Autoimmunity, Autoinflammation and Immunodeficiency in Vasculitis

Abstracts of the 20th International Vasculitis & ANCA Workshop, Dublin, Ireland 3-6 April 2022.

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Introduction

It is remarkable to consider that it is now 34 years since the inaugural ANCA workshop was hosted by Alan Wiik and Neil Rasmussen in Copenhagen. In the intervening period the bi-annual meeting has served as an important waypoint in our collective journey to develop our understanding of vasculitis and improve the care we provide to those affected. Each meeting is characterised by striking advances in basic science, epidemiological and clinical outcomes research. However, many challenges remain. Collectively we must commit to overcome these through continued scientific collaboration and study, to enhance patient experiences and outcomes.

Mark Little
Michael Clarkson
Chairpersons, 20th International Vasculitis & ANCA Workshop

With the evolutionary change of conference style gatherings, we welcomed the global vasculitis community of patients, practitioners, researchers and educators both virtually and in-person to Ireland. In so doing, we built upon the strong tradition and success of previous *International Vasculitis & ANCA Workshops* in translating advances in basic science and clinical research into demonstrable improvements in the management, outcome, and experience for patients living with vasculitis. COVID-19 has underscored the importance of collaborative networks, scientific development, and excellence in clinical care. Over 450 abstracts have been accepted, including first-author submissions from 180 institutions in 47 countries. These remarkable numbers emphasise that, notwithstanding the life changing events brought by the pandemic, this research community remains vibrant and resilient, whilst also maintaining a tremendous will for sharing novel ideas and learning. Areas of interest spanning autoimmunity, immunodeficiency and autoinflammation include Covid 19, bioinformatics, -omics, biomarkers, genetics, clinical trials, and newer therapeutics amongst many more. Herein this Supplement, we hope you enjoy reading the accepted abstracts for the *20th International Vasculitis & ANCA Workshop*.

Allyson Egan
Chair of the Scientific Organising Committee,

Disclosures: Mark Little has received grant funding from Vifor pharma, HRB, Vasculitis UK and Meath Foundation. Michael Clarkson has received grant funding from HRB. Allyson Egan has no disclosures.

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1. 1988 Copenhagen (A. Wiik, N. Rasmussen)
2. 1989 Noordwijkerhout (F.van der Woude, C. Kallenberg)
3. 1990 Washington, DC (C. Jennette, R. Falk)
4. 1992 Lubeck (W. Gross)
5. 1983 Cambridge (M. Lockwood, C. Pusey)
6. 1995 Paris (P. Lesavre, L.H. Noel)
7. 1996 Rochester (R. DeReeme)
8. 1998 Birmingham (P. Bacon)
9. 2000 Groningen (C. Kallenberg, J.W. Cohen Tervaert)
10. 2002 Cleveland (G. Hoffman, L. Calabrese)
11. 2003 Prague (V. Tesar)
12. 2005 Heidelberg (K. Andrassy)
13. 2007 Cancun (L.F. Flores-Suarez)
14. 2009 Lund-Copenhagen (M. Segelmark, N. /Rasmussen)
15. 2011 Chapel Hill (R. Falk, C. Jennette)
16. 2013 Paris (L. Guillevin)
17. 2015 London (C. Pusey, A. Salama)
18. 2017 Tokyo (Y. Arimura)
19. 2019 Philadelphia (P. Merkel)
20. 2022 Dublin (M. Little, M. Clarkson)

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Diagnosis & Classification

1. ANCA Positivity and ANCA Associated Vasculitis in Patients with Rheumatoid Arthritis

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Background: Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) with rheumatoid arthritis (RA) has been reported rarely, and studies have found ANCA positivity in RA. The objective of the study was to describe a cohort of patients with RA and AAV and to compare patients with RA+AAV to those with RA+ANCA positivity without AAV.

Methods: In this retrospective study, a cohort of patients with RA+ANCA positivity evaluated at an academic center were included. Data abstracted included demographics, seropositivity, ANCA specificity, clinical characteristics of RA, diagnosis of AAV and clinical features of AAV.

Results: The study included 77 patients, mean (±SD) age 60.2 (17.2) years, 78% female. ANCA serologies included perinuclear (p)-ANCA in 58%, cytoplasmic (c)-ANCA in 26%, myeloperoxidase (MPO) in 43% and proteinase 3 (PR3) in 26%. Twenty patients (26%) were p-ANCA/MPO positive, 3 patients (4%) c-ANCA/PR3 positive, 7 patients (9%) were p-ANCA/PR3 positive and 1 patient (1%) was c-ANCA/MPO positive.
Twenty-five patients (32%) had a diagnosis of AAV; 9 (36%) microscopic polyangiitis (MPA), 8 (32%) granulomatosis with polyangiitis (GPA), 1 (4%) eosinophilic granulomatosis with polyangiitis (EGPA), 1 (4%) GPA versus rheumatoid vasculitis (peripheral ulcerative keratitis, scleritis, sudden hearing loss, MPO positive). In 6 patients (24%) diagnosis was unclassifiable (1 interstitial lung disease attributed to vasculitis, 3 cutaneous vasculitis with ulcerations, 1 case of multiple digital infarctions from vasculitis, 1 leukocytoclastic vasculitis). Clinical manifestations of AAV included pauci-immune glomerulonephritis in 40%, cutaneous vasculitis in 28%, sino-nasal disease in 24%, mononeuritis multiplex or ocular disease in 12% each. Diagnosis of RA preceded vasculitis in 92% cases, was concurrent in 4% and followed vasculitis in 4%. Among patients with RA+ANCA positivity but no diagnosis of AAV, 1 patient had nasal septal perforation with polyposis, 1 patient had vasculitic rashes with neuropathy attributed to vasculitis from RA, 2 patients had retinal vasculitis.
A comparison of patients with RA+AAV, and patients with RA+ANCA without AAV is in Table 1. A higher proportion of patients with ANCA positivity via indirect immunofluorescence and antibody specificity to MPO or PR3 had a clinical diagnosis of AAV. These findings remained significant even when the 6 patients with unclassifiable disease were excluded.

Conclusions: AAV in RA included an even number of cases of GPA and MPA. The diagnosis of RA almost always preceded the diagnosis of AAV, and renal involvement was the most commonly present manifestation of AAV. There was uncertainty regarding attribution of isolated cutaneous vasculitis to RA or AAV. Many patients with RA and no vasculitis had positive MPO or PR3 antibodies. The presence of ANCA via IIF with MPO or PR3, even if

discordant, separated patients with RA+AAV from those without vasculitis highlighting the need for clinical vigilance in this subset of patients with RA. The immune mechanisms underlying this rare overlap need to be elucidated.

Disclosures: None.

Table 1: Comparison of patients with rheumatoid arthritis (RA) and diagnosis of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) to patients with RA with positive ANCA but no evidence of AAV

Variable	RA+AAV N=25	RA+ANCA without AAV N=52	p-value
Mean (±SD) age, years	59.3 (17.3)	60.6 (17.3)	0.69
Female sex, N (%)	20 (80)	40 (77)	1
Race, N (%)			0.17
Caucasian	15 (60)	17 (33)	
Black	2 (8)	2 (4)	
Asian	2 (8)	8 (15)	
Other	4 (16)	17 (31)	
Unknown or Declined	2 (8)	8 (15)	
Ethnicity, N (%)			
Hispanic/Latino	12 (48)	10 (19)	0.01
Seropositivity, N (%)	16 (64)	28 (54)	0.45
RhF positive	13 (56)	21 (41)	0.31
CCP positive	7 (32)	20 (43)	0.44
RhF and CCP positive, N (%)	4 (18)	13 (27)	0.56
p-ANCA	18 (72)	27 (52)	0.14
c-ANCA	8 (32)	12 (23)	0.42
MPO	15 (60)	18 (35)	0.05
PR3	8 (32)	12 (23)	0.42
p-ANCA/MPO or c-ANCA/PR3	16 (64)	7 (14)	<0.001
Any positive ANCA on IIF and positive ELISA	20 (80)	11 (21)	<0.001
Joint erosions on x-ray	7/19 (37)	11/42 (26)	0.55

SD = standard deviation, N= number, RhF = rheumatoid factor, CCP = cyclic citrullinated peptide, p-ANCA = perinuclear ANCA, c-ANCA = cytoplasmic ANCA, MPO = myeloperoxidase, PR3 = proteinase 3, IIF = indirect immunofluorescence, ELISA = enzyme linked immunosorbent assay

2. Clinical Characteristics and Reliability of a Self-Reported Diagnosis of Large-Vessel Vasculitis

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Background: To compare the clinical characteristics and determine the reliability of a self-reported diagnosis of giant cell arteritis (GCA) or Takayasu's arteritis (TAK) from an international, internet-based cohort.

Methods: Patients with GCA and TAK enrolled in an internet-based registry were included. Data provided by patients were collected through standardized forms, including type of vasculitis, symptoms, results of diagnostic testing, and medication use. The percentage of patients who met the 1990 American College of Rheumatology (ACR) classification criteria were calculated. For the 2012 Chapel Hill Consensus Conference (CHCC) definitions, age >50 years and report of a positive biopsy or imaging were used as surrogates for a diagnosis of GCA, and age <50 years with diagnosis on imaging were used as surrogates for a diagnosis of TAK.

Results: The study included 250 patients with self-reported diagnoses (126 GCA and 124 TAK). GCA cohort: The cohort was 80% female, mean (±SD) age 65 (±11.9) years. Mean (±SD) age at diagnosis of GCA was 62 (± 13.5) years. 9 patients (7%) reported age <50 years old at the time of diagnosis (range 31 to 48 years). Of these, 2 patients had a temporal artery biopsy with 1 reported as positive in a 48-year-old. 93 patients (74%) reported having a temporal artery biopsy which was positive in 59 patients (63%). Abnormal imaging was reported in 39 patients (31%), 27 of whom also reported symptoms of limb claudication. The self-reported clinical symptoms of GCA are in Table 1. 87% met ACR classification criteria and 60% met the CHCC definition for GCA (93% met either, 87% met both). TAK cohort: The cohort was 94% female, mean (±SD) age 42 (±15) years. Mean (±SD) age at diagnosis of TAK was 35 (±14.3) years. Twenty-six (21%) patients with TAK were age ≥50 years at diagnosis, 15 patients (12%) with symptom onset at age ≥50 years. 97/112 patients (87%) reported blood pressure discrepancy in the upper extremities. Abnormal imaging was reported in 115 patients (93%). The self-reported clinical symptoms of TAK are outlined in Table 1. The subset of 26 patients ≥50 years old reported similar manifestations as the other patients with TAK, including abnormal angiogram (92%), limb claudication (77%), upper extremity blood pressure discrepancy (77%), bruits (77%). 95% of patients met ACR classification criteria. 75% met the CHCC definition for TAK; the majority who failed to meet the definition criteria did so on account of age. 96% patients met either ACR classification criteria or CHCC definition with 74% meeting both.

Conclusions: Patients with a self-reported diagnosis of GCA or TAK were able to reliably provide information about their symptoms and diagnosis. Clinical symptoms and treatments reported were consistent with what would be expected. The majority in both cohorts met ACR classification criteria or CHCC definitions. The high proportion of patients ≥50 years diagnosed as TAK likely reflects the uncertainty in clinical practice in this age group and classification by

phenotype. These results provide support for the feasibility of conducting some types of research in these rare diseases through online registries.

Disclosures: None.

Table 1: Clinical manifestations in patients with a self-reported diagnosis of giant cell arteritis and Takayasu's arteritis

Clinical Manifestation	GCA* N=126	TAK* N=124
Weight loss >10 pounds	48/74 (65%)	65/118 (55%)
Fever >100.4° F	38/98 (39%)	41/89 (46%)
Myalgia	79/113 (70%)	96/116 (83%)
Headache	102/117 (87%)	70/104 (67%)
Scalp tenderness	93/121 (77%)	29/104 (28%)
Tenderness of temples	98/122 (80%)	36/107 (34%)
Vision loss	33/121 (27%)	28/115 (24%)
Pain/morning stiffness >30 minutes	89/115 (77%)	81/114 (71%)
Dizziness, syncope	60/106 (57%)	74/118 (63%)
Stroke	3/119 (3%)	17/115 (15%)
Chest pain or heart attack	21/119 (18%)	39/109 (36%)
Rash (including livedo, nodules)	34/109 (34%)	34/114 (30%)
Renal problems	15/119 (13%)	21/120 (18%)
Absent/weak pulse	25/91 (28%)	103/118 (87%)
Limb claudication	70/111 (63%)	82/116 (71%)
Bruit, neck/upper chest	9/111 (8%)	81/114 (71%)
Bruit, abdomen	5/111 (5%)	41/108 (38%)
Elevated blood pressure	41/103 (40%)	69/109 (63%)
Abnormal angiogram	31/117 (26%)	104/119 (87%)
Temporal artery biopsy	93/126 (73%)	9/117 (8%)
Abnormal ESR or CRP	106/119 (89%)	100/114 (88%)
Medication use for vasculitis		
Prednisone	121/124 (98%)	115/121 (95%)
Methotrexate	41/124 (33%)	81/121 (67%)
Azathioprine	0	35/121 (29%)
Mycophenolate mofetil	3/124 (3%)	31/121 (26%)
Anti-TNF therapy	2/124 (2%)	43/121 (36%)
Tocilizumab	18/124 (15%)	7/121 (6%)

* Numerator is the number of patients with this manifestation or treatment use; denominator is number of patients who responded Yes/No (response of "I don't know" excluded), data presented as number.
GCA=giant cell arteritis, TAK=Takayasu's arteritis, N=number, ESR=erythrocyte sedimentation rate, CRP=c-reactive protein

3. Takayasu arteritis presents at an older age in Northern European population

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Background: The definition of Takayasu arteritis includes the age of onset of disease as being <50 years. It has been reported most frequently in young females from Asian populations. We investigated whether the epidemiological features are the same in Norfolk, UK, where the population is predominantly of Northern European ancestry.

Methods: In our centre, cases are classified using validated international criteria. The electronic records of our vasculitis clinic were reviewed to identify all individuals with a new diagnosis of large vessel vasculitis between 2011-2020 who met a modified ACR 1990 criteria for Takayasu arteritis. The original criteria include decreased brachial artery pulse, bruit over subclavian arteries or aorta, and arteriogram abnormality. The respective modifications of these three criteria were to accept decreased radial pulse as well as the brachial pulse, bruit over the axillary artery as well as the subclavian artery, and abnormality of positron emission tomography and/or ultrasonography instead of arteriograms.

Results: 14 individuals met the modified ACR 1990 criteria for Takayasu arteritis. 2 of them also met the criteria for GCA and were excluded. 12 individuals were classified as having Takayasu arteritis. 10 were female. The mean (standard deviation) age at diagnosis was 68.4 (7.6) years. None of individuals were <40 years old. On presentation - 8 had upper limb claudication, 6 had pulse discrepancy, 3 had a blood pressure difference >10 mm Hg systolic, 7 had an audible bruit over either subclavian or axillary artery. The diagnosis was confirmed on positron emission tomography in all 12. Ultrasonography of extracranial arteries was abnormal in 6 as well. The mean (standard deviation) ESR was 53.6 (35) and CRP was 40.6 (32.2).

Conclusions: Takayasu arteritis can present at an older age in Norfolk, UK, where the population predominantly has Northern European ancestry. This has implications for treatment, identification of immunogenetic factors and disease classification.

Disclosures: None

4. Subgrouping ANCA-Associated Vasculitis According To Antibody Specifity and Clinicopathologic Classification

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Objectives: In this study we aimed to evaluate the effects of classification based on clinicopathological criteria and ANCA specificity in our AAV patients, retrospectively.

Methods: We reviewed the medical records of all patients diagnosed as AAV between January 2014 and December 2018 in our department. Patients were categorized as granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) according to the 2012 Chapel Hill

consensus nomenclature. Patients with available ANCA ELISA results were included. Associations between mortality, renal survival and AAV subgroups were analyzed using Kaplan Meier survival curves.

Results: A total of 61 AAV (45 [73.7%] GPA, 16 [26.2%] MPA, 44 [72.1%] PR3 positive and 17 [27.8%] MPO positive) patients were included. Patients' characteristics are summarized in table 1. Overall, both the GPA and anti-PR3 subgroups exhibited renal involvement less frequently (p=0.015 and p=0.012 respectively) and ear, nose or throat involvement more frequently than did the MPA and anti-MPO subgroups (both p<0.001). Renal survival was median 30 (IQR 61.75) months for MPA patients and 48 (IQR 82.5) months for GPA patients (p=0.506) during a median follow-up duration of 50 (0-184) months. Overall survival was median 38.5 (IQR 78.2) months for MPA patients and 57 (IQR 73.0) months for GPA patients (p=0,305). According to ANCA subtypes both renal and overall survival were better in PR3 positive group (p=0.018 and p=0.023 respectively).

Conclusions: In this study, which included a limited number of patients, classification by ANCA subtype appears to be a stronger criterion for predicting prognosis in AAV patients. However, multicenter studies are needed to confirm this trend.

Disclosures: None.

Table 1. Demographic and clinical characteristics of ANCA-associated vasculitis patients

	GPA (n=45)	MPA (n=16)	Total (n=61)
Sex, male (n) (%)	28 (62)	9 (56)	37 (61)
Age at diagnosis, mean (SD) (years)	50.3±2.6	62.4±2.7	53.2±15.3
ANCA subtype			
MPO-ANCA	4 (9)	13 (81)	17 (28)
PR3-ANCA	41 (93)	3 (19)	44 (72)
Organ/system involvements (n) (%)			
Kidney	32 (71)	16 (100)	48 (79)
Lung	37 (84)	15 (94)	52 (87)
ENT (ear-nose-throat)	36 (82)	0 (0)	36 (60)
Eye	9 (21)	0 (0)	9 (16)
Cardiac	0 (0)	0 (0)	0 (0)
GI	3 (7)	0 (0)	3 (5)
CNS	1 (2)	0 (0)	1 (2)
MNM	1 (2)	1 (6)	2 (3)
FFS; (n) (%)			
0	9 (24)	0 (0)	9 (17)
1	21 (55)	3 (19)	24 (44)
>2	8 (21)	13 (81)	21 (39)
Creatinine max. (mg/dl) (median, IQR) (at diagnosis)	2.08 (5.18)	3.27 (3.53)	2.52 (4.77)
ESRD development (n) (%)	9 (20)	4 (29)	13 (22)
Hemodialysis at diagnosis (n) (%)	13 (42)	9 (56)	22 (39)
Plasmapheresis at diagnosis (n) (%)	12 (29)	11 (69)	23 (40)
Overall Mortality (n) (%)	7 (16)	6 (38)	13 (21)

Follow-up duration (months), median (min-max)	57.0 (0-184)	38.5 (0-130)	50.0 (0-184)

5. Diagnostic algorithm to evaluate the clinical significance of small-vessel vasculitis surrounding a normal temporal artery

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Background: Systemic vasculitides are complex and heterogeneous diseases with overlapping features that frequently pose a diagnostic challenge to clinicians. The temporal artery biopsy (TAB) is the primary modality for establishing a diagnosis of giant cell arteritis (GCA) but, occasionally, TAB show small vessel inflammation (SVI) surrounding a spared temporal artery as the only pathologic finding. Ultimate diagnosis and, consequently, optimal treatment remain uncertain in these patients**. Objective:** To analyze the final diagnosis of patients with SVI surrounding a spared temporal artery after a pre-established diagnostic algorithm and to identify clinical and laboratory findings with potential usefulness in predicting the ultimate diagnosis.

Methods: Patients with TAB showing SVI were subjected to the diagnostic algorithm displayed in figure 1, completed by at least 1 year follow-up. Clinical and laboratory features at the time of diagnosis were recorded. The algorithm led to the following final diagnosis: GCA, other systemic vasculitis (other SV) and unclassifiable vasculitis. Chi-squared and ANOVA tests were used for statistical comparison using IBM SPSS Statistics 20.

Results: From 1998 to 2017, 826 TAB were performed in our institution. Biopsy disclosing SVI surrounding a normal temporal artery was described in 82 (10%) patients. In all patients TAB was selected as the first invasive procedure because GCA was initially considered the most likely diagnosis. 17 patients declined to undergo subsequent work-up to complete the diagnostic algorithm and 14 died or were lost to follow –up before completing 1 year. All of them were excluded. The study cohort consisted of 47 patients (27 women and 20 men) aged 74.2±9.4 years followed for 55.16±55.20 months. 36 (76%) fulfilled at least 3 ACR classification criteria for GCA. In 17 patients the final diagnosis was consistent with GCA based on the absence of small vessel vasculitis (SVV) in other territories, large-vessel inflammation by imaging or subsequent development of aortic aneurysm; in 19 SVV was subsequently

demonstrated in other territories and were diagnosed with other SV (11 ANCA-vasculitis, 1 cryoglobulinemia, 2 PAN, 5 vasculitis associated to autoimmune diseases) and in 11 diagnosis remained undetermined.

Conclusion: SVV surrounding a spared temporal artery is a relevant but equivocal finding in TAB. After a detailed diagnostic work-up most patients can be diagnosed with GCA or other systemic vasculitis although diagnosis remains uncertain in some cases. Search for more accurate molecular biomarkers is necessary for a better interpretation of these findings.

Disclosures: Lecturing/Consulting fees from Janssen, Meeting attendance support from Roche and Boehringer

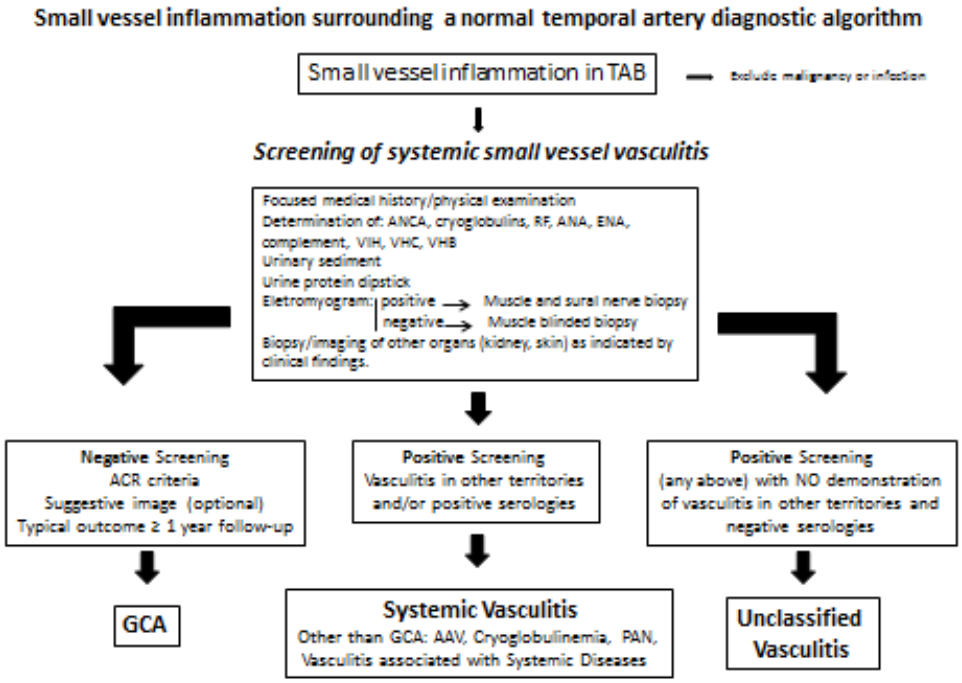

Fig 1

6. Anti-Collagen II Antibodies in Patients with Relapsing Polychondritis

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Background: Relapsing polychondritis (RP) is a heterogenous systemic inflammatory disease that affects multiple organ systems, in particular, cartilaginous structures. Clinical presentations in RP are variable, making recognition and diagnosis of the disease challenging. Testing for anti-collagen II (CII) antibodies have been proposed as a diagnostic tool t RP; however, the data remains inconclusive as to what percentage of RP patients have anti-CII antibodies and

the value for diagnosis. Our objectives were to evaluate the utility of anti-CII antibody as a diagnostic tool in patients with RP.

Methods: Patients 18 years and older were recruited into a prospective observational cohort of RP. Diagnosis of RP was made using McAdams or Damiani's diagnostic criteria for RP. All patients referred for evaluation of RP with anti-CII antibodies measured were included. Patients with VEXAS syndrome were excluded. Anti-Cll antibodies were assayed via a clinically certified ELISA test (Mayo Clinic, Rochester, MN) in all patients evaluated from July 2019 to October 2021. Clinical features were compared between patients with a diagnosis of RP stratified by presence of anti-CII antibody results using Fisher's exact test or Wilcoxon rank sum test as appropriate.

Results: 60 patients were tested for anti-CII antibodies, from those nine patients (15%) had elevated levels. Two patients did not meet diagnostic criteria for RP and, from those, one patient had elevated anti-CII antibodies. 58 patients met diagnostic criteria for RP and were included on further analysis. Seven patients (12%) had repeated measurements. One patient had an initial positive anti-CII, with a follow up negative value. Six patients (10%) had an initial negative anti-CII, with all of the repeat values remaining negative except for one patient. Patients with a diagnosis of RP with elevated anti-CII antibodies compared to those without elevated antibodies have significantly higher prevalence of genital ulcers (38% vs 8%, p = 0.01), sicca symptoms (88 vs 38%, p = 0.01) and a diagnosis of MAGIC ((mouth and genital ulcers with inflamed cartilage) syndrome (38% vs 8%, p=0.01). There were no statistical differences between the groups for age of disease onset, sex, other clinical manifestations, elevated inflammatory markers, treatment, organ damage, ICU admissions or death.

Conclusion: Anti-CII antibodies have a limited role as a diagnostic test and biomarker of disease activity in RP. Presence of anti-CII antibodies may be associated with specific clinical symptoms and may be enriched in a subset of patients with RP who have mucocutaneous disease. This subset is commonly referred to as MAGIC syndrome. Whether anti-CII antibodies provide pathogenic insight for a smaller subset of patients with RP remains to be determined.

Disclosures: None

7. Chronic Fatigue Syndrome (CFS), Cognitive Failure and Anxiety in ANCA-associated vasculitis

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Objective: Chronic fatigue is a major burden of disease in patients with ANCA-Associated Vasculitis (AAV) which results in a decreased quality of life. The prevalence of fatigue in AAV is, however, unknown. The aim of our study is to evaluate the presence of chronic fatigue in

patients with a diagnosis of AAV i.e., granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis or microscopic polyangiitis, and to identify potential clinical and biopsychosocial determinants.

Methods: 59 participants included in our study completed the validated DePaul Symptom Questionnaire (DSQ). Patients were labelled with “Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS)” when they fulfilled the Canadian Consensus Criteria for ME/CFS. Disease activity was scored using Birmingham Vasculitis Activity (BVAS), whereas the Vasculitis damage index (VDI) was used to evaluate damage. Mental comorbidities where analyzed to understand potential biopsychosocial factors related to chronic fatigue. To assess anxiety and depression we used the Hospital Anxiety and Depression scale (HADS). We also used the Cognitive Failure Questionnaire (CFQ) to estimate the frequency of cognitive failure. Sleep quality was assessed using The Pittsburgh Sleep Quality Index (PSQI). Statistical analysis was carried out using Fischer’s exact test.

Results: We found that 32/59 (54%) of AAV patients fulfilled the case definition for ME/CFS. There was no relationship between the presence of ME/CFS and BVAS (p=0.5), VDI (p=0.78), sleep disorders (p=0.8), depression (p=0.09) or C-reactive protein (p=0.2399) in our study population. However, a substantial statistically significant correlation was present in patients with AAV suffering from ME/CFS, cognitive failure (p=0.004) and/ or anxiety (p= <0.001).

Conclusion: Chronic fatigue affects AAV patient’s mental wellbeing. From our analysis we conclude that chronic fatigue, cognitive failure and/or anxiety co-occur independently of vasculitis disease activity. We postulate that therapies aimed at improving anxiety may be utilized as adjunct agents for patients with AAV suffering from Chronic fatigue.

Disclosure: Dutch Kidney Foundation (17PhD01) Arthritis Society (19-0558)

8. Dysregulated glucose and lipid metabolism in glucocorticoid naïve GCA patients at diagnosis

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Background: Giant cell arteritis (GCA) is an autoinflammatory disorder that affects the large and medium arteries in elderly people. Approximately 40-60% of patients with GCA also have overlapping polymyalgia rheumatica (PMR). PMR is a common rheumatological disease that affects the proximal large joints in the shoulders and hips. Long-term glucocorticoids (GCs)

administration is still the mainstay of therapy for GCA and PMR patients. However, GCs can cause GC-related adverse events including hypercholesterolemia, hypertension, diabetes mellitus, cataract, and infections. Therefore, novel GC-sparing treatment options are needed. Previous studies reported a negative association between metabolic features such as cholesterol, fasting blood glucose and BMI in the development of GCA. However, data are limited. Here, we aimed to explore the metabolic features in two independent GC-naïve GCA/PMR patient cohorts and to elaborate on the prevalence of comorbidities in patients at the time of diagnosis and during treatment.

Methods: This study included two cohorts from Aarhus (Denmark) and Groningen (The Netherlands, GCA/PMR/SENEX (GPS) cohort). The GPS cohort consisted of 50 GCA and 44 PMR patients. From the Aarhus cohort, 52 GCA and 25 PMR patients were included (Aarhus cohort). As a representation of the general population, we also included data of participants of the Lifelines cohort study (n=591), which includes participants from the northern population of the Netherlands. Patients in the GPS cohort were also prospectively followed with visits at 3 months, 1, 2, 3, 4 and 5 years. Laboratory measurements and comorbidities (diabetes mellitus, hypercholesterolemia, hypertension, obesity and cataract) were assessed at each visit.
Results: In GCA patients (GPS cohort), we observed higher HbA1c and glucose levels before treatment compared to the general population. In contrast, LDL, HDL and cholesterol levels as well as BMI were lower in GCA patients suggesting a disturbed lipid and glucose metabolism in newly diagnosed GCA patients. Similar findings were seen in the Aarhus cohort, thereby validating our findings in the GPS cohort. Next, we investigated whether comorbidities were associated with levels of acute-phase markers (CRP, ESR) at the time of diagnosis. Except for cataract, none of the comorbidities were associated with CRP or ESR. In the early phase of GC treatment, the prevalence of diabetes increased in GCA patients, but not in PMR patients. The prevalence of cataract and obesity was increased in GCA patients upon long-term (5 year) treatment.

Conclusions: Here, we show a dysregulated lipid and glucose metabolism in newly diagnosed GCA patients. GC treatment resulted in the development of comorbidities in GCA patients, emphasizing the high need for improved GC-sparing treatment options.

Disclosures: None.

9. Characterization of patients with normal inflammatory markers in giant cell arteritis

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Objectives: Giant cell arteritis (GCA) is the most common form of vasculitis in people over the age of 50 years old. Inflammatory markers, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are typically elevated at the time of diagnosis and prompt suspicion for

this disease. Given the severe potential consequences of a missed diagnosis, we aimed to study the frequency and clinical correlation of normal inflammatory markers in patients with confirmed GCA.

Methods: Electronic medical records of patients diagnosed with GCA by rheumatologists at the University of Alberta between April 2012 and December 2017 were retrospectively reviewed. For inclusion, patients must have 1) met ACR 1990 classification criteria for GCA, 2) had confirmed disease by either temporal artery biopsy or advanced imaging (PET/CT, MRA, CTA) and 3) had either ESR and/or CRP prior to glucocorticoid administration available. Patients were grouped according to the presence of either normal or elevated ESR or CRP (normal ESR defined as ≤25mm/hr, normal CRP as ≤8mg/L.) Groups with elevated versus normal inflammatory markers were compared with respect to demographics, symptoms, comorbidities, medications, and clinical outcomes.

Results: Of 81 total GCA patients, 42 met above study inclusion (38 with available ESR, 41 with available CRP, and 37 with both.) Among confirmed cases, 21.6% of patients had either a normal ESR or CRP pre-treatment (21.1% with normal ESR, and 9.8% with normal CRP,) while 5.4% of patients had both normal ESR and CRP. See Table 1 for distribution of inflammatory markers observed. Upon limiting the sample to the 34 patients with biopsy-confirmed disease, 20.0% had either normal ESR or CRP and 6.7% had both normal markers. No significant differences in age, sex, comorbidities, or symptoms were observed between patients with elevated versus normal inflammatory markers. Patients with normal ESR were less likely to receive steroid-sparing agents than patients with elevated ESR (0.0% vs 50.0%, p=0.013), however, and were less likely to relapse (12.5% vs 56.7%, p=0.045).

Conclusion: Twenty percent of biopsy- or imaging-confirmed GCA patients have either a normal ESR or CRP at diagnosis, and both tests are normal in 5-7% of patients. No clinical features reliably distinguish cases with normal inflammatory markers, but normal ESR may predict a lower risk of future relapse. These findings highlight the importance of routinely checking both ESR and CRP in cases of suspected GCA and maintaining a high index of suspicion in those with typical symptoms or signs.

Disclosures: None.

Table 1. Case distribution according to inflammatory marker value

Cut-off Value	Number of Cases	Relative Percent
ESR $\leq$ 25	8/38	21.1%
ESR 26-49	5/38	13.2%
ESR $\geq$ 50	25/38	65.8
CRP $\leq$ 10	4/41	9.8%
CRP 11-20	3/41	7.3%
CRP 21-30	5/41	12.2%
CRP 31-50	8/41	19.5%
CRP > 50	21/41	51.2%

10. Validation of Angiographic Patterns of Disease in a Turkish Cohort of Patients with Takayasu's Arteritis

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Background: Previous studies using computer-driven methods have identified subsets of patients with Takayasu's arteritis (TAK) based on angiographic patterns of disease. These subsets were consistent between independent cohorts in North America and India, however, the prevalence of each subset differed between continents. The objective of this current study was to validate in an independent cohort from Turkey angiographic patterns of disease in TAK and determine if the prevalence of these patterns is more similar to cohorts from India, North America, or neither.

Methods: Angiograph data were derived from records of patients with TAK from 12 tertiary rheumatology centers in Turkey. All patients underwent whole-body angiography of the aorta and branch vessels, with categorization of involvement (stenosis, occlusion, or aneurysm) in 13 arterial territories. K-means cluster analysis was performed to identify subgroups of patients based on pattern of angiographic involvement.

Results: Data from 421 patients in the cohort in Turkey were available for analysis. Using K-means clustering, three distinct clusters were identified for the Turkish patients; these three clusters we identical to those previously identified in the Indian and North American cohorts (Table 1). Patients in Cluster 1 have significantly more disease in the abdominal aorta, renal, and mesenteric arteries ($p < 0.01$). Patients in Cluster 2 have significantly more bilateral disease in the carotid and subclavian arteries ($p < 0.01$). Compared to Clusters 1 and 2, patients in Cluster 3 have asymmetric disease with fewer involved territories ($p < 0.01$).

The prevalence in each of the three clusters for patients from Turkey (current analysis) compared to the prevalences for patients from North America (NA) and India (previously published data) differed. The distribution of patients among the three clusters was quite similar among patients from Turkey and NA, but these two cohorts differed in this respect from patients from India. Patients from Turkey and NA were more likely to fall within Clusters Two (India: 27% vs NA: 35% vs Turkey: 35%) and Three (India: 32% vs NA: 41% vs Turkey: 44%), while patients from India were more likely to fall within Cluster One (India: 41% vs NA: 24% vs Turkey: 21%).

Conclusions: This study provides strong, independent confirmation that there are distinct subsets of Takayasu's arteritis based on angiographic disease. These patterns are consistent between continents; however, the prevalence of each pattern differs. Genetic and/or environmental factors may contribute to patterns of angiographic disease in patients with TAK.

Disclosures: None

Table 1. Arterial distribution in clusters for a Turkish cohort of patients with Takayasu's arteritis

	Cluster One n = 90	Cluster Two n = 148	Cluster Three n = 183
Ascending aorta	18 (0.20)	39 (0.26)	32 (0.17)
Aortic arch	14 (0.16)	18 (0.12)	24 (0.13)
Thoracic aorta	29 (0.32)	40 (0.27)	35 (0.19)
Abdominal aorta	44 (0.49)	30 (0.20)	51 (0.28)
Left subclavian	63 (0.7)	107 (0.72)	112 (0.61)
Right subclavian	34 (0.38)	104 (0.7)	45 (0.25)
Innominate	5 (0.06)	38 (0.26)	14 (0.08)
Left axillary	8 (0.09)	18 (0.12)	19 (0.1)
Right axillary	6 (0.07)	19 (0.13)	12 (0.07)
Left carotid	43 (0.48)	129 (0.87)	50 (0.27)
Right carotid	33 (0.37)	125 (0.84)	9 (0.05)
Left vertebral	17 (0.19)	14 (0.09)	19 (0.10)
Right vertebral	10 (0.11)	16 (0.11)	6 (0.03)
Left renal	77 (0.86)	7 (0.05)	9 (0.05)
Right renal	67 (0.74)	8 (0.05)	10 (0.05)
Mesenteric	65 (0.72)	26 (0.18)	31 (0.17)
Left iliac	9 (0.1)	4 (0.03)	11 (0.06)
Right iliac	10 (0.11)	3 (0.02)	13 (0.07)
Left femoral	3 (0.03)	2 (0.01)	0 (0)
Right femoral	0 (0)	3 (0.02)	2 (0.01)

11. Characteristics of Inflammatory Arthritis in Polyarteritis Nodosa

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Background: Polyarteritis nodosa is a small to medium vessel vasculitis that can be limited to cutaneous manifestations or occur as a systemic disorder. Arthralgia has widely been reported in polyarteritis nodosa, but true inflammatory arthritis is seemingly rare in the literature. When inflammatory arthritis does occur, it has been reported to have a predilection for the lower extremities and treatment options are unclear. We report on a case series of 22 patients with a co-diagnosis of cutaneous polyarteritis nodosa and inflammatory arthritis.

Methods: Advanced Text Explorer software was utilized to identify chart notes that contained the phrases "cutaneous polyarteritis nodosa" and "inflammatory arthritis". A thorough chart review was conducted on the 34 resulting patients. Twelve patients did not have a diagnosis of cutaneous polyarteritis nodosa and/or a diagnosis of inflammatory arthritis so were excluded.

The charts were then reviewed for pertinent demographic information, clinical history, lab values, pathology, synovial fluid analysis, and imaging results.

Results: Of the 22 patients included, 16 (72.7%) were female with an average age of 40 at diagnosis (18-78). The arthritis most often involved the ankles (91.3%), followed by feet (43%), hands and wrists (35% each), and sacroiliitis/low back (13%). Six of the patients (27%) had erosive disease. In 77.7% of the patients cutaneous PAN preceded the inflammatory arthritis or co-occurred. Average time between diagnoses was 4.25 years. C-reactive protein was elevated in 10 (45%) and ESR in 5 (23%). ANA was positive in 23% and ANCA in 14%. Treatments varied widely with success reported most often using methotrexate (positive response in 7 of 10 patients treated). The average number of treatments utilized at the time of last follow-up was 3.4.

Conclusions: Inflammatory arthritis in association with polyarteritis nodosa has a predilection to begin in the ankles and progresses to an oligoarthritis that can be difficult to treat with current immunosuppressive medications. Further research into the pathophysiology and treatment options of this oligoarthritis are indicated.

Disclosures: None

12. Negative vs. Positive Antineutrophil Cytoplasmic Antibody Granulomatosis with Polyangiitis: A Case-Control Study

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Objectives: To characterize clinical features, management and outcomes of ANCA-negative GPA patients in comparison to age and sex matched patients with ANCA-positive GPA, and to describe patients who seroconverted from ANCA-negative to ANCA-positive GPA.

Methods: We conducted a single-center, sex and age matched case-control with ANCA-negative vs. ANCA-positive GPA evaluated at our institution from January 1, 1996, to December 31, 2015. We also performed a case crossover study of the seroconverts. Clinical data and outcomes were retrospectively abstracted from electronic medical records.

Results: We identified 110 patients with ANCA-negative GPA, predominantly female (65%) with median age of 55 (IQR 39-65) years at time of diagnosis. Disease severity was milder in ANCA-negative GPA (BVAS/WG score = 2 vs. 6, $p<0.0001$). Mucous membranous/eye manifestations were more frequent in ANCA-negative GPA, whereas general symptoms (arthralgias, fever, weight loss, myalgias), pulmonary, and renal involvement were more frequent in ANCA-positive GPA. ANCA-positive GPA patients relapsed more at 60 months (21.8% vs. 9.1%, $p=0.009$) compared to ANCA-negative GPA and had a shorter time to event ($p=0.043$). Patients with general manifestations, BMI > 30 kg/m^2 and necrotizing

granulomatous inflammation were more likely to relapse. In 16 ANCA seroconverts, patients had higher mean BVAS/WG score (p<0.0001), and increased incidence of relapses (p=0.004) after the seroconversion. Necrotizing granulomatous inflammation on biopsy in ANCA-negative GPA patients was identified as a risk factor for ANCA-positive seroconversion.

Conclusion: ANCA-negative GPA patients have milder disease and decreased frequency of relapse. ANCA seroconversion portends higher disease severity and an increased frequency of relapses.

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Table 1. Clinical characteristics and outcomes of patients with ANCA negative Granulomatosis with Polyangiitis (GPA) who seroconverted into positive ANCA GPA (n=16).

Diagnosis	ANCA – negative period				Seroconversion	ANCA – positive period					Last contact	
Age, Sex	Clinical Presentation	BVAS/WG	Remission-induction	Relapse (n)	Time to seroconversion (months)	Clinical Presentation	ANCA type	BVAS/WG	Remission-induction	Relapse (n)	Follow-up (years)	Status
46, M	ENT	3	PDN	1	12	Neuro	PR3	6	PDN, MTX	1	15	Deceased
53, F	ENT	1	PDN	0	53	ENT	PR3	1	PDN, MTX	3	13	Alive
71, M	Lung	3	PDN, CYC	1	42	Lung	PR3	3	PDN, CYC	3	5	Alive
53, F	ENT	1	PDN	1	128	ENT, Lung	PR3	3	PDN	2	13	Alive
29, M	Lung	1	TMP/SMX	0	6	Lung	PR3	2	PDN	2	23	Alive
73, M	Lung	1	PDN	1	1	Lung	PR3	1	PDN	2	6	Deceased
22, M	ENT, Lung	2	PDN, CYC	0	148	ENT, Lung, Kidney	PR3	6	PDN	2	21	Alive
50, F	ENT	3	PDN	0	31	Lung	PR3	2	PDN, MTX	5	19	Alive
55, F	Kidney	4	PDN, CYC	0	102	ENT	MPO	1	PDN	1	11	Deceased
16, F	Lung	1	PDN	0	45	ENT, Neuro	PR3	6	PDN	1	9	Alive
47, M	ENT	2	PDN, CYC	1	48	ENT, Lung	PR3	4	PDN	1	3	Alive
47, F	ENT	3	TMP/SMX	0	9	ENT	MPO	3	PDN	3	17	Alive
61, M	ENT	4	PDN	0	13	ENT, Lung, Kidney	MPO	8	PDN, CYC	1	16	Alive
77, F	ENT	1	PDN, CYC	0	80	ENT, Neuro	MPO	4	PDN	2	13	Alive
67, F	Lung	2	PDN, MTX	1	44	Lung, Kidney	MPO	4	PDN	1	11	Alive
46, M	ENT	4	PDN, CYC	0	222	ENT	PR3	1	PDN	1	8	Alive

- **Increased incidence of relapse (20 vs. 6, p=0.004). Risk for >1 Relapse – OR = 1.11, 95%CI 0.203-2.432, p=0.097, vasculitis and granulomatous inflammation present at the biopsy of the time the patients were ANCA-negative GPA.**
- **Higher BVAS/WG at the time of seroconversion (3 vs. 2, p<0.0001). Risk for severe disease - OR = 1.52, 95%CI 0.93-2.50, p=0.093.**

13. Clustering of anti-neutrophil cytoplasmic antibody-associated vasculitis - using a pre-processed harmonised dataset

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Background: The sub-classification of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) has been a long-standing debate. Unsupervised learning has previously been used for partitioning of phenotypic groups, but as AAV is a rare disease, small sample sizes have been a limiting factor. Here we attempt clustering of a small dataset harmonised to the FAIRVASC ontology, allowing potential future inclusion of an additional 6000 AAV patients from the FAIRVASC collaboration registries to the cluster model.

FAIRVASC is a research project seeking to federate AAV registries across Europe using semantic web technologies (https://fairvasc.eu).

Methods: This study used a dataset of 292 patients from southern Sweden, classified as granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA), according to the European Medicines Agency algorithm. The dataset was pre-processed from a relational database format to a resource descriptive framework (RDF) graph-based data model, harmonising the dataset to a FAIRVASC standard. Factor analysis of mixed data (FAMD) and agglomerative hierarchical cluster analysis on principal components (HCPC) was used to develop a cluster model, including organ pattern, ANCA status, serum creatinine, C-reactive protein, gender, and age at diagnosis. The generated clusters were evaluated by baseline characteristics, mortality, and renal outcome.

Results: The analyses involved data for 163 subjects with GPA and 129 with MPA. The clustering model resulted in two larger clusters and three smaller ones. The larger clusters were a predominantly anti-PR3 positive cluster of young (mean 57.5 years at diagnosis) patients with ear-nose-throat involvement and a favourable outcome (Cluster 1), and a predominantly anti-MPO positive cluster with severe kidney involvement and high rates of mortality and end-stage kidney disease (Cluster 5). The three smaller clusters differed in terms of organ involvement and ANCA status at diagnosis, one with severe lung and renal involvement and a poor outcome (Cluster 3) and two with similar outcome, one ANCA negative (Cluster 4), and one with peripheral nerve involvement (Cluster 2). The descriptive characteristics of the clusters are presented in table 1.

Conclusions: Our analysis suggests five clusters of AAV patients based on baseline features, associated with different mortality and renal outcome. The investigation acts as a proof of concept of the FAIRVASC ontology and infrastructure for the harmonisation of heterogeneous AAV datasets. The cluster model may in the future readily include an unprecedented number of European AAV patients.

Disclosures: None

Table 1. Baseline characteristics and outcome of 292 patients with AAV by diagnosis and cluster affiliation

	Diagnosis		Cluster				
	GPA	**MPA**	**Cluster 1**	**Cluster 2**	**Cluster 3**	**Cluster 4**	**Cluster 5**
Demographics							
Age, years	62.9 (16.5)	70.8 (13.6)	57.5 (17.1)	65.3 (13.8)	67.0 (13.0)	65.8 (18.1)	73.3 (11.6)
Male	98 (60)	64 (50)	50 (54)	18 (62)	20 (77)	12 (63)	62 (50)
Female	65 (40)	65 (50)	43 (46)	11 (38)	6 (23)	7 (37)	63 (50)
Diagnosis							
GPA	163 (100)	0 (0)	85 (91)	20 (69)	17 (65)	10 (53)	31 (25)
MPA	0 (0)	129 (100)	8 (9)	9 (31)	9 (35)	9 (47)	94 (75)
Organ pattern							
General	135 (83)	90 (70)	76 (82)	25 (86)	24 (92)	10 (53)	90 (72)
Musculoskeletal	77 (47)	51 (40)	48 (52)	13 (45)	19 (73)	2 (11)	46 (37)
Cutaneous	16 (10)	14 (11)	6 (6)	2 (7)	4 (15)	6 (32)	12 (10)
Eyes	14 (9)	5 (4)	11 (12)	2 (7)	4 (15)	0 (0)	2 (2)
Ear-nose-throat	108 (66)	4 (3)	78 (84)	10 (34)	8 (31)	7 (37)	9 (7)
Lung	100 (61)	41 (32)	49 (53)	13 (45)	25 (96)	8 (42)	46 (37)
Pulmonary haemorrhage	13 (8)	9 (7)	0 (0)	2 (7)	19 (73)	1 (5)	0 (0)
Cardiovascular	10 (6)	6 (5)	0 (0)	12 (41)	0 (0)	3 (16)	1 (1)
Abdominal	4 (2)	5 (4)	0 (0)	0 (0)	0 (0)	9 (47)	0 (0)
Renal	89 (55)	124 (96)	43 (46)	13 (45)	23 (88)	12 (63)	122 (98)
Central nervous system	6 (4)	2 (2)	5 (5)	1 (3)	0 (0)	0 (0)	2 (2)
Peripheral nervous system	14 (9)	7 (5)	0 (0)	21 (72)	0 (0)	0 (0)	0 (0)
Laboratory							
PR3-positive	123 (75)	32 (25)	77 (83)	20 (69)	18 (69)	6 (32)	34 (27)
MPO-positive	33 (20)	93 (72)	16 (17)	9 (31)	7 (27)	3 (16)	91 (73)
ANCA-negative	7 (4)	4 (3)	0 (0)	0 (0)	1 (4)	10 (53)	0 (0)
S-Creatinine, µmol/L	174.8 (186.1)	320.3 (251.3)	110.4 (97.2)	126.7 (107.3)	322.1 (280.1)	281.3 (293.9)	337.2 (240.8)
CRP, mg/L	108.5 (83.4)	87.8 (80.2)	94.3 (79.1)	125.2 (73.6)	143.2 (96.4)	98.5 (102.9)	88.1 (77.4)
Cluster							
Cluster 1	85 (52)	8 (6)	93 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Cluster 2	20 (12)	9 (7)	0 (0)	29 (100)	0 (0)	0 (0)	0 (0)
Cluster 3	17 (10)	9 (7)	0 (0)	0 (0)	26 (100)	0 (0)	0 (0)
Cluster 4	10 (6)	9 (7)	0 (0)	0 (0)	0 (0)	19 (100)	0 (0)
Cluster 5	31 (19)	94 (73)	0 (0)	0 (0)	0 (0)	0 (0)	125 (100)
Outcome							
Death	56 (34)	82 (64)	20 (22)	13 (45)	11 (42)	10 (53)	84 (67)
ESKD	14 (9)	34 (26)	2 (2)	2 (7)	7 (27)	2 (11)	35 (28)
Follow up, years	7.5 (5.5)	6.0 (5.2)	8.9 (5.3)	6.3 (4.3)	4.5 (4.4)	7.4 (5.9)	5.8 (5.4)

Categorical variables are number (%). Continuous variables are mean (SD).
GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis, MPO, myeloperoxidase; PR3, proteinase 3; ANCA, anti-neutrophil cytoplasmic antibody; S-Creatinine, Serum Creatinine; CRP, C-reactive protein; ESKD, end-stage kidney disease.

14. ANCA-IIF technique improvement and its impact on the positivity rate of ANCA tests

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Background: The detection of antineutrophil cytoplasmic antibodies (ANCA) by indirect immunofluorescence (IIF) with ethanol-fixed neutrophils is subject to substantial differences across laboratories. A low positivity rate of the IIF-ANCA test compared to the literature was observed at a reference laboratory and the test's protocol needed to be revised. This study aims to assess the impact of improvements in the IIF-ANCA technique on the positivity rate of ANCA tests.

Methods: A cross-sectional study with serum samples from patients with ANCA-associated vasculitis (AAV), autoimmune hepatitis (AIH) and ulcerative colitis (UC) was performed. A paired analysis was performed for IIF-ANCA results using the traditional method and a modified protocol after a series of specific adjustments in the technique based on the protocol of IIF-ANCA test performed at a national-wide private laboratory in Brazil (Fleury Laboratory). ANCA specificity was assessed by a third generation ELISA kit for anti-PR3 and anti-MPO antibodies.

Results: At disease presentation, the positivity rate of IIF-ANCA tests performed at the reference Immunology laboratory in the Federal University of São Paulo, Brazil was 32.3% in AAV, AIH and UC patients. Meanwhile, sera from the same patients tested by other laboratories using IIF-ANCA and ELISA yielded a higher positivity rate of 75.0% and 72.7%, respectively. Modifications in the IIF-ANCA technique were performed and serum samples were tested in pairs for the traditional and modified IIF-ANCA technique. Patients were analyzed regardless of the disease activity status. A significantly increase in the positivity rate (14.8% vs. 34.3%; p=0.0002) and median ANCA titers [1/40 (1/30 – 1/160) vs. 1/80 (1/40-1/80); p=0.0003] were observed in AAV, AIH and UC patients. UC had the highest increment in positive IIF-ANCA results from 5.3% to 36.8%. The positivity rate of PR3-ANCA and MPO-ANCA was not associated with the positivity of the IIF-ANCA technique.

Conclusions: Adjustments in the IIF-ANCA protocol led to a significant improvement in the positivity rate and on ANCA titers in AAV, AIH and UC patients. Nonetheless, there was poor agreement between MPO- or PR3-ANCA and both IIF-ANCA techniques.

Disclosures: None.

Epidemiology, Registries, Informatics

15. Rare diseases: making environmental health studies' data as open as possible

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Background: Researchers are confronted with increased data protection risks when trying to publish in an open manner data related to their studies into environmental factors related to rare diseases, even if the data is pseudonymised. Identification risks exist for the patients being studied, in terms of singling out an individual, data linking with other sources, or inferencing certain data from the linked data. In addition, effective anonymization methods cannot be applied without losing the value of the data for research with low sample sizes, as in rare diseases. For example, permuting the environmental observations would affect the temporality of the data or introducing noise would affect the magnitude of the values. Both methods can potentially hide the signal that the researchers are looking for.

Methods: The approach we recommend is to publish example patient event-environmental linked data and its associated metadata, which could be shared as Open Data following the Findable Accessible Interoperability and Reusability (FAIR) guiding principles. In our approach, we recommend the example data and metadata are described using the Resource Description Framework (RDF), a standard graph data model, following W3C standards and recommendations for statistical data (RDF Data Cube), dataset descriptors (DCAT), provenance and lineage (PROV-O); and data protection domains (DPV). We then recommend that the data and associated metadata is published in an open repository preferred by your community generating a unique Digital Object Identifier (DOI) for the dataset.

Results: An example of a dataset that has been published in an open manner according to our proposed approach can be found at the following DOI: https://doi.org/10.5281/zenodo.5544257. The dataset is an example result of associating air pollution and weather data subsets to particular health events within a region in the Republic of Ireland, together with the relevant metadata fields. The implementation of the FAIR guiding principles was applied on the necessary metadata and a Data Protection Impact Assessment, in accordance with the GDPR, was created, therefore ensuring good data protection practices were met to assess the necessary risks that could arise.

Conclusions: The approach proposed would facilitate data publication as open as possible for researchers studying rare disease environmental risk factors. Furthermore, the data pre-processing step will be recorded in the metadata (i.e., a transparent record) enhancing the data re-use of researchers in the community and stakeholders.

Disclosures: None.

16. Epidemiology and Clinical Characteristics of Adult-Onset IgA Vasculitis in Southern Sweden

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Background: IgA vasculitis (IgAV) is the most prevalent primary childhood vasculitis in Sweden, but the disease is considerably rarer in adults. Patients with adult-onset IgAV have more severe organ involvement and worse long-term renal outcomes compared to children. This study aims to describe the epidemiology, clinical characteristics, and outcomes of adult-onset IgAV in Skåne, southern Sweden.

Methods: The study area consisted of Skåne, the southernmost region of Sweden, with an adult (≥18 years) population of 990 464 on 31 December 2010. Adult patients assigned the ICD-10 code D69.0 between 2000 and 2019 were retrospectively identified in a population-based database. Medical records were reviewed to validate the diagnosis of IgAV and abstract data. Patients defined as IgAV according to the 2012 Chapel Hill Consensus Conference Nomenclature of Vasculitides with a biopsy-proven diagnosis were included. The incidence rate and point prevalence (p.p.) were estimated per 1 000 000 adults. The p.p. was estimated on 31 December 2019.

Results: Fifty-nine patients (19 women) were classified as having adult-onset IgAV. The median age at diagnosis was 38 (IQR 24−55) years. The annual incidence rate was 3.0 per 1 000 000 adults and was higher among men than women (4.0 vs 2.0/1 000 000, *P*=0.004). The incidence rate decreased with age, with the highest rate in the group aged 18−27 years (Table 1). The point prevalence was estimated to 45.3 /1 000 000 adults and was higher among men (58.7 vs 31.8/1 000 000, *P*=0.03). Ninety-seven percent of patients presented with non-thrombocytopenic purpura, 78% with renal involvement, 59% with arthritis/arthralgia and 39% with gastrointestinal symptoms. At onset of the disease, 66% received oral corticosteroids (mean dose 40 ± 19 mg/day), three patients (5%) were treated with oral cyclophosphamide (150 mg/day), and one received plasmapheresis. Sixteen patients (27%) started immunosuppressive treatment later during follow-up, most commonly azathioprine. Patients were followed for a median time of 6.5 (IQR 2.8−11.8) years. One patient (35-year-old woman) developed end-stage renal disease 11 years after diagnosis of IgAV and underwent a kidney transplant. In total, five deaths (8%) were observed. Causes of death included malignancy (n=2), stroke (n=1), femur fracture (n=1) and unknown (n=1). The mean age at death was 83 ± 10 years.

Conclusions: The incidence of adult-onset IgAV in southern Sweden was comparable with that described in most other European studies. The long-term renal outcome was better than previously reported and the prognosis appears to be favourable.

Disclosures: None.

Table 1 Incidence rate and point prevalence of biopsy-proven IgAV per 1 000 000 adult (≥18 years) inhabitants in Skåne, Sweden, 2000−2019.

	No. of cases	Incidence (95% CI)
All	59	3.0 (2.2−3.8)
Sex-specific incidence rate		
Men	40	4.0 (2.8−5.3)
Women	19	2.0 (1.1−2.9)
Age-specific incidence rate		
18-27	18	5.7 (3.0−8.3)
28-37	11	3.3 (1.4−5.3)
38-47	11	3.3 (1.4−5.3)
48-57	6	1.9 (0.4−3.4)
58-67	5	1.8 (0.2−3.3)
68-77	5	2.3 (0.3−4.4)
≥78	3	1.8 (0.0−3.9)

	No. of cases	Prevalence (95% CI)
All *	49	45.3 (32.6−58.0)
Sex-specific point prevalence		
Men	32	58.7 (38.3−79.0)
Women	17	31.8 (16.7−46.9)

* All patients that were alive and living in the study area on the date of the point prevalence estimates (31 December 2019)

17. Description of an Internet-Based Cohort with a Self-Reported Diagnosis of Polyarteritis Nodosa

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Background: Polyarteritis nodosa (PAN) is form of medium-vessel vasculitis with an estimated annual incidence of 1 per million. The rarity of the disease makes traditional center-based approaches to research in PAN challenging. The purpose of this study was to describe an internet-based cohort of participants with a self-reported diagnosis of PAN, and, to determine how many patients met established criteria for this disease.

Methods: Participants with a self-reported diagnosis of PAN were included in a prospective, internet-based, longitudinal registry from November 2014 to May 2020. All patients completed standardized forms collecting data on disease manifestations, diagnostic testing, and treatment. Patients reporting a history of a positive test for ANCA (n=19) were excluded. Results: 80 participants (58% female) self-reported a diagnosis of PAN without a history of ANCA. Two participants reported a history of hepatitis B viral infection. Race/ethnicity

distribution: 87% Caucasian/White, 9% Asian, 8% Hispanic/Latino, 5% African American/Black, and 1% Native American. Enrollment included participants from across the world including North America (57), Europe (8), Australia (3), Asia (2), and South America (1). The mean age of onset of symptoms and diagnosis was 42.7 (SD 0.28) and 44.1 (SD 0.30) years. Only 13 participants (16%) were > 65 years old at the time of registration. Four participants were < 18 years old at the onset of symptoms. Patients reported that the diagnosis was made based on biopsy (75%), symptoms (51%), laboratory studies (46%), or angiogram (25%) (Table). The most common manifestations of vasculitis included: nerve damage (87%), muscle pain (86%), skin involvement (76%), weight loss (60%), and testicular pain (53% of males) (Table). Blood clots were reported in 18%. 6 participants reported only skin involvement. The majority (83%) of patients reported that a rheumatologist was their treating physician. The most common drug exposures included glucocorticoids (86%), cyclophosphamide (49%), and azathioprine (45%). 95% of participants met the 1990 American College of Rheumatology Classification Criteria for PAN. 95% of participants met the 2012 Chapel Hill Consensus Conference Definition of PAN.

Conclusion: In an internet platform based on self-reported patient information, most patients met well-established criteria for PAN and reported disease manifestations in similar frequencies to published data from physician-reported cohorts. These results support the use of online patient cohorts to conduct research in PAN.

Disclosures: JS: consulting for ChemoCentryx. PM: consulting for the following institutions: AbbVie, AstraZeneca, Biogen, Boeringher-Ingelheim, Bristol-Myers Squibb, Celgene, ChemoCentryx, CSL Behring, Forbius, Genentech/Roche, Genzyme/Sanofi, GlaxoSmithKline, InflaRx, Insmed, Jannsen, Kiniksa, Magenta, Pfizer, Sparrow, Talaris. They received research support from: AstraZeneca, Boeringher-Ingelheim, Bristol-Myers Squibb, Celgene, ChemoCentryx, Forbius, Genentech/Roche, Genzyme/Sanofi, GlaxoSmithKline, InflaRx. They receive royalties from: UpToDate.

Table: Means of diagnostic confirmation and manifestations of polyarteritis nodosa.

Confirmation of diagnosis based on	Number (%)
Biopsy	60 (75)
Symptoms	41 (51)
Labs	37 (46)
General imaging	23 (29)
Angiogram	20 (25)
I don't know	1 (1)
Vasculitis-related manifestations	Number/responses (%)
Nerve damage	65/75 (87)
Muscle pain	62/72 (86)
Rash	59/78 (76)
Weight loss	47/78 (60)
Testicular pain (males)	18/34 (53)
Hypertension	27/74 (36)
Kidney problems	25/75 (33)

18. Clinical features and outcome in systemic polyarteritis nodosa patients since 2005: data from 196 patients

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Background: The etiological landscape of systemic polyarteritis nodosa (PAN) have substantially changed since hepatitis B virus (HBV) vaccination and the description of new entities such as adenosine deaminase 2 (ADA2) deficiency or myelodysplastic syndrome (MDS) associated PAN. Recent data regarding systemic PAN characteristics and predictors of relapse are lacking.

Methods: Retrospective study including patients with systemic PAN referred to the French Vasculitis study Group (FVSG) from 2005 to 2019. Clinical characteristics, associated conditions and long-term outcomes were collected in order to identify predictors of relapse.

Results: Overall, 196 patients with systemic PAN were included. The most frequent clinical manifestations were constitutional symptoms (84%), cutaneous symptoms (67%), musculoskeletal symptoms (58%) and neurological symptoms (54%). Secondary PAN represented 28% of patients and were associated with MDS (9%), active cancer (7%), lymphoproliferative disorder (4%), autoinflammatory syndrome (4%) and hypereosinophilic syndrome (2,5%). No patient had active HBV infection at the time of PAN diagnosis. Most of the patients (98%) received a first line treatment with steroids alone (41%) or associated with an immunosuppressive agent (58%) achieving remission in 173 (90%) cases whereas 20 (10%) patients were non responders. During a median follow-up of 43 (16-90) months, 76 (39%) patients experienced a relapse after a median interval of 23 (8-45) months. Overall, 25 (13%) patients died with a 1-, 5- and 10-years overall survival rate of 91.4%, 88.8% and 87.8% respectively. In multivariable analysis, age >65 years (OR 2.11, 95% CI 1.27 to 3.51, P=0.004), severe gastrointestinal (GI) involvement (OR 2.57, 95% CI 1.40 to 4.71, P=0.002) and skin involvement (OR 1.99, 95% CI 1.21 to 3.29, P=0.007) were associated with a higher risk of relapse, while treatment with cyclophosphamide was associated with a decreased risk of relapse (OR 0.56, 95% CI 0.35 to 0.90, P=0.016).

Conclusions: Although HBV vaccination allowed a decreased incidence of HBV related PAN, 28% of systemic PAN in France are associated with another condition. The rates of relapse remain high, especially in patients with GI or cutaneous involvement.

Disclosures: none

19. Predictors of Relapse in Giant Cell Arteritis

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Background: Giant cell arteritis (GCA) is a systemic vasculitis which manifests as headaches and ischemic symptoms that can lead to vision loss. Treatment of GCA often requires more than a year of glucocorticoids, with or without a glucocorticoid-sparing agent, and can be complicated by episodes of recurrence. Here, we evaluate predictors of GCA recurrence over a decade at a tertiary hospital.
Methods: We conducted a retrospective chart review for patients with GCA followed at the Hôpital du Sacré-Coeur de Montreal from 2010 through 2020. Data extracted included patient's age, sex, baseline comorbidities (diabetes and hypertension), clinical features (weight loss, fatigue, headache, jaw claudication or polymyalgia rheumatica) and prednisone dose at initial presentation. We analyzed these factors as predictors of relapse, including survival analyses for time to first relapse.

Results: Among 93 patients, 23 (25%) had disease recurrence over a median follow-up of 562 days (IQR 368 days). Eighty (86%) patients were female. Thirteen (14%) had diabetes, whereas 52 (56%) had hypertension at baseline. For clinical features, 42 (45%) patients had weight loss, 46 (49%) had fatigue, 84 (90%) had headache, 58 (62%) had jaw claudication and 38 (41%) had PMR. There were no differences in relapse risk by demographic factors, comorbidities, or initial presenting clinical features. However, patients that received a higher dose of prednisone at presentation were shown to have less risk of relapse [hazard ratio (HR) .97 (95% CI 0.95, 1.00)].

Conclusions: Our study did not demonstrate diabetes, hypertension or clinical features at initial presentation to be associated with higher relapses. A higher dose of initial prednisone results was associated with less relapses.

Disclosures: None

20. No evidence that sun exposure can decrease the risk of vasculitis

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Background: The aetiology of vasculitis remains elusive. An important environmental factor that might increase the risk of developing vasculitis pertains to a lack of sun exposure. Sun exposure is the most important source of vitamin D, and vitamin D deficiency is associated with rheumatological autoimmune disorders. Our hypothesis was that regular sun exposure can affect the risk of developing vasculitis, and our prediction was that vasculitis is less common in people that sunbathe often, go on sun vacations, and/or use tanning beds compared to people that avoid sun exposure. Furthermore, we investigated the relation between cardiovascular risk factors and the risk of vasculitis.

Methods: The 'Melanoma inquiry of Southern Sweden' ('MISS') was a large prospective cohort study concerning risk factors for melanoma. MISS started in 1990 by sending out an initial questionnaire to almost 40000 women in southern Sweden. We focus on the follow-up questionnaire to which 24106 women responded to in the years 2000-2001. Following previous studies, sun exposure was determined by the response (dichotomized into 'ever' or 'never') to questions regarding sunbathing behaviour, summer and winter sun vacations, and tanning bed use. Based on how many questions were responded to with 'ever', a new variable was then created that grouped women into having low, moderate, and high sun exposure. We gathered ICD codes assigned by physicians between 1998 and 2019 from the Skåne Healthcare Register for 17209 women. We identified women with an ICD code for any type of vasculitis, hypertension, hyperlipidaemia, and diabetes. The risk of developing vasculitis was analysed using cox proportional hazard models. The follow up time spanned from the date of filling in the questionnaire until the date of developing vasculitis, date of death, or until the end of follow-up (2019-12-31). First, the importance of several covariates was considered in separate models: age (<50, 50-60, >60), smoking (ever / never), obesity (yes / no), education (primary school, high school, university / college, other), cardiovascular disease at start of study (yes / no), and diabetes at start of study (yes / no). In addition, diagnoses based on ICD codes of hypertension, hyperlipidaemia and diabetes after start of study were considered as time-dependent covariates. After evaluation of the covariates a full model with sun exposure, and covariates for age, smoking, cardiovascular history, hypertension and hyperlipidaemia was constructed.

Results: In the 16256 women with sufficient information on sun exposure behaviour and medical history, we identified 200 vasculitis diagnoses, mainly pertaining giant cell arthritis (83% of the vasculitis diagnoses). The most important factor determining the risk of vasculitis was age, with the risk of vasculitis increasing with age. Women that never smoked were more likely to develop vasculitis compared to women that smoked. However, there was no indication that women that had the greatest sun exposure were less likely to develop vasculitis compared to women that avoided sun exposure (Table 1).

Conclusions: Our study shows that variation in sun exposure did not lead to differences in the risk of developing vasculitis. Factors such as protective clothing, use of sunscreen, nutrition,

drug exposure and genetic factors may have modulated the effect of sun exposure on vitamin D levels and vasculitis. Current or previous smoking was associated with a reduced risk of vasculitis compared to women that never smoked.

Disclosures: None.

Table 1: Hazard ratios (HR) and 95% confidence interval (CI) for multivariable cox proportional hazard model showing the relation between different levels of sun exposure and other covariates and the risk of developing vasculitis.

Variable	Reference	Level	HR	LowerCI	UpperCI
Sun exposure	Low	Moderate	1.1	0.66	1.82
		High	0.97	0.55	1.71
Age (years)	<50	50-60	2.41	1.56	3.74
		60+	3.97	2.59	6.08
Smoking	Never	Ever	0.72	0.54	0.95
History of cardiovascular disease	No	Yes	1.07	0.65	1.76
Hypertension	No	Yes	1.14	0.8	1.63
Hyperlipidaemia	No	Yes	1.11	0.71	1.72

21. Withdrawn

22. Outcome of ANCA associated vasculitis with renal involvement. Data from Polish POLVAS registry.

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Rehabilitation, , Warsaw, Poland, [12]Department of Internal Medicine and Rheumatology, Medical University of Silesia, , Katowice, Poland

Background: ANCA-associated vasculitis (AAV) with renal involvement is an important cause of ESKD.

Methods: This retrospective, multicenter, cohort study reports features and outcome of 464 AAV patients with kidney involvement isolated from the cohort of 995 AAV patients diagnosed between 1990 and 2021 in 11 Polish reference centers.

Results: Diagnosis included granulomatosis with polyangitis (GPA), 336 patients (73%) and microscopic polyangiitis, 128 patients (27%). Median age at presentation was 52 years and 63 years, respectively (p< 0.001), Men in this cohort constituted 56% and 49%, respectively (p< 0.001). Median maximum creatinine concentration at presentation was 2 mg/dL and 1.23 mg/dl, respectively (p = 0.028). Median maximum CRP level at presentation was 65 mg/dl and 38 mg/dl respectively (P = 0.024). ANCA was negative in 3% of the patients. Double positity was noted in 2%. The duration of follow up was 58 months and 37 months, respectively (p< 0.001). Cumulative patient's survival at 5 years was 90 % and 78%, respectively (p< 0.001). In the multivariable Cox model, mortality was associated with the diagnosis of MPA, age, cardiopulmonary complications, CRP > 25mg/dl, active smoking (p< 0.001). Creatinine concentration at diagnosis was not associated with increased mortality. Plasmapheresis did not affect 5 year survival in both groups. MPA patients more frequently required haemodialysis. Cumulative 5-year patient's survival on dialysis was similar in both groups.

Conclusion: The significant risk factors for greater mortality in AAV with renal involvement were active smoking, CRP > 25 mg/dl at presentation, MPA diagnosis, age, and cardiopulmonary complication. The maximal median creatinine concentration, as well as plasmapheresis did not affect survival. Significant morbidity and mortality are still associated with the diagnosis of AAV.

Disclosures: None

23. Variations in Takayasu arteritis characteristics in a cohort of patients with different ethnic backgrounds

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Objectives: We aimed to describe differences in disease characteristics and outcomes in Takayasu arteritis (TA) patients with different ethnic backgrounds.
Methods: This was a retrospective cohort study consisting of TA patients seen at specialty vasculitis clinics from five academic hospitals across Canada. Disease features, treatments and outcomes were compared between Caucasian and non-Caucasian patients.

Results: The cohort included 113 patients, of which 51 were Caucasian. Over 50% of the non-Caucasian patients were Asian. Compared to non-Caucasians, Caucasian patients had higher CRP and ESR at diagnosis (33.6mg/l versus 9.4mg/l, p=0.033; and 51mm/h versus 24mm/h, p=0.047; respectively), and were less likely to have baseline cardiovascular comorbidities including dyslipidemia (11.8% versus 29%, p=0.037). There were no significant differences between ethnicity groups for other disease characteristics or outcomes.

Conclusion: Ethnicity did not appear to play a significant role in determining disease characteristics and outcomes when comparing TA patients from various ethnic backgrounds living in the same country.

Disclosures: None

Table 1. Characteristics at diagnosis and disease outcomes of different ethnicity groups				
	All patients (n = 113)	**Caucasians (n = 51)**	**Non-Caucasians (n = 62)**	**p**
Age at diagnosis (mean, SD)	33.09 (12.01)	33.22 (12.65)	32.98 (11.56)	0.92
Female	102 (90.3)	48 (94.1)	54 (87.10)	0.34
Cardiovascular comorbidity	75 (66.4)	32 (62.7)	43 (69.4)	0.55
Diabetes	13 (11.5)	3 (5.9)	10 (16.1)	0.14
Hypertension	55 (48.7)	25 (49.0)	30 (48.4)	1.00
Dyslipidemia	24 (21.2)	6 (11.8)	18 (29.0)	**0.037**
Smoking history	19 (17.0)	12 (23.5)	7 (11.5)	0.13
Obesity	13 (11.5)	6 (11.8)	7 (11.3)	1.00
Follow-up duration, years (median, IQR)[a]	9 (6.0-18)	9 (5.7-13.3)	7 (4-9.5)	**0.026**
Presenting symptoms				
Constitutional	60 (53.1)	31 (60.8)	29 (46.8)	0.19
Eye	13 (11.5)	7 (13.7)	6 (9.7)	0.56
Neurological	31 (27.4)	15 (29.4)	16 (25.8)	0.68
Cardiovascular	95 (84.1)	41 (80.4)	54 (87.1)	0.44
Respiratory	14 (12.4)	8 (15.7)	6 (9.7)	0.40
Gastrointestinal	11 (9.7)	4 (7.8)	7 (11.3)	0.75
Dermatological	11 (9.7)	6 (11.8)	5 (8.1)	0.54
Laboratory results at diagnosis				
Creatinine, µmol/l (median, IQR)	62 (54.8-67.3)	57.5 (52.8-65.5)	63 (56.5-72.8)	0.063
ESR, mm/h (median, IQR)	35 (18-69.8)	51 (21.8-84.8)	24 (12-55.3)	**0.047**
CRP, mg/l (median, IQR)	20.5 (4.3-51.6)	33.6 (13.6-67.1)	9.4 (3.9-47.8)	**0.033**
Elevated creatinine	3/58 (5.2)	1/25 (4.0)	2/33 (6.1)	1.00
Elevated ESR	58/83 (69.9)	30/39 (76.9)	28/44 (63.6)	0.23
Elevated CRP	54/81 (66.7)	27/35 (77.1)	27/46 (58.7)	0.099
Complications				
Any complication	69 (61.1)	31 (60.8)	38 (61.3)	1.00
Severe ischemic event, any	27 (23.9)	16 (31.4)	11 (17.7)	0.12
Stroke or TIA	11 (9.7)	5 (9.8)	6 (9.7)	1.00
ACS or ischemic cardiomyopathy	11 (9.7)	8 (15.7)	3 (4.8)	0.063
Ischemia induced blindness	0	0	0	-
Limb ischemia	6 (5.3)	3 (5.9)	3 (4.8)	1.00
Bowel ischemia	5 (4.4)	4 (7.8)	1 (1.6)	0.17
Other complications, any	58 (51.3)	26 (51)	32 (51.6)	1.00
CHF	5 (4.4)	4 (7.8)	1 (1.6)	0.17
Renal hypertension	33 (29.2)	14 (27.5)	19 (30.6)	0.84
Pulmonary hypertension	6 (5.3)	1 (2.0)	5 (8.1)	0.22
Aortic complication[b]	36 (31.9)	17 (33.3)	19 (30.6)	0.84
Death	1 (0.9)	1 (2)	0 (0)	0.45
Both SIE and other complications	16 (14.2)	11 (21.6)	5 (8.1)	0.057
Surgical intervention[c]				
Aortic surgery	13 (11.6)	8 (15.7)	5 (8.2)	0.25
Revascularization	27 (24.1)	10 (19.6)	17 (27.9)	0.38
Cardiac	7 (6.3)	4 (7.8)	3 (4.9)	0.70
CABG	3 (2.7)	2 (3.9)	1 (1.6)	0.59
Stent	5 (4.5)	3 (5.9)	2 (3.3)	0.66
Non-cardiac	21 (18.8)	6 (11.8)	15 (24.6)	0.095
Renal	7 (6.3)	1 (2)	6 (9.8)	0.12
Other	14 (12.5)	5 (9.8)	9 (14.8)	0.57
Relapse within follow up-period[d]				
Total relapses (mean, SD)	1.25 (1.60)	1.52 (1.68)	1.03 (1.49)	0.11
0	54 (48.2)	19 (38)	35 (56.5)	0.059
1	20 (17.9)	10 (20)	10 (16.1)	0.63
≥2	38 (33.9)	21 (42.0)	17 (27.4)	0.11

Data are presented as number (%) of patients unless otherwise indicated. Values in bold are statistically significant. IQR: interquartile range; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein SIE: serious ischemic event; TIA: transient ischemic attack; ACS: acute coronary syndrome; CHF: congestive heart failure; CABG: coronary artery bypass graft

[a]Defined from time of diagnosis to last study visit

[b]Includes aortic aneurysm, dissection and insufficiency

[c]Data available for 51 Caucasian and 61 non-Caucasian patients

[d]Data available for 50 Caucasian and 62 non-Caucasian patients

24. Predictors of Cancer in Patients Diagnosed with Giant Cell Arteritis in Western Norway 1972-2012

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Background: Giant cell arteritis (GCA) is the most common systemic vasculitis in adults, and the number of incident cases worldwide is projected to increase. Evidence as to whether or not GCA confers an added risk of cancer is conflicting.

Objective: Our aim was to investigate possible predictors of cancer in a large and well-characterized Norwegian cohort of GCA-patients.

Methods: This is a hospital-based retrospective cohort study including patients diagnosed with GCA during 1972-2012. Patients were identified through computerized hospital records using the International Classification of Diseases coding system. Clinical information was extracted from patients' medical journals and national registries. Further details about the inclusion process have been published previously. Data on the occurrence of cancer was obtained from the Cancer Registry of Norway. We investigated predicting factors using Cox proportional hazards regression. Selected variables were first analyzed in univariate and block regression models (block 1: clinical features including histology, block 2: laboratory and treatment factors, block 3: demographic and traditional risk factors). Variables included in the final multivariate model were selected on the following basis: P-value <0.1 in univariate or block regression or otherwise deemed clinically significant.

Results: A total of 881 patients were included following validation of the GCA diagnosis. Among these, 767 cases (71.8% women, mean age 72.5 (SD 9)) had no registered cancer prior to GCA diagnosis and were included in a time-to-event analysis, with first cancer as the event. During the observation period, 120 patients (15.6%) were diagnosed with a first cancer. We found no significant difference in the risk of malignancy compared to population controls matched according to age, sex and county of residence, but for the controls we lacked further data on potential cancer risk factors. Within the GCA-cohort we found no significant associations with the risk of cancer for the variables we could adjust for (Figure 1). Neither typical clinical findings of GCA, initial laboratory parameters nor initial or maximal (before first tapering) Prednisolone dose were predictive of cancer risk.

Conclusions: In our large cohort of GCA-patients the risk of cancer was found to be like that of population controls and no specific GCA-symptom, finding, laboratory-parameter or treatment factor were found to be predictive of cancer risk. However, our data are limited by incomplete or missing data on some cancer risk factors such as use of hormones, body mass index and family history of malignancy. Furthermore, our analyses were not able to confirm the known association of cancer with smoking and advancing age. This may be due to small numbers.

Disclosures: None

25. Prevalence, clinical phenotype and complications of large vessel giant cell arteritis: systematic review and meta-analysis

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Background: Giant Cell Arteritis (GCA) is a heterogenous systemic granulomatous vasculitis involving the aorta and any of its major tributaries. Despite increased awareness of large vessel involvement, studies reporting incidence, clinical characteristics and complications of large-vessel GCA (LV-GCA) show conflicting results due to inconsistent disease definitions, differences in study methodologies and the broad spectrum of clinical presentations. The aim of this systematic literature review was to better define LV-GCA based on the available literature.

Methods: Published studies indexed in MEDLINE and EMBASE were searched from database inception to 9 May 2021. Studies were included if they presented cohort or cross-sectional data on a minimum of 25 patients with LV-GCA and reported on epidemiology, clinical presentation, diagnosis, treatment and/or complications. Control groups were included if data was available on patients with limited cranial GCA (C-GCA). Covidence was utilized to assist with study selection and data extraction (https://www.covidence.org/) and data was quantitatively synthesised with application of a random effects meta-regression model to account for differences in variance and quality between studies, using Stata.

Results: The search yielded 3,488 results, of which 46 were included. 1,012 duplicates were removed and a further 2,430 did not meet eligibility criteria. Diagnostic criteria for LV-GCA differed between papers but was typically dependent on imaging or histopathology. Patients with LV-GCA were generally younger at diagnosis compared to C-GCA patients (69.8 vs 73.6 years), had longer delay to diagnosis (3.75 vs 1.6 months) and lower rates of positive temporal artery biopsy (OR 0.52, 95% CI: 0.3, 0.92). Fewer LV-GCA patients presented with cranial manifestations such as headache (OR 0.23, 95% CI: 0.17, 0.32) and only 53% met the 1990 ACR Classification Criteria for GCA, where it was not required as inclusion criteria. Vasculitis was detected most commonly in the thoracic aorta, followed by the subclavian, brachiocephalic trunk and axillary arteries. The cumulative mean prednisolone dose at 12-months was 8430mg for LV-GCA patients, 47% experienced at least 1 relapse, and 25% of deaths observed during follow-up were directly attributable to LV-GCA.

Conclusions: Patients with LV-GCA have distinct disease features when compared to C-GCA, and this has implications on diagnosis, treatment strategies and surveillance of long term sequalae.

Disclosures: None

26. Anti-Neutrophil Cytoplasmic Antibody (ANCA) in a General Population Without ANCA associated Vasculitis (AAV)

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Background: Currently it is hypothesized that many systemic autoimmune diseases occur due to environmental risk factors in addition to genetic risk factors. Anti-Neutrophil Cytoplasmic Antibody (ANCA) is mainly associated with three systemic autoimmune disease including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA). It is known that ANCA can be positive before clinical symptoms in patients with known diagnosis of GPA and ANCA titers rise before clinical manifestations appear. However, prevalence of ANCA among general population is not well known. It has not been described as well how many of people with positive ANCA eventually develop clinical manifestations of AAV.

Objective: This study aims to estimate prevalence of ANCA in general population without ANCA associated Vasculitis. It also describes natural disease course of people with positive ANCA without AAV. Risk factors for positive ANCA are also analyzed.

Method: This is a single center retrospective study at Center for Preventive Medicine of St. Luke's International Hospital in Tokyo. ANCA was checked among the patients who wished to between 2018 and 2019. St. Luke's Health Check-up Database (SLHCD) was utilized to collect the data. The patients whose serum was measured for ANCA were identified. The data for basic demographics, social habits, dietary habits and laboratory data were extracted. The charts of the patients with positive ANCA were reviewed.

Results: Sera of total 1204 people were checked for ANCA. Of these 1204 people, 587 (48.8%) are male and the mean age was 55.8 years (32.6 to 79). There were 11 patients with positive ANCA. Myeloperoxidase ANCA (MPO-ANCA) was positive for 3 patients and proteinase 3 ANCA (PR3-ANCA) was positive for 8 patients. Of these 11 patients, 5 were male (45.5%) and the mean age was 54.6 years. Two patients had history of autoimmune disease (primary biliary cirrhosis and ulcerative colitis). Five patients were evaluated by rheumatologists with the median follow-up period of 274 days. None of them developed clinical signs and symptoms of ANCA associated Vasculitis. Four out of five patients had ANCA checked later, two of which turned negative. The prevalence of ANCA in this cohort was 0.9% (95% confidence interval [95% CI]: 0.5% to 1.6%). Univariate analysis was performed to identify risk factors of positive ANCA. The variables analyzed include age, gender, body mass index (BMI), smoking habits, alcohol intake, dietary habits (fruits, fish, red meat), hypertension, dyslipidemia, and laboratory data. None of these variables demonstrated statistically significant differences except for positive rheumatoid factor (ANCA positive group: 33 % vs ANCA negative group: 9.1%, p value = 0.044).

Conclusion: The prevalence of ANCA in this cohort was 0.9% (95% CI: 0.5% to 1.6%). None of them who had a follow-up developed AAV during the follow-up period. Longer follow-up and more patients are necessary to determine natural course of people with positive ANCA.

Disclosure: None

27. Association of Rituximab- vs. Cyclophosphamide-Based Remission Induction Strategies with Risk of ESRD & Death in AAV

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Background: The RAVE trial established the non-inferiority of rituximab (RTX) vs cyclophosphamide (CYC) for remission induction of ANCA-Associated Vasculitis (AAV). Patients in RAVE were followed for 18 months so little is known regarding the long-term outcomes of these remission induction strategies in real world practice. Here, we evaluated the association of remission induction treatment strategy with the risks of end-stage renal disease (ESRD) and death, two key outcomes in AAV.

Methods: The data source was a consecutive inception cohort of PR3- or MPO-ANCA+ AAV patients assembled in a large healthcare system between 2002 and 2019. Baseline demographics and disease-specific features, including baseline manifestations and laboratory values, were extracted from the electronic health records (EHR) and data warehouse. The primary exposure was RTX- vs CYC-based remission induction regimens, ascertained by manual review. ESRD and vital status, the composite primary outcome of interest, were ascertained by EHR review as well as linkage to the United States Renal Data System and National Death Index, respectively. We also assessed the risk of relapse. A propensity score (PS) model for treatment with RTX vs CYC was created using demographic and disease-specific variables present at baseline, including age, sex, comorbidities, ANCA type, AAV manifestations, and renal function. We first examined the association of RTX vs CYC with the risk of ESRD or death in unadjusted and multivariable adjusted Cox proportional hazard models. We then performed the same analysis after one-to-many matching RTX users to CYC users by PS. Follow-up was truncated 5 years after treatment initiation.

Results: We identified 596 patients who received RTX- or CYC-based regimens. The mean (SD) age was 61 (17) years, 252 (42%) were male, and 516 (87%) were White. The majority were MPO-ANCA+ (417, 70%) and had renal involvement (413, 69%). The mean (SD) BVAS/WG score was 5.1 (2.2). Baseline demographics were similar between RTX- and CYC-users. RTX-users had a higher BVAS/WG (5.3 [2.4] vs 4.8 [1.9], p<0.001) and a higher eGFR (37.5 [13.5-69.3] vs 22.6 [8.8-56.8], p=0.02). Over a total follow-up of 40,311 days, there were 130 events (ESRD or death). The incidence of the primary outcome was 3.4/1,000 days in RTX-users vs 3.0/1,000 days in CYC-users (Table 1). In the multivariable adjusted Cox model (n=596), the risk of ESRD or death was similar in RTX- vs CYC-users (HR 1.21, 95% CI 0.80 to 1.82). Our results remained similar in analyses limited to those with renal involvement and those with any major disease. Baseline demographics and disease-specific features were well-balanced after PS-matching. In the PS-matched analysis (n=351), the risk of ESRD or

death was similar in RTX- vs CYC-users (HR 1.25, 95% CI 0.79-1.98). During follow-up, there were 77 relapses. There was no difference in the association of RTX- or CYC-users with risk of relapse in multivariable analyses (HR 0.84, 95% CI 0.54-1.33). These findings remained stable in subgroup analyses and propensity-score matched analyses (HR 0.89, 95% CI 0.48-1.66).

Conclusions: In this large multi-center AAV cohort, there were no significant differences in the risk of ESRD or death associated with RTX- vs CYC-based therapy for remission induction. No differences were observed in risk of relapse with RTX- vs CYC-based induction strategies. Our observations remained consistent in analyses using propensity score matching to robustly address confounding by indication. These results will inform the care of patients with AAV for whom there remains some uncertainty regarding initial choice of immunosuppression.

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Table 1: The Association of Rituximab- vs Cyclophosphamide-Based Remission Induction Regimens with the Composite Outcome of ESRD or Death

	RTX-Based Treatment	CYC-Based Treatment
Standard Cox Regression		
Entire Cohort	353	243
Number of Events	72	58
Follow Up (person years)	20882	19429
Incidence Rate (/1000 years)	3.40 (2.70, 4.20)	3.00 (2.20, 3.80)
Unadjusted (HR, 95% CI)	1.12 (0.78, 1.60)	1.0 (Ref)
Partially Adjusted*	0.96 (0.67, 1.39)	1.0 (Ref)
Fully Adjusted^	1.21 (0.80, 1.82)	1.0 (Ref)
Renal Involvement Only		
Number of Events	56	49
Follow Up Time	13972	12925
Incidence Rate	4.00 (3.00, 5.10)	3.80 (2.70, 4.90)
Unadjusted	0.98 (0.66, 1.46)	1.0 (Ref)
Partially Adjusted*	0.88 (0.59, 1.31)	1.0 (Ref)
Fully Adjusted†	0.84 (0.55, 1.28)	1.0 (Ref)
Major Involvement Only		
Number of Events	65	52
Follow Up Time	15889	15126
Incidence Rate	4.10 (3.10, 5.10)	3.40 (2.50, 4.40)
Unadjusted	1.11 (0.75, 1.62)	1.0 (Ref)
Partially Adjusted*	0.97 (0.66, 1.42)	1.0 (Ref)
Fully Adjusted**	1.01 (0.67, 1.52)	1.0 (Ref)
Propensity-Score Matching	131	219
PS-Matched	1.25 (0.79, 1.98)	1.0 (Ref)

Adjusted for age, sex, race, smoking; ^Adjusted for age, sex, race, smoking, ANCA type, CCI score, BVAS Score, GFR, CRP, ESR; † Adjusted for age, sex, race, smoking, ANCA type, CCI score, GFR; **Adjusted for age, sex, race, smoking, ANCA type, CCI score, GFR, BVAS

28. Development and Validation of a Simulation Model for Maintenance Treatment in ANCA-Associated Vasculitis

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Background: ANCA-associated vasculitis (AAV) care has evolved over the last two decades with several approaches to remission maintenance. However, these approaches have trade-offs regarding the risk of flare, infection, end-stage renal disease (ESRD), and other outcomes which impact morbidity, mortality, and costs. We developed a simulation model to project

clinical outcomes in individuals with specific disease features, which can be used to inform clinical decision-making and identify uncertainties that strongly affect outcomes.

Methods: We developed a state-transition, microsimulation model of people with AAV (TreeAge Pro Healthcare 2020). Individuals remain in or transition between health states monthly. At model start, individuals draw for demographic and disease-specific characteristics and then transition between the active AAV or inactive states (i.e., relapse/remission, stratified by major/minor severity) and are at risk for severe infection, ESRD, or death. Transition rates are stratified by demographic and disease-specific characteristics. The distribution of baseline demographics (i.e., age, sex, ANCA type, renal involvement) are from the MAINRITSAN 2 trial, which compared fixed-schedule rituximab (RTX) to a tailored approach based on rising ANCA or B cell titers for remission maintenance. We obtained probabilities of relapse, severe infection, and ESRD from MAINRITSAN 2, and other clinical trials, cohort studies, and national registries. We estimated mortality based on disease-specific features and background age- and sex-adjusted rates derived from US life tables. We then used the AAV model to project outcomes with tailored vs fixed schedule RTX among people in remission at baseline over 28 months, as studied in MAINRITSAN 2. To evaluate external validation, we repeated these steps and compared projected outcomes of fixed treatment in the AAV model to those observed in MAINRITSAN 1 and an observational study of continuous B cell depletion by Pendergraft, et al. We used mean average percent error (MAPE) and coefficient of variation of root mean-square error (CV-RMSE) to assess how the model-projected outcomes compared to those observed in MAINRITSAN 1 and 2, as well as the observational study.

Results: Over 28 months, the AAV model projected fewer minor and major relapses with fixed vs tailored RTX (7.4% vs 9.7% and 4.5% vs 7.0%). More patients had at least one severe infection in the fixed vs tailored group (20.5% vs 11.4%). ESRD was uncommon in both groups (0.3% vs 0.3%). Relapse free survival at 28 months was higher in fixed vs tailored treatment (85.2% vs 81.6%). Compared to the MAINRITSAN 2 trials results (Table 1), the projected rates of relapse-free survival, relapse, severe infection, ESRD, and death in the AAV model were similar with acceptable MAPE. When evaluating the projected relapse-free survival observed in the AAV model to that observed in MAINRITSAN 2, the CV-RMSE indicated good fit (CV-RMSE 2.2% for fixed treatment and 2.4% for tailored treatment). Similar observations were made when comparing the projected outcomes of the AAV model to those observed in MAINRITSAN 1 and the observational study. Limitations include that we made assumptions regarding differences in mortality rates during active vs inactive disease states.

Conclusions: We established the face validity and internal and external validation of a novel AAV state-transition model that projects key outcomes, including minor and major relapse, severe infection, ESRD, and death. This model can be adapted to compare other strategies (e.g., azathioprine) and incorporate other health states (e.g., steroid toxicity), quality of life, and costs.

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Table 1: Comparison of AAV Model Projected Outcomes with MAINRITSAN 2 Outcomes Over 28 Months

	Fixed Treatment			Tailored Treatment		
	AAV Model	MAINRITSAN 2	MAPE	AAV Model	MAINRITSAN 2	MAPE
Relapse-Free	85.2%	86.0%	1%	81.6%	84.0%	3%
≥ 1 Minor Relapse	7.4%	6.2%	19%	9.7%	8.6%	13%
≥ 1 Major Relapse	4.5%	3.7%	21%	7.0%	7.4%	5%
≥ 1 Infection	20.5%	19.8%	4%	11.4%	10.2%	12%
ESRD*	0.31%	1.2%	1%	0.31%	0%	0%
Death*	3.4%	3.7%	0%	2.8%	1.2%	2%

*Due to the rarity of these events, MAPE for these comparisons were calculated as ESRD-free or survival

29. Interstitial Lung Disease in ANCA-Associated Vasculitis: Associated Factors, Radiographic Features, and Mortality

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Background: Despite treatment advances, ANCA-associated vasculitis (AAV) remains associated with excess morbidity and mortality. Interstitial lung disease (ILD) is an increasingly recognized manifestation of AAV, but its prevalence, characteristics, and outcomes remain poorly defined. Additionally, most studies of AAV-ILD have been performed in AAV cohorts assembled in Asia where MPO-ANCA+ disease is highly prevalent. We sought to characterize factors associated with AAV-ILD and mortality in AAV-ILD in a large North American-based AAV cohort.

Methods: AAV-ILD cases were identified by screening a consecutive inception PR3- or MPO-ANCA+ AAV multi-center cohort assembled between 2002 and 2019 for ICD-9/10 codes relevant to the diagnosis of ILD. Each case identified by this screen then underwent a manual review of the electronic health record (EHR) and available chest imaging. Two board-certified radiologists reviewed all available computer tomography (CT) scans of the chest for each patient to assess for interstitial lung disease and classify the type of ILD. Demographics, AAV disease features, results of pulmonary function tests, and comorbidities were extracted from the EHR. The baseline Birmingham Vasculitis Activity Score/Wegener's Granulomatosis

(BVAS/WG) was determined for each patient. All-cause mortality was assessed by linkage to the National Death Index. Univariate analyses were used to assess the association of demographic- and disease-specific factors with AAV-ILD. Unadjusted and adjusted Cox proportional hazard models with age as the time scale were used to assess the association of AAV-ILD with death among patients with AAV.

Results: Of 684 patients in the MGB AAV Cohort, 91 (13%) had ILD which preceded the diagnosis of AAV by a mean of 2.2 years (Table 1). AAV-ILD patients were older (67 vs 60 years, $p<0.001$) than patients without ILD but the distribution of sex and race was similar. The proportion of ever smokers (57% vs. 50%, $p=0.23$) was similar among those with and without AAV-ILD. AAV-ILD patients were more often MPO-ANCA+ (93% vs. 65%, $p<0.001$); among MPO-ANCA+ patients (n=470), 85 (18%) had ILD whereas 6 (3%) of 208 PR3-ANCA+ patients had ILD. The majority of ILD was fibrotic (76%) and UIP was the most common ILD type (40%). The mean baseline forced vital capacity (FVC) % predicted was 80.8% (19.6%) and the mean baseline DLCO % predicted was 56.2% (22.7%). Over 4,708 years of follow-up there were 37 deaths in the AAV-ILD group and 149 in the non-ILD group (incidence rates of 68.4 vs 35.8 / 1,000 person years). AAV-ILD was associated with a 47% higher risk of death (aHR 1.47, 95% CI 1.01, 2.15) compared to AAV patients without ILD.

Conclusions: In a large North American cohort of AAV patients, we estimated the prevalence of AAV-ILD as 13% and observed strong associations with MPO-ANCA positive disease. Indeed, nearly 1 in 5 patients with MPO-ANCA+ AAV had ILD which is likely an underestimate given the retrospective nature of this study. In most cases, AAV-ILD was present prior to or at the time of AAV diagnosis, highlighting that it is a feature that may precede other manifestations of AAV. Compared with AAV patients without ILD, those with ILD have a higher risk of all-cause mortality. Additional studies are needed to understand appropriate screening approaches to ILD in this population and the response of ILD in AAV to conventional AAV treatment regimens.

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Table 1. Patient Demographics and Clinical Features

Characteristic	AAV (n=593)	AAV-ILD (n=91)	p-value
Demographics			
Age, mean (SD)	58 (18)	67 (12)	< 0.001
Age at ILD Identification	N/A	66 (12)	
ILD at or prior to AAV diagnosis	N/A	77 (85)	
Male	238 (40)	42 (46)	0.28
Race			0.67
White	515 (87)	76 (84)	
Black	11 (2)	3 (3)	
Asian	10 (2)	1 (1)	
Other	57(10)	11 (12)	
Ever Smoker	298 (50)	52 (57)	0.23
ANCA status			< 0.001
MPO-ANCA +	385 (65)	85 (93)	
PR3-ANCA +	208 (35)	6 (7)	
Organ involvement			
Head and neck	269 (45)	25 (27)	0.001
Pulmonary	266 (45)	63 (69)	< 0.001
Pleurisy	21 (4)	4 (4)	0.76
Nodules/cavities	127 (21)	22 (24)	0.55
Endobronchial involvement	10 (2)	1 (1)	1.00
Alveolar hemorrhage	80 (13)	12 (13)	1.00
Respiratory failure	23 (4)	5 (5)	0.40
Renal	390 (66)	52 (57)	0.11
Neurologic	55 (9)	8 (9)	0.88
AAV disease activity			
BVAS/WG, mean (SD)	5 (2)	4 (2)	0.006
Charlson Comorbidity Index, mean (SD)	2 (2)	2 (3)	0.11
Mortality	151 (25)	36 (40)	0.005

30. Lower frequency of comorbidities prior to onset of giant cell arteritis; a population-based study

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Background: Advancing age, female sex and white race are risk factors for development of giant cell arteritis (GCA). Recently metabolic features such as lower fasting blood glucose (FBG) were thought to predispose to GCA. However, the risk factors for development of GCA remain incompletely understood. We aimed to assess the frequency of comorbidities and metabolic risk factors at, and prior to, onset of GCA.

Methods: We conducted a retrospective case-control study of patients diagnosed with incident GCA in a geographically defined population from 01/01/2000 till 12/31/2019. Two age- and sex-matched controls were identified for every GCA case and assigned an index date corresponding to the incidence date of GCA. Twenty-five chronic conditions from either the Charlson, Elixhauser, or Rheumatic Disease Comorbidity Index were identified using ICD-9 diagnosis codes within a two-year lookback period; 2 or more codes ≥30 days apart were used to define a comorbidity. Prevalence of comorbidities, clinical and laboratory data among cases and controls were compared at incidence date and 5 years prior. Subjects with less than one year of diagnosis history were excluded from each analysis. Medical records of all subjects were manually abstracted for comorbidities and laboratory data at incidence date, at 5 years, and at 10 years prior to incidence date. Comparisons were performed using Chi square, Fisher exact, or rank-sum tests. Additional analyses for association between lab outcomes and GCA were performed using logistic regression models, adjusted for age, sex, smoking status (ever/never), and BMI.

Results: The cohort included 129 patients with GCA (74% female, mean age at diagnosis 77 years) and 253 controls. At GCA incidence/index date, the prevalence of diabetes mellitus (DM) was lower in patients with GCA (5% vs 17%; p=0.001). At 5 years prior to incidence/index date, cases had a lower prevalence of DM (2% vs 13%; p<0.001) and hypertension (HTN) (27% vs 45%; p=0.002) as compared to controls. The mean number (SD) of comorbidities at 5 years prior to incidence/index date was lower [0.7 (1.0)] in cases than controls [1.3 (1.4)] (p<0.001) (Table 1). Moreover, at 5 years prior to incidence/index date, cases had a significantly lower median Fasting Blood Glucose (FBG) (96 vs 104 mg/dL; p <0.001) and BMI (25.8 vs 27.7 kg/m^2; p-value=0.018) as compared to controls. At 10 years prior to the incidence/index date, the median FBG among cases was also lower (93 vs 98 mg/dL; p<0.001), although BMI was not significantly different at that time point. Total cholesterol (median 211 vs 201 mg/dL; p=0.029), low-density lipoprotein (LDL) (123 vs 112 mg/dL; p=0.056), and high-density lipoprotein (HDL) (62 vs 57 mg/dL; p=0.013) were higher among cases compared with controls at 5 years prior to incidence/index date, and no different at 10 years prior. Logistic regression analysis at 5-years and 10-years prior to GCA diagnosis/incident date showed a significant association between GCA and lower FBG, OR 0.965 (95%CI 0.944-0.983) for 5-years prior and OR 0.975 (95%CI 0.952-0.993) for 10-years prior to GCA diagnosis. Higher total cholesterol and LDL were also significantly associated with GCA at 5 years prior OR 1.008 (95%CI 1.001-1.016) and OR 1.009 (95%CI 1.001-1.019) respectively, but this was not at found at 10-years prior to diagnosis.

Conclusions: Development of GCA was associated with a lower prevalence of DM and HTN, and lower total number of comorbidities, at 5 years prior to incidence date. FBG and BMI were also lower among individuals who later developed GCA, suggesting that metabolic factors influence the risk of GCA. Future studies to elucidate the patho-mechanisms underlying these observations are warranted.

Disclosures: E. Matteson, Boehringer Ingelheim, Gilead Sciences; C. Turesson, Bristol-Myers Squibb, Roche, Abbvie, Bristol-Myers Squibb, Nordic Drugs, Pfizer, Roche; K. Warrington, Eli Lilly, Kiniksa.

31. Frequency of Immune Checkpoint Inhibitor-Induced Polymyalgia Rheumatica

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Background: Immune checkpoint inhibitors (ICPIs) induce immune-related adverse events (irAEs) such as skin disorders, gastrointestinal disorders, thyroid dysfunction, type 1 diabetes mellitus, lupus nephritis, and vasculitides. Information on ICPIs-induced vasculitides is limited, and predictors for this condition have not been identified. Therefore, we have examined the frequency of immune checkpoint inhibitor-induced vasculitides by analyzing the data recorded in the Japanese Adverse Drug Event Report (JADER).

Methods: Data from April 2004 to March 2020 were extracted from JADER database, and vasculitides as an immune-related adverse event was defined according to the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. The reporting odds ratio (ROR), which evaluates the AE signals according to previous reports. Adverse event signals were recognized as significant when the ROR estimates and lower limits of the corresponding 95% confidence intervals exceeded 1.

Results: The use of nivolumab showed a significant signal for vasculitides. Furthermore, significant signals of Polymyalgia rheumatica (PMR) were detected in the patients treated with nivolumab, pembrolizumab, and ipilimumab. In addition, the frequencies of nivolumab- and pembrolizumab-induced PMR were higher in patients aged ≥70 years and female patients, respectively. PMR was reported in 38 patients treated with nivolumab; 31 (82%) of these were either in recovery or in remission. Further, PMR was reported in 17 patients treated with pembrolizumab; 13 (76%) of these were in recovery or remission, while three (18%) were not. PMR was reported in 12 patients treated with ipilimumab; seven (58%) of these were in recovery or remission.

Conclusions: Careful monitoring for PMR is required when the patients are aged > 70 years and have been treated with nivolumab and when the patients are women and have been treated with pembrolizumab.

Disclosures: None.

32. Age and time-dependent increase in incident anti-glomerular basement membrane (anti-GBM) disease-a nation-wide cohort study

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Background: Anti-GBM disease is a rare type of severe small vessel vasculitis that can lead to pulmonary haemorrhage and kidney failure. Epidemiologic studies of unselected patients have been challenged due to the low disease incidence and non-relapsing nature. Accordingly, we examined incidence and outcomes based on data from multiple Danish nationwide healthcare registries.

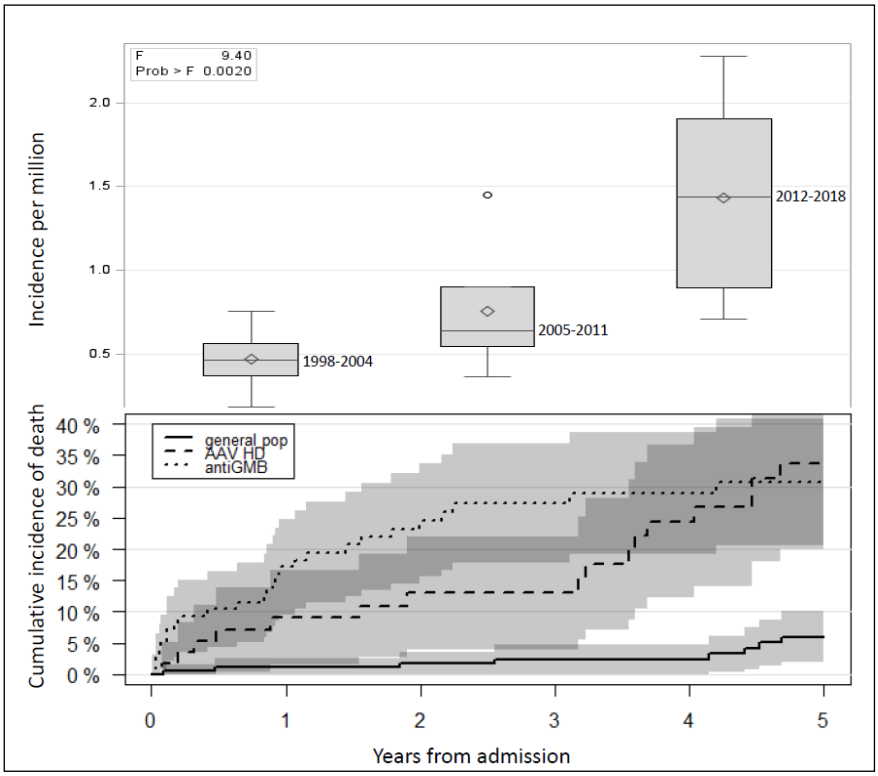
Method: All patients with incident anti-GBM disease defined by ICD10 code DM31.0A between 1998 and 2018, were ascertained by cross-referencing of data from the Danish nationwide administrative registries. Controls were matched 2:1 by Exposure Density Sampling on age and sex. Risks of death was compared based on adjusted absolute risk ratios (ARR) and cumulative incidences assessed based on the Aalen-Johansen estimator.

Results: We identified 97 patients with incident anti-GBM disease from the Danish National Patient Registry corresponding to an overall incidence of 0.91 (SD 0.6) cases/million/year. Cumulative frequencies of AAV diagnoses exhibited significant seasonal variation, with the highest number of incident cases observed during spring and fall (P=0.014). Incidence increased with age with 0.76 (SD 0.4), 1.5 (SD 1.04) and 4.9 (SD 2.6) cases/million/year for patients < 45, 45-75 and >75 years, respectively. Mean age at time of diagnosis was 52.4 (SD 22.8) years with an equal distribution of men and women (51.6%). A total of 45 (58.4%), 60 (61.9%) and 61(62.9%) patients had commenced haemodialysis at day 30, 180 and 360 after first day of admission, respectively. 36 (37.1%) patients were registered as having had an ICU stay and plasma exchange was employed in 74.2% of the cases. There was a significant increase in incidence of anti-GBM disease over time [1998-2004: 0.50 (SD 0.2); 2005-2011: 0.80 (SD 0.4); 2012-2018: 1.4 (SD 0.5), P=0.02] (figure 1); these findings were sustained in sub-analyses of gender and age groups >45 years, with the highest increase in incidence amongst patients between 45-75 years. The trend in incident anti-GBM tests in the northern administrative region of Denmark during 1998-2012 was decreasing, and there was no correlation between the incident anti-GBM testing and ICD10 registered anti-GBM disease during the period (P=0.43). Five-year mortality was 34.4%, and among the primary contributing causes of death were cardiovascular disease (52.9%), vasculitis (23.5), cerebral disease (23.5%) and infection (17.7%). Risk of death from anti-GBM disease was higher than the background population [ARR 5.27 (CI 2.45-11.3, P< 0.001)] and comparable to patients with incident ANCA-associated vasculitis (AAV) dependent on dialysis at day 30 after first day of admission [ARR 0.82 (CI 0.48-1.41, P= 0.50)] (figure 1).

Conclusion: Incidence of anti-GBM disease increased over the test period, possibly related to temporal demographic changes, as incidence increased with older age. Mortality remained high and was comparable with an age- and sex-matched cohort of dialysis-dependent AAV patients.

Disclosures: None

Figure 1. Incidence and mortality in anti-GBM disease during 1998-2018



33. An update on the epidemiology of Behçet's disease in southern Sweden

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Background: Behçet's disease (BD) is a variable-vessel vasculitis with a distinct geographical distribution of high prevalence along the ancient Silk Route, extending from eastern Asia to the Mediterranean. The prevalence and incidence rate in southern Sweden have previously been estimated to 4.9 per 100,000 adults and 0.2 per 100,000 person-years, respectively. Since then, the proportion of the population of non-Swedish ancestry has increased in southern Sweden. Furthermore, immigration patterns might have an increasing influence on epidemiology of BD. This study is aimed to update the epidemiology of BD in southern Sweden.

Methods: The study area was the county of Skåne with an adult (≥18 years) population of 1 080 664 on 31st of December 2019. Patients assigned to the ICD-10 code M35.2 between 1998 and 2019 were retrospectively identified by search in population-based data base. Patients fulfilling the International Study Group diagnostic criteria for BD were included. The point prevalence per 100 000 adults was estimated on the 31st of December 2019. Incidence rate of BD was estimated per 100 000 adult person-years. Non-Swedish ancestry was defined as a person being born outside of Sweden or with two parents born outside of Sweden. A case was considered incident when the diagnosis was made within Skåne with a minimum of 3 years of residence in Sweden prior to diagnosis.

Results: 101 patients fulfilling the diagnostic criteria for BD were identified (61 men and 40 women). The point prevalence was 9.1/100 000 adults (95% CI 7.3, 10.9) and higher among the population of non-Swedish ancestry (19.3 vs. 4.8/100 000, p = 0.001) and higher among men (11.2 vs 7.0/100 000, p =0.027). There were 58 adult incident cases diagnosed between 1998 and 2019. The incidence rate was 0.3/100 000 person-years (95% CI 0.2,0.3) and was higher among the population of non-Swedish ancestry 0.7 vs. 0.2/100 000, p =0.001). There was no significant increase in incidence rate of BD over time (Table 1). All patients presented with oral ulcerations, 90% with genital ulcerations, 84% with skin lesions and 53% with eye disease. 18% experienced thromboembolic events, 14 men and 4 women.

Conclusions: The prevalence of BD in southern Sweden has increased since last estimated. The incidence rate of BD has not increased significantly during the study period, despite an increased proportion of the population being of non-Swedish ancestry. Although the study was in a population-based setting the low sample size is a limitation.

Disclosures: None.

Table 1. Incidence-rate of Behçet's disease in adults in southern Sweden 1998-2019.

Period	Cases	Person-years	Incidence rate (95% CI)	Rate ratio (95% CI)
1998-2005	16	7178222	0.2 (0.1;0.3)	
2006-2012	19	6826433	0.3 (0.2;0.4)	1.3 (0.6;2.5)
2013-2019	23	7325315	0.3 (0.2;0.4)	1.4 (0.8;2.7)

34. Post-induction ANCA Titer Does Not Predict Relapse, Mortality, or Renal Outcomes: A Target Trial Emulation Study

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Background: ANCA-associated vasculitis (AAV) is associated with disease relapse as well as increased risk of end-stage renal disease (ESRD) and death. In most cases, circulating ANCA targeting proteinase-3 (PR3) or myeloperoxidase (MPO) are present and may be pathogenic. Studies of the association of post-treatment ANCA titers with future outcomes have yielded conflicting results. We evaluated the association of achieving a negative ANCA titer during the first year of treatment with risk of relapse, ESRD, and death.

Methods: Cases were obtained from a consecutive inception cohort of AAV patients who received care at a large multi-hospital system between 2002-2019. All cases were PR3- or MPO-ANCA+. Mortality data were obtained from the National Death Index and ESRD status from the United States Renal Data System. Data regarding baseline covariates and relapses during follow up were obtained from the electronic health record. Missing data was accounted for using multiple imputation. To address confounding and immortal-time biases, we performed a target trial emulation study to examine the association of post-induction ANCA titer with risk of ESRD or death and relapse using a previously described cloning, censoring and weighting approach. We designed a hypothetical trial with two management strategies: “achieve a negative titer” or “does not achieve negative titer” within 180 days of induction. “Clones” of each patient were included in each hypothetical treatment arm and censored when they violated the assigned management strategy. The composite outcome – risk of ESRD or death within five years – and secondary outcome of relapse was estimated using Cox models after accounting for informative censoring using inverse-probability-of-censoring weighting and adjusting for baseline covariates.

Results: The study included 674 patients (mean age: 60 years; 59% female; 87% white) with 46.7 $\pm$ 19.1 months of mean follow up. The majority were MPO-ANCA+ (68%) and had renal manifestations (64%). Rituximab (RTX)-based induction strategies were used in 52%. 28% achieved a negative titer within one year of induction. In the target trial (Table 1), the HR for the primary outcome of ESRD or death was 0.95 (95%CI 0.68-1.34) in the group that achieved a negative titer compared to the group that did not. In analyses stratified by remission induction strategy, the HR for ESRD or death was 1.05 (95%CI 0.67-1.66) in RTX-based and 0.96 (95%CI 0.54-1.72) in cyclophosphamide (CYC)-based regimen users when comparing those who achieved a negative titer vs those who did not. The HR for ESRD or death was 0.93 (95%CI 0.48-1.80) in the PR3-ANCA+ and 0.93 (95%CI 0.63-1.38) in the MPO-ANCA+ groups that achieved a negative titer. There was no association of achieving a negative ANCA titer with risk of relapse (HR 0.70, 95% CI 0.36-1.34). Our results persisted in analyses examining the association of achieving an ANCA titer within 365 days with these outcomes.

Conclusion: In this target trial using a large cohort of AAV patients, achieving a negative ANCA titer within one year of induction was not associated with improved outcomes. This finding was seen in both RTX- and CYC-treated patients. These findings suggest that post-induction ANCA titers have limited ability to predict mortality and ESRD outcomes in AAV.

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Table 1: The Association of Achieving a Negative ANCA Titer with Relapse, ESRD, and Death

	Achieves Negative Titer HR (95%CI) (n=674)	Does Not Achieve Negative Titer (n=674)
All Patients		
ESRD or Death	0.95 (0.68, 1.34)	Ref
ESRD	1.00 (0.67, 1.48)	Ref
Death	0.81 (0.51, 1.29)	Ref
Relapse	0.70 (0.36, 1.34)	Ref
PR3-ANCA+		
ESRD or Death	0.93 (0.48, 1.80)	Ref
ESRD	0.74 (0.43, 1.26)	Ref
Death	0.95 (0.37, 2.42)	Ref
Relapse	0.79 (0.20, 3.15)	Ref
MPO-ANCA+		
ESRD or Death	0.93 (0.63, 1.38)	Ref
ESRD	1.05 (0.64, 1.72)	Ref
Death	0.78 (0.45, 1.34)	Ref
Relapse	0.76 (0.35, 1.63)	Ref
RTX or RTX/CYC Treated		
ESRD or Death	1.05 (0.67, 1.66)	Ref
ESRD	0.93 (0.58, 1.49)	Ref
Death	0.99 (0.55, 1.78)	Ref
Relapse	0.69 (0.30, 1.59)	Ref
CYC Only Treated		
ESRD or Death	0.96 (0.54, 1.72)	Ref
ESRD	1.14 (0.58, 2.25)	Ref
Death	0.65 (0.28, 1.53)	Ref
Relapse	0.65 (0.20, 2.11)	Ref
TPE Treated		
ESRD or Death	1.20 (0.82, 1.75)	Ref
ESRD	1.07 (0.74, 1.54)	Ref
Death	1.07 (0.59, 1.93)	Ref
Relapse	0.46 (0.03, 6.07)	Ref

ANCA = antineutrophil cytoplasmic antibody, CYC = cyclophosphamide, ESRD = end-stage renal disease, MPO = myeloperoxidase, PR3 = proteinase-3, RTX = rituximab

35. Air pollution risk factors for disease onset appear shared across systemic vasculitis and other autoimmune diseases

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Background: Recent studies have identified long-term air pollution exposures as a risk factor for several autoimmune diseases. It is, however, unknown if these effects are generic or disease specific. In this study, we assessed the cumulative impact of long-term air pollution exposures on systemic vasculitis onset and other inflammatory autoimmune diseases.

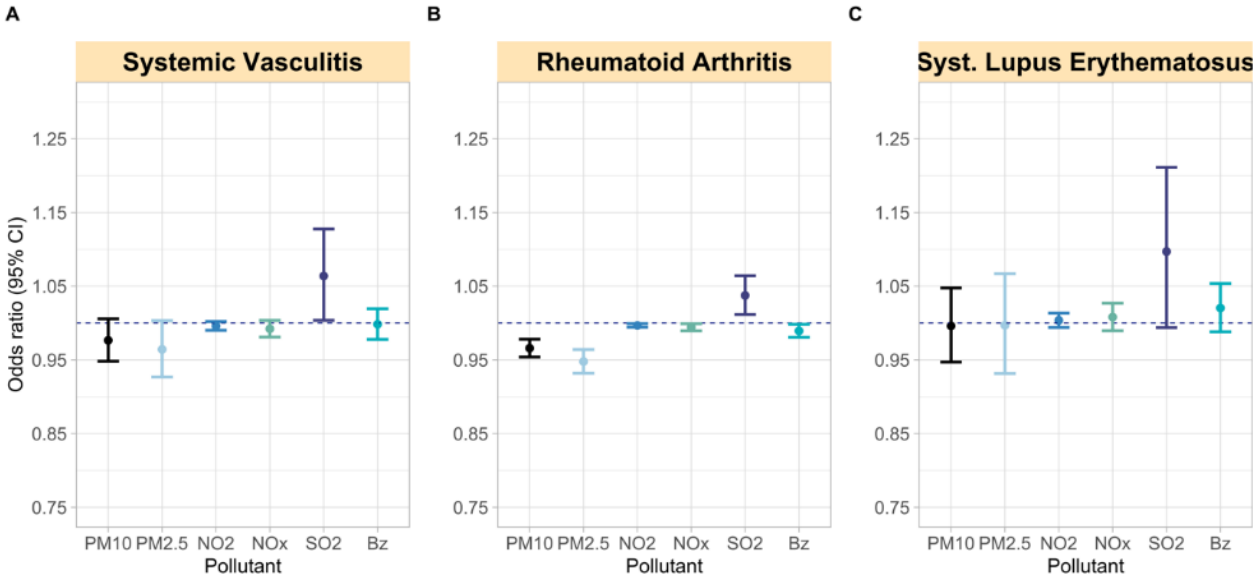
Methods: We undertook a case-control analysis using data from the UK Biobank (UKB) general population cohort. UKB enrolled over 500,000 adults, aged 37–73 years, between 2006 and 2010. Retrospective and prospective health outcomes data are linked from the UK national health service (NHS), death register and self-report information. Participants with systemic vasculitis (ICD-10 M30-31, n=1,206), rheumatoid arthritis (ICD-10 M05-06, n=6,451),

systemic lupus erythematosus (ICD-10 M32, n=401), ankylosing spondylitis (ICD-10 M45, n=624) or psoriatic arthritis (ICD-10 M07, n=812) were classified into case groups and were each compared with the remainder of the UKB cohort who served as controls (n=487,942). Long-term air pollution data on particulate matter (PM_{10}, $PM_{2,5}$), nitrogen oxides (NO_2, NO_X), sulphur dioxide (SO_2) and benzene (Bz) were linked for each participant's place of residence ($1km^2$ grid location based on postcode) annually from 2001-2018. This data was sourced from the UK department for environment, food, and rural affairs (Defra). Multivariable logistic regression models adjusting for age, sex, education, ethnicity, Townsend deprivation score, smoking and alcohol intake, time spent outdoors, and population density were used to assess the link between air pollution and inflammatory autoimmune disease status.

Results: A $1\mu g/m^3$ increase in annual mean SO_2 was associated with 6.4% increased odds of systemic vasculitis (OR: 1.064, 95% CI: 1.004 - 1.128). We observed similar associations in the other disease groups: a $1\mu g/m^3$ increase in SO_2 was associated with 3.7% (OR: 1.037, 95% CI: 1.011 – 1.064) and 9.7% (OR: 1.097, 95% CI: 0.994 – 1.211) increased odds of rheumatoid arthritis and systemic lupus erythematosus, respectively (Figure 1). PM_{10} and $PM_{2,5}$ were inversely associated with rheumatoid arthritis while no significant associations were observed for Bz, NO_2 or NO_X in relation to any of the disease groups.

Conclusion: This is the first large scale study to evidence a link between long-term air pollution exposures and systemic vasculitis onset. Specifically, SO_2 may be a risk factor for systemic vasculitis, but also other autoimmune diseases. Further work is needed to validate these results in cohorts with clinically well-defined disease phenotypes.
Disclosures: None to declare

Disclosures: None to declare
Figure 1: Relationships between long-term residential air pollution exposures (2001-2018) and (A) systemic vasculitis, (B) RA and (C) systemic lupus erythematosus in UK Biobank



36. The association between ambient UVB dose and ANCA-associated vasculitis relapse and onset

Jennifer Scott[1], Enock Havyarimana[2], Albert Navarro-Gallinad[3], Jason Wyse[4], Arthur White[4], Jos van Geffen[5], Michiel van Weele[5], Julie Power[6], Neil Basu[2], Mark A. Little[1], Lina Zgaga[7] ;
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Background: The etiology of ANCA-associated vasculitis (AAV) and triggers of relapse are poorly understood. Vitamin D (vitD) is an important immunomodulator, potentially responsible for the observed latitudinal differences between granulomatous and non-granulomatous AAV phenotypes. A narrow ultraviolet B spectrum induces vitD synthesis (vitD-UVB) via the skin. We hypothesised that prolonged periods of low ambient UVB (and by extension vitD deficiency) are associated with the granulomatous form of the disease and an increased risk of AAV relapse.

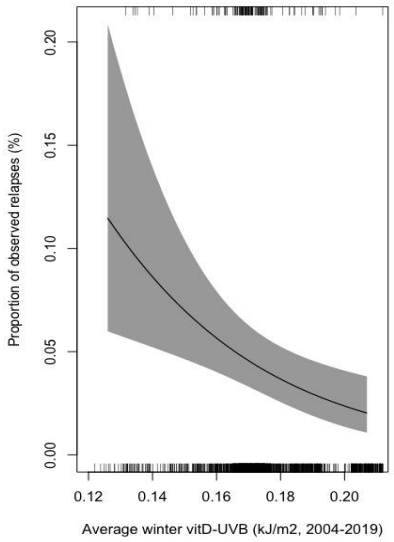
Methods: Patients with AAV recruited to the Irish Rare Kidney Disease (RKD) (n=439) and UKIVAS (n=1961) registries were studied. Exposure variables comprised latitude and measures of ambient vitD-UVB, including cumulative weighted UVB dose (CW-D-UVB), a well-validated vitD proxy. A novel n-of-1 study design was used to examine relapse risk. Multi-level models and logistic regression were used to examine the effect of predictors on AAV relapse risk, phenotype and serotype.

Results: Residential latitude was positively correlated (OR:1.41, 95% CI 1.14-1.74, p=0.002) and average vitD-UVB negatively correlated (0.82, 0.70-0.99, p=0.04) with relapse risk, with a stronger effect when restricting to winter measurements (0.71, 0.57-0.89, p=0.002). However, these associations were not restricted to granulomatous phenotypes. We observed no clear relationship between latitude, vitD-UVB or CW-D-UVB and AAV phenotype or serotype.

Conclusion: Our findings suggest that low winter ambient UVB and prolonged vitD status contribute to AAV relapse risk across all phenotypes. However, development of a granulomatous phenotype does not appear to be directly vitD-mediated. Further research is needed to determine whether sufficient vitD status would reduce relapse propensity in AAV.

Disclosure: None

Figure 1: Effects plot demonstrating the marginal effect of average winter vitD-UVB (kJ/m2) on relapse risk, after adjustment for confounders.



37. Defining ear chondritis: Data from 685 patients with relapsing polychondritis

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Background: Ear chondritis is often considered the pathognomonic feature of relapsing polychondritis (RP). Although painful redness and swelling of the pinna and a resultant cauliflower ear are universally recognized as chondritis, the complete spectrum of symptoms associated with ear chondritis have not been well described. The study objective was to seek patient input to help characterize ear chondritis.

Methods: An online survey was administered in English or Spanish to participants with self-reported RP. Participants were asked questions about their ear pain, including quality, location, duration, aggravating/alleviating factors, timing of onset and duration. Participants were included who reported age ≥ 18 years, a diagnosis of RP confirmed by a physician, and sufficient symptoms to meet McAdams or Damiani's diagnostic criteria. Participants were categorized as having "typical ear chondritis" if they reported ear pain localized to the pinna with associated redness and swelling. Atypical presentations of ear chondritis were also considered.

Results: A total of 685 participants from five continents completed the survey. Among them, 659 met inclusion criteria for subsequent analysis. Most participants were female (n=574; 87%), white (n=548; 83%) and from the United States (n=484;74%). The median age was 50 years (interquartile range = 41-58). In total, 593 (90%) patients reported ear pain, 227 (38%) had "typical ear chondritis", and 98 (16%) had cauliflower ear. Ear pain was most described as

burning (n=334, 56%) or throbbing (n=295, 50%). The most common location of pain was the pinna (n=373, 63%). Participants reported ear redness (n=454, 76%) and swelling (n=349, 53%). Some patients experienced isolated redness (n=130, 22%) and swelling (n=25, 4%). The most common aggravating factors were minor trauma (n=371, 62%) and stress (n=358, 60%). The most common alleviating factor was avoidance of touching the ear (n=374, 63%). Pain was most frequently reported during the daytime (n=355, 60%) and most likely to occur in either ear at different times (n=310, 52%). Onset could be gradual (n=198, 33%) or sudden (n=155, 26%). Pain typically lasted a few hours (n=175, 30%) or 2-3 days (n=130, 22%). The majority of patients who had pinna pain also had pain in other parts of the ear (e.g. mastoid process, inner ear, whole ear) at some point (n=394, 67%). In patients with cauliflower ear, the most common location of pain was the pinna (n=57, 58%) followed by pain inside the ear (n=53, 54%). Most participants reported at least two different types of pain (n=420, 64%).

Conclusions: Ear chondritis in patients with RP has a wide range of clinical presentations and characteristics beyond the typical triad of redness, swelling, and pain localized to the pinna. The description of pain often significantly varies within the same patient. Knowledge of the various distinct characteristics of ear involvement in RP may help physicians recognize and monitor the disease more effectively.

Disclosure: None

38. Coexistence of Vasculitides in Patients with Inflammatory Bowel Disease

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Background: The extraintestinal manifestations of Inflammatory Bowel Disease (IBD) are identified in 6%-40% of patients. Systemic vasculitides may present as extraintestinal manifestations of IBD. The purpose of this updated study was to determine the frequency of vasculitides (large, medium, or small vessel) in a cohort of patients with IBD.

Methods: This is a retrospective chart review of patients from 12/2004 until 08/2021 at a single tertiary medical center using the HERON registry, REDCAP database, and the electronic medical records (EMR). A cohort of patients with ICD-9 and ICD-10 diagnosis codes for inflammatory bowel disease including Crohn's disease (CD), ulcerative colitis (UC), microscopic colitis (MC), and indeterminate colitis (IC) were identified. Patients with vasculitides including giant cell arteritis (GCA), Takayasu's arteritis (TAK), polyarteritis nodosum (PAN), aortitis, ANCA-associated vasculitis, granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), CNS vasculitis, cryoglobulinemic vasculitis, leukocytoclastic vasculitis (LCV), and rheumatoid vasculitis were identified. One-sided student's t-tests were used for statistical analysis.

Results: The EMR/HERON query yielded a total of 4100 patients with IBD. There were 844 patients with concomitant ICD-9 or ICD-10 diagnoses codes for vasculitides. A total of 33 patients (0.80%) had concomitant vasculitis and IBD, but 3 patients had to be excluded due to lack of detailed records. Of the 30 patients (0.73%), there were 13 patients (43%) with CD, 12 (40%) with UC, 3 (10%) with MC, and 2 (7%) with IC (Table 1). Sixteen (53%) of patients were female and 14 (47%) were male. The mean age of diagnosis of IBD was 33.6 years old and the mean age of diagnosis of vasculitis was 40.3 years old. The difference in age between the diagnosis of vasculitides and IBD was 6.7 years (p=0.02). In 57% of cases IBD was diagnosed before vasculitis. The most common vasculitis diagnoses included LCV (9, 30%) and GPA (5, 17%). ANCA serologies were present in 27% of patients. Of the 30 patients, 3 (10%) developed vasculitis following IBD treatment with adalimumab.

Conclusions: In this cohort of patients with IBD, a small percentage of patients developed vasculitis (over 0.7%) with an estimated prevalence of 730 per 100,000. In most cases, IBD was diagnosed prior to vasculitides which could indicate that vasculitis may have developed as a secondary process in some patients.

Disclosures: Data was obtained using HERON, supported by CTSA Award # UL1TR000001 and REDCAP.

Table 1. Cohort of patients with coexisting IBD and vasculitis:

Patient Number	Gender	IBD	Age at diagnosis of IBD (years)	Biopsy-proven IBD	Vasculitis Diagnosis	Age at diagnosis of vasculitis (years)	Biopsy-proven vasculitis	ANCA Serologies	Imaging evidence of vasculitis	Medications Used for Treatment of IBD and vasculitis
1	Male	UC	58	Yes	GPA	60	No	Negative	None	AZA, SSZ, RTX
2	Male	CD	41	Yes	LCV	44	Yes	Negative	None	ADA, steroids
3	Male	UC	39	Yes	LCV	55	Yes	Negative	None	Steroids
4	Female	CD	Unknown	Unknown	GPA	42	Unknown	Positive	None	CYC
5	Male	UC	60	Yes	GPA	41	No	Positive	None	CYC, MTX, steroids
6	Female	CD	21	Yes	CNS angiitis	16	No	Negative	Yes	MTX, AZA, IFX, steroids
7	Male	UC	21	Yes	UV	22	Yes	None	None	GOM, steroids
8	Male	UC	18	Yes	ANCA vasculitis	67	No	Positive	None	RTX, steroids
9	Male	UC	15	Yes	LCV	44	Yes	Positive	None	Steroids
10	Female	MC	70	Yes	GCA/RA	69	No	Negative	None	LEF, ETN, MRA, steroids
11	Female	CD	21	Yes	LCV	23	Yes	Positive	None	ADA, IFX, UST, steroids
12	Female	UC	25	Yes	PAN	26	Yes	Unknown	None	AZA, IFX
13	Male	IC	24	Yes	TAK	32	No	Negative	Yes	MTX, IFX, AZA
14	Female	UC	24	Yes	Kawasaki	2	Unknown	Unknown	Unknown	GOM, ADA, steroids
15	Female	CD	48	Yes	Behcet	30	No	Negative	Yes	APR, AZA, MTX, steroids
16	Female	IC	33	Yes	EGPA	37	No	Negative	None	AZA, steroids
17	Male	CD	13	Yes	GPA	21	Yes	Positive	None	AZA, steroids
18	Female	CD	17	Yes	LCV	31	Yes	Negative	None	ADA, IFX
19	Male	UC	23	Yes	UV	23	Yes	Negative	None	MTX, IFX
20	Female	CD	Unknown	Unknown	TAK	57	No	Unknown	Yes	MTX
21	Male	UC	20s	Yes	LCV	Unknown	Unknown	Unknown	None	SSZ, steroids
22	Male	CD	30	Yes	LCV	41	Yes	Negative	None	ADA, IFX, steroids
23	Female	MC	Unknown	Unknown	Rheumatoid vasculitis	69	Yes	Negative	None	MTX, SSZ, RTX,
24	Male	UC	28	Yes	PAN	27	Yes	Negative	Negative	AZA, ADA, MTX, steroids
25	Female	CD	47	Unknown	LCV	49	Yes	Negative	None	None
26	Female	MC	81	Unknown	GCA/ Scleroderma	79	Yes	Negative	None	SSZ, HCQ, steroids
27	Female	CD	22	Yes	LCV	36	No	Positive	None	IFX, AZA
28	Female	UC	45	Yes	GPA	51	No	Positive	None	IFX, MTX, RTX
29	Male	CD	Early 20s	Yes	IgAV	64	Yes	Negative	Negative	IFX, ADA, AZA, steroids
30	Female	CD	16	Yes	HUV	12	Yes	Negative	None	MTX, ADA, UPA, HCQ, RTX, UST, steroids

39. Update on the epidemiology of ANCA-associated vasculitis in southern Sweden – a 23-year study

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Methods: The study area comprises 14 municipalities in southern Sweden with a total adult population of 623 872 in 2019. All adult (age ≥18) patients diagnosed with AAV from 1997 to 2019 in the study area were eligible for this study. The diagnosis of AAV was verified by case record review and the European Medicines Agency algorithm was employed for classification. Age and sex- specific incidence rates were estimated and the variation in incidence rate according to seasons was studied. Prevalence estimations were caried out at 4 time-points: January 2003, 2010, 2015 and 2020. Patients diagnosed with AAV prior to 1997 were included in prevalence estimates if they were alive and living in study area at time of p.p. estimation. Data on the following comorbidities at time of p.p. January 2020 was acquired from national registries: cancer, diabetes mellitus, stroke, myocardial infarction and hypertension).

Results: In total 422 patients were included. Of these, 372 patients (47% female) were diagnosed with new onset AAV between 1997 and 2019. Of the incident cases, 192 were

classified as granulomatosis with polyangiitis (GPA), 157 as microscopic polyangiitis (MPA) and 23 as eosinophilic GPA (EGPA). The mean age at diagnosis was 64.3 years for all patients, 64.5 for men and 64.1 for women. Patients diagnosed with MPA were older at time of diagnosis (mean age 69.5) compared to those with GPA (mean age 61.5) and EGPA (mean age 51.8). The average annual incidence rate per million adults was 29.9 (95%CI 26.6–32.9) for all AAV, 15.3 (95%CI 13.1–17.4) for GPA, 12.8 (95%CI 10.8–14.8) for MPA and 1.8 (95%CI 1.1–2.6) for EGPA. Incidence rate is increasing with age. Age-specific incidence rates for MPA and MPO-positive disease are highest in patients aged 85 and older, whereas overall AAV, GPA and PR3 positive disease show peak incidence rates in patients between 70-84 years and decrease in older age. Patients were followed from diagnosis of AAV to death or 2020-01-01. During the follow-up time 204 out of 422 patients (48%) died. At date of p.p. (2020-01-01), 218 patients were alive in the study area. The p.p. of AAV per million adults was estimated to 339.8 (GPA: 200, MPA: 106, EGPA: 34). The p.p. per million adults increased during the study time and was 216.3 in January 2003, increased to 312.5 in 2010, 338.7 in 2015 and 340 in January 2020. The prevalence was higher in men compared to women at all prevalence estimations.

Conclusions: The annual incidence rate is relatively stable during the study period. Incidence rates are increasing with age, however peak age differs according to disease phenotype. The prevalence of AAV has increased during the study period and is higher in males.

Disclosures: None

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Diagnosis	*N. of prevalent cases*	Prevalence/ million adults (95% CI), 1 Jan 2020	*N. of incident cases*	Incidence per million adults (95% CI)
AAV, all	*212*	340 (294, 386)	*372*	29.9 (26.6, 32.9)
Men	*111*	360 (293, 427)	*198*	32.6 (28.1, 37.1)
Women	*101*	320 (257, 382)	*174*	27.3 (23.3, 31.4)
GPA, all	*125*	200 (165, 236)	*192*	15.3 (13.1, 17.4)
Men	*73*	237 (183, 291)	*111*	18.3 (14.9, 21,7)
Women	*52*	165 (120, 209)	*81*	12.7 (10, 15.5)
MPA, all	*66*	106 (80, 131)	*157*	12.8 (10.8, 14.8)
Men	*30*	98 (63, 132)	*78*	12.8 (10, 15.7)
Women	*36*	114 (77, 151)	*79*	12.4 (9.7, 15.1)
EGPA, all	*21*	34 (19, 48)	*23*	1.8 (1.1, 2.6)
Men	*8*	26 (8, 44)	*9*	1.5 (0.5, 2,4)
Women	*13*	41 (19, 64)	*14*	2.2 (1, 3.4)

40. Vasculitides as Medication-Associated Adverse Events Based on a National Database Reporting System

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Background: Vasculitides have been reported as adverse events (AEs) related to a wide variety of medications. For the present study, we aimed to analyze the vasculitides reported to a national AE spontaneous reporting system from October 2012 through September 2021.

Methods: All spontaneous reports of vasculitis related to any medications from October 1st, 2012, to September 30th, 2021, were retrieved from the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database. We performed a descriptive analysis of demographics, medications, and type of vasculitis based on 25 Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) codes. Medications identified as the primary suspect in individual case safety reports (ICSRs) were retrieved by their product active ingredient. RStudio v1.4.1717 was used for general data analysis and the R package openEBGM v0.8.3 was used for the calculation of the Empirical Bayes Geometric Mean (EBGM) as the disproportionality score with its 90% two-sided credibility interval, frequently used in safety signal detection models. Drug-event combinations with an EBGM 5% lower limit credibility interval ≥ 2 were considered significant. An EBGM score of 2 indicates that the drug had at least 2 times as many reports for the AE as expected.

Results: During the study period, we retrieved 10,404 ICSRs reporting 10,931 AEs of vasculitis associated to a medicinal product as the primary suspect for that AE. Patient's mean age was 56.5 years, and 61% of them were female. Of the 25 PTs selected, the generic term "Vasculitis" was the most frequently reported AE (29.1%), followed by "Hypersensitivity vasculitis" (14.9%), "Polymyalgia rheumatica" (7.7%), "Anti-neutrophil cytoplasmic antibody positive vasculitis" (ANCA-associated vasculitis) (6.2%), and "Cutaneous vasculitis" (5.4%). Of the total ICSRs with vasculitis AEs, 90% were expedited because they reported serious, unexpected AEs. Eighty drug-event combinations were disproportionately reported. The 20 strongest associations are shown in Table 1. Of those, the strongest association was observed for alemtuzumab and Goodpasture's syndrome (anti-glomerular basement membrane disease), followed by minocycline and polyarteritis nodosa, palivizumab and Kawasaki's disease (KD), then ribavirin and cryoglobulinemia, ezetimibe and microscopic polyangiitis, and so on. Some medications were associated with more than one AE, such as infliximab with Takayasu's arteritis (TAK), Behcet's syndrome (BS) and Henoch-Schönlein purpura (IgA vasculitis); adalimumab with BS and TAK; hydralazine with ANCA-associated vasculitis and renal vasculitis; and rituximab with granulomatosis with polyangiitis (GPA) and cryoglobulinemia.

Conclusions: Many different vasculitides were reported as AEs in the national database. Some of the medications were associated with the diseases they treat, which raises concern for a possible confounding by indication. In other cases, the events were already known as adverse reactions, as for example alemtuzumab and Goodpasture's syndrome or montelukast and eosinophilic granulomatosis with polyangiitis. In other cases, no label or publication references were found, as for palivizumab and KD. These latter cases may raise a concern for potential safety signals that should be investigated. The improved understanding of the mechanism of action of drugs associated to some of these AEs may help to elucidate the pathogenesis of vasculitides.

Disclosures: None

Table 1. The 20 Strongest Statistically Significant Drug-Event Combinations for Drug-Associated Vasculitis

Product	AE	N	EBGM 05	EBGM	EBGM 95
Alemtuzumab	Goodpasture's syndrome	22	41.43	59.76	83.98
Minocycline	Polyarteritis nodosa	69	23.48	28.76	34.92
Palivizumab	Kawasaki's disease	6	16.8	35.17	66.79
Ribavirin	Cryoglobulinemia	29	16.12	22.14	29.8
Ezetimibe	Microscopic polyangiitis	7	14.63	28.83	52.25
Sofosbuvir	Cryoglobulinemia	56	14.61	18.31	22.7
Paroxetine	CNS vasculitis	6	13.77	28.84	54.8
Apremilast	Behcet's syndrome	68	13.11	16.07	19.55
Monteleukast	EGPA	131	12.76	14.77	17.01
Albuterol	EGPA	76	10.73	13.01	15.67
Buprenorphine	Cryoglobulinemia	8	10.27	19.3	33.72
Mepolizumab	EGPA	46	10.1	12.96	16.43
Ledipasvir/Sofosbuvir	Cryoglobulinemia	21	9.62	14	19.83
Hydralazine	ANCA-associated vasculitis	314	9.41	10.34	11.34
Ibuprofen	Henoch-Schönlein purpura	6	9.19	19.42	37.07
Phenytoin	Pulmonary vasculitis	5	8.38	19.58	40.09
Propylthiouracil	ANCA-associated vasculitis	35	8.37	11.16	14.64
Fluticasone propionate	EGPA	19	8.08	12.01	17.3
Human IgG	Kawasaki's disease	9	7.4	13.44	22.82
Cefotaxime	Kawasaki's disease	4	7.34	20.66	47.01

AE: Adverse event. N: Number of drug-event combinations. EBGM: Empirical Bayes Geometric Mean. EBGM 05: Lower limit of the 90% credibility interval of EBGM. EBGM 95: Upper limit of the 90% credibility internal of EBGM. The table is sorted in decreasing order of EGBM 05. CNS: Central nervous system. EGPA: Eosinophilic granulomatosis with polyangiitis. ANCA: Anti-neutrophil cytoplasmic antibody.

41. Subgrouping and personalized risk evaluation for outcome prediction in ANCA associated vasculitis (AAV)

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Objectives: In the most severe cases AAV can lead to end stage kidney disease or death. Since etiology and detailed pathogenesis of AAV is not known, the prediction of disease outcome is challenging. Early identification of patients who are likely to develop disease

exacerbation is crucial, as timely intensification of treatment may reverse the course of the disorder, preventing severe organ dysfunction (e.g. end stage kidney disease) and death. Thus, there is an unmet need for tools able to identify patients with the high risk of organ dysfunction and death.

Methods: We present here two approaches (sub phenotyping of patients and individual patient computed risk evaluation) to identify subjects with high risk of chronic replacement therapy (CRRT) and death based on retrospective data from Polish national AAV registry (POLVAS). The parameters used were: demographic data and laboratory parameters, specific organ involvement, ANCA specificity and time between selected stages of the disease. First approach is based on latent class analysis (LCA) followed by logistic regression to subcategorize patients (GPA, n = 417, MPA, n = 106) and to identify sub phenotypes with the highest risk of CRRT and death. Second approach is based on two machine learning (ML) classifiers, which by analyzing clinical information allow assigning computed risk for CRRT and death in an individual patient (GPA, n = 565, MPA, n = 135). We have evaluated several different approaches to build the ML models (including logistic regression, support vector machines, random forests), and obtained the best results for the gradient boosting algorithm implementation called LightGBM. It works as a sequential ensemble of so-called weak learners (decision trees) finally combined in a one prediction model.

Results: LCA used on our AAV cohort identified four sub phenotypes, including three previously proposed and revealing a fourth clinically relevant sub phenotype. Logistic regression analysis revealed significant differences in the risk of CRRT and death between these subgroups. Using ML approach, we obtained a prediction model performance (ROC AUC of 0.85 for CRRT and 0.82 for death) which we consider clinically relevant.

Conclusions: We consider results obtained encouraging. They may offer a new insight into the course of the vasculitis based on data available at diagnosis and create solid foundations for better capture of temporal relations between clinical events and towards potential clinical decision support system.

Disclosures: None

42. A prospective multi-centre national cohort study of 397 patients with ANCA-associated Vasculitis

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Background: There is a need for interoperable national registries to enable reporting of real-world long-term outcomes and their predictors in Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).

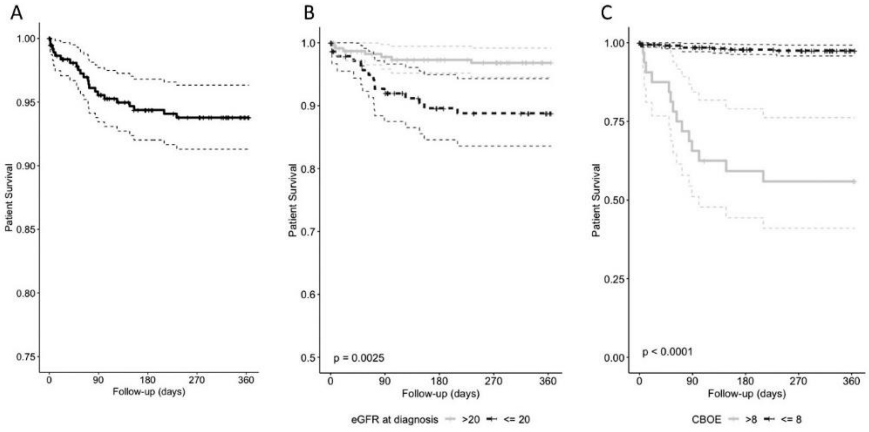
Methods: The Irish National Rare Kidney Disease (RKD) registry was founded in 2012. To date, 842 patients with various forms of vasculitis have been recruited across eight Nephrology, Rheumatology and Immunology centres. We focus here on patient- and disease-characteristics, treatment and outcomes of the 397 prospectively recruited patients with AAV.

Results: Median age was 64 years (IQR 55-73), 57.9% were male, 58.9% had microscopic polyangiitis and 85.9% had renal impairment. Cumulative 1- and 5-year patient survival was 94% and 77% respectively. Median follow-up was 33.5 months (IQR 10.7-52.7). After controlling for age, baseline renal dysfunction (p=0.04) and the burden of adverse events (p<0.001) were independent predictors of death. End-stage-kidney-disease (ESKD) occurred in 73 (18.4%) patients; 1- and 5-year renal survival was 85% and 79% respectively. Baseline severity of renal insufficiency (p=0.02), usCD163 level (p=0.002) and “sclerotic” Berden histological class (p=0.001) were key independent determinants of ESKD risk.

Conclusion: Long-term outcomes of Irish AAV patients are comparable to other reported series. Our results emphasise the need for personalisation of immunosuppression, to limit treatment toxicity, particularly in those with advanced age and renal insufficiency.

Disclosure: None

Figure 1. Overall (A), kidney function stratified (B) and combined burden of adverse events (CBOE) stratified (C) probability of patient survival over first year post diagnosis.



43. Vasculitis Patients Suffering Stroke Have Comparable Clinical Presentation and Outcome to Non-Vasculitis Patients

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Background: An increased incidence of stroke has been shown among patients with giant-cell arteritis (GCA) and Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). With this study we aimed to identify differences in clinical presentation and outcomes from stroke, between systemic vasculitis- and non-vasculitis patients.

Methods: The study cohort consist of 1527 patients with systemic vasculitis [SV: 1202 giant cell arteritis (GCA) and 325 ANCA associated vasculitis (AAV)] diagnosed in a defined geographic area in southern Sweden between January 1st 1997 – December 31st 2016. All SV patients diagnosed with stroke after the onset of their SV until December 31st, 2018, were identified by linking the SV cohort to the RIKSSTROKE, a Swedish national registry covering all stroke cases treated at a specialized stroke unit in Sweden (ICD-10 diagnoses; cerebral infarction (I63), - haemorrhage (I61), or unspecified haemorrhage or infarction (I64)). For each case with SV and stroke, 10 controls matched by sex, age, county of admission, and year of admission +/- 2 years, were identified from the RIKSSTROKE registry. Clinical data from time of admission to the stroke unit and data from 3-month follow-up were retrieved from Riksstroke and compared between SV and controls.

Results: 143 (9.4%) cases with SV, 127 with GCA (10.6%) and 16 with AAV (4.9%), were diagnosed with stroke after the onset of SV during the study period. Table 1 summarizes the clinical and demographic characteristics of patients and controls. A history of previous stroke was less common among patients with SV than their controls (14.2% vs. 27.4%, p=0.001), as was use of statins at admission (16.1% vs. 28.1, p=0.005). Prevalence of smoking and atrial fibrillation did not differ between patients with SV and controls, but there was a trend to a lower prevalence of antihypertensive therapy, and diabetes mellitus, among patients with SV (Table 1). Neither radiographic diagnosis (haemorrhage or ischemic infarction), nor level of consciousness at admission differed between cases with SV and controls. Frequency of thrombolysis treatment did not differ between cases and controls. Duration of hospital admission (9.1 vs. 10.3 days) and the occurrence of stroke related complications (deep vein thrombosis, pneumonia, or fracture) during admission were similar between cases and controls. Mortality rates at 3-month follow-up were identical in cases and controls (21.7%).

Conclusions: In this population-based cohort study, we found that patients with SV who were admitted with stroke were less likely to have a previous history of stroke than non-vasculitis patients matched by sex, age, county-, and year of admission. On the other hand, we found no major differences in baseline clinical characteristics, admission related complications, nor mortality at 3-month follow-up. The impact of vasculitis features, as well as glucocorticoids and other anti-inflammatory therapies, on the risk and outcome of stroke needs further studies.

Disclosures: None

Table 1: Clinical characteristics of patients with systemic vasculitis (SV) and non-vasculitis controls in relation to admission with stroke

Variable	Non-vasculitis	SV	*p*
n of events	1,430	143	-
Demographics			
Age, mean (SD)	80.1 (8.4)	80.4 (8.5)	0.70
Female Sex, n (%)	885 (63.7)	92 (64.3)	0.88
Baseline clinical characteristics			
Current smoker, n (%)	127 (12.0)	16 (14.8%)	0.41
Diabetes, n (%)	263 (20.2)	21 (15.7)	0.21
Antihypertensive treatment, no. (%)	764 (59.0)	67 (50.4)	0.05
Atrial fibrillation, n (%)	445 (32.9)	42 (30.0)	0.49
Previous stroke, n (%)	377 (27.4)	20 (14.2)	0.001
Baseline treatment			
ACE-I/ARB, n (%)	35 (20.2)	5 (33.3)	0.23
Beta-blocker, n (%)	250 (41.0)	18 (29.0)	0.07
Ca-Inhibitor, n (%)	107 (17.6)	8 (12.9)	0.35
Diuretic, n (%)	220 (36.1)	14 (22.6)	0.03
ASA	510 (39.5)	46 (34.9)	0.29
Clopidogrel	45 (4.0)	3 (2.5)	0.43
Warfarin	125 (9.7)	14 (10.6)	0.74
Statin	316 (28.1)	19 (16.1)	0.005
Clinical presentation			
Radiographic diagnosis			0.88
I61 - intracerebral haemorrhage, n (%)	199 (14.3)	21 (14.7)	-
I63 - cerebral infarction, n (%)	1143 (82.2)	116 (81.1)	-
I64 - haemorrhage or infarction, n (%)	48 (3.5)	6 (4.2)	-
Level of consciousness			0.09
Fully awake, n (%)	1,023 (78.8)	102 (77.3)	-
Lowered but responsive, n (%)	177 (13.6)	25 (18.9)	-
Unconscious, n (%)	98 (7.6)	5 (3.8)	-
Treatment			
Thrombolysis, n. (%)	89 (6.6)	11 (8.0)	0.48
Complications & outcome			
Duration of admission	10.3 (11.3)	9.1 (8.8)	0.32
DVT, n (%)	8 (0.9)	0	0.36
Fracture, n (%)	8 (0.9)	0	0.36
Pneumonia, n (%)	47 (5.4)	3 (3.4)	0.41
Deceased at 3m., n (%)	310 (21.7)	31 (21.7)	1.0
Worsened mobility or deceased at 3months. , n (%)	609 (48.4)	63 (50.0)	0.73

ACE-I: Angiotensin-converting-enzyme inhibitors; ARB: Angiotensin II receptor blocker; ASA: acetylsalicylic acid; DVT: deep vein thrombosis; Ca-inhibitors: Calcium channel inhibitors; SV: systemic vasculitis

44. Differences in phenotype and treatment of GPA and MPA in Europe, Japan, and the US

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Background: There are known geographical differences in the epidemiology, clinical presentation, and management of antineutrophil cytoplasmic antibodies (ANCA)-associated

vasculitis. Currently, the pandemic of coronavirus disease 2019 (COVID-19) may provide additional uncertainty. In this retrospective observational study, we evaluated the phenotypes, treatments, and outcomes in Europe, Japan, and the United States (US) using contemporary cohorts of GPA and MPA.

Methods: Patients with new-onset or severe relapse of GPA/MPA as classified by the Chapel Hill Consensus Conference classification between January 2020 and July 2020 were included in this study. Patients were enrolled from 7 sites in Europe (72 GPA, 65 MPA), 20 sites in Japan (19 GPA, 54 MPA), and 5 sites in the US (25 GPA, 19 MPA). We assessed baseline characteristics including demographics and clinical presentations, treatment regimens, and glucocorticoid doses in the three regions. End-stage renal disease (ESRD)-free survival at 1 year were compared using the adjusted survival curves.

Results: There was no clear gender difference in GPA/MPA throughout the regions, and median age [interquartile range (IQR)] was 65 [57–73], 76 [71–82], and 70 [64–76] in Europe, Japan, and the US, respectively. For each region, patients were numerically older in MPA than GPA. Regarding atypical ANCA-status, that is, MPO-ANCA positivity in GPA (overall, 31 out of 116) was more prevalent in Japan (58%) and the US (44%) than in Europe (13%); PR3-ANCA positivity in MPA (overall, 16 out of 138) was more prevalent in Europe (15%) and the US (21%) than in Japan (3.7%). The frequency of lung involvement in GPA was consistent in each region, ranging from 52–60%, whereas those in MPA were more common in Japan (69%) than in Europe (39%) and the US (32%). The frequency of kidney involvement in GPA was inconsistent: 67% in Europe, 42% in Japan, and 88% in the US, whereas in MPA it was common in almost all patients in all regions. In Europe, Japan, and the US, the frequency of use of cyclophosphamide was 57%, 29%, and 34%, and that of rituximab was 63%, 40%, and 86%, the median oral prednisone dose (mg/day) was 40, 40, and 60 at the beginning and 5, 10, and 5 at 6 months, respectively. In Japan, 13 out of 73 patients (18%) were treated with glucocorticoid alone. The ESRD-free survival rates at 1 year in Europe, Japan, and the US were 78%, 80%, and 81%, respectively, calculated from the covariate-adjusted survival curves.

Conclusions: Although the investigator's specialty should be considered, there are still regional differences in remission-induction regimens and glucocorticoid use, perhaps reflecting the diversity of clinical phenotypes of AAV. In the early stages of the COVID-19 pandemic, there was no apparent difference in ESRD-free survival among the three regions.

Disclosures: TK received consulting fees from Chugai. AK received consulting fees from Otsuka, Vifor Pharma, UriSalt, Catalyst Biosciences, and Alexion. DG received consulting fees from ChemoCentryx and Aurinia. YK received research grants from Asahi-Kasei and Chugai, and consulting fees from Asahi-Kasei, Chugai, and Pfizer.

45. Occupational exposure and granulomatosis with polyangiitis: new findings by using a job exposure matrix

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Background: Study of the environmental risk factors of granulomatosis with polyangiitis (GPA) may be more informative by analysing occupational exposure rather than occupational categories. We investigated occupational exposure associated with GPA incidence among pre-selected Swedish workers.

Methods: Data were retrieved from the Knight et al. report on occupational risk factors for Wegener's granulomatosis, a case–control study. The authors selected 32 occupations involving contact with animals and various airway exposures and compared the occupations held before an index date among GPA cases and general-population controls. For our purpose, we converted the reported occupations according to the 1968 International Standard Classification of Occupations and estimated occupational substance exposure by using the online Canadian Job Exposure Matrix (JEM). Then, substances showing the same relative frequency between cases and controls in each physicochemical category were combined. Finally, the frequency of the constituted groups was compared between cases and controls by chi-square test. $P<0.05$ was considered statistically significant.

Results: The Knight et al. study identified 392 GPA cases and 3,612 controls holding at least 1 of the 32 studied occupations (odds ratio 1.1, 95% confidence interval 1.0 to 1.3). The JEM estimated that the 32 occupations were exposed to 136 substances distributed among 6 categories of dusts, liquids, gases and fumes. GPA cases were more frequently exposed to a combination of organic gases, liquids and vapours and a combination of organic dusts as compared with controls (31.7% vs 30.5%, p=0.002, and 5.0% vs. 4.6%, p=0.03). Conversely, controls were more frequently exposed to a combination of inorganic fumes, liquids and vapours and a combination of inorganic dusts than cases (5.3% vs. 4.9%, p=0.006, and 7.5% vs. 6.9%, p=0.003). Cases and controls did not differ in exposure to inorganic and organic mixtures or inorganic gases (8.6% vs 8.6%, p=0.99, and 8.4% vs 8.2%, p=0.34). The Table shows substance combinations.

Conclusions: This large and comprehensive study suggests that GPA incidence could be associated with a combination of organic gases, liquids, vapours and dusts, which agrees with previously reported associations of the disease with farm, livestock or organic solvent exposures. Polycyclic aromatic hydrocarbons were highly represented in the organic group and deserve further investigation as a GPA risk factor. An inverse or no association between GPA incidence and the combined inorganic substances may be related to their attributed adjuvant role. Results are more specific in this supplementary analysis as compared with the original study. However, the population attributable fraction of suggested risk factors for the risk of GPA seems low. A dose–time response analysis may increase the effects of found associations.

Disclosures: None

Table. Substances retrieved in the job exposure matrix classified by physicochemical properties. Combined substances for case–control frequency comparisons are in **bold** and *italics*.

Organic gases, liquids and vapours		Organic dust		Inorganic fumes, liquids and vapours		Inorganic dust		Inorganic and organic mixtures		Inorganic gases	
Substance	%	Substance	%	Substance	%	Substance	%	Substance	%	Substance	%
PAHs	***25.9***	***Wood d.***	***31.6***	***Welding f.***	***16.0***	***Abrasive d.***	***10.4***	***Diesel Eng. e.***	***22.1***	***Carbon monoxide***	***22.8***
Petroleum cuts	***16.6***	***Grain d.***	***16.3***	***Metal oxide f.***	***11.5***	***Alumina***	***10.4***	***Engine e.***	***21.2***	***Nitrogen oxides***	***22.6***
MAHs	***6.9***	***Urea formal.***	***10.3***	***Iron f.***	***6.1***	***C. asbestos***	***10.1***	***Other paints***	***14.1***	***Sulphur dioxide***	***15.6***
Al. aldehydes	***6.9***	***Phenol formal.***	***10.0***	***Manganese f.***	***6.0***	***Insulation d.***	***9.2***	***Propane e.***	***3.1***	***Ammonia***	***12.4***
Organic solvents	***6.8***	***Cellulose***	***3.1***	***Calcium f.***	***5.2***	***Metallic d.***	***6.7***	***Soot***	***2.7***	***Hydrog. Sulph.***	***13.4***
Formaldehyde	***6.3***	***Flour d.***	***1.4***	***Aluminium f.***	***5.0***	***Mild steel d.***	***6.6***	***Coal d.***	***2.1***	***Hydrog. chloride***	***2.9***
Alkanes C1-C4	***4.3***	***Starch d.***	***1.4***	***Inorg. acids***	***4.4***	***Glass f.***	***6.4***	***Inks***	***1.4***	***Chlorine***	***0.9***
Methane	***3.7***	***Sugar d.***	***1.3***	***Chromium f.***	***4.4***	***A. asbestos***	***6.3***	***Plastic f.***	***1.1***	***Hydrogen***	***0.9***
Synth. adhesives	***2.7***	***Melamine formal.***	***1.0***	***Copper f.***	***4.2***	***Stainless S.***	***3.4***	***Coal gas***	***0.7***	***Chlorine dioxide***	***0.5***
Benzene	***2.5***	***Cotton d.***	***0.6***	***Zinc f.***	***4.2***	***Brass d.***	***1.1***	Liquid fuel c.	10.1	***Ozone***	**4.5**
Lubricating oils	***2.5***	***Fur d.***	***0.6***	***Nickel f.***	***3.8***	***Bronze d.***	***0.4***	Wood paints	8.0	Hydrog. fluoride	3.6
Toluene	***2.5***	***Hair d.***	***0.6***	***Tin f.***	***3.7***	C. Silica	11.8	Metal coating	5.3	-	-
Al. alcohols	***0.9***	***Cork d.***	***0.2***	***Sulph. acid***	***2.5***	Mineral wool	6.8	Pyrolysis f.	4.9	-	-
Ar. alcohols	***0.8***	***Polystyrene***	***0.2***	Caustic sol.	2.1	Silicon carb.	5.3	Coke d.	1.8	-	-
Al. ketones	***0.7***	***Polyurethanes***	***0.2***	Lead f.	16.0	Sulfur	5.3	Graphite d.	1.5	-	-
Chl. alkenes	***0.5***	***Isocyanates***	***0.2***	Soldering f.	2.7	-	-			-	-
Phenol	***0.5***	Plastic d.	6.5	Silver f.	2.3	-	-			-	-
Methanol	***0.3***	Fabric d.	4.5	-	-	-	-			-	-
Isopropanol	***0.2***	Synthetic fi.	3.9	-	-	-	-			-	-
Mineral spirits	4.3	Nylon fi.	3.9	-	-	-	-	-	-	-	-
VOL	1.8	Organic dyes	0.8	-	-	-	-	-	-	-	-
U. Hydrocarbons	1.7	Cellulose nitrate	0.8	-	-	-	-	-	-	-	-
Chl. Alkanes	0.5	-	-	-	-	-	-	-	-	-	-
Cutting fluids	0.3	-	-	-	-	-	-	-	-	-	-
Total	100		100		100		100		100		100

PAHs: polycyclic aromatic hydrocarbons; Al: aliphatic; Synth: synthetic; Ar: aromatic; Chl: chlorinated; VOL: volatil organic liquids, U: unsaturated, d: dust; formal: formaldehyde; fi: fibre; f: fumes; Inorg: inorganic; A: amphibole; S: steel; carb: carbide; Dies: diesel; e: emissions; c: combustions; Hydrog: hydrogen; Sulp: sulphide

46. Seasonal incidence of giant cell arteritis or polymyalgia rheumatica

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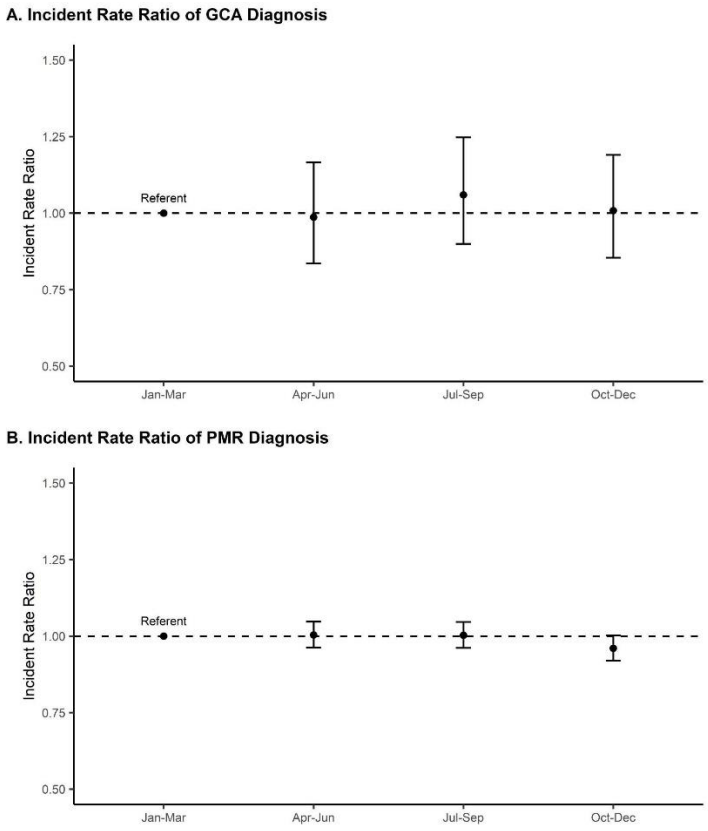
Background*:* Prior studies have observed a seasonal pattern in the incidence of both polymyalgia rheumatica (PMR) and giant cell arteritis (GCA), but neither finding has been consistently replicated in larger cohort studies or meta-analyses. The objective of this study was to describe seasonal patterns among incident cases of GCA and PMR.

Methods: A retrospective cohort study was conducted using data from the TriNetX (Cambridge, MA, USA) electronic health records database, which includes records from multiple United States health organizations. Patients with GCA were identified using validated case-finding algorithms (PPV 79%), which required (1) 2 encounters with GCA diagnostic codes (ICD-9-CM 446.5/ICD-10 M31.6 or M31.5) that occurred at least 30 days apart and (2) at least one moderate-high dose prednisone prescription (greater than or equal to 20mg/day of prednisone or one dose of 500mg or greater intravenous methylprednisolone). Patients with PMR were identified using 2 encounters with a PMR diagnostic code (ICD-9-CM 725/ICD-10 M35.3) at least 30 days apart, any dose of prednisone, and not meeting the criteria for GCA. The index date was defined as the first date of moderate-high dose prednisone for GCA and the first date of any prednisone prescription for PMR. Patients who were under 50 years of age or had less than 1 year of follow up prior to the index date were excluded. The incident rate ratio (IRR) was calculated using unconditional maximum likelihood estimations and confidence intervals were calculated using Wald normal approximation intervals.

Results: We identified 1,129 cases of GCA and 17,023 incident cases of PMR who were followed for 149,005 patient-years prior to their index date of diagnosis. The mean age for incident cases of GCA was 73.9 years (SD 8.1) and the mean age for PMR was 72.3 (SD 8.5). Most patients were female (69%% GCA, 59% PMR) and reported white (79% GCA, 85% PMR) or black (10% GCA, 6% PMR) race/ethnicity. There were no significant differences in the incidence rate ratio of GCA diagnoses as compared to January-March for April-June (IRR 0.99, 95% confidence interval (CI) 0.84-1.17), July-September (IRR 1.06, CI 0.90-1.25), or October-December (IRR 1.01, CI 0.85-1.19) (Figure 1A). There were also no significant differences in the incidence rate ratio of PMR diagnoses as compared to January-March for April-June (IRR 1.00, 95% confidence interval (CI) 0.), July-0.96-1.05, September (IRR 1.00, CI 0.), or O0.96-1.05, or October-December (IRR 0.96, CI 0.92-1.00) (Figure 1A).

Conclusions: In this large analysis of an electronic health records database, there were no seasonal patterns in the diagnosis of GCA or PMR. These results do not support the existence of a seasonal pattern in diagnosis for either disease but require validation in a better-characterized cohort.

Disclosure: Sebastian Sattui receives research funding related to clinical trials by AstraZeneca (MANDARA). Michael Putman receives research funding related to clinical trials by Abbvie (SELECT-GCA) and AstraZeneca (MANDARA).



47. Increased risk of death in patients with double positive serology of anti-GBM antibodies and ANCA

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Background and Aims: Double positivity of anti-GBM and ANCA serology is uncommon but may represent a distinct disease entity of small vessel vasculitis. Previous research has been challenged by low disease incidence, and conflicting results pertaining to risk of death and ESRD. Accordingly, we examined incidence and outcomes based on data from multiple Danish nationwide healthcare registries.

Method: All patients with incident positive anti-GBM serology between 2013 and 2018 were identified from 4 of 5 administrative regions in Denmark. Serological positivity was defined as serum concentrations exceeding the upper reference level. Double positivity was defined by either presence of PR3-ANCA or MPO-ANCA within a margin of 30 days from inclusion. Baseline information and clinical diagnoses defined by administrative diagnoses were subsequently ascertained by cross-referencing of data from the Danish nationwide administrative registries. Risks of death or ESRD were compared based on adjusted absolute risk ratios (ARR) and cumulative incidences assessed based on the Aalen-Johansen estimator.

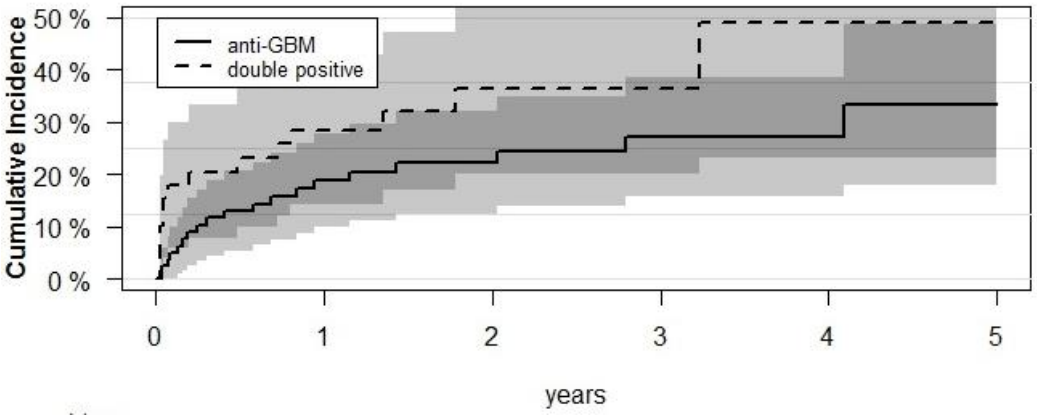
Results: A total of 118 patients with positive anti-GBM serology (4.4 cases/million/year) were identified. Concomitant ANCA serology was tested in 104 (88.1%), with 39 patients (37.5%) demonstrating double positivity (20 and 13 patients positive for PR3-ANCA (51.3%) and MPO-ANCA (33.3%), respectively, and 6 patients positive for all autoantibodies (5.8%)). Mean follow-up for the total study population was 1.9 (SD ±1.6) years. Compared with patients positive for anti-GBM alone, double positivity was associated with female gender (61.5%, P=0.02), and more frequent employment of plasma exchange (53.8%, P=0.04). No difference was observed with regard to age (63.2 years [SD 18.5], P=0.60), and mean anti-GBM concentration (125.5 [SD 182.4] IU/L vs. 108.9 [SD 212.7] IU/L, P=0.30). One-year mortality was 17.7% (n=14) in patients positive for anti-GBM alone, and 28.2% (n=11) in patients positive for both anti-GBM and ANCA. Double positive serology was associated with increased risk of death (ARR 2.10 [CI 1.20-3.65], P=0.009) (figure); however, there was no difference in risk of ESRD (ARR 1.28 [0.66-2.50], P=0.46). Of all identified patients, only 32 (27%) were diagnosed with anti-GBM disease according to ICD10 code (1.2 cases/million/year). In patients with confirmatory serology and ICD-10 code, 13 (40%) had double positive serology (46.2% PR3-ANCA and 53.8% MPO-ANCA). In the subset of patients with confirmatory ICD-10 code,

double positivity was associated with male gender (63.2%, P=0.07), numerical lower mean age (56.1 [SD 25.2], P=0.50), and increased mean anti-GBM concentration (333.3 [SD 278.7] vs 150.7 [SD 146.5] P= 0.026). There was no difference in risk of death or ESRD between the two groups.

Conclusion: Double positivity of anti-GBM and ANCA serology plausibly defines a distinct group of patients and is associated with a higher risk of death. While the association between an ICD10-confirmed diagnosis of anti-GBM disease and anti-GBM serology is well established, the significance of serology alone remains uncertain.

Disclosures: None

Figure. Mortality in patients with single anti-GBM antibodies and double positive serology



48. The golden touch: using MIDAS to uncover associations between environmental factors and vasculitis flare

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Background: Patients with ANCA Vasculitis are at risk of disease flare. We hypothesise that flares may be driven by exposure to one or more environmental factors, such as weather patterns or specific pollutants. Investigating this is challenging because: 1) Flare events can occur at any time – i.e., they are observed *unevenly*, unlike environmental data that is gathered on a fixed periodic basis (e.g., daily). 2) Exposures to environmental factors likely have a cumulative impact on the risk of flare, and the nature of this cumulative relationship is unknown. 3) There are many environmental exposures that could impact flare; these need to be sifted objectively to isolate those that may elevate risk. This work develops a regression method which can identify correlations between flare risk and cumulative exposures. The methods are demonstrated on synthetic data constructed by reference to a clinical database of patients with ANCA vasculitis.

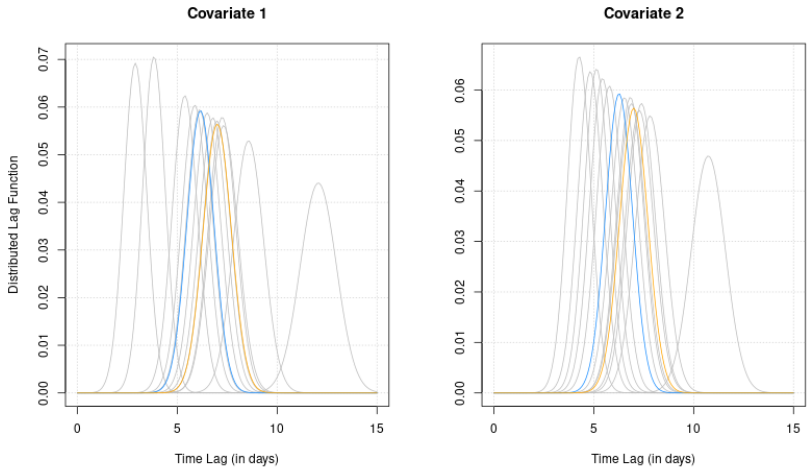
Methods: The method is based on the Mixed Data Sampling (MIDAS) model. We generalised this method, in a Bayesian framework, to handle unevenly sampled response data, addressing challenge (1) above. This method incorporates a data-driven approach to determine how an environmental exposure has a cumulative effect over time, addressing challenge (2). A further novel generalization we make to MIDAS regression modelling is to incorporate Bayesian stochastic model search, allowing us to search over the many possible combinations of environmental factors that could impact flare risk. This can tell us with what probability an environmental factor had any influence on a flare event. We illustrated the current state of the model with results from a synthetic data simulation study. The response data was simulated to be heavily imbalanced (20% positive events, 80% non-events) to reflect the real-life rarity of flare events. We also simulated many 'pollutants', but only two of which actually influenced the occurrence of synthetic flares. This was repeated 12 times to evaluate how closely the model can retrieve the parameters we used to create the data.

Results: The results for the two synthetic pollutants that generated the flares are given in figure 1. The algorithm was highly effective at filtering out the junk pollutants, though note that these results are based on a somewhat idealised scenario. A potential problem can arise from the sometimes periodic (or *seasonal*) nature of time series. Other simulations revealed that the method may have difficulty determining over what lags the effect is distributed when seasonal peaks occur close together. Regardless, even in such cases, the algorithm was still able to ascertain an effect, which is the important feature.

Conclusions: We have described a regression method for quantifying the time-lagged association between an unevenly sampled response variable and evenly sampled covariates. This approach was developed to uncover a correlation between the probability of a subject suffering a flare event and their environmental exposure, but we envisage the approach being useful for many other applications.

Disclosures: None

Figure 1. The 12 simulation results (in grey), their overall average (in blue) and the actual value (in orange) for the two non-junk synthetic pollutants. The plot displays the inferred *Distributed Lag* Functions.



49. Seasonal Variation in GCA

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Background: Giant Cell Arteritis (GCA) is the most common primary systemic vasculitis in adults, occurring in individuals over age 50, most frequently in women (3:1, F:M) and in those of Northern European descent. While genetic factors likely contribute to the increased incidence in Northern Europe, environmental triggers are also likely to play a role. Cyclical and seasonal fluctuations in incidence have been demonstrated in some cohorts. It is plausible that environmental triggers may play a role in inducing vascular inflammation but may also contribute to the differing patterns of disease seen in GCA. **Aim:** The objective of this study is to investigate the seasonal variation in the incidence of GCA.

Methods: This study used data from the St Vincent's University Hospital GCA registry of 340 patients who were prospectively recruited from three hospital sites, in Dublin, over a 7-year period. We looked at month and year of onset of GCA symptoms and the variation in clinical phenotype at diagnosis, investigating for trends based on season of diagnosis.

Results: We had complete data for 5 years: 2012-2016 inclusive. Over these 5 years, 306 patients were diagnosed with GCA, 65% females and 35% males with a mean age of 71. Based on the date of onset of symptoms, we found an overall peak in the incidence of GCA in late spring / early summer and another smaller peak in late autumn / early winter. 64% presented with uncomplicated cranial GCA, 22% of patients had an ischaemic complication at diagnosis, 11% of patients presented with PMR with subclinical vasculitis and 3% with only constitutional symptoms. We did not observe any seasonal variation in these phenotypes.

Conclusion: We found a seasonal variation in the incidence of GCA with peaks in the late spring / early summer and late autumn / early winter. Following on from this study, by using data from the international TABUL and DC VAS datasets, we aim to investigate further the seasonal, cyclical and geographical variation in incidence in GCA.

Disclosures: None

50. Hospital-Based Frequencies of Primary Vasculitides at Eastern Mediterranean: A Longitidunal Analysis at 7th year

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Background: Primary vasculitides are very rare diseases and distribution of vasculitides differ according to geographic region. Since October 2014, vasculitis patients diagnosed in any departments of Hacettepe University Hospitals are prospectively recorded in University

Vasculitis Research Centre (HUVAC) database. Distribution of patients at 2nd year was presented in 2017. This study is aimed to report the 7th year results and to compare with them with 2nd year data.

Methods: All patients are re-evaluated according to the 2012 revised Chapel Hill nomenclature criteria. Pediatric patients fulfilled the Ankara 2008 criteria for the respective childhood vasculitis. Electronic patient records are periodically searched for the possible vasculitis patients having any of the 10th revision of the International Statistical Classification of Diseases (ICD-10) code for the particular vasculitides. Recently we are also recording vasculitis mimickers.

Results: A total of 2464 patients were recruited until 24th November 2021. 514 (20.9%) of them were pediatric patients. The most frequently seen vasculitis among adult patients was Behcet's Disease whereas in pediatric patients it was HSP/IgA Vasculitis (Table). Granulomatous polyangiitis (GPA) was the most common small vessel vasculitis in adults. Takayasu arteritis was more frequent than giant cell arteritis among the adult patients. No differences was found in the comparison of distribution of vasculitides 2nd year with 7th year (p>0.05 for all).

Conclusions: Distribution of vasculitides at 2nd and 7th year was similar. Thus we suggest that this is a true reflection of vasculitides in our country. Behcet's Disease is the most frequent vasculitis as expected. However, Takayasu arteritis is more common than GCA in adult patients. GPA is the most common small vessel vasculitis in adulthood. IgA vasculitis and Kawasaki's disease were frequently seen paediatric vasculitis.

Disclosures: No disclosures related to this abstract.

Table. Longitidunal distribution of vasculitides among adult and paediatric patients (%)

		ADULT		PEDIATRIC	
		April 2016 (n=677)	**Nov 2021 (n=1661)**	**April 2016 (n=205)**	**Nov 2021 (n=500)**
Variable vessel vasculitis	Behcet's syndrome,%	51.9	51.9	25.3	15.8
Large vessel vasculitis	Giant cell arteritis,% Takayasu's arteritis,%	4.6 12.3	5.4 10.9	0 2.9	0 3.4
Medium vessel vasculitis	Kawasaki disease,% PAN,%	0 3.4	0 3.1	16.6 3.9	14 6.6
Small vessel vasculitis	AAV,% • GPA,% • EGPA,% • MPA,%	11.6 • 9.0 • 2.0 • 0.6	12.1 • 8.3 • 3.1 • 0.7	1.5 • 1.0 • 0.5 • 0	1.0 • 0.8 • 0.2 • 0
	IgA vasculitis	4.0	3.8	44.9	52.8
Others (single organ, secondary vasculitis etc.)		12.1	12.7	4.9	6.2
Mimickers			289		14

51. Kawasaki Disease in Japan: A spatiotemporal evaluation of epidemiological features and linkage to wind-borne agents

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Background: Kawasaki Disease (KD) is an acute systemic vasculitis that mainly affects children younger than 5 years old. Although KD has been diagnosed in over 60 countries across several continents, its incidence is the highest in East Asia, particularly in Japan. After more than five decades since its discovery and active research, the etiology of KD is yet to be elucidated. Recent studies have analyzed the association between KD and diverse environmental factors, with some advances pointing towards a relevant role of the atmospheric transport of a wind-borne agent triggering the disease. While some candidates have been proposed, the actual nature of this agent(s) is still unknown. We sought to characterize the seasonal dynamics in KD incidence for all of Japan and across its 47 prefectures, and to propose etiological candidates driving these dynamics.

Methods: Onset and admission dates of 393,376 KD patients in Japanese hospitals from 1970 to 2018 were collected from the biennial nationwide epidemiological surveys of KD in Japan. For cases during the 1979-2018 period (369,480), the prefecture of the hospital of admission was also collected. 92 weekly air samples were measured at the Noto Ground-based Research Observatory (NOTOGRO), at the tip of the Noto peninsula in the Ishikawa prefecture in Japan, from August 2014 to March 2016. These samples were subsequently analyzed for the concentrations of 57 different metals, general PM1, PM2.5 and PM10 content was quantified, and DNA was extracted and sent for metagenomic analysis to quantify abundances of bacterial and fungal clades. A combination of classical time-series methods such as modified ARIMA models and spectral analysis are used to decompose the epidemiological series data into its trend and seasonal components at different frequencies. To study association between the measured environmental variables and KD incidence, a combination of lagged correlation analyses and more complex methods such as Scale Dependent Correlation (SDC) are used.

Results: KD incidence in Japan data shows a strong increasing trend from 2000 onwards, with a marked yearly seasonal effect with maxima in January/February and minima in October/November. The amplitude of the yearly seasonal component has also been increasing together with the trend. The features observed at the national level are consistent for the data of most prefectures when stratifying the epidemiological records at the regional level. The temporal variability of several of the measured environmental factors were found to be moderately associated with the temporal changes in incidence of KD in the region, more so when considering transient couplings between the variables.

Conclusions: The coherence between the trend and seasonal patterns of KD incidence in Japan and among its individual prefectures points towards a common source potentially driving

the etiology of the disease. The coherences between some of the environmental factors and the temporal changes of incidence in the disease warrant further and deeper study, ideally at higher temporal resolutions.

Disclosures. None

52. Analysis of flares in a single centre cohort of Eosinophilic Granulomatosis with Polyangiitis patients

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Background: Eosinophilic granulomatosis with polyangiitis (EGPA) is a heterogeneous disease with a variable, relapsing course. Real-world data regarding specific characteristics of flares in these patients are scarce. We aim to describe and analyse the flares presented in a single-centre cohort of EGPA patients.

Methods: Medical charts of EGPA patients diagnosed since 2008 were reviewed to describe demographics, clinical characteristics at diagnosis and at flare, number of flares, disease activity at flare, treatment of the flares, damage accrual, and laboratory results. The definition of flare was the same used in the MIRRA trial[1].

Results: A total of 38 EGPA patients were diagnosed since 2008 and followed regularly at our department. All the patients fulfilled both the ACR/EULAR newly released classification criteria and the MIRRA trial classification criteria for EGPA. Nineteen of them were male and 19 were female, with a mean age of 54.6 years. Baseline characteristics, along with an in-depth description of flares are summarized in table 1. A total of 190 flares were registered in 31 of 38 patients during a cumulative follow-up of 256.77 years, while in the remaining 7 patients without flares the cumulative follow-up accounted for a total of 28.55 years. Thus, the yearly rate of flares was 0.74. The main clinical symptoms at flare were asthmatic (77% of flares), followed by ear, nose and throat (ENT) symptoms (34% rhinitis, 24% sinusitis) being those that may be attributable to vasculitis (alveolar haemorrhage, peripheral nervous system involvement, nephritis, skin purpura, or arthritis) the least frequent (less than 5%), together with constitutional symptoms (around 5%). Lab tests could be requested in a minority of cases when the patients were symptomatic, relying the diagnosis of flare on the clinical judgement of the treating physician. When eosinophils (requested only in 50 flares), CRP (52 flares) and ESR (30 flares) were evaluated, in almost half of the tests (26 flares for eosinophils; 27 flares for CRP; 20 flares for ESR) the results were within normal ranges. ANCA were the least requested test (only in 27 flares), being positive by immunofluorescence also in half of the tests (14 flares). The mean dose of prednisone at the moment of flare was 8.95 mg/day. All the flares required an increase in the dose of prednisone, with a mean increase of 20.69 mg/day of prednisone, reaching mean doses up to 29.59 mg/day to treat the flare.

Conclusions:
The main characteristics of the flares of a well-defined cohort of EGPA patients were described. Asthma was the most common cause of flare (77% of flares), followed by ENT symptoms, being those attributable to vasculitis the least common. Lab test regarding eosinophils, CRP, ESR or ANCA were normal/negative in up to half of the tests. Flares occurred already at medium doses of prednisone and required high increases of prednisone doses for its treatment, which was the main treatment.

Disclosures: Maria C Cid has received consulting fees from GSK, Abbvie and Janssen, a research grant from Kiniksa Pharmaceuticals and lecturing fees from Vifor and GSK. Georgina Espígol-Frigolé has received consulting fees from Janssen.

Baseline characteristics at diagnosis		
Age at diagnosis, mean (range, ±SD) years	54.6 (26.3-84.0, ±12)	
Male, n (%)	19 (50%)	
Female, n (%)	19 (50%)	
BVAS, mean (range, SD)	13 (0-33, 8)	
VDI at 1st year of follow-up, mean (range)	1.67 (0-6)	
VDI at last year of follow-up, mean (range)	3.00 (0-9)	
General characteristics of the flares		
Flares, n	190	
Patients with flares, n	31/38	
Flares per patient, mean (range)	6.3 (1-30)	
Total length of follow-up, years (range per individual patient)	285.3 (0.33-14.08)	
	In patients with flares	*In patients without flares*
	256.8 (0.80-14.08)	28.6 (0.33-9.67)
Yearly rate of flares	0.74	
BVAS at flare, mean (range, SD)	3 (1-28, 3)	
Symptoms at flare		
Asthma, n of flares (%)	147 (77%)	
Fever, n of flares (%)	11 (6%)	
Weight Loss, n of flares (%)	2 (1%)	
Pulmonary Infiltrates, n of flares (%)	9 (5%)	
Pleural Effussion, n of flares (%)	4 (2%)	
Skin Involvement, n of flares (%)	1 (1%)	
Rhinitis, n of flares (%)	64 (34%)	
Paranasal Sinuses Involvement, n of flares (%)	40 (21%)	
Peripheral Nervous System Involvement, n of flares (%)	9 (5%)	
Cardiomiopaty, n of flares (%)	1 (1%)	
Renal Involvement, n of flares (%)	0 (0%)	
Arthralgias, n of flares (%)	10 (5%)	
Arthritis, n of flares (%)	1 (1%)	
Myalgias, n of flares (%)	10 (5%)	
Lab results at flares		
Eosinophils*, mean (range, SD) cells x10^9	1377 (0-24680, 3698)	
CRP**, mean (range, SD) mg/dL	2.3 (0-26.2, 4.21)	
ESR^{T}, mean (range, SD) mm/h	20 (4-100, 20.3)	
ANCA^{TT} positivity (IIF)	14/27	
pANCA (IIF)	13	
cANCA (IIF)	0	
Anti-MPO titters, mean (range)	208 (18.5-588.7)	
Treatment of flares		
PDN dose at flare, mean (range) mg/day	8.95 (0-50)	
Increase of PDN, mean (range) mg/day	20.63 (5-90)	

*: Only requested in 50 flares; **:Only requested in 52 flares; ^{T}: Only requested in 30 flares; ^{TT}: Only requested in 27 flares

53. Data quality in ANCA-associated vasculitis: an analysis of the FAIRVASC registries

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Background: The FAIRVASC project seeks to federate the data of seven ANCA-associated vasculitis registries across Europe using semantic web technology. A high standard of data quality (DQ) is required for the types of data analysis planned for the FAIRVASC architecture. We sought to design and implement a DQ assessment of the FAIRVASC registries.

Methods: A Data Quality Group was established within the consortium. This group consisted of individuals from a variety of specialist backgrounds including clinician scientists, health informaticians, statisticians and computer scientists. DQ domains selected for evaluation were Uniqueness, Consistency, Completeness and Correctness. These dimensions were prioritised by investigator consensus from a pool of nine candidate dimensions drawn from the literature and assessed using statistical methods and tools developed through prior published research. A DQ worksheet was designed using an iterative approach. A representative at each registry used the worksheet to evaluate their local registry DQ.

Results: Registry participants identification numbers were 100% unique across all seven registries. Consistency of data class was 100% across all measured variables. Consistency on logic testing was 99.9% across all registries. Completeness was 94.3% across all registries. Correctness was still under assessment at the time of this report. Where missing data were present due to an assessed variable not being present in a registry dataset, these were removed prior to analysis. Percentages represent the mean of summary percentages reported for each registry as a whole and were not adjusted for registry size.

Conclusions: This analysis demonstrated a high level of DQ across the initial seven FAIRVASC registries. The registry data were therefore deemed highly suited to FAIRVASC objectives including epidemiological analysis of European data and cluster analysis to determine novel disease phenotypes. Future work will include a DQ improvement process with multiple potential objectives such removal of duplicates, selection of highest quality records, imputation of missing values, re-entry of data and increased specificity of registry metadata.

Disclosures: None

54. FAIRVASC: A semantic web approach to rare disease registry integration

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Background: Rare disease data is often fragmented within multiple heterogeneous siloed regional disease registries, each containing a small number of cases. These data are particularly sensitive, as low subject counts make the identification of patients more likely, meaning registries are not inclined to share subject level data outside their registries. At the same time access to multiple rare disease datasets is important as it will lead to new research opportunities and analysis over larger cohorts.

Methods: To enable this, two major challenges must therefore be overcome. The first is to integrate data at a semantic level, so that it is possible to query over registries and return results which are comparable. The second is to enable queries which do not take subject level data from the registries.

Results: To meet the first challenge, this paper we present the FAIRVASC ontology to manage data related to the rare disease anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV), which is based on the harmonisation of terms in seven European data registries. It has been built upon a set of key clinical questions developed by a team of experts in vasculitis selected from the registry sites and makes use of several standard classifications, such as Systematized Nomenclature of Medicine - Clinical Terms (SNOMED-CT) and Orphacode. It also presents the method for adding semantic meaning to AAV data across the registries using the declarative Relational to Resource Description Framework Mapping Language (R2RML). To meet the second challenge, a federated querying approach is presented for accessing aggregated and pseudonymized data, and which supports analysis of AAV data in a manner that protects patient privacy. For additional security, the federated querying approach is augmented with a method for auditing queries (and the uplift process) using the provenance ontology (PROV-O) to track when queries and changes occur and by whom.

Conclusions: The main contribution of this work is the successful application of semantic web technologies and federated queries to provide a novel infrastructure that can readily incorporate additional registries, thus providing simultaneous access to harmonised data relating to unprecedented numbers of patients with rare disease from nearly 10,000 patients with vasculitis, while also meeting data privacy and security concerns.

Disclosures: None

55. The Birmingham Vasculitis Activity Score (BVAS) Ontology

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Background: The Birmingham Vasculitis Activity Score (BVAS) is a validated tool for assessment of disease activity in patients with different forms of vasculitis. It is used as an internationally recognised tool in vasculitis clinical trials, real world data collections, registries and in routine clinical practice. While BVAS is standardised, there is no standard approach to representing BVAS data within registries and currently no machine-readable digital description of the BVAS standard. The Web of Data is an initiative to make data open and interconnected, stored and shared across the World Wide Web using web technologies. An ontological description of BVAS, based on these technologies, will therefore serve two purposes. The first is to provide a structure for storing and publishing BVAS data in a way that can be queried over the web, thus supporting semantic interoperability between registries for the purpose of doing analysing federated data SNOMED-CT. Efforts are currently underway to make vasculitis registries across Europe and Australia interoperable and machine readable. These make it possible to add additional semantics using standard classifications, thereby allowing automated and standardised mapping of BVAS data to the pattern of organ involvement in patients with vasculitis.

Methods: The ontology was developed using a standard methodology using freely available and open-source tools. In addition, a set of R2RML mappings have been developed for uplifting Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) BVAS data into Resource Description Framework (RDF), along with a set of samples SPARQL queries for querying this data.

Conclusion: This ontology will support exposure of BVAS data in a machine readable and FAIR manner.

Disclosure: None.

56. Different epidemiologic profiles of systemic vasculitis between two referral centers from Brazil and Peru

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Background: Little is known about the epidemiologic features of systemic vasculitis in South American countries. This study aims to compare the prevalence of systemic vasculitides in two vasculitis referral centers from Brazil and Peru.

Methods: This is a descriptive cross-sectional study performed in two vasculitis referral centers from Brazil and Peru. All patients above 18 years of age with at least 6 months of follow-up and who met classification or diagnosis criteria for the most common systemic vasculitides were included in the study. Demographic data were also collected.

Results: A total of 562 patients with systemic vasculitis were analyzed, 345 (61.4%) of them from Brazil and 217 (38.6%) from Peru. The frequency of Behçet's disease (37.9% vs. 1.8%; $p < 0.0001$), Takayasu arteritis (TAK) (25.2% vs. 6.9%; $p < 0.0001$), and giant cell arteritis (9.8% vs. 0.9%; $p < 0.0001$) was significantly higher in the Brazilian center compared to the Peruvian center. On the other hand, the frequency of microscopic polyangiitis (MPA) (67.3% vs. 2.8%; $p < 0.0001$) and renal-limited vasculitis (2.8% vs. 0.0%; $p = 0.009$) was significantly higher in the Peruvian center. No significant differences were found between both centers concerning granulomatosis with polyangiitis (GPA) (13.0% vs. 14.8%; $p = 0.567$), polyarteritis nodosa (4.0% vs. 1.8%; $p = 0.146$), cryoglobulinemic vasculitis (3.1% vs. 0.9%; $p = 0.081$), eosinophilic granulomatosis with polyangiitis (2.8% vs. 2.3%; $p = 0.670$), IgA vasculitis (0.5% vs. 0.0; $p = 0.850$) and urticarial vasculitis (0.2 vs. 0.5%; $p = 0.740$). At diagnosis, Brazilian patients with TAK, GPA and MPA were younger than Peruvian patients. No differences were found regarding the age at disease presentation for the other systemic vasculitides (Table 1). The female gender is predominant amongst patients with systemic vasculitis from both countries.

Conclusions: Significant epidemiologic differences in the frequency of systemic vasculitis are observed between a vasculitis referral center from Brazil and from Peru. MPA is the most frequent vasculitis in the Peruvian center while BD and TAK are the most common forms of vasculitis in the Brazilian center. Further studies are needed to unravel if these differences are due to genetic and/or environmental factors.

Disclosures: None.

Table 1. Demographics features of vasculitis patients from Brazil and Peru.

Vasculitides	Age at diagnosis (years)		*p*	Female gender		*p*	F:M ratio	
	Brazil	Peru		Brazil	Peru		Brazil	Peru
Behçet's disease	31.0 (24.8-41.0)	41.5 (35.5-49.0)	0.073	62.7%	75.0%	0.253	1.6:1.0	3.0:1.0
Takayasu arteritis	28.9 ± 13.4	36.9 ± 12.7	0.013*	88.9%	95.2%	0.219	7.7:1.0	19.0:1.(
Giant cell arteritis	71.0 (60.8-78.0)	70.5 (68.0-73.0)	#	59.6%	100.0%	0.493	1.4:1.0	1.0:0.0
Granulomatosis with polyangiitis	45.3 ± 14.4	55.3 ± 14.4	0.001*	63.0%	52.9%	0.244	1.8:1.0	1.1:1.0
Microscopic polyangiitis	48.6 ± 17.3	60.5 ± 11.6	0.0003*	75.0%	71.5%	0.769	3.0:1.0	2.5:1.0
Eosinophilic granulomatosis with polyangiitis	50.2 ± 14.2	48.0 ±15.6	0.786	72.7%	20.0%	0.105	2.6:1.0	0.2:1.0
Polyarteritis nodosa	29.2 ± 18.6	41.5 ± 18.9	0.250	47.0%	50.0%	1.000	0.8:1.0	1.0:1.0
Cryoglobulinemic vasculitis	56.5 (40.5-64.5)	43.0 (42.0-44.0)	#	81.8%	50.0%	0.324	6.0:1.0	1.0:1.0

57. Drug Associated ANCA Vasculitis: A Single Center Experience

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Background/ Objectives: The trigger that induces antineutrophil cytoplasmic antibodies (ANCA) that lead to systemic vasculitis is largely unknown. Over the years, there have been associations noted between certain drugs and ANCA associated vasculitis; primarily hydralazine, propylthiouracil (PTU), methimazole, cocaine adulterated with levamisole, minocycline, and more recently, allopurinol. The aim of this study was to further elucidate the characteristics of the correlation between these drugs and detection of ANCA.

Methods: We conducted a retrospective analysis of 3997 patients from 1989-2021 with a newly detected ANCA test for myeloperoxidase (MPO) and/or proteinase-3 (PR3) antibodies at the Massachusetts General Hospital (MGH) ANCA laboratory. For each new ANCA-positive patient, a limited discussion was held with the ordering clinician to review implications of the positive test and to identify exposure to any suspected culprit drugs at the time of positive ANCA test. Electronic medical records of cases managed at MGH were also reviewed.

Results: Of the 3997 patients (mean age: 73 years, 60% female) with a newly positive ANCA test from 1989 to 2021, 434 patients (mean age: 68 years, 63% female) were found to have exposure to one or more culprit drugs prior to detection of ANCA, representing 11% of the total cohort. Hydralazine exposure was noted in 149/434 (34.3%) of patients, cocaine/levamisole exposure in 107/149 (24.7%) patients, with the remainder of patients with PTU (50/434, 11.5%), minocycline (46/434, 10.6%) and methimazole (14/434, 3.2%) exposure. We found 68 of 434 patients (15.7%) were treated with allopurinol prior to a positive ANCA test. MPO-ANCA positivity was a predominant feature in the drug-associated cohort, representing 378/434 (87%) of drug associated cases. The median MPO titer in the drug-associated cohort was 5 times higher compared to the median MPO titer of the total ANCA positive cohort. The median MPO titer of the hydralazine group was 15 times higher compared to the entire cohort. 34 of 59 patients (57.6%) with double positive MPO and PR3-ANCA had a culprit drug exposure prior to ANCA detection.

Conclusions: The true prevalence of drug-associated cases is likely underrepresented as medication exposure at the time of a positive ANCA test were unknown in many cases. Our data suggest that patients with high MPO-ANCA titers and/or double positive MPO and PR3-ANCA should be investigated for any of these likely culprit drugs.

Disclosures: None

	n (%)	MPO-ANCA n (%)	PR3-ANCA n (%)	MPO- and PR3-ANCA n (%)	MPO-ANCA titer median (IQR), units*
Total ANCA positive cohort	3997 (100)	2804 (70.2)	1134 (28.4)	59 (1.4)	98 (22 - 511)
Drug-associated ANCA cohort	434 (11)	378 (87.1)	22 (5.1)	34 (7.8)	524 (50 – 2455)
Hydralazine	149 (34.3)	145 (97.3)	1 (0.7)	3 (2)	1433 (222 – 7578)
Cocaine/levamisole	107 (24.7)	73 (68.2)	11 (10.3)	23 (21.5)	1332 (207 – 4525)
Propylthiouracil	50 (11.5)	44 (88)	1 (2)	5 (10)	178 (59 – 1152)
Methimazole	14 (3.2)	14 (100)	0 (0)	0 (0)	19 (12 – 71)
Minocycline	46 (10.6)	39 (84.8)	4 (8.7)	3 (6.5)	37 (15 – 131)
Allopurinol	68 (15.7)	63 (92.6)	5 (7.4)	0 (0)	205 (54 – 2234)

Table 1: Analysis of drug-associated ANCA vasculitis patient cohort.
n = number, IQR = interquartile range
* = upper limit of positive MPO assay range set at 5.6 units

Public Health & Health Services Research

58. Disease modifying anti-rheumatic drug (DMARD) therapy laboratory monitoring for toxicity in rheumatology patients

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Background/ Objectives: Review of blood results for monitoring DMARDs is performed manually in our department and subject to human error with up to 200 starters per month. In the last 6 months at least 3 patients have had abnormalities which were missed, highlighting a significant clinical risk. The aim of the project was to develop, test and implement an automated algorithm to detect and act on significant blood abnormalities in patients starting DMARD therapy for a range of rheumatic diseases, including vasculitis.

Methods: We created a system to automatically analyse laboratory results supplied by our laboratory according to threshold values recommended by the British Society for Rheumatology (BSR). We imported data into a specifically designed database to provide analyses based on BSR guidelines. The data are immediately ready for review by a clinician, grouped as: normal, mildly abnormal (exceeding the upper or lower limit of normal for our laboratory), missing (individual values not recorded), or abnormal (outside the threshold values advised by the BSR); records with consecutive results showing a trend towards abnormality are also recorded. The clinician has the responsibility to review all records and endorse them after taking appropriate action where required.

Results: We tested the system on 2 cohorts of 100 and 227 sets of blood tests respectively and confirmed that it is more rapid and robust than a manual process. We compared each record with a manual evaluation of the data on a spreadsheet. We identified more abnormalities using the new system than were found on manual inspection (29% vs 10%, Chi square $P<0.001$). The manual inspection took 3 hours to prepare the data for evaluation; the new system performed the same task in under 1 minute. Table 1 shows the summary data for 100 test records, assessed manually and then using the algorithm, followed by real data using 1347 records from 395 patients initiating DMARDs (requiring action on 0.67% of all records: 2 missing results and 7 significantly abnormal results; in a further 7.4%, trending values were detected). Subsequent manual inspection of the test records defined as abnormal by the algorithm confirmed that the new system had correctly identified abnormalities in every case.

Conclusions: We have developed a blood monitoring system for patients initiating DMARDs, capable of processing up to 10,000 results per session. The system is practical, more efficient, and more accurate than a manual process for DMARD monitoring for any patients receiving immunosuppressive therapies.

Disclosures: None

Table 1. Analysis of blood results

	N (total no of records)	Normal	Mildly abnormal	Significant missing values	Trending values	Abnormal/ no action required	Abnormal / action required
Test data set 1 (manual)	100	90	0	-	-	0	10
Test data set 1 (algorithm)	100	71	0	0	-	0	29
Live data (algorithm)	1347	1017	129	2	99	93	7

59. Giant Cell Arteritis Hospital Standards (GHOST) - Mapping Specialised services for GCA care across England

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Background: The end objective of this project is to map services essential to delivering high quality care in Giant Cell Arteritis (GCA) across England, identifying gaps in provision and thereby hopefully help to remove inequalities. To do this however, there must first be agreement on what these best practice services and standards are.

Methods: A steering committee was formed comprising 18 expert representatives from each of the 13 clinical regions in England, and included rheumatology, ophthalmology, allied health professional and patient representation. A modified Delphi process was commenced with each member initially providing 5 aspects of service they felt were essential for best practice GCA care. From the 65 answers, the common themes were identified by creation of a word cloud and then condensed into domains of practice. These domains were then ranked by each member in order of perceived importance. The top 10 domains taken forward for further review were clinical pathways, patient access, Rheumatology involvement, Ophthalmology involvement, ultrasonography provision, temporal artery biopsy provision, PET-CT scan provision, glucocorticoid treatment, patient education and multi-disciplinary team working. Domains identified as separate areas but not quite making it into the top 10 were Tocilizumab provision, audit and governance and research. With the later 2 in particular, it was felt these are overarching principles which should run through all aspects of clinical work. Group consultation was undertaken to discuss the relevant aspects, and from this, 3 quality metrics and 1 summary statement were devised for each domain. Rheumatology and Ophthalmology provision were amalgamated, as it was felt these were equally as important, with similar requirements. On the first pass of voting all except ‘patient access’ achieved over 75% agreement amongst the steering committee members. After group consultation and amendment, ‘patient access’ also achieved the minimum 75% agreement cut-off.

Results: The final statements can be seen in table 1 below.

Discussion: By devising specific quality metrics in addition to the recommendation statements above, it is envisaged these standards can be easily used as an audit tool to identify gaps and development needs in GCA services.

Disclosures: None

Table 1. Final summary statements for each domain of best practice care for GCA.

Domain	Statement of recommendation
Clinical pathways	1.1 There should be an established pathway for the investigation and care of individuals with suspected GCA, which is agreed across primary and secondary care, with clear entry and exit points, and clear time frames for initiation of investigations and glucocorticoid treatment.
Patient access	Patients with suspected new or relapsing disease should always be able to access a clinician with appropriate expertise or a helpline, leading to a preliminary management plan within 24 hours of patient access and a definitive review within 2 working days.
Rheumatology & Ophthalmology provision	1.2 There should be nominated leads in rheumatology and ophthalmology with an interest in GCA who coordinate care, collaborate with the other specialities in the hospital, and run dedicated CTD/Vasculitis clinics for follow-up of patients with GCA.
Ultrasonography provision	1.3 Diagnostic ultrasonography for GCA should be adequately resourced with high-quality equipment and cross-cover to ensure that it is not dependent on a single machine or operator. Diagnostic ultrasonography for GCA should be performed within 7 days of starting prednisolone and the images should be reported using validated definitions and stored in the medical records.
Temporal artery biopsy	1.4 Temporal artery biopsy provision should be adequately resourced and should not be dependent on a single surgeon. The biopsy should be of an adequate size, harvested within 4 weeks of starting prednisolone and reported in a standardised manner.
PET scan provision	1.5 PET scan for large vessel vasculitis should be done within 7 days of the request and reported by an experienced radiologist.
Glucocorticoid treatment	1.6 There should be a provision and protocol for intravenous glucocorticoid. The shared care of oral prednisolone should include a written tapering plan and monitoring of complications of long-term glucocorticoid therapy.

60. Trends in Hospital Admissions in People with ANCA-associated Vasculitis Before and During the COVID19 Pandemic

Myron Odingo[1,3], Megan Rutter[1,2,3], Peter C. Lanyon[1,2,3], Matthew J. Grainge[1], David J. Groves[1,3], Mary Bythell[3], Jeanette Aston[3], Sarah Stevens[3], Fiona A. Pearce[1,2,3]
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Background/ Objectives: People with ANCA-associated vasculitis (AAV) have high rates of hospital admissions for their vasculitis. They may have emergency admissions at the time of diagnosis, or day case admissions to receive immunosuppressive treatment. We describe the

trends in emergency and day case admissions over the past 9 years, and the effect of the COVID-19 pandemic.

Methods: We extracted Hospital Episode Statistics data for the financial years 2012/13 to 2019/20, publicly available from NHS Digital, and supplemented these with provisional data for 2020/21 from the National Congenital Anomaly and Rare Disease Registration Service, using their legal permissions (CAG 10-02(d)/2015) because the publicly available data had not been released yet. We extracted all emergency and day case admission rates with ICD-10 codes for each AAV subtype: granulomatosis with polyangiitis, microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (M313, M317 and M303 respectively), in the primary position denoting main admission diagnosis. We used England population estimates from the Office for National Statistics as the denominator for rates. We calculated Poisson confidence intervals to quantify the difference in rates across the financial years between 2012/13 and 2020/21.

Results: Rates of day case admissions per 1,000,000 for AAV increased from 49.1 (95% CI 47.2 - 50.9) in 2012/13 to 63.3 (95% CI 61.2 - 65.4) in 2019/20, then decreased by 26.4% to 48.6 (95% CI 46.7 - 50.4) in 2020/21 (see table). The trends in emergency admissions were relatively unchanged between 2012/13 and 2019/20 (mean 6.7 per 1,000,000), and there was no significant decrease in emergency admissions during the COVID-19 pandemic in financial year 2020/21.

Conclusions: Day case admission rates increased between 2012/13 and 2019/20 but decreased during the COVID-19 pandemic. Emergency admission rates for people with AAV remained relatively unchanged, despite the context of the significant disruption and reconfiguration of healthcare services. Further research using patient-level data is needed to establish whether the reduction in day case activity is due to fewer people being diagnosed with new or relapsing disease, and therefore fewer remission induction infusions being administered, or due to postponement of planned remission maintenance treatment due to perceived risk from COVID-19 infection. Alternatively, the reduction in day case admissions may reflect a change in clinical practice to preferentially use oral rather than IV agents. All of these changes in healthcare delivery may have future consequences both for clinical practice and individual patient care and outcomes post-pandemic.

Disclosures: P. Lanyon: received funding for research from Vifor Pharma. FAP has received funding for research from Vifor Pharma.

Table: ANCA associated vasculitis (AAV)** crude incidence rates by financial year					
Year	**English population**	**Emergency admissions**	**Day case admissions**	**Emergency Admissions - rate per 1,000,000***	**Day case crude admissions - rate per 1,000,000***
2012/13	53493700	410	2624	7.6 (6.9 - 8.4)	49.1 (47.2 - 50.9)
2013/14	53865800	406	2795	7.5 (6.8 - 8.3)	51.9 (50.0 - 53.8)
2014/15	54316600	398	2658	7.3 (6.6 - 8.0)	48.9 (47.1 - 50.8)
2015/16	54786300	368	2504	6.7 (6.0 - 7.4)	45.7 (43.9 - 47.5)
2016/17	55268100	365	2953	6.6 (5.9 - 7.3)	53.4 (51.5 - 55.4)
2017/18	55619400	329	2901	5.9 (5.3 - 6.6)	52.2 (50.3 - 54.1)
2018/19	55977200	330	3450	5.9 (5.3 - 6.5)	61.6 (59.6 - 63.7)
2019/20	56287000	350	3564	6.2 (5.6 - 6.9)	63.3 (61.2 - 65.4)
2020/21	56550000	385	2746	6.8 (6.1 - 7.5)	48.6 (46.7 - 50.4)

*Crude incidence rate (95% confidence interval)
**AAV includes microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA) and granulomatosis with polyangiitis (GPA).

61. Time to diagnosis after referral to a hospital of ANCA-associated vasculitis patients in the Netherlands

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Background: Diagnosing patients with anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) can be challenging due to its rarity, complexity and wide variety of symptoms. Diagnostic delay may lead to delayed treatment potentially leading to progressive disease and chronic damage. Few studies have addressed real-life diagnostic pathways to identify opportunities to improve the diagnostic phase for AAV patients. Therefore, we evaluated the diagnostic phase of AAV patients in the Netherlands.

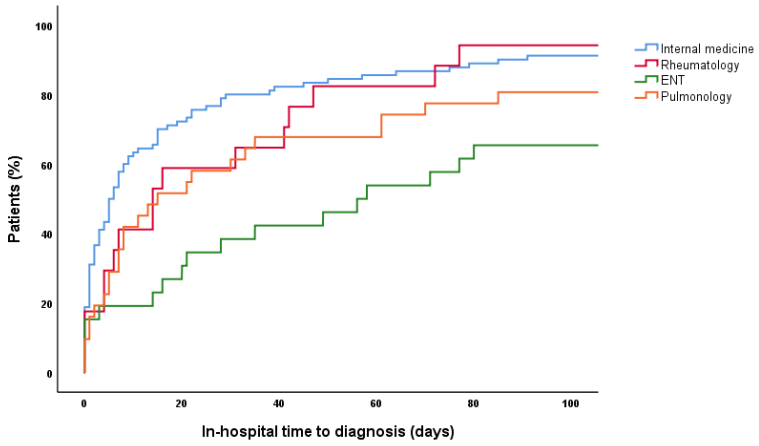
Methods: This study is a retrospective, observational study of electronic medical records data in hospitals focusing on diagnostic procedures during the first assessment until diagnosis.

Results: 230 AAV patients in 9 Dutch hospitals diagnosed with mainly granulomatosis with polyangiitis (73%) and generalized disease (72%) with major organ involvement (kidney, heart, lungs and nervous system) were included. First assessments upon hospital presentation was performed by a specialist in internal medicine (including nephrology) (52%), pulmonology (14%), ear-nose-throat (ENT; 13%) and rheumatology (10%). The median time to diagnosis after referral was 13 days [IQR 2-49] with a difference between patients with generalized and non-generalized disease (9 days [IQR 1-43] vs 22 days [IQR 3-73], p=0.094). The median time to diagnosis after referral in patients with their first assessment by a specialist from internal medicine was 6 days [1-25], rheumatology 14 days [4-45], pulmonology 15 days [5-70] and ENT 57 days [16-176] (p=0.004). A total of 219 biopsies were performed in 187 patients (81%). Histopathological support for AAV diagnosis was observed in 86% of kidney biopsies (84/98), 64% of lung biopsies (14/22), 34% in ENT biopsies (21/61) and 30% of skin biopsies (7/23).

Conclusion: In the Netherlands, AAV is predominantly diagnosed and managed by specialists from internal medicine. Diagnostic delay was associated with non-generalized disease and ENT-involvement as presenting symptom. Additionally, ENT biopsies had a very low diagnostic yield in contrast to kidney and lung biopsies. Awareness of these data and a multidisciplinary approach with early referral to internal medicine when AAV is suspected in difficult-to-diagnose cases may help reducing delay in AAV diagnosis.

Disclosures: none

Figure 1. A Kaplan Meier curve of the in-hospital time to diagnosis (days) of patients primarily assessed by a specialist from internal medicine (blue), rheumatology (red), ear-nose-throat (ENT; green) and pulmonology (orange).



62. Characterisation of systemic vasculitis outcomes across a nation: do different models of care matter?

Enock Havyarimana[1], Matthew Rutherford[1], Warren James[2], Prof Corri Black[2], Neil Basu[1], Rosemary Hollick[3]
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Background/Objectives: Care models employed to manage systemic vasculitis typically vary between regional health care systems. It is unknown if such differences result in geographical variation in outcomes. In this population based national study of individuals with ANCA associated vasculitis (AAV) and Giant Cell Arteritis (GCA) we aimed to explore geographical variation in key outcomes across the nation of Scotland where variation in regional vasculitis care models are known to exist.

Methods: Patients' ≥16 years with ≥ 1 ICD-10 code for AAV [Granulomatosis with Polyangiitis (GPA) - M31.3; Microscopic Polyangiitis (MPA) - M31.7; Eosinophilic granulomatosis with polyangiitis (EGPA) - M30.1] or GCA [M31.5 and M31.6] between 1996 and 2021 were identified from the population based Scottish hospitalisation registry (>90% population coverage). Each patient was matched with up to 5 general population controls (with a previous record of hospital admission) by age (+/-2 years), sex and health service region of residence. Incidence rates of serious infection, cardiovascular and cancer rates for AAV and GCA cohorts compared to matched controls were analysed using Poisson regression, adjusted for age, sex, deprivation and population density metrics. In each cohort, a stratified analysis per health board of treatment compared incident rate ratios (IRRs) for clinical outcomes across health service regions in Scotland, to the national average. We assessed heterogeneity in outcomes between health service regions using I^2 (index of heterogeneity).

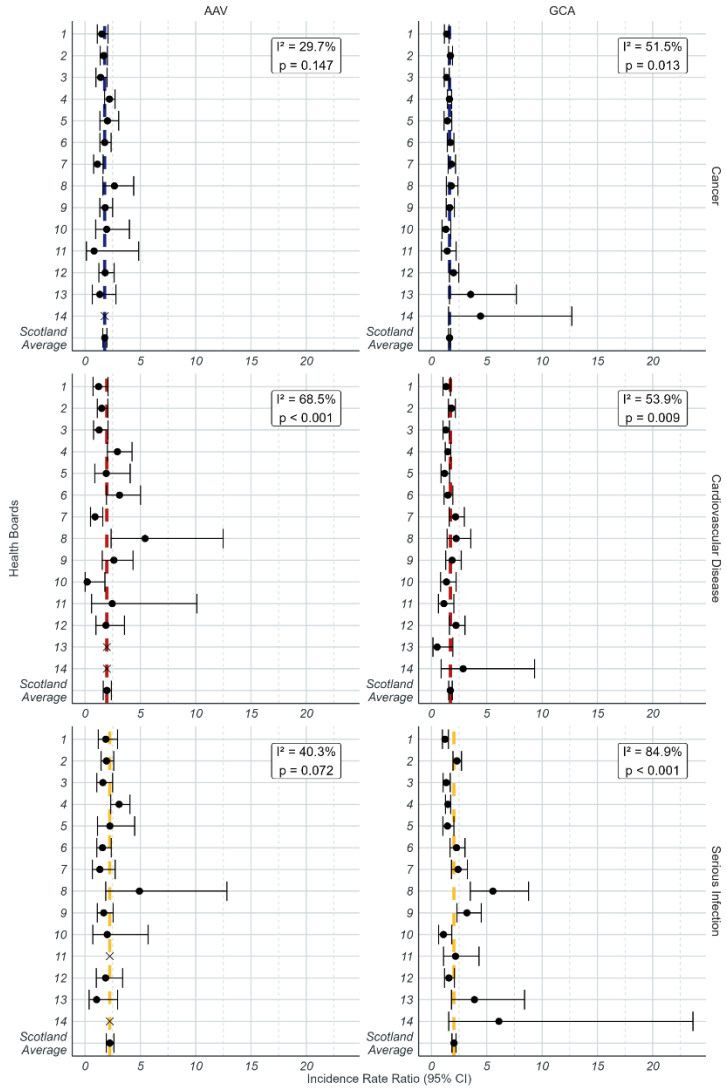
Results: A total of 1943 patients with AAV (median age 61.2 years [IQR 49.5 – 70.9]; 50.2% male) and 9715 population controls (median age 61.3 years [IQR 49.4-70.7]; male 50.2%) were identified with a median follow up time of 6.6 and 8.4 years respectively. Risk of serious infection requiring hospital admission, cardiovascular disease and cancer was higher in AAV patients than in matched controls (serious infection: IRR 2.24 [95% confidence interval (CI) 1.91, 2.62]; cardiovascular disease: IRR 1.98 [95% CI 1.65, 2.38]; cancer: IRR 1.78 [95% CI 1.60, 1.98]. 7107 patients with GCA (median age 75.2 years [IQR 68.1-81.3]; 28.2% male) and 10,030 hospital controls (median age 75.3 years [IQR 68.1-81.3]; male 28.2%) were identified with a median follow up time of 5.3 and 6.0 years respectively. Risk of serious infection, cardiovascular disease and cancer was higher in GCA patients than in matched controls (serious infection: IRR 2.04 [95% confidence interval (CI) 1.87, 2.23]; cardiovascular disease: IRR 1.71 [95% CI 1.57, 1.88]; cancer: IRR 1.64 [95% CI 1.55, 1.74]. There was significant geographical heterogeneity in some outcomes across health boards compared to the Scottish

average, particularly for cardiovascular disease in AAV (I^2 = 68.5%, p=0.000), and serious infection in GCA (I^2 = 84.9%, p=0.000), see Figure 1.

Conclusions: There is geographical variation in key clinical outcomes for AAV and GCA patients across health service regions in Scotland. These findings emphasise the importance of identifying key elements of care models underpinning effective care for patients with systemic vasculitis to support regional service planning and improve outcomes.

Disclosures: None

Figure 1. Clinical outcomes in AAV and GCA across health service regions in Scotland



63. Characterising AAV and GCA vasculitis services across UK and Ireland – priorities for collaborative care

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Background/ Objectives: The Vasculitis Outcomes In relation to Care Experience Study (VOICES), aims to understand the key patterns of service configuration underpinning effective care. In collaboration with the UK and Ireland Vasculitis Society (UKIVAS) and the Scottish Systemic Vasculitis Network (SSVN), an online questionnaire explored a range of service features including size, service model, human resources, facilities, organisation and processes of care.

Methods: Vasculitis services across nephrology and rheumatology in 87 UKIVAS sites, plus 11 Scottish regional health boards, were approached to complete the survey between Nov 2020 and June 2021.

Results: We received 59 responses from 51 Trusts/Health Boards across Scotland (n=11), England (n=33), Wales (n=2), and Ireland (n=5). This included an equal split of respondents from nephrology and rheumatology working across a range of healthcare settings; teaching hospitals, tertiary referral centres, and district general hospitals. 2/3rds said their service was recognised by NHS England as a specialised centre. 86% had a local care pathway for GCA and 63% had a local care pathway for AAV. 73% were able to see vasculitis patients for follow up at least weekly; 19% daily; and 23% indicating less frequent follow up (monthly or less). Vasculitis patient were seen in a range of different clinics; dedicated/subspecialty plus other clinics that included general and/or flare clinics. 41% held joint vasculitis clinics with other specialties, most commonly rheumatology, nephrology, ENT and respiratory, and a smaller number with dermatology and ophthalmology. 30% held parallel clinics with a broader spread of specialties, predominately rheumatology, nephrology, ENT and respiratory. In patient management of vasculitis was mainly under the care of individual specialties, with a smaller proportion reporting the presence of a dedicated in-patient vasculitis team or review team. 80% have the opportunity to discuss vasculitis patients at an MDT; most commonly local speciality meetings, followed by local primary vasculitis and regional vasculitis MDTs. As an outcome of MDTs, almost 50% reported proposing changes in patient management; 30% recommending prescription of biologics; 25% requesting additional investigation; 25% recording MDT outcomes to their health board/trust. All respondents had the ability to provide biologic and cytotoxic infusions, the majority of which was available within their own specialty day unit or use of another day unit facility (average wait time for urgent cases 2.7 days (range 1-10 days)). 52% have Specialist Nurses working directly within their vasculitis service. Activities included; infusion delivery, nurse-led clinics and patient advice line. 94% have staff trained to administer

cytotoxic therapy, and 70% would find a regional or training module helpful. 88% enter data to a national registry, mostly commonly by research nurses senior clinicians and research assistants. 48% have a local database, most commonly completed by senior clinicians.

Conclusions: Priorities for services include support for; specialist nurse led care, delivery of timely biologics/cytotoxic infusions, and support for MDT meetings. Other priorities in light of the COVID-19 pandemic include support for remote care delivery and hybrid care pathways. From the survey we have identified key pillars of service underpinning effective care for patients with systemic vasculitis to support regional service planning and improve outcomes.

Disclosure: None

64. Tertiary referral Autoimmune Inpatient Service: Multi-professional model of care addressing key milestones in patient care

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Background/ Purpose: The multi-disciplinary Vasculitis & Lupus Service at Addenbrooke's Hospital Cambridge, is composed of the Outpatient Clinic Service, the Inpatient Autoimmune Service and the Academic and Education Section. Close liaison between the inpatient and outpatient services facilitates rapid access to consultation, therapies, admission and discharge for patients. The Autoimmune inpatient service has a designated on-call Consultant and Registrar, with a specialist interest in autoimmune disease, comprising of Nephrologists and Rheumatologists. On-call responsibilities include the direct management and consults service for inpatients with autoimmune disease and those in whom the diagnosis is suspected and require diagnostic input and expertise.

Methods: The inpatient service was reviewed for 8 weeks with the aim to delineate the inpatient population, the reasons for admission, demographics, diagnosis, interventions, length of stay and weekly turnover. It sought to investigate key constituitive components inputting to the Inpatient Autoimmune service, to capture multi-organ specialist review and the workings of a multi-disciplinary service.

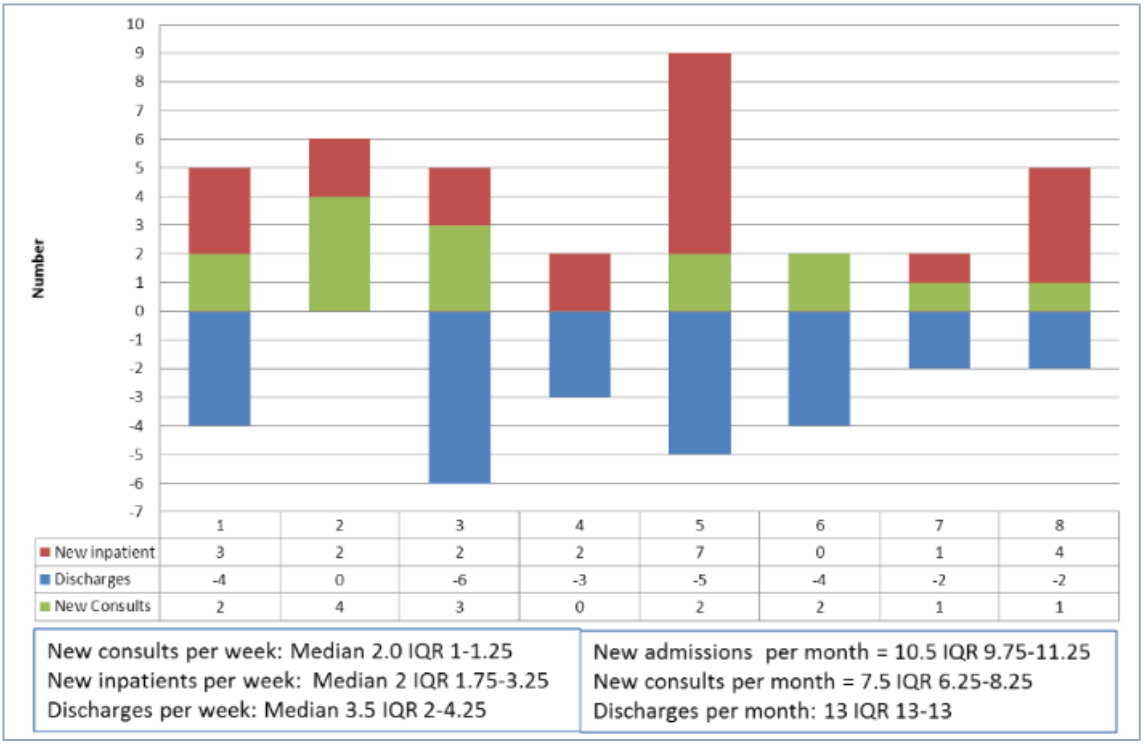
Results: Regarding in-patients, 28 were under the direct care of the service during the 2-month study. The median age was 59 years (46-69), 19 (67.9%) were female and 9 (32.1) were male. The median length of stay was 6.5 days [IQR 5-12.75], the range was 2-43 days. For in-patients with a pre-existing diagnosis of autoimmune disease (n=18), this included vasculitis (n= 9, 50%), lupus (n=4, 22%), unconfirmed (n= 3, 16%) and rheumatoid arthritis (n= 1, 5.6%). The referral source for their admission was clinic (n=15, 53.6%), the emergency department (n=8, 28.6%), and transfer from other hospitals (n=5, 17.9%). The reason for their admission was related to autoimmune disease activity in 16 (57%) – relapse (4), newly diagnosed (6) or diagnostic work-up (6). In a further 12 patients (42%) – 7 had infections, 1 hip fracture, 2 DVT/PE and 2 GI bleeds. 7 (25%) had evidence of an acute kidney injury at

presentation. 3 had renal biopsies, 4 line insertions for dialysis and 4 patients had PLEX. Patients had inter-disciplinary review by 17 other specialities, with respiratory review most frequent (13%), followed by rheumatology and haematology (11%). During the period of the study, none of the patients required intensive care. The median number of patients seen per day was 6 [IQR 4.75 – 6.25], with a median number of 4 inpatient admissions [IQR 3-6] and 1 consult [1-2]. The median number of new admissions per month was 10.5 [IQR 9.75-11.25] and new consults reviewed per month 7.5 [IQR 6.25-8.25], with the number of discharges 13 per month. Regarding the 15 consults cases that were seen over two months, the reason for referral was to confirm the diagnosis of autoimmune disease in 40%, review for consideration of a possible diagnosis of autoimmune disease in 27% and to provide management advice in 33 with a known pre-existing autoimmune disease. The referring disciplines were respiratory (27%), general medicine (20%), obstetrics and gynaecology (13%), neurology, rheumatology, ENT, emergency department and gastro-enterology (7%), other hospitals (7%).

Conclusion: The in-patient service was directly responsible for inpatient care and for the provision of a consultation service within the hospital, regionally and nationally. The service provided expertise in newly suspected vasculitis to both confirm and exclude the diagnosis. Multi-disciplinary organ management was engaged by the vasculitis team ensuring a timely coordinated management approach for patients. The inpatient service enabled rapid inpatient admission to facilitate early commencement of treatment, with discharge to vasculitis clinic minimizing inpatient stay, and implementing a longer term outpatient management plan.

Disclosures: David Jayne’s disclosures of commercial conflicts for companies with marketed products for 2021 are: Astra-Zeneca, Aurinia, BMS, Boehringer-Ingelheim, GSK, Janssen, Novartis, Roche/Genentech,Takeda & Vifor. AE, CB have nothing to declare.

Table 1. The In-patient Vasculitis Service at the Vasculitis and Lupus Unit, Addenbrooke's Hospital, Cambridge.



	1	2	3	4	5	6	7	8
New inpatient	3	2	2	2	7	0	1	4
Discharges	-4	0	-6	-3	-5	-4	-2	-2
New Consults	2	4	3	0	2	2	1	1

New consults per week: Median 2.0 IQR 1-1.25
New inpatients per week: Median 2 IQR 1.75-3.25
Discharges per week: Median 3.5 IQR 2-4.25

New admissions per month = 10.5 IQR 9.75-11.25
New consults per month = 7.5 IQR 6.25-8.25
Discharges per month: 13 IQR 13-13

Reproductive Health & Management

65. Comparing birth-rates, gestational diabetes and non-standard deliveries between Takayasu Arteritis patients and a general population

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Background: Takayasu arteritis (TAK) is a chronic, inflammatory vasculitis of the aorta and primary branches, particularly prevalent in women of childbearing age. We studied pregnancy outcomes for women with TAK compared to the general population.

Methods: All people in England with an ICD-I0 diagnostic code for TAK from 1997/98 to 2020/21 were identified from Hospital Episode Statistics (HES) using National Congenital

Abnormality and Rare Disease Registration Service (NCARDRS) data (CAG 10-02(d)/2015). To improve precision of estimated date of diagnosis, we used an English Hospital case register of 122 people with TAK and analysed all HES admissions occurring between the clinically-confirmed diagnosis date and the first TAK ICD-10 code. We identified codes which indicated likely TAK-related activity, and then applied these to the whole NCARDRS cohort. Maternity-related ICD-I0 and OPCS-4 code admissions after the estimated diagnosis date were extracted and age-specific values were calculated for number of births, TAK patient years and birth rates. ONS published national data was used for comparison.

Results: We identified 1,437 people with TAK. Between 2001 and 2021, there were 133 babies born (129 singleton, 2 twin births, no stillbirths) to 85 mothers. Mean maternal age at first delivery was 32.2 years (SD 5.3, median 33.2), above the UK mean of 27.8. See the table for age-specific birth rates compared to a 2019 general population. Overall birth rate in women with TAK was 62.5% of the national England/Wales rate. Gestational diabetes (GDM) was present in 13/131 deliveries (9.9%) but large variation in UK prevalence estimates makes national comparison difficult. Mothers with GDM had median age of 37 and delivery was by C-section in 9/13 cases. For non-GDM, 50% (95% CI: 41%, 59%) were C-section, significantly higher than the UK level of 26%. 12% were vacuum and/or forceps assisted deliveries, approximately equal to the general population.

Conclusions: The birth rate in women with TAK is lower than the general population and C-section rates higher. Causes are complex and might include personal choice, physician recommendation or reduced fertility related to disease activity or cytotoxic treatment. These findings highlight the importance of equitable access to specialist pre-conception counselling for people with rare autoimmune diseases.

Disclosures: None

Table 1.

Age-specific birthrates for Takayasu Arteritis in England compared to a national population

Females with TA					England & Wales 2019			Delivery method	
Ages	Number of babies	Patient years	Number of patients	Rate	Number of births	Population	Rate		N
12 - 19	1	191	53	5.2 (0.1, 29.2)	17,683	2,597,046	6.8	C-Section	68
20 - 24	9	339	96	26.5 (12.1, 50.4)	86,260	1,791,201	48.2	Vacuum	9
25 - 29	27	585	161	46.2 (30.4, 67.2)	172,301	1,970,004	**87.5**	Forceps	7
30 - 34	51	802	202	63.6 (47.3, 83.6)	207,331	2,004,089	**103.5**	Other	48
35 - 39	34	924	234	36.8 (25.5, 51.4)	120,559	1,978,036	**60.9**	TOTAL	132
40 - 44	11	980	256	11.2 (5.6, 20.1)	26,700	1,799,995	14.8		
45 - 49	0	936	250	0.0 (0.0, 3.9)	2,228	1,978,611	1.1		
	133	4,757	1,252	28.0 (23.4, 33.1)	633,062	14,118,982	**44.8**		

Rates are per 1000 patient years with 95% Poisson CI
Patient years is time between diagnosis and end of follow up
Deliveries include one twin birth
Boldface = a statistically higher rate than females with TA (p<0.05)

66. Takayasu's Arteritis and Pregnancy: A Meta-analysis

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Background: Takayasu's arteritis is a systemic autoimmune disease characterised by a large vessel vasculitis. It is characterised by inflammation of vessel walls which can lead to stenosis, occlusion, dilation, or aneurysm formation. It usually affects women of childbearing age, with 90% of patients diagnosed < 30 years of age, and previous studies suggest it is associated with adverse pregnancy outcomes. There is a vast discrepancy within the literature; some studies suggest preeclampsia occurring in 4.5% of patients, while others suggest a rate of 61%. The purpose of our work was to determine the prevalence of both maternal and foetal outcomes in patients with Takayasu's arteritis through a systematic review and meta-analysis.

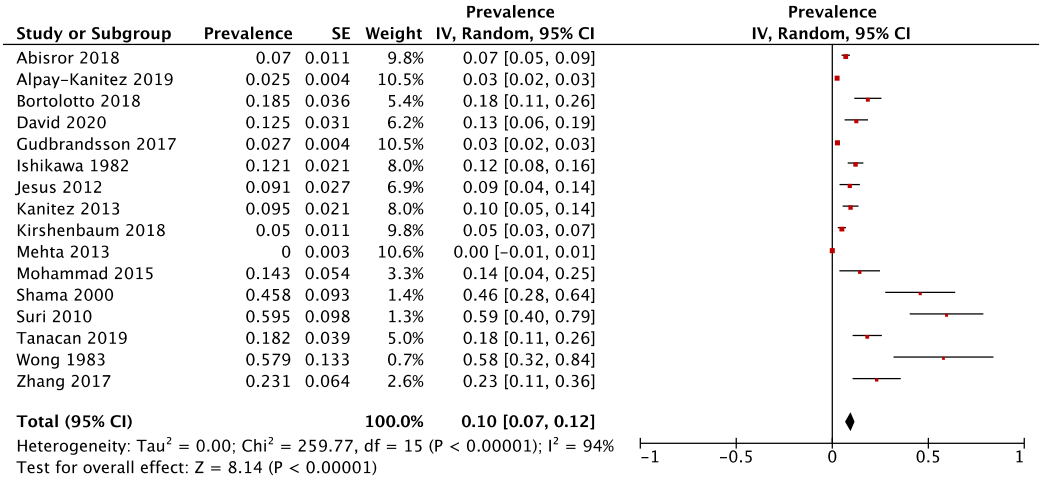
Methods: We performed a systematic review of the literature using Medline, Web of Science, and the Cochrane library from their inceptions until March 26, 2021, to identify studies that reported pregnancy outcomes in patients with Takayasu's arteritis. Demographic information, maternal outcomes, foetal outcomes, prednisolone use, and information on disease activity were extracted from studies. Two authors independently selected the studies, extracted the data and assessed for risk of bias.

Results: Our systematic review identified 6638 abstracts, of which 23 articles were included. The miscarriage rate was 11 [7-16] % and an intrauterine death rate of 1[0-3] %. Preeclampsia was reported in 10[7-12] % of patients (Figure 1). Preterm delivery occurred in 15[12-19] %. New hypertension in pregnancy was reported in 12[8-16] %. Intrauterine growth restriction occurred in 16[10-21] % of pregnancies. The prevalence of caesarean sections among Takayasu patients was 28 [22-28] % (Figure 2). In terof foetal outcomes, low birth weight was associated with 16[10-21] % of live births (Figure 3). Flares of vasculitis occurred in 11[8-15] % of patients. The prevalence of caesarean sections, preterm birth and preeclampsia increased over the time.

Conclusions: There is a high prevalence of both maternal and foetal adverse outcomes in pregnant patients with Takayasu's arteritis, who require careful management by a multidisciplinary team during pregnancy.

Disclosures: none

Figure 1: Prevalence of preeclampsia in Takayasu's arteritis patients



67. Fertility, Early Menopause, and Pregnancy outcomes of patients with Takayasu's arteritis

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Background: Reproductive health of Takayasu's arteritis (TA) is an important issue since it is commonly seen at childbearing ages. Systemic inflammation and used treatments in TA, may affect male and female reproductive organs leading to infertility, maternal and fetal morbidity and also early menopause. A novel proposed disease clusters for TA (C1: Abdominal Predominant, C2: Aortic Arch Predominant, C3: Focal Disease) was recently published. Pregnancy complications might differ among these subtypes. **Objectives:** We aimed to evaluate the fertility, early menopause and pregnancy (PG) outcomes of TA patients before TA diagnosis and after TA diagnosis. Additionally, pregnancy morbidities after TA diagnosis, were detail analysed for each TA cluster.

Methods: In the prospective database of the Hacettepe University Vasculitis Research Centre (HUVAC), 202 TA patients (female =184) meeting the 1990 ACR criteria were registered by the end of February 2020. Demographic and clinical features, comorbidities, distribution of vascular involvement, obstetrical histories and outcomes were retrospectively evaluated. TA patients were classified according to a novel proposed disease clusters (C1: Abdominal Predominant, C2: Aortic Arch Predominant, C3: Focal Disease). Infertility was defined as not

being able to get pregnant after one year (or longer) of unprotected sex. Menopause before the age of 45 was defined as early menopause (EM).

Results: 120 patients who could be reached out gynaecological records and marriage status, were included into the study. Of 96 married TA patients, 12(12.5%) had infertility. We identified 235 pregnancies in 82 female TA patients (beforeTA diagnosis: 200 pregnancies, after TA diagnosis: 35- two patients were diagnosed during pregnancy. Compared to before TA diagnosis, maternal complications were significantly more common in after TA group [22 (11.0%) vs. 9 (25.7%), p=0.048]. Most frequent maternal complication was gestational hypertension and was seen in 4 (12.1%) patients (Table 1). Fetal complications were frequent in both before and after TA diagnosis [21.5%vs.34.2%, p=0.18 respectively] and seen as prematurity, IUGR and LBW. According to novel disease subsets, afterTA patients classified into C1 (n=3; 15.7%), C2 (n=9; 47.3%) and C3 (n=6; 31.5%). One patient could not be classified. There was no difference for the obstetrical outcomes among these subgroups. 20 (16.7%) of 120 patients had early menopause.

Conclusion: Compared to general population in Turkey, infertility (12.5% vs. 8.1%) and early menopause ratios (16.7% vs. 7.6%) seem to be increased in TA patients. (1,2). Pregnancies after TA diagnosis had more maternal complications. Fetal complications were more frequent not only after TA but also before TA diagnosis. Chronic inflammation even before TA diagnosis might have impact on increased infertility and fetal complications.

Table 1.

	Pregnancies Before TA (n=200)	Pregnancies After TA (n=35)	
Number of Patients	71	19	Not performed
Age at first pregnancy	21.7 (5.0)	27.6 (5.0)	
Age at TA diagnosis, years mean (SD)	38.2 (13.1)	24.0 (6.6)	
Disease duration, year mean (SD) (TA diagnosis-1. Pregnancy)	NA	4.2 (3.6)	
Comorbidities/CV Risk factors n(%)	n (%)		p
- Smoking - Dyslipidaemia - Hypertension - Diabetes mellitus	22 (31) 14 (19.7) 29 (40.8) 8 (11.3)	3 (15.8) 1 (5.3) 9 (47.4) 0 (0)	>0.05
Maternal Complications	n (%)		
Numbers of pregnancies with any maternal complications	22 (11.0)	9 (25.7)	0.048
- Gestational hypertension - PROM - GDM - Bleeding (Antepartum/postpartum) - Preeclampsia - Infection - Placenta previa - Placental abruption	6 (3.0) 6 (3.0) 0 (0) 6 (3.0) 0 (0.0) 5 (2.5) 0 (0) 0 (0)	4 (12,1) 1 (3.0) 1 (2.9) 2 (6.1) 0 (0.0) 1 (3.0) 1 (3.0) 0 (0)	Not performed
Fetal Complications	n (%)		p
Numbers of pregnancies with any fetal complications	43 (21.5)	12 (34.2)	0.180

- LBW - IUGR - Preterm birth - CNS complications - Cardiovascular complications - RDS_BPD - NICU admission - Other - Neonatal death - Retinopathy of prematurity - Necrotizing enterocolitis - Stillbirth	16 (8.0) 20 (1.0) 13 (6.5) 2 (1.0) 3 (1.5) 4 (2.0) 12 (6.0) 5 (2.5) 5 (2.5) 1 (0.5) 0 (0) 7 (3.5)	6 (18.2) 6 (17.1) 7 (21.2) 1 (3.0) 0 (0) 0 (0) 1 (3.0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0)	Not performed
Delivery	n (%)		P
Vaginal delivery	128 (64)	6 (18.2)	<0.001
Cesarean delivery	24 (12)	15 (42.9)	<0.001
Spontaneous abortus	21 (10.5)	7 (21.2)	0.088
Termination of pregnancy	18 (9.0)	7 (21.2)	0.061
Abbreviations: BPD: Bronchopulmonary dysplasia, CNS: Central nervous system, GDM: Gestational diabetes mellitus, IU: Intrauterine. IUGR: Intrauterine growth restriction, LBW: Low birth weight, NICU: Neonatal Intensive Care Unit, PROM: Premature rupture of membranes, RDS: Respiratory distress syndrome			

68. A meta-analysis of pregnancy outcomes in Behcet's Disease

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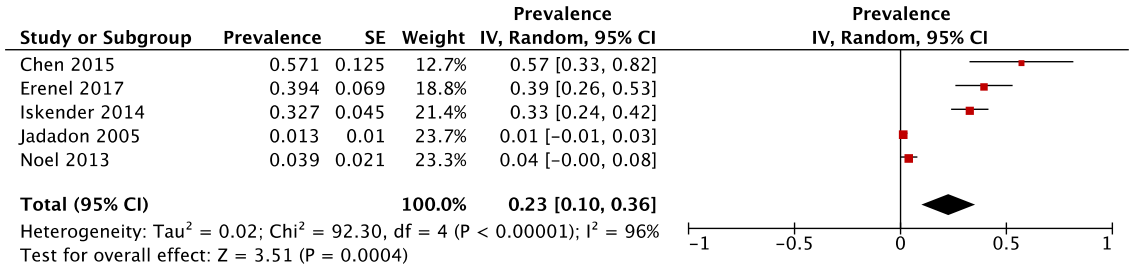
Background: Behcet's disease, a systemic inflammatory disease, commonly presents with episodes of acute inflammation, oral and genital ulcers, skin lesions and uveitis. It presents most commonly during the second and third decades of life, therefore frequently involves women during their reproductive years. The objective of our work was to determine the effect of Behcet's disease on pregnancy by evaluating the prevalence of fetal and maternal complications through systematic review and meta-analysis.
Methods: We performed a systematic review of the literature using Medline, Web of Science, and the Cochrane library from their inceptions until March 26, 2021. Studies were included if they presented the frequency of complications in cohorts of pregnant patients with a diagnosis of Behcet's disease. Studies were selected by two independent reviewers and statistics were performed using REVMAN5.4.

Results: We identified 6638 studies and 16 were included in the meta-analysis. Among patients' with Behcet's disease during pregnancy the pooled prevalence of caesarean section was 23% (CI 10-36% , Figure 1), miscarriage 11% (CI 8-14%), pre-term birth 11% (CI 8-15%, Figure 2), intrauterine growth restriction 6% (CI 3-9%), intrauterine death 4% (CI 2-7%), new hypertension 6% (2-10%), pre-eclampsia 4% (CI 3-6%) and 27% of women reported worsening of symptorelated to Behcet's disease during pregnancy (CI 20-34 , Figure 3).

Conclusion: One in ten had a pre-term delivery, one in four delivered their baby caesarean section and approximately one quarter of patients' experienced worsening of symptorelated to Behcet's disease during pregnancy. These results show the importance of close monitoring of patients with Behcet's disease during pregnancy – both for pregnancy complications and for worsening Behcet's symptoms.

Disclosures: None

Figure 1. Forest plot analysis of cesarian sections in patients with Behcet's disease



Genetics, Epigenetics, Microbiome

69. Interrelation Between Immune-Related microRNA Signature and Inflammatory Histopathological Features of Giant Cell Arteritis

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Background: Inflammation-driven thickening of arterial wall is a typical feature of giant cell arteritis (GCA). Nevertheless, there is still a scarcity of in-depth information on the distinct cellular composition of inflammatory infiltrates in temporal artery biopsies (TABs) from GCA patients, including their immune-related microRNA (miRNA) signatures, which may significantly differ between patients and lead to different clinical outcomes. The aim of this study was to evaluate the association between the expression signature of selected immune-related miRNAs with quantitatively assessed immune cell subsets comprising inflammatory infiltrate in TABs from patients with GCA, and thus highlight the role of altered miRNA expression in impaired regulation of arterial inflammation in GCA.

Methods: The study included 46 formalin-fixed, paraffin-embedded TABs from clinically diagnosed treatment-naïve patients fulfilling the American College of Rheumatology 1990

classification criteria, including 30 histologically positive and 16 negative GCA TABs. Non-GCA controls included 22 histologically negative TABs from age-matched patients with refuted clinical suspicion of GCA. Quantitative assessment of histological parameters was performed using histopathological and immunohistochemical techniques, and miRNA expression analysis by quantitative real-time PCR. Computational analyses were performed by employing the miRDB database and the STRING online prediction tool.

Results: Our quantitative histopathological assessment revealed that intense transmural mononuclear inflammatory infiltrates in TAB-positive GCA arteries predominantly comprised $CD3^+$, $CD4^+$ and $CD8^+$ T lymphocytes, $CD68^+$ macrophages, and variable numbers of $CD20^+$ B lymphocytes, multinucleated giant cells and eosinophil granulocytes. Overall, the lymphocyte infiltrate fraction was characterized by a strong nuclear overexpression of the nuclear factor of activated T cells, cytoplasmic 1 (NFATC). Moreover, we determined a significant overexpression of pro-inflammatory miRNAs miR-132-3p/-142-3p/-142-5p/-155-5p/-210-3p/-212-3p/-326/-342-5p/-511-5p and a significant under-expression of regulatory immune-related miRNAs miR-30a-5p/-30b-5p/-30c-5p/-30d-5p/-30e-5p/-124-3p in TAB-positive GCA arteries, whose expression levels significantly associated with most evaluated histopathological parameters. Notably, we revealed miR-132-3p/-142-3p/-142-5p/-155-5p/-212-3p/-511-5p as major promoters of arterial inflammation and miR-30a-5p/-30c-5p/-30d-5p as putative regulators of NFATC signaling in TAB-positive GCA arteries.

Conclusions: Our study demonstrated that an altered pro-inflammatory miRNA signature favors enhanced T cell-driven inflammation and macrophage activity in TAB-positive GCA arteries. Furthermore, dysregulation of several immune-related miRNAs seeto contribute crucially to GCA pathogenesis, through impairing their regulatory activity towards T cell-mediated immune responses driven by the calcineurin (CaN)/NFAT signaling pathway, indicating their therapeutic, diagnostic and prognostic potential.

Disclosures: None.

70. HLA region is associated with a higher genetic risk in male patients with Behçet's Disease

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Background: Behçet's disease is an inflammatory disease characterized by recurrent oro-genital ulcers and multisystemic organ involvement. The disease tends to be more severe in men than women. However, the reasons for this gender effect is unknown. This study was undertaken to investigate sex-specific genetic effects in Behçet's disease.

Methods: A total 1368 male patients and 970 female patients with Behçet's disease from Turkey were included in this study. Genotyping was performed using an Infinium ImmunoArray-24 v.1.0 or v.2.0 BeadChip, or extracted from available genotyping data. Following imputation and extensive quality control measures, genetic association was performed comparing male to female patients. In addition, a weighted genetic risk score using previously identified genetic susceptibility loci for Behçet's disease was calculated and compared between men and women with the disease.

Results: Genetic association analysis comparing male to female patients with Behçet's disease revealed an association with male sex in *MICA* within the HLA region with a GWAS level of significance (rs2848712, OR= 1.45, P= $1.10x10^{-8}$). Genetic risk score analysis showed significantly higher genetic risk for Behçet's disease in male compared to female patients. This difference in genetic risk was largely attributed to higher genetic risk within the HLA region in male compared to female patients, including in *HLA-B*/*MICA* (rs116799036, P= $2.61x10^{-8}$) and in *HLA-C* (rs12525170, P= $8.69x10^{-7}$).

Conclusions: Men with Behçet's disease are characterized by higher genetic risk compared to female patients. This genetic difference is largely explained by risk within the HLA region. These data suggest that genetic factors might contribute to differences in disease presentation between men and women with Behçet's disease.

Disclosures: Pre-print https://www.medrxiv.org/content/10.1101/2021.12.08.21266919v1

71. A high-throughput amplicon screen for somatic UBA1 variants in Cytopenic and Giant Cell Arteritis cohorts

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Background: Somatic mutations in the gene encoding the major E1 ubiquitin ligase, *UBA1* (X-linked), were recently identified as a cause of VEXAS, a late-onset acquired auto-inflammatory syndrome. Patients with VEXAS are typically male, aged over 60 years with a severe systemic inflammatory disorder, cytopenia and dysplastic features in their bone marrow. Differential diagnoses for patients subsequently found to have VEXAS include relapsing polychondritis, Sweets syndrome, myelodysplastic syndrome (MDS), giant cell arteritis (GCA) and undifferentiated systemic autoinflammatory syndrome (uSAID). We therefore sought to screen DNA from individuals with a non-diagnostic cytopenia or GCA, for known VEXAS-associated mutations.

Methods: We developed a multiplexed UBA1 amplicon sequencing assay, allowing quick screening of large cohorts while also providing sufficient sequencing depth to identify somatic mutations to an allele frequency <1%. Using this assay, we screened genomic DNA from 612 males diagnosed with GCA (patients recruited into UKGCA consortium), and bone marrow derived DNA from 1,055 cases with an undiagnosed cytopenia.

Results: 1,667 DNA samples were screened for variants in *UBA1* exon 3 by amplicon sequencing. In total, 1,650 (98.9%) of samples had a read depth >100 and all 1,667 (100%) had a read depth >30. Seven individuals were identified with a UBA1 mutation (Table 1), all present in the cytopenic cohort (n=7/1,055, 0.66%). No variants were identified in the GCA cohort. All variants identified have been published as a cause of VEXAS and either lead to substitution of Met41 or affect the canonical splice acceptor site. On average, the variant allele frequency (VAF) of the mutation was 44.1% (range:29.5%-59.3%). All variants were confirmed by Sanger sequencing. Six of the patients were identified from the 595 male cytopenic cases (1.00%). Interestingly, 1 patient was from the 460 cytopenic female cases. (0.02%). A whole genome SNP array on bone marrow extracted genomic DNA of the female case (P2) revealed a normal X chromosome dosage, with no indication of loss of heterozygosity over *UBA1*. The VAF of P2 was 33%, within the range observed in the male cases (range: 19%-52%).

Conclusions: Our study suggests that, despite the overlap in clinical features, VEXAS is rarely misdiagnosed as GCA but identified 1.0% of males with an undiagnosed cytopenia have VEXAS. The identification of a *UBA1* variant in a female case adds further evidence that VEXAS should not be ruled out as a differential diagnosis in females with VEXAS-like symptoms.

Disclosures: None

Table 1.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Demographics							
Deceased	Yes	Yes	Yes	Yes	Yes	Yes	No
Gender	M	F	M	M	M	M	M
Current age or age of death	76	86	77	63	86	76	75
Age at referral for hematological investigations	73	77	77	55	85	75	67
Investigations							
Peripheral blood findings Hemoglobin (Hb) g/L, White blood cells (WBC) 10x9/L, Neutrophils (Neu) 10x9/L, Platelets (Plt) 10x9/L	Hb 82, WBC 2.1 neut 0.3, plt 90	Hb 95, WBC 3.8, plt 98	Hb 104, WBC 2.63, Neut 0,76, plt 176	N/A	N/A	Hb 81, WBC 3.8, neut 1.96, plt 211	HB 103, WBC 5.88, Neu 2.76, Plt 90
Karyotype	Loss of Y in 12/20 cells	N/A	Normal	N/A	N/A	t(8;10) ? Constitutional	Normal
Mutations (myeloid panel)	No reportable mutations	No reportable mutations	*ASXL1* c.1771_1772insA p.Tyr591Ter (VAF 7%)	No reportable mutations	p.Lys721ArgfsTer58 (Vaf 55%)	No reportable mutations	No reportable mutations
UBA1 mutation	c.121A>G, p.Met41Val (VAF 51%)	c.122T>C, p.Met41Thr (VAF 29.5%)	c.121A>G, p.Met41Val (VAF 39.0%)	c.121A>G, p.Met41Leu (VAF 59.3%)	c.122T>C, p.Met41Thr (VAF 45.1%)	c.118-1G>C, p.splice (VAF 35.2%)	c.122T>C, p.Met41Thr (VAF 49.5%)
Bone marrow features							
Cellularity	Increased	Increased	Reduced	No trephine	Increased	Increased	Increased
Erythropoiesis	Expanded with minimal dysplasia (<10%). occasional vacuoles in erythroblasts.	Minimal dysplasia (<10%)	Minimal dysplasia (<10%)	N/A*	Minimal dysplasia (<10%) occasional vaculoated eryrthroblasts	minimal dysplasia (<10%)	Reduced
Granulopoiesis	Expanded, with minimal dysplasia (<10%). Vacuoles in promyelocytes.	Minimal dysplasia (<10%). Vacuoles in promyelocytes	Minimal dysplasia (<10%). Vacuoles in promyelocytes	N/A*	Expanded, minimal dysplasia (<10%). Vacuoles in promyelocytes	Expanded, minimal dysplasia (<10%). Vacuoles in promyelocytes	Expanded, minimal dysplasia (<10%).
Megakaryocytes	Normal number with occasional atypical forms	Normal number with occasional atypical forms	Normal size and morphology	N/A*	Increased with normal morphology	Normal size and morphology	Increased with normal morphology
Bone marrow vacuoles	Yes	Yes	Occ	N/A*	Yes	Yes	Yes
Bone marrow diagnosis	Reactive	Reactive	Non-diagnostic	Non-diagnostic*	Reactive	No evidence of disease	Non-diagnostic
Inflammatory history							
Inflammatory features/rheumatological dignosis	Pulmonary infiltrates, unprovoked DVT, periorbital oedema	Fever, WT loss, pulmonary infiltrates, DVT, C-ANCA positive (MPO and PRE negative) vasculitis	unexplained fevers, weight loss, arthritis	Pyoderma gangrenosum-like skin leasion, fevers, uSAID	Not known	Skin rash, fevers non-specific vasculitis	Fevers, Relapsing polychondritis
Steroid responsive	Yes	Yes	Not treated	Yes		Yes	Yes
*Bone marrow sample inadequate for morpholicical assessemnet/diagnosis							
M-male; F-female; VAF-variant allele frequency; N/A-not available							

72. Abstract withdrawn

73. Genetic explanation for increased risk of relapse in patients with PR3-ANCA

Dhruti Chen[1], Claudia Aiello[1], Demoris McCoy[1], Taylor Stamey[1], Candace Henderson[1], Jiajin Yang[1], Susan Hogan[1], Yichun Hu[1], Caroline Poulton[1], Lauren Blazek[1], Vimal Derebail[1], Eveline Wu[1], Charles Jennette[1], Ronald Falk[1], Dominic Ciavatta[1]

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Background: The role of autoantigen levels in ANCA Vasculitis and clinical consequences are not yet fully understood. Genome-wide association studies found associations between single nucleotide polymorphisupstream of the *PRTN3* gene, encoding proteinase 3 (PR3), and GPA/PR3-ANCA serotype[1-3 4, 5] . The risk variant rs62132293 (G-allele) was identified as an expression quantitative trait locus for *PR3* expression in healthy controls.[5] We sought to elucidate the clinical impact of rs62132293 in patients with ANCA Vasculitis. We postulated that the variant is associated with increased target autoantigen transcription and a more severe disease phenotype.

Methods: ANCA vasculitis patients (n=401) were followed longitudinally. Patients and healthy controls were genotyped for rs62132293 (C- or G-allele). Gene expression was quantified by RT-qPCR from total leukocyte RNA of 298 patients. Kaplan-Meier estimates and log rank test

were used to assess differences in time to relapse, and proportional hazards models were used to model the effect of genotype and ANCA serotype on relapse-free survival.

Results: We genotyped C/C in 179 (44%) and 62 (48%), C/G in 181 (45%) and 54 (41%), and G/G in 41 (10%) and 14 (11%) of patients and healthy controls, respectively. For all genotypes *PRTN3* gene expression was elevated in patients compared to healthy controls. In the patient cohort (MPO-ANCA and PR3-ANCA, n=298), variant carriers had significantly elevated *PRTN3* gene expression compared to non-carriers (effect size 0.24). *MPO* gene expression did not differ by genotype.
Risk of relapse was higher in PR3-ANCA compared to MPO-ANCA (HR 1.48, 95% CI 1.09,2.02). The frequency of relapse among PR3-ANCA patients was similar between heterozygotes (C/G, 70.4%) and homozygotes (G/G, 72.2%), suggesting variant carriage (one or two copies) was associated with relapse. We combined carriers (C/G; G/G) to analyze for serotype specific relapse risk. PR3-ANCA variant carriers had reduced relapse free survival and 1.66-fold increased risk of relapse compared to MPO-ANCA (HR 1.66, 95% CI 1.08, 2.54) while there was no difference among non-carriers (HR 1.23, 95% CI 0.77, 1.98).

Conclusion: Our study is the first to correlate the risk allele, marked by rs62132293, with increased autoantigen gene expression in patients and show an impact on clinical phenotype. We found higher *PRTN3* gene expression among variant carrying patients. We postulate increased transcription of *PRTN3* results in higher protein expression and availability of PR3 autoantigen. In the presence of corresponding ANCAs there is more severe disease. In a longitudinal cohort of 401 ANCA patients, we found a 1.66-fold increased risk of relapse among PR3-ANCA patients carrying the variant compared to the MPO-ANCA patients. Together this highlights the impact of rs62132293 on PR3 autoantigen levels and disease relapse. While this variant may not fully explain severity of PR3-ANCA, it highlights the genetic contribution to autoantigen expression and clinical disease.

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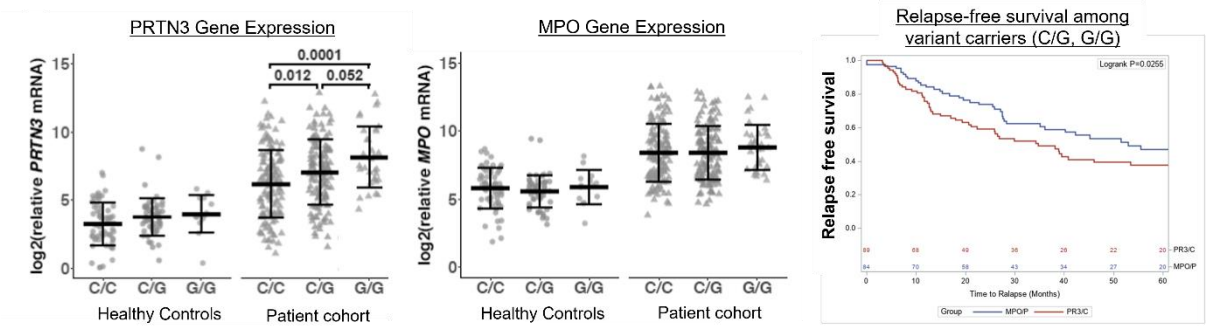
Figure 1:



74. Cross-Phenotype Analysis of Genome-Wide Data Reveals New Risk Loci Shared Across Systemic Vasculitides

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Background: Systemic vasculitides comprise a heterogenous group of complex diseases characterized by blood vessel inflammation. Their aetiologies are poorly understood but it is well established that genetic factors play a crucial role. We aimed to investigate the shared genetic component across systemic vasculitides by combining genomic data from clinically distinct conditions as a single phenotype.

Methods: We performed a meta-analysis of genomic data across the major phenotypes of systemic vasculitides (giant cell arteritis, Takayasu arteritis (TA), Kawasaki disease (KD), IgA vasculitis, ANCA associated vasculitis including ANCA-negative eosinophilic granulomatosis with polyangiitis) including more than 5,000 cases and 30,000 controls. We used the R package ASSET to identify the subset of phenotypes best contributing to the association. In addition, potential functional roles of the associated variants were queried using publicly available databases.

Results: Our analysis revealed independent 8 genome-wide significant loci shared by at least two of the conditions analyzed that were newly associated with at least one of the phenotypes. Among them, we identified known important loci in autoimmune disorders such as *CTLA4*, *PTK2B and IL12B.* While most signals showed the same direction effect for all associated phenotypes, two loci presented opposite effects. For example, the minor allele of rs6898844-*IRF1-AS1*, previously reported to confer risk to EGPA, had a protective effect in KD and TA in our study. *In silico* functional annotation suggested that some of these pleiotropic variants could play a regulatory effect. As an example, rs128738-*P4HA2* has been described to alter the expression level of several genes, such as *P4HA2*, *SLC22A5* or *ACSL6*.

Conclusions: Our results identified new loci with pleiotropic effects in systemic vasculitides, shedding light into our knowledge of the genetic component underlying these disorders.

Disclosures: None.

75. Methylation and Transcriptome Signatures of Monocytes Reveal Novel Pathways Involved in Giant Cell Arteritis Pathogenesis

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Background: Giant cell arteritis (GCA) is an immune-mediated large-vessel vasculitis with a complex etiology mediated by the interplay between both genetic and epigenetic factors. Several immune cells have been linked to its pathophysiology, including CD14+ monocytes that are crucial in the systemic and local inflammatory processes. Considering that the integration of -omics data has proven to be effective in yielding insight into our understanding of the molecular bases of complex diseases, we aimed to perform an integrative analysis of DNA methylation and gene expression profiling of CD14+ monocytes in GCA.

Methods: CD14+ monocytes were positively sorted by flow cytometry from whole blood of 31 healthy controls and 82 GCA patients within three different clinical status (active, in remission with glucocorticoid (GC) treatment, and in remission without treatment). Subsequently, DNA methylation profiling with the Illumina Infinium Methylation EPIC array and RNA-sequencing were carried out for an epigenome- and transcriptome-wide association study, respectively. MatrixEQTL R package was used to determine the correlation among DNA methylation changes and gene expression alterations.

Results: The results revealed a profound dysregulation in both the methylome and gene expression landscape of CD14+ monocytes of GCA patients. In particular, monocytes from patients with active disease showed a more pro-inflammatory phenotype compared to controls and patients in remission. As examples, response to interleukin-6 (IL-6) and IL-1 as well as IL-11, that emerged as a new cytokine pathway implicated in GCA, were dysregulated in monocytes from active patients. Furthermore, monocytes from patients in remission with treatment presented an anti-inflammatory phenotype when comparing with controls and patients in remission without treatment, with overexpression of glucocorticoid receptor-target genes and downregulation of genes involved in crucial pathways of the inflammatory process. Finally, the integrative analysis allowed identifying new genes with a potential role in GCA pathogenesis, such as *ITGA7* and *CD63*, as well as genes mediating the molecular response to GC in GCA, including *FKBP5*, *ETS2*, *ZBTB16*, and *ADAMTS2*.

Conclusions: Overall, the first analysis of the methylation and transcriptomic profiles of monocytes from GCA patients has provided evidence of genes and pathways that contribute to the pathogenic role of this cell type in GCA as well as to the molecular response to GC treatment.

Disclosures: The authors declare no conflicts of interest. This work has been performed as part of the HELICAL Innovative Training Network, a European Commission funded project under the Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 813545.

76. Gene expression profile of temporal artery tissue and whole blood in giant cell arteritis

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Background: Giant cell arteritis (GCA) is a systemic vasculitis affecting adults over age 50. Diagnosing GCA is notoriously challenging, as there are no reliable blood biomarkers and temporal artery biopsy (TAB) has a sensitivity of only approximately 80%. Thus, patients suffer both from missed diagnoses and over-treatment. This study seeks to identify differentially expressed transcripts in the blood and TAB of patients with GCA relative to controls, as determined by RNA-sequencing (RNA-Seq).

Methods: Blood (PAXgene tubes) and formalin-fixed paraffin-embedded (FFPE) TAB tissue from patients undergoing TAB for suspected GCA were evaluated by RNA-Seq. Samples

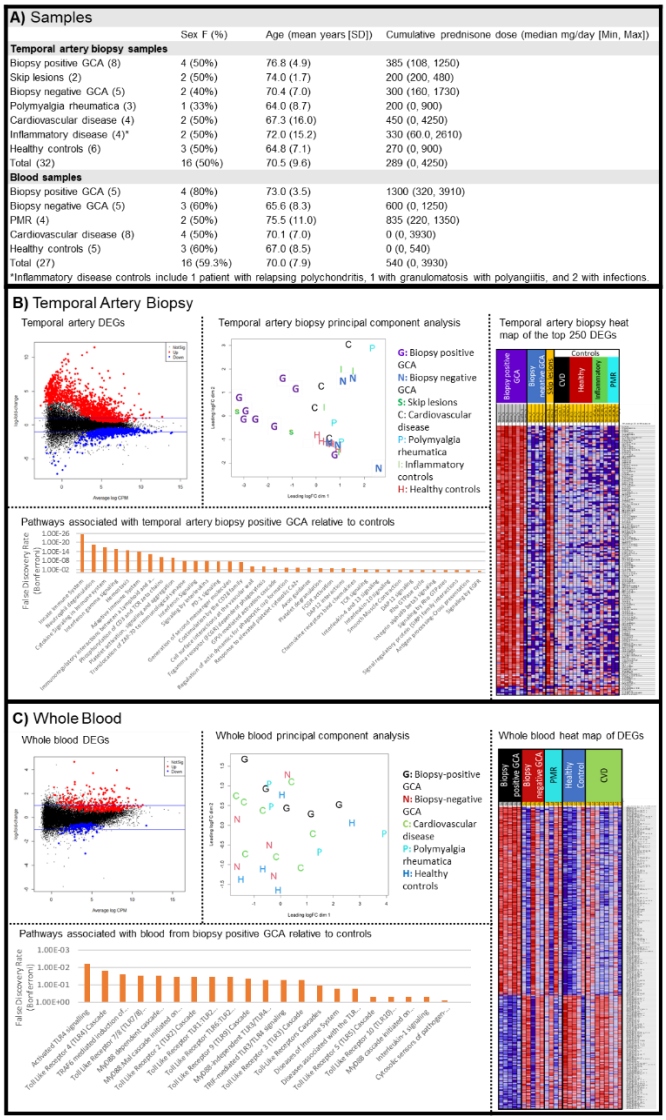
representative of biopsy positive GCA, biopsy negative GCA (negative biopsy but clinically diagnosed with GCA), polymyalgia rheumatica (PMR), non-vasculitic ischemia, other inflammatory diseases, and healthy controls (patients who underwent temporal artery biopsy but were not diagnosed with any disease) were included. Significantly differential expressed genes (DEGs) were considered as having a fold change (FC) > 1.5 and a false discovery rate (FDR) <0.05. Pathway analysis of significantly DEGs was performed using Reactome. Age, sex, and cumulative corticosteroid exposure pre-sample collection were included as covariates in the models.

Results: 32 TAB and 27 whole blood samples were included in the analysis, including 8 biopsy positive GCA TABs and 5 biopsy positive GCA whole blood samples. (Fig. 1A) The majority of patients had glucocorticoid exposure pre-sample collection, and all samples were above age 50. TAB expression (Fig. 1B) of biopsy positive GCA TABs revealed 1493 up- and 681 down-regulated transcripts relative to control groups (healthy controls, non-vasculitic ischemic cardiovascular disease, PMR, and inflammatory controls). Skip lesions samples (n=2) overlapped substantially with biopsy positive GCA, despite being histologically unaffected. Biopsy negative GCA TAB gene expression did not show any DEGs relative to controls. Pathways significantly associated with biopsy positive GCA expression included innate immune pathways, interferon gamma and other cytokine signalling, PD-1, and integrin alphaIIb beta3 signalling, among others.Whole blood expression (Fig. 1C) showed 351 up- and 168 down-regulated transcripts relative to controls (healthy controls, cardiovascular disease, and PMR.) Biopsy positive GCA samples clustered together, however there was overlap with control groups. Biopsy negative GCA did not show any significant DEGs relative to healthy controls. Pathways associated with biopsy positive GCA DEGs included toll like receptor and MyD88 pathways, among others.

Conclusions: The TAB gene expression signature distinguishes biopsy positive GCA from controls, while biopsy negative GCA tissue is not significantly different from controls. A preliminary analysis of skip lesions shows substantial overlap with biopsy positive GCA, which is surprising and suggests that skipped areas may represent early lesions, however this requires further evaluation. The lack of similarly between skip lesions and biopsy negative GCA calls into question the hypothesis that biopsy negative GCA is caused by skip lesions. Whole blood biopsy positive GCA gene expression shows fewer DEGs and an expression signature that overlaps with control groups. Whole blood expression in biopsy negative GCA is not substantially different from controls. Strengths include common GCA mimics as control groups (nonvasculitic ischemia and PMR) and the evaluation of both biopsy positive and biopsy negative GCA. Limitations include a small samples size and the difficulty in accurately diagnosing biopsy negative GCA.

Disclosures: The authors believe that they have no relevant conflicts.

Figure 1. Temporal artery biopsy and whole blood gene expression



77. Monogenic Mimics of Behçet's Disease

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Background: Behçet's Disease (BD) is a rare autoinflammatory vasculitis with a broad spectrum of symptoms, including oral and genital ulcers, uveitis, skin rashes, arthralgia, and internal organ inflammation. BD is polygenic, and multiple risk alleles across numerous genes have been associated with the disease, the strongest association of which is with HLA-B*51. There is, therefore, no single genetic hallmark of BD, making diagnosis challenging.

It has recently been discovered that many rare monogenic diseases can present with symptothat are indistinguishable from BD[1]. It is vital that BD is differentiated from these so-called 'monogenic mimics', as the treatments and prognoses can differ.
The aim of this study was to undertake whole exome sequencing in an unselected cohort of patients from the UK with clinically diagnosed BD to investigate the possibility of a monogenetic pathogenesis.

Methods: Patients were recruited from five hospitals in London, Birmingham, and Oxford. The only inclusion criterium was a clinically suspected diagnosis of BD. Patients' DNA was whole exome sequenced, and analysis performed using three approaches: [A] Rare variants in the ~400 genes of our in-house vasculitis and inflammation panel were manually assessed.
[B] Potential disease-causing variants were prioritised based on connection to phenotype using Exomiser[2]. [C] HLA genotype was obtained using OptiType[3].

Results: A total of 33 patients were recruited, 13 female, median age 13 yrs, range 3-51 yrs. The genetic analysis for this cohort remains in progress, however of the 18 cases analysed thus far, we have identified nine probable monogenic cases:
Four cases of Haploinsufficiency of A20 with five novel *TNFAIP3* mutations (p. p.G316S, p.S548Dfs, p.M112Tfs, p.C657fs, p.E661Nfs)
One case of ISG15 deficiency with a novel homozygous *ISG15* mutation (p.Q16X)
One case of TRAF3 deficiency caused by a dominant *TRAF3* mutation (p.R118W)
Two cases associated with a novel heterozygous *MEFV* mutation (p.T707I)
One case of Tumour necrosis factor receptor associated periodic syndrome (TRAPS) with a pathogenic low penetrance *TNFRSF1A* mutation (p.R121Q)
Of the remaining patients for whom a monogenic cause could not be identified, we classified four as having classical BD, three of which were HLA-B*51 positive, and one patient with Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA). The remaining patients remain under analysis, unsolved or classified as having a functional disorder. The functional consequences of the novel mutations discovered in this study are under investigation.

Conclusions: This work has expanded the genotypic spectrum of autoinflammatory diseases that can mimic BD. The genetic diagnoses made in this study have enabled clinicians to make informed decisions regarding individuals' treatments and prognoses, highlighting the importance of next generation genetic sequencing in patients with suspected BD. The analysis workflow designed for this study offers a template for which genetic characterisation of BD-like disease could be implemented more routinely, both for identification of monogenic diseases, and for HLA-typing.

Disclosures: None.

78. Clonal Hematopoiesis Across the Age Spectrum in Patients with Systemic Vasculitis

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Background: Clonal hematopoiesis (CH) is characterized by somatic mutations in hematologic precursor cells leading to a survival advantage of a single clone. Incidence of CH increases with age in healthy people, but is also associated with increased risk for all-cause mortality and cardiovascular disease and influence myeloid IL-1b and IL-6 production. Small studies report increased prevalence of CH in various inflammatory diseases. To what extent age versus inflammation underlies these associations is unclear. In this study, vasculitis patients with giant cell arteritis (GCA), ANCA-associated vasculitis (AAV), or Takayasu's arteritis (TAK) were screened for CH to determine the relationship between CH and vasculitis in a cohort of patients with vasculitis representing a wide age spectrum.

Methods: Error-correcting targeted sequencing was used to screen participants for peripheral blood somatic variants in 40 genes related to CH. Patients with vasculitis (GCA, AAV, TAK) were studied in 2:1 age-matched design compared to healthy controls (HC). Variants were called if the variant allele fraction (VAF) > 0.5% and if the variants were predicted to impair protein function. Logistic regression was used to assess associations of age and vasculitis with CH. Relative contribution of predictor variables was assessed using standardized beta coefficients. Clinical features were compared using Fisher's exact test, Wilcoxon rank sum test, or logistic regression as appropriate. Correlation between clone size and clinical features was assessed by linear regression.

Results: The prevalence of CH was 53.8% (28/52) in GCA, 34.8% (16/46) in AAV, 13.0% (9/69) in TAK, and 14.5% (12/83) in HC. Median age for GCA, AAV, TAK, and HC was 72 (range: 50-88), 60 (range: 19-77), 33 (range: 3-71), and 51 (range: 3-88) years, respectively. Using logistic regression modeling, age and vasculitis were independently associated with CH (Age: B=0.05, standardized b=0.96, p<0.0001; Vasculitis: B=0.53, standardized b=0.46, p=0.004). Of the 109 somatic mutations identified, the most common affected genes were *DNMT3A* (n=69, 63%) and *TET2* (n=19, 17%). Vasculitis patients with CHIP had lower percent lymphocytes (17.7% vs 25.4%, p=0.03) and higher absolute neutrophil counts (6.0 vs 5.1 K/uL, p=0.04) in peripheral blood than those without CH. Adjusting for daily prednisone dose, the neutrophil-to-lymphocyte ratio was significantly associated with presence of CH (B=0.07, p=0.02). Among patients with mutations, clone size was positively associated with age (B=0.01, p=0.002) and monocyte count (B=0.83, p=0.01).

Conclusion: Patients with vasculitis can harbor somatic mutations in bone marrow that are reflected in peripheral blood. There is a complex relationship between age, inflammation and CH. Age is 2.1x more strongly associated with CH than vasculitis, but each are independent contributors. CH is associated with skewing of peripheral blood counts towards myeloid lineages in patients with vasculitis. Mechanison how CH directly contributes to vasculitic

pathogenesis and the effect of systemic inflammation on mutagenesis and clonal selection are areas of active investigation.

Disclosures: None

79. Deep intronic mutation in patients with adenosine deaminase 2 deficiency

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Background: Deficiency of adenosine deaminase 2 (DADA2) is an autosomal recessive inflammatory disease caused by loss-of-function mutations in the ADA2 gene. Most patients with DADA2 exhibit systemic vasculopathy consistent with polyarteritis nodosa, but large phenotypic variability has been reported. Patients with DADA2 are deficient of ADA2 activity in plasma. We sometimes, however, experience cases in which no apparent mutations are found in the ADA2 gene, even in these definitive diagnosed cases. In this report, we present two siblings who have a deep intronic mutation which thought to result in aberrant splicing and nonsense mediated mRNA decay (NMD).

Methods: Now 24 and 21 years old siblings with DADA2 were enrolled. The older brother had repeated episodes of cerebral infarction and hemorrhage from the age of 10. He was diagnosed with DADA2 at 21 years of age due to deficiency of ADA2 activity in plasma. The younger brother revealed persistent elevation of CRP and an episode of cerebral ischemia at the age of 18, then he was diagnosed with DADA2 as same as his older brother.

Results: An analysis of whole exon sequencing in these siblings and their parents revealed E328K mutation in ADA2 gene, pathogenic mutation reported in past, in the allele derived from the mother. But no mutation other than SNPs were found in the allele derived from the father. Large deletion nor insertion was also not suggested. Then we analysed mRNA expression of ADA2 gene by deep sequencing and revealed aberrant splicing. As a result of whole genome analysis, an unreported mutation was found in the deep intron. The analysis in silico had suggested aberrant splicing due to this deep intronic mutation. mRNA analysis, using RNA extracted from the peripheral blood mononuclear cells, revealed a clear extra band in the sibling's cells, but not in normal controls. NMD inhibition by cycloheximide made the extra band clearer. In a minigene system, the antisense oligo, that suppress aberrant splicing by this deep intronic mutation, reduced extra band and increased normal band. These results suggest that the deep intronic mutation would induce aberrant splicing, the abnormal mRNA be degraded by NMD, and ADA2 expression be decreased.

Conclusions: This is the first report of DADA2 patient with a deep intronic mutation in the ADA2 gene. Large deletion/insertion/duplication etc. have been analysed for patients with

DADA2 with unknown mutations, but whole-genome analysis including deep intron region would be considered necessary in future.

Disclosures: We have no COI about our presentation.

80. Clinical characteristics of patients with ANCA-associated vasculitis with and without alpha-1 antitrypsin deficiency alleles

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Background: There are multiple reasons to suspect that alpha-1 antitrypsin (A1AT) genotype impacts disease characteristics in ANCA-associated vasculitis (AAV). A1AT serves as the predominant endogenous inhibitor of proteinase 3 (PR3), a major target antigen of ANCA, and interferes with ANCA-induced activation of both monocytes and neutrophils. Additionally, two separate, large genome wide association studies found that mutations in SERPINA1, the gene encoding A1AT, are associated with increased risk of developing AAV. This report describes the clinical characteristics of a large cohort of patients with AAV with and without A1AT deficiency.

Methods: DNA was obtained from patients with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) and linked to clinical data utilizing standardized for Demographics and clinical characteristics are described and compared between patients with and without A1AT deficiency alleles.

Results: Genotype data from a total of 2145 unique patients with GPA and MPA were identified and analyzed. While 1805 (84.2%) of these patients had normal A1AT genotype (MM), 340 patients (15.9%) had at least one A1AT deficiency allele (Z and/or S) – 203 (9.5%) with any S alleles, 142 (6.6%) with any Z alleles. Among these, was the most frequently identified abnormal genotype with 186 patients (8.7%), followed by MZ (127, 5.9%), SS (12, 0.6%), ZZ (10, 0.5%), and SZ (5, 0.2%). Clinical characteristics of patients with and without A1AT deficiency alleles are presented in Table 1. Mean age at AAV diagnosis was similar among patients with (48.3 ± 15.9 years) and without A1AT deficiency alleles (48.4 ± 17.8 years among those with MM, p=0.950), as was sex (51.0% female among those with deficiency alleles vs. 49.2% among MM, p=0.533). Hispanic, Latino, or Spanish origin was more common among patients with A1AT deficiency alleles (4.4% of patients with any deficiency alleles vs. 0.8% without, p=0.001). Patients with deficiency alleles were more frequently described as having a clinical phenotype of GPA (90.3% with deficiency alleles vs. 83.5% MM, p=0.003),

and were more frequently PR3-ANCA positive (74.5% with deficiency alleles vs. 63.3% MM, p<0.001). However, more patients with deficiency alleles were ANCA-negative as well (5.2% with deficiency alleles vs. 2.9% MM, p=0.029).

Conclusions: In this large cohort of patients with AAV nearly 1/6 had one or more A1AT deficiency allele. MS, a genotype that is often not associated with clinically significant decrease in A1AT levels, was the most frequently identified abnormal genotype among these patients with AAV. While the sample size was small for homozygous and compound heterozygous deficiency genotypes, the presence of A1AT deficiency alleles was associated with ethnicity, clinical phenotype, and ANCA serotype. Further investigation is needed to evaluate relationships with specific disease manifestations, including organ involvement, relapsing course, and cumulative damage.

Disclosures: Merkel: Consulting: AbbVie, AstraZeneca, Boeringher-Ingelheim, Bristol-Myers Squibb, ChemoCentryx, CSL Behring, Dynacure, EMDSerono, Forbius, Genentech/Roche, Genzyme/Sanofi, GlaxoSmithKline, InflaRx, Jannsen, Kiniksa, Kyverna, Magenta, MiroBio, Neutrolis, Novartis, Pfizer, Sparrow, Takeda, Talaris. Research Support: AbbVie, AstraZeneca, Boeringher-Ingelheim, Bristol-Myers Squibb, ChemoCentryx, Eicos, Forbius, enentech/Roche, Genzyme/Sanofi, GlaxoSmithKline, InflaRx, Sanofi, Takeda. Royalties: UpToDate. Remaining authors: None

Table 1. Clinical characteristics of patients with ANCA-associated vasculitis with and without alpha-1 antitrypsin deficiency alleles

Characteristic	Any Deficiency Allele	MM Genotype	*P* value (Chi-square)
Age at diagnosis, mean ± standard deviation N=899 (145, 754)	48.3 (15.9)	48.4 (17.8)	0.950
Female, n (% of genotype) N=2124 (335, 1789)	171 (51.0%)	880 (49.2%)	0.533
Ethnicity: Hispanic, Latino, or Spanish origin, n (% of genotype) N=851 (137, 714)	6 (4.4%)	6 (0.8%)	0.001
Clinical phenotype GPA, n (% of genotype) MPA, n (% of genotype) Indeterminate or unknown, n (% of genotype) N=1813 (289, 1524)	 261 (90.3%) 11 (3.8%) 17 (5.8%)	 1273 (83.5%) 140 (9.2%) 111 (7.3%)	 0.003 0.002 0.393
ANCA Specificity PR3-ANCA only, n (% of genotype) MPO-ANCA only, n (% of genotype) PR3- & MPO-ANCA, n (% of genotype) Atypical ANCA, n (% of genotype) ANCA-Negative, n (% of genotype) N=2077 (306, 1788)	 228 (74.5%) 56 (18.3%) 6 (2.0%) 0 (0.0%) 16 (5.2%)	 1131 (63.3%) 427 (23.9%) 28 (1.6%) 1 (0.1%) 51 (2.9%)	 <0.001 0.032 0.614 0.029

Sample size (N) values represent the total number of patients with available data on specific characteristic (any deficiency allele, MM genotype).

81. Altered Gut Microbiota Profile in Patients with Takayasu Arteritis

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Background: Takayasu arteritis (TAK) is a large non-specific vasculitis of unknown etiology that causes occlusive or dilated lesions in the aorta and its major branches, pulmonary arteries, and coronary arteries. In recent years, the prognosis and quality of life of patients with large vessel vasculitis have been improving with advances in treatment, mainly with immunosuppressive agents and biological agents. However, there are cases with exacerbation of vascular lesions even when serological inflammatory markers are quiescent. Thus the identification of biomarkers to assess the appropriate disease course of this disease is required. Notably, patients with TAK are more susceptible to inflammatory bowel disease, such as ulcerative colitis, at a higher rate than the general population. It has been also reported that dysbiosis of gut microbiota is also involved in the development and exacerbation of various diseases, such as inflammatory bowel disease and rheumatoid arthritis. Based on these backgrounds, we hypothesized that the intestinal microbiota of patients with TAK might have some influence on the pathogenesis of the disease through the patients' intestinal immunity. There have been no reports investigating about gut microbiota in large vessel vasculitis to date. The objective of this study is to investigate (1) whether the gut microbiome of patients with TAK is different from that of healthy subjects, and (2) the relationship between gut microbiome and clinical features.

Methods: We extracted gut microbiota-derived DNA from the stool of patients with TAK and controls, and then 16S rRNA sequencing were performed using MiSeq system (Illumina) targeting the V1-V2 regions. Paired-end sequences were analysed with Qiime2 to clarify the differences between the two groups and to evaluate whether the differences in gut microbiota and their composition rates are associated with the clinical characteristics and course of the patients. Moreover, PICRUSt2 was performed for predictive functional composition metagenomes in patients with TAK using MetaCyc Metabolic Pathway Database. The relationship between clinical events and bacteria abundances was examined. Clinical events include cardiovascular surgery or endovascular treatment due to aneurysm, angiostenosis, and dysfunction of the aortic valve.

Results: Untreated TAK patients had increased relative abundance of Marinifilaceae and decreased relative abundance of Bifidobacteriaceae. In addition, predictive functional

composition of metagenomic analysis by PICRUSt2 suggests that there were increased expression of enzyme pathways involved in the synthesis of hydrogen sulfide and formaldehyde. In patients with TAK including post-treatment patients, the higher the fecal abundance of a particular bacterium, such as Streptococcus, the higher the risk of having an aneurysm amenable to cardiovascular surgery or endovascular treatment.

Conclusions: Altered gut microbiota is observed in the patients with TAK, and some bacteria may be useful for identifying patients with poor prognosis.

Disclosures: None

82. Differential effects of miR-184, overexpressed in GPA, on PRTN3 and AKT2 in a granulocyte model

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Background: MicroRNAs (miRNAs) regulate a wide range of biologic and pathologic processes including inflammation mainly through translational repression. Previously, we screened nasal tissue from granulomatosis with polyangiitis (GPA) patients for 847 miRNAs and found a disease associated signature of 21 differentially expressed miRNAs compared to healthy controls and chronic rhinosinusitis. MiR-184 was most over expressed in nasal tissue from GPA (13.4fold) and it is predicted to target the proteinase-3 (PR3) gene PRTN3. First, we aimed to confirm if any of 21 GPA-associated miRNAs including miR-184 downregulates PRTN3 or its alternative transcript in vitro. The second objective was to validate miR-184 as a putative regulator of PR3 on mRNA and protein level in a granulocyte model.

Methods: The inhibitory capacity of miRNAs on PR3 mRNA was estimated by a dual-luciferase reporter system. The sequences of the alternative (132bp longer) and the regular 3'UTR-PRTN3 were cloned and inserted into the pmirGLO vector and co-transfected with 21 miRNA mimics into HeLa cells. Co-transfection with *Caenorhabditis elegans* miRNA 67 mimic (cel-miR-67) was used as negative control. Statistical significance was evaluated by students t-test adjusted for multiple comparisons (Holm-Sidak). NB4 cells were differentiated by all-transretinoic acid for 24h. Granulocyte-like differentiation was analyzed by FACS, qPCR and western blot. Endogenous miR-184 expression was examined by miRNA-specific PCR. miR-184 and the GPADH miRNA control were transfected using lipofection. Downregulation of target genes and proteins were analyzed by qPCR after 24h and by western blot after 48h.

Results: From the selected 21 miRNAs there were remarkable differential effects of let-7f, miR-184 and miR-708. Let-7f (-29,2%) and miR-708 (-23,6%) both showed a suppression of the alternative 3'UTR-PRTN3 but no effect on the regular 3'UTR-PRTN3 while miR-184 only suppressed the regular 3'UTR (-17,5 %) and not the alternative variant (fig. 1-2).

NB4 cells were differentiated into a CD11b+/CD14- granulocyte-like phenotype expressing PR3 mRNA and protein. Endogenous miR-184 expression was not found. Downregulation of GAPDH by control miRNA was validated on protein level. We could not confirm that miR-184 regulates PR3 on mRNA or protein level down, but we could show a downregulation of AKT2 on mRNA and protein level by miR-184.

Conclusions: Disease specific miRNA signatures together with an increased PRTN3 level and in alternative PRTN3 mRNA in GPA suggest an epigenetic dysregulation of PRTN3 expression in GPA. To our knowledge this is the first analysis in GPA showing that miRNAs can differentially regulate the regular and the alternative 3'UTR variants of PRTN3-mRNA. As miR-184 is markedly upregulated in GPA, a repression of PRTN3 is to be anticipated, possibly as a reaction to previous neutrophil activation with PRTN3 overexpression. However, we could not confirm downregulation of PR3 on mRNA or protein level in the NB4 granulocyte model. But AKT2, an alternative validated target of miR-184, was downregulated serving as positive control of our cell model. Interestingly, AKT2 is involved in cell death mechanism such as apoptosis. Since miR-184 is highly overexpressed in nasal tissue of GPA patients, the miR-184/AKT2-axis might represent a potential new link to mechanisof cell death regulation, driving autoimmunity in GPA.

Disclosures: S. Schinke: grant by vasculitis foundation Kansas City, MO 64188. Other authors: none

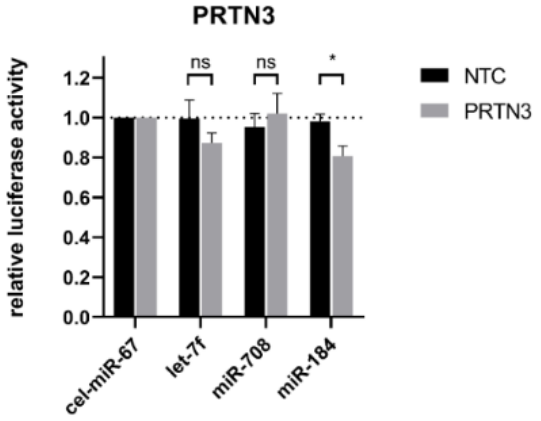

Fig. 1: Dual-luciferase reporter assay with the regular 3'UTR of PRTN3 cloned into the pmirGLO vector compared to empty vector (NTC). Significant effect for miR-184 (17,5 %), miR-708 no effect and let-7f small but not significant reduction in luciferase activity (12,3 %). Data represent 3 independent experiments with triplicate measurements. miR-184 was tested 6 times. *P<0.05; ns = not significant; error bars display standard deviation.

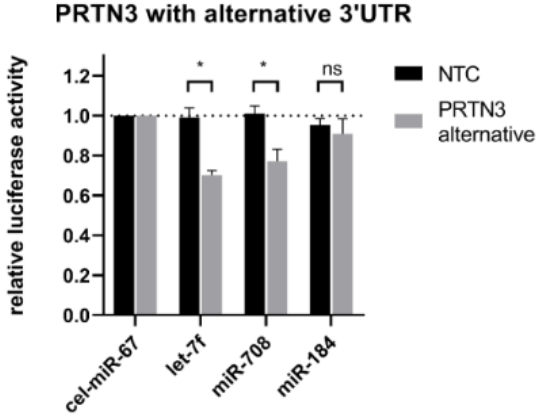

Fig. 2: Dual-luciferase reporter assay with the alternative 3'UTR of PRTN3. Significant effects of let-7f (29,2 %), miR-708 mimic (23,6 %), miR-184 (no significant reduction) in luciferase activity. 3 independent experiments with triplicate measurements. *P<0.05

83. Screening for monogenetic vasculitides: the Great Ormond St Hospital Experience

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Background: Next generation genetic sequencing (NGS) is now firmly established as part of the routine diagnostic workup of vasculitis, and has been a disruptive but welcome addition to the diagnostic armamentarium, facilitating precision medicine in this space. The growing number of genes that have been identified to cause monogenic vasculitides and

vasculopathies now encompass not only vasculitis but also autoinflammatory conditions with occasional vasculitis, immunodeficiency, and hematologic manifestations (1–4). Genetic vasculopathy mimicking vasculitis are also a concern. We describe diagnostic yield in a cohort of 339 patients referred to our autoinflammation centre of excellence (GOSH-ACE) since 2015.

Methods: A NGS custom gene panel validated for vasculitis and inflammation (5), and whole-exome sequencing approach with virtual panel analysis was used to screen 339 patients with unknown but suspected autoinflammatory/ vasculitides. Genetic variants present in more than 1% of individuals (1000G and gnomAD databases) were excluded, and the remaining rare variants subsequently classified according to pathogenicity.

Results: Of the 288 cases with demographics, there were 51% males; median age 13 years, range 1-70 years. Pathogenic or likely pathogenic (class 5 or 4) variants were detected in 119/339 patients (35%). A definite new genetic diagnosis was made in 31/339 cases (9%; Table). Seventy-four/339 patients (22%) had at least 1 class 4 variant requiring further workup to fully establish a true genotype-phenotype correlation. The commonest disease-causing genes (i.e. affecting more than one case in this cohort) with class 5 pathogenic mutations were: *ADA2*, *MEFV, C1QB* and *TREX1* (Table). Vasculopathic mimics of vasculitis included neurofibromatosis and Marfan syndrome.

Conclusions: NGS is now fully embedded as a routine diagnostic test for vasculitis of the young, with overall diagnostic yield (definite, or possible genetic diagnosis) of 10-22% respectively. Precision medicine is thus now possible for these cases, with profound impact on treatment ranging from no immunosuppression (vasculopathy) to targeted treatment with biologics or hematopoietic stem cell transplantation, and in the future gene therapy. Clinicians should be aware that the diagnostic yield of this approach is profoundly influenced by what genes are included in virtual panel analyses, the pre-test odds of genetic disease in the population tested, and by operator expertise since reporting of genetic results is not yet fully automated.

Disclosures: None

Table. Class 5 mutations detected resulting in a confirmed genetic diagnosis

Gene ID	Variants	Clinical diagnosis	Number of cases
ADA2	p.G47R (x2), p.G47W, p.N370K	DADA2	4
C1QB	p.M95fs, p.G96Afs*49,	Complement deficiency	2
C3	p.R1042G	Complement deficiency	1
C6	p.Q274Rfs*45	Complement deficiency	1
CYBA	p.P157Q	Chronic granulomatous disease	1
FBN1	p.R1170H, p.P404Hfs*43	Marfan syndrome	2
GLA	p.G271S	Fabry disease	1
ISG15	p.Q16X	Interferonopathy	1
MEFV	p.V726A (Het x2), p.S208C (Hom), p.M694V (Hom), p.M694V (Hom)	FMF	5
NFI	p.Q543X	Neurofibromatosis	1

PIK3R1	c.336+1G>A	SHORT syndrome (AD)	1
PRF1	p.A91V (Hom)	HLH	1
PSTPIP1	p.G403R	Autoinflammatory; pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA)	1
PTEN	p.V217D	Cowden syndrome 1	1
RNF213	p.D4013N	Moyamoya	1
SLC29A3	p.F316V (Hom)	H-syndrome	1
TMEM173	p.C206Y	Autoinflammatory; SAVI	1
TNFAIP3	p.R271X	Autoinflammatory syndrome, A20 deficiency, familial, Behcet-like	1
TRAF3	p.R118W	Encephalopathy, acute, infection-induced, Herpes-specific, 5 (IIAE5)	1
TREX1	p.D18N (x2)	AGS (interferonopathy)	2
WAS	p.E131K	Immune deficiency	1

84. Genetic variation in efficacy and toxicity of cyclophosphamide in the treatment of ANCA vasculitis

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Background: Cyclophosphamide remains as the key immunosuppressive drugs for induction treatment of ANCA-associated vasculitis (AAV). It can produce serious side events such as myelotoxicity, infections and malignancies. To advance the mission of personalised medicine, we sought to identify genetic polymorphism associated with occurrence of adverse events and/or reduced efficacy.

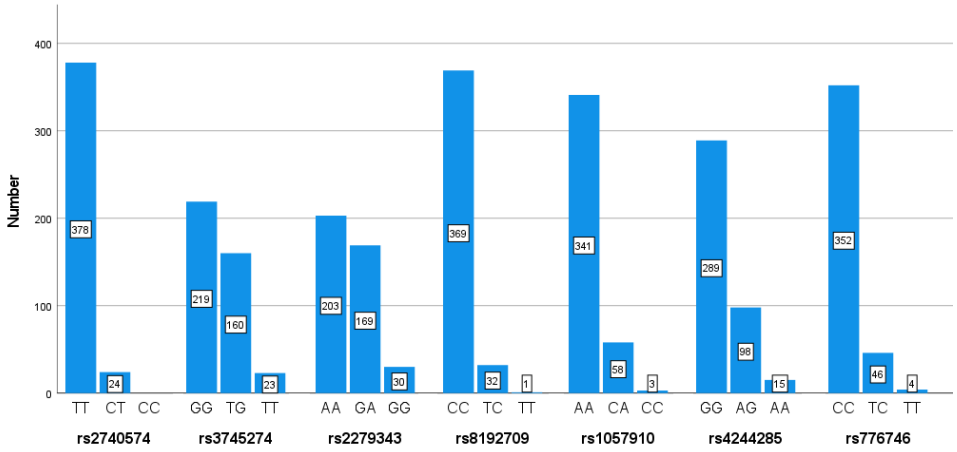
Methods: A cohort of 402 patients with diagnosis of AAV from two centres who had been treated with at least 2g of cyclophosphamide was recruited. We investigated the following SNPs in gene regions encoding proteins related to cyclophosphamide metabolism: rs2740574, rs3745274, rs2279343, rs8192709, rs1057910, rs4244285 and rs776746. Their demographic characteristics, disease course and adverse effects were recorded.

Results: Different alleles were recorded for the population, with the distribution seen in the graph bellow. The specific association between these SNPs and outcomes is currently under analysis.

Conclusions: This study may help guide the election of treatment according to patients SNPs.

Disclosures: None.

Figure 1.



85. Identification of a Novel Susceptibility Locus for Small Vessel Vasculitis with Autoantibodies Against Myeloperoxidase

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Background: ANCA-associated vasculitides (AAV) are rare but aggressive autoimmune disorders. The pathogenesis of the disorders is complex and still poorly understood; only a few genetic loci have been associated with AAV. The aim of this project was to identify and characterize novel susceptibility loci for AAV positive for myeloperoxidase (MPO) or proteinase 3 (PR3) ANCA.

Methods: Genetic association analyses were performed after Illumina sequencing of 1853 genes and subsequent replication with genotyping of candidate single-nucleotide polymorphisms (SNPs) in a total cohort of 1110 Scandinavian cases with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) and 1589 controls. Data were analysed using logistic regression with a P value threshold for significance of $< 9.1 \times 10^{-7}$. A novel AAV-associated SNP was analysed for allele-specific effects on gene expression using luciferase reporter assay.

Results: Associations between PR3-ANCA positive (+) AAV and the *HLA-DPB1*, *HLA-DPA1* and *SERPINA1* genes and between MPO-ANCA+ AAV and the HLA–DQB1 locus identified in previous genome-wide studies were confirmed in the present study. In addition, a rare SNP located in the *BACH2* gene (rs78275221) was identified as significantly associated with MPO-ANCA+ AAV ($P = 7.9 \times 10^{-7}$, Odds ratio = 3.0 in meta-analysis). The rare allele of the novel disease-associated SNP affected downstream gene expression in primary endothelial cells, specifically.

Conclusion: This study confirms previous findings of genetic associations specific for PR3-ANCA+ and MPO-ANCA+ AAV, respectively. A novel susceptibility locus for MPO-ANCA+ AAV was identified, where the disease-associated SNP may facilitate the development of autoimmunity through a negative effect on gene expression in specific cell types.

Disclosures: None.

86: Digital spatial profiling of glomerular gene expression in pauci-immune glomerulonephritis

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Background: Pauci-immune focal necrotizing glomerulonephritis (piFNGN) is a remitting and recurring disease characterized by asynchronous focal necrosis of glomerular tuft segments resulting in scarring and loss of renal function. The lesions evolve over time during active disease phases and appear as heterogeneous patterns of injury in renal biopsies. Characterization of the underlying molecular processes using expression profiling is difficult

because most methods involving analysis of bulk tissue, or dissociated single cells, disregard the heterogeneity of discrete lesions. Here, we use digital spatial profiling (DSP) to characterize protein and transcript expression in individual, morphologically distinct glomeruli from patients with piFNGN.

Methods: 18 biopsies showing piFNGN were used for DSP according to assay's instructions. Circular tissue annotations containing glomeruli were manually placed for analysis with the Nanostring GeoMX protein (n=120), immuno-oncology RNA (n=72) and Cancer Transcriptome Atlas (n=48) panels. Glomerular histomorphology was evaluated in adjacent serial sections. Expression data was processed by log transformation, quantile normalization and batch effect correction.

Results: DSP demonstrated the differences in the expression of proteins and RNA targets between injured and apparently normal glomeruli that were expected based on previous studies of renal biopsies from vasculitis patients and transplant donors. In addition, DSP identified heterogeneous RNA and protein expression among individual glomeruli from the same biopsy and among glomeruli with similar morphological patterns of injury. This enabled us to identify differential gene expression signatures that correlated with morphological patterns of injury, and indicated involvement of specific inflammatory pathways.
Conclusions: Our findings demonstrate the utility of DSP for characterizing heterogeneity of focal glomerular injury and identifying pathways of renal pathobiology in morphologically distinct lesions.

Disclosures: None

Innate Immunity

87. Siglec-9 engagement attenuates ANCA-mediated neutrophil activation

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Background: Sialic acid-binding Ig-like lectin 9 (Siglec-9) is constitutively expressed on neutrophils and monocytes. The expression and potential role of siglec-9 in ANCA-associated vasculitis (AAV) is yet to be determined. We aimed to examine the expression of siglec-9 in patients with AAV and explore the impact of siglec-9 engagement on ANCA-mediated neutrophil responses *in vitro*.

Methods: Leukocytes and serum were isolated from peripheral venous blood of AAV patients and siglec-9 expression was measured by flow cytometry and ELISA, respectively. Immunohistochemistry was performed on kidney biopsies of AAV patients with AAGN and stained for siglec-9, recombinant siglec-9 Fc chimera and leukocyte markers. Functional studies were done using healthy donor neutrophils in the presence of ANCA and siglec-9 mAb to investigate its role in ANCA-induced ROS production and neutrophil extracellular traps (NETs) formation.

Results: We found increased serum siglec-9 expression in active AAV compared to remission AAV and a positive correlation with disease activity. Neutrophils and intermediate (CD14+/CD16+) monocytes from PR3-AAV patients displayed higher siglec-9 expression compared to MPO-AAV patients. Siglec-9 expression in AAGN was restricted to areas of active inflammation. Using recombinant siglec-9 Fc chimera protein in immunohistochemistry experiments, we identified glomerular endothelial cells to express siglec-9 ligands. ANCA stimulation of primed neutrophils was associated with siglec-9 shedding. Siglec-9 engagement using anti-siglec-9 mAb was associated with reduction in ROS production and NETs formation compared to isotype control.

Conclusion: Siglec-9 expression correlates with disease activity in AAV. Surface expression of siglec-9 on key cellular players in AAV pathogenesis, is biased towards PR3-AAV. The biologic relevance of this finding is unclear. Our *in vitro* experiments support a potential role for siglec-9 in attenuating ANCA-mediated neutrophil responses. Further work is required to determine the nature of siglec-9 ligand on endothelial cells and relevance of our findings on neutrophil-endothelial interactions *in vivo*.

Disclosures: None

88. Role of Neutrophil Extracellular Trap Formation in Systemic Vasculitides

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Background: Neutrophil extracellular trap (NET) formation, the release of decondensed chromatin and granular proteins from activated neutrophils, is essential in innate immunity. NET formation plays also an important role in autoimmune diseases, including anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV), a disease that affects small blood vessels. Whether NET formation and autoimmunity against NET antigens such as extracellular histones, a common autoantigen in other autoimmune diseases including systemic lupus erythematosus and rheumatoid arthritis, occurs in Takayasu's arteritis (TAK) and giant cell arteritis (GCA), two forof large vessel vasculitis (LVV) is unknown. The objective of this study was to compare levels of NET formation and anti-histone antibodies in AAV and LVV.

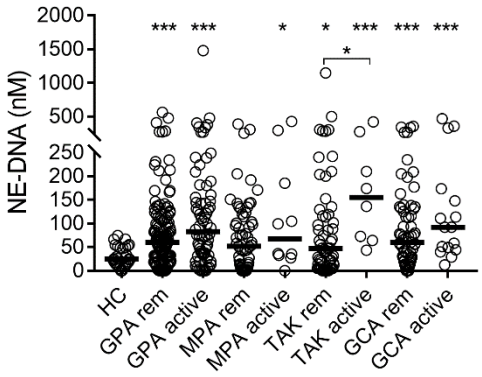
Methods: NETs (neutrophil elastase (NE)-DNA complexes) and anti-histone antibodies were analyzed in plasma samples of healthy controls (n=30), and patients with AAV (granulomatosis with polyangiitis (GPA, n=196), microscopic polyangiitis (MPA, n=74)), TAK (n=66), and GCA (n=82), at times of remission or flare. Physician global assessment (PGA) was used for evaluation of disease activity.

Results: NE-DNA complexes were significantly elevated in the plasma of patients with AAV and LVV, both at flare and remission, compared to healthy controls (HC), except for patients with MPA at remission (Figure 1A). In patients with TAK, but none of the other conditions, NE-DNA complexes were significantly elevated at time of flare as compared to remission ($p<0.05$), and NE-DNA levels correlated with PGA ($r=0.28$, $p<0.05$). Levels of NETs did not correlate with markers of general inflammation, such as C-reactive protein. Only patients with TAK had significantly higher levels of anti-histone antibodies in their circulation regardless of disease activity ($p<0.01$) (Figure 1B). In patients with TAK, presence of NETs correlated with levels of anti-histone antibodies ($r=0.35$, $p<0.01$).

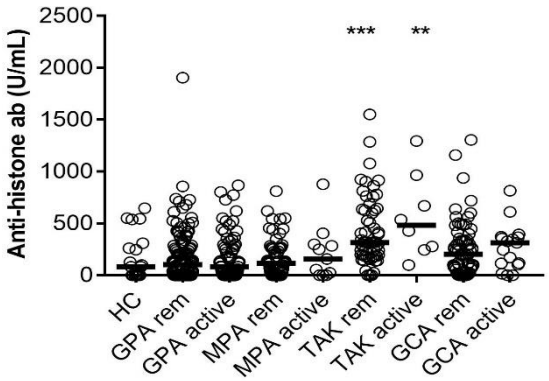
Conclusions: NETs, as assessed by NE-DNA complexes, are elevated in both AAV and LVV suggesting a potential common disease link in vasculitides. Presence of anti-histone antibodies in TAK suggests that NETs may be a source of autoantigens in this disease. Further studies are required to explore the role of NETs and anti-histone antibodies in the pathogenesis of vasculitides.

Disclosures: None

Figure 1. Levels of NE-DNA complexes and anti-histone antibodies in patients with vasculitis. Levels of A) NE-DNA complexes and B) anti-histone antibodies were analyzed in healthy controls (HC), and patients with vasculitis at times of remission (rem) and active disease. Statistical analyses were done by Mann-Whitney U test with *$p<0.05$, **$p<0.01$ and ***$p<0.001$. Unless otherwise indicated, all analyses are compared to healthy controls. Each circle represents an individual sample, with the bar representing the median of the group. GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; TAK: Takayasu's arteritis; GCA: giant cell arteritis.



A.



B.

89. The role of monocyte subsets and CSF2 in the pathogenesis of ANCA-induced glomerulonephritis

Anthony Rousselle[1], Alexander Mildner[2], Janis Sonnemann[1], Doerte Lodka[1], Kerstin Amann[5], Markus Bieringer[3], Udo Schneider[4], Ralph Kettritz[1], Achim Leutz[2], Phillip Enghard[1], Adrian Schreiber[1]

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Background: Activation of myeloid cells by circulating anti-neutrophil cytoplasmic autoantibodies (ANCA) is essential in the development of ANCA –associated vasculitis (AAV) and necrotizing crescentic glomerulonephritis (NCGN). In contrast to neutrophils, the contribution of classical and non-classical monocyte subsets in AAV remains poorly described. Classical monocytes are released from the bone marrow into circulation where they can differentiate into non-classical monocytes. This differentiation is under the control of the CCAAT/enhancer binding protein β (C/EBPβ) transcription factor. Colony stimulating factor 2 (CSF2) is a cytokine which stimulates stem cells to produce myeloid cells. Recent studies have put in evidence that high level of CSF2 is present in patients with autoimmune diseases and is an important pathogenic factor by modulating monocyte functions. Our work aimed to investigate the contribution of both monocyte subsets and the involvement of CSF2 in ANCA-associated NCGN.

Methods: To assess the differential role of both monocyte subsets, myeloperoxidase$^{-/-}$ (MPO$^{-/-}$) mice were immunized with murine MPO, irradiated and subsequently transplanted with hematopoietic cells from either WT, CCR2$^{-/-}$ or C/EBPβ$^{-/-}$ mice. Mice were sacrificed and examined 6-8 weeks following transplantation. CSF2 expression was studied in kidney and urine of mice with AAV and was used *in vitro* for the stimulation of human and murine monocytes. The contribution of CSF2 *in vivo* was investigated in MPO$^{-/-}$ mice transplanted with bone marrow cells from CSF2rb$^{-/-}$ mice following the procedure described above. Finally, we quantified urinary monocytes and CSF2 levels in patients with AAV.

Results: CCR2$^{-/-}$ chimeric mice showed a reduction in circulating Ly6C^{hi} classical monocytes and were protected from the development of renal damage compared to WT chimeric mice. In contrast, C/EBPβ$^{-/-}$ chimeric mice lacking non-classical monocytes developed glomerular necrosis and crescent formation to the same extend as WT chimeric mice. Kidney and urinary CSF2 protein levels were upregulated in mice with AAV. *In vitro*, CSF2 increased the ability of ANCA-stimulated monocytes to release interleukin-1β (IL1-β) and induce the polarization of CD4^{+} T-cells into T helper 17 (T_H17) effector cells. CSF2rb$^{-/-}$ chimeric mice were protected from glomerulonephritis and exhibited reduced numbers of kidney T_H17 cells. Finally, we found increased numbers of both urinary classical monocytes and CSF2 levels in patients with active kidney AAV. In addition, kidney CSF2 expression was also increased in these patients.

Conclusions: Classical, but not non-classical, monocytes are important mediators of renal damage in AAV. CSF2 is a crucial pathological factor in AAV by modulating monocyte pro-inflammatory functions. Classical monocytes and CSF2 levels were increased in urine from patients with AAV. Our data suggest that monocytes and CSF2 might represent novel interesting therapeutic targets.

Disclosures: none

90. Low ANCA IgG Sialylation Levels Enhance anti-MPO induced NCGN in a murine model

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Background/Objective: ANCA induced vasculitides are induced by binding of anti-MPO or anti-PR3 IgG to the autoantigen expressed on the membrane of myeloid cells. However, ANCA titers only loosely correlate with disease activity in an individual ANCA patient. Glycosylation of IgG and especially of autoantibodies are an important regulator of the pathogenicity of autoantibodies. In AAV it has been described that glycosylation of ANCA IgG is changed in active AAV and that antibody glycosylation influences the binding ability to Fc receptors. However, only few publications show a direct connection of glycosylation pattern and cellular functionality in AAV-concerning processes. Our work aimed to understand the role of IgG sialylation in the pathogenicity of ANCA IgG.

Methods: Flow cytometry was used to analyse the glycosylation status of patients-derived B cells compared to healthy controls. IgG isolated from patients with active disease were in vitro sialylated and desialylated. These modified antibodies were used in PMN stimulation assays to analyse the effect of the sialylation status on ROS production (Ferricytochrome C assay), NETs

induction (Sytox, fluorescence microscopy) and IL-1b secretion (ELISA). Anti-MPO NCGN was induced in WT mice by passive transfer of IgG from MPO-immunized either MPO-deficient mice (normal IgG) or MPO/St6gal1-DKO mice (hyposialylated IgG). Histological evaluation of kidney sections as well as blood and kidney flow cytometry were performed.

Results: Flow-cytometric analysis of the glycosylation status of B cells from active patients revealed a reduced level of sialic acid, terminal galactose and fucose compared to healthy controls. Sialylation of IgG derived from active patients resulted in reduced ROS-production of PMNs whereas desialylation did not further increase ROS-production compared to unmodified IgG. Furthermore, NETs formation was also reduced by sialylation. Finally, mice receiving IgG from MPO/St6gal1-DKO (hyposialylated IgG) had increased disease severity shown by elevated frequencies of crescentic or necrotic glomeruli compared to mice receiving IgG from MPO-KO mice.

Conclusion: Glycosylation and especially sialylation of IgG influences disease severity in AAV. IgG sialylation had a protective effect, seen by reduced ROS production and NETs formation in sialylated IgG samples in vitro. Nevertheless, there seeto exist a certain threshold, where further lowering sialic acid frequency does not result in increase of PMN activity (ceiling effect). We finally found a profound impact of IgG sialylation on ANCA-induced NCGN severity in an animal model, where sialic acid-deficient anti-MPO IgG worsens disease. In summary, we here for the first time provide data, that IgG sialylation directly regulates severity of ANCA-induced NCGN.

Disclosures: None.

91. In ANCA disease, blockade of certain inflammatory mediators improves kidney disease but worsens lung disease

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Background: Kidney disease with glomerulonephritis (GN) and lung disease (LD) with capillaritis/microabscesses/granulomatosis are common components of ANCA disease. Targeted blockade of innate immune system inflammatory mediators has been shown to be effective therapy for ANCA glomerulonephritis (GN). In this study, we used a murine model of MPO-ANCA disease to compare the effects of knockout (KO) of multiple innate immune system components on GN and LD.

Methods: Anti-MPO IgG purified from MPO KO mice immunized with murine MPO was injected iv into wild-type C57BL/6j mice (WT B6), and mice with KO of complement factors B (FB), complement factor I (CFI), C5, bradykinin 1 receptor (B1R), LFA-1, Mac-1, or CCR2. Proteinuria, hematuria and leukocyturia were monitored, and mice were sacrificed at day 6 and kidney and lung tissue obtained for pathologic examination. GN was scored based on %

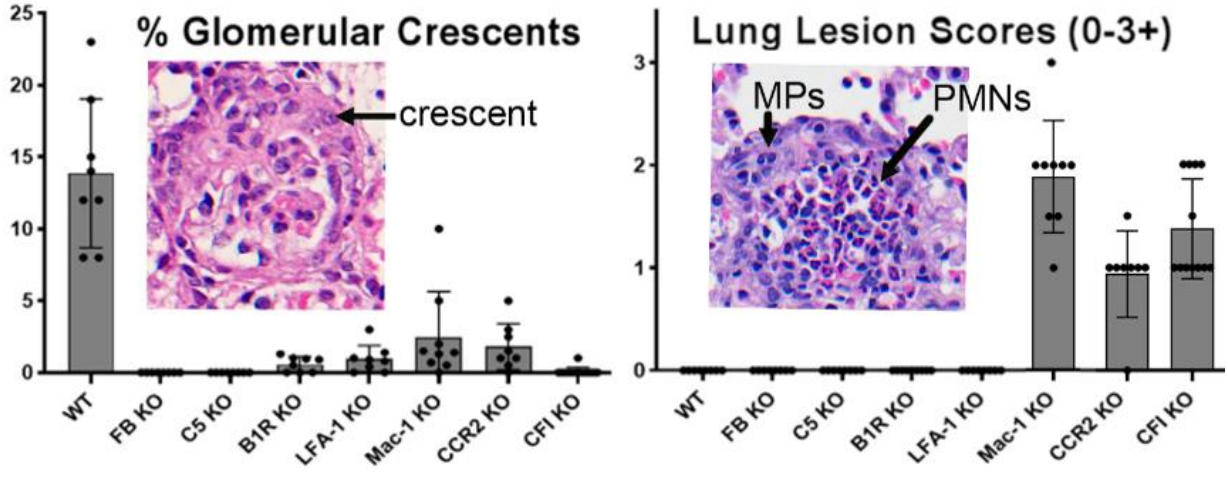
glomeruli with crescents, and lungs scored based on microabscess/granuloma formation (0-3+).

Results: All WT B6 mice developed GN with crescents, but none developed LD. All mice with KO of any innate immune components tested had prevention or amelioration of GN. However, all mice with KO of Mac-1, CCR2 or CFI developed multiple small lung microabscesses/granulomas histologically identical to human ANCA lung disease. The Figure shows % glomeruli with crescents (left) and semiquantitative score of lung lesions (right) with a central core of neutrophils (PMNs) surrounded by a thin rim of macrophages (MPs).

Conclusions: In a preclinical model of ANCA disease, blockade of some but not all components of innate immunity prevents or reduces GN but facilitates LD. We hypothesize that reduced MP recruitment to early sites of lung injury caused by ANCA-activated PMNs allows initiation of microabscesses that are the precursors to lung granulomatosis. Blockade of mediators that sufficiently prevent early lung injury by PMNs do not result in LD even if macrophages are impaired. These observations raise the possibility that some treatment strategies that are effective for ANCA GN may exacerbate ANCA LD.

Disclosures: PH, HX and JCJ disclose research funding from NIH NIDDK, ChemoCentryx and Alexion. JCJ discloses consultant services for BioCryst Pharmaceuticals and ChemoCentryx. All other authors have no disclosures.

Figure 1.



92. Aberrant Phenotype Of Circulating Antigen Presenting Cells in Giant Cell Arteritis and Polymyalgia Rheumatica Patients

Miss. Rosanne Reitsema[1], Bernd-Cornèl Hesselink[2], Kornelis van der Geest[1], Annemieke Boots[1], Elisabeth Brouwer[1], Peter Heeringa[2], Yannick van Sleen[1]
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Background: Giant Cell Arteritis (GCA) and Polymyalgia Rheumatica (PMR) are overlapping diseases occurring exclusively in people older than 50 years. Antigen-presenting cells (APCs), including monocytes and dendritic cells (DCs), are main contributors to the immunopathology of GCA and PIn GCA tissues, DCs may be prone to activation, leading to chemokine production and recruitment of CD4+ T-cells and monocytes to the arterial wall. However, little is known about APC phenotypes in the peripheral blood at the time of GCA/Pdiagnosis. Therefore, we aimed to investigate the phenotype of the circulating APCs in GCA and Ppatients.

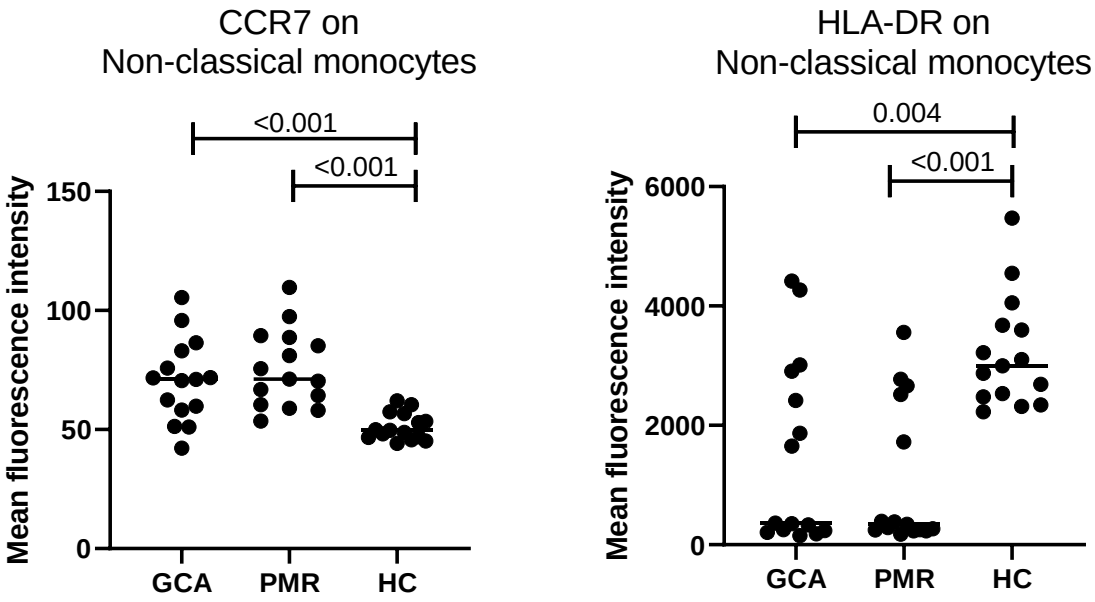
Methods: APCs among peripheral blood mononuclear cells (PBMCs) of treatment-naive GCA and Ppatients were compared to those in age- and sex-matched healthy controls (HCs) using flow cytometry (n=15 in each group). Using a 14-colour panel, we identified three monocyte subsets: classical (CD14+CD16-), intermediate (CD14+CD16+), and non-classical (CD14lowCD16+) monocytes. DC subsets were defined as CD14/CD16/CD19 negative cells with high Human Leukocyte Antigen – (HLA-DR) expression, and were subdivided in CD303+CD11c- plasmacytoid DCs (pDCs), CD11c+CD141+ conventional DCs (cDC1) and CD11c+CD1c+ conventional DCs (cDC2). Each of these subsets was analysed for expression of Toll-like receptor 4 (TLR4), TLR2, CD86, CCR7, Programmed death- ligand 1 (PD-L1), CD40, HLA-and CD11c by assessing the mean-fluorescence intensity of these markers.

Results: Compared to HCs, non-classical monocytes of GCA and of Ppatients had a significantly lower expression of TLR2, HLA-and CD11c, whereas CD86 expression was significantly lower on non-classical monocytes of Ppatients only. In contrast, CCR7 expression by non-classical monocytes of GCA and Ppatients was significantly higher (Figure 1). Expression of CD40 appeared to be lower in Ppatients' intermediate monocytes. Even though no phenotypical and numerical differences were observed for DCs in the peripheral blood, cDC2 counts correlated negatively with CRP levels (r=-0.64 for GCA, r=-0.43 for PMR).

Conclusions: Circulating non-classical monocytes, but not DCs, display an altered phenotype in GCA and Ppatients at diagnosis. These cells, thought to be pro-inflammatory and representing the end stage of monocyte maturation in the blood, display features of decreased activation. The results suggest an exhausted or an early senescent phenotype of non-classical monocytes possibly caused by the inflammatory process. Moreover, their increased CCR7 expression could indicate an increased capacity to migrate to tissues expressing high CCR7 ligands, a notion to be further investigated.

Disclosures: AB was a consultant for Grünenthal Gmbh until 2017. EB and KSMvdG as employees of the UMCG received speaker/consulting fees from Roche paid to the UMCG.

Figure 1. Mean fluorescence intensity of CCR7 and HLA-on non-classical monocytes in GCA and Ppatients compared to HCs (n=15 per group).



93. A prospective study of NET-formation in ANCA-associated vasculitis using bioimpedance analysis

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Background: In ANCA-associated vasculitis (AAV), the neutrophil plays a central role. Recently, neutrophil extracellular traps (NET) have been implicated in the pathogenesis of AAV. Several groups have stated ANCAs and/or serum components of AAV patients can induce NETs. There is accumulating evidence that NET formation is increased during active AAV in contrast to remitted patients. We hypothesize that serum from active AAV patients has a higher NET-inducing activity than treated AAV patients in remission. To test this hypothesis, we developed a high content method to measure NET formation using the xCelligence Real-Time Cell Analysis.

Methods: Patients were included from the PROMAVAS study, i.e., a prospective longitudinal study in active AAV patients at Maastricht UMC, between April 2019 and June 2021. Clinical data were obtained from the PROMAVAS database. Serum samples were obtained at the time of active disease (T0), 6 weeks (T1) and 6 months (2) after initiating therapy. Consenting healthy donors were recruited as healthy controls (HC). For NET formation assays healthy control neutrophils were seeded in 96-wells E-plate VIEW and incubated for 4 hours with PMA (25nM, positive control), AAV serum (20% v/v) or HC serum (20% v/v) in the presence or absence of the PAD4 inhibitor (PAD4i; a NET-formation inhibitor). Cell-index (CI) reflecting

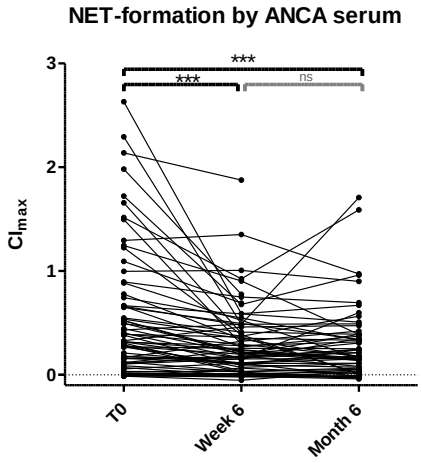
NET-formation was recorded continuously per well by the xCelligence. CI was validated as NET-formation signal by (immuno)fluorescence (IF) visualizing nuclear integrity (DAPI), extracellular free DNA (SYTOX green) and citrullinated histone 3 (CitH3).

Results: Seventy-two patients (M:F; 46:26) were included with a mean age of 63 (±13) years. PR3-, MPO-ANCA or both were detected in 38 (53%), 33 (46%) and 1 (1%), respectively. Renal (*n*=41; 59%) and pulmonary (*n*=33; 47%) involvement were the predominant organs involved. Patients were treated either Rituximab (*n*=43; 60%), cyclophosphamide (*n*=16; 22%) or both (*n*=13; 18%). At 6 months 68 (96%) patients were in remission according to a BVAS of 0. Death occurred in 5 (7%) patients. ANCA serum showed increased NET formation reflected by increased nuclear swelling, cell membrane expansion and CitH3 positivity compared to HC serum (IF, both *n*=7). Accordingly, using bioimpedance, these ANCA and HC sera showed increased CI-max values (median, 3.44 vs. 1.35, resp., *P*<0.001). Incubation with PAD4i inhibited these CI-max values (median AAV vs. HC, 0.07 vs. 0.06, resp., *P*=0.8), indicating CI-max values reflect NET formation capacity. Using bioimpedance, active AAV sera (*n*=72) showed increased NET formation compared to HCs (*n*=12) (median, 0.38 vs. 0.11, respectively, *P*=0.001). In all ANCA sera, the presence of NETs was confirmed by effective inhibition with PAD4i (median AAV-uninhibited vs. AAV-PAD4i, 0.38 vs. 0.04, resp., *P*<0.001) and staining for extracellular free DNA. MPO-ANCA serum showed more NET-formation compared to PR3-ANCA serum (0.50 vs. 0.29, resp., *P*=0.006) and NET formation correlated mildly with serum creatinine (Rho=0.24, *p*=0.048). NET formation did not correlate with BVAS, ANCA titre or age at presentation. NET formation capacity decreased after treatment initiation after six weeks and remained low after 6 months (both *P*<0.001; Wilcoxon signed rank, Figure 1).

Conclusions: Active AAV serum shows increased NET formation capacity compared to HC. Bioimpedance is a useful technique to assess NET formation in AAV. Longitudinal serum samples from AAV patients show a decline in NET formation capacity following immunosuppressive therapy after 6 weeks and 6 months, indicating this technique can be helpful to assess treatment efficacy.

Disclosures: none

Figure 1. NET formation capacity by active AAV serum at presentation (T0), and week 6 and month 6 after treatment initiation showing an overall reduction in NET formation.



94. The Age-Old Question of ANCA-Associated Vasculitis

Isabella Batten[1], Mark W. Robinson[3], Amrita Dwivedi[2], Pamela O'Neill[2], Mark A. Little[2], Nollaig M. Bourke[1]
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Background: Unlike most autoimmune disorders, ANCA-associated vasculitis (AAV) tends to develop later in life, with an average age of onset of about 62 years. Although chronological age is considered a major risk factor involved in AAV development and progression, the underlying mechanisdriving this remain unknown. “Inflammageing” refers to the chronic, low-grade inflammation that occurs in older individuals and is characterised by increased resting levels of inflammatory mediators such as IL-6 and TNFa. Inflammageing has been associated with the development of most, if not all, age-related diseases. Despite this, it’s role in AAV pathogenesis has never been thoroughly explored. We hypothesise that immunological changes associated with ageing and inflammageing drive AAV pathogenesis and aim to investigate the effect of age on innate immune cell function in response to stimulation with ANCA.

Methods: Blood samples were collected from healthy younger (<35 years old) and older (>60 years old). Immune cells (PBMC and neutrophils) were isolated, plated and stimulated with anti-myeloperoxidase (MPO) as well as positive and negative controls for 1-4 hours. Supernatants from these cells were used to measure cytokine release using ELISA. RNA was extracted from cell pellets to measure gene expression using qPCR. Fixed cells were analysed by flow cytometry to measure NETosis and reactive oxygen species (ROS) production.

Results: PBMCs isolated from older individuals show significantly increased IL-6 gene expression and cytokine production in response to anti-MPO compared to those isolated from younger individuals. No significant differences in TNFa gene expression or cytokine production were noted between PBMCs isolated from younger and older individuals. No significant differences in NETosis or ROS production by anti-MPO stimulated neutrophils were observed between the cohorts.

Conclusions: Ageing may result in heightened pro-inflammatory cytokine production in response to ANCA and promote AAV pathogenesis. However healthy ageing does not seem to alter ROS production or NETosis in innate immune cells isolated from healthy donors. Increased sample numbers are needed in order to confirm these findings and these experiments are ongoing.

Disclosures: None

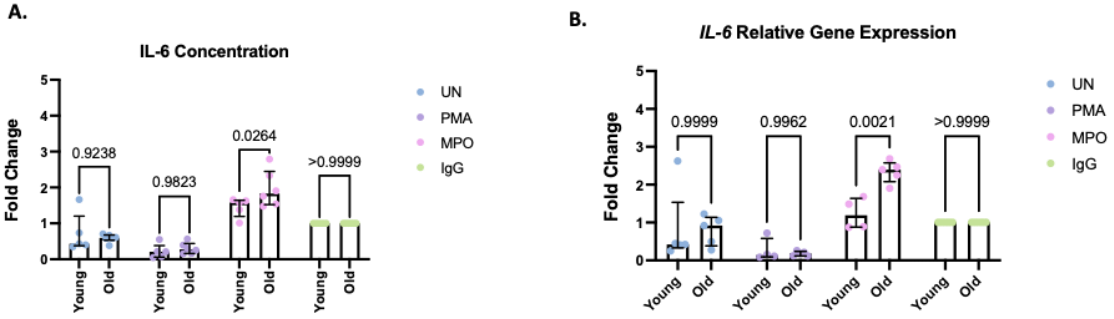

Figure 1: Relative *IL-6* gene expression and protein concentration from isolated PBMCs. PBMCs were isolated from the whole blood of young (<35 years old; n=5) and old (>60 years old; n=6) volunteers and incubated for 4 hours with either no stimulation (UN), Phorbol 12-myristate 13-acetate (PMA), myeloperoxidase (MPO) or an IgG control. (A.)Supernatants were collected and IL-6 concentration was measured using ELISA. (B.)RNA was extracted from the cell pellets and qPCR was used to quantify *IL-6* gene expression and all data is shown relative to the expression of the endogenous control gene *RPL27* and normalised to the IgG control measures ($2^{-\Delta\Delta CT}$).

95. Identification of Monocyte Gene Signatures in Blood and Nasal Tissue of ANCA-Associated Vasculitis Patients

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Background: ANCA-associated Vasculitis (AAV) is a chronic autoimmune disease, comprising two clinical syndromes, granulomatosis and polyangiitis (GPA) and microscopic polyangiitis (MPA), affecting a variety of organs ranging from the kidney to the respiratory tract that without treatment has a poor prognosis. Although the function of neutrophils in AAV has been well

described, the contribution of monocytes and macrophages to disease has received less attention although they have some functional similarities in the context of this disease.

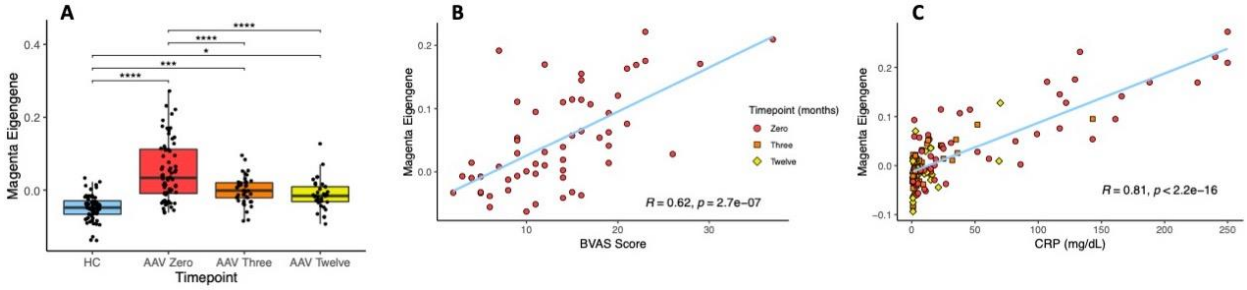
Methods: We sought to gain insight into the role monocytes play in the pathogenesis of AAV by exploring transcriptomic profiles of circulating CD14 monocytes generated using either microarray (42 GPA, 30 MPA and 64 healthy controls) or single-cell RNA-Sequencing (14 GPA and 6 healthy controls), and macrophages in matching nasal tissue in the latter cohort. Data analysis was performed using Bioconductor 3.9, and Seurat 4.0 in R (3.6 and 4.0, respectively).

Results: Weighted gene co-expression network analysis of the microarray dataset identified two modules of co-expressed genes that were associated with both the presence of disease (Panel A) and its extent as assessed by BVAS and CRP (Panel B and C). Functional annotation of these modules using gene set enrichment suggested they were comprised of genes involved in the complement pathway, and pro-inflammatory pathways, such as IL-6/JAK/STAT3 signalling. The association of these signatures with disease activity was validated in the single-cell RNA-sequencing dataset and preservation of these signatures was seen in the nasal tissue.

Conclusions: More biomarkers and prognostic markers are needed in AAV to help physicians better understand each patient's disease and tailor treatment plans. Monocyte transcription signatures offer the potential as new biomarkers of disease activity and understanding the role of monocytes in AAV pathogenesis and persistence.

Disclosures: None

Image 1. Magenta Signature correlates with Disease Activity



96. Disrupted LFA-1/ICAM-1 axis in intermediate monocytes from patients with active ANCA vasculitis

Miss. Carolina A. Herrera[1], Dominic Ciavatta[1], Meghan Free[1], J. Charles Jennette[1], Ronald Falk[1]

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Background: Monocytes migrate to tissues via chemotactic gradients and contribute to the development of inflammation and organ damage in ANCA vasculitis. One specific signaling axis involved in monocyte trafficking and adhesion is the LFA-1/ICAM-1 axis. Monocytes expressing lymphocyte function-associated antigen-1 (LFA-1) bind to the intracellular adhesion receptor 1 (ICAM-1), facilitating endothelial adhesion, however monocytes are heterogeneous and the involvement of LFA-1/ICAM-1 in different monocytes subsets (classical $CD14^{+}CD16^{-}$, intermediate $CD14^{+}CD16^{+}$, non-classical $CD14^{dim}CD16^{+}$) remains unexplored in ANCA vasculitis. Since monocyte subsets are phenotypically and functionally different, we aimed to investigate the involvement of the LFA-1/ICAM-1 in different monocyte subsets during ANCA vasculitis relapse and remission. We hypothesize that the LFA-1/ICAM-1 axis is disrupted in intermediate (pro-inflammatory) monocytes during active ANCA vasculitis.

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from 53 ANCA vasculitis patients and 31 healthy controls who were enrolled according to IRB guidelines. Patients were diagnosed according to the Chapel Hill Consensus Conference and disease activity was assigned based on the Birmingham Vasculitis Activity Score. Peripheral blood and urinary monocyte subset frequencies and monocyte LFA-1 surface protein expression were quantified by flow cytometry. Serum and urinary soluble ICAM-1 (sICAM-1) levels were measured by ELISA.

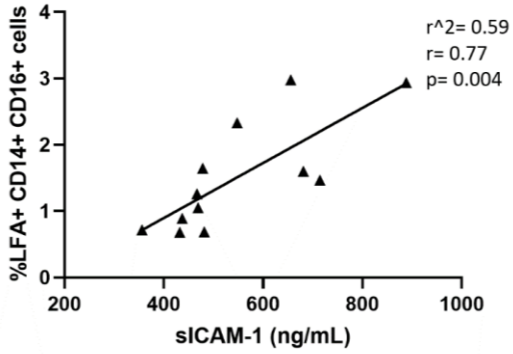
Results: We found that intermediate monocytes are elevated in ANCA vasculitis patients with active disease ($p=0.0004$) and exhibit decreased surface expression of LFA-1 ($p=0.008$) compared to healthy controls. Additionally, sICAM-1 levels were significantly increased in the serum of ANCA vasculitis patients with active renal disease compared to patients in remission ($p=0.003$) and healthy controls ($p=<0.0001$). In paired serum from longitudinal ANCA vasculitis active and remission pairs, sICAM-1 levels were significantly elevated during active disease compared to remitting disease ($p=0.0008$). Furthermore, we found a positive correlation between the frequency of intermediate monocytes expressing LFA-1 and levels of circulating sICAM-1 ($r=0.77$, $p=0.004$). Lastly, the percentage of urinary monocytes was elevated in ANCA vasculitis patients compared to healthy controls ($p=<0.0001$), and urinary sICAM-1 levels were elevated in active ANCA vasculitis patients with disease flare compared to healthy controls ($p=0.034$).

Conclusions: An increased frequency of intermediate monocytes during active disease and decreased surface expression of LFA-1 on intermediate monocytes in the periphery are consistent with shedding of LFA-1 during disease flare. Elevated sICAM-1 levels in the circulation and in the urine during active disease suggest recruitment of monocytes to sites of inflammation and point to an increased shedding of endothelial membrane-bound ICAM-1 from inflamed tissues. The positive correlation between $LFA\text{-}1^{+}$ intermediate monocytes and circulating levels of sICAM-1 suggests an expansion of intermediate monocytes and increased recruitment of these cells to tissues during disease flare. These data support the active involvement of intermediate monocytes during disease relapse and propose an important role for the LFA-1/ICAM-1 axis in the recruitment of intermediate monocytes to sites of inflammation. Intermediate monocytes and/or the LFA-1/ICAM-1 axis may serve as potential

therapeutic targets to inhibit migration of pro-inflammatory intermediate monocytes, ameliorating tissue inflammation and damage in ANCA vasculitis.

Disclosures: None

Figure 1. Serum sICAM-1 ELISA. Correlation of %LFA-1$^+$ intermediate (CD14$^+$CD16$^+$) monocytes and serum sICAM-1. ANCA vasculitis patients N=12. Statistics: Linear regression analysis and Pearson correlation.



97. Altered neutrophil phenotype and function in ANCA Vasculitis and COVID-19 highlights a disease specific response

Miss. Amrita Dwivedi[1], Aisling Ui Mhaonaigh[1], Miss. Isabella Batten[1], Conor Finlay[1], Stuart Phelan[2], Mark A Little[1,2]
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Background: Aberrant neutrophil activation is one of the key contributing factors in the ANCA vasculitis (AAV) immunopathology. A distinct subset of neutrophil is increased in AAV patients and associates with disease severity. This neutrophil subset is termed low-density granulocytes (LDGs), because they appear in the PBMC fraction of density separated blood, moreover, LDGs have been reported in COVID-19 (C-19). AAV and C-19 share similar pathways involved in disease mechanism such as high levels of neutrophil extracellular traps (NETs) and subsequent widespread endothelial dysfunction. We therefore hypothesize that these neutrophil subsets represent a disease specific response and possess distinct phenotypic and functional characteristics depending on the disease context.

Methods: LDGs were isolated using a modified Percoll gradient preparation and analysed by multiparametric flow cytometry in patients with active and remission AAV, in mild and severe C-19 patients and in healthy controls (HC). The phenotyping panel included CD15, CD66b, CD16, CD10, CD62L, CD63, PD-L1, LOX-1, CXCR2 and CXCR4. We used UMAP dimensionality reduction technique to characterise the LDG populations within each cohort. We

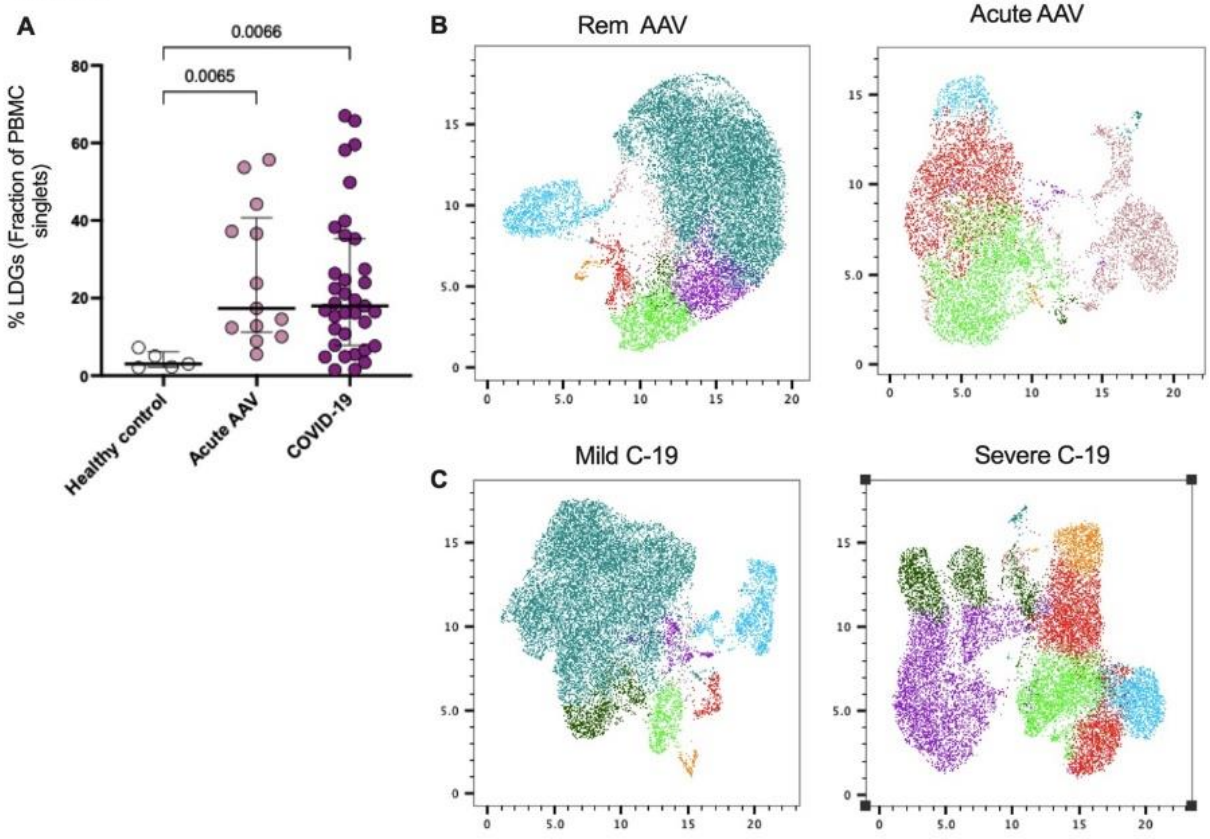
then assessed the production of reactive oxygen species (ROS) and NETs from LDGs following PMA and fMLP stimulation using dihydrorhodamine123 assay and DNA dye-based flow assay respectively.

Results: We found increased levels of LDGs in AAV and C-19 patients which associated with disease severity. UMAP analysis of LDGs from remission AAV and mild C-19 yielded 1 major (over 70% of cells) and 3 minor (>5%) sub-populations in each cohort. The phenotype of the predominant cluster identified was $CD16^{+}CD62L^{+}CXCR2^{+}CXCR4^{lo}LOX\text{-}1^{-}CD63^{+}$ suggesting mature neutrophils. However, the LDG populations within acute AAV and severe C-19 were more complex. We identified 3 sub-populations in acute AAV: $CD16^{+}CD62L^{+}CXCR2^{+}CXCR4^{+}LOX\text{-}1^{hi}CD63^{+}$, $CD16^{+}CD62L^{-}CXCR2^{+}CXCR4^{-}LOX\text{-}1^{hi}CD63^{+}$ and $CD16^{-}CD62L^{-}CXCR2^{-}CXCR4^{+}LOX\text{-}1^{hi}CD63^{lo}$. Severe C-19 sub-populations comprised 2 major (>20%, $CD16^{-}CD62L^{lo}CXCR2^{lo}$ and $CD16^{hi}CD10^{lo}CD62L^{+}LOX\text{-}1^{-}$) and 4 minor (>10%) sub-populations. In addition to these phenotypic differences, we also observed different ROS and NET production capability in LDGs, especially enhanced NET production in fMLP stimulated LDGs from acute AAV.

Conclusion: LDGs are significantly elevated in AAV and C-19, but their phenotypic and functional characteristics appear to be very different. Our results show that LDGs are comprised of several distinct sub-populations within acute AAV and severe C-19. AAV LDGs may possess enhanced functional response thereby suggesting a disease specific role for these neutrophil subsets.

Disclosures: None

Figure 1.



98. Biomechanical phenotype of circulating myeloid cells is altered in ANCA associated vasculitis

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Background: Real Time-Deformability Cytometry (RT-DC) is a novel technique able to identify morpho-rheological characteristics of individual cells such as size, deformability, and elasticity. Cells in suspension flow through a microfluidic channel at a set rate while hydrodynamic force is applied, leading to reversible deformation of individual cells from shear stress and pressure gradients. Cell brightness and area can be used to identify cell populations within whole blood. It is possible to characterise a morpho-rheological phenotype of major leucocyte subsets simultaneously using only 50µl of whole blood. Pathological activation of immune cells in vivo can lead to decreased cell deformability, reducing their ability to traffic through microvasculature and potentially increasing the capacity for endothelial damage and vascular inflammation. The morpho-rheological characteristics of immune cells in ANCA associated vasculitis (AAV) are unknown.

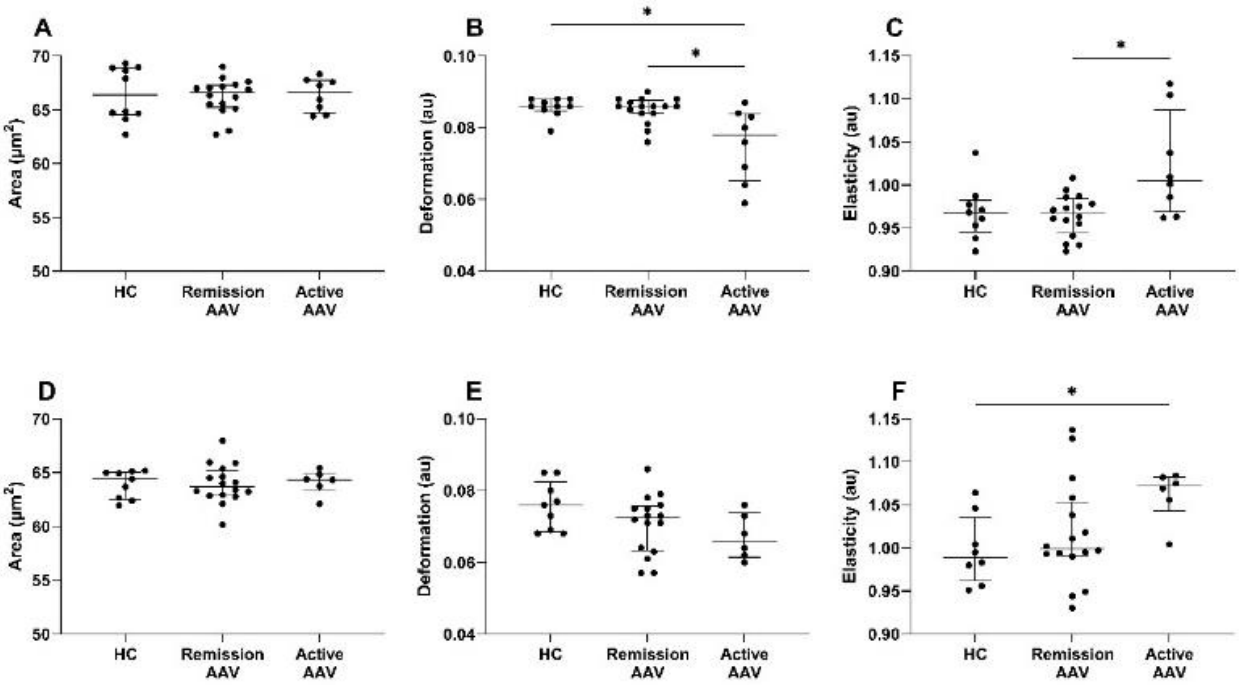
Methods: Whole blood from healthy controls (HC), patients with active AAV, and patients with AAV in remission was analysed using RT-DC. Anticoagulated blood was diluted 1:20 in CellCarrierB (1xPBS/0.6% methylcellulose). Cell suspensions were drawn into a 1ml sample syringe on a syringe pump (neMESYS, Cetoni) of the AcCellerator (Zellmechanik), an extension for an inverted microscope (Zeiss). Syringes connected to polymer tubing were attached to the sample inlet of a Flic20 PDmicrofluidic chip (Zellmechanik), containing reservoirs connected by a measurement channel with a 20x20 μm^2 cross-section. RT-DC measurements were collected at a flow rate of 0.12 µL/s using a high-speed CMOS camera (Mikrotron) to capture images of cells as they reached the end of the microfluidic channel at a frame rate of 2000 frames/second. ShapeOut software was used to calculate cell size, deformation, and elasticity.

Results: RT-DC analysis of whole blood showed no difference in neutrophil size between patients with active AAV (n=8), patients with AAV in remission (n=16), and HC (n=10) (Figure 1A). Neutrophils from patients with active AAV were significantly stiffer than patients in remission or HC, displaying decreased deformation (Figure 1B; median 0.078, 0.086, and 0.087 au respectively, p=0.007) and increased elasticity (Figure 1C; median 1.005, 0.968 and 0.968 au respectively, p=0.03). In patients with AAV (active and remission), there was a strong inverse correlation between neutrophil deformation and disease activity as measured by BVAS score ($r=-0.77$, $p<0.0001$). There was no correlation of neutrophil physical properties with renal function or neutrophil count. Monocytes demonstrated morpho-rheological properties similar to neutrophils, with no difference in cell size between patients with active AAV (n=6), patients with AAV in remission (n=16), and HC (n=9) (Figure 1D). Monocytes from patients with active AAV had lower deformation (Figure 1E; median deformation 0.066, 0.073, and 0.076 for active AAV, remission AAV, and HC respectively) and higher elasticity than those from patients in remission or HC (Figure 1F; median elasticity 1.072, 0.999 and 0.989 for active AAV, remission AAV, and HC respectively, p=0.04). There was no difference in morpho-rheological characteristics of lymphocytes between the three groups.

Conclusion: Neutrophils and monocytes from patients display distinct physical properties in active AAV which correlate with disease activity. This phenotype of increased cell stiffness may lead to increased neutrophil retention in pulmonary and renal microvasculature, thus increasing the potential for neutrophil-endothelial cell interactions and microvascular damage. These parameters can be rapidly measured using a small volume of whole blood; thus RT-DC may be a useful technique to aid identification of disease activity in AAV and to guide treatment.

Disclosures: None

Figure 1. Morpho-rheological properties of circulating leucocytes in AAV
(A)-(C) Neutrophils, (D)-(F) Monocytes. Data are shown as median with IQR, statistical comparison by Kruskal-Wallis test, with Dunn's post-test comparison; *p<0.05 **p<0.01.



99. Neutrophil mediated T-cell suppression in ANCA vasculitis and Covid-19

Aisling Ui Mhaonaigh[1], Amrita Dwivedi[1], Makala Carroll[1], Conor Finlay[1], Mark A Little[1]

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Background: ANCA vasculitis (AAV) and Covid-19 (C-19) share many pathological characteristics including widespread endothelial dysfunction, a strong association with neutrophil activation with NETosis and a pro-thrombotic coagulation phenotype. We have previously defined a specific neutrophil fraction in AAV present in the PBMC layer of separated cells: Low Density Granulocytes (LDGs). We now hypothesise that these LDGs are also present in C-19 and sought to compare their phenotype with those present in AAV. Of particular interest is the expression of intracellular Arginase 1 (Arg-1), an enzyme linked to T cell suppression.

Methods: LDGs were isolated using a modified percoll gradient preparation and analysed by traditional and imaging flow cytometry in patients with active and remission ANCA vasculitis, in those with severe moderate and mild C-19, and in healthy controls (HC). The phenotyping panel included CD14, CD15, CD16, CD10, CD33, CD62l. Intracellular Arg-1 was quantified following cellular permeabilisation. We then tested the effect of cultured neutrophil supernatants from C-19 of varying severity on T-cell proliferation and function.

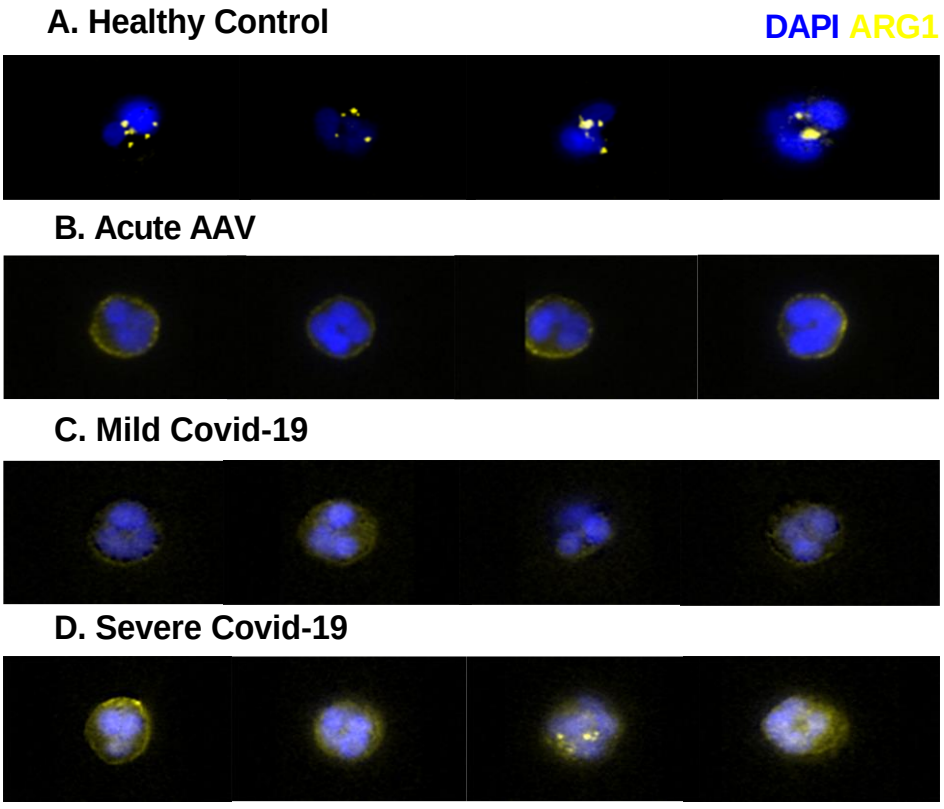
Results: We identified extensive LDG populations in both AAV and Covid-19 peripheral blood which were associated with disease severity. HC had uniformly high Arginase expression. We observed a distinct Arg-1 expression pattern in LDG populations from AAV and C-19.

Intracellular Arg-1 levels were reduced in LDGs from patients with acute AAV; conversely, reduced Arg-1 expression was associated with mild disease in C-19. Using imaging flow cytometry, we observed that the intracellular distribution of Arg-1, which was distinctly granular in HC, was diffusely cytoplasmic in severe C-19 and virtually absent in mild C-19. Consistent with this, levels of Arg-1 in blood were elevated in mild disease and neutrophil supernatants from these patients more effectively inhibited t cell proliferation.

Conclusion: LDGs are markedly elevated in both AAV and C-19, but their expression of Arg-1 and effect on T-cell function appears to be different. Our results suggest a block on Arg-1 release from LDGs in severe C-19, which may contribute to the observed hyper-inflammation in this condition.

Disclosures: None

Figure 1. Imaging Flow Cytometry highlights altered mature neutrophil Arg-1 expression in AAV, Covid 19 and healthy controls. Neutrophils were defined as $CD15^{+}$ $CD16^{+}$ singlets. Representative images of neutrophils shown.



100. Longitudinal Pattern of Circulating Complement Activation in ANCA Vasculitis

Eveline Wu[1], Elizabeth McInnis[2], Kristin Kennedy[2], Lauren Blazek[2], Dhruti Chen[2], Mary Collie[2], Yichun Hu[2], Susan Hogan[2], Caroline Poulton[2], Candace Henderson[2], Charles Jennette[3], Ronald Falk[2], Donna Bunch[2]
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Background: There is accumulating evidence that alternative complement pathway activation is important in ANCA vasculitis pathogenesis. Our group was the first to show that complement activation occurs in both MPO-ANCA and PR3-ANCA vasculitis.[1] Objectives for this study were to investigate complement system activation in a longitudinal cohort of MPO-ANCA and PR3-ANCA vasculitis and evaluate for potential relationships between complement activation measures and clinical characteristics.

Methods: Subjects included 39 patients with ANCA vasculitis (18 MPO-ANCA, 21 PR3-ANCA) and 10 healthy controls. 20 patients had paired samples obtained during disease activity and remission, and 16 had samples obtained during long-term remission off therapy for ³2 years (LTROT). Plasma was obtained from blood collected in EDTA tubes including 100 µg/mL futhan per prior report.[1] Levels of Bb, C3a, C5a, sC5b-9, properdin, and C4d were measured by ELISA and median values reported. Group comparisons were made using Wilcoxon two-sample test. Paired data were analyzed with paired signed-rank test. A p-value of <0.05 was considered statistically significant. Bonferroni correction was applied for multiple comparisons when applicable.

Results: Of the 39 ANCA vasculitis patients, 25 were male and median age was 59 years. Compared to healthy controls, patients with active ANCA vasculitis had higher levels of C3a (128.30 vs. 34.00 ng/mL, p<0.0001), sC5b-9 (217.60 vs. 149.04 ng/mL, p=0.01), and C4d (2.39 vs. 1.02 µg/mL, p=0.004). Compared to patients in remission, patients with active ANCA vasculitis had higher levels of Bb (0.79 vs. 0.65 µg/mL, p=0.003), C3a (128.30 vs. 53.67 ng/mL, p<0.0001), and sC5b-9 (217.60 vs. 135.20 ng/mL, p<0.0001) and lower levels of properdin (14.30 vs. 18.04 µg/mL, p=0.009). Compared to patients with active ANCA vasculitis, those with LTROT status had lower levels of Bb (0.79 vs. 0.63 µg/mL, p=0.003), C3a (128.30 vs. 53.31 ng/mL, p<0.0001), and sC5b-9 (217.60 vs. 144.81 ng/mL, p<0.002). Among the patients with paired active-remission samples, levels of Bb (0.79 vs. 0.66 µg/mL, p=0.03), C3a (128.25 vs. 63.22 ng/mL, p=0.01), C5a (7.94 vs. 5.32 ng/mL, p=0.0001), and sC5b-9 (218.98 vs. 130.48 ng/mL, p<0.0001) were higher and properdin (14.58 vs. 17.89 µg/mL, p=0.04) lower during active disease compared to remission. Evaluating disease manifestations among patients with paired active-remission samples, levels of C5a (8.96 vs. 5.51 ng/mL, p=0.0006) and sC5b-9 (218.77 vs. 132.44 ng/mL, p=0.0001) were higher and properdin lower (14.10 vs. 16.08 µg/mL, p=0.04) among the 15 patients with renal involvement during active disease. In contrast, no difference was observed in any analyte in the 5 patients with paired active-remission samples and without renal involvement during active disease.

Conclusions: Complement activation occurs in both MPO-ANCA and PR3-ANCA vasculitis, and the activation profile differs by disease activity with higher Bb, C3a, C5a, and sC5b-9 levels and lower properdin levels during active disease compared to remission in our longitudinal cohort. More study is needed to determine if complement activation measures correlate with specific disease manifestations, in particular renal involvement, or can reliably predict those patients who can safely discontinue therapy.

Disclosures: Elizabeth McInnis has investments in Chemocentryx, otherwise none

B/T-cell Biology & Targets

101. Production mechanism of anti-glomerular basement membrane antibody in anti-neutrophil cytoplasmic antibody-associated vasculitis

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Background: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is sometimes complicated by anti-glomerular basement membrane (GBM) disease. Proteases, including elastase, released from neutrophils activated by ANCA are implicated in the pathogenesis of AAV. Epitopes of anti-GBM antibody exist in the α3-subunit non-collagenous (NC1) domain of collagen type IV [Col (IV)]. This region, called α3(IV)NC1, is structurally cryptic. This study aimed to determine the production mechanism of anti-GBM antibody in AAV.

Methods: We first examined whether α3(IV)NC1 could be revealed by the digestion of formalin-fixed, paraffin-embedded (FFPE) normal kidney sections and Col (IV) by proteases, including neutrophil elastase, using immunohistochemistry (IHC) and enzyme-linked immunosorbent assay (ELISA). Next, the reveal of α3(IV)NC1 and the infiltration of CD11c+ macrophages in the affected kidneys of patients with AAV and other diseases were evaluated by IHC and immunofluorescent staining using FFPE sections. Finally, the production of anti-GBM antibody in AAV rats was determined by ELISA.

Results: α3(IV)NC1 was revealed by the digestion of FFPE normal kidney sections and Col (IV) by proteases. Although the reveal of α3(IV)NC1 was observed in sclerotic glomeruli regardless of causative diseases, CD11c+ macrophages near α3(IV)NC1 were characteristics of AAV. Anti-GBM antibody was produced subsequent to ANCA in some AAV rats. IHC

demonstrated the reveal of α3(IV)NC1 in affected renal tissues and the infiltration of CD11c+ macrophages around the sites.

Conclusions: The collective findings suggest that, in AAV, proteases released from neutrophils activated by ANCA digest Col (IV) and result in the reveal of α3(IV)NC1, CD11c+ macrophages present GBM epitopes, and then the host's immune system produce anti-GBM antibody. This corresponds to the concept of intermolecular epitope spreading, which is related to disease conversion and complication. For example, the implication of intermolecular epitope spreading has been discussed in a conversion from pemphigus vulgaris to pemphigus foliaceus and in a complication of Hashimoto's thyroiditis with Graves' disease. To our knowledge, this is the first report suggesting that intermolecular epitope spreading is involved in the production of anti-GBM antibody in AAV.

Disclosures: Pre-print: https://www.researchsquare.com/article/rs-322082/v1

102. Maintenance of Remission is Influenced by HLA-DPB1*04:01 and Interaction with PR3225-239

Dhruti Chen[1], Elizabeth McInnis[1], Eveline Wu[1], Katherine Stember[1], Susan Hogan[1], Yichun Hu[1], Candace Henderson[1], Lauren Blazek[1], Simon Mallal[2], Edita Karosiene, Bjoern Peters[3], John Sidney[3], Eddie James[4], William Kwok[4], J. Charles Jennette[1], Dominic Ciavatta[1], Ronald Falk[1], Meghan Free[1]
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Background: GWAS identified the risk allele HLA-DPB1*04:01 in ANCA vasculitis and observational studies associate this risk allele with relapse. As HLA are the focal point of immune system initiation to antigen, these interactions can define immunological remission and/or antigen non-responsiveness. The specific HLA combined with the cognate peptide facilitates activation of an autoreactive immune response (including T and B cells). We hypothesized that PR3-ANCA vasculitis patients exhibit a specific interaction between cognate PR3 peptide and HLA-DPB1*04:01, and in the absence of this HLA-peptide interaction, long-term remission is achieved and maintained.

Methods: ANCA vasculitis patients were followed longitudinally. Peripheral blood mononuclear cells (PBMCs) from patients and healthy controls with HLA-DPB1*04:01 were tested for HLA-DPB1*04:01 expression and interaction with a PR3 peptide identified via in silico and in vitro assays. Tetramers (HLA/peptide multimers) identified autoreactive T cells.

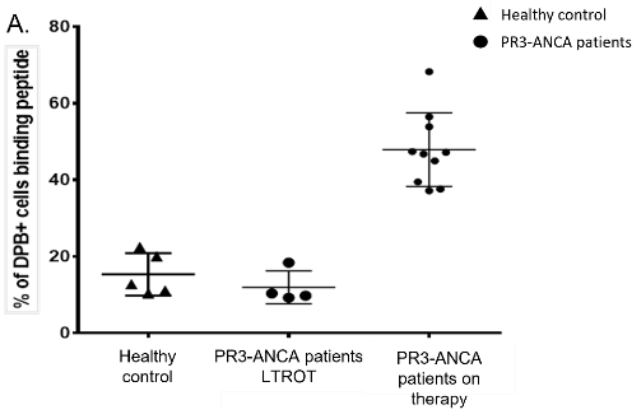
Results: Carriers of the risk allele HLA-DPB1*04:01 were less likely to maintain remission in PR3-ANCA vasculitis, (HR for relapse 2.06 (1.01,4.20)). This effect was not observed in the MPO-ANCA or the combined patient cohort. We confirmed that mRNA and surface protein expression of HLA-DPB1 among patients and controls was not different, therefore we

examined how highly specific peptide binding between HLA-DPB1*04:01 and PR3 may influence disease status. In silico predictions demonstrated strong affinity between $PR3_{225-239}$ and HLA-DPB1*04:01 that was confirmed by in vitro binding. The interaction was tested in ex vivo flow cytometry studies of fluorescently labelled peptide and patient PBMCs. Patients in long-term remission off therapy had lower PR3 peptide and HLA overlap, indicating immunological remission (Figure). To further investigate the pathogenic role of HLA-DPB1*04:01, we utilized tetramers (HLA multimers) loaded with $PR3_{225-239}$ to identify autoreactive CD4+ T cells in the circulation of patients (scrambled peptide $MPO_{447-461}$ as negative control). We examined tetramer positivity of PBMCs directly ex vivo versus 14 day expansion in vitro in response to specific peptides. CD4+ T cells were detectable by PR3-specific tetramers after 14 day in vitro expansion in response to $PR3_{225-239}$. We found greater CD4+ T cell reactivity to $PR3_{225-239}$ compared to scrambled peptide in our cohort. This strengthened our conclusion that HLA-DPB1*04:01 and $PR3_{225-239}$ drive the adaptive immune response in some patients with PR3-ANCA vasculitis. The CD4+ T cell response during active disease and remission was tested using paired samples. Despite limited paired samples, we found that in half of the active patients, T cell reactivity to $PR3_{225-239}$ was high only during periods of disease activity and exhibited low to no reactivity during disease remission.

Conclusion: While the risk allele HLA-DPB1*04:01 has been previously associated with PR3-ANCA vasculitis, the biological underpinnings were unclear. These studies demonstrate that HLA-DPB1*04:01 and $PR3_{225-239}$ affinity is dynamic and lack of interaction may be the basis for immunological remission. We hypothesized that it could determine the subsequent immune response of T cell activation and maintenance of immunological remission. We found that $PR3_{225-239}$ presented by HLA-DPB1*04:01 is specifically recognized by autoreactive T cells and may explain why PR3-ANCA vasculitis patients with HLA-DPB1*04:01 are unable to maintain disease remission.

Disclosures: J.C.J has the following disclosures: Grant support from Medimmune (2017-2019). E.Y.W. receives consulting and Advisory Board fees from Pharming Healthcare, Inc. and receives research funding from AstraZeneca and Bristol-Myers Squibb. All other authors have no financial conflicts of interest to disclose.

Figure PR3-ANCA patients in long term remission and healthy controls have low level of interaction of PR3 peptide with HLA-DPB1 expressing cells. FITC-labeled PR3 peptide ($PR3_{225-239}$) was incubated with PBMCs and subsequently stained with flow cytometry antibodies to identify DPB1+ APCs that were also positive for FITC-labeled PR3 peptide. LTROT=long-term remission off therapy



103. CD19 CAR T cells prevent the development of ANCA-induced NCGN in a mouse model

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Background: ANCA induced vasculitides and NCGN are potentially life threatening and current therapies rely largely on cytotoxic drugs or B cell depleting antibodies. Chimeric antigen receptor T cells (CAR T cells) are genetically modified to express a protein consisting of intracellular T cell receptor domains coupled to an extracellularly expressed antibody domain. The specificity of the antibody part determines which target cells are bound and destroyed by the CAR T cells. The use of CAR T cells in autoimmune diseases is a promising new therapeutic approach. As ANCA are important inductors of ANCA-associated vasculitides (AAVs) depletion of ANCA-producing B cells could be potentially beneficial for AAV therapy. Here we wanted to clarify whether CD19 CAR T cells are able to deplete B cells including ANCA-producing B cells and by that remove disease-inducing ANCAs and prevent disease onset.

Methods: To assess the potential of a CD19 CAR T cell treatment approach, anti-MPO NCGN was induced by immunization of $MPO^{-/-}$ mice with murine MPO, subsequent irradiation and transplantation with hematopoietic cells from WT mice. Additionally, CD19 CAR T cells and

SP6 CAR T cells (control) were transferred intravenously. Effects on disease severity were analyzed by histological examination of kidney sections and by kidney, blood and bone marrow flow cytometry analysis.

Results: CD19 CAR T cells showed a stable engraftment in the transplanted animals as both two and five weeks after administration the cells were detectable in bone marrow, spleen and peripheral blood. Furthermore, mice receiving CD19 CAR T cells had a strongly reduced frequency of CD19-expressing endogenous B cells in the bone marrow, spleen and peripheral blood. This resulted in decreasing anti-MPO titers in CD19 CAR T treated animals. Finally, analysis of kidney histology revealed protection from NCGN induction with a decrease in crescentic or necrotic glomeruli in CD19 CAR T treated animals.

Conclusion: Our data suggest that depletion of CD19 B cells by administration of CD19 CAR T cells is an effective therapeutic option in murine anti-MPO induced NCGN.

Disclosures: None.

104. A cytokine-mediated role of B cells in giant cell arteritis

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Background: Giant cell arteritis (GCA) is vasculitis of large- and medium-sized arteries classically regarded as a T cell and macrophages mediated disease. B cells are clearly detected in the inflamed arteries, but their exact role in the pathogenesis of GCA is unclear. As the knowledge on the antibody-independent functions of B cells is growing, we sought to determine cytokine production by B cells in GCA and their effect on macrophages, crucial players in the pathogenesis of GCA.

Methods: We performed immunohistochemistry on temporal artery (n=11) and aorta tissue (n=10) form GCA patients to detect lesional B cells and cytokines (IL-6, GM-CSF, TNFα, IFNγ, and IL-10). The capacity of circulating B cells to produce cytokines was assessed *in vitro* by stimulating PBMC with CpG and PMA from treatment-naïve GCA patients (n=11), polymyalgia rheumatica patients (PMR, n=10) and 15 age- and sex-matched HCs. Intracellular detection of cytokines by B cells (effector: IL-6, GM-CSF, TNFα, IFNγ and regulatory: IL-10) was performed using flow cytometry. To assess the skewing potential on macrophages, THP-1 derived macrophages were exposed to conditioned medium from stimulated B cells followed by qPCR analysis of IL-23, IL-6, IL1β, MMP9 and YKL40 mRNA expression.

Results: B cells in GCA-affected arteries express IL-6, GM-CSF, TNFα, IFNγ and IL-10. Stimulated peripheral B cells from GCA patients showed enhanced frequencies of IL-6+ (median (IQR); 44 (41-52)) and TNFα+IL-6+ B cells (12 (8-24)) compared to HC (28 (23-39) and 6 (4-24) respectively). Production of effector cytokines by B cells was diminished after glucocorticoid treatment. *In vitro* B cell conditioned medium was capable of skewing macrophages towards a pro-inflammatory and tissue destructive phenotype expressing IL-6, IL-1β, TNFα, IL-23, YKL40 and MMP9.

Conclusions: Our results indicate that B cells may contribute to the vasculopathy in giant cell arteritis via antibody independent functions. Cytokines produced by activated B cells can influence the vascular wall microenvironment and polarize macrophages towards a proinflammatory and tissue destructive phenotype known to be active at the site of vascular inflammation. Our data provide a rationale for B cell targeted therapy in GCA patients.

Disclosures: none.

105. Identification of central tolerance checkpoints for autoreactive proteinase 3+ B cells in human bone marrow

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Background: Autoreactive proteinase 3 ($PR3^+$) B cells have recently been phenotypically and functionally characterized, and the presence of defective central antigen-independent and peripheral antigen-dependent checkpoints in patients with ANCA-associated vasculitis (AAV) has been shown. This work aimed to investigate the central tolerance-checkpoint controlling immature $PR3^+$ B cells in the bone marrow (BM), before their migration into the periphery as transitional B cells.

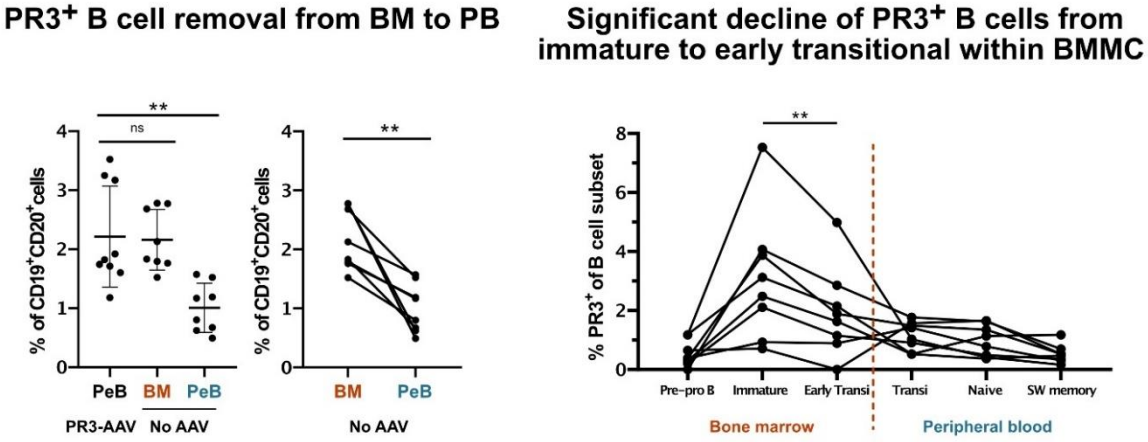
Methods: By flow-cytometry, using PR3 as ligand to target autoreactive $PR3^+$ B cells, we investigated 1) the presence and the specific phenotypic features of $PR3^+$ B cells in BM mononuclear cells (BMMC) of non-vasculitis controls (No-AAV), comparing them to paired peripheral blood mononuclear cells (PBMC) of No-AAV and PBMC of PR3-AAV patients, and 2) the central tolerance-checkpoints for $PR3^+$ B cells.

Results: The proportion of PR3^{+} B cells within BMMC (median [IQR25-75%]; 1.98%[1.77-2.75]) was higher than within PBMC of No-AAV (0.9%[0.63-1.44], p<0.01 by paired comparison) and similar to their proportion within PBMC of PR3-AAV patients (1.82%[1.66-3.21]; p>0.05). When focusing on immature/transitional CD24^{++}CD38^{++}B cells only in No-AAV, we observed distinct phenotypes within BMMC versus PBMC (i.e. higher proportion of CD27^{-} CD10^{+} and lower expression of CD21, IgD, IgM within BMMC versus PBMC), representing two separate developmental steps of B cell maturation. Within CD24^{++}CD38^{++} B cells, BMMC contained the greatest proportion of PR3^{+} B cells as compared to PBMC (3.35%[1.99-4.92] versus 1.23%[0.62-1.55], p<0.01). We observed a significant decline of the PR3^{+} fraction from T1-like/immature subset (IgD^{-}IgM^{+}; 2.80%[1.23-4.02]) to T2-like/early transitional subset (IgD^{+}IgM^{+}; 1.76%[0.96-2.68], p<0.01) in BMMC, while no significant reduction was observed between the latter subset and the transitional compartment of PBMC (1.26%[0.62-1.56], p>0.05).

Conclusions: To prevent PR3-related autoimmunity, autoreactive PR3^{+} B cells pass a stringent selection in the BM, and their removal by central tolerance-checkpoint activity occurs mainly between T1-like/immature to T2-like/early transitional B cells of BMMC.

Disclosures: Specks have received research grants from Roche/Genentech.

Figure 1.



106. Elevated STAT3/PIM1 Expression in T Cell Subsets of Granulomatosis with Polyangiitis Patients

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Background: Granulomatosis with polyangiitis (GPA) is an autoimmune disease characterized by inflammation of the microvasculature in various organs. Aberrations in several T cell subsets, both numerical and functional, have been identified in GPA patients. However, their significance for GPA pathogenesis remains unclear. Here, we applied single-cell RNA sequencing (scRNA-seq) of peripheral blood mononuclear cells (PBMCs) to capture the transcriptional signatures of T cell subsets associated with active disease in GPA.

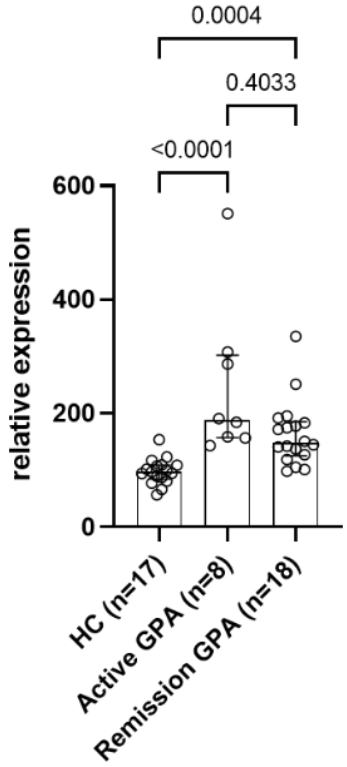
Methods: PBMCs of active GPA patients (n=3) and healthy age-and sex-matched donors (n=3) were subjected to droplet-based scRNA-seq (10x Genomics). Analysis of scRNA-seq data was performed using BioTuring Browser (https://bioturing.com/bbrowser) and Seurat package. Validation of differentially expressed genes was subsequently performed by quantitative PCR (qPCR) on bulk flow-sorted naïve CD4+ T cells (CD4+Tnaive), CD4+ effector memory T cells (CD4+TEM), and CD4+ regulatory T cells (CD4+Tregs) derived from active and remission GPA patients and healthy donors.

Results: Differential expression analysis of scRNA-seq datasets revealed that mRNA expression levels of the serine/threonine kinase; proviral integration site for Moloney murine leukemia virus (PIM1) and its transcription factor STAT3 were upregulated in T cells from active GPA patients including subpopulations of CD4+Tnaive, CD4+TEM, and CD4+Tregs. qPCR analysis of bulk flow-sorted CD4+Tnaive, CD4+TEM, and CD4+Tregs of active GPA patients confirmed elevated expression levels of PIM1 in all subsets compared to those of healthy controls whereas STAT3 expression was significantly upregulated in CD4+Tnaive and CD4+TEM subsets. Interestingly, qPCR analysis of CD4+Tnaive and CD4+TEM from remission patients demonstrated that PIM1 expression was still upregulated suggesting persistent T cell activation (figure 1).

Conclusions: These data indicate that the STAT3/PIM1 signaling pathway is activated in T cells from GPA patients. Interestingly, previous studies have shown that PIM1 mediated phosphorylation of FOXP3 impairs the suppressive capacity of Tregs which may explain the defective Treg function known to exist in GPA patients (1,2). Further functional studies are warranted to determine whether PIM1 inhibition is a rational therapeutic approach in GPA.

Disclosures: None

Figure 1. *PIM1* mRNA expression is upregulated in bulk sorted CD4+T_{EM} in GPA patients with active disease and in remission compared to healthy controls. Kruskal-Wallis test ($p<0.05$).



107. Method Development for the Detection of Proteinase 3-specific B Cells in Granulomatosis with Polyangiitis

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Background: Granulomatosis with polyangiitis (GPA) is a severe, relapsing, autoimmune disease predominantly affecting the small blood vessels of the airways and kidneys. In GPA, an autoimmune response is present against proteinase 3 (PR3), which is a protein primarily located in the granules of neutrophils. Moreover, GPA is considered to be a B cell-mediated autoimmune disease since pathogenic PR3-anti-neutrophil cytoplasmic antibodies are present and B cell depletion therapy is efficacious. Unraveling the biology of PR3-specific B cells is of high interest because this may provide insights into the differentiation and maturation process of PR3-specific B cells, and may aid in the identification of novel therapeutic targets and relapse risk biomarkers. However, sensitive techniques to specifically detect, isolate, and characterize these low-frequency cells are lacking. Therefore, we aimed to develop a flow cytometry-based detection method for the specific identification and isolation of PR3-specific B cells from the peripheral blood of GPA patients.

Methods: Native human PR3 was fluorescently labeled with Alexa Fluor 647 (AF647) or R-Phycoerythrin (PE) and their binding characteristics to anti-human PR3, anti-human elastase,

and anti-human epithelial glycoprotein-2 hybridoma cells were determined by flow cytometry. Freshly isolated or frozen peripheral blood mononuclear cells (PBMCs) from GPA patients in remission (n=5), with active disease (n=1), and healthy donors (n=2) were dual stained with PR3-AF647 and PR3-PE, and the presence of PR3-specific B cells was studied by flow cytometry.

Results: PR3-AF647 and PR3-PE separately bound to anti-human PR3 hybridoma cells specifically. Combining PR3-AF647 and PR3-PE resulted in higher specificity to anti-human PR3 hybridoma cells and lower background staining. PR3-AF647$^+$PR3-PE$^+$ B cells could be detected from the PBMCs of GPA patients and healthy donors and the frequency of PR3-AF647$^+$PR3-PE$^+$ B cells within the total B cell population was higher in GPA patients (mean: 0.58%; 0.02-1.48) compared to healthy donors (mean: 0.12%; 0.04, 0.2,).

Conclusions: These preliminary data suggest that circulating PR3-specific B cells can be detected in GPA patients and healthy donors with a PR3-AF647/PR3-PE dual staining. However, whether the detected B cells can produce PR3-anti-neutrophil cytoplasmic antibodies, thereby confirming the validity of the detection method, needs to be determined.

Disclosures: None

108. CD4+ α3(135-145)-specific T cells in human Goodpasture Disease are enriched for Tscm and Th1 cells

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Background: Goodpasture disease is defined by autoimmunity to the non-collagenous domain of the α3 chain of type IV collagen (α3(IV)NC1). Autoantibodies are readily measurable and central to the diagnostic algorithm. Antigen-specific cellular responses also have an important role in immunopathogenesis, but are difficult to assess in this and in other autoimmune diseases. This study defines the antigen-specific CD4$^+$ T cell population in blood from patients with Goodpasture disease.

Methods: Peripheral blood samples were collected from 14 patients with Goodpasture disease at the time of first presentation, and isolated peripheral blood mononuclear cells (PBMCs) were assessed by flow cytometry. Antigen-specific cells were identified by staining with HLA-DR15 (DRA1*01:01/DRB1*15:01)-α3$_{135\text{-}145}$ tetramers, which identify cells specific to the immunodominant T cell epitope of α3(IV)NC1. CD4$^+$ T cell subpopulations and their chemokine receptor expression profiles were characterised with a surface stain panel comprising CD3,

CD4, CD8, CD25, CD127, CD45RA, CCR7, CD95, CXCR3, CCR6, CCR4 and CXCR5. Nonparametric continuous paired variables were analysed by Wilcoxon signed rank test.

Results: $\alpha3_{135\text{-}145}$ specific cells were enriched in memory stem ($CD45RA^+CCR7^+CD95^+$) T cells (Tscm) compared with the overall $CD4^+$ T cell pool (median % of conventional T cells 16.66% vs 5.32%, p=0.03), and comprised fewer naïve-like $CD45RA^+CCR7^+CD95^-$ cells (33.64% vs 50.24%, p=0.0001). A minority of $\alpha3_{135\text{-}145}$-specific $CD4^+$ cells were $CD127^{lo}CD25^{hi}$ regulatory T cells (median 4.35%). A Th2 ($CXCR3^-CCR6^-CCR4^+$) chemokine receptor expression profile was prominent across total and antigen-specific $CD4^+$ T cells. However, the $\alpha3_{135\text{-}145}$-specific population showed a significant skew towards T cells with effector function, specifically Th1 ($CXCR3^+CCR6^-$) polarisation (median % of antigen-experienced T cells 8.52% vs 2.74%, p=0.04), with a trend towards more Th17 ($CXCR3^-CCR6^+$) (9.55% vs 2.71%, p=0.07) and Th1/Th17 ($CXCR3^+CCR6^+$) (3.44% vs 0.15%, p=0.06) polarisation.

Conclusions: Examination of the circulating $CD4^+$ $\alpha3_{135\text{-}145}$-specific T cell population implies a role for T cell-mediated autoimmunity in patients with Goodpasture disease, including long-lived Tscm cells (as described in rheumatoid arthritis and type 1 diabetes). Chemokine receptor expression profiles suggest that, in addition to Th2-mediated antibody responses, Th1- and potentially Th1/Th17 and Th17-polarised T cells are enriched in assessing antigen-specific T cell responses.

Disclosures: None

109. Study of pathogenic T-helper cell subsets in Asian Indian patients with Takayasu arteritis

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Background: Relapses and refractory disease are a challenge in management of patients with Takayasu arteritis (TAK). In the present study, we quantified pathogenic CD4+memory T-helper cells bearing surface markers CD161 and/or p-glycoprotein (MDR1) in patients with TAK.

Methods: Peripheral blood mononuclear cells of 21 patients with TAK and 16 age-matched controls were stained with anti-CD3, anti-CD4, anti-CD45RA-, anti-CD161 and anti-p-glycoprotein antibodies and subjected to flow cytometry by FACS ARIAIII. Follow up sample was immunophenotyped for 18 patients. Intracellular staining for interleukin-17 and *interferon-*Ɣ was performed for 18 patients at 2 visits and 11 controls. The clinical details of patients were

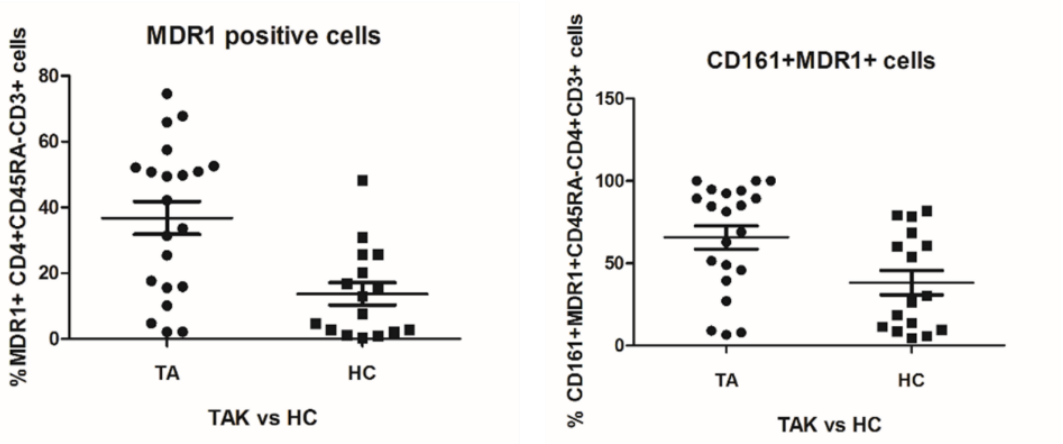
recorded prospectively. Surgical arterial biopsies of 6 TAK patients and 5 non-inflammatory controls were subjected to immunohistochemistry with anti-CD161 and anti-p-glycoprotein.

Results: Among memory CD4+ T cell pool, frequency of MDR1+ and CD161+MDR1 cells was significantly higher in TAK than in controls at baseline visit (p=0.002 and 0.01 respectively). After stimulation, frequency of CD161+cells with intracellular IFN-Ɣ expression was higher in TAK than controls (p=0.028). Modal fluorescence intensity of CD161+MDR1+ CD45RA-CD4+ cells normalized to the MFI value of MDR1+CD161-CD45RA-CD4+ subset was higher in patients with active disease as compared with stable disease (p=0.041). Among 6 surgical biopsies from patients with TAK, 4 and 5 stained positive for CD161 and MDR1 respectively. Only one of the 5 control biopsy stained positive for CD161 and MDR1. On serial sampling, frequency of MDR1+ and CD161+MDR1+ memory CD4+ cells decreased significantly in only patients who had complete/partial response to treatment at 6 months (p=0.047 and 0.02 respectively).

Conclusion: MDR1+ and MDR1+CD161+CD4+ memory T-helper cells are increased in patients with TAK. Decrease in frequency of these cells is associated with response to treatment during subsequent follow up.

Disclosures: None. This study is funded by CMC, Intramural and Indian Rheumatology Association research grant to Ruchika Goel.

Figure 1. Frequency of MDR1+ and CD161+MDR1+ T helper cells in TAK patients and healthy controls (HC)



110. Neutralizing the IL-7Ra (CD127) limits injury in experimental anti-MPO glomerulonephritis

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Background: Human data suggests that signaling through the IL-7Rα (CD127) may be important in ANCA-associated glomerulonephritis. These studies use a model of glomerulonephritis mediated by anti-MPO cellular autoimmunity to examine the presence and the phenotype of IL-7Rα$^+$ (CD127$^+$) and IL-7Rα$^-$ T cells in the kidney and the function of IL-7Rα in murine cell mediated anti-MPO glomerulonephritis (GN).

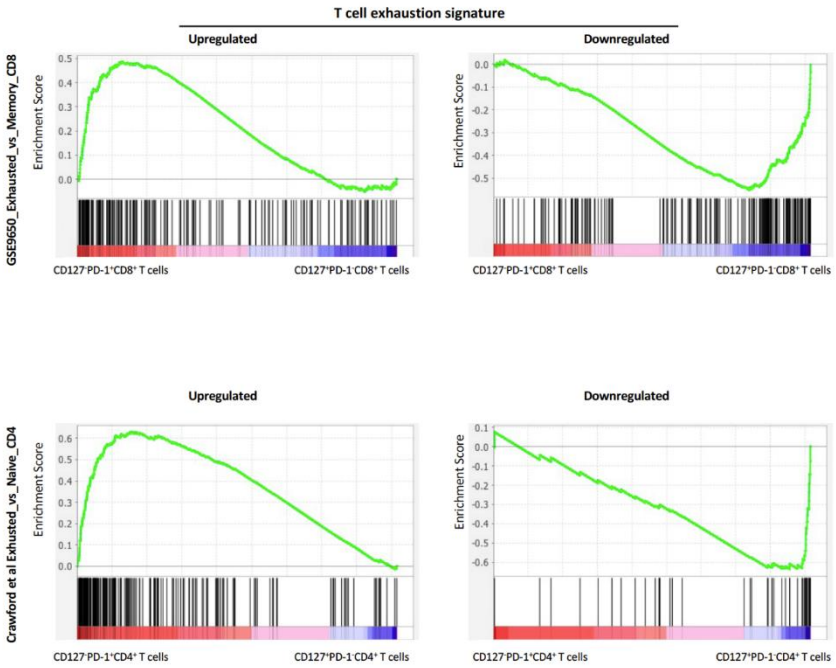
Methods: Experimental anti-MPO glomerulonephritis was induced by immunizing mice with 20ug rMPO in FCA day 0 and 20ug rMPO in FIA on day 7. On day 17, low dose sheep anti-mouse anti-basement membrane (BM) globulin was administered to transiently recruit neutrophils to glomeruli, lodging MPO there and allowing T cell recognition of MPO as the autoantigen. Experiments ended on day 21. Leukocyte accumulation was examined by flow cytometry and immunostaining, injury by histology and albuminuria. CD127$^+$PD-1$^-$ and CD127$^-$PD-1$^+$ CD4$^+$ and CD8$^+$ T cells from kidneys of mice with anti-MPO GN were isolated by FACS, total RNA was extracted from each cell population and whole transcriptomic profiling was performed using next-generation sequencing (Illumina NextSeq550). Differentially expressed genes were identified by linear modelling and an empirical Bayes method (Degust webtool, Victorian Bioinformatics Consortium) with an Fthreshold of 0.05 as indicated to determine significance. Gene set enrichment analysis (GSEA, Broad Institute) was performed to assess whether specific biological pathways or signatures were significantly enriched between different cell populations. The IL-7Rα was neutralized by administering non-depleting anti-IL-7Rα antibodies (0.5mg, alternate days).

Results: Control ovalbumin-immunized mice given anti-BM globulin developed minimal renal injury, while MPO-immunised mice given anti-BM globulin developed albuminuria, with focal and segmental glomerular lesions. Numbers of intrarenal CD4+ and CD8+ T cells that were either CD127$^+$ or CD127$^-$PD-1$^+$ were increased in mice with anti-MPO GN compared with control OVA immunized mice receiving anti-BM globulin. Proportions of these cells within their respective CD4$^+$ or CD8$^+$ subset remained similar. In mice with anti-MPO GN, there were 2,541 and 1,664 genes differentially expressed between intrarenal CD127$^-$PD-1$^+$ and intrarenal CD127$^+$PD-1$^-$ CD8$^+$ and CD4$^+$ T cells respectively, including *Il7r* and *Pdcd1* (PD-1). There was a substantial overlap of the differentially expressed genes between CD8$^+$ and CD4$^+$ T cells. Both the CD127$^-$PD-1$^+$ CD8$^+$ and CD4$^+$ T cells were enriched for previously described T cell exhaustion signatures (Figure 1), which predict prognosis in autoimmune disease and viral infection. As CD127$^-$ (IL-7Rα$^-$) cells are not likely to be major contributors to injury, the IL-7Rα (CD127) was neutralised in the effector phase of disease after the induction of anti-MPO autoimmunity (commencing day 16). Compared to control IgG, anti-IL-7Rα antibodies limited glomerular and interstitial injury, reduced albuminuria and reduced the numbers of glomerular and interstitial CD4+ and CD8+ T cells, and macrophages. This was associated with reduced intrarenal chemokine and cytokine expression (*Cxcl10*, *Ccl20* and *Ccl2*, *Il6* and *Tnf*).

Conclusions: Both activated and exhausted CD4+ and CD8+ cells are present within kidneys in murine anti-MPO GN. In this model, neutralising activated T cells via the IL-7Rα (CD127) limits intrarenal inflammation and disease.

Disclosures: None.

Figure 1: Gene set enrichment analysis in sorted intrarenal T cells from mice with anti-MPO GN.



111. Target-to-B! Prospective immunophenotyping in ANCA vasculitis PROMAVAS study design and interim analysis on clinical outcome

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Background: ANCA-associated vasculitis (AAV) is an autoimmune disease characterized by antibodies against myeloperoxidase (MPO) and proteinase-3 (PR3) in most patients. The resulting inflammatory response in the small to medium sized blood vessels can lead to organ damage and subsequently to potential life-threatening disease. Cyclophosphamide (CYC) and rituximab (RTX) are potent drugs for the induction of remission, but relapse rates remain high. The identification and prediction of patients at risk, on the other hand, is very difficult in daily practice. As a part of the Target-to-B consortium, a Dutch national project supporting overarching research in the field of B-cell mediated diseases, we set up a prospective cohort of AAV patients. The main objective for this study is to monitor the immune phenotype over time,

before and after start of immunosuppressive therapy, and to integrate and correlate these findings with clinical outcome data.

Methods: Patients with a major disease presentation of AAV requiring remission-induction therapy, who are either newly diagnosed or have relapsing disease, are included in the Prospective Maastricht ANCA Vasculitis (PROMAVAS) study. Clinical and routine laboratory parameters, as well as research specimen are collected before and 6 weeks, 3 months, 6 months, and 1 year after therapy. After this, sampling takes place on a yearly basis. Laboratory parameters include renal function, CRP, MPO- or PR3-ANCA and immunoglobulin levels, B- and T-cell subsets, urine spot analysis, and in addition we collect serum, plasma, DNA, RNA, PBMC, urine and, when applicable, tissue samples. Clinical data include organ involvement, therapy, previous disease presentations, and disease duration at baseline and relapse rate, infections, renal function, malignancy, and mortality during follow-up.

Results: Since 2019, we have screened 101 patients and included 85 patients. Currently, 56 patients are followed for at least one year, with a median follow-up of 22 months (IQR 16-26). An interim analysis on clinical data in this group of patients has been performed. Of these patients, 27 (48.2%) presented with MPO-ANCA positivity, 28 (50.0%) with PR3-ANCA positivity, and 1 (1.8%) with both. Thirty-eight (67.9%) of the patients had biopsy proven renal involvement, with a baseline median serum creatinine level of 236 µmol/L (IQR 149-307). Baseline characteristics of the total cohort and the patients followed for at least 1 year are depicted in Table 1. In addition to corticosteroids in all patients, 30 (53.6%) patients were treated with RTX (2 x 1000mg) and 5 (8.9%) with a combination of RTX (2 x 1000mg) and CYC IV (2 x 15mg/kg), both followed by RTX maintenance depending on ANCA levels, B cell counts, and clinical symptoSixteen (28,6%) patients were treated with oral CYC for 3-6 months, followed by azathioprine for 2 years. Five patients received a different remission-induction regimen. During follow-up, 6 patients died after a median of 6 months (IQR 1-9), of which 2 died due to a SARS-CoV-2 infection. Twelve patients had a major relapse after a median of 15 months (IQR 12-19). The majority of the patients with disease relapse had renal involvement (73%), was treated with RTX without additional CYC (73%), and had PR3-ANCA positivity (82%).

Conclusion: With this ongoing prospective study we were able to set up a large, unique, and well-described cohort of AAV patients that is linked to an extensive biobank. We are planning to perform experiments in cooperation with the consortium on deep immune cell phenotyping in the nearby future. The insights that will be gained will help to better identify active disease, evaluate treatment effects, and predict future relapses.

Disclosures: None

Table 1. Baseline characteristics of the total AAV cohort and the patients followed for at least 1 year.

	Total cohort, N = 85	>1 year follow-up, N = 56

Age in years, median (IQR)	66 (57-74)	66 (55-74)
Male, n(%)	53 (62.4)	37 (66.1)
ANCA type, n(%) MPO PR-3 Double positive	 39 (45.9) 44 (51.8) 2 (2.4)	 27 (48.2) 28 (50.0) 1 (1.8)
Diagnosis, n(%) MPA GPA	 25 (29.4) 60 (70.6)	 16 (28.6) 40 (71.4)
De novo, n(%)	48 (56.5)	27 (48.2)
BVAS, median (IQR)	14 (12-18)	15 (12-18)
Renal involvement, n(%)	54 (63.5)	38 (67.9)

112. Identification of GCA specific T-cell clones

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Background: Arterial wall inflammation in giant cell arteritis (GCA) is characterised by T-cell infiltration and the formation of granulomas with macrophages. A strong MHC II association with GCA suggests that antigen-specific immune processes may play a crucial role in GCA pathogenesis. However, to date there have been limited studies investigating the prevalence of T-cell clones in GCA lesions. Here we present an analysis on T-cell receptor (TCR) repertoires of blood and temporal artery biopsy samples from 26 GCA patients. We aimed to identify disease specific T-cell clones shared by GCA patients. Analysis of TCR sequences is a first step towards identifying a potential auto-antigen.

Methods: We compared the TCR sequences identified through bulk TCR sequencing of blood and biopsy tissue of GCA patients to those found in control groups. Controls were made up of 41 patients with paroxysmal nocturnal haemoglobinuria (PNH), 30 healthy subjects as well as a publicly available additional dataset containing TCR repertoires of 627 healthy individuals.

Results: We identified 49 TCRs that exclusively occur in GCA patients. Each of them was found in the biopsy samples of at least 8 different GCA patients. These T-cells may be involved in the disease processes and were also detected in the blood of the patient as well as the biopsy. The GCA-specific TCRs show preferential use of certain V and J segments, which is in line with the known MHC association of GCA. Clustering of patients based on the TCRs identified in their biopsy samples results in three distinct patient groups that did not correlate with age or sex of the individuals. Further studies are underway to expand this cohort and explore association with GCA clinical phenotype.

Conclusions: These preliminary results suggest that certain TCRs are typical for and specific to GCA patients. Further studies will investigate association with more refractory disease and

persistence following treatment, to determine if they may identify a subgroup of patients who would benefit from T-cell targeted therapies. Further analysis of sequence patterns may ultimately reveal whether these TCRs bind a common autoantigen providing further insights into disease pathogenesis.

Disclosures: AWM reports no conflicts of interest with the content of this manuscript. She has received research grant and educational funding or undertaken consultancy for the following pharmaceutical companies in the last 5 years: AstraZeneca, Kiniska Pharmaceuticals, Regeneron, Roche/Chugai, Sanofi and Vifor.

113. Studies on the mechanism of the dysregulation of t-cell interferon- γ production in ANCA-vasculitis patients

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Background: T cells play an important role in pathogenesis of ANCA vasculitis. Predominant presence of $CD4^+$ T cell subsets and proinflammatory cytokines such as IFN-γ in inflammatory lesions implies that T cells during remission contribute to autoantibody generation and subsequent disseminated vasculitis. Previously, we have shown that B cells are unable to down regulate IFN-γ production by activated $CD3^+$ T-cells from AAV patients during remission, in contrast to healthy control. The aim of this study is to investigate the mechanisfor this dysregulation of IFN-γ production.

Methods: To reveal mechanisfor B-cell inhibition of T-cell IFN-γ production, inhibitors of the following molecules were added to co-cultures of cells from healthy controls (HC): PDL1, CTLA4, IL-10, B- and T- lymphocyte attenuator (BTLA) protein. Sandwich ELISA were used to measure IFN-γ and other cytokines in culture supernatants. Intracellular staining for Foxp3 was used to enumerate Treg cell generation. The effect of recombinant IL-10 on IFN-γ production of isolated T cells was assessed in both HC and AAV patients in remission. This effect was studied in different T cell subsets ($CD3^+$, $CD4^+$, $CD8^+$,$CD45RO^+$, $CD45RO^-$, Th1, Th2, Th17) after sorting by FACS.

Results: The inhibition of IFN-γ in HC (n=4) was attenuated by blocking PDL1, CTLA4, BTLA or IL-10 on activated $CD3^+$ T cells in co-culture with B cells. However, this attenuation was markedly higher by blocking the IL-10 receptor compared (343 pg/ml), with the other blockers (298 pg/ml, 287 pg/ml, 265 pg/ml, p=0.028, p=0.027, p=0.057 respectively). Addition of recombinant IL-10 to activated $CD3^+$ T-cells increased numbers of Treg cells in both AAV patients (p=0.001, n=10) and HC (p=0.004, n=4), but supressed IFN-γ secretion only in HC; activated T-cells alone vs activated T cell + recombinant IL-10 (395 pg/ml vs 297 pg/ml, p=0.013), not in AAV patients; activated T-cells alone vs activated T cell + recombinant IL-10 (322 pg/ml vs 327 pg/ml, p=0.484). Preliminary data from the T-cell subsets indicate that IFN-γ

production is elevated and unresponsive to regulation primarily in the Th1 and Th17 subpopulations in cells from AAV patients (n=3) (regardless of whether they are in remission or active disease).

Conclusions: Suppression of T-cell's IFN-γ production is mainly mediated by IL-10 in HC, but in AAV patients this mechanism seeto be absent. The importance of these preliminary findings is unclear but signalling pathways downstream of IFN-γ are possible to target pharmacologically.

Disclosures: None

114. Effects of tocilizumab on ex-vivo peripheral blood mononuclear cells from patients with GCA

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Background: Giant –cell arteritis (GCA) is a chronic granulomatous vasculitis affecting individuals aged ≥50 years. Glucocorticoids (GCs) are only effective therapy able to induce disease remission but most patients relapse when GC are tapered and suffer from GC-related toxicity. Interleukin-6 (IL-6) is a pleiotropic cytokine that may play a pivotal role in GCA pathogenesis since its transcripts are increased in vascular lesions and elevated serum levels have been reported in active GCA patients. Recently, blocking IL-6 receptor with tocilizumab (TCZ) has demonstrated effectiveness in reducing GCA flares and sparing GC. However, 40% of patients still relapse when GCs are discontinued, indicating heterogeneity in TCZ-response. Therefore, identifying predictors of response to TCZ is crucial. TCZ strongly reduces systemic symptoand acute-phase reactants but little is known about the effects of TCZ on vascular lesions or peripheral blood mononuclear cells (PBMCs). The aim of this study was to investigate transcriptomic changes induced by IL-6 and TCZ+IL6 on *ex-vivo* PBMCs from patients in clinical remission.

Methods: PBMCs were isolated from 17 patients in remission and 5 age and sex – matched controls using Lymphoprep™ density gradient. Fourteen patients were receiving prednisone (<5mg/day) and 4 patients were in sustained remission without prednisone. PBMCs were exposed to recombinant human (rh) IL-6 (IL6 group) (20 ng/ml) and combination of rhIL-6 and TCZ (20 µg/ml) (TCZ+IL6 group) and cultured for 24h. Total RNA was extracted from cells using TRIzol™ reagent. RNA (100ng/sample) was processed using nCounter Prep Station screening for 256 genes from Human Inflammation Nanostring panel. Barcode counts were processed with nSolver 4.0 Software. Normalized data were analysed using R Studio 4.0.3 and paired or unpaired Wilcoxon tests were applied.

Results: Total count of PBMCs was significantly lower in GCA compared to controls (1.26±0.43, 2.53±0.2 cell/ml, respectively; p<0.0001). At transcriptomic level, 64 transcripts were differentially expressed between controls and patients, even considered in clinical remission; 5 transcripts were increased and 59 were decreased in GCA. After stimulation with IL-6, 12 transcripts were increased and 34 decreased respect to baseline condition. A total of 113 transcripts were differentially expressed between IL-6 group and TCZ+IL6 group. After correction for multiple comparisons, 73 transcripts remained significant (FDR<0.05), of which 63 transcripts were increased with TCZ exposure. However, 8 transcripts that were increased with IL-6 stimulation, decreased their expression after exposure to TCZ: STAT3, HIF1A, CCL2, CCR1, BCL6, MYC, TLR2 and C3AR1; all of them being target genes of STAT3.

Conclusions: Patients with GCA in clinical remission still have transcriptomic differences with healthy controls. Tocilizumab reduces expression of STAT3 and 7 other transcripts downstream from STAT3, important for differentiation of naïve T helper cells to follicular T helper cells (BCL6), cell growth/apoptosis (MYC), monocyte trafficking and activation (CCL2, CR1), activation of IL-6 (TLR2) and hypoxia (HIF1A). Validation is in process. Studies in active, treatment-naïve patients are ongoing.

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115. Circulatory peripheral T helper (PTH) cells in PR3 ANCA associated vasculitis (PR3 AAV)

Seerapani Gopaluni[1], David Jayne[1]
[1]*University of Cambirdge, Cambridge, UK*

Background: Evidence from different strands supports the importance of CD4 T cells in disease pathogenesis and in the persistence or relapse of disease activity in ANCA associated vasculitis (AAV). A subset of T helper cells expressing PD1 but not CXCR5 (referred to as peripheral T helper (PTH) cells) were shown to help B cell survival and proliferation at sites of inflammation in rheumatoid arthritis and lupus. This study was aimed at understanding the relevance of these cells in PR3-ANCA positive AAV (PR3 AAV).

Methods: Blood samples from 21 patients with active PR3 AAV, 51 PR3 AAV patients in remission, 20 age-matched disease controls (giant cell arteritis, SLE, IgA Vasculitis) and 37 healthy volunteers (HV) were obtained, along with paired urine samples from 28 of the PR3 AAV patients. Lymphocytes were extracted from the samples for flowcytometric and functional analyses. Kidney biopsy samples from patients with active nephritis were stained for the presence of PTH cells.

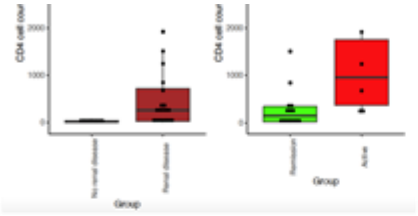
Results: PR3 AAV patients, either in remission or with active disease had a higher proportion of circulatory PTH (cPTH) cells compared to HVs and disease controls. Further, the ratio between cPTH and circulatory TFH (cTFH) cells was also higher in PR3 AAV patients compared to both HVs and disease controls, suggesting a skewing of CD4 T cells towards a cPTH phenotype. The proportion of cPTH cells was higher in PR3-AAV patients with elevated inflammatory markers, CRP ($p=0.034$) and ESR ($p=0.03$). In a subset of 15 patients sampled before and 3 months after induction therapy there was a reduction in the proportion of cPTH cells ($p=0.041$) as well as the proportion of activated (HLA-DR+) cPTH cells ($p=0.05$) suggesting a correlation with disease activity. PR3 AAV patients with active renal disease had a higher number of CD4 T cells/dL in urine ($p=0.023$) and a higher proportion these were PTH cells ($p=0.024$) compared to those in remission. Immunofluorescent staining of kidney biopsy samples from PR3 AAV patients with nephritis revealed the presence of CD4 T cells expressing PD1 infiltrating the tubules of kidney tissue.

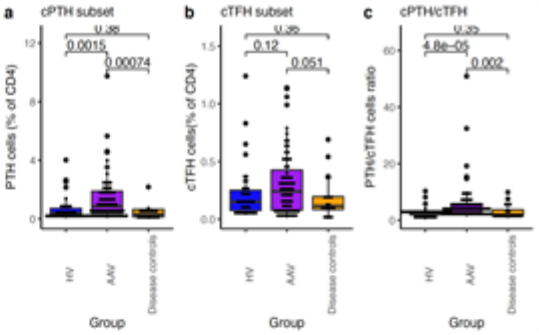
Conclusions: In the current study, CD4 T cells were present in the urine of PR3-AAV nephritic patients and were reduced or disappeared as remission was achieved, and 25% of urinary CD4 T helper cells were of a PTH phenotype, expressing PD1+ but not CXCR5. As histological studies also found CD4+PD1+ cells infiltrating the tubules and interstitium of the kidney these observations are consistent with a nephritogenic role for this subset. cPTH cells were expanded in the peripheral circulation of patients with PR3-AAV irrespective of their disease status when compared to age-matched HVs and disease controls reflecting the persistence of T cell dysregulation despite apparent control. In paired samples, the frequencies of cPTH cells and activated cPTH within the CD4 compartment fell with treatment, suggesting an association with disease activity. cPTH cells were also higher in patients with increased inflammatory markers.

Disclosures: The authors have no financial disclosures relevant to the submitted work.

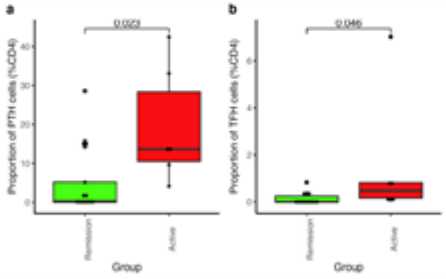
Figure 1.

CD4 T cells/dL of urine in a) PR3 AAV patients with or without renal disease b) patients with or without active renal involvement

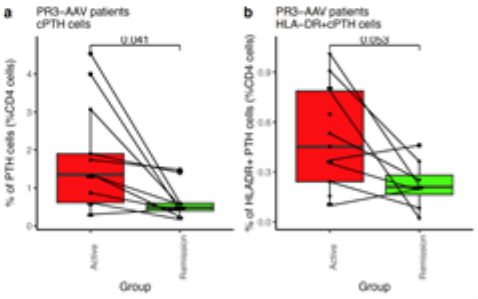




cPTH cells are higher in proportion in PR3-AAV patients compared to HVs or disease controls. Comparison of all PR3-AAV patients (both in remission and with active disease) with other controls. Plot a) PR3-AAV patients have more cPTH cells compared to other



Urinary CD4 T cells have a higher proportion of uPTH cells and very few uTFH cells. uPTH cells are higher in proportions in patients with active nephritis compared to patients in remission. Plot depicting the distribution of a) uPTH cells b) uTFH cells in patients with active nephritis and in remission.



The proportion of a) cPTH cells and b) activated cPTH (HLA-DR+) cells reduced with induction treatment (paired samples obtained 3 months after treatment).

116 Peripheral T helper cell gene signature in patients with PR3 ANCA associated vasculitis

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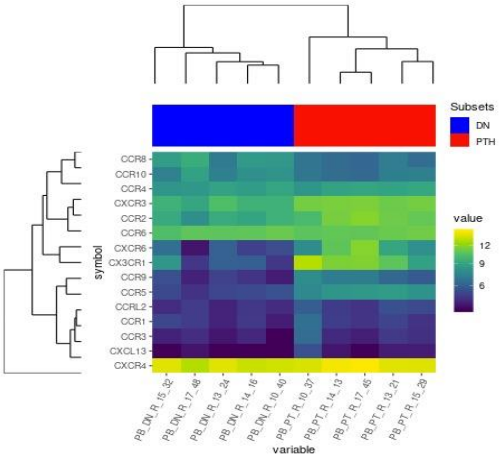
Background: A subset of T cells with the phenotype CD4+PD1+CXCR5- (called peripheral T helper cells (PTH)) were shown to infiltrate renal tubules and in the urine of PR3 ANCA associated vasculitis (PR3 AAV) patients with active nephritis. Circulating PTH cells (cPTH) were shown to correlate with disease activity and PR3 AAV patients had higher proportion of these cells compared to age matched healthy volunteers and disease controls. This study evaluated the nature of these cells by studying the transcriptome of flow sorted cPTH, circulating TFH (cTFH) (CXCR5+PD1+) and double negative (cDN) CD4 T cells in greater detail. The gene signature of cPTH cells was validated by studying candidate genes expressed by urinary lymphocytes obtained from AAV patients with nephritis.

Methods: Peripheral blood mononuclear cells (PBMC) from 5 independent PR3 AAV patients in remission were flow sorted to obtain cPTH, cTFH and cDN samples. At least 1000 – 10,000 cells were sorted from PBMCs and subjected to RNA sequencing (SMART-Seq v4 Ultra low input RNA kit for sequencing). In a parallel and independent experiment, urine samples from patients with active nephritis were tested for the expression of a set of genes (TGFB1, PRF1, VIM, FOXP3, CD25, CCL5 (RANTES), GZMB, CD3, TBX21, CD20, CCL2, CXCR3, CDH1 (E-cadherin), NKCC2, VEGFA, CD46).

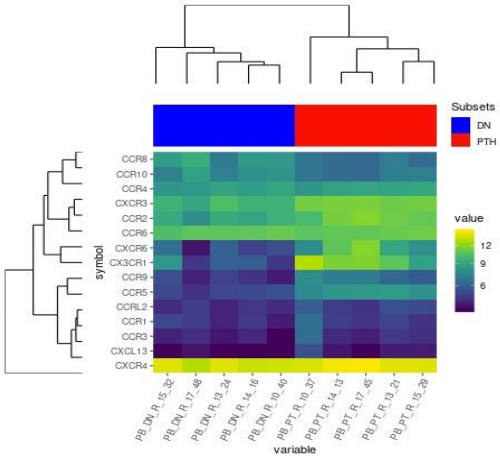
Results: Differential gene expression analysis between cPTH and cDN cells resulted in 832 upregulated and 702 down-regulated genes. The cPTH cell transcriptome, when compared to cDN T cells, was enriched for cytotoxic genes such as Granzyme A (GZMA), Granzyme B (GZMB), Granzyme K (GZMA), Perforin-1 (PRF1), C-C Motif Chemokine Ligand 5 (CCL5), Natural Killer Cell Granule Protein 7 (NKG7) and genes implicated in cell proliferation such as RRM2, DLGAP5, CDC20, TOP2A, BIRC5. Further, these cells were also enriched for chemokine receptor genes, such as CX3CR1, CCR2, CCR5, CXCR3 that aid the trafficking of these cells to sites of inflammation. Similarly, cPTH cells differentially expressed cytotoxic and chemokine receptors when compared to cTFH cells. mRNA expression of urinary lymphocytes from an independent cohort of patients with and without active nephritis revealed differential expression of similar cytotoxic genes (GZMB, PRF1, CCL5, VIM). Genes that aid B cell differentiation such as CXCL13, IL-21 were not enriched in cPTH cells.

Conclusions: Transcriptomic analysis of flow-sorted cPTH cells from patients suggested, these cells to be proliferating activated CD4 T cells when compared to cTFH or cDN cells. This supports the hypothesis that cPTH cells could be pathogenic effector cells. Surprisingly, they were enriched for cytotoxic genes (GZMH, GZMK, PRF1, NKG7, CCL5, GNLY, SLAMF7, CD160) and chemokine receptors (CCR2, CCR9, CCR5, CX3CR1, CXCR3, CXCR6) that may aid their migration to sites of inflammation and partake directly in tissue inflammation and damage. Genes that help B cell differentiation were not enriched in cPTH cells. All the samples for the transcriptomic study were from patients in remission and this signal could be specific to patients with active disease or to the cells exclusively found at the sites of inflammation.

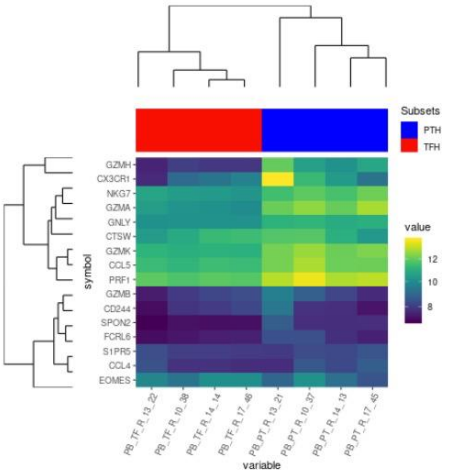
Disclosures: The authors have no financial disclosures relevant to the submitted work



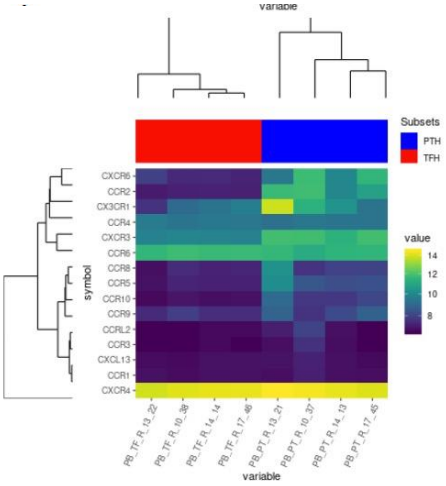
Heatmap showing that cPTH cells, when compared to cDN cells, were enriched for cytotoxic genes such as GZMA, GZMB, PRF1, CCL5, NKG7



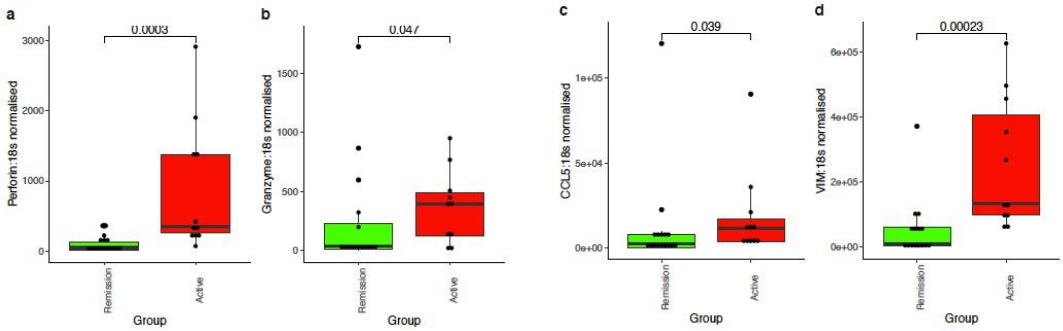
Heatmap showing that cPTH cells are enriched for chemotactic genes such as CX3CR1, CCR2, CCR5, CXCR3. These receptors may aid the migration of cPTH cells to sites of inflammation.



Heatmap showing that cPTH cells were enriched for cytotoxic genes compared to cTFH



Heatmap showing that cPTH cells upregulate chemokine receptors when compared to cTFH cells



Plot showing the results of urinary lymphocyte mRNA analysis from samples obtained before and 6 months after induction therapy in AAV patients with renal involvement. This shows that active nephritis in comparison to remission is associated with higher expression of cytotoxic genes such as a) PR1F515b) GZMB and c) CCL5 as well as d) VIM.

117. Peripheral T helper like cells in secondary lymphoid organs in PR3 ANCA associated vasculitis

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[1]University of Cambirdge, Cambridge, UK, [2]Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

Background: Only 2% of the lymphocytes circulate in the blood stream whilst 40% reside in lymph nodes. We have shown that a specific CD4 T cell subset expressing PD1+CXCR5- (referred to as circulatory PTH cells), was hyper-expanded in the peripheral blood of patients. This subset was cytotoxic in nature and was identified in the inflamed kidney tissue and urine of patients with active nephritis. Using single cell transcriptomic analysis, the cytotoxic gene signature predominantly came from a CD28low cluster that had higher expression of cytotoxic, activation and chemokine gene sets. cPTH cells were clonally expanded and had features consistent with persistent antigenic stimulation, a core feature of chronic auto-immune and inflammatory conditions. In this study, the presence of phenotypically similar cells within secondary lymphoid organs (SLOs), their transcriptomic profile and clonal relationship in comparison to cPTH cells was investigated.

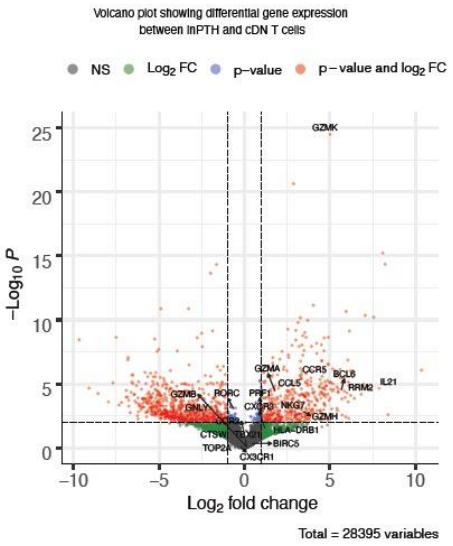
Methods: The most easily accessible lymph node (LN) in the inguinal region was selected by ultrasound and samples obtained by core needle biopsy and/or fine needle aspiration under local anaesthesia. Paired blood samples were obtained for PBMC extraction. Lymph node biopsy samples were mashed and run through a 70um strainer and made into single cell suspension. Samples from lymph nodes (prefixed with “ln”) and PBMC (prefixed with “c”) were stained with fluorochromes for phenotyping. PTH, T follicular helper cells (TFH), CXCR5+PD1- and double negative (DN) subsets from LN and PBMC were flow sorted from samples that had at least 400 cells of each subset and were subjected to RNA sequencing (SMART-Seq v4 Ultra low input RNA kit for sequencing).

Results: In 17 subjects, paired pre and post-induction therapy lymph node and peripheral blood samples were available. Another 11 subjects provided samples either at the time of active disease (n=7) or when in remission (n=4). In total, 45 procedures were performed, and 42 samples were obtained. 20 samples were obtained from patients in remission and 22 samples were obtained from patients with active disease. Procedure was well tolerated with no complications other than minor bruising. Cell yield was highly variable and usually low (median of 2102 (range: 21 to 65000)). LNPTH cells (PD1+CXCR5-), were identified in LN lymphocytes in similar proportions to that observed in the peripheral blood. The proportion of lnPTH cells was higher than conventional lymph node T follicular helper (lnTFH) cells (0.93 vs 0.19, $p < 0.001$). Transcriptomic data from the 4 subsets from 5 AAV patients (in remission) was available for analysis. Differential gene expression analysis of lnPTH cells against cDN cells revealed enrichment for cytotoxic genes (GZMK, GZMA, NKG7, CCL5, PRF1) and chemokine receptor genes (CCR5, CXCR3 and CXCR6) but not CCR2 or CX3CR1 unlike cPTH cells. CRTAM, a precursor gene of cytotoxic effector cells, was also upregulated in lnPTH cells, possibly indicating that the circulating cytotoxic CD4 T cells develop within the SLOs and

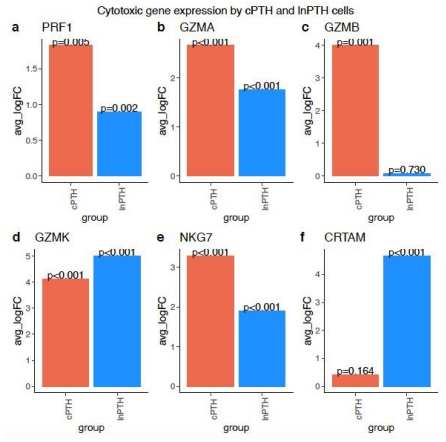
lnPTH cells could be their precursors. In TCR clonality analysis, the overlap coefficient between cPTH and lnPTH cells was highest in comparison to other subsets. Similarly, cTFH cells have higher overlap coefficients with lnTFH cells. This data suggests that the cPTH cells and lnPTH cells may have a common precursor or that lnPTH cells could be the precursors of cPTH cells.

Conclusions: The safety and tolerability of percutaneous lymph node biopsy as research tool was demonstrated. Cell yield, though poor, was adequate to perform transcriptomic analysis. Cells that were phenotypically similar to cPTH cells were present within the lymph nodes in similar proportions to peripheral blood. Transcriptomic analysis showed that lnPTH cells share cytotoxic gene signatures with cPTH cells. TCR clonality analysis demonstrated evidence for clonal relationship amongst cPTH, lnPTH and lnTFH cells.

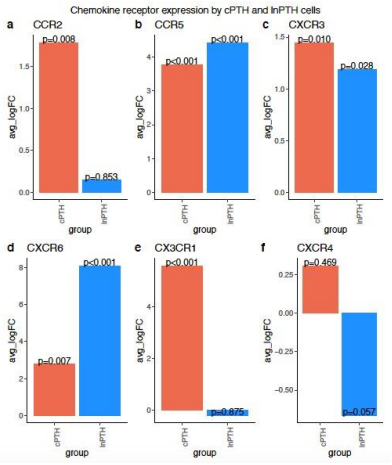
Disclosures: The authors have no financial disclosures relevant to the submitted work



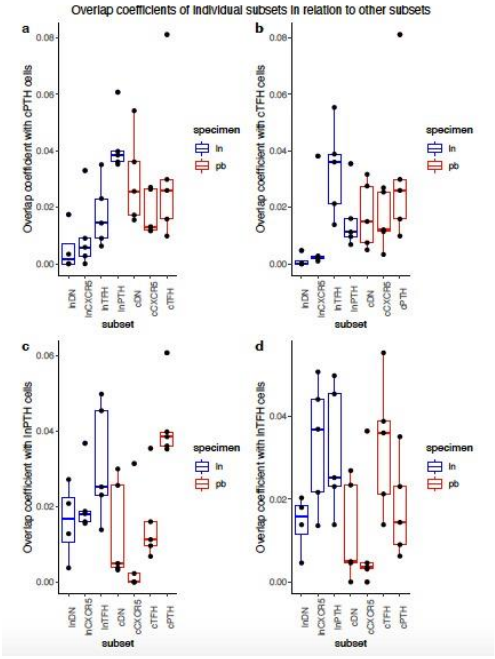
Volcano plot showing selected relevant genes differentially expressed between lnPTH cells and cDN CD4 T cells (reference group - left side of the plot). Genes enriched by cPTH cells were identified in this plot to show the similarities between cPTH and lnPTH cells. Further, BCL6, IL21 were also upregulated suggesting similarities with lnTFH cells



Plots showing relative expression of cytotoxic genes by cPTH and lnPTH in comparison to cDN cells. They have a similar expression for most of the cytotoxic genes except for GZMB, which was exclusively expressed by cPTH cells. lnPTH cells express CRTAM, a gene known to be expressed by cytotoxic precursor cells.



Plots showing the relative expression of chemokine receptors by lnPTH and cPTH cells in comparison to cDN cells. cPTH cells have a higher expression of CCR2 and CX3CR1 which were not expressed by lnPTH cells. Expression of CCR5, CXCR3 and CXCR6 was similar between the two subsets.



TCR clonal overlap coefficient plots. Within each plot, the overlap coefficient of a subset in relation to other subsets is shown a) Highest overlap coefficient of cPTH cells is with lnPTH cells; b) highest overlap coefficient of cTFH cells is with lnTFH cells; c) lnPTH cells share clones mostly with cPTH and lnTFH cells; d) lnTFH cells shares most clones with lnPTH and cTFH cells.

118. Changes in the frequency of T-regulatory cell subsets can distinguish disease activity in ANCA vasculitis

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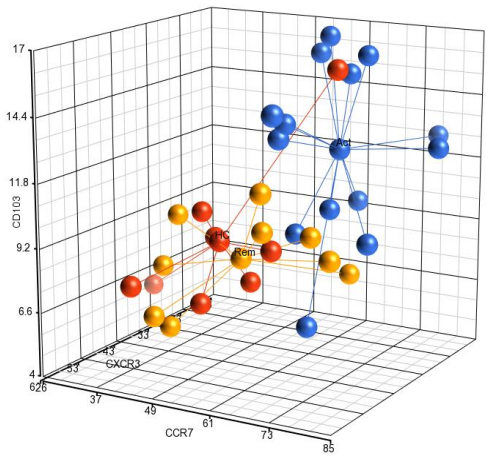
Background: Anti-neutrophil cytoplasmic autoantibody (ANCA) vasculitis is characterized by cycles of remitting and relapsing stages. Previous data demonstrate that T-regulatory cells (Tregs) are defective in ANCA vasculitis and that the expression of a FoxP3 variant lacking exon 2 in CD4+ T cells (FoxP3Δ2) is negatively correlated with suppressive capacity. Furthermore, the major grade of Treg dysfunctionality is exhibited during active disease suggesting that Treg biology could be exploited as a biomarker of disease activity and as a therapeutic target in ANCA vasculitis. Previous studies regarding Tregs in ANCA vasculitis examined bulk Tregs. However, with the recent advances in Treg biology, it is evident that Tregs are a heterogeneous group of immunoregulatory cells. Changes in the phenotype, frequency, and suppressive capacity of Treg subsets have been identified in other autoimmune diseases. However, in ANCA vasculitis, Treg heterogeneity and its implications in disease prognosis and treatment remain unexplored. We hypothesized that changes in the frequency of Treg subsets will distinguish disease activity in ANCA vasculitis.

Methods: Patients with ANCA vasculitis and healthy controls were enrolled according to approved study guidelines Institutional Review Board (IRB study 97-0523). Active disease and remission were defined as a BVAS ≥ 3 or BVAS of 0 and with or without clinical and/or laboratory evidence of disease within 3 months of the sample, respectively. Blood samples from study participants were collected to measure the frequency of Treg subsets using Mass Cytometry, and data were analyzed using Cytobank. Non-parametric Mann-Whitney test was used to assess the significance of the changes in the frequency of Treg subsets. Non-parametric discriminant analysis using Normal Kernel Density estimation was applied to determine the optimal combination of Treg markers to distinguish disease activity status. A value of p £ 0.05 was considered significant for both statistical methods.
Results: We found that patients in remission have expanded frequency of Tregs regardless of the administration of Rituximab. No association between disease activity and the frequency of FoxP3Δ2 CD4+ T cells were observed in our cohort. Additionally, FoxP3Δ2 CD4+ T cells are $CD127^{high}$ and $CD25^{low}$ suggesting that they are not bonafide Tregs. Interestingly, both CCR7+ and CD103+ Tregs are expanded during active disease. In contrast, CXCR3+ Tregs are decreased during active disease and their frequency was negatively correlated with the BVAS score. We also discovered that CXCR3+ Tregs are preferentially reduced in patients with renal involvement. Furthermore, we demonstrated that a combination of the frequency of CXCR3+, CCR7+, and CD103+ Tregs more accurately distinguishes disease activity than individual markers.

Conclusions: Little is known about what underlies Treg dysfunctionality in ANCA vasculitis. This is the first study to identify changes in specific Treg subsets and their possible implications in disease. Understanding Treg heterogeneity and implications for organ involvements could open an avenue for the development of new therapeutic approaches. Our data demonstrate, that changes in the frequency of CXCR3+, CCR7+, and CD103+ Tregs reflect disease activity. Further studies will examine whether these subsets are the underlying cause of Treg dysfunctionality in ANCA vasculitis. Furthermore, as CXCR3 Tregs have been shown to be protective against autoimmune diseases in murine models, they are poised to become a prime candidate for new therapies tailored to patients with renal ANCA vasculitis.

Disclosures: None.

Figure 1



A combination of the frequency of CXCR3+, CCR7+, and CD103+ Tregs distinguishes active disease in ANCA vasculitis: The frequency of CXCR3+, CCR7+, and CD103+ was measured using Mass cytometry and plotted in a three-dimensional plot. Non-parametric discriminant analysis using Normal Kernel Density estimation was applied to

119. Single-cell transcriptome profiling of rituximab-resistant tissue B cells in ANCA-associated vasculitis

Mark Mcclure[1], Mathew Coates[1], Miss Jacinta Lee[1], Kelvin Tuong[1], John Ferdinand[1], Seerapani Gopaluni[1], Rachel Jones[1], David Jayne[1], Menna Clatworthy
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Background: Failure of rituximab to adequately deplete tissue B cells may contribute to remission failures and high relapse rates seen after a single induction course of rituximab for ANCA-associated vasculitis (AAV). There is very limited information on the impact of rituximab on tissue B cells in AAV.

Methods: We performed flow cytometric assessment (n=7) and transcriptomic profiling (n=2) of blood and nasal tissue lymphocytes before and after rituximab 1g x 2 on a prospective cohort of patients with PR3-AAV. Nb: this is an interim report of early data from an ongoing project.

Results: Flow cytometric and scRNA-seq analysis of sequential nasal mucosal biopsies revealed incomplete depletion of B cells in the tissue after rituximab. Both analytical methods indicated that the residual nasal B cells were predominantly antigen-experienced mature B cells (memory and plasma cells), suggesting that antigen-inexperienced cell types (naïve and transitional) were more susceptible to rituximab-induced depletion in the tissue. This was in contrast to the effect of rituximab on the circulating peripheral B cell pool for which there was near-complete depletion of B cells, by standard FACS, without preferential targeting of specific subtypes. Persistent nasal B cells had expression profiles suggesting the capacity for antigen presentation and production of proinflammatory cytokines. Quantification of predicted cell-cell interactions based on receptor-ligand expression revealed several predicted interactions between B and T cell ligands and receptor gene expression, highlighting a complex interplay of stimulatory and inhibitory signalling pathways within the tissue microenvironment, and also revealing some potential mechanisof rituximab resistance.

Conclusion: Examination of tissue lymphocytes demonstrates a failure of a single course of rituximab (1g x 2) to deplete B cells and a change in the repertoire to a memory phenotype likely to be relevant to early relapse after rituximab.

Disclosures: The authors have no financial disclosures relevant to the submitted work

120. ERAP1 Mediates Immunogenicity in HLA-B51+ Behçet's Disease Pointing to Pathogenic CD8 T Cell Effectors

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Background: HLA-B51 is a definite risk factor for Behçet's disease (BD). A coding variant of ERAP1, Hap10 – with low peptide-trimming activity – vastly potentiates this risk, but is mechanistically unclear. Here, we aimed to test the hypothesis that low or absent ERAP1 activity alters CD8 T cell immunogenicity through changes in the HLA-B51 peptidome and shapes the CD8 T cell immune response in affected subjects.

Methods: We generated HLA-B51^{+}ERAP1 KO LCL clones using CRISPR-Cas9, performed mass spectrometry of the immunoprecipitated MHC-class I peptidome with subsequent computational deconvolution for HLA-B51-binding peptides. We then assessed single cell (ICS), bulk (ELISA) and proliferative (CFSE) CD8 effector (IFNG, granzyme-B, perforin) T cell responses through stimulation of allogeneic donor cells with WT vs KO LCL and determined

ERAP1 haplotypes in 49 untreated Turkish BD subjects with ocular and/ or vascular involvement as well as healthy donors (HD) whose PBMC were profiled using multicolor flow cytometry panels. To assess cellular composition and clonotypes at a disease-relevant effector site, we performed single cell RNA sequencing with TCR analyses of intraocular cells in BD uveitis.

Results: WT and KO peptidomes differed significantly ($p< 0.0005$ Fisher's exact test) with a distinct shift of peptide length frequencies exceeding 9-mer (binding optimum) in the KO vs WT. This held true for computationally deconvoluted HLA-B51 binders. IFNG secretion from CD8 T cells stimulated with KO LCL was significantly different from WT (ICS, $p=0.0006$; ELISA, $p=0.0059$) as were CD8 T cell proliferation and ICS of perforin/ granzyme-B^+ CD8 T cells. Analysis of 133 T, B, NK, and monocyte cell populations revealed a predominance of CD8 T and NKT cell subset in HLA-B51+/Hap10+ BD vs HLA-B51+/Hap10- BD and HD, accounting for 80% of all populations reaching significance ($p< 0.05$, Mann-Whitney). Naive and effector memory CD8 T cell subsets were inversely correlated. Cohen's effect sizes were large (>0.8) or very large (>1.2). CD8 T cells in BD uveitis showed differential subset distribution in between the eye and peripheral blood as well as oligoclonal expansions.

Conclusions: We show that the absence of functional ERAP1 alters human CD8 T cell immunogenicity. This is mediated by an HLA-class I peptidome with a propensity for longer peptides above 9mer and suggests a loss or de-novo presentation of peptide-HLA-B51 complexes to cognate CD8 TCR. The reciprocal changes in antigen-experienced vs naive CD8 T cell subsets in affected subjects point to the biologic significance of HLA-B51/Hap10 in BD. CD8 T cell subset analyses in between peripheral blood and the eye during uveitis point to the non-random localization of CD8 T cells into that compartment. Collectively, our findings suggest that an altered HLA-B51 peptidome modulates the immunogenicity of CD8 effector T cells in ERAP1-Hap10 carriers with BD and underlines their potential importance in BD pathogenesis.

Disclosures: None

Cytokines, Immunomodulators & Cell Biology

121. Chemokine profile in the peripheral blood and vascular tissue of patients with Takayasu arteritis

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Background: Takayasu arteritis (TAK) is characterized by chronic inflammation, and multiple immune cells participate in the development of TAK. The aim of this study is to explore the chemokine spectrum in peripheral blood as well as vascular tissue from patients with TAK, and investigate its potential role in the pathogenesis of TAK.

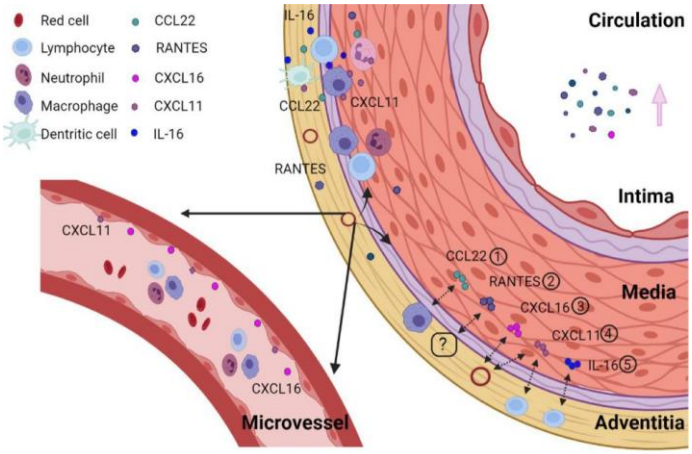
Methods: A total of 58 naive patients with TAK and 53 healthy controls were enrolled in this study from Zhongshan Hospital, Fudan University, Shanghai, China, between January 1st and December 31st, 2020. Among the study participants, 50 patients with TAK and 48 healthy controls were selected for serum examination, while the remaining 8 patients and 5 controls were selected for vascular tissue examination.

Results:
The patients with TAK and healthy controls selected for serum examination were matched for age (TAK: 34.44 ± 13.25 years, Control: 37.85 ± 5.10 years, p = 0.27) and female:male ratio (TAK: 41:9, Control: 36:12, p = 0.40). Among the 50 patients with TAK, 40 (80%) had active disease at the time of enrollment. No significant differences were observed in the clinical characteristics (p > 0.05 for all parameters) of patients (n = 5) selected for chemokine screening and those selected for chemokine validation (n = 45).
The main reasons for surgery were aortic regurgitation (n = 7) and renal artery occlusion (n = 1). Thus, ascending aortic specimens (n = 7) and a renal artery specimen (n = 1) were obtained. In addition, apparently normal specimens (control) of the ascending aorta (n = 3) and abdominal aorta (n = 2) were obtained from donors for heart transplantation (n = 3) and liver transplantation (n = 2). Increased expression of CCL22, RANTES, CXCL16, CXCL11, and IL-16 in the peripheral blood of patients with TAK. Among the 31 chemokines, the average signal of 12 chemokines was over 15% higher in patients with TAK than in the healthy controls: CCL22, RANTES, CXCL16, CXCL11, IL-16, CCL1, XCL1, CX3CL1, CXCL1, CCL17, CCL19, and CCL20. In contrast, the average signal of four chemokines (CXCL10, CXCL7, CCL18, and CXCL4) was 15% lower in patients with TAK than in the healthy controls.
Correlations between the changes in these chemokines were also analyzed, and the results indicated similar trends in the changes in CCL22, CXCL16, and IL-16 levels after treatment.
A proposed model illustrating chemokines discovered in the present study and their potential role in the pathogenesis of TAK was shown in Figure 1.

Conclusions:
CCL22, RANTES, CXCL16, CXCL11, and IL-16 are identified as the major chemokines that may involve in the recruitment of immune cells in the vascular tissue of patients with TAK. Additionally, the persistently high levels of CCL22, CXCL11, and IL-16 observed after treatment might suggest their participation in vascular chronic inflammation or fibrosis and demonstrate the need for developing more efficacious treatment options.

Disclosures: none

Figure 1.



122. Molecular Imaging to Identify Neutrophil Activation in ANCA-Vasulitis

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Background: Anti-neutrophil cytoplasmic antibody (ANCA)-vasculitis (AAV) is a small-vessel vasculitis caused by pathogenic autoantibodies directed against proteinase 3 (PR3) or myeloperoxidase (MPO) (1). Leukotrienes (LT)s are bioactive signaling lipids derived from arachidonic acid (AA) (2, 3) and have been suggested to play a role in inflammatory diseases (4), acting as a signal relay molecule that increases recruitment range and enhances directional migration (5). LTs initiate and amplify innate and adaptive immune responses made by leukocytes and play a central role in their recruitment to inflamed sites (6,7). We have shown that 5-lipoxygenase (5-LO), the 5-lipoxygenase-activating protein (FLAP), and LTC_4 synthase are assembled in novel macromolecular complexes on the nuclear envelope to initiate LT synthesis (8-12). 5-LO is a cytosolic protein that moves to the nuclear envelope in a calcium dependent manner. FLAP is an integral membrane protein that behaves as a scaffold protein to present AA to 5-LO. Mast cells and monocytes generate LTC_4 and LTB_4 while neutrophils only synthesize LTB_4. Chemoattractants recruit neutrophils out of the peripheral circulation to inflamed tissues and interactions between complement, neutrophils and ANCA contribute to the onset and amplification of AAV (13,14). C5a and its receptor, C5aR, play a central role in ANCA-mediated neutrophil recruitment and activation. We showed that priming healthy human neutrophils with granulocyte macrophage-colony stimulating factor (GM-CSF) prior to C5a stimulation produces LTB_4 in a time-dependent manner. Figure 1 illustrates the evolution of the following neutrophil states: 1) resting state, 2) following C5a-priming and antigen translocation to the surface, ANCA and LTB_4 bind 3) activated state and transmigration. Our goal is to leverage a new understanding of lipids and protein-protein interactions using novel molecular imaging techniques to predict disease activity in AAV.

Methods: *Cell Isolation and treatment:* Neutrophils were isolated from peripheral blood of healthy donors and from patients with active AAV. Cells were left untreated or primed with 1 ng/mL GM-CSF for 45 min then treated with 50 nM C5a for 0, 2, 4, 6, 8 and 10 min. *Imaging and analysis:* Following treatment, cells were prepared for direct Stochastic Optical Reconstruction Microscopy (dSTORM) combined with computational analysis (Clus-DoC), Fluorescence Lifetime Imaging Microscopy (FLIM) and Enzyme Immunosorbent Assays (EIA).

Results: EIA data show that LTB_4 production was minimal in cells untreated from a healthy donor (45 pg/ml), however after priming and activation levels increased to 280 pg/ml. Comparatively, LTB_4 levels in untreated neutrophils from a patient with active disease started at 1484 pg/ml and increased to 1980 pg/ml following priming and activation, suggesting that peripheral neutrophils in patients with active AAV are pre-activated and are making LTB_4. STORM illustrates 5-LO and FLAP association on the nuclear envelope of neutrophils from a representative healthy donor only after priming and cell activation. Neutrophils from a representative patient with AAV show 5-LO and FLAP associated in both untreated and primed and activated conditions. FLIM revealed that in neutrophils from healthy donors that were primed with GM-CSF and activated with C5a for 0, 2, 4, 6, 8 and 10 min, the FLIM t_1 values decreased (suggesting a close interaction) at the same time LTB_4 levels increased. In contrast, neutrophils from patients with AAV that were primed with GM-CSF and activated with C5a for 0, 2, 4, 6, 8 and 10 min, the FLIM t_1 values remained constant (suggesting no change) and priming and cell activation did not synthesize LTB_4.

Conclusions: Circulating neutrophils from patients with AAV are pre-activated defined by the interaction of 5-LO:FLAP on the nuclear membrane and subsequent production of LTB_4.

Disclosures: None.

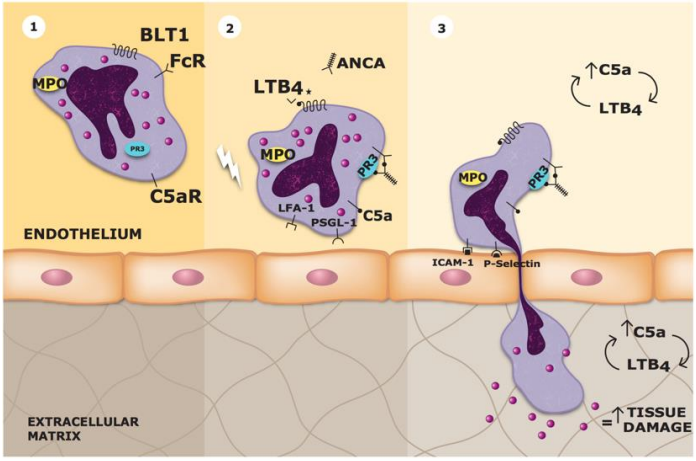

Figure 1. Model of the LTB_4/C5a amplification loop in neutrophil transmigration (created by Schmider).

123. Methionine oxidation compromises protective AAT effects in PR3-ANCA vasculitis

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Background: PR3 is a major autoantigen in ANCA-associated vasculitis (AAV) and a neutrophil serine protease (NSP) inhibited by alpha1-antitrypsin (AAT). Increased PR3 and decreased AAT were suggested as disease mechanisfor PR3- but not MPO-AAV. We systematically assessed PR3 and AAT in AAV patients and healthy controls (HC), characterized mechanistic interactions between PR3 and AAT, and identified disease-related modifiers of this interaction.

Methods: We measured PR3 and AAT in 110 AAV patients and 51 HC and explored correlations with clinical parameters. We produced recombinant wild-type (wt)- and mutant (mu)-AAT to study the interaction of AAT with PR3, including membrane-presented PR3 (mPR3) on the neutrophil surface by FRET assay, flow cytometry, surface plasmon resonance measurements (SPR), and neutrophil superoxide release. Plasma AAT from AAV patients and AAT exposed to ANCA-activated neutrophils were analyzed by quantitative targeted mass spectrometry, namely Parallel Reaction Monitoring (PRM) to detect unmodified and oxidized AAT variants.

Results: We found that the PR3 and AAT pools were increased in both active PR3- and MPO-AAV. The increased PR3 pool correlated with markers of inflammation (CRP), kidney injury (creatinine, erythrocyturia), and autoimmunity (ANCA ELISA), in PR3- but not MPO-AAV patients. In HC, plasma AAT showed an inverse correlation with neutrophil mPR3 that was not observed in AAV patients. Mechanistically, wt-AAT dose-dependently displaced PR3 from the neutrophil membrane by competing with the PR3-presenting CD177 receptor for PR3 binding thereby reducing neutrophil activation by PR3- but not MPO-ANCA. Neutrophil mPR3 depletion was less efficient when using active PR3-AAV patient plasma compared to remission and HC plasma at the same AAT concentration. We identified AAV-related plasma factors that modified mPR3, AAT, and the PR3:AAT interaction. Compared to HC and remission PR3-AAV, plasma AAT from active PR3-AAV patients showed increased methionine (Met) oxidation at Met residues 351 and 358 in the reactive center loop that are critical for the efficient encounter of mature NSPs. This oxidative modification was recapitulated by AAT exposure to ANCA-

activated neutrophils *in vitro*. Oxidized AAT did not interact with PR3 and did not reduce the proteolytic PR3 activity, mPR3 on neutrophils, or neutrophil activation by PR3-ANCA. Conclusions: PR3 and AAT are increased in active PR3- and MPO-AAV patients. The increased PR3 pool correlates with inflammation, kidney injury, and autoimmunity in PR3- but not MPO-AAV patients. AAT controls mPR3 and thereby PR3- but not MPO-ANCA induced neutrophil activation. We identified AAV-related factors that modify mPR3, AAT, and the PR3:AAT interaction.

Disclosures: No disclosures with relevance to this study

124. Investigating the contribution of platelets to inflammation in ANCA Associated Vasculitis.

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Background: The release of Neutrophil Extracellular Traps (NETs) causes endothelial damage in numerous inflammatory pathologies including ANCA associated vasculitis (AAV). The mechanisdriving these cellular processes are yet to be fully characterised. Autoantibodies are likely to make a significant contribution, however, other factors must be considered given that ANCA titre does not correlate well with NET production[1] and an ANCA negative subpopulation comprise up to 10% of cases.[2] Thrombocytosis is well described in acute AAV, and a raised platelet-to-lymphocyte ratio is significantly associated with disease severity.[3] Platelets are implicated neutrophil activation and NETosis in both infective and sterile inflammation including AAV, with TLR 9 and monomeric CRP being pathways of interest.[4,5] Platelets themselves become activated by NETs in the circulation creating a positive feedback loop, propagating the inflammatory state. We have used descriptive methods to examine the inflammatory phenotype of acute AAV and have established an *in vitro* Platelet-Neutrophil co-culture model to characterise platelet-induced NETosis.

Methods: GraphPad PRISM was used to analyse biochemical data related to 103 acute AAV presentations. Tests used included multilinear regression, T-Test and Mann Whitney-U test. Neutrophils and platelets were isolated from whole blood using density gradient and centrifugation techniques. Results were analysed using immunofluorescence and ELISA.

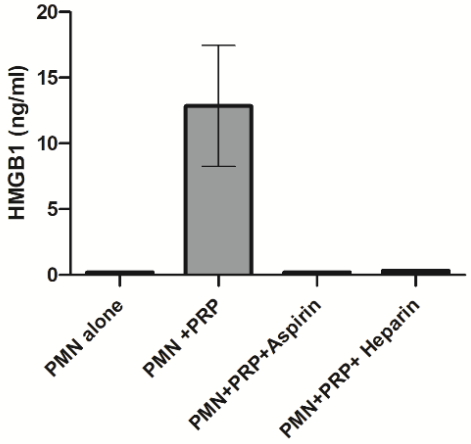
Results: Multilinear regression analysis of biochemical parameters of 103 initial presentations of AAV to our centre identified a significant positive association between platelet count and ESR (p=0.0008). A subgroup of thrombocythaemic patients (platelet count >400 $x10^9$/L) (n=26) had significantly raised ANCA titre (p=0.009), ESR (p=0.0000006), CRP (p=0.000005) and neutrophil count (p=0.000002) when compared to those with normal platelet counts.
In vitro work using platelet-neutrophil co-culture has demonstrated a reduction in supernatant myeloperoxidase (MPO) concentration when inhibitors of platelet activation (Prostaglandin E1 or Apyrase) are added to culture. Additionally, we found reduced supernatant High Mobility Group Box 1(HMGB1) concentration when aspirin or heparin are added to the culture (Figure

1). HMGB1 serum levels have been implicated as biomarkers of AAV disease activity. These readily available therapeutic agents provide an interesting avenue for future investigation in AAV patients, with potential to interrupt the positive inflammatory feedback loop between platelets and neutrophils.

Conclusions: Elevated platelet counts are associated with elevated markers of inflammation and autoimmunity in AAV patients. This positive feedback loop between platelet activation and NETosis may have therapeutic implications for AAV patient management.

Disclosures: None

Figure 1. Supernatant HMGB1 Concentration



Abbreviations (PMN: Polymorphonuclear leucocyte, PRP, platelet rich plasma)

125. Endothelial cell ferroptosis promotes renal damage in ANCA-induced glomerulonephritis

Anthony Rousselle[1], Doerte Lodka[1], Janis Sonnemann[1], Ralph Kettritz[1], Adrian Schreiber[1]
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Background: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are systemic autoimmune diseases characterized by inflammation of small blood vessels and organ damage, including necrotizing and crescentic glomerulonephritis (NCGN). ANCA are circulating immunoglobulin G (IgG) autoantibodies directed against either myeloperoxidase (MPO) or proteinase 3 (PR3), both antigens being expressed by neutrophil granulocytes and monocytes. ANCA bind to these surface antigens and provoke the activation of both myeloid cell subsets. The persistent inflammation leads to endothelial and renal cell necrosis. In contrast to apoptosis, necrosis has long been thought to be an uncontrolled event. However, this dogma has been challenged over the last decade. Ferroptosis is a new type of programmed cell death characterized by the production of ROS- and iron-dependent lipid

peroxidation leading to membrane rupture. The Acyl-CoA Synthetase Long Chain Family Member 4 (ACSL4) enzyme play a crucial role in the generation of lipid peroxides. Ferroptosis has been described to play a role during acute kidney injury. Our work aimed to investigate the contribution of ferroptosis in endothelial cell death during ANCA-associated NCGN.

Methods: To analyse the biological significance of ferroptosis in endothelial cells *in vivo*, we bred $ACSL4^{lox/lox}$ mice with transgenic mice expressing the Cre recombinase under the control of the endothelial Tie2 promoter to obtain $ACSL4^{\Delta EC}$ mice. These mice were further crossed with myeloperoxidase$^{-/-}$ ($MPO^{-/-}$) mice to generate $MPO^{-/-}$ $ACSL4^{\Delta EC}$ chimeric mice. These animals were immunized with murine MPO, irradiated and subsequently transplanted with hematopoietic cells from C/57BL6J (WT) mice. Mice were sacrificed and analysed 6-8 weeks following transplantation. Ferroptosis was investigated *in vitro* using human umbilical vein endothelial cells and ANCA-stimulated neutrophils. Cell death and lipid peroxidation were detected by flow cytometry. Ferrostatin-1 (Fer-1) and siRNA against ACSL4 were used to inhibit ferroptosis.

Results: We found increased lipid peroxidation (4-HNE staining) in kidney section of mice with AAV. $MPO^{-/-}$ $ACSL4^{\Delta EC}$ chimeric mice were protected from the development of renal damage compared to WT chimeric mice suggesting that ferroptosis in endothelial cells play an important role in the development of ANCA-induced glomerulonephritis. *In vitro*, we found that ANCA-activated neutrophils induce endothelial cell death and this effect was prevented by inhibition of ferroptosis with Fer-1 and siRNA against ACSL4. In contrast, inhibition of either necroptosis or apoptosis did not have any effects. In addition, ferroptosis inhibition alleviated the accumulation of lipid peroxides and endothelial dysfunction induced by ANCA-activated neutrophils.

Conclusions: ANCA-activated neutrophils induce ferroptosis in endothelial cells *in vitro*. Ferroptosis is induced in endothelial cell in vivo and play a major role in the development of vasculitis and ANCA-associated renal damage. Further experiments are warranted to decipher the mechanism(s) by which ferroptosis regulate the development of AAV. Altogether, our data suggest that ferroptosis is an important mediator in the development of AAV and might represent a novel interesting therapeutic target.

Disclosures: none

126. Mitochondrial Reactive Oxygen Species Inhibition Attenuates Neutrophil Extracellular Trap Formation And Inflammation In MPO-ANCA Vasculitis

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Background: A key feature of myeloperoxidase anti-neutrophil cytoplasmic antibody associated (ANCA) vasculitis (MPO-AAV) is the observation of neutrophil extracellular traps (NETs) in the glomerular lesions of kidney biopsies. NETs are a unique form of cell death that release highly injurious proinflammatory mediators that are destructive to nearby tissue. The DNA back bone of the NET acts as a reservoir which biologically enhances the activity of myeloperoxidase the autoantigen in MPO-AAV. NETs contain highly proinflammatory mtDNA, mitochondrial reactive oxygen species (mtROS) and histones which contribute to inflammation. Oxidative stress is a key inducer of NET formation mediated by (ROS). These studies aim to investigate the therapeutic potential of a mtROS inhibitor SKQ1 to inhibit NET formation and reduce inflammation in an experimental model of MPO-AAV, without impairing host defence.

Methods: C57Bl/6 mice were used to isolate peritoneal thioglycolate elicited neutrophils. Neutrophils were stimulated to NET *in vitro* with either ANCA, LPS, PMA or Ionomycin (to stimulate all pathways to NET formation) and compared to SKQ1 treated neutrophils. Confocal imaging was used to analyse NET formation and contents (MPO, citrullinated histones, Mitotracker, MitoSox, and Sytox green). *In vitro* Zymosan phagocytosis assays were used to investigate if SKQ1 interfered with neutrophil phagocytosis. Experimental anti-MPO GN was induced in C57Bl/6 mice by myeloperoxidase (MPO) immunisation and GN triggered using a subnephritogenic dose of anti-glomerular basement membrane globulin (anti GBM Ig). Therapeutic intervention with (SKQ1 daily n=8 or vehicle n=8) was administered after the establishment of MPO autoimmunity until termination of the experiment.

Results: *In vitro* NET formation was significantly attenuated with SKQ1 regardless of NET stimuli (all, P>0.05, compared to control). Confocal microscopy demonstrated that NETs contained large quantities of mtDNA, and mtROS colocalised with MPO. *In vitro* nanomolar concentrations of SKQ1 inhibited NET formation without interfering with neutrophil phagocytosis via zymosan phagocytosis assays. SKQ1 *in vivo* in an experimental model of MPO-AAV was able to significantly reduce inflammatory cells recruited to the glomerulus with a reduction in neutrophils, CD4 T cells, CD8 T cells and macrophage influx (all, P <0.05 compared to vehicle control). SKQ1 significantly reduced glomerular segmental necrosis, autoimmunity to MPO [measured by delayed type hypersensitivity reaction (DTH)] and MPO specific T cells from the draining lymph nodes (all, P>0.05). SKQ1 significantly attenuated the number of glomerular NETs and extracellular deposition of MPO when compared to the control group.

Conclusions: SKQ1 therapeutically targets NET formation without impairing neutrophil bactericidal killing capacity *in vitro. In vivo* administration of SKQ1 prevented NET formation and attenuated inflammation in an experimental model of MPO-AAV. This data provides strong pre-clinical evidence that SKQ1 could have potential for clinical translation.

Disclosures: No disclosures.

127. Active Takayasu Arteritis is associated with plasma and cellular measures of endothelial dysfunction

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Background: Takayasu Arteritis (TA) is a form of Large Vessel Vasculitis (LVV) characterised by granulomatous inflammatory lesions affecting the aorta and its branches. The accurate assessment of disease activity and progression can be a major challenge in TA. An improved undertanding of disease pathogenesis is required to facilitate the development of novel tools to aid clinical decision-making.
Due to its central role in vascular health and disease, we hypothesise that endothelial dysfunction is an important factor in TA disease progression. To explore this concept, we first investigated the association between plasma markers of endothelial dysfunction and disease activity. Second, we sought to understand the molecular basis of endothelial dysfunction in TA by studying blood endothelial cells derived from TA patients.

Methods: A panel of endothelial dysfunction markers including soluble (s)VCAM1, sICAM1, sE-selectin, sP-selectin, Plasminogen Activator Inhibitor 1 (PAI-1), soluble thrombomodulin (sTM), von Willebrand Factor (vWF) and the vWF cleaving protease ADAMTS13, were measured by ELISA in the plasma of 135 TA patients and 52 healthy control (HC) subjects matched for age and sex. TA patients were classified as active (n=42), grumbling (n=22) or stable (n=71) through assessment of clinical and radiological features, physician impression, CRP, ESR and Indian Takayasu clinical Activity Score (ITAS). The established TA disease activity marker pentraxin 3 (PTX3) was also quantified to provide additional assessment of disease activity status. For endothelial cell analyses, endothelial colony-forming cells (ECFC) were generated from PBMC of 6 patients with active TA and 5 HC. After confirmation of endothelial purity by flow cytometry ($CD31^+/CD144^+/CD146^+/CD45^-/CD14^-$), ECFC phenotype was interrogated by pro-inflammatory activation assays and by bulk RNA-seq analysis. Plasma markers were analysed using non-parametric statistical methods and data is presented as median [IQR]. For TNFα dose response experiments, non-linear least squares regression analysis was applied. After quality control and mapping (Salmon), RNA-seq data was analysed for differential expression using EdgeR. $P>0.05$ was considered significant.

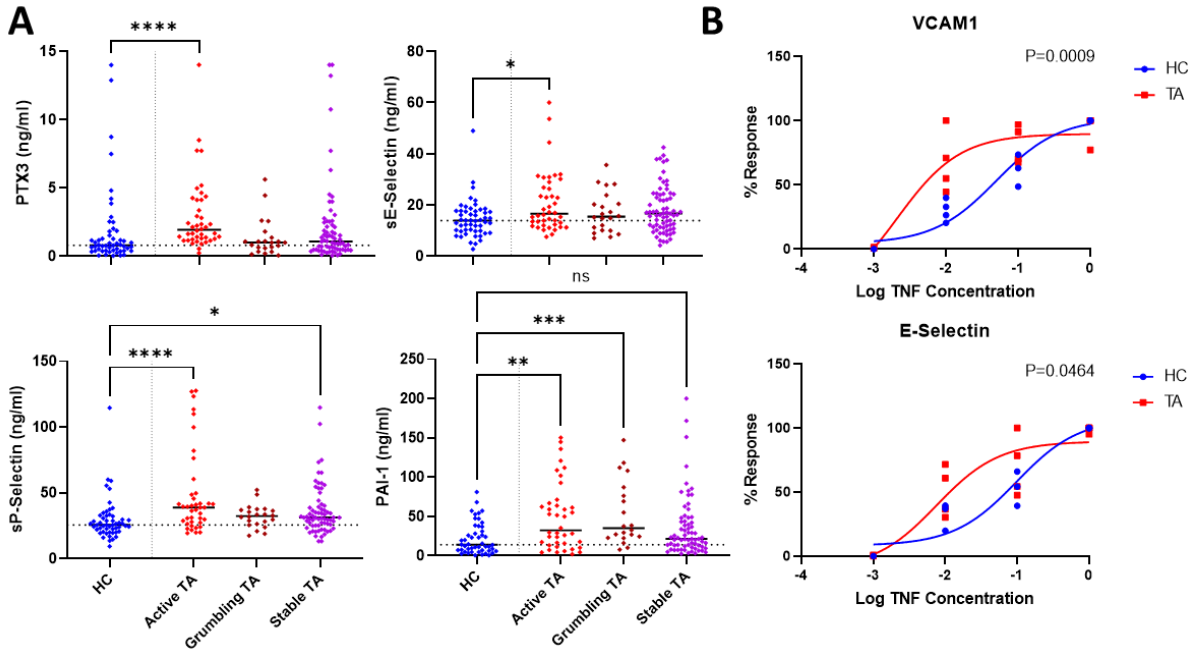
Results: Plasma levels of PTX3, sE-selectin, sP-selectin and PAI-1 were elevated in active TA patients in comparison to HC (+2.3 [1.5-4.2] fold, $p<0.0001$; +1.2 [0.9-1.8] fold, $p=0.026$; +1.5 [1.1-1.9] fold, $p<0.0001$; +2.3 [1.1-4.6], $p=0.004$ respectively, Fig 1A). Furthermore, concentrations of sP-selectin correlated with ITAS and PTX3 (rho= 0.19, $p=0.033$; rho=0.4, $p<0.0001$ respectively). Levels of sVCAM1, sICAM1, VWF, sTM were not increased in active TA. ECFCs derived from patients with active TA demonstrated significantly higher sensitivity to TNFα-mediated induction of VCAM1 and E-selectin mRNA in comparison to HC ($p=0.0009$ and $p=0.0464$ respectively, Fig 1B). Consistent with this pro-inflammatory phenotype, RNA-seq

analysis of TA ECFC revealed increased expression of inflammation and immunoregulatory genes including E-selectin, ZNF580, MICA, TNFSF4, and IL7R.

Conclusions: Herein, we describe a pattern of endothelial dysfunction in active TA which includes increased plasma levels of soluble cell adhesion molecules E-selectin and P-selectin and the pleiotropic fibrinolytic regulator PAI-1. In particular, P-selectin levels may represent a useful, novel disease activity marker. Plasma findings were consistent with the pro-inflammatory phenotype observed in ECFCs derived from patients with active TA. Future work will aim to understand how this molecular pattern of endothelial dysfunction contributes to TA disease progression.

Disclosures: RM has no disclosures.

Figure 1: Assessment of plasma and cellular endothelial dysfunction parameters in active Takayasu Arteritis



128. The NLRP3 inflammasome, IL-1 and IL-18 in experimental anti-MPO glomerulonephritis

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Background: The NLRP3 inflammasome responds to cellular stress by activating the pro-inflammatory cytokines IL-1β and IL-18. MCC950 is a specific NLRP3 inflammasome inhibitor. Neutrophil proteases are the dominant activators of IL-1β in passive anti-MPO antibody

transfer models, but the role of the NLRP3 inflammasome in active and T cell autoimmunity in MPO-AAV is not known. These studies aimed to determine the therapeutic potential of NLRP3 inflammasome inhibition and assess the role of its targets. IL-1β and IL-18 in experimental anti-MPO glomerulonephritis.

Methods: To assess anti-MPO autoimmunity, mice were injected with 20ug rMPO in FCA and studied at 10 days. For anti-MPO GN, mice were immunised with 20ug rMPO in FCA day 0 and 20ug rMPO in FIA on day 7. On day 16, low dose of sheep anti-mouse anti-basement membrane globulin was administered to transiently recruit neutrophils to glomeruli. Experiments ended on day 19. Experiments used *Nlrp3*-/- mice, WT mice treated with MCC950 (20mg/kg daily), IL-1RA (anakinra) or a neutralizing anti-IL-18 antibody, and *Il18*-/- mice. Renal and immunological (ELISPOT, flow cytometry) endpoints were studied. Glomerular neutrophil recruitment was assessed after 4 hours by administering 10μg LPS, then 1mg of the mouse anti-mouse anti-MPO monoclonal antibody clone 1D1.

Results: After immunization, *Nlrp3*-/- mice had fewer activated CD4+T cells and decreased Th1 responses. Compared to WT mice. *Nlrp3*-/- mice developed less 24-hour albuminuria and glomerular and interstitial histological injury, with fewer macrophages and neutrophils. Compared with saline treated mice, mice with anti-MPO GN that were treated with MCC950, from day 0 (first immunisation) developed less histological injury and albuminuria with lower proportions of activated T cells and lesser Th1 and Th17 responses. MCC950 reduced MPO-stimulated IFN-γ production (ELISPOT) and T cell activation, with fewer $CD62L^{-}CD44hi$ cells. When treatment was commenced at day 9 (after autoimmunity had been established), albuminuria was limited but glomerular histological changes were not significantly reduced, and treatment from day 16 (at the time of anti-basement membrane antibody administration) did not significantly reduce glomerular histology or albuminuria. Acute anti-MPO antibody or anti-basement membrane globulin induced acute neutrophil recruitment was similar in MCC950 treated and control mice. Anti-MPO antibody induced acute neutrophil recruitment was not affected by IL-1RA (anakinra) or by anti-IL-18 antibody treatment. Anakinra treatment limited disease at day 19 of the active model of anti-MPO GN, but *Il18*-/- mice and WT mice treated with anti-IL-18 antibodies were not protected from nephritis.

Conclusions: The NLRP3 inflammasome promotes T cell responses and disease in experimental anti-MPO GN. In this active model, endogenous IL-1 but not endogenous IL-18 promotes disease.

Disclosures: None.

129. Adeno Associated Virus Vector Delivery of DNase I Attenuates Inflammation in Experimental MPO-ANCA Associated Vasculitis

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Background: A hall mark of Myeloperoxidase Anti Neutrophil Cytoplasmic Antibody Associated Vasculitis (MPO-AAV) is the accumulation of dying neutrophils in glomerular lesions. Cell death via the release of neutrophil extracellular traps (NETs) containing MPO and proinflammatory extracellular DNA (ecDNA) promotes injurious inflammation. Under homeostatic conditions endogenous ecDNA is cleared by DNase I however in uncontrolled inflammation there is pathological consumption of DNase I. We have shown in a murine model of MPO-AAV that exogenous DNase I is therapeutic but twice daily intravenous (i.v.) infusions are required to achieve this outcome. To address the translational challenge of the short half-life of the enzyme, this study sought to use an adeno associated virus vector (AAvec) to deliver a DNase I transgene to the liver. We hypothesised that hepatocytes would secrete a steady supply of enzyme into the circulatory system that would attenuate both MPO-driven autoimmunity and kidney inflammation by clearing NETs, the major reservoir of MPO.

Methods: A 20-day model of MPO-AAV was induced in C57/Bl6 mice by subcutaneous immunisation with MPO on day 0 and 7. Glomerulonephritis was triggered by i.v. administration of subnephritogenic anti-glomerular basement membrane antibody on day 16. A single dose of [10^{11}vg] AAvec-DNase I (*n*=8) given after the establishment of autoimmunity to MPO (on day 10), was compared to mice given (i) a control AAvec-GFP (*n*=8) (ii) i.v. DNase I (10mg/kg, *n*=8) or (iii) vehicle control (*n*=8).

Results: AAvec-DNase I increased enzyme activity (>200-fold above physiological levels) and was as effective as twice daily i.v. DNase I in reducing glomerular segmental necrosis and recruitment of CD4 T cells, neutrophils and macrophages (all, $P < 0.05$ when compared to AAvec-GFP or vehicle control). Generation of MPO-specific IL-17 and IFNɣ cells from the draining lymph nodes, or the generation of MPO-ANCA was not significantly reduced with administration of i.v. DNase I, however AAvec-DNase I significantly reduced both the generation of MPO-ANCA and MPO-specific IL-17 and IFNɣ cells (all, $P<0.05$ when compared to AAvec-GFP control, and i.v. DNase I group). NETs and extracellular deposition of MPO were significantly reduced with AAvec-DNase I and i.v. DNase I when compared to controls (all, $P<0.05$). AAvec-DNase I and i.v. DNase I significantly reduced the number of apoptotic cells as seen by Caspase 3 staining and increased the amount of detectable DNase I within the kidney ($P<0.05$ for both analyses when compared to control groups).

Conclusions: A single dose of AAvec-DNase I is superior to twice daily i.v. DNase I for therapeutic targeting of ecDNA in experimental MPO-AAV. This pre-clinical data supports the translational development of a gene therapy to target ecDNA for treatment of MPO-AAV.

Disclosures: No disclosures

130. Monocyte subpopulations and monocyte-related chemokines profile in the peripheral blood from patients with Takayasu arteritis

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Background: Takayasu arteritis (TAK) is a chronic large-vessel granulomatous vasculitis that affects the aorta and its main branches. The pathogenesis of TAK is poorly understood. Although a macrophage-rich vessel wall granulomatous inflammation is a hallmark of TAK pathology, no previous studies have analyzed the monocytes' role in the pathogenesis of the disease. Therefore, this study aito evaluate the distribution of monocytes subpopulations and the monocyte-related chemokines profile in the peripheral blood of TAK patients and healthy controls (HC).

Methods: A cross-sectional study with a control group was performed. TAK patients were evaluated for current disease activity and current therapy. Monocyte's subpopulations were identified by flow cytometry according to the surface expression of CD14 and CD16 as classical ($CD14^{+}CD16^{-}$), intermediate ($CD14^{+}CD16^{dim}$), and non-classical ($CD14^{dim}CD16^{high}$) in the peripheral blood. Multiplex was used to measure serum monocytes-related chemokines including CCL2, CCL3, CCL4, CCL5, CCL7, CXCL10 and CX3CL1.

Results: Thirty-two consecutive TA patients and 30 HC were evaluated. TAK patients presented a higher number of circulating intermediate monocytes compared to HC [25.0 cells x 10^6/L (16.6-52.0) vs. 17.2 cells x 10^6/L (9.2-25.3); $p < 0.014$]. Active disease was associated with monocytosis ($p = 0.003$) along with the increase of the classical ($p = 0.002$) and intermediate ($p = 0.004$) subtypes compared to HC. However, no significant differences were found between disease activity and the remission states in TAK (Table 1). Prednisone use reduced the percentage of non-classical monocytes [3.7% (1.3-4.1) vs. 6.9% (3.9-8.5); $p = 0.011$]. TAK patients had lower CCL3 [6.22 pg/mL (4.9-8.1) vs. 9.3 pg/mL (5.7-14.7); $p = 0.009$] and CCL4 [37.4 pg/mL (24.6-47.9 vs. 45.4 pg/mL (37.8-63.7); $p = 0.008$] levels than HC, whereas CCL22 levels were higher in active TAK compared to the remission state (2030.5 ± 982.5 pg/mL vs. 1222.3 ± 552.6 pg/mL; $p = 0.008$). Therapy glucocorticoids, immunosuppressive agents or biologics did not impact serum chemokines concentrations. In TAK patients, CCL4 concentration correlated with the number of total monocytes (Rho = 0.441; $p = 0.012$) and classical monocytes (Rho = 0.400; $p = 0.023$) in the peripheral blood.

Conclusion: TAK is associated with altered distribution of monocytes subtypes in the peripheral blood compared to HC and CCL22 is the chemokine mostly associated with active disease in TAK.

Disclosures: The authors declare no conflicts of interests.

Table 1. Monocyte's subsets in the peripheral blood of TAK patients presenting active disease, TAK patients in remission, and healthy controls.

Variables	Active TAK (n = 6)	TAK in remission (n = 26)	Healthy controls (n = 30)	*p*
Total monocytes, cells x10^6/L	976.1 (601.6-1504.8)	465.8 (288.9-718.5)	461.26 (313.9-544.1)	0.022*
Classical monocytes, cells x10^6/L	818.8 (572.8-1280.3)	404.0 (258.5-647.0)	420.7 (278.0-506.4)	0.018*
Classical monocytes, %	88. 5 (80.5-91.7)	88.6 (83.9-91.6)	90.9 (87.5-94.7)	0.279
Intermediate monocytes, cells x10^6/L	55.4 (28.4-127.0)	22.3 (15.8-35.7)	17.2 (9.2-25.3)	0.008*
Intermediate monocytes, %	6.5 (4.6-8.1)	5.5 (4.1-7.2)	3.7 (2.8-6.7)	0.153
Non-classical monocytes, cells x10^6/L	43.3 (12.4-161.9)	19.1 (8.4-40.5)	14.2 (6.5-28.3)	0.183
Non-classical monocytes, %	4.4 (2.6-10.9)	5.1 (3.3-7.5)	3.4 (1.4-6.8)	0.345

TAK – Takayasu arteritis, n – number of patients, * - significant differences. *Post hoc* analyses for total monocytes: active disease vs. remission (p = 0.038), active disease vs. healthy controls (p = 0.003*), remission vs. healthy controls (p = 0.706). *Post hoc* analyses for classical monocytes: active disease vs. remission (p = 0.026), active disease vs. healthy controls (p = 0.002*), remission vs. healthy controls (p = 0.755). *Post hoc* analyses for intermediate monocytes: active disease vs. remission (p = 0.053), active disease vs. healthy controls (p = 0.004*), remission vs. healthy controls (p = 0.082). Bonferroni's correction for *post hoc* analyses (p = 0.016).

131. Role of inflammatory induced TPO and thrombocytosis on kidney remodeling in Rapidly progressive glomerulonephritis

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Background: Rapidly progressive glomerulonephritis (RPGN) is a severe pathology induced by chronic inflammation of glomerular capillaries and driving glomerulosclerosis. This leads to rapid loss of kidney functions and drive renal failure (PMID:3287904). Current treatments (high-dose of corticosteroids) are associated with high morbi-mortality and poor prognosis. So, better insights into the pathophysiology of the RPGN are needed to unravel new therapeutic strategies. Platelets are known to be involved in the acute phase of inflammatory RPGN induced by auto-antibodies (PMID:16709860) but little is known about their contribution to glomerulosclerosis. Platelet production is mediated by thrombopoietin (TPO), which regulates megakaryocyte expansion in the bone marrow and platelet release in the blood stream (PMID:27358871). Interestingly, it is known that pro-inflammatory cytokines, such as IL6, can

contribute to TPO production (PMID:11675343). Our hypothesis is that local kidney inflammation during RPGN induces TPO production, which overstimulates megakaryopoiesis, promotes glomerulosclerosis through platelets and worsen RPGN.

Method: We used a mouse model of RPGN induced by a nephrotoxic serum (NTS) containing anti-glomerular basement membrane (anti-GBM) antibodies to reproduce the human disease. Systematic analysis of platelet count showed that NTS-injected mice developed a thrombocytosis compared to non-immune serum injected mice (control mice). Using a multiplex bead-based assay, we observed an increase of multiple hematopoietic growth factors in the plasma of NTS-injected mice. TPO concentration steadily increased over 7 days, as compared to control mice. Immunofluorescent staining and mRNA analysis in tissue lysate revealed a kidney specific TPO production following the injury, which was not observed in the liver or lungs. Albumin-creatinine ratio (ACR) measurement in urine and histological analysis revealed that thrombocytosis induction was correlated to albuminuria and renal fibrosis in NTS-injected mice. To get a better insight on inflammation induced TPO, thrombocytosis and RPGN progression we treated mice with immunosuppressive drugs (dexamethasone). This treatment inhibited the NTS-dependent thrombocytosis, plasmatic TPO elevation and drastically reduced renal fibrosis, in NTS-injected mice. To know if IL6 is involved in TPO production during RPGN, we neutralized the cytokine using an anti-IL6. This treatment only mildly reduced NTS-dependent thrombocytosis, failed to prevent TPO increase in plasma and had no impact on renal fibrosis and ACR in urine. This suggest that inflammation is a key process in TPO production and kidney remodeling during RPGN. However, TPO production and kidney fibrosis are not only IL6-dependent in this model, suggesting that other mediators are involved. Finally, to determine the role of platelets in RPGN, we depleted them using a neutralizing antibody (R300) in NTS-injected mice. Platelet depletion significantly reduced NTS-induced increase in ACR and prevented glomerulosclerosis, suggesting that platelets are involved in glomerulosclerosis, however platelet depleting therapeutic approach is not suitable for human disease.

Conclusion: Altogether, our data suggest that in RPGN, local inflammation increases renal production of TPO which stimulates megakaryocyte’s expansion and NTS-dependent thrombocytosis, which contribute to glomerulosclerosis.
Perspectives: We will investigate which inflammatory mediators contribute to TPO production in RPGN and how platelets contribute to fibrosis, potentially via growth factors, as TGFβ and PDGF, stored in alpha granules and released upon activation.
This work could lead to the development of new potential therapeutic strategies targeting thrombocytosis to prevent RPGN progression.

Disclosures: None

132. Roles of Transglutaminase, Protein Crosslinking Enzyme, in Antibody-mediated Glomerulonephritis

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Background: Transglutaminase (TGase) is an enzyme that catalyses the covalent bond between glutamine and lysine residue of proteins in on Ca^{2+} dependent manner. TG2, an isozyme of TGases, is expressed in glomerular and proximal tubular cells and is well known to promote extracellular matrix accumulation leading to the progression of kidney fibrosis. TG2 null mouse (TG2KO) exhibited normal development and postnatal growth. The elevated TG2 expression in glomerulus has been observed in human kidney specimen of IgA nephropathy, or in animal models such as rat diabetic nephropathy and mouse antibody-mediated glomerulonephritis (GN). Recently, we have reported that the distribution of TG2 expression does not correlate with its activity. To elucidate roles of TG2 in GN, we analysed TG2 expression in crescentic GN of wild type (WT) and TG2 null (TG2KO) mice and in glomerular cells in response to several inflammatory stimuli.

Methods: Necrotizing crescentic GN was induced by intravenous injection of nephrotoxic serum in pre-immunized mice with rabbit IgG (NTS-GN). Renal function and histology were assessed in TG2 null (TG2KO) and wild type (WT) mice. TG2 activity was visualized using TG2 specific substrate peptide labelled with FITC (FITC-pepT26, HQSYVDPWMLDH). Glomerular TG2 activity was evaluated by fluorescent intensity and quantified using Image J software (NIH). Glomerular disease activity was semi-quantified by Periodic Acid-Schiff (PAS) positive index from the average of 20 glomeruli (ratio of PAS positive area in a glomerulus; 0%, 0; 0-25%, 1; 25-50%, 2; 50-75%, 3; 75-100%, 4). Cellular TG2 expressions were detected by immunoblot analysis in immobilized mouse mesangial cells (MES13) and vascular endothelial cells (RCB1994) in response to tumour necrosis factor-α (TNF-α) and lipopolysaccharide (LPS). Statistical analyses were used with Student's t test or Wilcoxon rank sum test. If the p-value was less than or equal to 0.05, the result was accepted as statistically significant.

Results: TG2KO demonstrated severe proteinuria (258.6±243.6 vs 118.6±109.0 mg/gCr, $p<0.05$) and comparable histological glomerular injury compared to WT in initial phase of NTS-GN. On the other hand, severe proteinuria (182.3±156.6 vs 128.0±19.5 mg/gCr, $p=0.42$) and glomerular injury were observed in advanced phase of NTS-GN. Change of body weight from the baseline and BUN were not significantly different between TG2KO and WT. During the observation period, some of the TG2KO mice died. In WT, the glomerular TG2 activity was remarkably elevated in initial phase of the disease without the histological changes, and it was hardly detected in sclerotic glomeruli. TG2 expression in MES13 was elevated in response to

LPS stimulation, but not to TNF-α stimulation. On the other hand, elevated TG2 expression was observed in RCB1994 upon stimulation with both TNF-α and LPS.

Conclusions: Our data suggested that TG2 activity associates with primary inflammation and may have a protective role against the onset of NTS-GN, and that exogenous inflammatory signals that induce TG2 expression are diverse in glomerular cell types.

Disclosures: None.

133. Role of kynurenine metabolizing enzymes and tryptophan metabolites in antibody mediated glomerulonephritis.

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Background: Tryptophan (TRP), which is one of the essential amino acids, is eventually metabolized to to nicotinamide adenine dinucleotide in kynurenine pathway, and its intermediate metabolites (Figure) potentially exert many biological activities. Although there are several studies indicating the involvement of indoleamine 2.3 dioxygenase (IDO), a rate limiting enzyme of kynurenine pathway, in onco-immunology, precise roles of TRP metabolism in autoimmune disorder is still controversial. For example, pharmaceutical inhibition of IDO for rheumatoid arthritis resulted in contradiction depending on the context of exploited animal models.
The objective of the current study is to elucidate the role of TRP metabolism in the progression of antibody mediated glomerulonephritis by using mice deficient in TRP-metabolizing enzymes involved in kynurenine pathway (KP).

Methods: We introduced antibody mediated crescentic glomerulonephritis by intravenous administration of rabbit anti-mouse nephrotoxic serum (NTS-GN) in several mouse strains deficient in KP-related enzymes (C57BL/6 mice background IDO1$^{-/-}$, IDO2$^{-/-}$, and kynurenine 3-monooxygenase; KMO$^{-/-}$) and in those wild-type mice (WT), and assessed kidney function (urinary protein, serum Cr and BUN) and kidney histology at day7 and 14. We intraperitoneally administrated clodronate-liposome for macrophage depletion and exogenous kynurenic acid (KYNA) for therapeutic intervention into IDO1$^{-/-}$ with NTS-GN every other day until day10.
In vitro, we analysed morphology of bone marrow derived neutrophils from IDO1$^{-/-}$, IDO2$^{-/-}$, KMO$^{-/-}$ or of KYNA-treated cells on immune-complex (IC) formed by BSA-anti-BSA antibody.

Results: IDO1$^{-/-}$ demonstrated severe renal dysfunction and histological glomerular damage (increased crescent formation rate and PAS-positive area) starting on day7 compared to WT. On the other hands, the functional and histological kidney damages in IDO2$^{-/-}$ was comparable to those in WT, and conversely, crescent formation at week 2 was significantly less in KMO$^{-/-}$ mice than in WT. Moreover, glomerular accumulation of esterase+ neutrophils was significantly more in IDO1$^{-/-}$ mice, but less in KMO$^{-/-}$ mice than in WT. Depletion of macrophages significantly ameliorated glomerular crescent formation in IDO1$^{-/-}$ mice.

The percentage of neutrophils presenting “spread” morphology among attaching cells on IC in IDO1$^{-/-}$ was significantly increased, whereas it in KMO$^{-/-}$ was reduced compared to WT. Treatment of KYNA in IDO1$^{-/-}$ with NTS-GN significantly diminished glomerular crescent formation, which associated with the amelioration of renal dysfunction, at day10. KYNA-treated IDO1$^{-/-}$ neutrophils demonstrated less percentage of “spread” cells on IC-coated dishes than non-treated cells.

Conclusions: Our data suggests that IDO1 or KMO-mediated alterations of TRP metabolism particularly in macrophages and neutrophils involve in the disease activity of NTS-GN. In addition, KYNA may contribute to the improvement of antibody-mediated glomerular damage by altering neutrophil activity in response to ICs.

Disclosures: None.

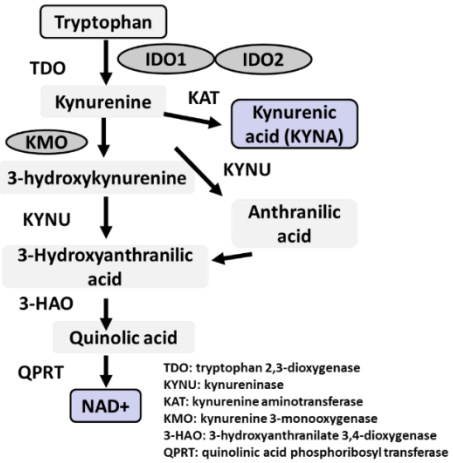

Fig. Kynurenine Pathway

134. The expression of inducible nitric oxide synthase and arginase-1 in patients with IgA vasculitis nephritis

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Background: Macrophages, categorized as M1 (calprotectin+ subtype) or M2 (CD163+ subtype), infiltrate glomerules and tubulointerstitium of the kidney of patients suffering from IgA vasculitis (IgAV). The number of tubulointerstitial CD163+ macrophages predicts chronic

kidney failure. Arginase-1 is the marker of all M2 macrophages, and inducible nitric oxide synthase (iNOS) is the marker of all classically activated M1 macrophage. iNOS shows the activity of inflammation when expressed on the epithelial cells of the intestine. However, the role of iNOS in the development of IgAV is still undetermined. Aim of this research was to determine the distribution of CD68+, iNOS+ and arginase 1+ cells in the kidney tissue of patients with IgAV, their quantity in regard to patients' histologic features and finally the interrelation between CD68+ cells CD3+ and CD56+ cells.

Methods: CD68+, iNOS+ and arginase1+ were marked with immunohistochemical methods while the double staining of iNOS, arginase-1, CD3 or CD56 with CD68 marker was achieved with double immunofluorescence in kidney biopsy samples of 22 patients with IgAV nephritis. Four patohistologic classifications were used in analysis: ISKDC, Haas, Oxford, and SQC classification.

Results: Number of CD68+ cells is similar in glomeruli [4,6 (2,6; 13,7)] and in tubulointerstitium [3,3 (2; 6,2)], [median (25. i 75. percentiles)]. There was a similar number of arginase-1+ and iNOS+ cells in glomerules, interstitium and tubules. Double-stained CD68+/iNOS+ cells were found in glomerules and tubules, with only a few CD68+/arginaza-1+ cells. Clusters of CD3+ lymphocytes were imprinting on the interstitium, however, less on the glomeruli. They were found near macrophage and tubular epithelia cells. CD56+ lymphocytes were rarely marked, mostly in glomeruli. Classification stages/total classification scores and all histological variables were evaluated for possible correlation with macrophage count. A statistically significant negative correlation was found between segmental glomerulosclerosis (Oxford classification) and arginase-1+ cells and an indication of negative correlations between arginase-1+ cells and segmental sclerosis, as well as adhesions (SQC classification) in the glomeruli.

Conclusions: Alongside CD68+ macrophages, tubular epithelia cells express CD68 and present an important source of iNOS, enclosed by CD3+ lymphocytes. The interrelationship of iNOS+CD68+ cells and lymphocites is yet to be explored, as well as their relationship with nephritis activity. Infiltration of glomeruli with arginase-1+ cells was highlighted as a possible negative predictor for segmental glomerulosclerosis, which should be further examined.
Disclosures: Research is supported by Croatian Science Foundation project IP-2019-04-8822 and University of Rijeka research grant No. Uni-ri-biomed-18-110.

135. Relevance of the angiotensin II system in temporal artery biopsies from patients with giant-cell arteritis

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Background: Retrospective studies have shown that treatment with angiotensin II receptor 1 (ATR1) blockers (ARB) was associated with lower relapse rate and glucocorticoid (GC)-sparing effect in patients with giant cell arteritis (GCA) (1,2). In this study, we investigate the expression and functional activity of the angiotensin II (ATII) system in temporal arteries (TA) from patients with GCA.

Methods: 40 GCA TA and 18 control arteries were analyzed. Expression of angiotensinogen (AGT), angiotensin-converting enzyme (ACE), ACE2, and ATR1 was investigated by quantitative real-time PCR in TA. Distribution of ATII system was qualitatively assessed by confocal microscopy. Effect of ATII and ATR1-blockade on selected cytokines was investigated in a co-culture system of PBMC and TA-derived VSMC. Modulation of the ATII system by GC was addressed using an *ex vivo* model of cultured TA. Multiplex Luminex system was used to quantify the concentration of 30 cytokines with inflammatory, Th1/Th2, chemokine, or growth factor activity in supernatants of cultured GCA TA incubated with ATII or ARB losartan.

Results: ACE and ACE2 mRNA transcripts were overexpressed and downregulated in GCA TA, respectively. By confocal microscopy, ATII, ACE, and ATR1 expression was qualitatively higher in GCA lesions (Figure 1A). The local ATII system identified in GCA lesions required multi-cellular cooperation as VSMC mainly expressed ATII and ATR1 while PBMC predominantly expressed ACE. *In vitro*, ATII increased mRNA expression of IL-1β, IL-6, CCL-2, ICAM-1, and VCAM in VSMC co-cultured with PBMC and of IL-1β, IL-6, TNF-α, CCL-2, ICAM-1, and VCAM-1 in PBMC. Losartan reversed these changes and reduced basal expression of IFN-γ, CCL-2, ICAM-1, and VCAM-1 in PBMC. In cultured GCA TA, dexamethasone reduced ACE gene expression and increased ATR1 and ACE2 transcripts (Figure 1B). Cytokine determination in supernatants of cultured GCA TA after incubation with ATII or losartan showed that ATII increased IL-6, VEGF, G-CSF, IL-15, CCL2, and CXCL9 concentration whereas losartan tended to augment anti-inflammatory IL-10, the latter also confirmed at mRNA level by RT-PCR (Figure 1C).
Conclusions. Our findings suggest that the ATII system may play a role in vascular inflammatory lesions of GCA and that observed anti-inflammatory effects of ARB in GCA may be mediated in part by increase of IL-10.

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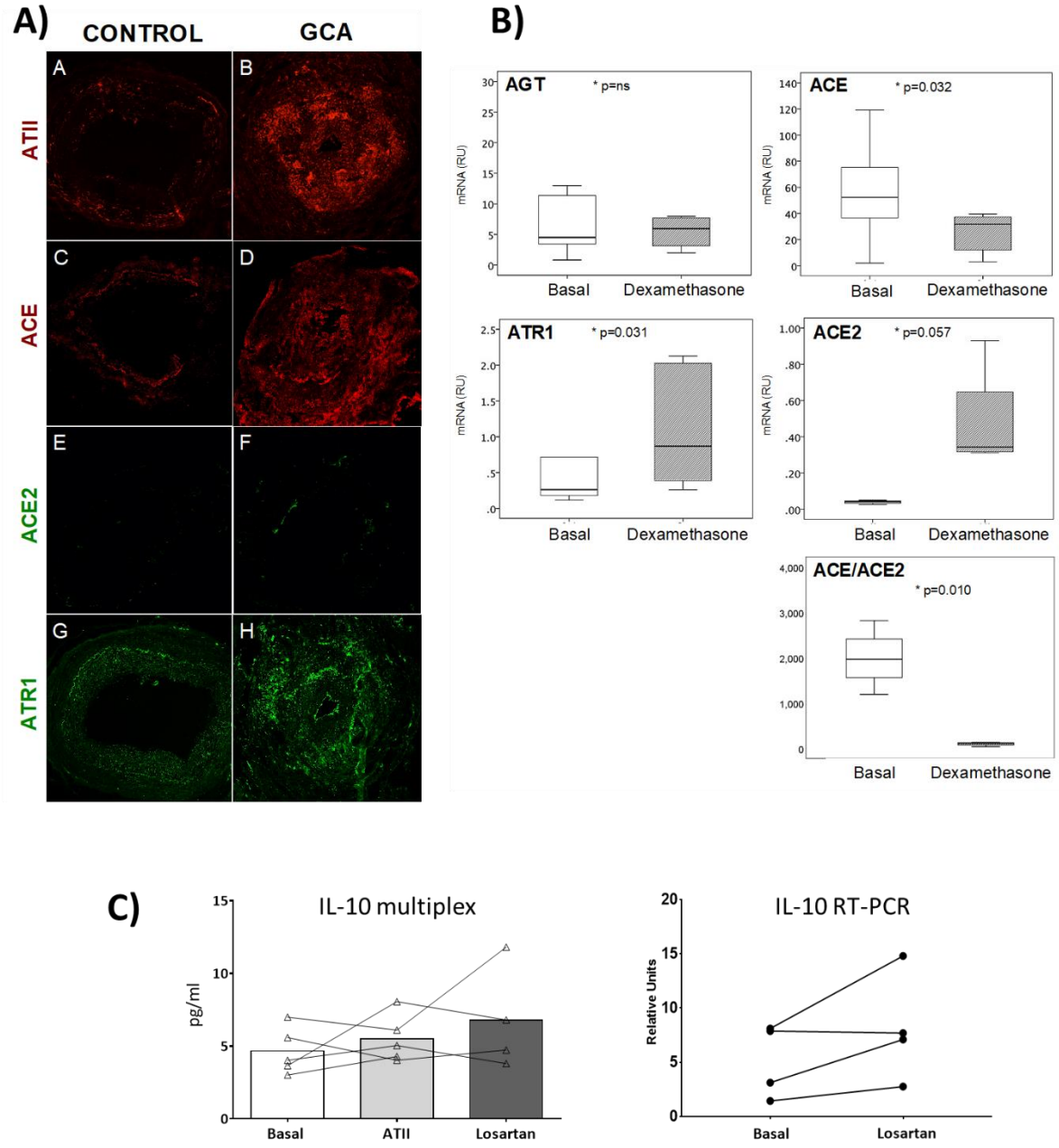
Figure 1. A) Expression of ATII system in TA sections from a control and a patient with GCA. B) Changes in mRNA concentration of AGT, ACE, ACE2, ACE/ACE2 ratio, and ATR1 induced by dexamethasone in cultured GCA TA. C) Quantification (left) of IL-10 in supernatant fluid of 5 cultured TA from patients with GCA incubated with ATII or losartan. Gene expression (right) of IL-10 in cultured GCA TA determined by RT-PCR.



136. New role for proteinase 3 in IL-16 bioactivity control in granulomatosis wit polyangiitis

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Background: The immunomodulatory cytokine IL-16 is increased in several inflammatory and autoimmune diseases, such as granulomatosis with polyangiitis (GPA). IL-16 recruits and activates different immune cells such as T cells, dendritic cells, or monocytes via CD4 as the main receptor. IL-16 is produced by a variety of immune and non-immune cells, but synthesis and storage of IL-16 is regulated differently depending on the cell type and stimulation3. For the biological activity of IL-16, proteolytic cleavage by caspase-3 in apoptosis dependent- and independent manner is required. Necrotizing granulomatous inflammation is a hallmark of granulomatosis with polyangiitis (GPA) with neutrophil dysregulation as a putative driver of chronic inflammation and autoimmunity. Earlier studies showed correlation of increased serum IL-16 with clinical parameters reflecting chronic inflammation in GPA, but functional evidence for a direct link between IL-16 and neutrophils in granulomatous inflammation is missing so far. In this study we aim to identify a functional link between increased release of IL-16, neutrophils, and the autoantigen proteinase 3 (PR3) regarding chronic inflammation and autoimmunity in GPA.

Methods: IL-16 was measured in sera of GPA patients (n = 40) and healthy controls (HC, n = 50) by ELISA and correlated with clinical features, such as disease activity (BVAS), creatinine, GFR, VDI and PR3-ANCA status. IL-16 protein expression was analyzed in peripheral blood mononuclear cells (PBMC) and polymorphonuclear cells (PMN) from GPA patients and HC (n = 5, each) by SDS-PAGE and western blot. Binding affinity of recombinant pro-IL-16 to fluorescently labeled native human PR3 was assessed by microscale thermophoresis. Cleavage of pro-IL-16 by active human PR3 was performed at various time points at 37°C. Cleavage products were analyzed using SDS-PAGE and western blot.

Results: Circulating IL-16 was significantly increased in GPA patients compared to HC. Elevated IL-16 levels positively correlated with BVAS, creatinine, VDI and PR3-ANCA status whereas there was a negative correlation with GFR. In isolated PMBC and PMN from GPA patients and HC we identified different expression patters of precursor and active forof IL-16. In healthy PBMC we found high amounts of precursor (80kD), pro-IL-16 (55kD) and active IL-16 (17kD). In contrast, PBMC from GPA patients had lower amounts of pro-IL-16 and no active IL-16, indicating activation and secretion of IL-16 due to inflammatory stimulation, as described earlier5. In GPA PMN we detected no precursor IL-16, but pro-IL-16 and its active form, in contrast to very low amounts of all IL-16 forin healthy PMN. Processing of IL-16 in neutrophils has been linked to apoptosis and the release of active IL-16 was dependent on secondary necrosis6. Interaction studies showed direct binding of recombinant pro-IL-16 to PR3 with a Kd

of 10 nM. In a subsequent cleavage assay we could confirm that PR3 processed pro-IL16 in a time-dependent manner.

Conclusions: Correlation of serum IL-16 with clinical features of GPA suggests that IL-16 could represent a marker of disease activity, tissue damage and autoreactivity. We showed that PBMC and neutrophils represent a source of IL-16 in GPA. By the identification of PR3 as an additional IL-16-processing enzyme we demonstrate a potential link between excessive PR3 expression and cell death dysregulation to IL-16 dependent mechanisas a driver of the chronic granulomatous inflammation and autoimmunity in GPA.

Disclosures: none.

137. Immunometabolism of monocytes in VEXAS syndrome is indicative of pro-inflammatory activation

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Background: VEXAS is an adult-onset inflammatory syndrome induced by an acquired mutation in the UBA1 gene[1]. Here, we investigated alterations in monocytes from VEXAS patients using a metabolomics-driven approach. The main purpose of this research is to highlight metabolic changes in pathways involved in the pathogenesis of this disease, paving the way for new therapeutic strategies.

Methods: Two patients with VEXAS and one healthy donor were evaluated. VEXAS diagnosis was confirmed by identification of p.Met41 status by Sanger Sequencing. Ultra-High-Pressure Liquid Chromatography-Mass Spectrometry was performed on monocytes purified by negative selection from peripheral blood and evaluated in 3 technical replicates. Production of TNFα and IL-6 was assessed via ELISA assay.

Results: Patient 1 was a 70-year man with fever, inflammatory arthritis, lung micronodules and skin manifestations; patient 2 was a 69-year man with polychondritis, fever, skin manifestations and lung micronodules. The healthy donor was 70-year man. Principal component analysis (PCA) showed that the metabolome of monocytes from VEXAS patients clustered independently from the control, with a PC1 higher than 50%, indicative of a profound metabolic rewiring. Hierarchical clustering analysis (HCA) of the top 50 significant metabolites confirmed these changes and clusters. T-Test analysis of the most significantly altered metabolites highlighted variations in glycolysis and TCA cycle. Specifically, pyruvate and lactate – modulators of both immune cells metabolism and cytokine production[2,3] - and citrate[5] fumarate[5], and succinate[4,5] – fundamental for controlling immune cell phenotype and

inflammation - were particularly increased in VEXAS patients. Moreover, the UBA1 mutation seeto affect Oxidative stress with a decrease in glutathione and glutathione disulfide[6], polyamines, such as spermine and spermidine[7], and increased sphingolipids as sphingosine-1-phosphate[8]. Compared to the control, VEXAS monocytes showed also a significantly enhanced production of TNFα and IL-6 ($p<0.01$).

Conclusions: We report the first data investigating the immunometabolism of VEXAS syndrome and reveal meaningful changes in pivotal metabolic pathways driven by the UBA1. These changes resemble those observed during activation (i.e. 'trained immunity') and likely represent the metabolic basis to enhanced cytokine production in this disease. These preliminary data highlight significant differences in essential metabolic pathways in monocytes from patients affected by VEXAS and open a new scenario for treatments targeting intermediates by-products of these metabolic processes. Further investigations in larger cohorts are mandatory.

Disclosures: The authors declare no competing financial interests.

138. Maladaptive activation of trained immunity in the pathogenesis of Giant Cell Arteritis

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Background: Giant cell arteritis (GCA) is a large-vessel vasculitis characterized by inflammation of the aorta and cranial arteries, leading to rampant systemic inflammation and irreversible ischemic complications. Macrophage activation and excessive cytokine production

are central to the pathogenesis of GCA, as confirmed by infiltration with myeloid cells at arterial biopsy and by the clinical efficacy of cytokine inhibitors (1). However, the mechanism responsible for this chronic inflammatory activation of monocyte/macrophages in GCA remains elusive. Trained immunity (TI) is a pro-inflammatory program induced in monocyte/macrophages upon sensing of some pathogens and characterized by immunometabolic and epigenetic changes, functionally resulting in enhanced cytokine production (2). In this study, we hypothesized that maladaptive activation of TI (i.e. in the absence of infection) may account for the development of detrimental inflammation in GCA. We specifically aimed at determining the mechanistic features of TI in GCA monocytes, and the therapeutic potential of targeting TI for the treatment of GCA.

Methods: We adopted a polyfunctional approach (UHPLC-Mass Spectrometry, chromatin immunoprecipitation PCR, ATAC sequencing, RNA sequencing, ELISA assays) to compare monocytes from a large cohort clinically active GCA patients (i.e. at diagnosis or during flares) to age- and sex-matched healthy controls (HD).

Results: Metabolomics studies revealed a profound immunometabolic rewiring in GCA monocytes, consistent with activation of TI (i.e. increased glycolysis, glutaminolysis through the TCA cycle, and cholesterol synthesis) (3). Epigenetic studies revealed changes in the epigenetic landscape, including H3K27Ac in enhancers of genes encoding cytokines (3), as well as increased accessibility of chromatin regions encoding for pro-inflammatory genes and effector immune mechanisRNA sequencing studies confirmed enhanced transcription of pro-inflammatory genes and pathways, both at baseline and following stimulation with LPS. ELISA assays revealed a significant increase in LPS-induced inflammatory cytokine production in GCA monocytes compared to HD, which represents the functional hallmark of TI. Furthermore, immunometabolic inhibition effectively dampened cytokine production by GCA monocytes (4).

Conclusions: Altogether, our findings indicate that deregulated TI is involved in the pathogenesis of GCA and identify druggable targets for alternative and/or complementary pharmacological treatment of GCA.

Disclosures: The authors declare no competing financial interests.

139. A passive model of anti-MPO dependent crescentic glomerulonephritis reveals matrix dysregulation

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Background: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are severe inflammatory disorders that often involve focal necrotizing glomerulonephritis (FNGN) and consequent glomerular scarring, interstitial fibrosis, and chronic kidney disease. Robust murine models of scarring in FNGN that may help to further our understanding of deleterious processes are still lacking. Here, we present an adapted murine model of severe FNGN that recapitulates both acute injury and the subsequent glomerular and interstitial scarring.

Methods: We modified a previously established model based on sequential administration of sub-proteinuric doses of antibodies to glomerular basement membrane (GBM) and myeloperoxidase (MPO), and bacterial lipopolysaccharides (LPS) using 8-week old female BL/6 mice. Mice were observed for up to 29 days after the initial treatment. In a separate set of experiments, mice additionally received either daily administration of the CXCR4 inhibitor AMD3100 or control vehicle over the course of 12 days.

Results: Dipstick positive hematuria occurred consistently and rapidly; glomerular necrosis and crescent formation were evident at 12 days without involvement of other organs, and progressive injury with glomerular and interstitial scarring was seen 29 days after the initial treatment. Concordantly, we observed substantial glomerular and interstitial infiltration by neutrophils, macrophages, T cells and expansion of myofibroblasts following injury. Using mass-spectrometric proteome analysis, we provide a detailed overview of the matrisomal and cellular changes in the model. We detected increased expression of a variety of matrisome components, including collagens, fibronectin, tenascin-C, which is consistent with tissue staining and transcriptomic data from renal biopsies from patients with AAV. Experimental inhibition of CXCR4 using AMD3100 led to a sustained histological presence of fibrin extravasates and reduced expression of specific chemokines, but did not markedly affect ECM composition.

Conclusions: Taken together, we demonstrate a FNGN model that enables the study of matrisomal changes both in an active and fibrosing stage of the disease and that can be used for therapeutic intervention, as exemplified by CXCR4 inhibition.

Disclosures: None

COVID-19 – Pathogenesis

140. Circulating levels of Annexin A1 are associated with severity of COVID-19

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Background: Coronavirus disease 2019 (COVID-19)–associated coagulopathy is driven by excessive Neutrophil Extracellular Trap (NET) formation, complement, and contact activation. The triangular relationship with its multiple amplifying feedback loops might include Annexin A1 (AnxA1), a pro-resolving inhibitor of neutrophil infiltration and activation.

Methods: We measured serum AnxA1 levels in 228 consecutive patients presented in our hospital during the first wave (21st March to 29th April 2020) with COVID-19. Disease severity was classified as mild (not admitted), moderate (admitted; requiring oxygen via nasal cannula) and severe patients (admitted; requiring oxygen via a face mask, or invasive ventilation or deceasing ≤7 days). AnxA1 levels at presentation and during follow-up were measured with an in-house developed ELISA. AnxA1 level were correlated with inflammatory markers (neutrophil count, C-reactive protein, Complement 5 and neutrophil lymphocyte ratio (NL-ratio)). Differences in endothelial as well as coagulation activation markers and circulating extracellular histone release were assessed between patients with normal and high AnxA1 levels.

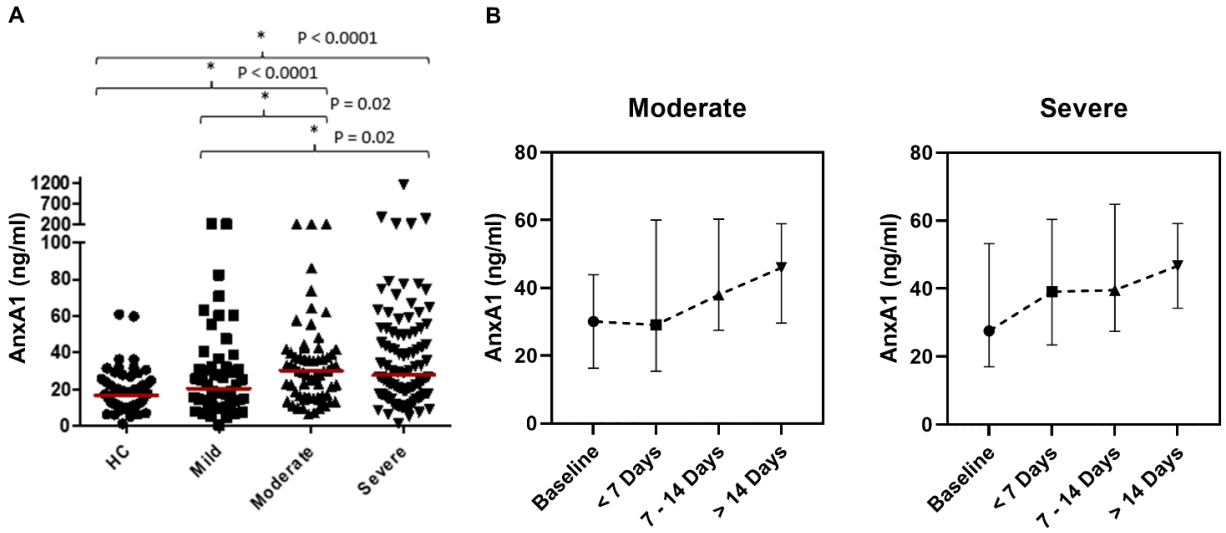
Results: Patients with moderate and severe COVID-19 had significantly increased baseline AnxA1 levels as compared to healthy controls ($p<0.0001$) and mild patients ($p=0.01$) (Figure 1A). AnxA1 levels increased during follow-up (Figure 1B).
Positive corelations between baseline AnxA1 levels and baseline neutrophil count ($rs(98)=0.294$, $p<0.0001$), C-reactive protein ($rs(98)=0.200$, $p<0.004$) and C5a ($rs(98)=0.192$, $p<0.008$) were only weak or not found (NL-ratio ($r_s(98)=0.055$, $p=0.457$).
Severe patients with elevated AnxA1 levels (>33,8 ng/ml) had significantly higher von Willebrand factor:antigen ($p=0.006$), FIXa:antithrombin ($p=0.026$), FXIa:antithrombin ($p=0.036$) levels at baseline compared to severe patients with normal AnxA1, respectively. No significant differences between these groups were found for complement 5a ($p=0.159$), plasma kallikrein:C1-esterase inhibitor ($p=0.673$) and thrombin:antithrombin ($p=0.989$) levels.
Circulating extracellular histones at baseline or follow-up tend to be more frequently detectable in severe patients with elevated AnxA1 (n=21, 51.2%) compared to patients with normal AnxA1 (n=19, 32.8%; $p=0.149$).

Conclusion: We conclude that serum AnxA1 levels are increased in patients with moderate and severe COVID-19 and are positively associated with the extent of endothelial activation/injury, coagulation activation and NET formation in severe COVID-19. The clinical significance of these findings in terof prognostic or therapeutic targets has to be further elucidated.

Disclosures: The authors have no disclosures to report.

Figure 1. Baseline Annexin A1 levels in healthy controls and patients with mild, moderate and severe COVID-19, respectively. Differences between groups were analysed by a Mann

Whitney U test. (A) Annexin A1 levels were significantly higher at baseline in patients with moderate and severe COVID-19 when compared to healthy controls and/or patients with mild COVID-19. (B) During the course of disease Annexin A1 levels further increased in patients with moderate and severe COVID-19. *Abbreviations: AnxA1, Annexin A1. HC, healthy controls.*



141. Retinal endothelial dysfunction in patients with acute COVID-19 and three months post-infection

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Background: Infection with SARS-CoV-2 can lead to severe organ dysfunction. Vascular involvement has been postulated early during COVID-19 pandemic. Endothelial activation and dysfunction by altering the integrity of vessel barrier, promoting pro-coagulative state, endothelial inflammation, and mediation of leukocyte infiltration is critical for disease progression. Retinal vessel analysis (RVA) provides insight into endothelial function. Static and dynamic parameters are reliable markers for systemic vascular alterations.
The aim of our study was to assess the endothelial function of the retinal vessels in patients with acute COVID-19 and three months post-infection.

Methods: Patients with PCR proven SARS-CoV-2 infection and a NIAID-OS (National Institute of Allergy and Infectious Disease Ordinal Scale) score ³3 were included. Study visits were performed at the end of hospitalisation for severe infection and three month later for follow-up. Results are preliminary, as the study is still ongoing. All patients underwent retinal vessel analysis (RVA, iMEDOS Health GmbH, Germany) for investigation of static and dynamic retinal vessel parameters. Endothelial function was compared to normative data from age matched

healthy individuals. Correlation of endothelial parameters with disease severity was sought. At 3 months after infection, all parameters were analysed again and compared to baseline.

Results: 31 patients (mean age 58 years, 8 female) were included. So far, 19 patients completed the 3 months visit, one patient died during follow-up (malignancy) and one was lost to follow-up. Median NIAID-OS score was 5 (range 4 - 7, SD ± 1), mean duration from first symptoto hospitalisation 8.4 ± 3.0 day and lenght of hospitalisation 13.7 ± 10.1 days. Nine patients required intensive care with a mean ICU time of 11.2 ± 6.0 days, 6 patients were on mechanical ventilation (mean 11.7 ± 1.7 days). Oxygen was required in 23 (74%) patients (mean 12.0 ± 8.7 days). Mean body mass index (BMI) was 27.2 ± 3.1 kg/m^2. Mean systolic and diastolic blood pressure at baseline were 127.8 ± 16.3 mmHg and 80.4 ± 11.6, respectively. Baseline static retinal vessel diameter parameters for either arteriolar (CRAE) or venular (CRVE) diameter were in the range of age-related normative values (mean CRAE 174 ± 27µm, normal: 196 ± 13 to 166 ± 17 µm; mean CRVE 225 ± 24µm, normal: 220 ± 15 to 199 ± 16 µm). Parameters of dynamic vessel analysis indicated endothelial dysfunction. Flicker-induced maximal arteriolar (aFID) and venular (vFID) dilatation were reduced compared to age-related normative values (aFID 1.27 ± 1.88%, normal: 3.74 ± 2.17 to 3.79 ± 2.43% and vFID 1.64 ± 2.48%, normal: 4.64 ± 1.85 to 3.86 ± 1.56%). Endothelial function improved significantly after three months compared to baseline (aFID 3.07 ± 2.50, p=0.001; vFID 4.82 ± 1.67, p<0.001), while static vessel diameter parameters remained stable. There was no correlation between static (CRAE, CRVE) or dynamic (aFID, vFID) endothelial function with severity of infection (NIAID-OS score) at baseline or follow-up.

Conclusions: This study indicates severe endothelial dysfunction at retinal vessels in patients with acute severe COVID-19 with no relation to disease severity. Three months post-infection flicker induced endothelial reaction recovered.

Disclosures: The authors declare that there is no conflict of interest.

142. Covid-19 Neurological Disease and CNS Inflammatory Vasculopathy

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Objective: To describe the clinicopathologic correlations of 141 confirmed postmortem cases of coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome-coronavirus -2 (SARS-CoV-2).

Background: Analysis of 50 cases of COVID-19 with available neuropathology revealed three CNS findings. First, hypoxia-ischemia does not account for all relevant neuropathological features. Second, elevated levels of circulating cytokines suggest activation of post-infectious immunity indicative of a cytokine storm, with increased hypercoagulability leading to a risk for thrombotic and hemorrhagic parenchymal tissue infarction. Third, a minority of cases have acute demyelinating encephalomyelitis-(ADEM) like features or indolent brainstem

encephalitis. Such cases may present with early altered sensorium and brainstem signs. Fourth, SARS-CoV-2 staining could not be confirmed due to paucity of available tissue specimens.

Design/Methods: Ninety-four additional cases with available postmortem CNS neuropathology showed four additional findings.

Results: First, positive SARS-CoV-2 genome by PCR testing is present in brain tissues especially in olfactory bulb neurons and glial cells lending support to a route of entry into the CNS and the importance of early anosmia. Second, SARS-CoV-2-positive neurons appear to be TUNEL positive and caspase-positive, displaying reversible pT231 Tau localization in some cell soma that may be highly neurotoxic and a driver of tauopathy. Third, expression of ACE2 in oligodendrocytes is associated with viral entry, while TMPRSS2 and TMPRSS4 staining is implicated in pruning of viral-decorating spikes. Fourth, meningeal and interstitial brainstem inflammation by cytotoxic T-cells coincides with the localization of SARS-CoV-2 viral proteins in cranial nerves and interstitial areas of lower brainstem encephalitis. The detection of brain microglial activation and sparse perivascular and leptomeningeal T-cell infiltrates correlates with critical illness encephalopathy.

Conclusions: Genetic diversity, recombination, and viral mutation carries the foreseeable risk of continued fatality due to the direct and indirect effects of SARS-CoV-2 that include inflammatory vasculopathy, encephalitis, silent infarctions, and critical illness encephalopathy.

Disclosures: None.

COVID 19 - Vaccination & Prevention

143. Antibody response to COVID-19 booster vaccine in patients with ANCA vasculitis on Rituximab

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Background: The COVID-19 vaccine has been associated with a suboptimal response in patients on immunosuppression. Albeit booster doses of the vaccine have led to an increase in number of patients (solid organ transplant recipients and patients with rheumatic disease) achieving an antibody response, a considerable proportion continue to demonstrate none. Administration of rituximab is associated with lower response to the initial vaccine series, with a paucity of data regarding its effect with respect to booster doses. We looked to elucidate the antibody response post booster vaccine doses in patients with anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) on maintenance rituximab, who had no response to the initial vaccine series.

Methods: AAV patients attending the vasculitis clinic at Johns Hopkins on rituximab therapy were screened for a completion of vaccine series and associated negative antibody response between January 2021 and September 2021. Immunoglobulin G antibodies to spike protein S1 subunit of on SARS-CoV-2 were measured using ELISA at least 1 month post completion of vaccination series and booster doses. Clinical demographics and immunological data were retrieved after review of the electronic health record. Fifteen patients with no demonstrable antibody response received a booster dose. B cell depletion was defined as absolute CD19 count of 0/mm^3. This study was approved by the Johns Hopkins Institutional Review Board.

Results: Of the 15 patients, 7 patients had a discernable antibody response to a booster dose. The median age (IQR) was 69 (62-73) years with 7 patients being female and 8 with granulomatosis with angiitis phenotype (rest with microscopic polyangiitis). Seven patients received the Pfizer vaccine, with 6 and 2 patients received Moderna and Johnson & Johnson (J&J) respectively (patients who initially received Pfizer or Moderna completed same booster types). All patients with CD19 depleted at the time of completion of first vaccine series, with 5/7 booster dose responders having B cell reconstitution at the time of administration of third dose of vaccine. Of note, the two patients that demonstrated antibody response despite complete B cell depletion initially received J&J and received booster Pfizer or Moderna doses.

Conclusion: This is the largest study to elucidate the antibody response to COVID-19 vaccine booster dose in patients on rituximab therapy. B cell reconstitution correlated with booster vaccine response, however, it was possible to generate an antibody response in patients with B cell depletion by combining different types of vaccines. This could be a viable strategy in generating immune response in patients with B cell depletion as consequence of rituximab, thus balancing the need for primary disease control with continued therapy and achieving an essential goal of vaccine immune response in a vulnerable population.

Disclosures: DG is a consultant to ChemoCentryx and Aurinia. SK has no disclosures

Table 1. Patient characteristics, immunosuppressive regime, immunological data and details of vaccine administration. F- female, IS- immunosuppression, J&J- Johnson & Johnson, M- male, MPO- myeloperoxidase, N- negative, PR3-proteinase 3, R- reconstitution, RTX- rituximab, S- corticosteroids, SCQ- subcutaneous immunoglobulin, U- undetectable

ID	Age	Gender	Ethnicity	ANCA type	Duration elapsed since booster (years)	Vaccine type	SP Ab post 2nd dose	CD19 levels at the time of 2nd dose	Booster vaccine type	Duration elapsed between first vaccine series and 3rd vaccine dose (months)	SP Ab post 3rd dose	CD19 levels at the time of 3rd dose	Relation of last RTX dose to 1st dose (months)	Relation of last RTX dose to 3rd dose (months)	IS regime
1	66	M	W	PR3	4	J&J	N	<1%	Pfizer	3	P	U	-4	-8	RTX
2	80	F	W	MPO	6	J&J	N	<1%	Moderna	4	P	U	-4	-9	RTX
3	69	F	W	MPO	8	Pfizer	N	<1%	J&J	3	N	U	-2	-6	RTX
4	66	F	W	PR3	3	Moderna	N	<1%	Moderna	5	P	R	-3	-10	RTX

5	69	F	W	PR3	3	Pfizer	N	<1%	Pfizer	6	N	U	-1	-8	RTX
6	69	F	W	PR3	6	Pfizer	N	<1%	Pfizer	6	N	R	-5	-11	RTX + S
7	73	M	W	MPO	8	Moderna	N	<1%	Moderna	7	P	R	-4	-11	RTX
8	55	M	W	MPO	4	Moderna	N	<1%	Moderna	6	P	R	-3	-10	RTX
9	50	M	W	PR3	21	Moderna	N	<1%	Moderna	6	N	U	-2	-9	RTX + S + SQIG
10	61	M	W	PR3	1	Pfizer	N	<1%	Pfizer	4	N	U	-7	-11	RTX
11	65	M	W	MPO	7	Pfizer	N	<1%	Pfizer	6	N	U	-6	-12	RTX
12	62	M	W	PR3	7	Pfizer	N	<1%	Pfizer	4	P	R	-5	-10	RTX
13	74	F	W	MPO	4	Moderna	N	<1%	Moderna	8	P	R	-1	-9	RTX
14	79	M	W	PR3	7	Pfizer	N	<1%	Pfizer	1	N	U	-5	-6	RTX
15	73	F	A	MPO	5	Moderna	N	<1%	Moderna	5	N	U	-1	-7	RTX

144. SARS-CoV-2 vaccine response in ANCA associated vasculitis patients

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Background: The development of COVID-19 vaccines and mass vaccination is a landmark achievement of modern medicine. Management of patients with anti-neutrophil cytoplasmic autoantibodies (ANCA) associated vasculitis (AAV) during the pandemic has been challenging. Immunosuppressive (IS) medications to control vasculitis are associated with severe COVID-19 infection and may impair immune response to the vaccine. In this study we aim to identify correlations between humoral response to the vaccine and IS medications used in the management of AAV.

Methods: A multicentre cross-sectional study was carried out across 3 centres, John Hopkins Hospital, Vasculitis centre, Baltimore USA, Royal Preston Hospital, UK and The University Hospital, Munich, Germany. One hundred and fifty-nine patients were included. Serum anti-spike IgG enzyme immunoassays were performed between 11th March 2021 and 19th August 2021. The cut off titre for positive humoral response was between >0.8 to >1.24 u/ml depending on the assays.

Results: Of the 159 patients included; mean age 65 ± 14 years, 55% developed detectable SARS-CoV-2 anti-spike antibodies. The use of Rituximab (RTX) was shown to be significant for a poor humoral response to COVID-19 vaccines (p= 0.01). For every 1g increase in the cumulative dose of RTX given, antibody seropositivity reduced by 10% (as shown in Table 1). Multivariate analysis demonstrated CD19 reconstitution was significantly associated with antibody production (p <0.001). Those that received RTX over 6 months prior to vaccination had a seven-fold increase in antibody production.

Conclusions: Our study has demonstrated a significant correlation with B cell depleting agents (Rituximab) and SARS-CoV-2 anti-spike antibody production following vaccination. We recommend CD 19 counts as a reliable marker for prediction of antibody production. Decisions to delay or change maintenance treatments should be made on balance with the risk of relapse and other risk factors. We recommend considering other immunosuppressive treatments such as Azathioprine as maintenance treatment, especially in those who are vulnerable to hospitalisation or severe COVID-19 infection.

Disclosures: DG is a consultant to ChemoCentryx and Aurinia Inc. The other authors have no other disclosures or competing interests.

Table 1: Odds ratios of SARS-CoV-2-anti-spike-antibody response to vaccination with AAV disease characteristics, co-morbidities, risk factors for COVID-19 infection, immunosuppression and vaccine type

	OR, 95% CI	P value
Demographics		
Age	0.99 (0.96, 1.01)	0.26
Sex, Females vs. Male	1.02 (0.54, 1.92)	0.94
AAV disease characteristics		
Active disease	1.67 (0.50, 6.49)	0.42
Renal	0.77 (0.27, 2.07)	0.61
Respiratory	1.02 (0.54, 1.93)	0.94
Cardiac	0.59 (0.11, 2.76)	0.5
Renal limited disease	0.70 (0.29, 1.66)	0.42
Co-morbidities		
Hypertension	0.69 (0.34, 1.38)	0.30
Diabetes Mellitus	0.87 (0.34, 2.22)	0.76
Cardiovascular disease	0.99 (0.48, 2.09)	0.98
Respiratory	0.70 (0.30, 1.62)	0.41
Renal transplant	0.51 (0.13, 1.87)	0.32
ESKD	0.51 (0.20, 1.25)	0.14
eGFR (ml/min.1.73m2)	1.01 (1.00, 1.02)	0.23
Vaccination characteristics		
Vaccine type		
Oxford- AstraZeneca	0.82 (0.38, 1.78)	0.61
Johnson & Johnson	0.19 (0.01, 1.33)	0.14
Moderna	1.35 (0.61, 3.08)	0.46
Pfizer-BioNTech	1.14 (0.60, 2.15)	0.69
Days between 1st & 2nd Vaccine	1.00 (0.99, 1.01)	1.00
Immunosuppression		
CNI	0.51 (0.13, 1.87)	0.32
MMF	1.08 (0.43, 2.82)	0.86
Azathioprine	0.80 (0.09, 6.81)	0.83
Steroid	1.32 (0.67, 2.63)	0.43
Rituximab	0.31 (0.12, 0.74)	0.01
Rituximab Therapy		
Vaccination <6 months of RTX	0.12 (0.06, 0.25)	<0.001
Vaccination >6 months of RTX	7.31 (3.66, 15.18)	<0.001
Days from last RTX to 1st vaccine	1.07 (1.04, 1.12)	<0.001
Cumulative RTX dose prior vaccine (g)	0.89 (0.80, 0.99)	0.05
CD 19 reconstitution	29.91 (11.71, 85.89)	<0.001

OR; odds ratio, CI; confidence interval, AAV; ANCA associated vasculitis, ESKD; end stage kidney disease, eGFR; estimated glomerular filtration rate (ml/min.1.73m2), CNI; calcineurin inhibitors. MMF; Mycophenolate, RTX; Rituximab, CD 19; Cluster of Differentiation 19, G; grams

145. Reactive arthritis secondary to mRNA vaccine with urticarial skin lesions with reversible rheumatoid serology

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Background: A 20-year-old female presented with swelling of hands and feet. 3 days earlier she received mRNA BNT162b2 vaccine. She had swollen lips (Fig. 1A), right ankle, (Fig. 1B), wrists and MCP joints (Fig. 1C). She developed urticarial-rash affecting her legs (Fig. 1D).

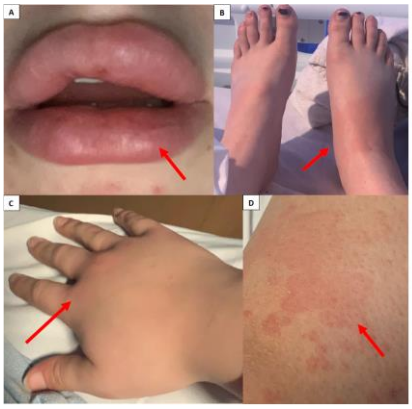
Methods: Her bloods revealed elevated CRP 138mg/L. Despite prednisolone 40mg daily she developed dyspnoea, pruritus, angioedema requiring IM adrenaline, IV chlorphenamine and hydrocortisone. Blood and urine cultures, Coronavirus PCR, Influenza and RSV were negative.

Results: HLA B27, hepatitis B, C, chlamydia, gonorrhoea and HIV were negative. RF and anti-CCP were elevated at 20.2IU/ml [Normal<12] and 96.9u/ml [0-3.1] respectively. ANA was positive with elevated DsDNA 14 IU/ml [0-10.1], but negative crithidia and ENA. Prednisolone was tapered over 6 weeks. 3 months after presentation there has been no recurrence with subsequent negative ANA, RF and anti-CCP.

Conclusions: Reactive arthritis [ReA] typically manifests as asymmetric oligoarthritis 1-4 weeks after an STI or gastrointestinal infection. SAR-CoV-2 infection may also cause a ReA [1]. Our case highlights a case of ReA with anaphylaxis secondary to the mRNA BNT162b2 vaccine. Our patient developed strongly positive rheumatoid serology indicating a possibility of early RA, but repeat serology was negative. Flare of rheumatoid arthritis after COVID-19 vaccination has been reported [2] however our patient had no further synovitis.

Disclosures: The authors have declared no conflicts of interest. No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript. The patient provided informed consent to publish this case.

Figure 1. Swollen and erythematous lips (A). Swelling of right ankle (B), Swollen MCP joints (C), urticarial skin lesions (D)



146. The Effect of Immunosuppressive Therapy on Adaptive Immune Responses to COVID-19 Vaccination in AAV Patients

Emma Leacy[1], Jean Dunne[1,2], Niall Conlon[1,2], Matthew Griffin[3,4], Aya Ibrahim[1], Gareth Brady[1], William McCormack[1], Lina Zgaga[1], Michelle O'Shaughnessy[5], Mark Little[1,6]
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Background: As the COVID-19 pandemic proceeds, it is vital to understand how immunosuppressive therapies impact vaccine immunogenicity, so that vaccine strategies encompassing timing, nature, and frequency of treatment, can be tailored to optimise efficacy in immunosuppressed patients. We profiled serological and whole blood immune cell responses to SARS-CoV-2 vaccination, according to immunosuppression exposure status in a national population of adults with ANCA vasculitis (AAV).

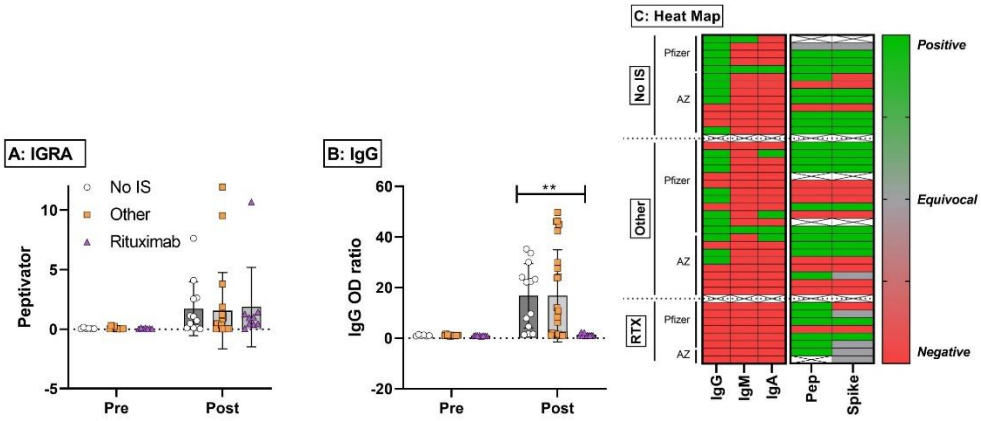
Methods: Patients were sampled before and after completion of a COVID-19 vaccine course, and again 4-6 weeks following their 3rd vaccine dose. Immunosuppression exposure was categorised as: i) No immunosuppressive therapy (including <10mg prednisolone currently); ii) Rituximab exposure (within previous 6 months, or at any time with persistent B-cell depletion); iii) Other immunosuppression (current prednisolone ≥10mg, cyclophosphamide within previous 6 months, or current use of another immunosuppressive agent). We measured IgG, IgM, IgA and antibodies capable of blocking Spike-ACE2 interaction against SARS-CoV2 Spike protein. A novel interferon gamma response assay (IGRA) was used to assess cellular interferon-γ release, using whole Spike protein, M&N protein and PepTivator SARS-CoV-2 peptides. Deep phenotyping of T cell responses was performed in selected cases.

Results: Results following the 2nd vaccine dose are presented here. Among the 50 patients studied, one was excluded because of serological/IGRA evidence of pre-vaccine SARS-Cov2 exposure. Median age was 65 (IQR 54-73) years, 28 (56%) were male, and 24 (48%) were immunosuppressed: 10 (20%) with Rituximab and 14 (28%) with “other” immunosuppression. 24 (49%) received the AZD1222/ChAdOx1 and 25 (51%) the BNT162b2 mRNA vaccine. Median time to post-vaccine blood sampling was 42 (IQR 35-57) days. T cell responses to SARS-CoV-2 were evident after 2nd dose vaccination in 89% of immunosuppressed patients: 57% of “other immunosuppression” exposed, and 83% of non-exposed patients had detectable cellular responses to SARS-CoV-2 (Fig 1A). In contrast, the serological response was impaired in patients exposed to Rituximab (0% had detectable IgG) compared to 77% with other immunosuppression (Fig 1B). Post-vaccine immune responses are summarised in Fig 1C.

Conclusions: In this national study of patients with AAV, exposure to immunosuppressive therapy – most notably Rituximab – significantly impaired serological response to COVID19 vaccine but had less impact on cellular responses in line with previous observations for other immunosuppressed cohorts. The clinical implications of these findings, immunosuppression choice, timing and frequency of vaccination, and clinical effectiveness of a predominant T-cell response invite further study.

Disclosures: None

Figure 1. Cellular (A) and serological (B) responses to SARS-CoV2 vaccination, and paired subject level binary results (C).



147. Long-term SARS-CoV-2 vaccine response in patients with ANCA-associated vasculitis

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Objectives: ANCA-associated vasculitis (AAV) patients under immunosuppressive therapy are at high risk of having a severe COVID-19 infection. At the same time, they are also less likely to develop a sufficient immune response after vaccinations. We therefore examined the antibody response over time in patients with AAV after complete vaccination against COVID-19.

Methods: In this monocentric observational cohort study, we enrolled 52 AAV patients (28 men and 24 women) (PR3-ANCA n=31, MPO-ANCA n=19, ANCA-negative n=2). Patients were tested for antibody response during routine follow-up visits up to 33 weeks after complete vaccination. SARS-CoV-2 spike antibody testing was performed with chemiluminescence immunoassays designed to detect antibodies against the SARS-CoV-2 spike protein (Elecsys Anti-SARS-CoV-2 S, Roche Diagnostics, Mannheim, Germany) in the Institute of Laboratory Medicine of the University Hospital Munich. According to the manufacturer's specifications, anti-SARS-CoV-2 S titres >0.8 U/mL are considered reactive (sensitivity 98.8% and specificity 99.9%). Anti-SARS-CoV-2 S titres <300 U/mL were defined as low antibody response.

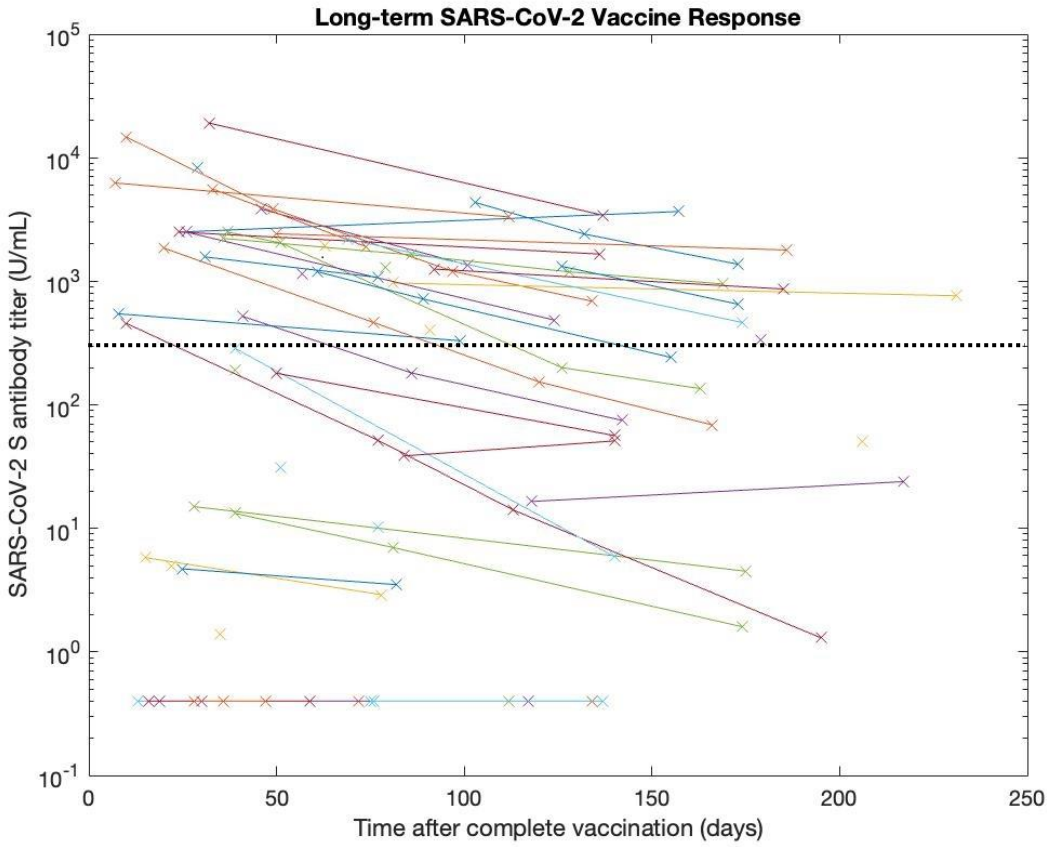
Results: 49 patients completed a series of two SARS-CoV-2 vaccinations. Three patients were infected with COVID-19 and subsequently received only one vaccination according to national recommendations. After complete vaccination, 41 patients (79%) developed a detectable anti-SARS-CoV-2 spike antibody response, with 14 patients (34%) showing low antibody response (<300 U/L). 11 patients (21%) remained without an antibody response. After having received

the vaccination, 22 patients underwent immunosuppressive therapy with Rituximab. Humoral response declined continuously during follow-up of up to 6 months (see figure 1). Rituximab treatment after vaccination resulted in substantial antibody decline. Four patients at present have received a booster, all of which demonstrate a significant antibody increase.

Conclusions: In our cohort, the majority of patients fortunately developed a detectable SARS-CoV-2 spike antibody titre after vaccination, although patients receiving Rituximab showed a diminished response. The observed decline in titres matches other studies‘ results and concerns for an increasing susceptibility to COVID-19 infection. Our preliminary data suggests a positive impact of booster vaccination also in AAV patients.

Disclosures: MF – Advisory Board/Study participation (Chemocentryx/Vifor; Alexion; Ablynx/Vifor; Alnylam). US – Advisory Board/Study participation (Chemocentryx/Vifor; Alexion; Ablynx/Vifor; Alnylam)

Figure 1



148. Immunogenicity of BNT162b2 vaccine against Alpha and Delta Variants in patients with systemic inflammatory diseases

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Objectives: The emergence of strains of SARS-CoV-2 exhibiting increase viral fitness and immune escape potential, such as the Delta variant (B.1.617.2), raises concerns in immunocompromised patients. We aimed to evaluate seroconversion, cross-neutralization and T-cell responses induced by BNT162b2 in immunocompromised patients with systemic inflammatory diseases.

Methods: Prospective monocentric study including patients with systemic inflammatory diseases and healthcare immunocompetent workers as controls. Primary end points were anti-spike antibodies levels and cross-neutralization of Alpha and Delta variants after BNT162b2 vaccine. Secondary end points were T-cell responses, breakthrough infections and safety.

Results: Sixty-four cases and 21 controls not previously infected with SARS-CoV-2 were analyzed. Kinetics of anti-spike IgG after BNT162b2 vaccine showed lower and delayed induction in cases, more pronounced with rituximab. Administration of two doses of BNT162b2 generated a neutralizing response against Alpha and Delta in 100% of controls, while sera from only one of rituximab-treated patients neutralized Alpha (5%) and none Delta. Other therapeutic regimens induced a partial neutralizing activity against Alpha, even lower against Delta. All controls and cases except those treated with methotrexate mounted a SARS-CoV-2 specific T-cell response. Methotrexate abrogated T-cell responses after one dose and dramatically impaired T-cell responses after 2 doses of BNT162b2. Third dose of vaccine improved immunogenicity in patients with low responses.

Conclusions: Rituximab and methotrexate differentially impact the immunogenicity of BNT162b2, by impairing B-cell and T-cell responses, respectively. Delta fully escapes the humoral response of individuals treated with rituximab. These findings support efforts to improve BNT162b2 immunogenicity in immunocompromised individuals (ClinicalTrials.gov number, NCT04870411).

Disclosures: None

149. COVID-IGRA' responses post SARS CoV2 vaccination in patients with primary (PID) and secondary (SID) Immunodeficiency

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Background: Patients with PID and SID are at risk from COVID disease. Patients with objective evidence of immunodeficiency have been advised to shield or cocoon, to reduce infection risk. Vaccination offers a possible pandemic exit strategy from these enforcted limitations for such groups. However, little is known about the effect of SARS-CoV2 vaccination on the immune system of patients with immunodeficiency conditions. We estbalished a robust, scalable 'COVID-IGRA'; A whole blood assay to measure IFN-g release (IGRA) after stimulation with SARS CoV2 antigens. We aimed to use this to assess post COVID vaccine IFN-g responses in controls including healthy older individuals and in patients in a variety of immunodeficiency states

Methods: Samples were drawn into 'Qiagen Monitor TM tubes' and after overnight incubation with SARS CoV2 membrane/ nucleopcapsid peptide mix, spike peptide mix (Miltenyi) or recombinant spike trimer protein, the supernatants were tested by ELISA for IFNγ level. Normal ranges were established using healthy controls pre-vaccination (n=32) and 28-40 days post vaccination (n=40). Patients with PID were invited to participate including Common Variable Immunodeficiency (CVID) (n=27), X-linked Agammaglobulinaemia (XLA) (n=8), other Inborn Errors of Immunity (IEI) (n=8). A comparator group of patients with symptomatic SID were recruited (n=13). This included 9 patients with rituximab treated ANCA vasculitis

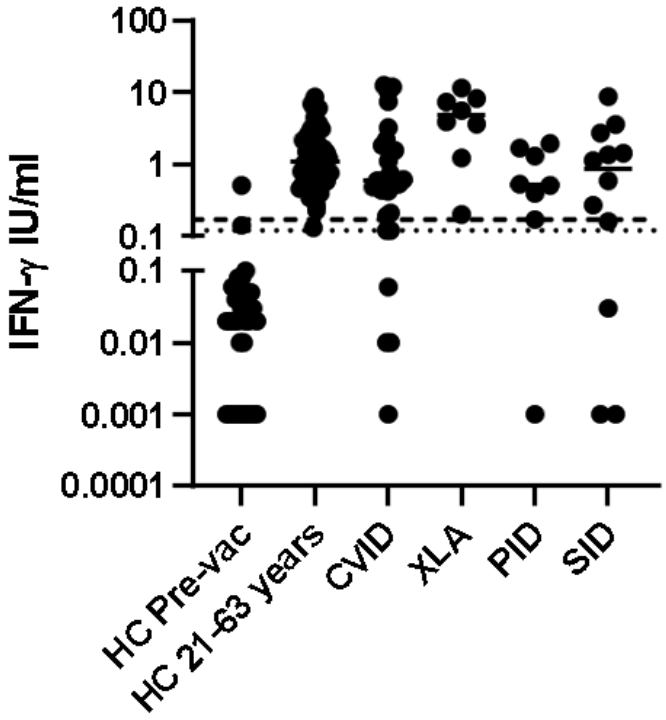
Results: Healthy control assay validation data demonstrated that the SARS CoV2 spike peptide antigen was able to discriminate accurately between pre and post vaccine samples (ROC AUC 0.99). Stimulation with whole spike protein was a less perfect recall antigen in the post vaccine state. 23/27 (85%) of patients with Common Variable Immunodeficiency (CVID) produced a post vaccine IFNg response in whole blood that was comparable to the reference range derived from healthy controls (Figure 1). 8/8 (100%) of XLA patients and 7/8 (87.5%) of other IEI patients produced a similar response. 9/13 (69%) patients with symptomatic SID produced a robust response. Patients with CVID who did not respond had a significantly higher disease severity score (42.75 v 13.8, $p<0.01$) than those who did respond. Membrane/Nucleocapsid antigen induced IFNg release was suggestive of prior natural infection.

Conclusions: We established and validated a COVID IGRA. Our assay is scalable, robust, reproducible and suitable for use in a routine diagnostic laboratory. Many patients with objective evidence of PID and SID immunodeficiency produce IFNg responses to SARS CoV2 antigens. However, a higher proportion of patients with SID, including patients on maintenance rituximab, failed to produce a normal IFNg response. Although numbers are small our data suggests that examination of this cohort is desirable. It is currently unknown whether cellular

immune responses such as IFNg release in response to recall antigens in the post vaccine state represent correlates of clinical protection. The high proportion of vaccinated PID and SID patients inducing IFNg production, comparable to healthy controls in conditions where humoral immunity is known to be compromised does indicate vaccines are inducing measurable cellular recall responses. This information may be useful in explaining the rationale for vaccination in immunocompromised cohorts. We propose further work correlating our assay with other COVID-IGRA methodologies and examining factors that may influence reduced cellular and humoral immune responses in similar cohorts.

Disclosures: NC's work is in part supported by an SFI grant 20/SPP/3685. The STTAR Bioresource for COVID-19 is also, in part, supported by an unrestricted grant from Takeda

Figure 1. Showing log IFNg levels in patients and healthy controls whole blood following stimulation with SARS CoV2 spike peptide mix. Dotted line = lower indeterminate range, Dashed line = upper indeterminate range.



150. Refractory ANCA associated Vasculitis (AAV) post Pfizer COVID-19 Vaccine

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Presentation of Case: A 57-year-old male with a history of hypertension and rosacea treated with hydralazine and minocycline respectively, presented to the hospital with dyspnea and lower extremity skin rash a week after completing the 2nd dose of Pfizer COVID-19 mRNA

vaccine. Skin rash started after the initial dose and got exacerbated by the subsequent dose. Physical exam was unremarkable except for lower extremity tender purpuric rash and pitting edema.

Diagnostic Testing: Laboratory tests revealed hemoglobin of 5.7 g/dL, elevated LDH (254 U/L), schistocytes on peripheral smear, and serum creatinine (sCr) of 5.2 mg/dL. Further evaluation showed serum albumin of 3.2 g/dL, CRP of 1.9 mg/dL, and negative anemia workup. Urinalysis showed microscopic hematuria, red blood cell casts, and a spot UPCR of 1.15 g/g. Serologies were notable for positive MPO-ANCA antibodies >100 units, and negative PR3. HIV and all hepatitis serologies were negative. Chest CT revealed bilateral upper and lower lobe perihilar ground-glass opacities. SARS-CoV-2 was ruled out.

Kidney biopsy demonstrated 14 nonsclerotic glomeruli, with 2 showing crescentic pauci-immune glomerulonephritis (GN) with 30% interstitial fibrosis and tubular atrophy.

Differential & Final Diagnosis: While pulmonary renal syndrome is the prototype presentation of anti -GBM disease, it can also be seen in, AAV and immune complex mediated GN. We infer our patient has AAV with microscopic polyangiitis involving skin, kidney, and lung, likely triggered by the vaccine given the temporal association with the receipt of the vaccine.

Discussion of Management: Patient received induction with methylprednisolone followed by prednisone taper and rituximab with a decrease in sCr to 3.36 mg/dL at the time of discharge. Hydralazine and minocycline were discontinued. Repeat rituximab was administered in a 2-week interval reaching a sCr nadir of 2.7 mg/dL, however, a week later patient was re-admitted with recurrent skin rash and worsening kidney function, sCr peaked at 6.7 mg/dL, p-ANCA titters increased to 1:640. In the setting of refractory vasculitis, he was treated with pulse methylprednisolone, plasma exchange, and a short course of oral cyclophosphamide. Gradual improvement of renal function ensued no requirement of dialysis in the interim. His vasculitis remains in remission with a sCr of 1.63 mg/dL.

Conclusions: Although the constellation of findings in our patient is suggestive of drug induced AAV set off by hydralazine and minocycline, the temporal relation between vaccine administration and the onset of vasculitis cannot be ignored. Recent literature has described increasing evidence of SARS-CoV-2 vaccine induced glomerular disease; thus far 6 cases of crescentic GN have been reported, 5 of them de novo and 1 relapsing, all had positive ANCA serology. While causality cannot be established, and its occurrence is rare, it is important to clarify whether the autoimmune response is a consequence of molecular mimicry, vaccine adjuvants, or a transient systemic proinflammatory cytokine response having T cells as important mediators triggering podocytopathies in genetically predisposed individuals. If this response could be a direct reaction to RNA- based vaccines remains to be elucidated. We suspect that a dysregulated immune response may have a role given suboptimal response to rituximab induction. It is imperative mechanisleading to de novo or relapsing glomerular disease are identified with continued reporting and surveillance of these rare occurrences.

Disclosures: None.

151. Vasculitis following SARS-CoV-2 vaccination

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Background: SARS-CoV-2 vaccination can rarely trigger a heightened inflammatory response, notably vaccine-induced immune thrombotic thrombocytopenia (VITT). Case reports also suggest an association with SARS-CoV-2 vaccination and vasculitic reactions.
Presentation of Case 1:
A previously well 60 year old female developed small joint arthritis and myalgia following a first dose of Astra-Zeneca ChAdOx1-S/nCoV-19 adenoviral vector SARS-CoV-2 (AZ) vaccine in January 2021. Two weeks after the second AZ vaccine dose (April 2021), her arthritis worsened and she developed numbness and progressive weakness in her hands. Eight months after symptom onset she was hospitalised with an abdominal vesicular rash, diarrhoea and vomiting.
Diagnostic Testing, **Diagnosis** and Management: CRP was elevated at 290 mg/L, liver function was abnormal (ALP 462 U/L, ALT 162 U/L) and she had a small pericardial effusion. Infection screen was normal apart from VZV DNA from her rash. Hepatitis screen and autoimmune serology were negative. CT excluded malignancy and found mild hepatic steatosis. She failed to respond to antibiotics and deteriorated, requiring non-invasive ventilation on intensive care. Further complications of radial artery and superficial venous thrombosis occurred in association with line insertions. Nerve conduction studies confirmed mononeuritis multiplex, sural nerve biopsy identified T cell infiltrate suggesting a vasculopathic process and bronchoscopy demonstrated diffuse alveolar haemorrhage. Dermatomal shingles was treated with aciclovir, following which intravenous methylprednisolone allowed rapid symptomatic improvement. Clinical findings along with exclusion of systemic infection and response to steroids led to a diagnosis of vaccine-induced ANCA negative small/medium vessel vasculitis. Given her disease severity she also received high dose oral prednisolone and cyclophosphamide which led to hospital discharge with CRP 39mg/L and improving liver function in October 2021.
Presentation of Case 2:
A 71 year old male presented with a lower limb purpuric rash, blisters on his fingers, arthritis and severe fatigue, eight days after a first dose of Pfizer-BioNTech BNT162b2 mRNA SARS-CoV-2 (Pfizer) vaccine (January 2021). He had previously treated bowel cancer in 2011.
Diagnostic Testing, **Diagnosis and Management**: CRP was elevated at 400 mg/L; however, autoimmune serology and blood cultures were negative. A lung nodule was identified on CT scan. A clinical diagnosis of small vessel vasculitis was made and he received 3 months of tapering prednisolone 40 mg/day with symptomatic improvement. He received a second Pfizer vaccine dose in April 2021, following which his symptorecurred and he was hospitalised with breathlessness. CT demonstrated a pulmonary embolism, skin biopsy demonstrated fibrinoid necrosis, perivascular inflammation and thrombi (leucocytoclastic vasculitis). Oral prednisolone 40mg/day was restarted and tapered over 6 months. Follow-up imaging showed lung nodule

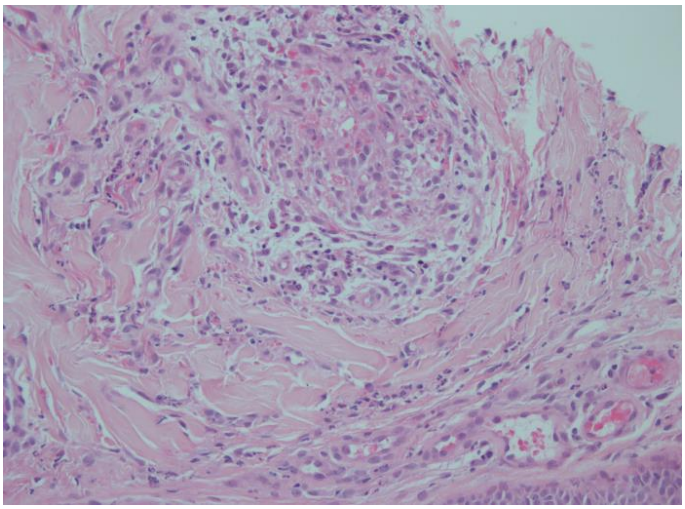
resolution. In November 2021 he was symptom free (CRP <4 mg/L) and he received a booster dose of the SARS-CoV-2 Moderna vaccine without complication.

Discussion: These two cases highlight a temporal association between SARS-CoV-2 vaccination and systemic vasculitis with thromboses. Both patients responded to glucocorticoids, with additional cyclophosphamide use in one due to severe disease. Vaccine-induced vasculitis is well described, in particular after influenza vaccination; although population studies suggest the incidence is rare. SARS-CoV-2 vaccination is extremely common, and reports of associated vasculitic reactions are limited, suggesting that SARS CoV-2 associated vasculitis is also rare.

Conclusions: Our report adds to the literature of a temporal association between Pfizer and AZ SARS-CoV-2 vaccination and de novo vasculitis. Awareness of this rare phenomenon is important for both diagnosis and treatments including glucocorticoids and anticoagulation.

Disclosures: Dr Jones has received grants/consultancy fees from GlaxoSmithKline, Vifor Pharma, ChemoCentryx and Roche**.** David Jayne's disclosures of commercial conflicts for companies with marketed products for 2021 are: Astra-Zeneca, Aurinia, BMS, Boehringer-Ingelheim, GSK, Janssen, Novartis, Roche/Genentech, Takeda & Vifor.

Figure 1. Skin biopsy from Case 2, with mid dermal perivascular inflammation, red cell extravasation and an organising vascular thrombus containing fibrin



152. COVID-19 Vaccination Perceptions in Vasculitis Patients

Imama Butt[1], Charmaine van Eeden[1], Jan Willem Cohen Tervaert[1], Alison Clifford[1], Elaine Yacyshyn[1]

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Background: Vaccination against SARS-CoV-2 is essential towards ending the COVID-19 pandemic. Previous international studies have demonstrated that a significant proportion of rheumatology patients are vaccine hesitant.[1] Patients with rheumatologic conditions, such as vasculitis and Autoimmune/Inflammatory Syndrome induced by Adjuvants (ASIA) syndrome, may be susceptible to contracting SARS-CoV-2 and developing poor outcomes.[2] Vaccination is important in managing and preventing rheumatic disease exacerbation. The objectives of this

study were to identify the factors implicated in vaccine-hesitant ASIA and vasculitis patients' decision-making around COVID-19 vaccination. Results from this study may help healthcare providers engage patients in discussion around their concerns and promote vaccine uptake.

Methods: Adult rheumatology patients seen at a Rheumatology Clinic in Edmonton, Canada were surveyed using an anonymous online questionnaire, between June and August 2021. The survey asked questions on demographics and medical history, vaccination and COVID-19, and informed decision-making. Survey responses were then analysed for statistical differences using chi-square analysis.

Results: The COVID-19 Vaccine Perceptions Survey had a response rate of 70.9%. Of the total 231 respondents, 121 patients had been diagnosed with either ASIA (n=18) or vasculitis (Takayasu's arteritis, GCA, ANCA-associated vasculitis, or IgA vasculitis) (n=103). The ASIA and vasculitis subgroups were not statistically different from patients with other rheumatic diseases in tergender, age, education level, or annual household income. However, compared to other rheumatology patients, ASIA and vasculitis patients had significantly shorter length of diagnosis of rheumatic disease ($p<0.001$), more rheumatic conditions ($p<0.001$), and had a higher proportion of patients on disability support income ($p=0.01$). At the time of the survey, 78.5% of patients in the ASIA and vasculitis subgroup had received one COVID-19 vaccine dose, with 11.6% of participants refusing vaccination. Compared to other responders, vaccine-hesitant ASIA and vasculitis patients were significantly more concerned about almost every aspect of available COVID-19 vaccines (e.g., safety ($p <0.001$), effectiveness ($p=0.02$)), and feared that they could contract SARS-CoV-2 from a vaccine ($p<0.001$). Similarly, the vaccine-hesitant ASIA and vasculitis subgroup was significantly less satisfied in the government's response to the COVID-19 pandemic (e.g., less trust in government-provided reports on vaccines ($p<0.001$) and COVID-19 ($p=0.04$)), significantly less confident in the information provided by their healthcare team ($p<0.001$), and less likely to involve them in their COVID-19 vaccine decision-making (e.g., more likely to report that healthcare providers had no role in vaccine decision-making ($p<0.001$)).

Conclusions: Vaccine-hesitant ASIA and vasculitis patients were significantly less confident in all aspects related to COVID-19 vaccines and the overall healthcare system (government and healthcare providers) involved in administration and promotion of vaccination. Healthcare teacan help dispel some of these worries by specifically addressing the vaccine-related concerns identified in this study and ensuring a more active role in supporting patients' vaccine decision-making.

Disclosures: I.N. Butt, None; C. van Eeden, None; J.W. Cohen Tervaert, None; A. Clifford, None; E. Yacyshyn, None

Table 1: Vaccine-hesitant ASIA and vasculitis patients' most significant concerns around COVID-19 vaccines and healthcare providers, in COVID-19 Vaccine Perceptions Survey participants.

Vaccine-hesitant patients with ASIA or vasculitis who responded:	Yes [n =] (% total responders)	No [n =] (% total responders)	Not Sure [n=] (% total responders)	p-value
COVID-19 vaccine concerns				
Speed of development	11 (26.8)	2 (3.2)	0	**<0.001**
Safety	13 (26.5)	0	0	**<0.001**
Components	11 (28.9)	0	2 (11.8)	**<0.001**
Severe adverse reactions	12 (26.1)	1 (1.5)	0	**<0.001**
Getting COVID-19 from vaccine	7 (53.8)	5 (5.3)	1 (14.2)	**<0.001**
Side effects	9 (26.5)	4 (5.1)	0	**0.003**
Impact on rheumatic condition	12 (19.4)	1 (2.0)	0	**0.008**
Risk of blood clots	10 (21.7)	2 (3.2)	1 (11.1)	**0.009**
Effectiveness	10 (17.9)	1 (2.0)	2 (20.0)	**0.02**
Health care provider perceptions				
Healthcare provider helped in decision to get COVID-19 vaccine	5 (5.8)	8 (22.9)	-	**0.006**
Spoken to healthcare provider(s) about getting a COVID-19 vaccine	7 (7.1)	6 (27.3)	0	**0.02**
Belief that providers can answer questions regarding COVID-19 vaccines	6 (6.6)	5 (27.8)	2 (18.2)	**0.02**

153. Cutaneous Leukocytoclastic Vasculitis Post COVID-19 Vaccination - a Review of Literature

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Background: In the fight against coronavirus disease 2019 (COVID-19), different types of vaccines, such as messenger RNA (mRNA) vaccines, viral vector vaccines and inactivated vaccines, have been rapidly developed. With a growing vaccinated population, uncommon adverse cutaneous reactions including leukocytoclastic vasculitis (LCV) have been increasingly observed and reported following immunization. Considering the lack of reviews that summarize the existing literature, we hereby reviewed various cases of LCV post-COVID-19 vaccination.

Methods: Data are obtained from manual search results of online databases, mainly PubMed, Semantic Scholar, Google Scholar and Web of Science. A number of keywords are used, including but not limited to, "coronavirus", "COVID-19", "SARS-CoV-2", "vaccine", coronavirus disease-19", "new coronavirus", "2019-nCoV", "novel corona virus", "novel coronavirus", "nCoV-2019", "2019 novel coronavirus", "coronavirus disease 2019", "leukocytoclastic vasculitis", "small-vessel vasculitis", "Cutaneous small-vessel vasculitis", "IgA vasculitis", "Henoch-Schönlein purpura", and "Urticarial vasculitis".

Results: We reviewed the currently available literature up to November 2021, including case reports, reviews, letters to the editor and comments, regardless of the vaccine type or target population. More than 30 cases of COVID-19-vaccine-related LCV have been reported,

ranging from IgA vasculitis to urticarial vasculitis. Cutaneous reactions typically developed from a few days to 2 weeks after vaccination, and resolved after glucocorticoid treatment. A temporal association between vaccination and LCV could be established, with recurrences observed in some cases after another dose of vaccine.

Conclusions: Although the number of published cases of post-vaccination LCV is relatively low, it is important for healthcare providers and patients to be aware of the possible cutaneous reactions associated with the COVID-19 vaccine in order to avoid complications and to be better prepared. The pathophysiological mechanisof post-vaccine LCV are still unclear in literature and the causative link is yet to be formally established. Further investigations are needed with the use of standardized methods for data collection and interpretation.

Disclosures: None

154. Humoral immune response after SARS-CoV-2 vaccination in systemic vasculitis - a Target to B! substudy

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Background: Vasculitis patients are at increased risk of negative outcome of a COVID-19 infection, both due to their disease and due the immunosuppressive treatments used. The aim of this study was to investigate the effect of various immunosuppressive therapies on the humoral immune responses after vaccination against SARS-CoV-2 in patients with systemic vasculitis.

Methods: The Target to B! SARS-CoV-2 study is a multicentre study, taking place in 7 Dutch academic hospitals. We present the data of 84 patients with systemic vasculitis (including large vessel vasculitis and ANCA-associated vasculitis) with various treatment regimens. SARS-CoV-2 receptor binding domain (RBD) antibodies were measured 28 days after completed SARS-CoV-2 vaccination.

Results: The results are demonstrated in table 1. Seven patients had prior SARS-CoV-2 infections, two of these were treated with rituximab (RTX). Six of these patients were seropositive after SARS-CoV-2 vaccination, except for one of the RTX treated patients. The seroconversion rate for the SARS-CoV-2 naive patients were high in patients without immunosuppression (8/8; 100%), whereas patients using immunosuppressive treatment other than RTX exhibited reduced seroconversion rate (30/38 78.9%) and this was even lower in patients using RTX (10/31; 32.3%). The effects of an additional, third vaccination and the B cell number at time of third vaccination on humoral immune responses is under current investigation.

Conclusions: RTX based immunosuppression in systemic vasculitis patients is associated with reduced, but not absent seroconversion rate after SARS-CoV-2 vaccination. Third or

booster vaccinations might be beneficial for these patients, although they might have to be timed properly in relation to RTX administration and B cell recovery.
Disclosures: *Funding by* ZonMw (The Netherlands Organization for Health Research and Development). On behalf of the T2B! immunity against SARS-CoV-2 study group

Table 1

	anti-CD20(+other(s))		corticosteroids		corticosteroids(+other(s))		MTX/MMF/PA/TOC	no systemic immunosuppression	Overall	
	no previous COVID-19 (N=31)	previous COVID-19 (N=2)	no previous COVID-19 (N=13)	previous COVID-19 (N=3)	no previous COVID-19 (N=18)	previous COVID-19 (N=2)	no previous COVID-19 (N=7)	no previous COVID-19 (N=8)	no previous COVID-19 (N=77)	previous COVID-19 (N=7)
AGE										
Mean (SD)	58.6 (14.0)	66.0 (9.90)	66.5 (7.49)	60.0 (9.54)	60.6 (8.25)	48.0 (15.6)	53.0 (13.9)	68.4 (9.55)	60.9 (12.0)	58.3 (12.0)
Median [Q1,Q3]	59.0 [52.5,67.5]	66.0 [62.5,69.5]	66.0 [61.0,72.0]	55.0 [54.5,63.0]	60.5 [56.3,67.0]	48.0 [42.5,53.5]	54.0 [47.5,60.0]	68.5 [64.0,75.0]	62.0 [55.0,69.0]	59.0 [54.5,65.0]
SEX										
Male	18 (58.1%)	2 (100%)	10 (76.9%)	2 (66.7%)	6 (33.3%)	1 (50.0%)	3 (42.9%)	6 (75.0%)	43 (55.8%)	5 (71.4%)
Female	13 (41.9%)	0 (0%)	3 (23.1%)	1 (33.3%)	12 (66.7%)	1 (50.0%)	4 (57.1%)	2 (25.0%)	34 (44.2%)	2 (28.6%)
vaccin										
Moderna	5 (16.1%)	0 (0%)	1 (7.69%)	0 (0%)	2 (11.1%)	0 (0%)	1 (14.3%)	1 (12.5%)	10 (13.0%)	0 (0%)
AZ	5 (16.1%)	0 (0%)	3 (23.1%)	0 (0%)	4 (22.2%)	0 (0%)	3 (42.9%)	1 (12.5%)	16 (20.8%)	0 (0%)
Pfizer/BioNTech	21 (67.7%)	2 (100%)	9 (69.2%)	3 (100%)	12 (66.7%)	2 (100%)	3 (42.9%)	6 (75.0%)	51 (66.2%)	7 (100%)
ISP										
no ISP	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	8 (100%)	8 (10.4%)	0 (0%)
ISP	31 (100%)	2 (100%)	13 (100%)	3 (100%)	18 (100%)	2 (100%)	7 (100%)	0 (0%)	69 (89.6%)	7 (100%)
diagnosis_VAS										
ANCA-vasculitis	29 (93.5%)	2 (100%)	5 (38.5%)	1 (33.3%)	14 (77.8%)	2 (100%)	3 (42.9%)	7 (87.5%)	58 (75.3%)	5 (71.4%)
other vasculitis	2 (6.45%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (28.6%)	0 (0%)	4 (5.19%)	0 (0%)
large vessel vasculitis	0 (0%)	0 (0%)	8 (61.5%)	2 (66.7%)	4 (22.2%)	0 (0%)	2 (28.6%)	1 (12.5%)	15 (19.5%)	2 (28.6%)
seroconversion_VD1										
seroconversion	2 (7.69%)	0 (0%)	6 (60.0%)	3 (100%)	3 (20.0%)	1 (50.0%)	1 (16.7%)	3 (50.0%)	15 (23.8%)	4 (57.1%)
no seroconversion	24 (92.3%)	2 (100%)	4 (40.0%)	0 (0%)	12 (80.0%)	1 (50.0%)	5 (83.3%)	3 (50.0%)	48 (76.2%)	3 (42.9%)
Missing	5 (16.1%)	0 (0%)	3 (23.1%)	0 (0%)	3 (16.7%)	0 (0%)	1 (14.3%)	2 (25.0%)	14 (18.2%)	0 (0%)
seroconversion_VD2										
seroconversion	10 (32.3%)	1 (50.0%)	11 (84.6%)	3 (100%)	13 (72.2%)	1 (100%)	6 (85.7%)	8 (100%)	48 (62.3%)	5 (83.3%)
no seroconversion	21 (67.7%)	1 (50.0%)	2 (15.4%)	0 (0%)	5 (27.8%)	0 (0%)	1 (14.3%)	0 (0%)	29 (37.7%)	1 (16.7%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (50.0%)	0 (0%)	0 (0%)	0 (0%)	1 (14.3%)

155. Humoral and cellular SARS-CoV-2 vaccine responses in patients with Giant Cell Arteritis and Polymyalgia Rheumatica

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Background: Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are overlapping autoinflammatory diseases that target almost exclusively people over 50 years. The diseases are commonly treated with immunosuppressive drugs such as glucocorticoids (GCs), methotrexate (MTX), leflunomide (LEF) and tocilizumab (TCZ). The recent SARS-CoV-2 pandemic has had tremendous effects on these patients, both medically and psychologically. Even though the SARS-CoV-2 vaccines have proven to be overwhelmingly efficient in preventing severe disease in the general population, little is known about their effect on patients with GCA and PIn particular, the effect of their immunosuppressive medication may substantially hamper their vaccine responses. Therefore, the objective of this study is to assess effectiveness of SARS-CoV-2 vaccination in GCA and Ppatients, based on humoral and cellular immunity.

Methods: We investigated the effectiveness of COVID-19 vaccination in GCA and Ppatients participating in our prospective GPS cohort in the Netherlands. We assessed immune responses to COVID-19 vaccines that are part of the 2021 national vaccination program. Participants were requested to visit the outpatient clinic twice: pre-vaccination and 4 weeks

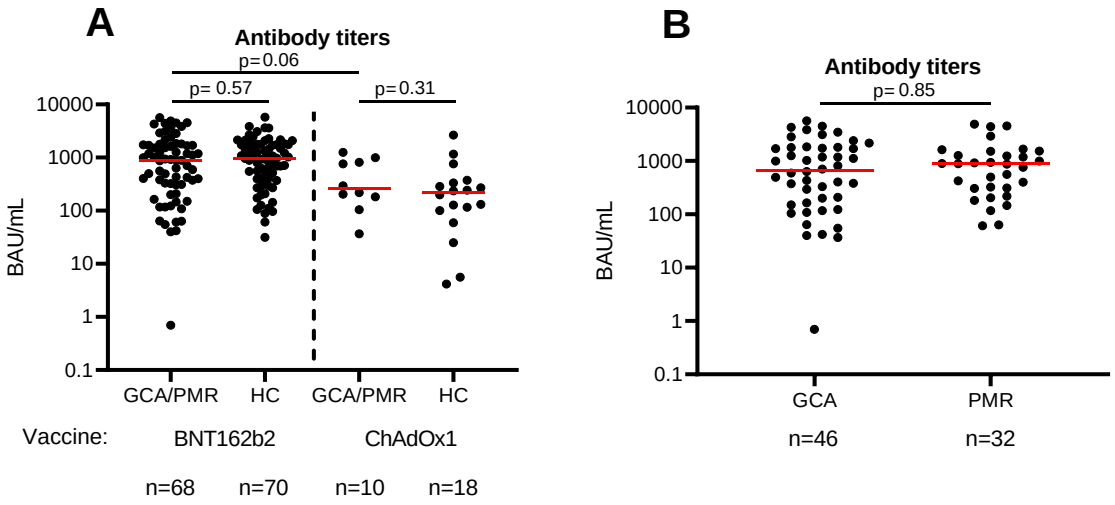
post-vaccination. Patients with a previous SARS-CoV-2 infection were excluded. In both pre- and post-vaccination samples, antibody titers against the Spike protein were assessed using the Multiplex Immuno assay. Antibody titers of patients were compared to age-, sex- and vaccine-matched control groups. The frequency of Spike-specific T-cells was assessed by an IFN-γ ELIspot assay with pre- and post-vaccination samples.

Results: After exclusion, 46 GCA patients, 32 Ppatients and 98 controls participated in this study. The total GCA/Ppatient population did not have reduced antibody titers compared to the control groups (Figure 1). No differences were observed between GCA and Ppatients. However, a linear regression analysis revealed three factors that were significantly associated with lower antibody titers in GCA/Ppatients: the use of MTX, the use of >10mg GCs and the ChAdOx1 vaccine. Evidence of cellular immunity, as assessed by ELIspot assay, was found in 65% of GCA/Ppatients. Antibody titers correlated positively with spot counts, indicating reduced cellular immunity in patients with a hampered humoral vaccine response.

Conclusions: As a patient population, GCA/Ppatients do not have a reduced vaccine response compared to other elderly individuals. However, patients using MTX and high dose GCs did show lower antibody titers after vaccination, which corresponds with findings in other patient populations suffering from autoinflammatory diseases. These patients may therefore face a higher risk of (potentially even severe) breakthrough infections, particularly when the time since the vaccination becomes longer.

Disclosures: Y van Sleen is under contract with Akston Biosciences. KSM van der Geest and E Brouwer received speaker fees from Roche.

Figure 1*: SASR-CoV-2 antibody titers in GCA and Ppatients after vaccination. In A, GCA/Ppatients are compared with age- and sex-matched controls. In B, GCA and Ppatients are compared. Data are expressed in BAU (binding antibody units).*



156. The immunological response to COVID-19 vaccination in patients with ANCA-associated vasculitis treated with rituximab

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Background: Landmark clinical trials have demonstrated efficacy of SARS-CoV-2 vaccination in preventing severe COVID-19, however most participants in these trials were healthy volunteers. In particular, vaccine performance in immunosuppressed individuals, such as those with ANCA-associated vasculitis (AAV) is unknown. Rituximab (RTX) has become an important treatment for AAV, however this B cell depleting agent has previously evidenced impaired humoral response following influenza vaccines and now there are similar concerns regarding reduced immunogenicity to SARS-CoV-2 vaccines. In this study, we aimed to characterise the immune response of the ChAdOx1 (Astra Zeneca) vaccine in RTX treated AAV patients. (1)

Methods: The OCTAVE trial was a UK based, multi-centre, multi-disease prospective cohort study designed to assess the immune response to SARS-CoV-2 vaccination in immunosuppressed individuals, including patients with AAV treated with RTX within the prior 12 months. Peripheral blood samples were taken for quantitative IgG response to SARS-CoV-2 spike antigen (anti-S) and IFNγ T cell responses to SARS-CoV-2 antigens at baseline (where possible), immediately prior to second SARS-CoV-2 vaccine dose and 28 days post-second dose. Results were compared to a group of healthy controls from the UK PITCH (Protective Immunity from T cells in Healthcare workers) study.

Results: Of 455 cases recruited for full immune response analysis, 29 had AAV and 93 were healthy controls. Baseline demographics were described (Table 1). At 4 weeks post-second SARS-CoV-2 vaccine dose 27.6% (8/29) AAV patients demonstrated anti-S seroconversion, compared to 100% (93/93) healthy controls. Further, 89.7% of AAV patients had an anti-S antibody response that was less that the lowest titre achieved in the healthy control group. When compared to other OCTAVE disease cohorts, AAV patients had the lowest serological conversion rate and lowest median anti-S titre. The median SARS-CoV-2 specific T cell response in the AAV group was 98 (IQR: 40-178) IFNγ secreting T cells / 10^6 peripheral blood mononuclear cells (PBMC), while the equivalent result in the healthy control group was 60 (IQR: 20-136) (Table 1).

Conclusions: Early analysis indicates that individuals with AAV have a substantially blunted antibody response to SARS-CoV-2 compared to a healthy population, but a comparable T-cell response. This may suggest that AAV patients have some degree of protection from SARS-CoV-2 vaccination, but clinical evaluation of this population is awaited. Analyses of additional immunological parameters, such as neutralising antibody responses and broader immunoglobulin analysis, are ongoing.

Disclosures: None relevant to this study.

Table 1: Demographics and anti-Spike seroconversion at 4 weeks in healthy controls and AAV patients

		Healthy controls	AAV
N (whole cohort)		231	30
Age; N (%)	18 – 40	186 (81%)	10 (33%)
	50 – 64	37 (16%)	12 (40%)
	65 +	7 (3%)	8 (27%)
	Missing data	1 (0%)	0 (0%)
Sex; N (%)	Female (%)	156 (68%)	16 (53%)
N (full immune response at 4 weeks)		93	29
Anti-S seroconversion; N (%)		93 (100%)	8 (27.6%)
Anti-S titre; U/ml [Median(IQR)]		11,514 (3,324-23,302)	0.4 (0.4-24.5)
IFNγ secreting T cells; per 10^6 PBMC [Median(IQR)]		60 (20-136).	98 (40-178)

157. Immunogenicity of SARS-CoV-2 vaccination in patients receiving immunosuppression

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Background: Patients receiving immunosuppression treatment are clinically vulnerable to coronavirus disease 2019 (COVID-19). Phase 3 trials of several vaccine candidates have shown proven immunological and clinical efficacy in the general population but excluded patients receiving immunosuppression or with renal impairment. In this study we describe immunological responses to vaccination with BNT162b2 mRNA or ChAdOx1 nCoV-19 replication-deficient adenoviral vector vaccines in patients with autoimmune glomerular and rheumatic diseases.

Methods: Immunological responses to vaccination were analysed in immunosuppressed patients (IS) and healthy volunteers (HV). In 443 patients, analysis of humoral responses were assessed at any time-point ≥21 days following two-dose vaccination. In a sub-group of 140 patients, and 70 HV analysis of both humoral and cellular responses were assessed at baseline, day 21 after first-dose, day and 6 months after second-dose. Serum was tested for antibodies to nucleocapsid protein using the Abbott Architect SARS-CoV-2 IgG chemiluminescent immunoassay (CMIA) and to spike protein using the quantitative Abbott Architect SARS-CoV-2 IgG Quant II CMIA. SARS-CoV-2 specific T-cell responses were detected using the T-SPOT® Discovery SARS-CoV-2 (Oxford Immunotec).

Results: 443 patients underwent assessment of humoral responses at a median of 31 days after second-dose vaccination. 62.5% received BNT162b2 (n=277) and 37.5% received ChAdOx1 (n=177), median vaccine interval was 65 days (IQR 35-76). Humoral response to vaccination was significantly lower than in those without prior natural infection (median anti-S 130.8 and 3171 BAU/ml respectively, p<0.0001). In infection-naïve patients multivariable analysis identified increasing age (OR 0.97, p0.01), rituximab treatment within 6 months of vaccination (OR 0.26, p=0.0002), B cell depletion at time of vaccination (OR 0.15, p<0.0001), and lower eGFR (OR 1.01, p=0.06) associated with decreased likelihood of seroconversion. When quantitative serological responses were analysed, time between vaccinations (Figure 1A), vaccine type (Figure 1B), and B cell depletion at time of vaccination (Figure 1C) were associated with decreased serological responses. There was inverse correlation between B cell count and anti-S titre (r=0.23, p=0.0005), and time since last rituximab treatment and anti-S titre (r=0.35, p<0.0001). In the sub-group of patients, following 2-dose vaccination, T cell responses were comparable between HV (n=51) and IS patients (n=43) with 83% of IS patients developing detectable T cell responses (Figure 1D). Magnitude of T cell responses was weaker in patients receiving treatment with tacrolimus (median 43 and 152 SFU/10^6 PBMC in patients treated with tacrolimus and not respectively, p=0.01). At 5-6 months after second-dose vaccination, anti-S titres were significantly lower in both IS (n=105 infection-naïve; median anti-S 11.2 BAU/m) and HV cohorts (Figure 1E; n=45 infection-naïve; median anti-S 107 BAU/ml). Similar to the earlier time point, T cell responses were comparable between IS (n=27, median 38 SFU/10^6 PBMC) and HV cohorts (Figure 1F; n=36, median 24 SFU/10^6 PBMC).

Conclusions: COVID-19 vaccines are immunogenic in the majority of patients with GN but serological responses are blunted, particularly in patients treated with rituximab. Age, eGFR, vaccine type and dosing interval also have an impact on seroconversion rates. T cell responses are comparable to HV and the majority of patients have detectable T cell responses to two-dose vaccination. Both serological and cellular responses have waned by 6 months after two-dose vaccination. Since patients with AAV are frequently of older age, treated with rituximab, and may have impaired GFR they are high risk of impaired vaccine responses and should be prioritized for further protective strategies.

Disclosures: PK and MW have received support to use the T-SPOT® Discovery SARS-CoV-2 by Oxford Immunotec.

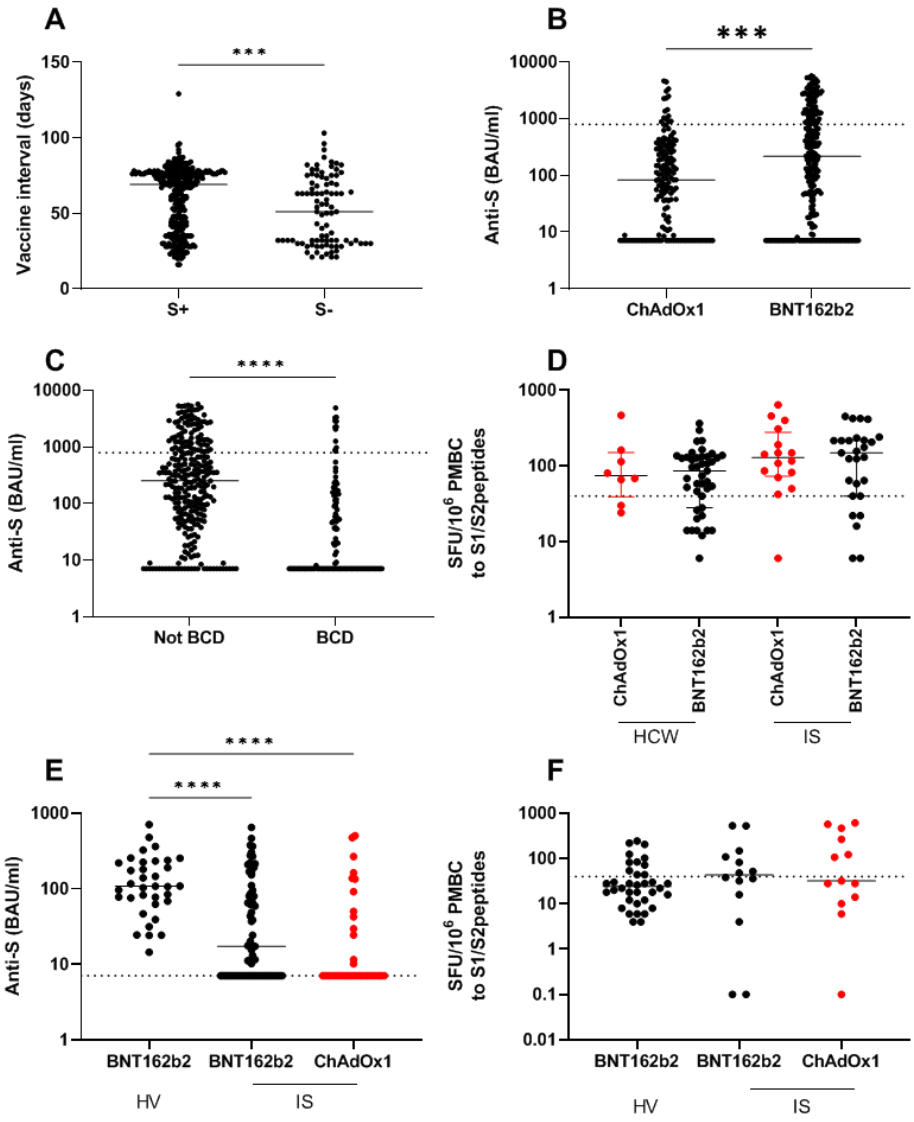

Figure 1. Immune responses to SARS-CoV-2 vaccination

158. Altered Antibody Response to SARS-CoV-2 Vaccination in Patients with Immune-mediated Disease on Immunosuppressive Therapy

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Background: The development of highly effective SARS-CoV-2 vaccines has provided the opportunity to combat the global COVID-19 pandemic. Vaccine trials that supported their authorization largely excluded individuals receiving immunosuppressive medications. While a growing number of studies have demonstrated impaired antibody production to SARS-CoV-2 vaccines among immunosuppressed patients, our understanding of the risk factors for suboptimal immune response remains incomplete. Following authorization of SARS-CoV-2 vaccines, we leveraged existing registries and multi-specialty clinics to collect longitudinal pre- and post-vaccine (prime-dose and booster) bio-samples.

Methods: We enrolled patients with immune-mediated disease who were currently on immunosuppressive therapy. Reactivity to the SARS-CoV-2 spike protein receptor binding domain (RBD) and N-terminal domain (NTD) were assessed by ELISAs using recombinant proteins produced in-house. Neutralizing antibodies were measured using a surrogate virus neutralization assay to determine the percent inhibition of RBD binding to ACE-2 (cPass, GenScript).

Results: To date, we have enrolled 80 patients (65% female, 81% white, age range 13 to 85; 56% vasculitis, 14% glomerular disease, 30% other) and 12 healthy controls not on immunosuppressive therapy. Sera from 64 patients collected 30 to 90 days after the prime vaccine series (41% Moderna, 59% Pfizer) has been tested (Table 1). Over half (34/64, 53%) developed neutralizing antibodies, all of whom had reactivity to RBD and NTD, including 4 patients who had received rituximab therapy within 3 months of their first vaccine dose. Thirty patients (47%) failed to develop neutralizing antibodies. Of these, 40% (12/30) showed reactivity to RBD and NTD. All healthy controls developed robust neutralizing antibodies and reactivity to RBD and NTD.

Conclusions: These data indicate that the antibody response following SARS-CoV-2 vaccination is altered in patients with immune-mediated disease. A substantial proportion of immunosuppressed patients developed reactive, but not neutralizing, antibodies to viral epitopes. Elucidating factors that contribute to sufficient humoral and cellular immunization is critical for the development of effective vaccination strategies for this vulnerable population.

Disclosures: None

Table 1. SARS-CoV-2 reactivity by medication type in patients with immune-mediated diseases				
Medication type	N (%)	RBD+	NTD+	Neut Ab+
Rituximab	30 (47%)	18 (60%)	18 (60%)	12 (40%)
AZA	4 (6%)	4 (100%)	4 (100%)	4 (100%)
MMF	15 (23%)	10 (67%)	11 (73%)	6 (40%)
Methotrexate	4 (6%)	4 (100%)	4 (100%)	4 (100%)
Other	11 (17%)	10 (91%)	8 (73%)	8 (73%)
Total	*64*	*46 (72%)*	*45 (70%)*	*34 (53%)*
Abbreviations: MMF – mycophenolate mofetil, AZA – azathioprine. “Other” includes tumor necrosis factor alpha inhibitor, janus kinase inhibitor, Plaquenil, prednisone, and Tacrolimus.				

159. SARS-COV-2 vaccine responses in immunosuppressed patient populations

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Background: Dialysis patients and immunosuppressed renal patients are at increased risk of COVID-19 and were excluded from vaccine trials. We conducted a prospective multicentre study to assess SARS-CoV-2 vaccine antibody responses in dialysis patients and renal transplant recipients, and patients receiving immunosuppression for autoimmune disease.

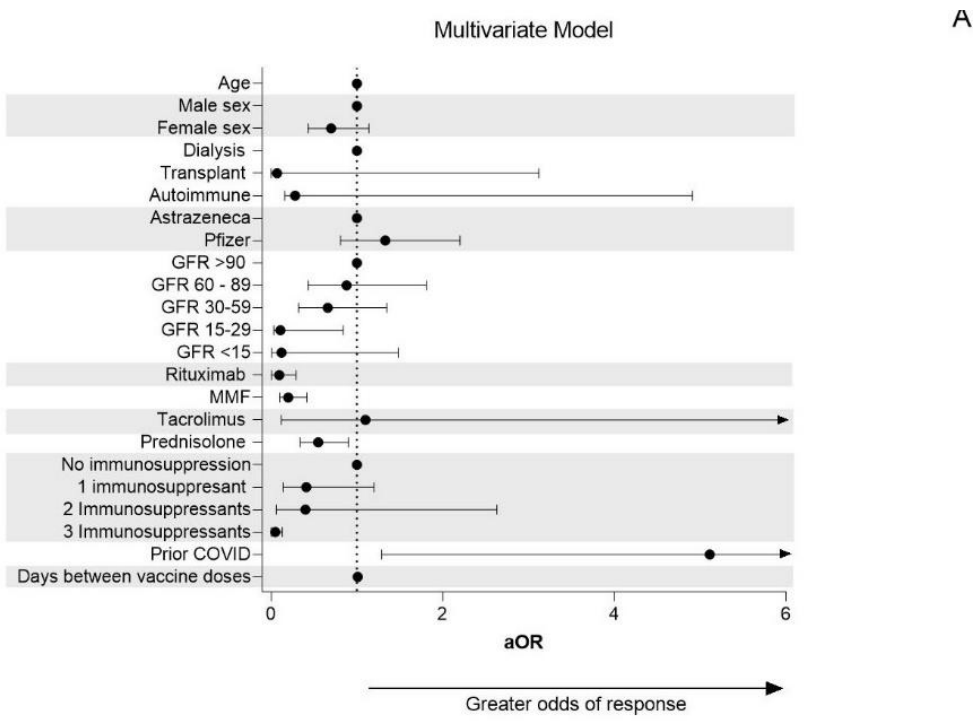
Methods: Patients were recruited from four UK centres (ethics:20/EM/0180) and compared to healthy controls (ethics:17/EE/0025). SARS-CoV-2 IgG antibodies to spike protein were measured using a multiplex Luminex assay, after first, second and third doses of Pfizer BioNTech BNT162b2(Pfizer) or Oxford-AstraZeneca ChAdOx1nCoV-19(AZ) vaccine. Clinical data on COVID19 infection and immunosuppression was collected from patient interviews and electronic medical records.

Results: 692 patients were included (260 dialysis, 209 transplant, 223 autoimmune disease (prior rituximab 128(57%)) and 144 healthy controls. 299(43%) patients received Pfizer vaccine

and 379(55%) received AZ. Median age was 62 (range 19 – 95) years. At time of assessment of second vaccine response prior PCR confirmed SARS-CoV-2 infection was documented in 39 individuals (6%). In the autoimmune population, disease subgroups were classified as: ANCA-associated vasculitis (AAV) 133 (60%); systemic lupus erythematosus (SLE) 27 (12%); large vessel vasculitis 11 (5%) and other 52 (24%). 128 patients had received rituximab, a median of 162 (IQR 110 – 275) days prior to vaccination Following two vaccine doses, positive responses occurred in 96% dialysis, 52% transplant, 70% autoimmune patients and 100% of healthy controls. In dialysis patients, higher antibody responses were observed with Pfizer vaccination. Predictors of poor antibody response were triple immunosuppression (adjusted odds ratio [aOR]0.016;95%CI0.002-0.13;p<0.001) and mycophenolate mofetil (MMF) (aOR0.2;95%CI 0.1-0.42;p<0.001) in transplant patients; rituximab within 12 months in autoimmune patients (aOR0.29;95%CI 0.008–0.096;p<0.001) and patients receiving immunosuppression with chronic kidney disease stage 4 (eGFR 15-29ml/min, aOR0.031;95%CI 0.11–0.84;p=0.021) (see Figure). After second vaccine dose median s-antibody titres correlated strongly with time from most recent rituximab treatment (Spearman's correlation coefficient 0.46; p<0.001), with increasing time from dose correlating with higher s-antibody titres. A lower median s-antibody was seen in those who had received Rituximab in the 6 months preceding a second vaccine dose (690 [IQR 175 – 12,767] compared to receiving a second vaccine dose greater than 6 months since most recent Rituximab treatment (27,975 (1,534 – 31,199); p<0.001.
Samples after third vaccine dose are currently being processed and analysis of antibody responses will be complete by April 2022.

Conclusions: Amongst dialysis, kidney transplant and autoimmune populations SARS-CoV-2 vaccine antibody responses are reduced compared to healthy controls. Following two vaccine doses a reduced response to vaccination was associated with rituximab in autoimmune patients, MMF and triple immunosuppression in transplant patients and immunosuppression use in CKD stage 4. Vaccine responses increased after second dose, suggesting low-responder groups should be prioritised for repeated vaccination. Greater antibody responses were observed with the mRNA Pfizer vaccine compared to adenovirus AZ vaccine in dialysis patients suggesting that Pfizer SARS-CoV-2 vaccine should be the preferred vaccine choice in this sub-group.

Disclosures: RS has received grants from GlaxoSmithKline (GSK) and Union Therapeutics**.** RJ has received grants/consultancy fees from GSK, Vifor Pharma, ChemoCentryx and Roche



160. Cellular/humoral Response to SAR-CoV-2 Infection and Vaccination in B cell Depleted Patients with Rituximab (RituxiVac)

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Background: The immune response to viral infections normally involves both humoral and cellular immunity. Patients on rituximab have prolonged B cell depletion and the humoral immune response is blocked. When the COVID 19 epidemic started in early 2020, virtually the entire population of the world had no detectable adaptive immunity. Thus, the immune responses of individuals infected with COVID 19, or vaccinated to COVID 19, or both, could be assessed starting with a clear slate. Among patients on rituximab with COVID 19, the immune response is without B cells.

Methods: We reviewed the available data on 630 patients who achieved B cell depletion during the COVID era (1/1/2020 to 7/26/2021) for the impact of SARS-CoV-2 infection and vaccination on their clinical and serologic course. T cell responses are being assessed in a subset of patients.

Results: After the last dose of rituximab, the median time to B cell recovery was 280 days (IQR, 272 – 363) (Figure 1A). Forty-seven patients contracted symptomatic COVID 19 while B cell depleted. Of these 47 patients, the infection occurred in 36 patients prior to vaccination (of

which 33 patients (91.7%) survived), in 3 patients during vaccination (of which 1 patient (33.3%) survived), and in 6 patients after vaccination (of which 5 patients (83.3%) survived). Two patients developed COVID 19 twice, once each before and after vaccination. Among the 6 total patients who died from COVID 19, additional risk factors were present in all, including advanced age (mean 74; range 57-92), CKD (n = 4), severe obesity (n = 2), cardiac disease (n = 2), and interstitial lung disease (n=1) (Figure 1C.) Antibodies to SARS-CoV-2 remained absent in all 41 surviving patients. Thirty-five COVID 19-naïve patients were identified who were vaccinated during B cell depletion and tested for SARS-CoV-2 spike antibodies. 33 of 35 had no detectable antibodies and 2 had very low levels of antibodies. Among 12 patients vaccinated during documented or imputed early B cell recovery, 6 had SARS-CoV-2 antibodies. Among 9 patients vaccinated after B cell recovery, 8 had SARS-CoV-2 antibodies (Figure 1D). T cell responses to SARS-CoV-2 peptides are being tested from an available subset of B cell depleted COVID survivors and from an available subset of B cell depleted vaccinated patients.

Conclusions: Rituximab treatment for autoimmune disease leads to prolonged B cell depletion. B cell depletion completely prevents a detectable antibody response to COVID 19. Nevertheless, among unvaccinated patients who contract SARS-CoV-2 infection, survival appears comparable to that of broader non-B-cell depleted populations with a similar degree of other risk factors. Recovery from COVID 19 without antibodies appears dependent on other aspects of the immune system and is presumably T cell driven. However, it remains to be seen if the current vaccines can provide protection from COVID 19 among B cell depleted patients. Studies of the T cell responses to SARS-CoV-2 infection and vaccination may lead to additional strategies for new vaccine creations.

Disclosures: In collaboration with Ragon Institute of MGH, MIT and Harvard. Funded by the Vasculitis and Glomerulonephritis Center, Ragon Insitute of MGH, MIT and Harvard, and Center for Disease Control and Prevention (DHHS).

Figure 1A

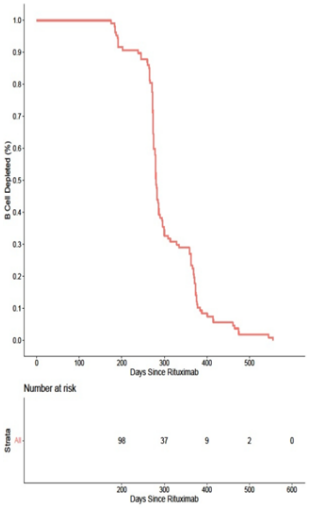


Figure 1B

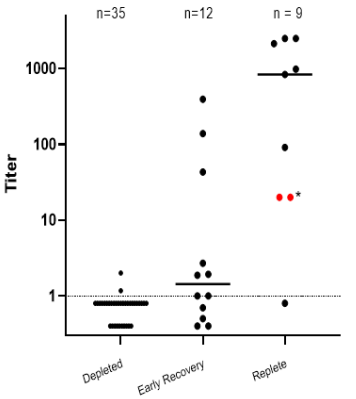
	1/1/2021-1/26/2021
Patients treated with rituximab - n	630
Total COVID19 (+) – n	47
COVID19 (+) prior to vaccination – n	36
COVID19 (+) during vaccination course – n	3
COVID19 (+) after completing vaccination course – n	6
COVID19(+) prior and after completing vaccination – n	2
Proportion of survival in patients with COVID19 (+) on rituximab–n(%)	41 (87.2)
Proportion of survival in patients with COVID19 (+) prior to vaccination–n(%)	33 (91.7)
Proportion of survival in patients with COVID19 (+) during vaccination course–n(%)	1 (33.3)
Proportion of survival in patients with COVID19 (+) after completing vaccination course–n(%)	5 (83.3)
Proportion of survival in patients with COVID19 (+) before and after completing vaccination–n(%)	2 (100.0)
Total Death – n	N = 6**

** risk factors described in figure 1C

Figure 1C

Groups	Demographics	Risk Factors
COVID19 (+) prior to vaccination	92y.o, male, white, non-Hispanic	Age (92 y.o.), CKD 3a, AKI, hypertension, malignancy (prostate cancer), chronic sinusitis, pulmonary nodules
	91y.o, female, white, non-Hispanic	Age (91 y.o.), CKD 3bAKI, hypertension
	70y.o, female, white, non-Hispanic	Age (70 y.o.), obesity (BMI: 42.5), hypertension
COVID19 (+) during the vaccination course	57y.o, male, White non-Hispanic	Age (57 y.o.), CKD 2, obesity (BMI 39.4) COVID (+) 1 day after 1st dose
	67y.o, male, white non-Hispanic	Age (67 y.o.) CKD 5, Paroxysmal atrial fibrillation congestive Heart Failure, Diastolic Congestive Heart failure Severe aortic stenosis, Mitral regurgitation
COVID19 (+) after completing vaccination	69y.o, male, White non-Hispanic	Age (69 y.o.), hypertension Cardiac disease and heart attack Dermatomyositis associated ILD DLCO 52% predicted

Figure 1D



Peripheral B-cell status during vaccination

B-cell Depleted is defined as CD20+ < 5, B-cell replete is defined as documented CD20+ ≥ 20
* two patients in the B-cell replete group have positive spike protein titer > 20 but the assay did not report the absolute titer.

COVID 19 - Risk factors & Outcome

161. Systemic vasculitides in the time of COVID-19 pandemic

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Background: COVID-19 pandemic significantly affected our routine rheumatological practice and the management of systemic vasculitides. To provide the best care for patients, daily practice has had to be adjusted overnight. We aimed to evaluate how successful we were in the management of systemic vasculitides during pandemic.

Methods: We analysed medical records of patients diagnosed with a systemic vasculitis before (Jan/2010-Feb/2020; overall 122 months) and during COVID-19 pandemic (Mar/2020 – Sep/2021; overall 19 months) at our secondary/tertiary medical centre. Variations in the frequency, delays to diagnosis (the symptom duration time until diagnosis) and the baseline activity of the most commonly diagnosed vasculitides, i.e. giant cell arteritis (GCA), IgA vasculitis, ANCA associated vasculitis (AAV) and cryoglobulinemic vasculitis (CryoV) were recorded. Disease activity/severity was assessed by the Birmingham vasculitis activity score (version 3) for small vessel vasculitides, and by assessing the development of permanent ischemic complications (permanent vision defect and/or ischemic stroke) in GCA.

Results: During the pandemic period, we diagnosed 122 new adult cases of GCA, IgAV, AAV, and CryoV (51, 33, 32, and 6 cases, respectively). Whereas the frequency per year of new GCA, IgAV and CryoV cases was comparable to pre-pandemic period, we diagnosed AAV nearly 3-times more frequently during the pandemic compared to average pre-pandemic year. Table 1 shows the median (interquartile range) symptom duration time and disease activity at presentation. In spite of the COVID-19 pandemic, neither was the symptom duration time longer nor was the baseline disease activity higher compared to the pre-pandemic decade.

Conclusions: The frequency of AAV increased during COVID-19 pandemic. Despite a lockdown during pandemic, we did not record any significant delay in diagnosing systemic vasculitides.

Disclosures: Authors have no conflict of interest to declare.

Table 1. Characteristics of vasculitides before and during COVID 19 pandemic

Vasculitis	No. of patients		Symptom duration time # (weeks)		Disease activity/severity*	
	Jan/2010 - Feb/2020	Mar/2020 - Sep/2021	Jan/2010 - Feb/2020	Mar/2020 - Sep/2021	Jan/2010 - Feb/2020	Mar/2020 - Sep/2021
GCA	341	51	4.3 (2.9 – 8.6)	3.0 (1.9 – 6.3)	11.1%	11.8%
IgAV	310	33	1.1 (0.7 – 2.4)	1.3 (0.7 – 2.0)	8 (3 – 14)	6 (2 – 10)
AAV	117	32	12.9 (5.6 – 36.4)	11.8 (4.3 – 26.8)	16 (11 – 22)	12 (6 – 19)
CryoV	57	6	25.7 (4.3 – 51.4)	7.5 (2.0 – 22.5)	11 (4 –19)	5 (2 – 10)

Legend: GCA giant cell arteritis; IgAV IgA vasculitis; AAV ANCA associated vasculitis; CryoV cryoglobulinemic vasculitis; # median and interquartile range (IQR); * determined as BVAS-3 (median, IQR) in IgAV and AAV, and as a percentage of patients with permanent vision defect or ischemic stroke in GCA.

162. Risks and treatment related aspects of COVID-19 in patients with ANCA associated vasculitis

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Background: Patients with ANCA associated vasculitis (AAV) require immunosuppressive therapy for disease control and prevention of relapse and may therefore be at risk for a severe disease course if infected by SARS-CoV-2. The disease itself and its consequences, for example kidney damage, may also increase the risk for a severe COVID-19 infection.
The objectives of this study was to analyse the outcome of COVID-19 in a large cohort of well characterized AAV patients regarding incidence and risk factors for development of severe infection.

Methods: Data were retrieved from March 2020 to May 2021 from the medical records of living patients from the AAV cohorts in Stockholm and Uppsala (n=310). Extracted data includes age, gender, ongoing immunosuppressive therapy, kidney involvement (ever), lung involvement (ever) and estimated GFR (eGFR). COVID-19 was confirmed either by a positive PCR test or by serology. Severe COVID-19 was defined as need of non-invasive ventilation, ICU care and/or death.

Results: The cohort comprised 232 patients with GPA, 56 with MPA and 22 with EGPA. 95% were ANCA positive (ever), the ANCA negative patients found mainly among the EGPA patients. 49% of the patients were female. During the study period 29 patients (9%) were diagnosed with COVID-19. The median age in the COVID-19 group was 60 (40-72) years, in the non-COVID group 68 (55-77) years (p=0.02). However, patients with severe COVID infection were older (p=0.07). Four deaths were related to COVID-19. Fifteen patients (52%) were on prednisolone treatment in the COVID-19 group and 130 (46%) in the non-COVID group, with significantly higher doses in the COVID-19 patients ($p < 0.01$). Concerning DMARD treatment, 65% were on (any) DMARD in both groups. However, induction therapy with either cyclophosphamide (CYC) and/or rituximab (RTX) and corticosteroids was more prevalent in the COVID-19 group, with 14% on induction in the COVID-group compared to 2.5% in the non-COVID group ($p<0.01$). Of the 29 COVID-19 cases, 9 (31%) had severe infection. Significant risk factors for severe COVID-19 was older age, impaired kidney function, higher steroid dose and ongoing induction therapy with cyclophosphamide (borderline risk for induction with CYC and /or RTX). RTX maintenance therapy was not associated with poorer disease outcome. See Table.

Conclusions: Patients with AAV were at risk for a more severe COVID-19 disease course. This risk is driven by known risk factors such as older age, but also of consequences of vasculitis i.e. impaired kidney function, and by treatment related factors. Higher steroid dose and ongoing induction therapy, reflecting higher disease activity, were significant risk factors in this group. More reassuring was that maintenance therapy with RTX was not associated with a severe disease course. The findings stress the need for continued shielding and prompt and effective vaccination in AAV patients.

Disclosures: None

Table 1. Characteristics comparing non-severe and severe COVID-19 infection

Subjects characteristics	Non-severe COVID-19	Severe COVID-19	p-value
Number of patients (%)	20 (69)	9 (31)	
Age (median, IQR)	51 (35.5-64.5)	69 (55.5-75.0)	0.02
Gender (F/M, %)	10/10(50/50)	4/5 (45/55)	ns
Diagnosis GPA/MPA/EGPA	16/3/1	6/2/1	ns
ANCA: None/PR3/MPO/both	2/15/3/0	2/5/2/0	ns
Lung involvement n (%)	13 (65)	6/9 (67)	ns
Renal involvement n (%)	11(55)	6/9 (67)	ns
eGFR (mL/min/1.7)	80.5(61.5-89.0)	53.0 (28.5-67.5)	0.01
Treatment			
Number on prednisolone	8(40)	7 (78)	ns
Prednisolone dose, mg/day (median, IQR)	5.0 (2.5-7.5)	7.5 (5.0-50.0)	0.02
DMARD (n, %)	12 (60)	7 (78)	ns
Induction therapy (rituximab and/or Cyclophosphamide) (n, %)	1 (5)	3 (33)	0.08

Cyclophosphamide induction (n, %)	0	2 (22)	0.05
Rituximab maintenance	7 (35)	1 (11)	ns

163. The course of COVID-19 in patients with Takayasu arteritis: Case series of 15 patients

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Background: The Coronavirus disease 2019 (COVID-19) has affected more than two hundred million individuals and many risk factors for increased mortality and morbidity in COVID-19 have defined. There are many studies evaluating the effect of immunosuppressants used in inflammatory rheumatic diseases in the course of COVID-19. (1,2) However, fewer data are available on the course of COVID-19 in patients with Takayasu arteritis (TAK). This study evaluated the characteristics and outcomes of TAK patients with COVID-19.

Methods: A phone survey was conducted among TAK patients that are followed up in our clinic between February 2021 and March 2021. All patients were asked whether they were diagnosed as COVID-19 during the pandemic. The patients who had a history of confirmed COVID-19 were asked about the symptoms, hospitalization status and the treatment received for COVID-19. Information about their chronic diseases were obtained from the patient files.

Results: Among 118 TAK patients, 15 had COVID-19 infection during the first year of pandemic, 13 of them were female and mean age was 42,5 ± 12,0 years. None of the patients had been vaccinated before the diagnosis of COVID-19. Nine of the patients were taking prednisone therapy and 3 of them were taking moderate to high doses of glucocorticoids during the infection period. Twelve patients were taking conventionally synthetic disease-modifying antirheumatic drugs (csDMARDs), 7 patients were taking biological disease-modifying antirheumatic drugs (bDMARDs), and 5 patients were taking a combination of csDMARD and bDMARD therapy when they were diagnosed with COVID-19. Two patients were hospitalized; one of them required nasal oxygen support and discharged after 5 days. The other patient was 61 years old and had multipl comorbidities and had admitted to intensive care unit for 5 days. One patient who had a mild COVID-19 disease had pulmonary thromboembolism 2 weeks after the infection and his symptoms resolved after starting anticoagulation therapy. All of the patients fully recovered and had no mortality related to COVID-19.

Conclusions: To our knowledge, this is the largest cohort reporting the course of COVID-19 in TAK patients. Our data suggest that there is no increased risk for morbidity or mortality related to COVID-19 in TAK patients.

Disclosures: None.

164. Increased Incidence of New and Relapsed Small Vessel Vasculitides During the COVID-19 Pandemic

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Background: In small vessel vasculitis autoimmunity develops in genetically susceptible individuals after an inciting event or exposure. Observational studies have found associations between viral and bacterial infections with systemic vasculitides. There have been case reports of concurrent ANCA associated vasculitis in patients that have tested positive for COVID-19 infection. We aimed to investigate the incidence of vasculitis in our centre over a year's period during the pandemic and compare it to a corresponding period before the pandemic.

Method: Data was collected on all patients that were diagnosed with new or relapsed vasculitis between April 2019 and March 2020 and compared to those diagnosed between April 2018 and March 2019.

Results: During the period 2019/2020 there was a total of 22 cases comprising 15 new diagnoses and 7 relapses whereas in the year 2018/2019 there were 9 cases made up of 7 new cases and 2 relapses. The demographics and clinical data of these patients are summarised in Table 1. Out of the 15 new cases diagnosed during the pandemic, 7 had a covid-19 test prior to their diagnosis of vasculitis, all of which were negative. After their diagnosis of vasculitis, 2 of them subsequently had a positive covid-19 test, 6 had a negative covid-19 test and 7 were not tested. Out of the 7 relapses during the pandemic, 4 were tested for covid-19 prior to their vasculitis relapse. All 4 of them tested negative. After their relapse 2 tested positive for COVID-19, 2 of them tested negative and 3 of them were not tested. Three of the patients with a new diagnosis of vasculitis during the pandemic died. The causes of death were unknown for two of them and COVID-19 for the remaining one. The death from COVID-19 occurred after their vasculitis diagnosis and induction treatment.Two of the patients that relapsed during the pandemic died. The causes of death were vasculitis for 1 of them and COVID-19 for the other.

Conclusion: There was 2.4 times the number of patients with new or relapsed cases of vasculitis in 2019/2020 compared to 2018/2019. Interestingly there were more cases of pANCA vasculitis during the pandemic compared to year before (8 cases versus 1). Whilst we hypothesised that the COVID-19 pandemic could partially explain the increase all the patients that were tested for COVID-19 prior to their diagnosis of vasculitis tested negative. However due to limited testing capacity in the early stages of the pandemic a substantial number of

patients were not tested for COVID-19. In addition we did not have access to serum COVID-19 antibody testing that might have identified past infections.
This study shows an increase in vasculitis incidence during the pandemic. It is possible that the presence of the virus in the environment could induce immunological effects in susceptible individuals without causing clinically apparent COVID-19 disease. Other factors such as lifestyle changes as a result of the pandemic can also be considered for the focus of future research.

Disclosures: None

Table 1

	2018/2019	2019/2020		2018/2019	2019/2020
New Diagnoses	7	15	Relapses	2	7
Age, Mean	69	72	Age, Mean	53	65
Female, n	5	8	Female, n	1	2
C-ANCA	4	6	C-ANCA	2	7
P-ANCA	1	8	P-ANCA	0	0
GBM	2	1	GBM	0	0
Immunosuppression			Immunosuppression		
Cyclophosphamide	6	13	Cyclophosphamide	0	3
Rituximab	1	2	Rituximab	2	4
COVID-19 Status			COVID-19 Status		
Pre-Diagnosis			Pre-Diagnosis		
Positive	N/A	0	Positive	N/A	0
Negative	N/A	7	Negative	N/A	4
Not Tested	N/A	8	Not Tested	N/A	3
Post-Diagnosis			Post-Diagnosis		
Positive	N/A	2	Positive	N/A	2

Negative	N/A	6	Negative	N/A	2
Not Tested	N/A	7	Not Tested	N/A	3

165. COVID-19 pandemic: outcomes among people with rare autoimmune rheumatic diseases during the second wave.

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[1]Lifespan and Population Health, University Of Nottingham, Nottingham, United Kingdom, [2]Department of Rheumatology, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom, [3]National Disease Registration Service, NHS Digital, London, United Kingdom

Background: To calculate the rates of COVID-19 infection and COVID-19-related death among people with rare autoimmune rheumatic diseases (RAIRD) during the second wave of the COVID-19 pandemic in England compared to the general population.

Methods: We used Hospital Episode Statistics data from the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) using their legal permissions (CAG 10-02(d)/2015) to identify all people alive 01 August 2020 with ICD-10 codes for RAIRD from the whole population of England. We used linked national health records (demographic, death certificate, admissions and PCR testing data) to calculate rates of COVID-19 infection and death up to 30 April 2021. Our primary definition of COVID-19-related death was mention of COVID-19 on the death certificate. General population data from Public Health England and the Office for National Statistics were used for comparison. We also describe COVID-19-related hospital admissions and all-cause deaths.

Results: We identified a cohort of 168,330 people with RAIRD (70.2% female, median age 61.7 (IQR 41.5 – 75.5)). 9,961 (5.92%) had a positive COVID-19 PCR test, which was similar to the general population (6.13%). The age-standardised infection rate ratio between RAIRD and the general population was 0.99 (95% CI 0.97-1.00). 1,342 (0.8%) people with RAIRD died with COVID-19 on their death certificate and the age-sex-standardised mortality rate for COVID-19-related death was 2.76 (2.63 – 2.89) times higher than in the general population. There was no evidence of an increase in deaths from other causes in the RAIRD population. 4432 (2.6%) people with RAIRD had a hospital admission with an associated diagnostic code for COVID-19 and 387 (0.2%) had an ICU admission with an associated diagnostic code for COVID-19.

Conclusions: During the second wave of COVID-19 in England, people with RAIRD had a 2.76x increased risk of COVID-19 related death compared to the general population, confirming the increased risk seen during the first wave of the pandemic. Unlike the first wave,

the risk of COVID-19 infection was similar between RAIRD and the general population. There was no evidence of increased risk of death from non-COVID-19 related causes.

Disclosures: FP & PCL are recipients of a grant from Vifor Pharma. Preprint: https://www.medrxiv.org/content/10.1101/2021.08.17.21260846v3.full

166. Rituximab – Patient Management and Outcomes in the Covid-19 era

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Background: Rituximab (RTX) is a chimeric anti-CD20 antibody that targets B-cells, leading to B cell depletion. It is the treatment of choice for many patients with systemic autoimmune inflammatory rheumatic and renal diseases. In the CoVid-19 era, vaccination of the general population and in particular the vulnerable immunosuppressed population is an essential component of the public health response. Evidence suggests that B cell-depleting therapy with RTX affects humoral immune responses after vaccination. It remains unclear whether RTX-treated patients can develop humoral and T-cell-mediated immune response against SARS-CoV-2 after immunization, and if not, are they susceptible to worse outcomes from CoVid-19 infection. There are also concerns that delaying rituximab to facilitate vaccination may lead to flares of the underlying disease and contribute to significant morbidity and/or mortality.

Methods: This is a retrospective observational cohort study of patients treated with RTX at a tertiary referral centre.The aim of this study was to determine a) changes in clinical practice in response to the CoVid-19 pandemic, b) the vaccination status of RTX-treated patients c) the incidence and outcomes CoVid-19 infection in RTX treated patients and d) any change in disease activity consequent to changes in RTX treatment schedules.

Results: A total of 210 patients were included in the study. This included 79 patients with rheumatoid arthritis, 55 with small vessel vasculitis, 25 with systemic lupus erythematosus (SLE), 9 with scleroderma, 5 with myositis, 4 patients with seronegative inflammatory arthritis, 4 with primary sjogrens syndrome, 1 with medium vessel vasculitis, 9 with other forms of connective tissue disease, 8 with membranous nephropathy, 2 with focal segmental glomerulosclerosis, 6 with minimal change disease, 1 with IgG4 disease, 1 with amyloid renal disease and one with an unspecified nephrotic syndrome. 94 patients had their treatment with rituximab delayed, primarily to facilitate augmented vaccination responses. Of these, 48 patients experienced a disease flare (51%). In contrast only 23 of 116 patients who continued RTX experienced a disease flare (19%). 42 patients in the study had their immunosuppression treatment changed for various reasons, predominantly to re-establish disease control following flare. Disease flare was most common in scleroderma, SLE, small vessel vasculitis and RA. At least 184 (87%) of patients were vaccinated against CoVid-19. 13 were not vaccinated, of which 7 chose not to be vaccinated, 2 tested positive for CoVid-19 before the roll out of the

vaccine programme and 4 died before the vaccine roll out. The vaccination status of 13 patents could not be ascertained. 16 patients (7.6%) contracted CoVid-19 infection during the pandemic. Of these, 6 were not vaccinated. 37.5% of infected patients required hospitalisation. One patient with RA died of CoVid-19 before the vaccination program commenced.

Conclusions: Managing patients on RTX in the CoVid-19 era is challenging. Withholding therapy associated with an enhanced risk of disease flare. The majority of our patients chose to be vaccinated. Those who contracted CoVid-19 despite vaccination had worse hospitalisation rates compared to the general population.

Disclosures: The authors have no financial disclosures relevant to the submitted work

167. Interplay between demographic, clinical and polygenic risk factors for severe COVID-19

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Background: Hospitalization and death from COVID-19 is an ongoing threat to public health and medical systems worldwide. We aimed to identify clinico-demographic and genetic risk factors for severe COVID-19 (hospitalization, critical care admission or death) utilising the population-based UK Biobank cohort from the pre-SARS-CoV-2 vaccination era. To improve biological understanding, we aimed to summarise the genetic risk for severe COVID-19 by developing a polygenic risk score (PRS) and applying this across ethnicities.

Methods: We identified UK Biobank participants diagnosed with COVID-19 in 2020. We derived and optimised a PRS for severe COVID-19 using publicly-available European and trans-ethnic COVID19-hg consortium GWAS summary statistics[1] and UK Biobank data. The performance of our PRS was evaluated in different ethnic subgroups. We estimated the risk of hospital or critical care admission within 28 days or death within 100 days following COVID-19 diagnosis (i.e., severe COVID-19), and assessed associations with demographic factors, immunosuppressant use, morbidities and PRS. Pathway analysis was performed using genetic variants from the final PRS.

Results: We included 9,560 patients followed for a median of 61 (interquartile range=34-88) days since COVID-19 diagnosis. The risk of severe COVID-19 increased with age and was higher in men, former or current smokers, those living in socio-economically deprived areas, for each additional 5 kg/m² increment of BMI between 25 and 40 kg/m², immunosuppressant users and individuals with morbidities, including autoimmune diseases, or a higher comorbidity count. An optimised PRS consisting of 133 genetic variants was independently associated with risk in both European and transethnic populations after adjustment for clinico-demographic risk factors; the highest PRS quintile compared with the lowest: adjusted odds ratio 1.32, 95%

confidence interval 1.11-1.58, R^2=2.35 x 10^{-3}, P= 6.23x10^{-4}. The magnitude of risk for the highest PRS quintile was equivalent to that reported for well-known risk factors, such as living in the most deprived areas or having cardiovascular disease. Pathway analysis revealed that our PRS was enriched for genetic variants in multiple immune-related pathways, including the "OAS antiviral response" and "Interleukin-10 signalling" pathways.

Conclusions: We provide evidence for targeted public health interventions, such as vaccine campaigns, for those with identified clinical and sociodemographic risk factors. This study conducted in the pre-SARS-CoV-2 vaccination era, emphasizes the novel insights to be gained from using genomic data alongside commonly considered sociodemographic and clinical factors in developing an understanding of severe COVID-19 outcomes. Our optimized PRS was independently associated with risk of severe COVID-19 and bioinformatic analysis demonstrated that host genetic variation in antiviral and immunoregulatory immune pathways may contribute to COVID-19 severity. Genetic variation in immune pathways offers the opportunity for guiding therapeutic strategies in severe COVID-19 and ultimately risk stratification for patients with autoimmune diseases requiring immunosuppressant therapy.

Disclosures: AWM has received research grant and educational funding or undertaken consultancy for the following pharmaceutical companies in the last 5 years: AstraZeneca, Kiniska Pharmaceuticals, Regeneron, Roche/Chugai, Sanofi and Vifor. MPR is employed by UCB Biopharma.

168. Vasculitis services during the COVID-19 pandemic: Characterising changing practices across the United Kingdom

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Background: The Vasculitis Outcomes In relation to Care Experience Study (VOICES), aims to understand the key patterns of service configuration underpinning effective care. An online questionnaire exploring the impact of COVID-19 pandemic on vasculitis service was conducted in collaboration with the UK and Ireland Vasculitis Society (UKIVAS) and the Scottish Systemic Vasculitis Network (SSVN).

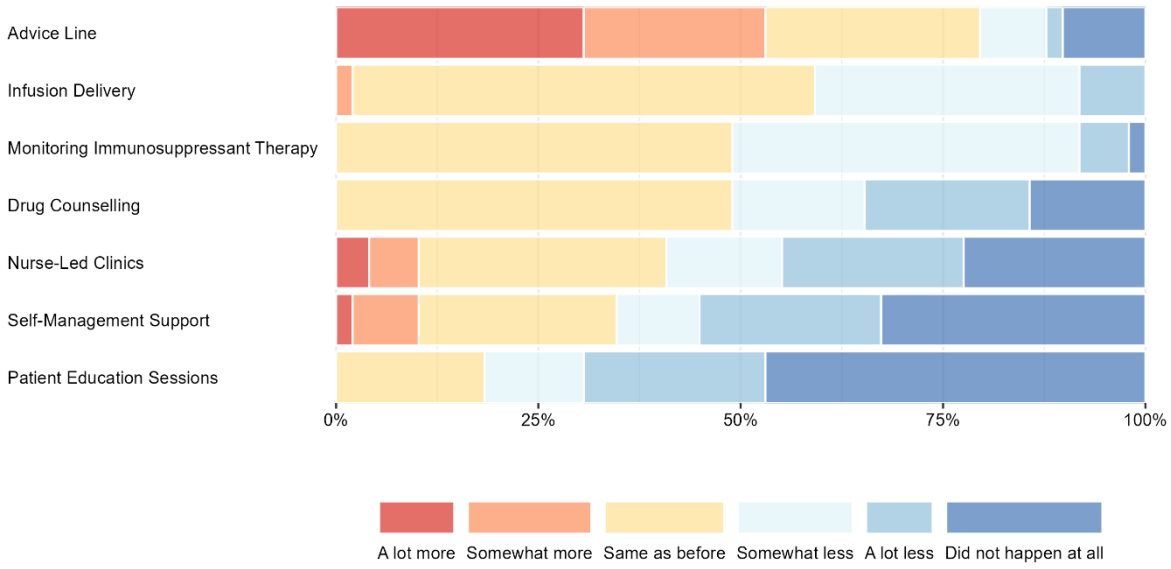
Methods: Vasculitis services across specialities in 87 UKIVAS sites, plus 11 Scottish regional health boards, were approached to complete the survey. 59 responses from 51 Trusts/Health Boards across Scotland (n=11), England (n=33), Wales (n=2), and Ireland (n=5) were collected.

Results: During COVID, wait-times for GCA services capable of providing an appointment for newly suspected GCA within 3 working days pre-COVID, were largely maintained. In some services, a shift towards longer wait-times occurred, whilst in others, times improved. For suspected AAV, most services were able to maintain similar wait-times for new patients. During lockdown 41% held fewer regular clinics or cancelled clinics completely. 16% of services held fewer regular clinics but replaced these with general and urgent access/flare clinics. Some nurse led- clinics occurred more frequently, others reduced frequency or stopped.
Triage processes included contacting all patients (by letter, email or telephone); patient triggered consultation (advice line or GP); and asynchronous consultation (clinical notes review, patient provided information, and blood tests) to identify those at high risk. During COVID-19, 94% undertook face to face (F2F) vasculitis consultations. Common indications for F2F consultation were relapse, diagnostic and disease activity assessment. 74% reported up to a quarter of remote consultations were converted to F2F consultation. Remote consultations were used to varying extents in existing vasculitis patients but much less commonly in new patients with suspected vasculitis. There was a rise in telephone and video consultations. Challenges for remote consultations include physical examination, urine analysis, phlebotomy, imaging, and reliable assessment of disease activity. Administrative and IT support for consultations could be an issue. Results indicated preference for this hybrid approach going forward. 38% of multidisciplinary meetings occurred less frequently, 21% were cancelled and 2% increased. Networks and vasculitis services roles during COVID-19 included case discussion, research, peer support, enablement of access to biologics, and educational updates for healthcare professionals. The pandemic impacted access to day-unit facilities for biologics and cytotoxic drug administration with 45% reported limited access for urgent cases only. Advice line activities increased significantly. Monitoring of immunosuppressants were similar in approximately 50% of respondents and reduced in others, see Figure 1.

Conclusions: During COVID-19, service flexibility included rapid access clinics, and adaptation to remote consultations. Priorities going forward include support for remote care delivery, hybrid care pathways, and provision of biologic / cytotoxic drug delivery. Identifying core components of vasculitis services to be maintained in times of significant health services pressure is essential.

Disclosures: none

Figure 1. Frequency of service activities during COVID -19 lockdown compared to usual



COVID 19 - Trials & Therapies

169. Bamlanivimab decreases severe outcomes of SARS-CoV-2 infection in ANCA vasculitis patients

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Background: Patients with ANCA-associated vasculitis (AAV) are more likely to have poor outcomes if infected with SARS-CoV-2.[1] Rituximab use is associated with blunted humoral and cell mediated immune responses to SARS-CoV-2 vaccine.[2] Monoclonal antibody treatment, specifically Bamlanivimab, has shown promise in reducing hospitalization and mortality rates for patients infected with SARS-CoV-2.[3] We studied the outcome of SARS-CoV-2 infection in AAV patients and the impact of Bamlanivimab on the risk of hospitalization and death.

Methods: We analyzed data for 20 patients with AAV who had received lymphocyte-depleting therapy (rituximab (75%), prednisone (15%), cyclophosphamide (5%), and azathioprine (5%)) and were subsequently diagnosed with SARS-CoV-2. After extracting demographic and clinical information from medical records, we performed descriptive statistics and bivariate comparisons using $\chi 2$ and Fischer's exact tests for categorical variables and t-tests and Welch unequal variances tests for continuous variables. Analyses were conducted in SAS V.9.4 (SAS Institute).

Results: Of 20 patients with a mean age of 61 years, 75% Caucasian and 60% MPO ANCA, 12 were hospitalized and 5 died of pneumonia or sepsis. The majority (75%) were treated with rituximab (Table 1). The median (IQR) time from last rituximab administration to SARS-CoV-2 diagnosis in the 15 rituximab treated patients was 18 (13 to 30) weeks. B cells were depleted in the 13 patients who had CD19 data. Four patients had received both doses of the SARS-CoV-2 vaccine with Pfizer or Moderna prior to SARS-CoV-2 diagnosis. Of these 4 vaccinated patients, 3 did not mount a humoral response; the single patient with a humoral response subsequently received treatment with rituximab for newly diagnosed AAV. The median (IQR) time between administration of the second dose of SARS-CoV-2 vaccine and SARS-CoV-2 diagnosis was 14 (8.3–23) weeks. The median (IQR) time from SARS-CoV-2 symptom onset to hospitalization was 3 (2–4) days. The median (IQR) duration of hospitalization was 8 (6.5–13.8) days. The median (IQR) time from SARS-CoV-2 symptom onset to death was 14 (11–49) days. Eleven patients (55%) required supplemental oxygen and five (25%) required mechanical ventilation. Eleven patients received dexamethasone, 10 received remdesivir and 3 patients received plasma therapy. Seven patients including 6 on rituximab therapy received treatment with the monoclonal antibody Bamlanivimab and hospitalization showed a statistically significant decrease in this group; hospitalization was required for one patient (14.3%) of those who received Bamlanivimab vs eleven (84.6%) of those who did not (P=0.0044). No patient who received Bamlanivimab died of SARS-CoV-2; 38.5% of those who did not receive Bamlanivimab died.

Conclusion: Managing AAV patients on rituximab therapy has been challenging due to risk of severe SARS-CoV-2 infection and impaired immune response to the SARS-CoV-2 vaccine. Our data demonstrates that Bamlanivimab decreases risk of severe outcomes offering hope in this vulnerable cohort. Early use of monoclonal antibody therapy should be advocated for in AAV patients on immunosuppressive therapy.

Disclosures: None.

Table 1: Demographic, co-morbidities, immunosuppressive treatment versus SARS-CoV-2 outcomes.

Variable	All Patients	Not Hospitalized	Hospitalized	Prob	Survived	Died	Prob
N	20	8	12		15	5	
Age (years)				0.0138			0.3913
Mean (Std Dev)	61.3 (15.4)	50.9 (14.2)	68.3 (12.2)		59.6 (4.1)	66.4 (14.0)	
Gender, n (col %, row %)				1.000			0.3034
Female	10 (50.0)	4 (50.0, 40.0)	6 (50.0, 60.0)		6 (40.0, 60.0)	4 (80.0, 40.0)	
Male	10 (50.0)	4 (50.0, 40.0)	6 (50.0, 60.0)		9 (60.0, 90.0)	1 (20.0, 10.0)	
BMI				0.8596			0.4263
Mean (Std Dev)	35.2 (6.2)	34.8 (8.7)	35.4 (4.2)		35.7 (6.9)	33.7 (3.5)	
Comorbidities, n (col %, row %)							
Hypertension				0.2553			1.000
No	4 (20.0)	3 (37.5, 75.0)	1 (8.33, 25.0)		3 (20.0, 75.0)	1 (20.0, 25.0)	
Yes	16 (80.0)	5 (62.5, 31.25)	11 (91.7, 68.8)		12 (80.0, 75.0)	4 (80.0, 25.0)	
Diabetes				0.2421			0.5395
No	17 (85.0)	8 (100.0, 47.1)	9 (75.0, 52.9)		12 (80.0, 70.6)	5 (100.0, 29.4)	
Yes	3 (15.0)	0 (0.0, 0.0)	3 (25.0, 100.0)		3 (20.0, 100.0)	0 (0.0, 0.0)	
Heart Disease				0.6027			0.5598
No	15 (75.0)	7 (87.5, 46.7)	8 (66.7, 53.3)		12 (80.0, 80.0)	3 (60.0, 20.0)	
Yes	5 (25.0)	1 (12.5, 20.0)	4 (33.3, 80.0)		3 (20.0, 60.0)	2 (40.0, 40.0)	
CKD				0.8367			0.2088
No	7 (35.0)	2 (25.0, 28.6)	5 (41.7, 71.4)		6 (40.0, 85.7)	1 (20.0, 14.3)	
Stage 3 and 4	10 (50.0)	5 (62.5, 50.0)	5 (41.7, 50.0)		8 (53.3, 80.0)	2 (40.0, 20.0)	

Stage 5	3 (15.0)	1 (12.5, 33.3)	2 (16.7, 66.7)		1 (6.67, 33.3)	2 (40.0, 66.7)	
Immunosuppressant Regimen, n (col %, row %)				0.6444			0.3025
Rituximab	13 (65.0)	7 (87.5, 46.7)	8 (66.7, 53.3)		12 (80.0, 80.0)	3 (60.0, 20.0)	
Prednisone	3 (15.0)	1 (12.5, 33.3)	2 (16.7, 66.7)		2 (13.3, 66.7)	1 (20.0, 33.3)	
Cyclophosphamide	1 (5.0)	0 (0.0, 0.0)	1 (8.3, 100.0)		0 (0.0, 0.0)	1 (20.0, 100.0)	
Azathioprine	1 (5.0)	0 (0.0, 0.0)	1 (8.3, 100.0)		1 (6.7, 100.0)	0 (0.0, 0.0)	
SARS-CoV-2 Vaccination, n (col %, row %)				0.6945			0.097
No		7 (87.5, 43.8)	9 (75.0, 56.3)		13 (86.7, 81.3)	3 (60.0, 18.8)	
Yes	4 (20.0)	1 (12.5, 25.0)	3 (25.0, 75.0)		2 (13.2, 50.0)	2 (40.0, 50.0)	
Bamlanivimab, n (col %, row %)				0.0044			0.1137
No	13 (65.0)	2 (25.0, 15.4)	11 (91.7, 84.6)		8 (53.3, 61.5)	5 (100.0, 38.5)	
Yes	7 (35.0)	6 (75.0, 85.7)	1 (8.33, 14.3)		7 (46.7, 100.0)	0 (0.0, 0.0)	

170. PROphylaxis for vulnerable paTiEnts at risk of COVID-19 infecTion (PROTECT-V) – a national platform trial

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Background: Several patient groups are more vulnerable to COVID-19 infection by virtue of demographics, underlying health conditions or as a consequence of treatments. Such vulnerable patients include individuals with kidney disease requiring dialysis, organ transplant recipients, or autoimmune diseases that require immunosuppression. Despite the introduction of widespread vaccination, there remains a need for antigen independent prophylactic agents against SARS CoV-2. No vaccine is completely effective, new variants of SARS CoV-2 are

emerging, and many immunocompromised vulnerable individuals are known to mount a suboptimal response to vaccination.

Methods: PROTECT-V is a platform trial to test prophylactic interventions against SARS CoV-2 infection in vulnerable patient populations at particularly high risk of COVID-19 and its complications, seeking to either prevent the disease from occurring or reduce the number of serious or life-threatening cases. In PROTECT-V, multiple agents can be evaluated on the same platform across multiple vulnerable populations and sharing placebo groups, with the option of adding additional treatments at later time points as these become available. Furthermore, PROTECT-V is also able to restrict interventions to particular subpopulations or patient groups, as well as adding additional vulnerable patient groups at a later stage such as patients with a sub-optimal vaccine response. The primary endpoint is symptomatic Covid-19 infection, and each agent will be independently evaluated in real time when the required number of events occur.

Results: The trial commenced with the first intervention, nasal niclosamide and matched placebo in a 1:1 ratio in February 2021. As of 30th November, 671 patients from 32 UK sites had been enrolled. The last independent data monitoring committee meeting was in October 2021 and it was recommended to continue the trial as it is. A second inhaled intervention, ciclesonide, will be added in the next few weeks. At that point, patients will be enrolled in a 2:1 ratio, active: placebo. In parallel to the repurposed drug arms, a monoclonal antibody arm, sotrovimab, will enrol vaccine non-responders in a 1:1 ratio, active: placebo. Potential future prophylactic agents such as alternative monoclonal antibody therapies, antivirals or nasal or inhaled agents may be proposed to the UK Prophylaxis Taskforce for endorsement to be included within the platform.

Conclusions: The PROTECT-V trial platform brings greater efficiency, running multiple sub-trials within one master protocol. It is an exemplar trial demonstrating the success of collaboration in the COVID-19 pandemic. The platform is jointly funded from charitable (LifeArc, Kidney Research UK, Addenbrooke's Charitable Trust), government funding (NIHR), and industry (Union Therapeutics for the niclosamide arm; GSK for the sotrovimab arm) sources and focuses on patient populations who are often excluded from clinical trials due to complex disease, but remain vulnerable to infection despite the success of vaccination.

Disclosures: RS receives research funding from Union Therapeutics and GSK, DD receives research funding from GSK.

Figure 1: PROTECT-V trial schema

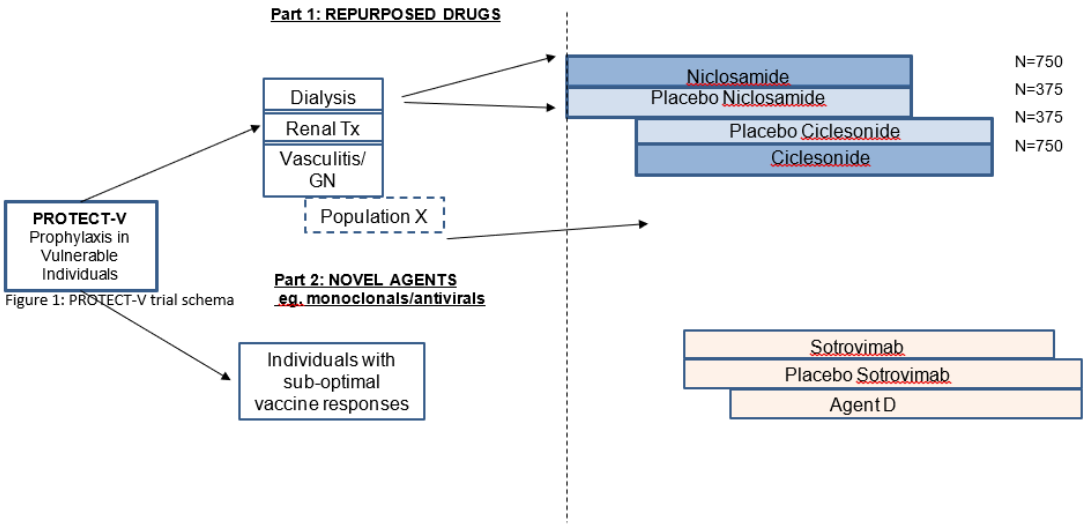

Figure 1: PROTECT-V trial schema

Omics & Vasculitis

171. Intrarenal single cell sequencing of MPO-ANCA associated glomerulonephritis patients reveal novel targetable treatment options

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Background: The etiopathogenesis underlying myeloperoxidase anti-neutrophil cytoplasmic antibody associated glomerulonephritis (MPO-ANCA-GN) remains incompletely understood. Furthermore, there are only limited treatment options and treatment resistance of MPO-ANCA-GN is still a common problem.

Methods: To identify new targeted treatment options, intrarenal single-cell RNA sequencing (scRNA-seq) was applied to kidney biopsies from MPO-ANCA-GN patients and control health kidney tissues to define the transcriptomic landscape at single-cell resolution. Intrarenal scRNAseq was also applied to a pre-clinical mouse model of MPO-ANCA-GN to show that this model of disease can be used to trial new targeted treatments.

Results: We found that kidney endothelial cells in MPO-ANCA-GN patients displayed increased expression of several genes, including *CD9* and *SPARC*, which were closely related to parietal epithelial hyperplasia and crescent formation. NF-κB pathway activation was confirmed in a variety of kidney cells in MPO-ANCA-GN patients. Kidney infiltrating immune cells of MPO-ANCA-GN patients were mainly enriched in inflammatory pathways including TNF signaling, IL-17 signaling and NOD-like receptor signaling. These findings were similar in our

pre-clinical mouse model of MPO-ANCA-GN. Furthermore, there was an overexpression of inflammasome related genes (*AIM2, IFI16*) in MPO-ANCA-GN patients. Treatment resistance was associated with increased infiltration of $CD8^+$ T cells, and elevated expression of *SPARC*, *LAMA4*, *IL33*, and *CFL1* in mesangial cells when compared with patients who achieved remission after induction therapy.

Conclusions: These results offer new insight into the pathogenesis of MPO-ANCA-GN, treatment resistance, and identify new therapeutic targets for MPO-ANCA-GN that can be tested in a pre-clinical model of disease.

Disclosures: none.

172. RNA sequencing of leukocytes reveals unique differences among groups of adult patients with IgA vasculitis

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Background: Immunoglobulin A vasculitis (IgAV) is a small vessel leukocytoclastic vasculitis, characterized by vascular IgA deposits. Renal involvement, found in up to 84% of patients, is associated with an increased risk of progression to chronic kidney failure. An invasive procedure of skin biopsy is still the golden standard for diagnosis. Omics data from NCBI-GEO and Array Express databanks is lacking from IgAV samples of adult patients. Thus, our aim was to perform RNA sequencing and identify differentially expressed genes and dysregulated molecular pathways in leukocytes of IgAV patients with renal involvement, patients with skin-limited IgAV and healthy controls (HC).

Methods: Peripheral blood leukocytes were collected from treatment-naive IgAV patients at time of diagnosis with: 1) renal complications (n=3), 2) skin-limited disease (n=3), and age-/sex-matched HC (n=3), in the University Medical Center Ljubljana. RNA was isolated from leukocytes and 100 bp paired-end sequenced using the Illumina HiSeq 4000 platform (25.9 to 30.8 million reads). Reads were mapped with Salmon tool onto the human transcriptome (Ensemble Release 104). Differentially expressed genes (log2 fold change $\geq |1|$, padj < 0.05) were computed using the R package DeSEQ2. Data were clustered using principal component analysis (PCA), KEGG pathway over-representation analysis (ORA) was performed with R package clusterProfiler and protein-protein interaction analyses were done using STRING analysis.

Results: PCA distinguished between IgAV (renal and skin-limited) and healthy controls, suggesting specific transcriptome signatures in IgAV. 300 genes were differentially expressed (220 up- and 80 down-regulated) in leukocytes between IgAV patients with renal involvement and healthy controls (HC), thereby representing renal-associated IgAV pathology and an

associated leukocyte mRNA signature. 198 genes were identified as differentially expressed (144 up- and 54 down-regulated) between skin-limited IgAV and HC. 67 overlapping genes were differentially expressed in both groups of patients in comparison to controls. 48 genes were differentially expressed between patients with renal involvement, as compared to those with skin involvement only. Differentially expressed genes in patients with renal involvement exhibited enriched KEGG Pathways involved in the Antigen processing and presentation (padj 0.0000043), Platelet activation (padj 0.0000010), the Natural killer cell-mediated cytotoxicity (padj 0.0070636), as analysed by ORA approach. Genes, differentially expressed in patients with skin-limited disease were enriched in the Antigen processing and presentation (padj 0.0000000), NOD-like receptor signaling (padj 0.0000226) and Platelet activation (padj 0.0459034) KEGG Pathways. Interestingly, using STRING analysis, an Interferon signaling Reactome pathway (FDR 3.01e -11) emerged in patients with skin-limited disease.

Conclusions: Here, we report an IgAV-associated leukocyte mRNA signature in adults. We showed, that it is possible to discriminate between patients with different organ involvement and healthy controls based on differentially expressed genes that regulate various innate immunity responses. Deregulated molecular pathways in patients with IgA vasculitis could serve as the basis for further investigations for potential clinically-relevant biomarkers and functional *in-vitro* studies deciphering organ-specific pathology in IgAV patients.

Disclosures: None

173. Global Transcriptomic Profiling Identifies Differential Gene Expression Signatures between Inflammatory and Non-inflammatory Aortic Aneurysms

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Objective: The goal of this study was to identify aortitis hallmark genes and pathways by utilizing a high-throughput gene expression profiling approach (RNA-seq).

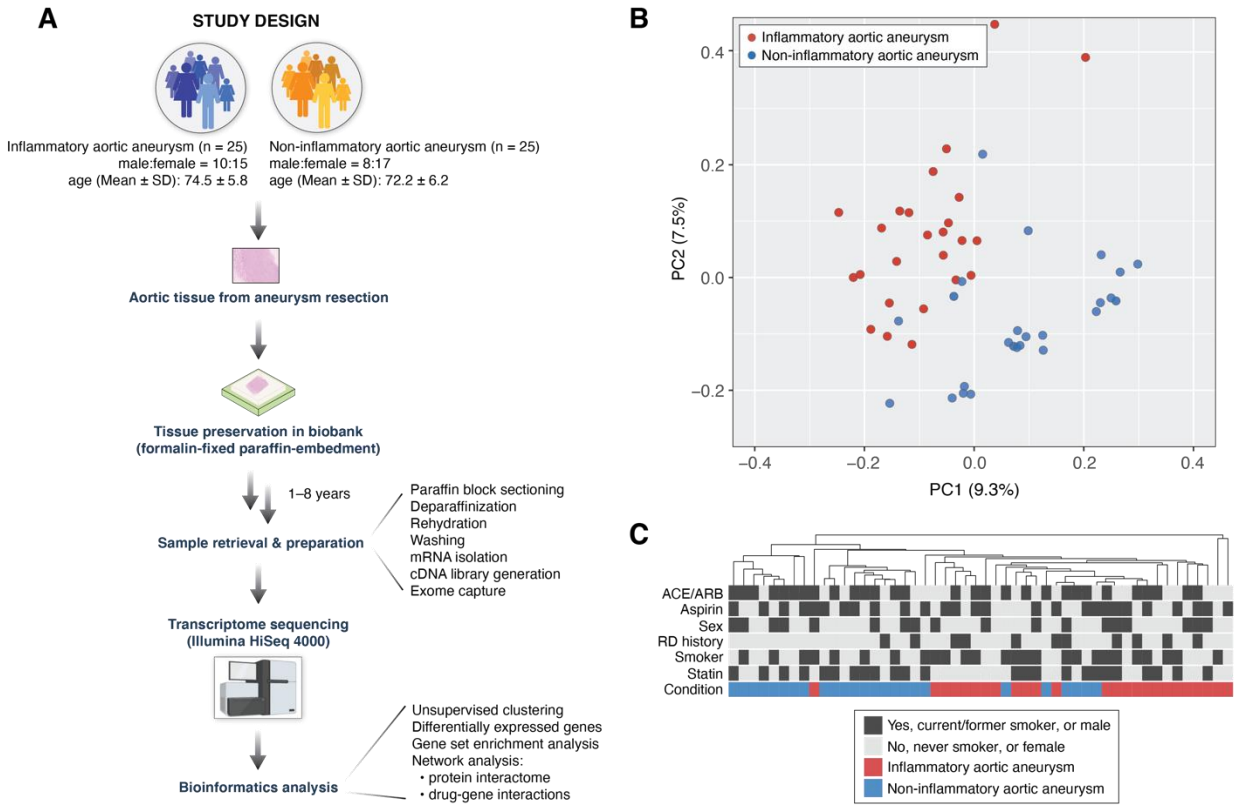
Methods: RNA-seq was performed on surgically resected aortic tissues from inflammatory (giant cell arteritis [GCA] with or without polymyalgia rheumatica [PMR] = 8; clinically isolated aortitis [CIA] = 17) and non-inflammatory (n = 25) aneurysms undergoing surgical aortic repair. Differentially expressed genes (DEGs) between the two patient groups were identified while controlling for clinical covariates. Gene set enrichment analysis was used to find enriched biological functions for the up/downregulated DEGs. A protein-protein interaction model, drug-gene target information, and DEGs were used to construct a pharmacogenomic network for identifying promising drug targets and potentially new treatment strategies in aortitis.

Results: Overall, gene expression patterns were more associated with disease state than with other clinical characteristics. We identified 159 and 93 genes that were significantly upregulated and downregulated, respectively, in inflammatory aortic aneurysms compared to non-inflammatory aortic aneurysms. We found that the upregulated genes were enriched in immune-related functions, including response to infectious microbial agents; whereas the downregulated genes were enriched in neuronal processes. Notably, gene expression profiles of inflammatory aortic aneurysms from patients with GCA/PMR were no different than those from patients with CIA. Finally, our pharmacogenomic network analysis identified genes that could potentially be targeted by immunosuppressive drugs currently approved for other inflammatory diseases.

Conclusion: We performed the first global transcriptomics analysis in inflammatory aortic aneurysms from surgically resected aortic tissues. We identified signature genes and biomolecular processes, while finding that CIA may be a limited presentation of GCA. Moreover, our computational network analysis revealed potential novel strategies for pharmacologic interventions. Looking ahead, we expect system-level analyses using high-throughput technologies to elucidate druggable disease mechanisms and next-generation biomarkers for the precise diagnosis and treatment of aortitis.

Disclosure: KJW receives clinical trial support from Kiniksa and Eli Lilly, and an honoraria from Chemocentryx.

Figure 1. Data analysis pipeline and clustering results on genome-wide expression (transcriptome) profiles of inflammatory and non-inflammatory aortic aneurysms. (A) Study design to investigate transcriptomic differences between inflammatory and non-inflammatory aortic aneurysms. (B) PCA on gene expression profiles (26,475 total genes) from 50 surgically resected aortic tissue samples across the two patient groups (inflammatory aortic aneurysm, n = 25; non-inflammatory aneurysm, n = 25). (C) Hierarchical clustering on all 50 gene expression profiles shows that samples cluster together by disease condition (inflammatory/non-inflammatory aortic aneurysms) more so than by any other clinical characteristic (i.e., ACE/ARB use, aspirin use, sex, RD history, smoking history, and statin use). Heatmap of gene expression profiles is not shown due to space constraints. PCA: principal component analysis; ACE/ARB: angiotensin converting enzyme inhibitors/angiotensin receptor blockers; RD history: history of other rheumatic diseases



174. Alterations in Amino Acid and Lipid Metabolism in ANCA-Stimulated Monocytes

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Background: Multiple metabolic pathways and intermediates are involved in inflammation. Altered immune cell metabolism is involved in the pathogenesis of ANCA-associated vasculitis (AAV). In particular, monocytes stimulated with ANCA show increased oxidative phosphorylation and glycolysis, with a more profound response to monoclonal myeloperoxidase (MPO) ANCA than proteinase-3 (PR3) antibodies. The aim of this work was to profile the metabolome of ANCA-stimulated primary monocytes.

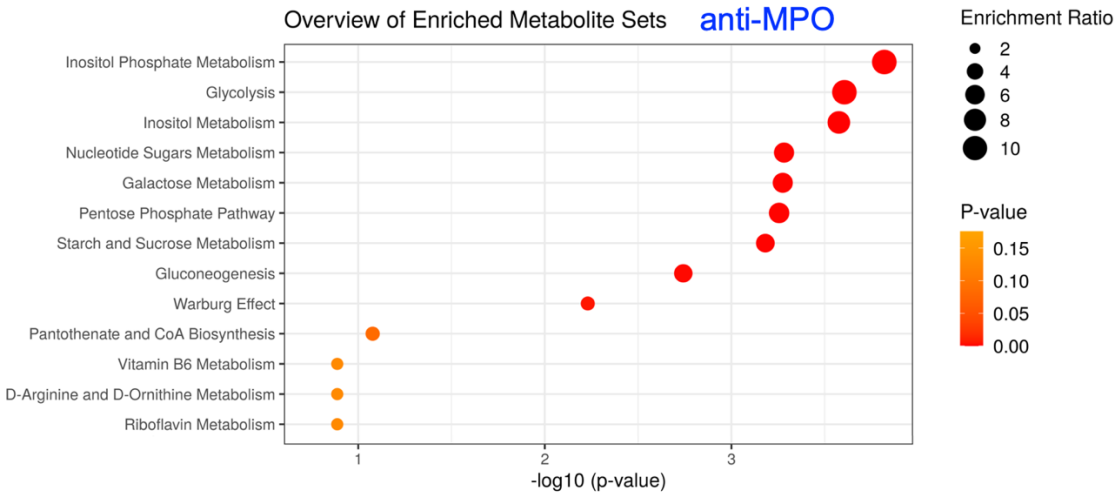
Methods: Monocytes from healthy donors (n=24) were isolated and stimulated with anti-MPO, anti-PR3 and lipopolysaccharide (LPS) for 4 hours. Cells were extracted using an optimised methanol-based extraction protocol and analysed by liquid chromatography–mass spectrometry (LC–MS). Targeted and untargeted analyses (relative to unstimulated cells) were carried out using Agilent MassHunter Profinder and Mass Profiler Professional. Cytokine production was measured by ELISA and flow cytometry was used to assess surface expression of MPO and PR3.

Results: Targeted metabolomic analysis showed increases in several amino acid and TCA cycle metabolites, notably phenylalanine, isomers leucine & isoleucine, and fumarate. These metabolic differences did not correlate with the increased cytokine expression observed in anti-MPO and LPS treated monocytes. Untargeted analysis confirmed alterations in amino acid and lipid metabolism in anti-MPO- (and LPS-) stimulated monocytes. Among the most significantly altered pathways in anti-MPO stimulated cells were inositol metabolism, glycolysis, and nucleotide metabolism (Figure 1). Anti-PR3 stimulation did not induce major changes in metabolism nor cytokine production. Monocytes expressed high levels of surface PR3, with greater variation in surface MPO expression, which showed a significant inverse correlation with age. A relationship between surface expression of MPO and intracellular concentrations of certain metabolites was also revealed.

Conclusions: Inflammatory and metabolomic activation of primary human monocytes occurs with anti-MPO, but not anti-PR3 stimulation. Early increases in amino acid and lipid metabolism are evident in anti-MPO treated cells and may be related to surface expression of MPO.

Disclosures: This work is supported by an Irish Research Council Enterprise Partnership Scheme in collaboration with Agilent Technologies Ireland Limited.

Figure 1: Pathway analysis of metabolites from untargeted metabolomic analysis of anti-MPO-stimulated primary monocytes



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175. Transcriptomic changes induced by mavrilimumab versus tocilizumab in ex-vivo cultured arteries from giant-cell arteritis patients

Marc Corbera Bellalta[1], Farah Kamberovic[1], Ferran Araujo[2], Roser Alba-Rovira[1], Georgina Espigol-Frigolé[1], Marco A Alba[1], Sergio Prieto-Gonzalez[1], José Hernández-Rodríguez[1], Patricia Pérez-Galán[2], Kent Bondensgaard[3], John F Paolini[3], Maria C Cid[1]
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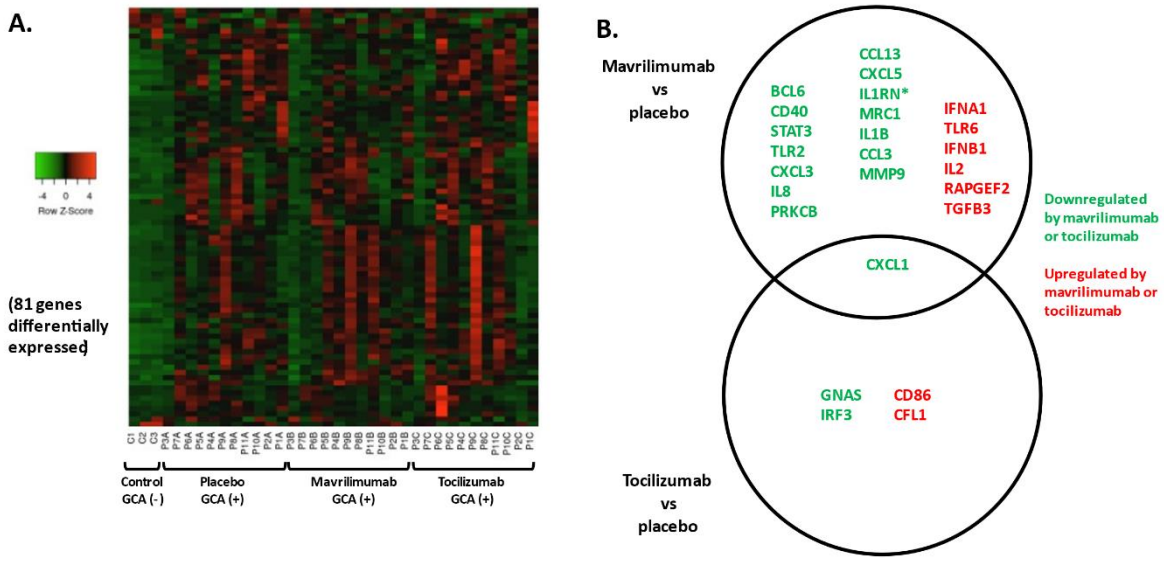
Background: Giant cell arteritis (GCA) is a chronic disease, and affected patients suffer from relapses and glucocorticoid (GC)-related toxicity. Targeted therapies are emerging with the aim of achieving better disease control and reducing GC exposure. Blocking IL-6 receptor with tocilizumab has been a major advance in the treatment of GCA. However, approximately 40% of patients treated with tocilizumab in combination with GCs experience a flare or tocilizumab-related adverse event. Blocking GM-CSF receptor a with mavrilimumab significantly reduced risk of relapse and improved sustained remission at week 26 vs placebo in a Phase 2 trial. Not all patients satisfactorily respond to any therapy, indicating heterogeneity in leading pathogenic pathways among patients. For these reasons, it is crucial to understand the specific impact of targeted therapies on vascular lesions. In this study we investigated transcriptomic changes induced by tocilizumab or mavrilimumab in *ex-vivo* cultured arteries from patients with GCA.

Methods: Temporal artery sections obtained for diagnostic purposes from 11 patients with histopathologically-confirmed GCA and 3 controls were cultured *ex-vivo* and exposed to placebo, mavrilimumab, or tocilizumab (both at 20 µg/mL) for 5 days. Of 11 GCA donors, 2 had received no treatment prior to biopsy, 2 had received a single prednisone (60 mg) dose, 1 had received 2 daily doses, and the remaining 6 had extended treatment; in prednisone-treated patients, mean (SEM) treatment duration was 17.9 ±8.7 days. Samples were homogenized, and total RNA was extracted with TRIzol reagent. 100 ng of RNA per sample were processed with Nanostring Inflammation gene expression assay (256 transcripts) and hybridized using nCounter Prep Station. Barcode counts from nCounter Digital Analyzer were processed with nSolver 4.0 Software. Normalised data were analyzed using R Studio 4.0.5 and IBM SPSS 22.0, and paired Wilcoxon tests were applied individually to each treatment comparison group for each analysed gene.

Results: 67 out of 250 transcripts were differentially expressed between arteries from GCA patients and arteries from control patients (all placebo-treated). Of those, only 9 transcripts remained significant after correction for multiple comparisons, with a false discovery rate ≤0.05. 81 transcripts were differentially expressed in at least one comparison across groups, due to disease effect only (67 transcripts) or treatment effect (25 transcripts), with an overlap of 12 transcripts differentially expressed due to both disease and treatment effect (Fig 1A). 15 transcripts were lower, and 6 were higher in the mavrilimumab group vs placebo; 3 transcripts were lower, and 2 were higher in the tocilizumab group vs placebo (Fig 1B). Most changes elicited between treatments were unique, but CXCL-1 was common (Fig 1B). None remained significant after correction for multiple comparisons.

Figure 1. (A) Heat map of differential expression of 81 genes in GCA (-) control and GCA (+) treated with placebo, mavrilimumab, or tocilizumab. (B) Venn diagram of genes differentially expressed in mavrilimumab versus placebo and tocilizumab versus placebo



Conclusions: Mavrilimumab and tocilizumab have a different transcriptomic impact on cultured arteries from patients with GCA, with some overlapping effects, although differential effects may have been attenuated by prior GC use. A better understanding of the impact of targeted therapies on vascular inflammation is needed to improve treatment options for patients with GCA.

Disclosures: MCC reports a research grant from Kiniksa; consulting for Janssen, GlaxoSmithKline, and AbbVie; educational support from GlaxoSmithKline, Roche, and Vifor; and meeting attendance support from Roche and Kiniksa. KB and JFP are employees and stockholders of Kiniksa Pharmaceuticals Corp. JFP is an inventor on patent applications related to mavrilimumab. Funding: Kiniksa Pharmaceuticals, Ltd.

176. Reduced Activation Thresholds Of CD8+ T Cells In Giant Cell Arteritis

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Background: Giant cell arteritis (GCA) is an immune-mediated vasculitis affecting the large- and medium-sized arteries. The role of CD8+ T cells in the pathogenesis of GCA is poorly understood despite the potential association with viral infections, HLA-class I genes and the involvement of CD8+ T cells in other vasculitides. Therefore, we performed a comprehensive phenotypic, transcriptomic and functional analysis of CD8+ T cells in GCA patients.

Methods: To assess the phenotype of circulating CD8+ T cells, we measured the frequencies of CD8+ T-cell differentiation subsets for markers of activation (CD69 and CD25) and proliferation (Ki-67+) in 14 newly diagnosed GCA patients and 18 age- and sex-matched healthy controls (HCs). Next, we assessed the proliferative capacity of CD8+ T cells upon anti-CD3 or anti-CD3/CD28 stimulation *in vitro.* To gain more mechanistic insights, we performed single cell (sc) RNA sequencing on peripheral blood mononuclear cells from three GCA patients and HCs. Lastly, immunohistochemistry was performed on GCA-affected arteries to detect CD3, CD8, Ki-67, TNF-α and IFN-γ expression whereas colocalization of Ki-67/ CD8 and IFN-γ/ CD8 was determined with immunofluorescence.

Results: The absolute number of circulating effector memory CD8+ T cells was decreased in GCA patients compared to HCs, whereas the percentages of Ki-67+ effector memory CD8+ T cells were increased. Circulating CD8+ T cells from GCA patients had reduced activation thresholds after *in vitro* stimulation and a gene expression profile concurrent with increased proliferation as assessed by scRNA sequencing. CD8+ T cells in GCA-affected tissues were present in all layers of the temporal artery biopsies whereas their location in the aorta was confined to the adventitia. The large majority of CD8+ T cells in the tissues expressed IFN-γ but not Ki-67.

Conclusions: In GCA, circulating CD8+ T cells demonstrate a proliferation-prone phenotype. Their lower activation thresholds could render CD8+ T cells more prone to react to antigens and to differentiate into pro-inflammatory cells. The finding that CD8+ T cells in tissues were Ki-67 negative suggests that these cells were recruited to the site of inflammation, rather than the result of local expansion. Vascular CD8+ T cells produce IFN- γ which could contribute to the local inflammation.

Disclosures: AB was a consultant for Grünenthal Gmbh until 2017. EB and KSMvdG as employees of the UMCG received speaker/consulting fees from Roche paid to the UMCG.

177. Molecular determinants of myeloperoxidase-ANCA glomerulonephritis: transcriptomic analysis across three species identifies the inflammasome as a conserved pathogenic pathway

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Trinity Translational Medicine Institute, Trinity College Dublin, Ireland.

Background: Human myeloperoxidase (MPO)-anti-neutrophil cytoplasm antibodies (ANCA) vasculitis causes crescentic glomerulonephritis that results in glomerular destruction. This has been modelled in rats (Experimental Autoimmune Vasculitis or EAV, an active model) and mice (Murine Experimental Vasculitis or MEV, a passive model). To investigate conserved and divergent molecular pathways involved in glomerular injury, we analysed the glomerular transcriptome in EAV, MEV and in humans with MPO-ANCA vasculitis. We reported previously that 179 (3.0%) of the 6006 genes with altered expression were common across all three

species, with 27 of these (0.4%) regulated in opposite directions between human and both rodent species.

Methods: Species-specific transcriptional networks were generated following glomerular microdissection and microarray analysis and compared with a co-citation network matching algorithm. Immunohistochemistry (IHC) was used to quantify tissue protein expression.

Results: The murine model shared more similarly regulated genes with the human disease than the rat model. Three molecular pathways, dedicated primarily to inflammation, integrin activation and antigen presentation, were upregulated in all three species. Of the 43 other co-regulated pathways (none of which were shared by both mouse and rat), 14 (12 and 2 in mouse and rat respectively) were regulated in the opposite direction between rodent and human, the core inflammasome component gene Pycard (also known as ASC) was strongly upregulated (Fig 1A) in all three tissues. We therefore went on to assess tissue protein expression of ASC speck in the inflamed glomeruli by IHC. We found similar marked upregulation of ASC speck in all three species (Fig 1b-D).

Conclusions: We have identified both conserved and divergent molecular pathways in the glomeruli of vasculitic glomeruli, the latter potentially exploitable as features underpinning the rapid recovery of rodent vasculitis with minimal scarring. The inflammasome pathway is also strongly upregulated in all three species, suggesting another potential therapeutic target.

Disclosures: None

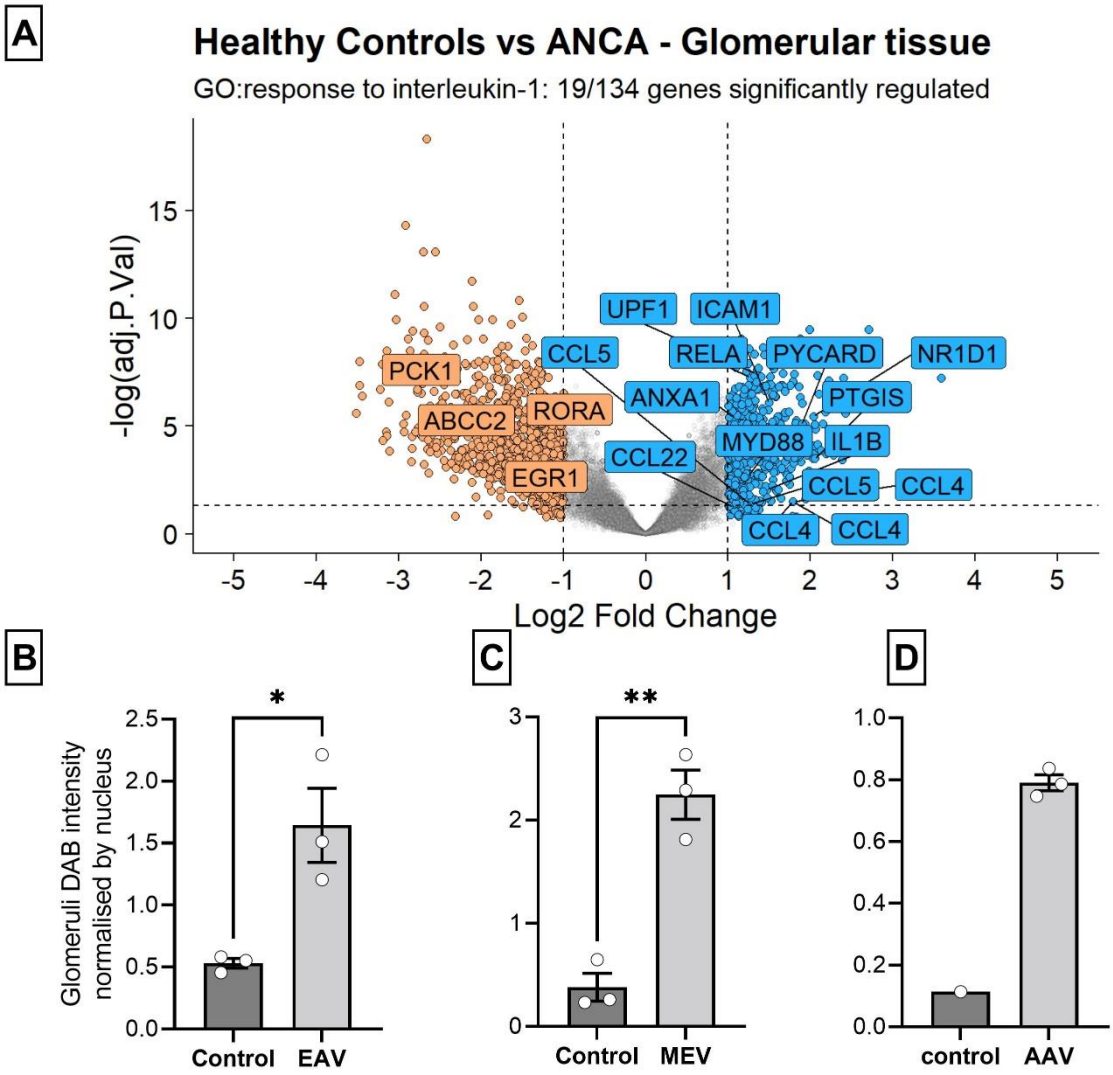

Figure 1. (A) Volcano plot illustrating upregulated and down-regulated genes in glomerular tissue of humans with MPO-AAV. Protein expression of ASC speck in glomeruli of (B) rats, (C) mice and (D) humans with MPO-AAV.

178. Longitudinal transcriptomic profiling of nasal epithelium in patients with granulomatosis with polyangiitis

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[1]University Of Pennsylvania, USA, [2]Washington University in St. Louis, USA, [3]Children's Hospital of Philadelphia, USA, [4]National Institute of Arthritis and Musculoskeletal and Skin Diseases, USA

Background: Epithelial cells lining the respiratory tract regulate immune responses and modulate host-commensal interactions. In particular, goblet cells and submucosal glands produce a protective layer of mucin-type glycoproteins, which are the primary component of mucus. We aimed to define the longitudinal changes in nasal epithelial gene expression associated with disease activity in patients with granulomatosis with polyangiitis (GPA).

Methods: Samples of nasal epithelial cells were obtained by nasal cytology brushes collected longitudinally from patients with GPA and healthy controls. Pre-relapse and relapse visits from 7 patients with GPA (“relapsing GPA”) were matched by immunosuppressive therapy to 2 visits each from 7 patients in stable remission (“non-relapsing GPA”). Relapse was defined as BVAS-WG >0. We performed bulk RNA-sequencing and unsupervised hierarchical clustering analysis of differentially expressed genes between relapsing vs non-relapsing GPA. Pathway enrichment analysis was performed using NCATS BioPlanet. Differentially expressed genes were mapped to cells using HuBMAP.

Results: There were data from a total of 36 visits among the 14 patients with GPA and 10 healthy controls. Among GPA patients, 86% were PR3-ANCA positive, 64% had prior history of sinonasal involvement, 64% had prior history of relapse; these characteristics were not significantly different between relapsing and non-relapsing groups. There were no significant differences between relapsing and non-relapsing GPA groups in use of topical nasal antibiotics, oral antibiotics, or sinus rinse at time of visit. At the relapse visit, 4 of 7 patients with relapse had clinically-apparent sinonasal involvement and 6 of 7 patients with relapse developed extra-rhinologic manifestations related to GPA. We found differential gene expression related to mucus production in the relapsing GPA group compared to the non-relapsing GPA or healthy control groups. For example, upregulation of the genes B3GNT6 (required for mucin-type core 3 O-glycosylation), GALNT6 (initiates mucin-type O-glycosylation), SPDEF (regulates goblet cell differentiation and mucus production), and MUC5AC (major glycoprotein component of mucus) were observed in the relapsing vs non-relapsing GPA groups. Enrichment analysis revealed pathways associated with O-linked glycosylation of mucins and O-glycan biosynthesis. Upregulated genes were mapped to goblet and submucosal gland cells which are known to produce mucins. Notably, the transcriptomic profiles were similar between the relapse and pre-relapse visits (many months before clinical manifestations of relapse occurred) and were similarly expressed in patients with or without sinonasal symptoms at time of relapse.

Conclusions: While it has been shown that mucus regulates microbiota and inflammation within the intestinal epithelium, a role for mucus in sinonasal autoimmunity has not previously been described. By performing RNA-seq gene expression profiling, we discovered a persistent signature related to mucus production (specifically mucin-type O-glycosylation) in patients with relapsing GPA but not in those in stable remission. This profile is present regardless of sinonasal symptoms and is detectable many months before active disease becomes clinically apparent. Our results suggest that alterations in homeostasis of mucin-producing cells may contribute to relapsing GPA and, given the established role of mucins in regulating microbiota, raise new questions about the role of mucins in mediating pathogenic host-microbial interactions in the sinonasal epithelium of patients with relapsing GPA.

Disclosures: None

179. Single cell transcriptomic analysis of T helper cells in PR3 ANCA associated vasculitis

Seerapani Gopaluni[1], John Ferdinand[1], Menna Clatworthy[1], David Jayne[1]
[1]*University of Cambridge, Cambridge, UK*

Background: CD4 T cells in ANCA associated vasculitis (AAV) patients, irrespective of their disease status, were shown to be in a state of persistent activation. We have shown that a subset of CD4 T cells, circulatory peripheral T helper cells (cPTH) expressing CD4+CXCR5+PD1-, were increased in the peripheral blood of PR3-AAV patients and that phenotypically similar cells were present in the kidney tissue and urine of nephritic patients. Bulk transcriptomic analysis indicated that cPTH cells were proliferating and were cytotoxic cells expressing chemokine receptors supporting migration to sites of inflammation. The primary aim of this study was to understand the composition of the cPTH cell subset, its heterogeneity, and the clonal relationship between circulatory TFH (cTFH) and cPTH cells.

Methods: Three patients with PR3-ANCA associated vasculitis (PR3 AAV), in stable remission on minimal immunosuppression with rising PR3-ANCA levels and three healthy volunteers (HV) were recruited. 100 mL of blood was obtained from each subject and PBMCs extracted. The samples were enriched for CD4 T cells by positive selection using magnetic cell sorting. For each subject, 160,000 cPTH cells, 80,000 cTFH and 300,000 each of CXCR5+PD1- and double negative (cDN) T cells were flow sorted and processed using 10x Genomics' single-cell RNA-seq (scRNA-seq) technology combined with feature barcoding technology. Cells were pooled in a ratio of 1:1:1:1

Results: After performing pre-processing and quality control steps, 19997 cells were obtained from the 6 subjects (3 patients and 3 HVs). The total number of cells from HVs was 13353 and from patients was 6644. Leiden clustering analysis resulted in 10 clusters and based on differential gene expression analysis each cluster was annotated. From bulk transcriptomic analysis (our previous work), a gene set (n=171) of significantly upregulated genes by the cPTH subset was used to derive enrichment scores. Clusters 7, 8 and 9 had higher enrichment

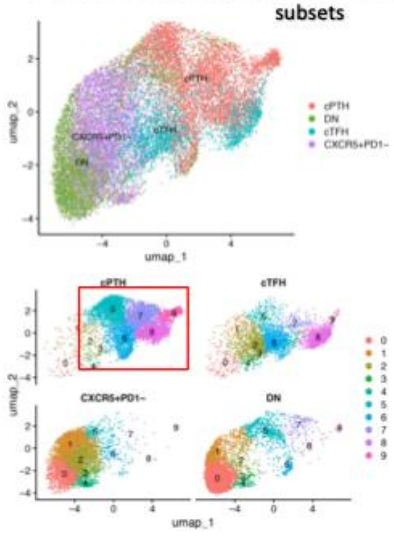
scores, with cluster 9 scoring the most. Further analysis of cluster 9 revealed these cells to be expressing low levels of CD28 (CD28low), higher levels of CX3CR1, genes of recent activation such as HLA-DR and CD69 and higher levels of cytotoxic genes (also suggested on reactome pathway analysis). Cluster 9 from patients when compared to HVs had higher expression of cytotoxic (GZMB, PRF1) and chemokine receptors (CX3CR1). TCR clonal diversity index was lower in patients compared to HVs across all clusters implying restricted repertoire. The diversity indices fell steeply for clusters 8 and 9 for both patients and HVs but the drop was more pronounced in patients, suggesting greater clonal expansion in these clusters. Clonal overlap analysis showed that TCR clones in cluster 9 frequently shared clones with T cells in cluster 8 and cluster 7, suggesting that cytotoxic CD4 T cells in cluster 9 possibly originated from cluster 7 (predominantly Th1 subset without cytotoxic gene enrichment), through cluster 8 (predominantly Th1 subset with cytotoxic gene enrichment). CD4 T cells of patients had low levels of expression of IL-7a possibly due to chronic antigenic stimulation of T cells.

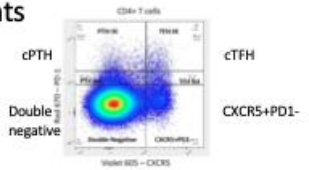
Conclusions: We have shown that cPTH cells express cytotoxic genes and that cells within clusters 7, 8 and 9 expressing GZMB, PRF1, CCL5, NKG7, GZMA are the predominant subset that contributed to the genes identified on bulk transcriptomics. Further, cells in cluster 9 were differentially expressed with patients having a higher expression of activation markers, CD69, HLA-DR and chemokine receptors such as CX3CR1, CXCR4, CXCR3. cPTH cells were not a homogenous group of cells and consisted of at least five different clusters, each expressing a predominant gene sets characteristic for either Th1, Th17, cytotoxic, TFH-like or CD28null subsets. TCR clonality analysis showed that these cells were clonally expanded and that they share clones mostly with Th1 phenotype subsets suggesting that they have common origins with other cPTH cells.

Disclosures: None

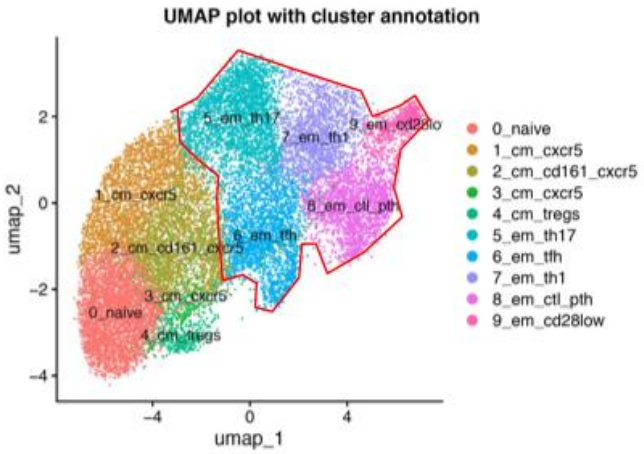
Single cell transcriptomics of sorted CD4 T cells from 3 patients and 3 healthy volunteers

cPTH cells are heterogenous and consist of at least different 5 subsets



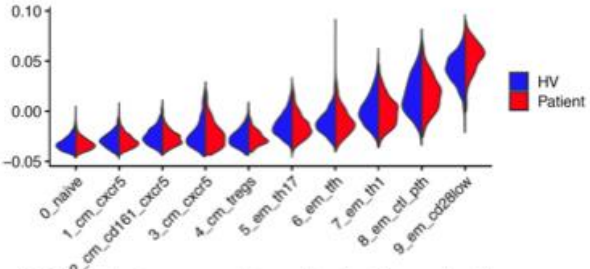


UMAP plot with cluster annotation

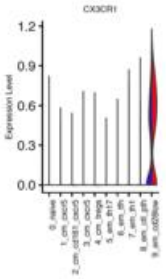


CD28low cluster transcriptome correlates closely with cPTH bulk transcriptome

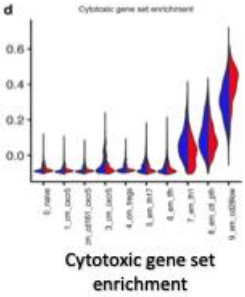
Enrichment scores of clusters for cPTH bulk transcriptomic gene set



CD28low cluster has highest expression of CX3CR1

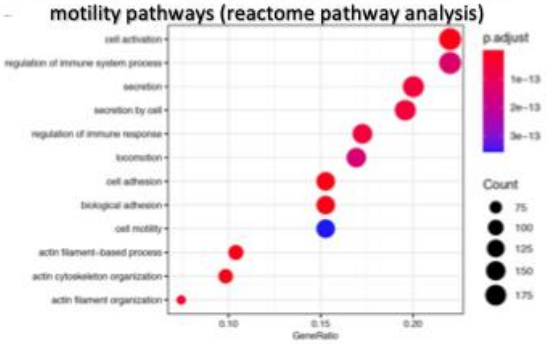


CD28low cluster has highest expression of cytotoxic gene signature



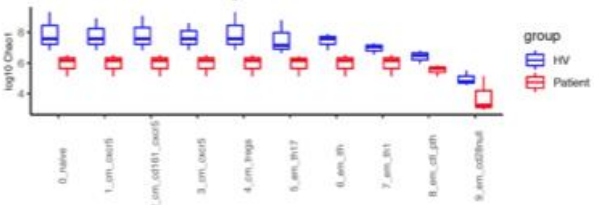
Cytotoxic gene set enrichment

CD28low cluster upregulates cell activation and cell motility pathways (reactome pathway analysis)



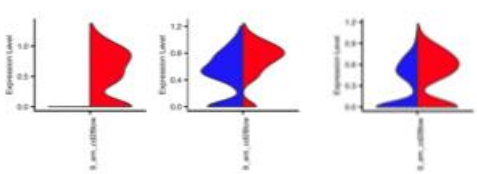
T cells are clonally restricted in patients compared to HV

Diversity indices of TCR clones

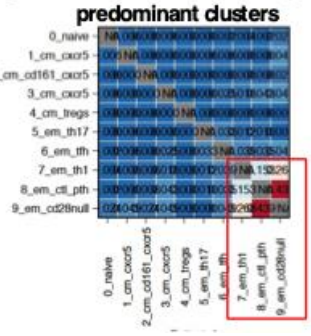


CD28low cluster differentially expresses cytotoxic genes and CX3CR1 between patients and HVs

GZMB, p <0.001 D=0.56 PRF1, p <0.001 D=0.35 CX3CR1, p <0.001 D=0.25



Significant clonal overlap amongst PTH predominant clusters



180. Deconvolution of transcriptomic data reveals immune cell landscape of inflammatory infiltrates in giant cell arteritis

Michal Zulcinski[1], Gary Reynolds[2], Lubna Shafi[1], Arundhati Chakrabarty[1], Mark Iles[1], Ann Morgan[1]
[1]School of Medicine, University of Leeds, Leeds, UK, [2]Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK

Background: Giant cell arteritis (GCA) is the most common form of vasculitis in people over 50 years old and can lead to serious ischaemic complications, such as permanent visual loss. It is characterized by inflammation in medium- and large-sized vessels, but the molecular events leading to different phenotypes remains largely unexplained. Current treatment choices are very limited and high glucocorticoid doses are required at disease onset, despite carrying a substantial risk of side effects. Better understanding of the molecular mechanisms underlying GCA is needed to discover alternative treatment options and to improve molecular stratification of GCA management. Our study aims to integrate bulk and single-cell transcriptomes generated from temporal artery biopsies to reveal cell-type-specific expression profiles associated with distinct histological patterns of arterial inflammation in GCA.

Methods: Patients from the UK GCA Consortium (UKGCA; *n*=41) and Newcastle and North Tyneside registry (NNT; *n*=9) were selected for the study. All UKGCA cases had a positive histological diagnosis as part of routine clinical care. RNA was extracted from formalin-fixed paraffin embedded temporal artery biopsies from UKGCA participants and subjected to next-generation sequencing, while cells from all (5 positive and 4 negative) NNT biopsies were dissociated from fresh tissue and subjected to single-cell RNA-sequencing, using 10x Genomics. Various clinical and histological variables, identified in a serial section, were recorded for each patient. Deconvolution analysis was performed using the MuSIC software (https://github.com/xuranw/MuSiC) to infer sample-specific cell-type proportions and to enable cell-type-specific differential expression analysis. All statistical testing for clinical and histological features was performed using the non-parametric Mann-Whitney-Wilcoxon test to avoid making parametric assumptions. False Discovery Rate was used to account for multiple testing.

Results: Transcripts differentially expressed in patients with specific histological features were identified. Those showing the strongest associations were: the presence of giant cells (1571 transcripts; FDR-corrected p-value <0.01) and the extent of inflammation in the intima, media and adventitia (3301, 2637 and 5359 transcripts respectively; all FDR-corrected p-values <0.01). The deconvoluted data for cell-type-specific differences revealed the myofibroblast population to have the strongest association with transcriptomic profiles which confirms the importance of vascular remodelling. Additional analyses to assess the influence of confounding factors on gene expression, in particular sex, age and duration of steroid treatment were also conducted, resulting in no clear evidence for a confounding effect from patients' age (UKGCA: 59-92; NNT: 64-84) or steroid treatment duration (UKGCA: 0-16 days; NNT: 4-13 days).

Gender was found to be a likely source of confounding and secondary to inclusion of the sex chromosomes in the analysis pipeline.

Conclusions: Our findings reveal a previously unreported landscape of cell population abundance levels in GCA biopsies and their associations with different inflammatory phenotypes. We also aim to provide novel insights into cell-type-specific expression profiles of both, transcripts already known to be involved in GCA pathogenesis, as well as novel molecular signatures that might have potential for therapeutic targeting. Although no clear confounding influence of unavoidable prednisolone exposure prior to biopsy was found, such effects will be further investigated in an expanded patient cohort. Ultimately, we aim to identify novel therapeutically amenable candidate genes and pathways involved in the inflammatory response.

Disclosures: AWM has received research grant and educational funding or undertaken consultancy for the following pharmaceutical companies in the last 5 years: AstraZeneca, Kiniska Pharmaceuticals, Regeneron, Roche/Chugai, Sanofi and Vifor.

181. Tissue immunophenotyping of three refractory cases of EGPA using single cell RNA sequencing

Matthew Coates[1], David Jayne[1]
[1]*University of Cambridge, Cambridge, United Kingdom*

Background: Eosinophilic granulomatosis with polyangiitis (EGPA) is a multisystem inflammatory disorder currently classified as an Antineutrophil Cytoplasmic Antibody (ANCA) associated vasculitis. Core features of the condition include eosinophilia and respiratory tract involvement, often manifesting as early and treatment resistant involvement of both the upper and lower respiratory tract. However, the underlying pathophysiology of EGPA remains poorly understood, with a particular lack of studies exploring the tissue immune response in the affected organs of subjects with the disease. Clinical phenotype varies within the condition, with an absence of ANCA and biopsy evidence of vasculitis in the majority of patients. Variations in clinical phenotype and genotype between ANCA positive and negative cohorts suggesting that the term could encompass at least two distinct conditions with similar clinical manifestations[1,2]. We aim to characterise the tissue immune response in MPO positive and ANCA negative EGPA using single cell transcriptomics. We show pilot data from a novel postnasal space biopsy technique, which we have used to sample respiratory tract secondary lymphoid tissue from EGPA subjects and controls, at a disease relevant site.

Methods: Subjects with active (BVAS>0) EGPA, disease controls with active GPA (Granulomatosis with polyangiitis) or Chronic rhinosinusitis, and healthy controls were recruited from Cambridge University Hospitals. EGPA was diagnosed based on MIRRA study criteria[3]. All subjects underwent single timepoint paired endoscopic postnasal space lymphoid tissue biopsy and peripheral blood samples. Biopsies were performed using topical local anaesthesia in the outpatient department. Tissue was minced, enzymatically digested (DNAse/Liberase)

and filtered to create a single cell suspension. Blood underwent density centrifugation (Histopaque 1077) for red cell removal. Single cell transcriptome libraries were created from the resulting fresh single cell suspensions using the 10x genomics platform. Transcriptomes were aligned with Cellranger software and processed in R and Python.

Results: Three EGPA subjects (one MPO ANCA positive, two ANCA negative), one Chronic rhinosinusitis subject, seven PR3 ANCA positive GPA, and six healthy controls were included in this pilot analysis. After quality control and preprocessing, 126822 cells were obtained, across 51 distinct celltypes. Celltypes included epithelial, stromal and immune cell populations, including germinal centre related celltypes. Eotaxins are chemokines with eosinophil chemotactic activity. Eotaxin expression profiles varied between ANCA positive and ANCA negative subjects and controls. Whilst Eotaxin 1(CCL11) and Eotaxin 2 (CCL24) predominated in the two ANCA negative subjects, Eotaxin 3 (CCL26) predominated in the MPO ANCA positive subject. Eotaxin expression in EGPA subjects was increased compared with healthy controls despite concurrent corticosteroid therapy. The source of Eotaxins also varied. Eotaxin 1 expression localised to a distinct cluster of Fibroblasts expressing Prostaglandin D2 Synthase, complement genes (C1S, C3), and the chemokines CXCL14 and RARRES2. Eotaxin 2 expression localised to a population of nasal macrophages expressing a tissue residency signature, and Eotaxin 3 was localised to the basal Epithelial cell cluster.

Conclusions: Postnasal space biopsy can be used to safety and effectively obtain adequate tissue samples in vasculitis for single cell transciptomics. This pilot data suggests that different Eotaxin profiles may exist in ANCA positive and ANCA negative EGPA, which persist during corticosteroid therapy.

Disclosures: None

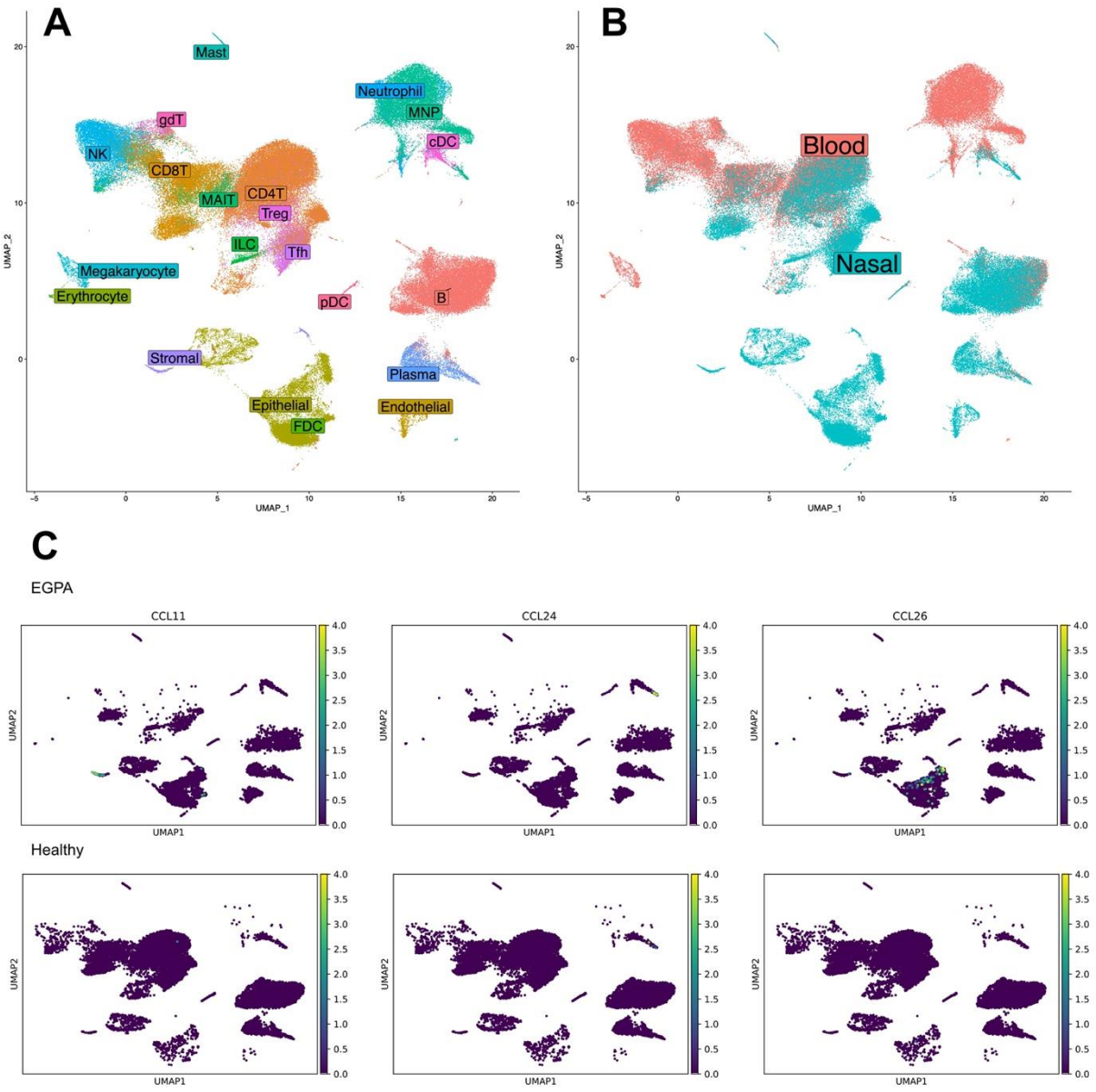


Figure 1: Uniform manifold projection (UMAP) of single cell RNA sequencing data in EGPA subjects and controls. A: Broad celltype named clusters. B: UMAP of celltype split by sample type. C: UMAP of Eotaxin expression in EGPA subjects and controls.

Imaging & Diagnostic Procedures

182. Point of Care Ultrasound in a Rapid-Access GCA/PMR Clinic

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Background: In recent years, temporal artery ultrasound (TAUS) has become a reliable alternative to temporal artery biopsy (TAB) for diagnosing Giant Cell Arteritis (GCA). There is also accumulating evidence that a substantial subset of Polymyalgia Rheumatica (PMR) patients have sonographic evidence of temporal artery inflammation in the absence of cranial symptoms. Early identification will help with earlier and more appropriate escalation of immunosuppressive therapy. Study objectives were to compare the diagnostic performance of TAUS with that of TAB and to define the prevalence of subclinical temporal artery inflammation in those presenting with PMR.

Methods: In August 2020, we established rapid-access GCA/PMR clinics in Tallaght University Hospital (TUH) and Cork University Hospital (CUH). ACR classification criteria for GCA and EULAR classification criteria for PMR were used as inclusion criteria. In most cases, patients were seen within 24 hours from referral. Referral sources included primary care physicians, emergency departments, acute medical units and TUH/CUH inpatients. All study participants had vascular ultrasound performed of both temporal arteries (all 3 branches) and both axillary arteries. TAB was performed where possible.

Results: 123 patients have been assessed in our clinic over 1 year. 100 were referred with a working diagnosis of GCA, of whom 57 ultimately had GCA diagnosed clinically. 23 had been referred with a working diagnosis of PMR, of whom 6 had sonographic evidence of temporal artery inflammation. 49 patients with suspected GCA had TAB performed. Using clinical criteria as the reference standard, US and TAB demonstrated the following diagnostic performance:

Conclusion: Ultrasound is a far more sensitive test than TAB for diagnosing GCA. In our model, hospital admission would have been avoided entirely in 50% of patients owing to the diagnostic accuracy and timing of ultrasound. Our data also adds to the evidence that suggests a significant proportion of pure-PMR patients have underplaying GCA at diagnosis. We propose that vascular ultrasound should be performed as routine in all PMR patients at baseline.

Disclosures: None to declare.

(n=57)	TAUS	TAB
Sensitivity	89%	41%
Specificity	91%	100%
Positive Predictive Value	93%	100%
Negative Predictive Value	87%	16%

183. Duration of Steroid Therapy and Temporal Artery Biopsy Positivity in Giant Cell Arteritis

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Background: Temporal artery biopsy (TAB) is an important investigational tool in the diagnosis of giant cell arteritis (GCA). Glucocorticoid therapy is also often used upon suspicion for GCA to prevent irreversible vision loss.[1] It is recommended to complete a TAB within 14 days of glucocorticoid initiation. However, data has conflicted as to how long biopsies remain positive, with one study demonstrating positivity of 44% up to 1 year.[1,2] The aim of this study was to investigate how duration of glucocorticoid exposure affected TAB positivity in a cohort of patients with suspected GCA.

Methods: Data were extracted from two sources: the McMaster GCA Database (n=52) and those enrolled in a trial evaluating imaging in the diagnosis of GCA (n=171).[3] Diagnosis of GCA was made clinically using all available material including features on history and exam suggestive of GCA, inflammatory markers, temporal artery magnetic resonance angiography, and temporal artery ultrasound. Individuals who underwent TAB as part of their diagnostic evaluation were included. Data concerning demographics and other investigations were extracted. Individuals were stratified by duration of glucocorticoid pre-treatment by weeks of therapy; those receiving six or more weeks of therapy were pooled due to low numbers. Descriptive statistics were performed and the impact of the duration of glucocorticoid therapy on TAB positivity was assessed using a two-sided Cochran-Armitage Trend test.

Results: Data from 223 patients were included. There were 48 TAB-positive and 175 TAB-negative cases. Stratified by TAB positivity, mean ages (standard deviation) of each subgroup were 73.5 (9.5) for positive TABs and 70.7 (10.6) for negative TABs respectively. 35 (72.9%) of the TAB-positive cases, and 123 (70.3%) of TAB-negative cases, were female. Forty-six (95.8%) TAB-positive cases, and 152 (86.9%) of TAB-negative cases, received glucocorticoids pre-TAB. No significant difference in length of glucocorticoid pre-treatment between groups existed. TAB-positive individuals were more likely to have vision loss, jaw claudication, constitutional symptoms, and elevated ESR and CRP ($p<0.01$). When stratified by weeks of

treatment, there were fewer TABs performed with longer duration of therapy ($p<0.01$) (Table 1). The Cochran-Armitage Trend test did not demonstrate a temporal trend between weeks of treatment and TAB positivity ($p=0.11$).

Conclusion: The results of this analysis suggest that glucocorticoid therapy does not affect TAB positivity to at least 6 weeks, with inconclusive data thereafter. These results suggest the recommendation of obtaining a TAB within 14 days of glucocorticoid initiation is unnecessarily conservative.

Disclosures: NK discloses grants or contracts from the following entities: BMS-supplied drugs and investigator-initiated clinical trial, Sanofi and 2020 GCA and PMR clinical trial, Abbvie and 2020/21 GCA clinical trial; Support for travel to an international meeting for MANDARA trial from Astra Zeneca; and participation on the Advisory Board for GCA CME November 2020 with Roche. SG discloses an honorarium provided for Pfizer for a speaking event; Sanofi: Clinical Trial 2020 in GCA and PMR; AbbVie: Clinical Trial 2020-2021 in GCA; Roche: Educational Grant; Novartis: Advisory Board.

Table 1: Diagnoses of GCA stratified by duration of glucocorticoid treatment pre-TAB.

Weeks of treatment	Number of patients	GCA diagnoses	Number of positive TABs
	223	118	48
0	57	23	8
1	46	28	11
2	45	25	10
3	26	8	6
4	21	10	4
5	10	8	3
6	18	16	6

184. Clinical-radiological correlation and prognostic value of baseline chest computed tomography in eosinophilic granulomatosis with polyangiitis

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Background: Eosinophilic granulomatosis with polyangiitis (EGPA) is characterized by vasculitis, blood and tissue eosinophilia and severe asthma. While high-resolution computed tomography (HRCT) is correlated to severity and prognosis in asthma, it has not been studied in EGPA.

Methods: Retrospective, multicenter observational study in three French hospitals, including EGPA patients with available chest HRCT before any systemic treatment between 2006 and 2019. Two experienced radiologists blind for clinical data evaluated HRCT images using semi-quantitative scoring ranging from 0 (absent feature) to 3 (severe) of six items: mucous plugging, bronchiectasis, bronchial wall thickening, mosaic perfusion, ground-glass opacities and consolidation. HRCT characteristics were correlated with clinical features and outcome at one year of follow-up.

Results: Among 46 patients, 38 (82.6%) had abnormal parenchymal findings on HRCT, that included bronchial wall thickening (69.6%), mosaic perfusion (63.0%), ground-glass opacities (32.6%), bronchiectasis (30.4%), mucous plugging (21.7%) and consolidations (17.4%). Patients were clustered into three groups depending on HRCT features: ground-glass pattern *i.e* with ground-glass opacities with or without bronchial abnormalities (group 1, 28.3%), bronchial pattern (group 2, 41.3%), and extra-pulmonary pattern without any major chest HRCT abnormality (group 3, 30.4%). Patients with bronchial pattern were older (median age 65 [52-72] *vs*. 48 [39-54] and 47 [35-53] years in groups 1 and 3, respectively), had less frequent cardiac involvement (31.6 *vs*. 46.2 and 42.9%), more frequent neurological involvement (47.4 *vs*. 30.8% and 28.6%) and positive ANCA (52.6 *vs*. 0.0 and 14.3%), and higher blood eosinophil count (median 7,510 [2,275-12,875] *vs*. 4,000 [2,750-7,600] and 4,250 [2,100-12,983]/mm^3), whereas patients with ground-glass pattern had more frequent ENT manifestations (92.3 *vs*. 68.4 and 64.3% in groups 2 and 3, respectively). Patients with ground-glass pattern showed worse prognosis with more frequent steroid-dependency (58.3 *vs.* 11.1 and 28.6%) and requirement for mepolizumab (25.0 *vs.* 11.1 and 7.1%). Conversely, patients with bronchial pattern had a better outcome with less frequent treatment failure, less frequent relapses (11.1 *vs*. 25.0 and 35.7% in groups 1 and 3, respectively), and higher rates of complete remission at 1-year (77.8 *vs*. 33.3 and 35.7%).

Conclusion: Chest HRCT at EGPA diagnosis is correlated to clinical features and patients' outcome, especially while studying ground-glass opacities and bronchial involvement. As in allergic asthma, HRCT could help clinicians to more appropriately manage EGPA patients.

Disclosure: The authors have no conflicts of interest to declare.

185. Carotid ultrasonography markers for neurological severe ischemic events in Takayasu arteritis with supra-aortic lesions

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Background: Takayasu's arteritis (TAK) is an idiopathic systemic vasculitis characterized by the involvement of the aorta and its major branches [1]. The supra-aortic arteries are often involved in TAK, with the reported prevalence ranging from 40% to 84% [2-3]. Importantly, patients with supra-aortic involvement carry a higher risk of neurological severe ischemic events (SIE) [4-5]. The common carotid artery (CCA) is the most affected artery and is more closely associated with neurologic symptoms than other supra-aortic arteries [6]. Ultrasonography (US) has been regarded as the most popular, user-friendly, and repeatable tool for the diagnosis and follow-up of CCA injuries. Our aim was to characterize TAK with supra-aortic involvement and determine the associations between clinical features, carotid US parameters, and neurological SIE.

Methods: Patients with supra-aortic involvement including brachiocephalic trunk, bilateral common carotid artery and internal carotid artery, and bilateral subclavian and vertebral artery and baseline carotid US examination were enrolled. Bilateral carotid diameter, intima-media thickness (IMT), and peak systolic velocity (PSV) were measured by US. Then, IMT/diameter ratio (IDR) was calculated. Risk factors associated with neurological SIE were analyzed by multivariate logistic regression.

Results: Totally, 295 patients were included, of whom 260 (88.1%) were female, and 93 (31.5%) experienced neurological SIE, with common carotid artery involved (81.7%). Involved supra-aortic artery distribution (p=0.04) and number (p<0.01) differed between neurologic and non-neurologic SIE subjects, showing higher prevalence of common carotid and vertebral artery involvement in cases with neurological SIE and 57.1% neurological SIE patients having more than four involved arteries. The left carotid IMT (p=0.03) and IDR (p<0.01) differed between patients with and without neurological SIE. The left carotid IDR (cut-off value ≥0.55, odds ratio [OR] 4.46; 95% confidence interval [CI] 2.05-9.71; p<0.01) and PSV (≤76 cm/s, OR 3.38; 95% CI 1.62-7.04; p<0.01) and involved supra-aortic artery number (≥4, OR 3.16; 95% CI 1.54-6.47; p<0.01) were independently associated with neurological SIE.

Conclusion: The left carotid IDR, PSV and involved supra-aortic artery number would perform as valuable markers for recognizing neurological SIE in TAK patients with supra-aortic lesions.

Disclosures: None.

186. Validating diagnostic GCA ultrasonography skills against an expert sonographer

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Background: Ultrasonography has become the recommended first line investigation for suspected giant cell arteritis (GCA). However, it is still not yet widely available in the UK due to a paucity of skilled rheumatologists. Effective training programmes have been developed, but subsequent hands-on practice is needed to become truly proficient. There is no consensus on the logistics of gaining the 'appropriate' level of skill. This project demonstrates a potential mechanism for validation against an expert sonographer.

Methods: Over a 6-month period, 12 scans of patients referred with suspected GCA were sequentially performed by first a trainee (FC) and then an expert sonographer (CM) on the same day. FC had theoretical knowledge and supervised practical experience but had not scanned independently prior to this project. CM has performed >1000 scans. 6 vascular territories considered to be the core GCA US data set (common, frontal and parietal branches of the superficial temporal artery, and the 1st, 2nd and 3rd part of the axillary artery) were marked as either 'normal' or 'halo'. CM was blinded to FC's results. Inter-observer reliability was calculated for all vascular territories using Cohen's kappa.

Results: A total of 144 vascular territories were scanned in 12 patients. Table 1 details the inter-observer variation, with a near perfect level of agreement demonstrated, kappa=0.90 (95% CI 0.83 – 0.98).

Conclusions: This is the first study that demonstrates a mechanism for validation of ultrasonography skills which will allow GCA US to become a feasible reality in clinical practice. This project demonstrates that after acquiring supervised training, near perfect levels of agreement can be arrived between a trainee and expert.

Disclosures: None

Table 1. Matrix of inter-observer variation for all vascular territories in 12 patients, k=0.90 (95% CI 0.83 – 0.98)

	FC positive	FC negative	Total
CM positive	48	4	50
CM negative	2	90	92
Total	50	94	

187. Combination of CT chest findings may help in differentiating GPA from PTB

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Background: Computed tomography (CT) chest findings of granulomatosis with polyangiitis (GPA) may mimic the abnormalities of post primary pulmonary tuberculosis (PTB). In tuberculosis endemic countries, it is essential to differentiate between these two conditions due to therapeutic implications. Aim of the present study was to compare the chest CT findings between GPA and PTB.

Methods: In this retrospective study, patients with GPA and lung involvement and patients with sputum positive PTB were included for analysis. Parenchymal lesions including nodules, masses, consolidation, ground glass opacities, cavities, traction bronchiectasis, pleural or pericardial involvement and presence of lymphadenopathy were compared between patients with GPA and PTB.

Results: Forty-five patients with GPA and 47 patients with PTB were included. Findings in GPA were nodules in 33 (73.33%), masses in 10 (22.22%), ground glass opacities in 18 (40%), consolidations in 19 (42.22%) and septal thickening in 19 (42.22%) patients. Cavitation of the nodules was noted in 21 (46.67%) and diffuse alveolar haemorrhage was present in 6 (13.33%) patients. Pleural involvement was noted in 5 (11.11%) patients. None of the patients had mediastinal or hilar lymphadenopathy. Findings that were significantly more common in PTB included centrilobular nodules ($p<0.0001$), consolidation ($p<0.0001$), cavitation ($p=0.022$), parenchymal bands ($p=0.001$), and lymphadenopathy ($p<0.0001$). Diffuse alveolar haemorrhage was the only finding that was significantly more common in GPA ($p=0.043$). Additionally, GPA was associated with significantly larger nodules ($p=0.003$).

Conclusion: Combination of CT chest findings may help in differentiating GPA from PTB in tuberculosis endemic areas.

Disclosures: None

188. Ultrasound with superb microvascular imaging and a novel developed grading scale diagnosing giant cell arteritis

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Background: Giant cell arteritis (GCA) is a systemic inflammatory disease primarily affecting an elderly population. Ocular ischemia is a serious complication, and rapid and reliable diagnosis is therefore important. High frequency ultrasound (US) and superb microvascular imaging (SMI) may provide more information regarding activity of the disease. SMI is a low-flow Doppler technology with high resolution and high framerate allowing detection of neovascularization. The aim of this study was to evaluate if US with SMI, in combination with a novel developed GCA grading scale, based on US vessel wall appearance and compression test, may be used to differ between active or stable disease, and provide a hint of the global burden of inflammation.

Methods: Fifty consecutive patients, 32 women and 18 men, mean age 74 years, with GCA suspicion, were investigated. Intima-media thickness (IMT) and vessel wall appearance was evaluated with high frequency US (Canon Aplioi800) in carotid and central arteries (linear transducer i11LX3) as well as in temporal arteries (hockeystick transducer i22LH8). SMI was used in the evaluation of neovascularization. Compression test was done at multiple locations of the temporal arteries. A theoretical model was created to characterize inflammatory vessel wall changes in temporal arteries (Table 1).
Grade I – Increased IMT, low-medium echogenicity with neovascularization and/or oedema extending into the media, and/or signs of inflammation outside the vessel walls, and positive compression test (highly active inflammation).
Grade II – As Grade I but without neovascularization and/or oedema and/or signs of inflammation outside the vessel walls (active inflammation).
Grade III – Increased IMT, increased echogenicity, and positive compression test (longstanding arteritis).
Widespread disease – Grade I, II or III with addition of inflammatory findings in facial, carotid and/or central arteries.

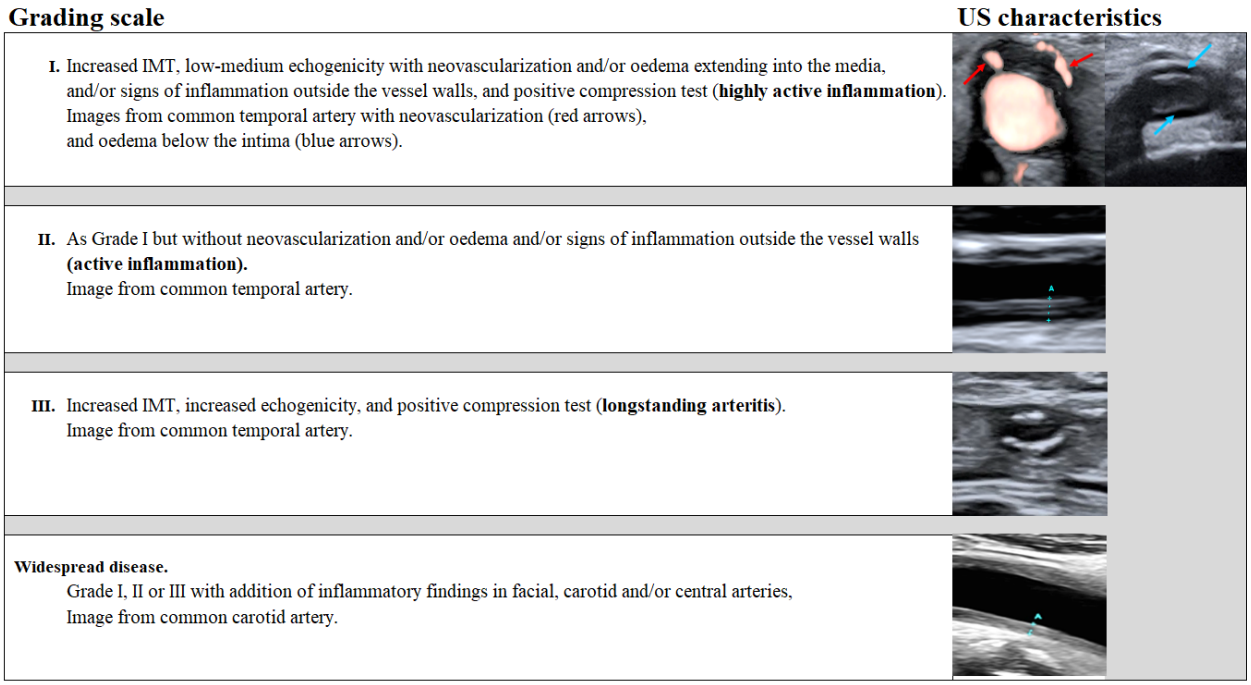
Results: Inflammatory changes were found in the temporal arteries in eighteen patients (36%), five (28%) of these patients also showed abnormalities in facial, carotid or central arteries. One patient demonstrated inflammatory changes restricted to carotid and central arteries.
Active arteritis, with increased IMT, and low-medium echogenicity of the increased vessel wall was found in fifteen cases. Neovascularization was detected with SMI in four patients; oedema extending into the media was visualized in one patient, and signs of inflammation outside the vessel walls in six cases. High echogenic vessel walls with increased IMT, indicating long-

standing arteritis were found in three patients. Seven patients were judged as Grade I, eight patients grade II, and three patients grade III.
IMT in the common temporal artery differed significantly between patients with and without positive ultrasound signs, 0.61±0.21 mm vs. 0.22±0.06 mm ($p<0.001$).

Conclusion: High frequency US with SMI seems to be a promising tool to detect and monitor inflammatory changes and differ between longstanding or newly developed/active GCA. The novel GCA grading system may aid in judging inflammatory activity and evaluate the global inflammatory burden. Further studies regarding the relation between vessel wall appearance, laboratory findings and clinical disease activity are warranted.

Disclosures: None.

Figure 1. Grading scale and US characteristics, IMT; Intima Media Thickness, US; Ultrasound



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189. Early Diagnostics in Giant Cell Arteritis: Comparing Ultrasound, Positron-Emission Tomography/Computed Tomography and Magnetic Resonance Imaging

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Background: Giant cell arteritis (GCA) requires rapid diagnosis and treatment to prevent severe complications. However, its low incidence, generic symptoms and nonspecific laboratory markers often result in a diagnostic challenge. The use of a temporal artery biopsy as a gold standard in GCA diagnosis is debatable, as it is time-invasive and has a low sensitivity. The use of imaging techniques is increasingly recognized because they are fast, non-invasive and have a higher sensitivity. However, a direct comparison between these techniques is lacking. This study aims to compare the diagnostic value of ultrasound (US), positron-emission tomography/computed tomography (PET/CT) and magnetic resonance imaging (MRI) with each other.

Methods: Patients were recruited for this nested-case control study from a prospective observational cohort study in Hospital Group Twente (ZGT), the ZGT GCA Early in Twente (ZGT-GET) cohort. Demographic and clinical information of patients with suspected GCA is collected. In the present study, 20 patients diagnosed with GCA (GCA+) and 20 patients suspected of but not diagnosed with GCA (GCA-) were included according to baseline diagnosis by the treating rheumatologist. Due to ethical considerations, this rheumatologist had access to all imaging results. Therefore, to avoid bias, the reference diagnosis will be determined by an expert panel based on clinical and laboratory parameters after 6 months follow-up. At baseline, patients underwent standard diagnostic work-up including US of at least the temporal and axillary arteries. A whole body PET/CT and a cranial MRI were performed within one week to minimize influence of treatment. Based on the aforementioned reference diagnosis, sensitivity and specificity of the 3 imaging techniques will be compared. Additional analyses will be performed to assess GCA manifestations and glucocorticoid use.

Results: In GCA+ patients, mean age was 72.1 years (SD 7.3) and 55.0% (n=11) were female. In GCA- patients, this was 69.2 years (SD 8.3) and 75.0% (n=15), respectively (Table 1). Follow-up is still ongoing, fortunately the results of the reference diagnosis, sensitivity and specificity of the imaging techniques will be available at the time of the conference.

Conclusions: This study compares sensitivity and specificity of US, PET/CT and MRI with each other when 6 months follow-up is available. Direct comparison of diagnostic accuracy is needed to determine the optimal imaging modality for early diagnostics in GCA.

Disclosures: none

Table 1 baseline characteristics

	GCA+[1]	GCA-[1]	p-value <0.05
Gender; %female (n)	55 (11)	75 (15)	0.02
Age; mean (SD)	72.1 (7.3)	69.2 (8.3)	
Clinical symptoms, %yes (n)			
New headache	100 (20)	85 (17)	
Visual impairment	20 (4)	5 (1)	
Scalp tenderness	65 (13)	40 (8)	
Jaw claudication	45 (9)	0 (0)	<0.001
Arm/leg claudication	0 (0)	5 (1)	
Constitutional symptoms[2]	84 (16)	70 (14)	
Polymyalgia Rheumatica	30 (6)	35 (7)	
CRP[3], median (IQR) mg/l	36 (17.0-135.0)	8 (1.0-27.0)	0.001
ESR[4], median (IQR) mm/h	77 (31.8-93.0)	26.5 (6.5-46.3)	0.002
Duration of symptoms, median time in days (IQR)	32.5 (18.3-55.5)	83.0 (21.0-186.0)	
Temporal artery biopsy, %yes (n)	10 (2)	0 (0)	
GCA indicated high-dose GC use, %yes (n)			
at time of US;	5 (1)	0	
PET/CT;	50 (10)	5 (1)	0.001
MRI	65 (13)	5 (1)	<0.001

[1]Giant cell arteritis; [2]Fever, fatigue or weight loss; [3]C-reactive protein; [4]Erythrocyte sedimentation rate

190. You can only treat what you see: the key role of imaging in vasculitis

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Presentation of Case: The case of a 69-year-old gentleman is presented, with known cardiovascular risk factors, and a previous ischemic heart disease with preserved ejection fraction. In addition, the patient had been diagnosed with rheumatic polymyalgia a year before, having been treated with a low dose of corticosteroids since then. The patient was admitted to the Emergency Room with a two month fever and headache history, complaining of malaise and arthromyalgias. The patient also presented a black spot in the left arm accompanied by a pruriginous rash in the left trunk without referring any insect bites. Although *Borrelia burgdorferi´*s serology was negative, the patient was empirically treated with doxycycline, with a good response of arthromyalgias, although with persistent fever. Moreover, the patient

acknowledged significant weight loss, being admitted to the Internal Medicine ward for further testing.

Diagnostic Testing: Initial patient evaluation focused on ruling out an infectious disease as the cause of the patients' symptoms. Therefore, numerous viral and bacterial serologies with a COVID-19 PCR test and lumbar puncture were performed, with negative results. Blood cultures were as well negative. Laboratory results showed an elevation of inflammatory markers such as an Erythrocyte Sedimentation Rate (ESR) level of 120 mm/hour, and a C - Reactive Protein (CRP) level of 200 mg/L, accompanied by normocytic normochromic anemia with hemoglobin of 11 g/dL and ferritin of 1500 µg/L. Further study of the patient was reached with a cranial, chest and abdominal computerized tomography (CT) scan, with no findings. Due to the persistence of inflammatory markers and fever, a PET scan was requested with a result of a hypermetabolic caption in large vessels (aortic, both carotids, subclavian and, to a lesser extent, in the iliac axes) being compatible with the diagnosis of giant cells arteritis (GCA) (Figure 1).

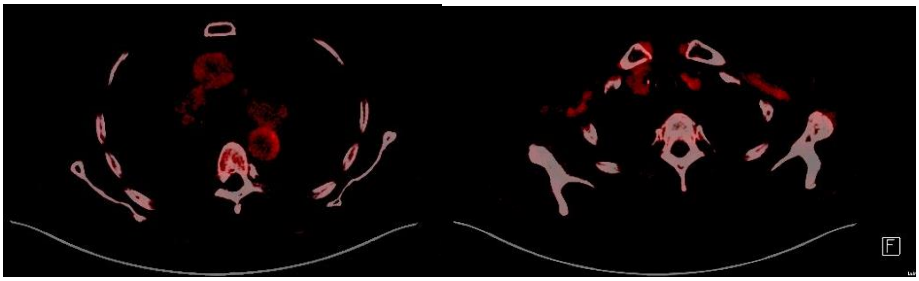
Differential & Final Diagnosis: Fever, presence of inflammatory markers and the imaging results were the clue of the differential diagnosis, suggesting a large vessel vasculitis. The two principal causes of this type of vasculitis are Takayasu's arteritis (TAK) and giant cells arteritis (GCA). The former was ruled out due to the epidemiology, headache and rheumatic polymyalgia prior history. The differential diagnosis of patients with inflammatory vascular diseases is crucial. It should include infectious diseases such as aortitis (like mycobacterial or syphilis aneurisms). Furthermore, other autoimmune disorders must be ruled out, for example Behçet's disease, and atherosclerosis, IgG4-related disease also considered. In this clinical case, four out of five diagnostic criteria for GCA were accomplished. These criteria were the age older than 50, the recent history of headache, Erythrocyte Sedimentation Rate elevation over 50 mm/hour and aortic involvement in PET scan.

Discussion of Management: The challenge of this clinical case is the differential diagnosis between the two principal large vessel arteritis, which are Takayasu's arteritis and giant cell arteritis. Treatment consists in high-dose corticoid therapy associated with tocilizumab or methotrexate. In the case presented, treatment with 60 mg of prednisone once daily was started, with the administration of calcium and vitamin D to prevent osteoporosis. As a glucocorticoid sparing agent, methotrexate 2.5 mg once weekly was also initiated, with folic acid supplements. In further follow up the patient kept asymptomatic with normalization of acute phase reactants. Glucocorticoid tapering dosage until maintenance treatment with prednisone 2.5 mg once daily was achieved, also with a decreasing methotrexate dosage.

Conclusion: Vasculitis diagnosis is a challenging process due to the lack of pathognomonic signs and frequent overlap between different diseases. Furthermore, GCA diagnosis is also hardened due to its late clinical presentation. Diagnosis must focus on the established classification criteria, supported by epidemiology and biopsy results in order to guide clinical practice. However, the fulfillment of all diagnostic criteria is not common. Therefore, more objective tests such as biopsy results and specific imaging tests, and clinical response to inmunosupresive treatment are crucial to diagnostic confirmation.

Disclosures: None.

Figure 1. PET scan results



191. A New Aid in Diagnosis of Childhood Onset Behcet disease: Venous Wall Thickness

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Background: Behçet's Disease (BD) is a systemic inflammatory disease that can involve both the arteries and veins. The lower extremity venous wall thickness (VWT) of BD patients was found to be significantly increased in adults, suggesting its use for the support of the diagnosis. The aim of this prospective study was to investigate the lower extremity VWT in childhood BD patients and incomplete BD and compare it to healthy age-matched controls.

Methods: Pediatric patients classified according to the 2015 international pediatric BD criteria in Hacettepe University Department of Pediatric Rheumatology were included in the study. Incomplete BD relied on the diagnosis of an expert. The control group was age and gender-matched healthy children. VWT measurements of the lower extremity veins including common femoral vein (CFV), superficial femoral vein (FV), vena saphena magna (VSM), vena saphena parva (VSP), and popliteal vein (PV) were recorded.

Results: In this cross-sectional study, VWT was measured in 30 patients (67% male) and 22 healthy controls (55%male). Twelve (40%) of 30 patients met the criteria for the diagnosis of BD. The remaining 18 (60%) had incomplete BD with at least one major organ involvement. The median age was 18 (range 9,5-25) years in the BD group and 17,3 (range 12-23,5) years in the control group. The median age at diagnosis was 12,2 (range 6-16) years. Three patients had a history of thrombosis in lower extremity veins and one patient had a history of upper extremity thrombophlebitis. Pulmonary artery thrombosis had been detected in one patient. Thrombosis of superior sagittal veins was present in six patients with neurological signs. The others had no vascular events. The median VWT values of both complete and incomplete BD patients were significantly higher than the control group in all veins, on both sides (Table 1). Although VWT measurements were higher in complete BD patients, the difference with incomplete BD patients was not significant.

Conclusions: Increased VWT was present not only in patients with vascular involvement but in those without as well. Incomplete BD is a major challenge in the paediatric practice which is due to the heterogeneous character and late appearance of the full clinical features. We suggest that VWT may be a new criterion in supporting the diagnosis of BD in a child. Cut-off values have to be validated in multiethnic populations for its widespread use.

Disclosures: None

Table 1. Venous Wall Thickness of BD Patients and Healthy Controls

Median (25p-75p), mm	Behcet's Disease Patients (n=30)	Healthy Controls (n=22)	P value
Right common femoral vein	0.77 (0.68-0.90)	0.59 (0.56-0.63)	**<0.001**
Right superficial femoral vein	0.67 (0.58-0.75)	0.51 (0.50-0.58)	**0.002**
Right vena safena magna	0.57 (0.40-0.65)	0.39 (0.35-0.41)	**0.001**
Right vena safena parva	0.64 (0.54-0.72)	0.48 (0.46-0.51)	**<0.001**
Right popliteal vein	0.43 (0.38-0.58)	0.29 (0.26-0.34)	**<0.001**
Left common femoral vein	0.78 (0.60-0.88)	0.56 (0.52-0.61)	**0.002**
Left superficial femoral vein	0.64 (0.54-0.81)	0.52 (0.46-0.54)	**0.001**
Left vena safena magna	0.49 (0.42-0.61)	0.37 (0.31-0.40)	**<0.001**
Left vena safena parva	0.63 (0.50-0.80)	0.48 (0.45-0.51)	**<0.001**
Left popliteal vein	0.40 (0.33-0.55)	0.30 (0.25-0.34)	**<0.001**

192. Too Many Ultrasounds? Developing Referral Criteria for a Fast-Track Temporal Artery Ultrasound Service

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Background: In January 2019 we introduced temporal and axillary ultrasound (TAUS) to the giant cell arteritis (GCA) diagnostic service at Leeds Teaching Hospitals Trust. Over the subsequent year we saw a steady increase in referral numbers. During the 2020 COVID pandemic, almost all referrals were sent for TAUS, but false-positives were sometimes observed in low-probability cases, usually due to atherosclerosis; this has been reported by others (De Miguel et al., 2017, Fernández-Fernández et al., 2020). The increasing number of TAUS conducted per week also raised concerns about sustainability of the service. However,

judgement of pre-test probability, even using risk scores, requires face to face evaluation by an individual with clinical expertise in GCA; this may delay referral for TAUS for patients with medium or high pre-test probability of GCA. As part of our service evaluation, we therefore examined our retrospective data to determine whether restricting TAUS to those with CRP>5.0mg/L was a reasonable option.

Methods: This was part of our ongoing service evaluation and was a retrospective analysis. We examined consecutive patients who had undergone TAUS for new presentation of GCA (excluding those having repeat scans for relapse assessment). The highest CRP before starting steroids was recorded, alongside the GCA diagnosis, defined by consultant confirmation of GCA diagnosis and continued treatment for GCA for at least 6 months following first presentation.

Results: We examined consecutive scans between 21st Jan 2019 and 25th Aug 2020. Of 293 scans done, 242 were new presentations of suspected GCA. Of these 242, 96 patients with new suspected GCA had a normal CRP (<5mg/L).
Of these 96, five patients were ultimately diagnosed with GCA. However, of these five, three were already taking long-term, low-dose steroids for polymyalgia rheumatica (PMR), and therefore this cannot be said to be a pre-steroid CRP. The fourth, who presented with visual loss, may have self-treated with prednisolone in the community prior to having the CRP drawn; over time, he had two negative TAUS and two negative TABs but was treated for GCA. The fifth had a negative TAUS and negative TAB but was treated for GCA due to a symptomatic response to steroid therapy.

Conclusions: After the introduction of TAUS for suspected GCA, nearly 40% of our referrals with suspected GCA had CRP<5mg/L but, excluding those with prior PMR, none of these had a positive TAUS or TAB. Therefore with agreement of our department we have now created a referral criteria for TAUS of a pre-steroid CRP>5mg/L (with exceptions possible at consultant discretion). Notably, our laboratory reference range for “normal” is <10mg/L in older patients but we chose to implement this more conservative definition of “normal” for the purposes of GCA diagnosis. Introducing this single TAUS referral criterion has resulted in a noticeable reduction in the number of TAUS required per month.

Disclosures: SM - Support from Roche/Chugai to attend EULAR 2019. Support from Pfizer to attend ACR 2021. Consultancy on behalf of my institution for: Roche/Chugai, AbbVie, AstraZeneca, Sanofi, Pfizer.

193. The utility of hybrid PET/MR imaging for disease monitoring in large vessel vasculitis

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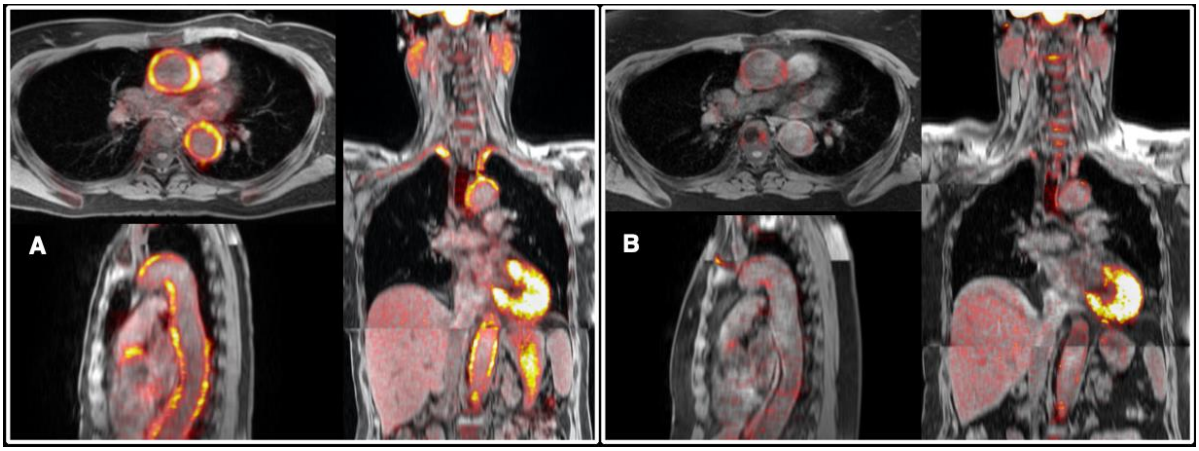
Background: Large vessel vasculitis (LVV), including giant cell arteritis (GCA) and Takayasu arteritis (TAK), is the most common primary vasculitis. Accurately determining disease activity in LVV is challenging, particularly once treatment has started, and can lead to both under-treatment, with resultant disease complications, and over-treatment, leading to adverse effects of toxic therapies. Hybrid PET/MR imaging utilises ~20% of the radiation dose associated with PET/CT and has potential as a diagnostic tool in LVV.[1] Here, we evaluated, for the first time, the potential of PET/MR for tracking LVV disease activity and monitoring treatment-response.

Methods: Patients aged ≥18 years with active LVV were recruited to this Scotland-wide prospective, observational study. The study consisted of 2 visits ≥6 months apart; at each visit clinical evaluation was followed by ^{18}F-fluorodeoxyglucose (FDG) PET/MR scanning (Siemens 3T Biograph mMR). Images were obtained from the Circle of Willis to iliac arteries, and included gadolinium-enhanced MR angiography. PET/MR images were assessed for disease activity qualitatively and semi-quantitatively, and compared with clinical assessment of disease activity.

Results: Thirty-nine PET/MR scans were performed in 24 patients with LVV (14 GCA, 6 TAK, 4 unspecified). Mean age was 61±15 years and 17 (71%) were female. Interpretation of PET/MR scans by a radiologist blinded to clinical details demonstrated a sensitivity of 77% and specificity of 88% for distinguishing active from inactive LVV. Investigator quantification of FDG uptake was then performed for each of 9 arterial segments on a scale of 0-3, and a cumulative PET Vasculitis Activity Score (PETVAS) calculated (0-27; higher scores indicate greater burden of disease).[2] PETVAS was higher in active *versus* inactive disease (15.6±7.0 *versus* 8.8±4.2, *P*=0.001), and higher in GCA *versus* TAK (14.9±7.0 *versus* 8.6±3.4, *P*=0.01). ROC analysis of PETVAS performance yielded an AUC of 0.78 and a suggested cut-off score of 12 for distinguishing active from inactive disease (sensitivity 73%, specificity 76%). In those with >1 scan, PETVAS fell significantly from baseline to follow-up (18.2±6.4 *versus* 9.1±4.5, *P*=0.0001), reflecting a reduction in disease activity over time (Figure – baseline (A) and follow-up (B) PET/MR imaging). MR metrics, including mural enhancement and mural signal, also differed between active and inactive disease. We observed correlations between PETVAS and acute phase reactants, but not with patient-reported fatigue scores.

Conclusions: PET/MR may be useful in tracking disease activity and assessing treatment response in patients with LVV. Based on our findings larger, prospective, multi-centre trials assessing the utility of PET/MR in LVV are now warranted.

Disclosures: none



194. A novel PET/MR score for assessment of disease activity in large vessel vasculitis

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Background: Monitoring disease activity in large vessel vasculitis (LVV) is challenging. Current imaging techniques do not reliably distinguish low-grade inflammation from atherosclerosis. Hybrid PET/MR provides structural and functional vascular imaging, and utilises ~20% of the radiation dose associated with PET/CT, allowing interval scanning.[1] We recently showed the potential utility of PET/MR for LVV disease monitoring. Novel scoring systems for disease quantification that incorporate both PET and MR metrics (as opposed to PET alone) are needed to optimise data extraction and clinical application. Here, we aimed to develop a PET/MR-specific disease activity assessment score for use in LVV.

Methods: Patients aged ≥18 years with active LVV were recruited to this national, prospective, observational study. The study consisted of 2 visits ≥6 months apart; at each visit clinical evaluation was followed by ^{18}F-fluorodeoxyglucose (FDG) PET/MR scanning (Siemens 3T Biograph mMR). Clinician's assessment of disease activity was used as the reference standard. For each of 12 arterial segments, we calculated PET (maximum standardised uptake value (SUV_{max}), SUV_{mean}, and target-to-background ratios (TBRs) based on comparison with venous bloodpool SUV), and MR metrics (mural thickness, T2 mural signal, and the presence of luminal abnormalities). Logistic regression modelling determined which metrics best predicted disease activity. These were then combined to form a weighted 'Vasculitis Activity using MR PET (VAMP)' score.

Results: Thirty-nine PET/MR scans were performed in 24 patients with LVV (14 GCA, 6 TAK, 4 unspecified; mean age 61±15 years; 17 (71%) were female). 22 patients (56%) had active disease based on clinical assessment at time of scan. In univariate analyses, TBRs using SUV_{mean} and T2 mural signal best predicted clinically active disease for PET and MR,

respectively. Informed by multivariate analysis, VAMP score was calculated as shown in Figure 1.

VAMP score was higher in active disease compared with inactive disease (3.7±3.0 *versus* 0.9±0.9; *P*=0.0008). ROC analysis demonstrated an AUC of 0.89 (*P*=<0.0001) and suggested a cut-off of 0.985 (rounded up to 1) to distinguish active from inactive disease. Using this cut-off, VAMP score distinguished active from inactive disease with a sensitivity of 95% and specificity of 82%, outperforming the established (PET-only) PET Vasculitis Activity Score (PETVAS) (sensitivity 73%, specificity 76%).

Conclusions: In our LVV cohort, a novel PET/MR-specific scoring system better distinguished active from inactive disease compared with established scoring systems. Validation in a large, independent cohort is now required.

Disclosures: none

Figure 1. VAMP score calculation equation

$$\frac{\text{Sum of } SUV_{mean} \text{ TBRs for all regions} + 0.5 \text{ if aortic mural signal increased} + 0.5 \text{ if great vessel mural signal increased}}{12}$$

195. Use of 18F-fluorodeoxyglucose Positron Emission Tomography to Standardize Clinical Trial Recruitment in Takayasu's Arteritis

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Background: Disease activity assessment can be challenging in Takayasu's arteritis (TAK), which can lead to difficulty in determining eligibility for enrollment into randomized clinical trials (RCTs). FDG-PET can complement clinical assessment of disease activity. The study objective was to assess whether data from FDG-PET should be incorporated into eligibility criteria for clinical trials in TAK.

Methods: The study was conducted in two parts. Part One was an international online survey among physicians with experience managing TAK to determine whether FDG-PET data influences decisions about enrollment in trials. Participants were asked background questions, including personal experience with use of PET. Clinical vignettes of commonly encountered clinical scenarios were presented, based on actual cases derived from a prospective,

observational cohort. In section A of each vignette, clinical symptoms, examination findings, acute phase reactant (APR) levels, and angiographic data were presented. Participants were asked if there was sufficient evidence of active vasculitis to enroll the patient into an RCT studying a new treatment agent (yes or no) and to rate level of confidence about their assessment (scale of 0-100). In section B, detailed information from the same patient's PET scan was presented and participants were again asked whether they would enroll the patient into an RCT (yes or no) and level of confidence about their assessment. Part Two used patient-level data from an observational cohort study in TAK to assess agreement regarding decisions about enrollment into trials, based on clinical assessment with and without incorporation of FDG-PET data. Generalized linear mixed models, adjusting for correlated data, were used to evaluate associations between PET activity, APR levels, and enrollment decisions.

Results: In Part One 68 physicians responded to the survey. Most physicians had used FDG-PET to diagnose TAK (82%) or monitor disease activity over time (66%). In Section A of the vignettes, greater variability in trial enrollment decision was observed in cases of constitutional symptoms alone (e.g. fatigue) and elevated APR levels (Cases 4-6) (Table 1). In Section B, level of confidence improved when PET findings aligned with clinical assessment from Part A (Case 1,3,8). In cases where PET findings did not align with clinical assessment in part A (e.g. absent clinical symptoms with active PET scan, "subclinical inflammation"), the degree of variability about whether to enroll/not enroll increased in Section B and level of confidence worsened (Case 2, 7). In cases with the highest variability about enrollment in Section A (Cases 4-6), PET activity drove the decision of whether to enroll in Section B and level of confidence improved (Table 1). In multivariable models, FDG-PET findings were 1.29 times more strongly associated with enrollment decisions compared to levels of APRs.
In Part Two, incorporation of FDG-PET data significantly improved agreement about enrollment decisions between raters, (IRR=0.68 [95%CI (0.67-0.69)] to IRR=0.88 [95%CI 0.87-0.89]; $p<0.01$).

Conclusions: Incorporation of FDG-PET data into the assessment of TAK influences decisions about enrollment of patients into clinical trials, improves physician confidence about clinical assessment, and could help reduce variability in study populations. Future trials in TAK should consider incorporating FDG-PET data into eligibility criteria.

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Table 1: Disease activity assessments from Section A and Section B of the clinical vignettes in the context of potential enrollment of the patient into a clinical trial for Takayasu's arteritis

Case	Clinical symptoms	Acute phase reactants	Section A: Enrolled (n, %)	Section A: Not Enrolled (n, %)	FDG-PET	Section B: Enrolled (n, %)	Section B: Not Enrolled (n, %)	Level of Confidence (Section Aà B)
1	Active symptoms (carotidynia, headache)	Elevated	54 (84%)	10 (16%)	Active	63 (98%)	1 (2%)	79%à93%
2	Symptoms of damage (stable arm claudication)	Normal	1 (2%)	61 (98%)	Active	20 (33%)	41 (67%)	74%à69%
3	Symptoms of damage (stable arm claudication)	Normal	0 (0%)	61 (100%)	Inactive	1 (2%)	60 (98%)	82%à91%
4	Fatigue	Elevated	19 (31%)	42 (69%)	Active	54 (89%)	7 (11%)	62%à80%
5	Fatigue	Elevated	16 (26%)	45 (74%)	Inactive	9 (15%)	52 (85%)	64%à75%
6	Fatigue	Elevated	24 (39%)	37 (61%)	Active	55 (90%)	6 (10%)	65%à80%
7	No symptoms	Normal	1 (2%)	60 (98%)	Active	21 (34%)	40 (66%)	83%à69%
8	No symptoms	Normal	2 (3%)	59 (97%)	Inactive	3 (5%)	58 (95%)	83%à93%

FDG-PET: 18F-fluorodeoxyglucose positron emission tomography

196. 18F-fluorodeoxyglucose positron emission tomography as a predictor of angiographic progression of disease in large-vessel vasculitis

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Background: There is limited prospective data characterizing arterial lesions over time in giant cell arteritis (GCA) and Takayasu's arteritis (TAK), the two main forms of large-vessel vasculitis (LVV). FDG-PET can detect vascular inflammation. Whether vascular PET findings predict angiographic change is unknown.

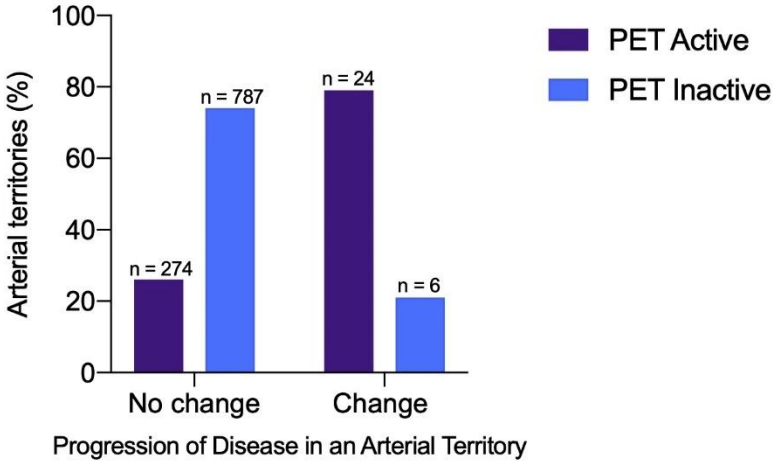
Methods: Patients with GCA or TAK were recruited into a prospective, observational cohort. All patients underwent magnetic resonance (MR) or computed tomography (CT) angiography and a follow-up study ≥6 months after baseline per a standardized imaging protocol. Arterial lesions, defined as stenosis, occlusion, or aneurysm, were evaluated in 4 segments of the aorta and 13 branch arteries by a central reader blinded to clinical status. Development of new lesions in these same territories was recorded, and existing lesions were characterized as improved, worsened, or unchanged over time. All patients underwent FDG-PET on the same date as angiography. Qualitative assessment of FDG uptake was performed in each corresponding arterial territory evaluated by angiography. Active vasculitis was defined as greater FDG uptake in the arterial wall compared to the liver by visual inspection. Conditional logistic regression using a within-person matched design selecting for cases of asymmetric angiographic progression in paired arterial territories (e.g. bilateral subclavian arteries) was performed to evaluate whether FDG-PET activity was independently associated with angiographic progression, controlling for all person-level confounders.

Results: 1162 arterial territories were evaluated from 70 patients with LVV (TAK=38; GCA=32). Over 1.6 years of median follow-up, new lesions developed only in 8 arterial territories, exclusively in 5 patients with TAK. Arterial lesions improved in 16 territories (GCA = 7, TAK = 9) and worsened in 6 territories (GCA = 1, TAK = 5). Typically, angiographic change was asymmetric in paired arteries (26/30 territories).
FDG-PET activity was evaluated in 1091/1162 (94%) of corresponding arterial territories. PET activity in an arterial territory at baseline was significantly associated with change in that arterial territory on follow-up angiography ($p<0.01$), with a sensitivity of 80% and specificity of 74% (FIGURE). Most arterial territories without PET activity at baseline remained unchanged over time by angiography, yielding a negative predictive value of 99%. Most territories with PET activity also did not show change over time, but of the territories with angiographic change, the majority had PET activity (24/30 territories). Using conditional logistic regression, an arterial territory with baseline PET activity had a 3-fold increased risk for angiographic progression of disease compared to the paired arterial territory without PET activity ($p<0.01$). In territories with baseline PET activity, the presence of concomitant wall thickening and edema

by angiography was associated with a 2.6-fold increased risk for angiographic change compared to territories with PET activity without concomitant wall morphologic changes.

Conclusions: Development of angiographic change was infrequent in this cohort of patients with LVV. Lack of PET activity was strongly associated with stable angiographic disease. Most cases of angiographic change were asymmetric in paired arterial territories with PET activity present only in the affected side at baseline. These data may inform recommendations for imaging monitoring in LVV.

Disclosures: None



197. Common Femoral Vein Thickness Measurement as a diagnostic test in Incomplete Behçet's Disease

Fatma Alibaz-Oner[1], Rabia Ergelen[2], Fatma Temiz[3], Seda Kutlug Agackiran[1], Efe Soydemir[2], Tulin Ergun[4], Haner Direskeneli[1]
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Background: Behçet's disease (BD) is characterized by recurrent oral and/or genital aphthous ulcers accompanied by cutaneous, ocular, articular, gastrointestinal and central nervous system lesions. Diagnosing BD can be a clinical challenge in patients presenting with a limited number of organ manifestations, especially with single major organ involvement. We reported the first controlled doppler ultrasound study showing increased common femoral vein (CFV) thickness in BD. We recently also showed that increased CFV thickness is a distinctive feature of BD, rarely present in other inflammatory or vascular diseases such as ankylosing spondylitis,

systemic vasculitides, venous insufficiency, and non-inflammatory DVT with a specificity higher than 80% for the cut-off value of ≥ 0.5 mm. We suggest that CFV thickness measurement is an easy, non-invasive diagnostic test for BD. In this study, we aimed to assess the diagnostic performance of CFV thickness measurement in patients with 'Incomplete' Behçet's Disease diagnosed by expert opinion.

Methods: We included 28 patients with incomplete BD (15 male, 12 female) diagnosed with expert opinion and followed in the Marmara University Behcet's Clinic. Demographic, clinical characteristics and treatment data were recorded during routine visits. Common femoral vein wall thickness was measured by an experienced radiologist at the same day.

Results: Median age was 34.3 years and median disease duration 2 years (0-16). Four patients were newly diagnosed. At follow-up onset, oral ulcers were present in 22 (78.6%), genital ulcers in 6 (21.6%), papulopustular lesions in 4 (14.3%) and pathergy positivity in 5 (17.9%) patients. Ten (35.7%) patients had familial BD. While 24 (85.7%) patients had major organ involvement, 4 (14.3%) patients had mucocutaneous disease. All patients except 1, had CFV thickness value above the cut-off value of ≥0.5 mm. Right CFV thickness was 0.71 (0.3-1.3) mm and left CFV thickness 0.72 (0.4-1.2) mm. Bilateral femoral vein thicknesses were similar in patients with and without an history of familial BD.

Conclusions: Diagnosing BD can be challenging in patients presenting with one major organ involvement such as oral ulcers and posterior uveitis, brain-stem disease or arterial aneurysms, especially in countries with a low prevalence. These patients are generally diagnosed as 'incomplete' BD by 'expert opinion'. Early diagnosis is of utmost importance in some of these cases, especially with venous thrombosis as their management differs from non-inflammatory venous thrombosis, necessitating immunosuppressive use rather than anticoagulant therapy. Our results show that CFV thickness measurement with Doppler US, a non-invasive, fast and cost-effective radiological modality, is a valuable diagnostic test in incomplete BD, especially with major organ involvement.

Disclosures: None

198. Lessons learned from a multidisciplinary approach to giant cell arteritis diagnosis

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Background: During the first year of offering TAUS, we advised clinicians not to change their usual practice with regard to requesting TAB. We set up a monthly multidisciplinary team

meeting (MDTM) with pathologists and sonographers to facilitate team learning. Here, we focus on lessons learnt from the results of patients who had both TAUS and TAB.

Methods: A positive ultrasound was defined as at least one non-compressible temporal artery halo and/or axillary artery intimal-medial thickening (>1.0mm) . A positive biopsy required the presence of inflammatory infiltrate in one or more arterial wall layers.

Results: 279 consecutive patients with suspected GCA had a first TAUS between 01/01/2019 and 30/08/2020. Mean age was 70 (range: 46-100); 74% female. 82/279 had TAB: results are compared with TAUS in Fig. 1. The sensitivity and specificity of TAUS compared to TAB was 17/23(74%) and 44/59(75%). 4 of the 5 TAB+/TAUS- cases were histologically mild: adventitial-invasive (n=2), focal inflammation (n=2). The fifth had clinically and histologically typical GCA but the TAB was performed before the ultrasound, suggesting that only one temporal artery branch was involved. In no case did the discrepancy seem likely to be explained by steroid therapy before TAUS (1 week or less for all 5). Of the 9 TAB-/TAUS+ cases, 2 TAUS showed focal halo (skip lesions) in cases with typical GCA clinically. 5 TAB had features of vascular ageing including intimal thickening, and had acute bacteraemia (n=2) or extensive prior history of atherosclerosis (n=3). The remaining 2 were genuinely uncertain cases and were both treated for GCA acknowledging diagnostic uncertainty.
Re-evaluating the equivocal ultrasound scans, six of the seven cases could be attributed to “bifurcation halo” ; in these cases, either the vessel was not fully compressible, or it had a halo appearance but was compressible. If the equivocal TAUS had been reclassified as negative, the specificity of TAUS compared to TAB would have improved to 50/59 (85%) without detriment to sensitivity.

Conclusions: In evaluation of suspected GCA, TAUS and TAB are usually but not always concordant. Using the MDTM and audit of discrepant results has enabled us as a team to learn lessons: The MDTM enables discrepant results to be discussed and this feedback allows clinical or imaging thresholds to be refined. TAB can detect cases that TAUS misses due to focal/adventitial inflammation. TAUS can detect cases that TAB misses due to skip lesions sparing sections of artery. False positive TAUS is usually explained by age-related intimal thickening. Isolated halo sign at a vascular bifurcation is not sufficient for a positive TAUS.
If MDTM reviews all cases, genuinely ambiguous cases are rare.

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Figure 1.

		TAB result		
		TAB positive	TAB Negative	TAB equivocal
USS result	USS positive	17	9	0
	USS negative	5	44	0
	USS equivocal	1	6	0

199. Comprehensive Assessment of Cranial and Orbital Vasculature on MRI in Patients with Giant Cell Arteritis

Rennie Rhee[1], Vatsal Bhatt[1], Shubhasrhee Banerjee[1], Madhura A. Tamhankar[1], Naomi Amudala[1], Sherry Chou[1], Morgan Burke[1], Peter A. Merkel[1], Jae W. Song[1]
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Background: Vessel wall MRI can depict changes consistent with arterial wall inflammation. Unlike temporal artery biopsy, MRI visualizes several full-length cranial arteries in a single scan mitigating the issue of sampling error. Furthermore, MRI evaluates orbital arteries posterior to the ocular globe, an area not visualized by ophthalmologic examination. While previous studies demonstrated good diagnostic performance of vessel wall MRI in evaluating temporal arteries in giant cell arteritis (GCA), little is known about changes to other cranial and orbital arteries. The goal of this study was to compare enhancement by MRI of multiple cranial and orbital arteries in patients with GCA versus controls.

Methods: Patients with suspected new or relapsing cranial GCA who underwent vessel wall brain and/or orbital MRI at presentation were included in the study. A clinical diagnosis of active ocular GCA or non-ocular GCA was determined by a rheumatologist and/or ophthalmologist and confirmed retrospectively. All MR images were scored by a single radiologist blinded to clinical data. Semi-quantitative integer scores of MRI enhancement were determined: scalp arteries were each scored 0, 1, 2, or 3 (score 2-3 defined as abnormal) and orbital structures were each scored 0, 1, or 2 (score 1-2 defined as abnormal). Differences in MRI findings between groups were determined using Fisher's exact test.
Results: 30 patients had scalp arteries visualized on vessel wall MRI (final clinical diagnosis: 11 with GCA; 19 non-GCA) and 35 patients had orbital structures visualized on MRI (final clinical diagnosis: 4 ocular GCA; 9 non-ocular GCA; 22 non-GCA). No patient in the non-GCA group had abnormal scalp artery enhancement. Among patients diagnosed with GCA, temporal

artery enhancement was the most common arterial abnormality (89%) followed by occipital artery enhancement (70%). One patient with GCA had isolated occipital artery enhancement without temporal artery involvement on MRI. Enhancement of the maxillary, facial, and external carotid arteries were seen in GCA but not in controls. In addition, MRI depicted multiple enhancing orbital structures which corresponded with vascular territories known to be affected by GCA; for example, optic nerve sheath and orbital intraconal fat enhancement were the most common findings on orbital MRI and corresponded to the anatomic location of the posterior ciliary arteries which are the main source of blood supply for the optic nerve (Figure 1C and 1D). No significant differences in orbital enhancement were observed between ocular and non-ocular GCA (all $P > 0.05$).

Conclusions : By comprehensively visualizing multiple cranial arterial territories, vessel wall MRI identified abnormal enhancement in arteries outside of the temporal arteries in patients with GCA vs controls. MRI enhancement was observed in orbital arteries known to be inflamed in ocular GCA. Interestingly, abnormal orbital enhancement was seen not only in clinically diagnosed ocular GCA patients (confirmed on fundoscopic exam) but also in a subset of patients without visual symptoms, suggesting that MRI may detect subclinical ocular disease in GCA. This study supports the possibility that vessel wall MRI may be a useful imaging tool that enhances current approaches to disease classification, risk stratification, and assessment of disease activity in GCA.

Disclosures: MAT – consultant for Horizon pharmaceuticals, UpToDate

200. PET/CT reveals high prevalence of extracranial vasculitis in giant cell arteritis

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Background: Giant cell arteritis (GCA) predominantly affects cranial arteries; however, vasculitis of the extracranial large blood vessels is also possible. The aim of this study was to analyze the prevalence of extracranial vasculitis in patients with GCA using PET/CT.

Methods: In this retrospective observational study we enrolled patients with GCA with or without polymyalgia rheumatica. All patients were older than 50 years of age, met the revised ACR criteria for GCA or had an evidence of large vessel vasculitis at FDG-PET/CT scan.

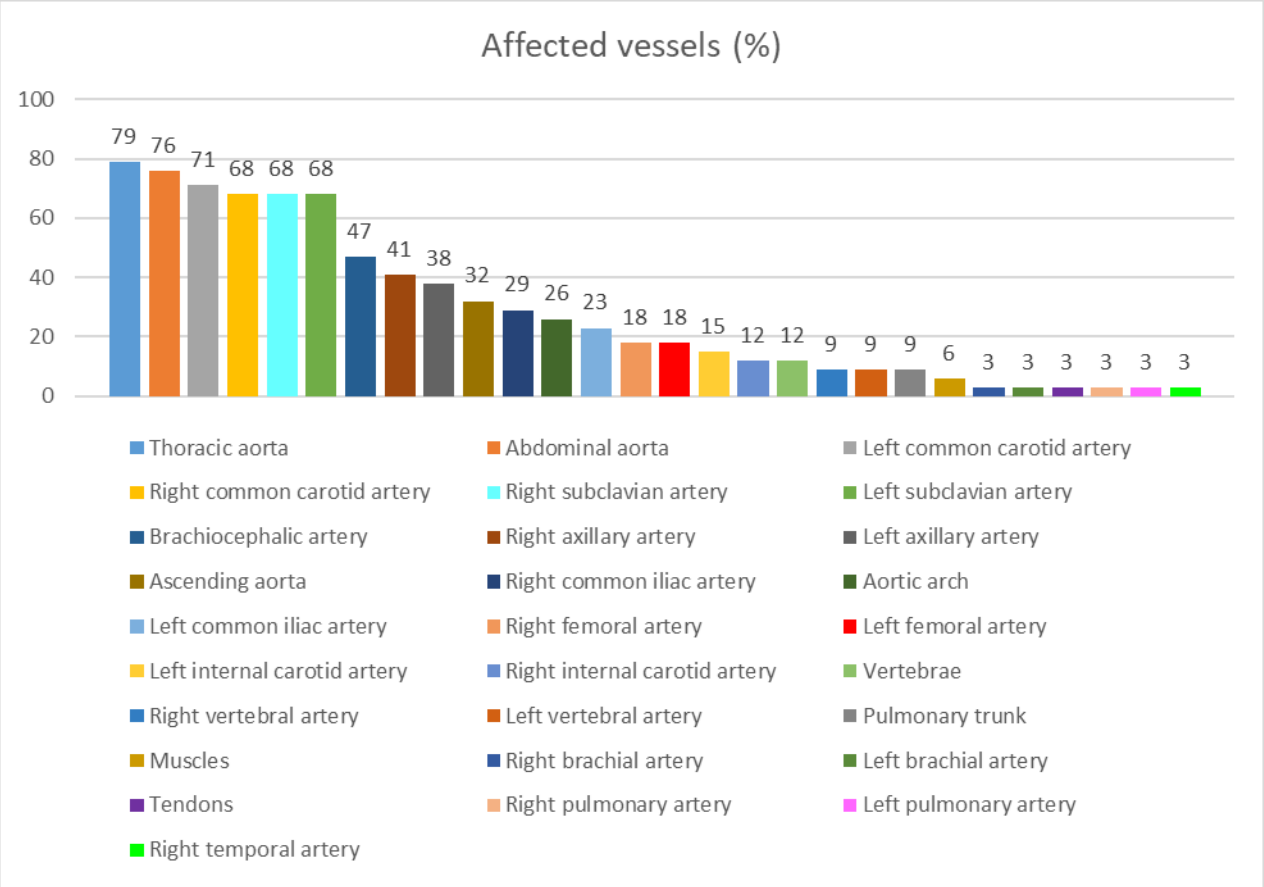
Results: Thirty-four patients (26 female, 8 male) with a median age of 63 (56.0, 67.0) years were included in the analysis. CRP levels and ESR were measured in 27 and 26 patients respectively. At the time of PET/CT median CRP level was 50.0 mg/L (16.3, 79.5), and median ESR was 65 mm/h (51.5, 92.0). Seven patients underwent PET/CT within 5-10 days after corticosteroid initiation, three received corticosteroid therapy for 8.5 months, and the other 24

had not received corticosteroids. The most common affected vessel was thoracic aorta (see Figure 1). Based on vascular involvement, patients were classified into 4 groups: in the vast majority of patients - 29 (85%) both cranial and large vessel involvement were observed, 2 (6%) of patients had only extracranial large vessel vasculitis, 2 (6%) of patients had only cranial arteritis and 1 (3%) patient had no signs of vascular inflammation. Vascular inflammation was visualized in the temporal arteries in 1 person (3 %) even though there were 17 patients who had a new temporal headache as one of their complaints. Among patients on corticosteroid therapy only one patient had no evidence of inflammation by FDG-PET/CT.

Conclusions: FDG-PET/CT imaging indicates a high prevalence of extra-cranial involvement in patients with GCA.

Disclosures: None

Figure 1.



201. Magnetic Resonance Imaging of Orbital and Scalp Arteries in Patients with Cranial Giant Cell Arteritis

Rennie Rhee[1], Vatsal Bhatt[1], Shubhasree Banerjee[1], Madhura A. Tamhankar[1], Naomi Amudala[1], Sherry Chou[1], Morgan Burke[1], Peter A. Merkel[1], Jae W. Song[1]
[1]University of Pennsylvania, United States

Background: In giant cell arteritis (GCA), there is a critical need to identify patients at risk for vision loss. MRI evaluates neurovascular anatomy posterior to the ocular globe, an area not visualized by ophthalmologic examination. Multiple case series and small cohort studies demonstrated that MRI can detect inflammation of orbital arteries in GCA-related ischemic optic neuropathy ("ocular GCA"). The aim of this study was to investigate MRI enhancement of orbital and scalp arteries in patients with suspected cranial GCA, including patients with or without visual symptoms.

Methods: Patients with suspected new or relapsing cranial GCA who underwent orbital and brain vessel wall MRI at presentation were included in the study. A clinical diagnosis of ocular or non-ocular GCA was determined by a rheumatologist and/or ophthalmologist and confirmed retrospectively. All MR images were scored by a single radiologist blinded to clinical data. Semi-quantitative integer scores of MRI enhancement were determined: 8 orbital structures were each scored 0, 1, or 2 (score 1-2 defined as abnormal) and included bilateral optic nerve sheath, optic nerve, intraconal orbital fat, and retrobulbar fat of posterior globe; 8 scalp arteries were each scored 0, 1, 2, or 3 (score 2-3 defined as abnormal) and included bilateral temporal arteries (stem, frontal, and parietal branches) and occipital arteries. MRI was considered diagnostic for GCA if at least 1 scalp and/or orbital artery had abnormal enhancement. A subgroup of patients with a clinical diagnosis of GCA underwent repeat MRI at month 1 to assess post-treatment changes in the composite orbital score (summation of scores for all bilateral orbital structures, possible range 0-16). Differences in MRI findings between groups were determined using Fisher's exact or Wilcoxon signed-rank test.

Results: The study included 30 patients with suspected cranial GCA: 25 new and 5 relapsing GCA. Of 30 patients, 11 had a clinical diagnosis of active GCA: 8 non-ocular and 3 ocular GCA. Of the 9 new diagnoses, 6 patients had a temporal artery biopsy consistent with GCA and 3 patients had negative biopsy. Compared to a clinical diagnosis of GCA, MRI had sensitivity of 83% (95% CI 52% to 98%), specificity of 94% (95% CI 73% to 99%), positive likelihood ratio of 15 (95% CI 2 to 102), and negative likelihood ratio of 0.18 (95% CI 0.05 to 0.63) for the diagnosis of GCA. Orbital enhancement on MRI was observed in 100% of patients with ocular GCA, 38% non-ocular GCA, and 11% without GCA ($P < 0.01$). Example MR images are shown in Figure 1B. Among 6 patients with an abnormal orbital MRI and a clinical diagnosis of GCA, all 6 patients had bilateral orbital enhancement including 3 patients without visual symptoms, 1 patient with unilateral visual symptoms, and 2 patients with bilateral visual symptoms. Follow-up MRIs were performed in 8 patients: all patients with orbital enhancement at baseline (n=4) had decreased composite orbital scores after 1-month treatment with

glucocorticoids (median composite orbital score: baseline = 6 [IQR 4.5-6] and 1-month = 3 [IQR 2-5]).

Conclusions: Vessel wall MRI of orbital and scalp arteries is a sensitive and specific diagnostic test for active cranial GCA. This study not only confirmed the presence of orbital MRI enhancement in patients with ocular GCA, similar to previous studies, but also is the first to demonstrate orbital MRI abnormalities in GCA patients without visual symptoms. These data validate the utility of cranial MRI for the diagnosis of GCA and generates a new hypothesis: orbital MRI detects “at-risk” subclinical ocular disease and may be a predictive biomarker of impending blindness due to GCA. Future studies may determine if cranial MRI can be used for risk stratification and treatment decision-making (e.g., high- vs low-dose glucocorticoids) as well as longitudinal disease surveillance in GCA.

Disclosures: MAT – consultant for Horizon pharmaceuticals, UpToDate

202. Comparison of abnormalities on thoracic CT-scans in subtypes of ANCA-associated vasculitis

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Background: Pulmonary manifestations are common in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Computed tomography of the chest is a sensitive method to detect pulmonary manifestations. Pulmonary abnormalities visible on CT scans in granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) have been described earlier, but studies comparing thoracic CT findings in GPA and MPA to EGPA are lacking. The aim of this study was to analyze chest CT scans from patients with GPA, MPA and EGPA using a standardized methodology.

Methods: Patients with GPA (N = 132), MPA (N = 54) and EGPA (N = 26) who were followed at a tertiary vasculitis referral center and had received at least one chest CT scan between 2005 and 2021 were included. All CT scans were retrospectively re-analyzed by an independent radiologist using a predefined protocol using a predefined protocol based on the Guidelines of the Fleischner Society.

Results: The most common pulmonary changes in GPA detected by CT were pulmonary nodules, ground glass opacities, and pulmonary emphysema (table). With the exception of one patient with EGPA, nodules with cavitation were found only in patients with GPA. Reticulation, bronchial wall thickening, and lymphadenopathy were slightly less common. Honeycombing was not observed in GPA, but was seen in a subset of patients MPA who displayed also other signs of interstitial lung disease. Consolidations and reticulations were primarily found in GPA and EGPA. The tree in bud-sign was found in similar frequencies between GPA, MPA and EGPA. Both NSIP and UIP Pattern are almost specific for MPA. Also a noticeable frequent association emerges between pulmonary venous congestion and MPA, while pericardial effusion is more common in MPA and EGPA.

Conclusions: Pulmonary manifestations in AAV are frequently detected on chest CT. Analysis of this large cohort shows that subtypes of AAV are characterized by individual patterns of pulmonary findings on CT.

Disclosures: none

Table. Thoracic CT findings in patients with AAV according to type of diagnosis. Values are N (%).

CT findings	GPA n= 132	MPA n= 54	EGPA n= 26	*P* GPA vs. MPA	*P* GPA vs. EGPA	*P* MPA vs. EGPA

Parenchymal involvement						
Nodules	73 (0,55)	13 (0,24)	11 (0,42)	5,0E-05 *	1,3E-01	3,8E-02
Nodules with cavitation	26 (0,20)	0 (0,00)	1 (0,04)	8,7E-13	5,2E-02	!
Consolidation	15 (0,11)	1 (0,02)	3 (0,12)	4,3E-02	7,3E-01	1,4E-02
Ground glass opacities	60 (0,45)	26 (0,48)	15 (0,58)	8,2E-01	2,7E-01	1,6E-01
Reticulation, peripheral	43 (0,33)	18 (0,33)	4 (0,15)	8,4E-01	1,0E-01	9,2E-02
Honeycombing	0 (0,00)	8 (0,15)	0 (0,00)	1,1E-06	!	4,9E-03
Bronchiectasis	11 (0,08)	8 (0,15)	2 (0,08)	1,3E-01	7,1E-01	8,7E-02
Peribronchovascular thickening	39 (0,30)	13 (0,24)	14 (0,54)	3,7E-01	3,1E-02	8,0E-04
Bronchial stenosis	8 (0,06)	5 (0,09)	11 (0,42)	4,4E-01	2,1E-07	5,4E-04
Emphysema	60 (0,45)	16 (0,30)	7 (0,27)	4,6E-02	8,0E-02	1,7E-01
Other abnormalities						
Lymph node enlargement	37 (0,28)	13 (0,24)	9 (0,35)	5,9E-01	3,0E-02	1,5E-01
Pleural effusion	11 (0,08)	6 (0,11)	2 (0,08)	5,5E-01	2,0E-01	6,3E-01
Pericardial effusion	3 (0,02)	6 (0,11)	7 (0,27)	3,4E-03	3,2E-07	7,3E-02
Disease Patterns						
Alveolar haemorrhage	4 (0,03)	5 (0,09)	3 (0,12)	7,2E-01	5,4E-02	7,5E-01
UIP**	1 (0,01)	7 (0,13)	0 (0,00)	2,0E-04	6,6E-01	5,5E-03
NSIP***	0 (0,00)	9 (0,17)	0 (0,00)	1,5E-06	!	2,7E-02
Other interstitial lung disease	7 (0,05)	1 (0,02)	3 (0,12)	2,9E-01	2,3E-01	6,3E-02
Scarring/ Reticulation	43 (0,33)	18 (0,33)	4 (0,15)	9,2E-01	8,0E-02	9,2E-02
Pulmonary venous congestion	2 (0,02)	6 (0,11)	0 (0,00)	3,4E-03	5,3E-01	7,7E-02

Normal CT	15 (0,11)	7 (0,13)	5 (0,19)	7,6E-01	5,6E-01	4,6E-01

* in Bold: p-value < 0,05 **Usual interstitial pneumonia, *** nonspecific interstitial pneumonia

Disclosures: None

203. Evaluation of CNN methods for computer-assisted morphometry in kidney biopsies from AAV patients

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Background: Although machine learning methods have just come out of their infancy, with the first AI-based decision support system for clinical diagnostics of prostate cancer having been approved by US FDA in September 2021, and the focus is on the field of oncopathology, AI techniques have also shown promising results in nephropathology, where AI based methods can exploit the large amount of information given by WSIs (Whole Slide Images). Visual assessments by pathologists don't make use of all the information due to the huge dimensions of images and consequent time constraints and human perception of complexity is limited, whereas machine learning techniques thrive with large amount of data and are able to find interdependencies that remain unrecognized in visual observation. Moreover, machine learning techniques already achieved performance levels comparable to human capabilities in several visual tasks. Glomerulosclerosis constitutes a critical prognostic marker for CKD progression as is IFTA, but its identification is based on the count of individual discrete structures, glomeruli, rather than an overall visual assessment. As a consequence, it suffers less variability in visual assessment, although still representing a tedious and time-consuming task for pathologists, which could be successfully automated via computer assisted techniques.

Methods: CNN (Convolutional Neural Network) architectures have been implemented and trained on a total of 3120 tiles (512x512 pixels) and finally evaluated on 878 tiles. U-Net architecture has been elected as being successful in several segmentation tasks within the biomedical field due to its remarkable capability to capture features at different resolutions via its contracting and expanding architecture. Consequently, several U-Net derived methods have been implemented and evaluated to assess whether alternative configurations could further improve diagnostic and prognostic fidelity in glomeruli segmentation. Data augmentation techniques have been applied to enhance variability within the training set and models have been evaluated with and without data augmentation.

Results: U-Net based methods show high stability in training as compared to other CNN techniques (e.g. Deep Convolutional Generative Adversarial Networks). Although yielding

promising results in terms of performance, metrics results are highly variable across the models due to the large number of possible parameters and configurations, and models often suffer from artifacts within the image prediction. Also, staining techniques seem to affect model performance, thus suggesting that specific stains are to be matched to specific segmentation tasks, which is also reflected by the use of different stains during pathologists' visual assessment of biopsy specimens.
Similarly, color normalization also needs to be taken into account in order to reduce colors variability across images in the training set, which could be a confounding factor.

Conclusions: Deep learning techniques can be applied for glomeruli segmentation reliably and prove to be able to capture informative features across the image at different resolution levels due to the several layers used in the contracting and expanding path. U-Net derived methods also show promise in terms of tailoring the use of conventional CNN networks towards specific needs, although suffering from the lack of optimization, which well-established methods enjoy. Further research is required to both optimize these methods and assess whether and under what terms medicine could benefit more from them, and to evaluate their use on a larger cohort and on a different training set, to evaluate the potential impact of variability across datasets on performance.

Disclosures: none

204. Pulmonary Artery Wall Thickness is Increased in Behcet's Disease

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Background: Behcet's Disease (BD) is a unique systemic vasculitis that mainly involves veins, in contrast to other vasculitides (1,2). Prior studies showed that pulmonary arteries have similar structure with systemic veins in terms of wideness, thin-walled, increased compliance and low resistance (3). We have recently showed increased venous wall thickness in lower extremity veins of BD patients. In this study, we aimed to assess pulmonary artery wall thickness by transthoracic echocardiography (TTE) in BD compared to healthy controls and patients with non-inflammatory pulmonary embolism (NIPE).

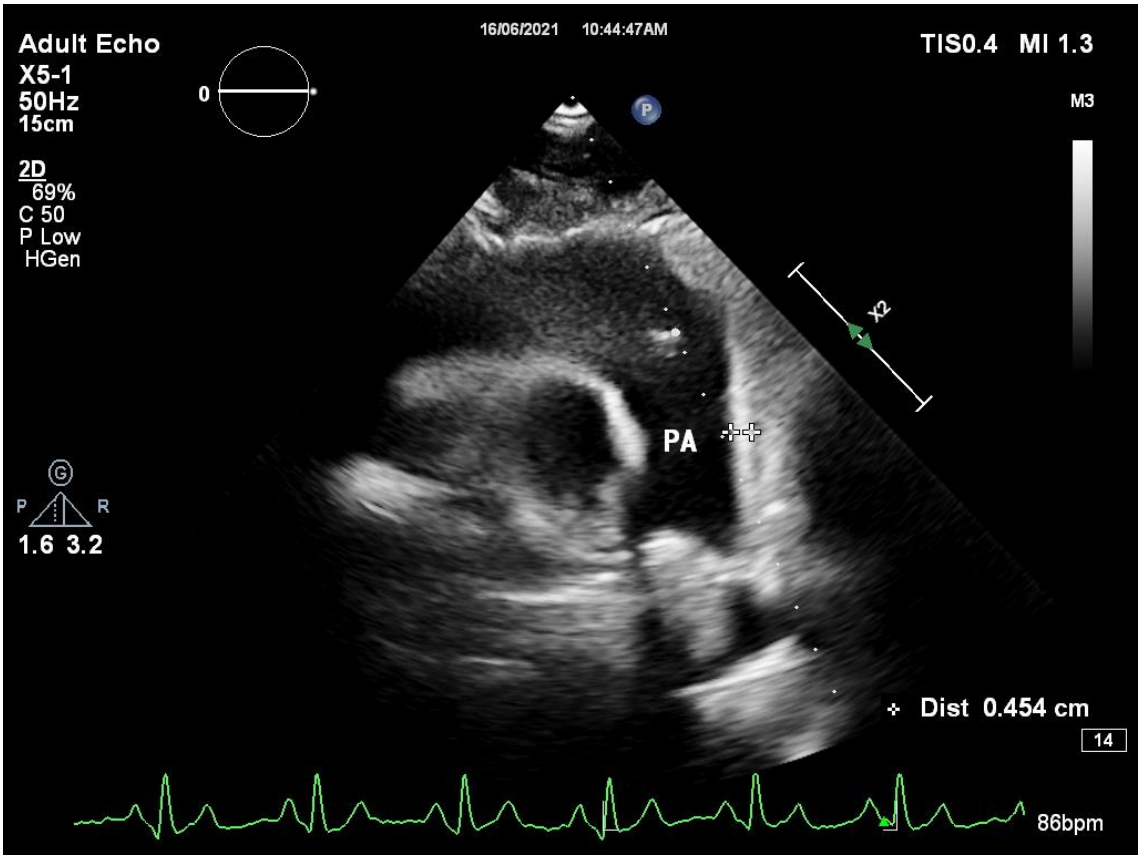
Methods: Patients with BD (n=77), NIPE (n=33) and healthy controls (n=57) were included in the study. Pulmonary artery wall thickness was measured with transthoracic echocardiography by a cardiologist blinded to cases. Pulmonary artery wall thickness was measured from the mid-portion of the main pulmonary artery (approximately 1 to 2 cm distal to the pulmonary valve) as demonstrated in Figure 1.

Results: Pulmonary artery wall thickness was significantly lower in controls (0.36 mm (SD:0.03) compared to NIPE (0.44 mm (SD:0.05) and BD (0.44 mm (SD:0.06) ($p<0.001$ for both). Pulmonary artery wall thickness was also found to be significantly higher in BD patients with major organ involvement (0.46 mm (SD:0.04) compared to healthy controls and NIPE ($p<0.001$ and $p=0.027$, respectively). In the subgroup analyses of patients with major organ involvement, pulmonary artery wall thickness was observed to be higher in patients with vascular (0.46 mm (SD:0.05), ocular (0.47 mm (SD:0.05) and neurologic (0.49 mm (SD:0.02) involvement ($p<001$ for all) and also in patients with a history of deep venous thrombosis (0.46 mm (SD:0.05) and pulmonary embolism (0.46 mm (SD:0.04) ($p=0.012$ and $p=0.039$, respectively) compared to BD patients with mainly mucocutaneous disease.

Conclusions: Increased pulmonary artery wall thickness suggest extensive vascular inflammation in patients with BD, not limited to venous vessels as previously shown. Assessment of pulmonary arteries by TTE, a feasible, commonly used modality, may be used for vascular wall research and routine practice in BD.

Disclosures: None

Figure 1



205. Does Vein Wall Thickness have prognostic value in Behçet's Disease? A prospective follow-up study

Kerem Abacar[1], Rabia Ergelen[2], Fatma Temiz[3], Yasin Yıldız[3], Tülin Ergun[4], Haner Direskeneli[1], Fatma Alibaz-Oner[1]
[1]Department of Internal Medicine, Division of Rheumatology, Marmara University School of Medicine, Istanbul, Turkey, [2]Marmara University, School of Medicine, Department of Radiology, [3]Marmara University, School of Medicine, Department of Internal Medicine, [4]Marmara University, School of Medicine, Department of Dermatology.

Background: We reported the first controlled doppler ultrasound study showing increased common femoral vein (CFV) thickness in Behçet's Disease (BD).[1] We also recently showed that increased CFV thickness is a distinctive feature of BD, rarely present in other inflammatory or vascular diseases with a specificity higher than 80% for the cut-off value of ≥ 0.5 mm.[2] However, the association between CFV thickness and any organ involvement, disease course or treatment during disease course has not been demonstrated so far. This study aimed to assess the longitudinal course and prognostic value of CFV thickness measurement during a prospective follow-up BD patients.

Methods: In this study, we included 195 patients with a diagnosis of BD. The clinical, demographic, treatment data and biomarkers were recorded during routine visits. Bilateral CFV thickness was measured with ultrasonography by an experienced radiologist at the same day. Patients were started to follow up prospectively with 3-6 months intervals and in any urgent visit.

Results: At baseline, 98.6% of patients had increased CFV wall thickness above the cut-off value of ≥0.5 mm. The baseline and last follow-up clinical characteristics were shown in Table 1. 139 of 195 patients had prospective clinical follow-up data with a mean of 26.5 (16.9) months. New major organ involvement or relapse leading to treatment change was seen in 39 (28%) patients. Among 22 (15.8%) patients with new major organ involvement, 12 had vascular , seven had ocular, two had neurologic and one had gastrointestinal involvement. Among 36 patients with only mucocutaneous disease at baseline, new major organ involvement developed in 9 patients during follow-up. These nine patients had higher baseline CFV thicknesses compared to patients without major organ involvement, however without reaching clinical significance (0.83 mm vs 0.73 mm for right CFV, 0.80 mm vs 0.73 mm for left CFV: p >0.05 for both). In 47 patients, the second CFV thickness measurement was done with a mean 19.8 months after the first visit. There was no statistically significant difference between the first and second CFV wall thickness measurements for both right and left CFVs (First vs. second for right CFV: 0.79 vs. 0.76 mm, p=0.26; for left CFV: 0.79 vs. 0.75 mm, p=0.26). We did not find any change in CFV wall thickness with the treatment modality, new organ involvement and relapses.

Conclusions: CFV wall thickness measurement with ultrasonography which is a new non-invasive diagnostic tool for BD, does not show a major change over time with treatment

modality, new organ involvement or disease relapses. However, our preliminary results suggest that mucocutaneous BD patients with higher CFV thickness may have a higher risk for the development of major organ involvement during follow-up. The long term results of our prospective cohort with increased patient numbers would clarify the prognostic value of CFV thickness in BD.

Disclosures: None

Table 1: The baseline and follow-up clinical characteristics of patients with Behçet's Disease.

	Baseline (n=139)	Last Follow-up (n=139)	Relapses or New Involvement during follow-up
Age mean (SD)	34.85 (8.27)		
Gender F/M ratio	43/96		
Pathergy (positive/negative)	59/44		
Right CFV Wall Thickness mean (SD) mm	0.791 (0.253)		
Left CFV Wall Thickness mean (SD) mm	0.797 (0.207)		
Oral Aphthous Ulcers n (%)	134 (95)	134 (95)	13 (9.4)
Genital Ulcers n (%)	84 (60.4)	89 (64.5)	6 (4.3)
Folliculitis n (%)	77 (55.4)	77 (55.4)	2 (1.4)
Erythema Nodosum n (%)	62 (44.6)	69 (49.6)	9 (6.5)
Arthritis (%)	48 (34.5)	48 (34.5)	10 (7.2)
Major Organ Involvement n (%)			
Vascular Involvement n (%)	84 (60.4)	96 (69.1)	35 (25.2)
Deep Venous Thrombosis (%)	61 (43.9)	65 (46.8)	6 (4.3)
Pulmonary Thrombosis n (%)	35 (25.2)	52 (37.4)	23 (16.5)
Sinus Venous Thrombosis n (%)	12 (8.6)	14 (9.9)	2 (1.4)
Thrombophlebitis n (%)	4 (2.9)	6 (4.3)	5 (3.6)
Vena Cava Thrombosis (%)	3 (2.2)	3 (2.2)	0

Pulmonary Aneurysm n (%)	1 (0.7)	2 (1.4)	2 (1.4)
Other Vascular Involvement n (%)	4 (2.9)	5 (3.6)	2 (1.4)
Neuro-Behcet n (%)	14 (9.9)	16 (11.5)	2 (1.4)
Uveitis n (%)	33 (23.7)	40 (28.8)	7 (5)
Entero-Behcet n (%)	8 (5.8)	9 (6.5)	1 (0.7)

206. Coronary arterial involvement can be observed in Takayasu's arteritis patients by coronary CT-angiography

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Background: Besides aorta and its main branches, coronary arterial involvement is also seen at a substantial rate in patients with Takayasu's arteritis (TAK). Computerized tomography (CT)-angiography, as a non-invasive assessment tool, has started to be used instead of conventional angiography in the evaluation of coronary arteries. However limited data is available for its role in TAK patients. In this study, we aimed to assess the coronary arterial involvement by coronary CT-angiography in TAK patients with or without symptoms and to compare clinical characteristics of patients with or without coronary arterial involvement.

Methods: Patients with TAK (n=49, F/M: 40/9, mean age: 42.61±9.95 years) followed in Marmara University Vasculitis Clinic and underwent coronary CT-angiography with or without cardiac symptoms were evaluated retrospectively. Data of four patients who were not suitable for coronary CT-angiography but underwent conventional angiography were also included. CT angiography findings in the coronary arteries were defined as osteal stenosis, stenosis, calcific plaque and aneurysm and patients were categorized into two groups as those with or without coronary artery pathology. Demographic data, cardiac symptoms, clinical findings, BMIs, angiographic Hata and Goel classifications, treatments received for TAK, acute phase reactants and lipid levels were compared.

Results: Coronary artery pathology was detected in 14 patients (28.7%). Only 9 patients had a history of angina and 6 had cardiac symptoms in this group. Calcific plaque was present in 11 (22.5%), coronary artery stenosis in eight (16.3%) and aneurysm, osteal stenosis and occlusion in one patient each (2.0%). RCA was involved in 20.4%, LAD in 28.6%, LMCA in 22.4%, Cx in 26.6% and more than one coronary arterial involvement in 26.5% of patients. In patients with coronary artery involvement, age (p=0.02), age at TAK diagnosis (p=0.004) and number of anti-hypertensive drugs (p=0.011) were significantly higher than those without

coronary artery involvement. History of angina (p=0.004) and statin use (p=0.001) were also significantly higher in patients with coronary artery abnormalities, whereas HDL levels were significantly lower (p=0.037). No significant differences were observed between the groups when gender, smoking history, diabetes, BMI, ITAS2010 scores, biological therapy use, angiographic classifications, aortic involvement, presence of cardiac symptoms, CRP, ESR, total cholesterol and LDL levels were compared (Table 1).

Conclusions: Coronary artery involvement which is an important cause of morbidity and mortality can be detected non-invasively by coronary CT-angiography in up to 1/3 of patients with Takayasu's arteritis, also in patients without angina and cardiac symptoms. Traditional cardiac risk factors are present more commonly in this group.

Disclosures: None

Table 1. Comparison of patient groups with and without coronary artery involvement

	Presence of Coronary Arterial Involvement (n=14)	Absence of Coronary Arterial Involvement (n=35)	
Age	49.29 (8.23)	39.94 (9.39)	*p=0.02*
Gender (F/M)	10/4	30/5	p=0.254
Disease duration	7.43 (6.42)	8.46 (6.25)	p=0.608
Age at TAK Diagnosis	41.21 (12.58)	31.37 (9.18)	*p=0.004*
Diabetes	3/14	1/35	p=0.065
Family History	4/14	7/35	p=0.706
Smoking History	8/14	25/35	p=0.122
BMI	25.08 (2.53)	25.17 (4.68)	p=0.930
Biological Therapy	4/14	15/34	p=0.317
CRP mean (SD)	4.45 (3.4)	8.68 (24.08)	p=0.642
ESR mean (SD)	22.5 (20.72)	25.06 (24.9)	p=0.991
ITAS2010 mean (SD)	0.57 (0.94)	0.51 (1.15)	p=0.869
LDL mean (SD)	102 (41.96)	112.44 (35.79)	p=0.398
HDL mean (SD)	46.23 (12.78)	55.12 (12.62)	*p=0.037*
Total Cholesterol mean (SD)	177.77 (44.09)	194.15 (48.98)	p=0.157

Cardiac Symptoms	6/14	2/35	p=0.159
Aorta Involvement	8/14	18/35	p=0.717
Statin Use	10/14	6/34	*p=0.001*
Number of Antihypertensives	1.79 (0.89)	0.85 (1.18)	*p=0.011*
Acetylsalicylic Acid	10/14	24/34	p=1
Angina History	9/14	6/35	*p=0.004*

(BMI: Body Mass Index, SD: Standard Deviation, ESR: erythrocyte sedimentation rate, ITAS: Indian Takayasu Activity Score, LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein)

207. **Involvement of Iliofemoral Arteries in PET/CT are associated with Atherosclerotic Risk Factors in Takayasu's Arteritis**

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Background: Iliofemoral artery disease, which is commonly observed in severe atherosclerosis, may also be present in Takayasu's arteritis (TAK). In this study we aimed to evaluate the characteristics of TAK patients with or without iliofemoral artery involvement in PET/CT.

Methods: Patients fulfilling ACR 1990 classification criteria for TAK and underwent PET-CT imaging were evaluated retrospectively. Demographic and clinical data were collected from patients' charts. Traditional cardiovascular risk factors: diabetes, hypertension, hyperlipidaemia, smoking history and body mass index (BMI) were recorded. PET Vascular Activity Score (PETVAS) was used to assess the quantitative PET activity.

Results: Seventy-one PET/CT scans of 52 (F/M: 42/10) patients with TAK were investigated. Mean age was 42.8±14.2 years and mean disease duration 5.6 ±5.3 years. The aortic arch (75%) was the most commonly involved artery. Iliofemoral arteries were involved in 9 (13%) patients. Patients with iliofemoral involvement were older (52.5±17.4 vs 39.9±12.4 years, p=0.036), had lower glucocorticoid (GC) dose (0 (0-7.5) vs 2.5 mg/day (0-80), p=0.049), higher CRP (36.1±28.1 vs 19.7±25.0 mg/L, p=0.041) and higher PETVAS (11.4±9.7 vs 4.2±3.9, p=0.018). Male gender (50% vs 14%, p=0.016) and current smokers (78% vs 35%, p=0.016) were also more present in the iliofemoral involvement group.

Conclusions: Involvement of iliofemoral arteries in PET/CT in TAK patients are associated with atherosclerotic risk factors more frequently. Therefore, anti-atherosclerotic approaches should be implemented more vigorously during the follow-up of TAK patients with lower extremity involvement.

Disclosures: None

Table 1. Characteristics of TAK patients with and without iliofemoral involvement in PET/CT.

	Patients with iliofemoral involvement (n=9)	Patients without iliofemoral involvement (n=62)	p
Age, years, mean±SD	52.5±17.4	39.9±12.4	0.036
Gender, male, n(%)	4 (50)	6 (14)	0.016
Disease duration, years, mean±SD	4.0 ± 5.6	5.7 ± 5.4	0.65
GC dose*, mg/d	0 (0-7.5)	2.5 (0-80)	0.049
Active disease**, n (%)	6 (67)	30 (48)	0.30
CRP, mg/l, mean±SD	36.1±28.1	19.7 ± 25.0	0.041
PETVAS, mean±SD	11.4±9.7	4.2 ± 3.9	0.018
Diabetes, n(%)	0 (0)	6 (11)	0.29
Hypertension, n(%)	4 (45)	29 (53)	0.64
Hyperlipidemia, n(%)	4 (45)	17 (31)	0.42
Smoking, n(%)	7 (78)	19 (35)	0.016
BMI, kg/m², mean±SD	21.9±3.5	24.3±4.1	0.105

* *methylprednisolone equivalent dose **According to Kerr criteria*

208. Incidental findings on PET/CT in patients with large vessel vasculitis

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Background: This study aims to shed light on the number and type of incidental findings detected on positron emission tomography (PET)/CT in a cohort of patients with large vessel vasculitis (LVV).

Methods: The scan reports from PET/CT studies along with the medical charts of a cohort of patients with LVV from a clinic in Edmonton, Alberta, Canada were retrospectively reviewed on Connect Care and Netcare. Incidental findings from PET/CT, along with follow up studies and their diagnosis were documented and analysed.

Results: The disease activity of 40 patients, with an average age of 65.8 years, was investigated using PET/CT. A total of 59 incidental findings were found in 28 (70%) patients. Of these findings, 45.8% were in the abdomen and pelvis. The most common incidental finding was lymphadenopathy (11.9%). Subsequent investigations of 7 patients confirmed pathological aetiology in 3 patients and benign findings in 4 patients.

Conclusions: Overall, out of the 40 patients studied with PET/CT, 7 (17.5%) had follow up investigations. Most of the incidental findings were insignificant, but a total of 3 (7.5%) patients needed further management for their incidental findings, this included metastatic adenocarcinoma, pheochromocytoma, and cerebral infarct. With the increased usage of PET/CT in the assessment of patients with LVV and older age, incidental findings may become a significant result. Further studies are needed to determine the significance of the relationship between these incidental findings and LVV.

Disclosures: None

Table 1. Summary of incidental findings by site

Site of incidental findings	Total findings	Incidental findings
Vascular, bursae and joints	8	Atherosclerosis (5) Bursitis (1) Joint arthropathy (1) Vertebral artery dissection (1)
Musculoskeletal	2	Congenital vertebral fusion (1) Spinal canal stenosis (1)
Head and neck	11	Meningioma (2) Thyroid nodule (2) Brain lesion (1) Enlarged palatine tonsil (1) Increased palatine tonsil uptake (1) Lymphadenopathy (1) Parotid gland lesion (1) Posterior tongue mass (1) Sinus cyst/polyp (1)
Chest	11	Lymphadenopathy (4) Lung nodule (3) Atelectasis (1) Bronchiectasis (1) Esophageal diverticulum (1) Pulmonary opacities (1)
Abdomen and pelvis	27	Diverticulosis (5) Cholelithiasis (4) Hepatic cyst (4) Lymphadenopathy (2) Renal cyst (2) Adnexal cyst (1) Atrophic kidneys (1) Colonic nodule (1) Decreased liver activity (1) Enlarged prostate (1) Increased cecal uptake (1) Pancreatic cyst (1) Portacaval mass (1) Stomach nodule (1) Suprarenal mass (1)

209. Increased Inferior Vena Cava Wall Thickness as a Sign of Venous Inflammation In Behcet's Disease

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Background: Vascular involvement of Behcet's disease (BD) involves both arterial and venous vessels of all sizes [1]. Femoral (superficial, deep, and common) and popliteal veins are the most frequently affected veins. We have previously shown that femoral wall thickness is increased in BD patients and can be used as a diagnostic test [2]. However, many other sites including vena cava inferior/superior and pulmonary arteries may also be involved [3]. Despite the dominance of venous vessel involvement, there is limited data assessing the large veins in BD. In this study, we aimed to assess inferior vena cava wall thickness (IVC) by transthoracic echocardiography (TTE) in BD compared with healthy controls.

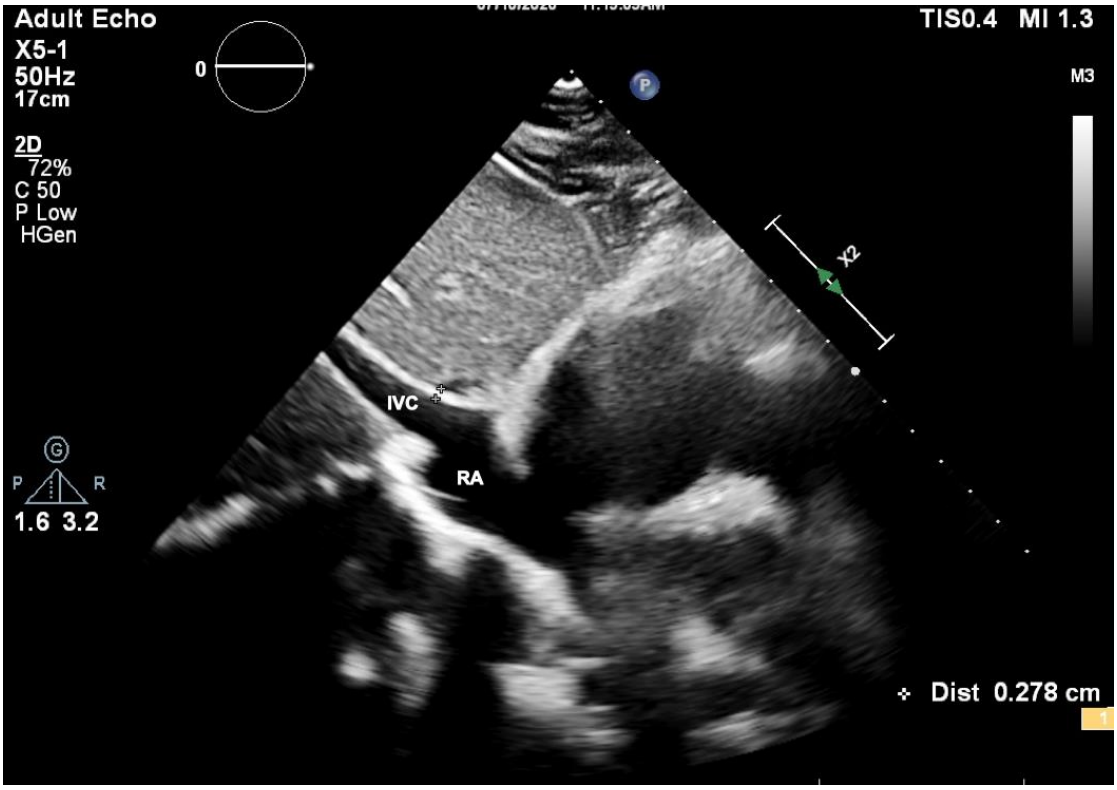
Methods: Patients with BD (n=70) and age and sex-matched healthy controls (n=51) were included in this study. Assessment of inferior vena cava (IVC) wall thickness was performed by an experienced cardiologist blinded to cases. Measurement of IVC wall thickness was made at end-expiration and approximately 0.5 to 2.0 cm proximal to the ostium of the right atrium as demonstrated in Figure 1.

Results: IVC wall thickness of patients with BD (0.29 mm (SD: 0.03) was significantly higher than healthy controls (0.26 mm (SD: 0.03) ($p<001$). Although IVC wall thickness was higher in patients with BD with vascular involvement (0.30 mm (SD:0.04) and history of pulmonary embolism (0.30 mm (SD:0.04)), the difference did not reach statistical significance. There was no difference between IVC wall thicknesses in patients who used immunosuppressive and anti-TNF treatments due to major organ involvement, compared to those who did not. Similarly, no difference is observed between IVC thicknesses among Behcet's patients according to age, gender and activity status at the last visit. Although no correlation was found between IVC wall thicknesses, disease duration, and BDCAF scores at the last visit in BD group, there was a low-grade correlation between age and VCI wall thickness ($r=0.31$, $p=0.09$).

Conclusions: Increased IVC wall thickness shows vasculitic involvement of large venous structures in BD and can be easily measured by TTE which is an easily accessible, noninvasive modality without radiation. The role of IVC wall thickness assessment for the diagnosis or management of BD requires further studies.

Disclosures: None

Figure 1.



210. A Case Presentation of Tuberculous Aortitis and Vasculitis

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Introduction: Tuberculosis (TB) aortitis is a rare manifestation of TB. The presentation of TB aortitis is usually associated with disseminated disease and can lead to a multitude of complications including aneurysmal dilatation of the aorta, perforation and even death. There is often a delay in diagnosing TA, due to a lack of awareness regarding this rare presentation of extrapulmonary TB.
Case Presentation: A 55-year-old Dentist of Irish descent, presented to his General Practitioner with a 2-month history of indigestion and retrosternal discomfort that failed to respond to oral Proton Pump Inhibitors. He was a fit 55-year-old gentleman who exercised avidly and was a non-smoker. His past medical history included a sigmoid colectomy in 2019 for diverticulitis, and a history of bowel obstruction in 2020 secondary to adhesions. He had no significant family history of note. He also has no known previous history of exposure to Tuberculosis. In the ensuing weeks, he developed additional symptoms of fatigue, malaise and occasional night sweats. He had no other relevant symptoms of note such as pyrexia, weight loss, cough, early morning stiffness, arthralgia or hemoptysis. His initial physical exam revealed no abnormalities. However, his laboratory investigations revealed a persistently

elevated C-Reactive Protein and Erythrocyte Sedimentation Rate (above 60mg/dl and 50mm/hr respectively).

Investigations: Due to his predominant upper GI symptoms he was initially investigated by surgical services. An Oesophago-Gastro-Duodenoscopy was normal, prompting a CT of thorax, abdomen and pelvis due to systemic symptoms. This revealed a 3-4mm right lower mild calcification of his abdominal aorta and common iliac vessels which were ectatic particularly on the left with stranding suggestive of vasculitis surrounding his distal aorta and proximal iliac vessels. He was thereafter referred to Rheumatology. He had ongoing systemic symptoms, intermittent epigastric pain and denied claudicating symptoms. He had no history of COViD 19 infection and was vaccinated in the weeks prior to symptom onset. A standard autoimmune screen, IgG 4 levels and Angiotensin Converting Enzyme levels were normal. HIV and syphilis testing were negative. A Positron Emission Tomography scan demonstrated significant fluoro-deoxy glucose -uptake within the right mediastinal node and a single pre-tracheal node. An endobronchial ultrasound with real- time guided transbronchial needle aspiration was then arranged. This demonstrated caseating granulomas and AFB (acid- fast bacilli) smear and cultures were positive and consistent with mycobacterium tuberculosis infection. A QuantiFERON test was positive.

Differential Diagnoses and Management: The differential diagnosis for this case was wide and varied. This patient was initially investigated for upper GI pathology including possible neoplasm which could have explained his constitutional symptoms. The findings of the CT TAP were suggestive of IgG4 disease and retroperitoneal fibrosis. Normal IgG4 levels and the avidity of nodal uptake led to biopsy which confirmed the diagnosis. He was treated with 2 months of quadruple therapy isoniazid, rifampicin , ethambutol, pyrazinamide and pyridoxine. His TB cultures grew a fully sensitive organism. A repeat CT TAP after 2 months of Quadruple Therapy showed interval reduction in the size of the right hilar lymph node and significant amelioration of the vascular inflammatory changes indicative of treatment response.

Conclusions: Tuberculous aortitis is an uncommon cause of large vessel vasculitis. Imaging and biopsy was critical in establishing definitive diagnosis in this case. There is some suggestion that dentists have an increased risk of tuberculosis due to working in close proximity to oral secretions. Risk factors for latent TB reactivation include immunosuppression and of relevance to the current era, there have been reports of reactivation following COViD19 infection.

Disclosures: None.

211. Differences in giant cell arteritis manifestations according to the ultrasound pattern of disease involvement

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Background: Giant cell arteritis (GCA) is the most common form of primary systemic vasculitis in patients aged >50 years. It predominantly affects the cranial arteries; however, extra-cranial disease involving the aorta and its major branches, known as large-vessel GCA (LV-GCA), can be present in 20-80% of cases, depending upon the imaging modality used for screening the disease. We aim to compare the clinical features and outcomes of GCA patients with exclusive cranial, exclusive LV and combined cranial and LV involvement.

Methods: Single centre observational retrospective study, using data from patients diagnosed with GCA registered at the Rheumatic Diseases Portuguese Registry (Reuma.pt). All patients underwent ultrasound of both temporal (TA) and axillary (AX) arteries ± facial (FA), occipital (OC), subclavian (SC) or common carotid (CC) arteries at the time of diagnosis. Only patients with the presence of “halo sign” in at least one of these arterial segments were included. Three groups of patients were established according to their ultrasound results: i) exclusive cranial-GCA in cases of TA, FA, or OC involvement; ii) exclusive LV-GCA in cases of AX, SC, or CC involvement; and iii) cranial- and LV-GCA in cases of both cranial and LV involvement. Univariate analysis was performed using T-test, Chi-square and ANOVA, as appropriate. Multivariate analysis was performed using logistic regression modelling.

Results: We included 81 patients with GCA, 55 (67.9%) females, with a mean ± SD age of 75.8 ± 8.6 years. Halo sign was found on the TAs of 66/81 (81.5%) patients, AXs of 38/81 (46.9%) patients, FAs of 37/71 (52.1%) patients, OCs of 15/58 (25.9%) patients, SCs of 27/46 (58.7%) patients and CCs of 12/57 (21.1%) patients. A total of 37 (45.7%) cases had exclusive cranial-GCA, 44 (54.3%) had cranial- and LV-GCA and 14 (17.3%) had exclusive LV-GCA. Table 1 summarises the differences between the three groups. Regarding clinical manifestations, exclusive cranial-GCA was more commonly associated with temporal headache, as opposed to exclusive LV-GCA, in which patients were less likely to experience temporal or frontal headache, as well as jaw claudication, scalp tenderness or a cranial ischemic event. Concerning physical examination, exclusive LV-GCA was associated with abnormalities of the upper limb arteries and lack of TA changes. No significant differences were found between groups regarding demographics, comorbidities, relapses or mortality. Multivariate analysis, adjusted for jaw claudication, scalp tenderness, frontal and temporal headache, cranial ischemic events, abnormalities of the TA and upper limb arteries on examination, was performed to assess the association between these variables and the three GCA groups. Occurrence of a cranial ischemic event was independently associated with a

lower probability of exclusive LV-GCA [OR: 0.069 95%CI: 0.009-0.526, p=0.010]. No other independent predictors were found.

Conclusions: GCA can encompass various patterns of vascular disease on ultrasound. LV involvement was frequently found in these patients, including in cases without evidence of cranial disease, highlighting the need to incorporate LV assessment in the diagnosis of GCA. Patients in the group of exclusive LV-GCA had fewer cranial manifestations and more abnormalities on upper limb arteries on examination than the other groups. Presence of a cranial ischemic event was an independent negative predictor for exclusive LV-GCA. No differences were found between groups regarding the clinical outcomes at two years. Further studies with longer time of follow-up are needed.

Disclosures: None

Table 1. Demographic and clinical characteristics of cranial-GCA vs cranial- and LV-GCA vs LV-GCA

	Exclusive cranial-GCA N=37 (45.7%)	Cranial- and LV-GCA N=30 (37.0%)	Exclusive LV-GCA N=14 (17.3%)	*p-value*
Demographic data				
Mean age at diagnosis, mean ± SD	76.6 ± 8.0	76.3 ± 8.4	72.6 ± 10.5	**p=0.574**
Female sex, n (%)	28 (75.7%)	18 (60.0%)	9 (64.3%)	p=0.374
Comorbidities at the time of diagnosis, n (%)				
Arterial hypertension	26 (70.3%)	20 (66.7%)	7 (50.0%)	p=0.391
Atrial fibrillation	5 (13.9%)	4 (13.3%)	2 (14.3%)	p=0.996
Carotid atherosclerosis	3 (8.3%)	3 (10.0%)	2 (14.3%)	p=0.820
Cerebrovascular disease	6 (16.7%)	4 (13.3%)	3 (21.4%)	p=0.791
Chronic renal disease	6 (16.7%)	5 (16.7%)	2 (14.3%)	p=0.976
Diabetes *Mellitus*	15 (40.5%)	10 (33.3%)	5 (35.7%)	p=0.826
Hypercholesterolemia	18 (48.6%)	12 (40.0%)	3 (21.4%)	p=0.209
Hypertriglyceridemia	1 (2.7%)	0 (0%)	0 (0%)	p=0.548
Hyperuricemia/Gout	1 (2.8%)	4 (13.3%)	2 (14.3%)	p=0.231
Ischemic cardiopathy	4 (11.1%)	4 (13.3%)	1 (7.1%)	p=0.832
Obesity	1 (3.1%)	2 (7.1%)	2 (14.3%)	p=0.380
Peripheral arterial disease	2 (5.6%)	3 (10.0%)	0 (0%)	p=0.431
Thyroid disease	4 (10.8%)	4 (13.3%)	1 (7.1%)	p=0.828
Clinical manifestations at the time of diagnosis, n (%)				
Fatigue	19 (51.4%)	10 (33.3%)	7 (50.0%)	p=0.111
Night sweats	3 (8.1%)	1 (3.3%)	2 (14.3%)	p=0.151
Fever	3 (8.1%)	1 (3.3%)	2 (14.3%)	p=0.151
Weight loss	19 (51.4%)	19 (63.3%)	7 (50.0%)	p=0.210
Arthralgia	13 (35.1%)	12 (40.0%)	4 (28.6%)	p=0.266
Arthritis	2 (5.4%)	2 (6.7%)	0 (0%)	p=0.224
Polymyalgia rheumatica	19 (51.4%)	15 (50.0%)	8 (57.1%)	p=0.254
Myalgia	12 (32.4%)	6 (20.0%)	2 (14.3%)	p=0.138
Jaw claudication	25 (67.6%)	18 (60.0%)	2 (14.3%)	**p=0.004**
Tongue claudication	5 (13.5%)	3 (10.0%)	0 (0%)	p=0.152
Arm claudication	1 (2.7%)	0 (0%)	1 (7.1%)	p=0.137
Leg claudication	0 (0%)	1 (3.3%)	0 (0%)	p=0.162
Scalp tenderness	12 (32.4%)	7 (23.3%)	0 (0%)	**p=0.037**
Headache – frontal	18 (48.6%)	12 (40.0%)	0 (0%)	**p=0.007**
Headache – occipital	11 (29.7%)	9 (30.0%)	2 (14.3%)	p=0.204
Headache – temporal	25 (67.6%)	17 (56.7%)	1 (7.1%)	**p=0.001**
Blurred vision	4 (10.8%)	6 (20.0%)	0 (0%)	p=0.083
Amaurosis fugax	3 (8.1%)	6 (20.0%)	0 (0%)	p=0.106
Permanent loss of vision	17 (45.9%)	12 (40.0%)	2 (14.3%)	p=0.112
Diplopia	3 (8.6%)	1 (3.4%)	0 (0%)	p=0.411
Cranial ischemic event[1]	20 (54.1%)	20 (66.7%)	3 (21.4%)	**p=0.020**
Transient ischemic attack	1 (2.7%)	2 (6.7%)	0 (0%)	p=0.501
Ischemic stroke	2 (5.4%)	4 (13.3%)	2 (14.3%)	p=0.463
Physical examination at the time of diagnosis, n (%)				
TA abnormality[2]	14 (37.8%)	9 (30.0%)	0 (0%)	**p=0.023**
Upper limb arteries abnormality[3]	0 (0%)	1 (3.3%)	2 (15.4%)	**p=0.042**
Arteritic anterior ischemic optic neuropathy	17 (47.2%)	13 (43.3%)	2 (14.3%)	p=0.092
Central retinal artery thrombosis	3 (8.1%)	3 (10.0%)	0 (0%)	p=0.487
Inflammatory markers at the time of diagnosis, mean ± SD				
ESR mm/hr	81.3 ± 30.2	84.5 ± 34.9	86.5 ± 29.3	p=0.787
CRP mg/dl	5.8 ± 5.4	6.0 ± 5.1	6.5 ± 5.6	p=0.973
Clinical course over the first two years of disease, n (%)				
At least one relapse	8 (47.1%)	5 (25.0%)	2 (50.0%)	p=0.321
Death	7 (29.2%)	4 (18.2%)	2 (28.6%)	p=0.664
Disease-modifying antirheumatic drugs, n (%)				
Methotrexate	15 (41.7%)	16 (53.3%)	8 (57.1%)	p=0.504
Azathioprine	1 (2.8%)	0 (0%)	0 (0%)	p=0.539
Tocilizumab	2 (5.6%)	3 (10.3%)	4 (28.6%)	p=0.069

[1] Cranial ischemic event include transient ischemic event, ischemic stroke or visual disturbances (central retinal artery thrombosis, arteritic anterior ischemic optic neuropathy, diplopia, permanent or transient visual loss). [2] Temporal artery abnormality on examination: tenderness, thickness of the artery or absent/reduced pulse. [3] Upper limb arteries abnormality on examination (excluding temporal arteries): tenderness, bruit or absent/reduced pulse on the axillary, humeral or radial arteries. SD: standard deviation; TA: temporal artery; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

212. The anteromedial ultrasound of the large vessels in patients with Giant Cell Arteritis

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Background: Giant cell arteritis (GCA) affects both the cranial and large vessels. Ultrasonographic studies have reported that large vessel vasculitis (LVV) in patients with GCA varies from 30% to 55%. This study aimed to investigate the rate of LVV in patients with GCA by using the anteromedial approach to examine the large supraaortic vessels in addition to the cranial arteries.

Methods: Patients with new-onset GCA referred to the Department of Rheumatology, Martina Hansens Hospital in Bærum, Norway, were examined between September 2017 and July 2021. The diagnosis was based on the typical clinical manifestations and verified six months after the diagnosis. All the patients were scanned by ultrasound, using the anteromedial approach for the supraaortic vessels (carotid, vertebral, subclavian, axillary proximally and distally) and the examination of the cranial vessels (temporal, facial). In a selected group of patients, the ascending aorta and the aortic arch were also examined. The anteromedial approach consists of a continuous ultrasound evaluation of the large supraaortic vessels with the patient prone. The examination utilized a GE S8 ultrasound machine and an Applio 800 with 9-12 Mhz linear probes for the large vessels and >18Mhz probes One hundred for the cranial arteries. The age, gender, CRP and the distribution of vasculitis in the vessels were recorded.

Results: One hundred twenty-three patients, 82 (85%) females, and 41 (25%) males, were diagnosed with GCA during the recruitment period. The mean age was 72,6 years (95% CI (71-74)) for the female patients and 73 years (95% CI (69-74)) for the male patients. Mean CRP was 99 mg/dl (95% CI (87-110)). Of the 123 GCA patients, 35 patients (28 %) had cranial GCA only, 21 patients (17%) had LVV only, and 67 patients (55 %) had mixed disease (both cranial and LVV GCA). Five patients suffered a visual loss (4%). Fifty-seven patients had an ultrasound evaluation of the ascending aorta, and arch and four of them had an increased diameter of the aortic area >= 40 mm. The temporal arteries were the most frequently involved cranial vessels in 81% of the patients,while the facial artery was involved in 41%. The large supraaortic vessels primarily involved were the right proximal axillary (33%), the left proximal axillary (32 %), the left distal axillary (32 %), the right distal axillary (31 %), and the subclavian (left 26% and right 30 %). The left carotid and vertebral were involved in 17 % of patients, while the right carotid in 9 % and right vertebral in 20% of the patients.

Conclusions: The anteromedial ultrasound examination revealed inflammation of the large supraaortic vessels in 72% of the GCA patients indicating that the involvement of supraaortic arteries is more common in GCA than previously reported. In our cohort, only a small percentage of patients (4%) suffered a visual loss.

Disclosures: None declared. Preliminary data published here: https://acrabstracts.org/abstract/the-anteromedial-ultrasound-examination-of-the-large-supraaortic-vessels-identifies-higher-rates-of-large-vessel-involvement-than-previous-reported-in-patients-with-giant-cell-arteritis/

Biomarkers

213. Routine application of PR3- and MPO-ANCA chemiluminescence immunoassays demonstrates enhanced detection rates

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Background: The sensitive and accurate detection of anti-neutrophil cytoplasmic antibodies (ANCA) against proteinase 3 (PR3) and myeloperoxidase (MPO) is crucial in the diagnosis and monitoring of patients with ANCA-associated vasculitides (AAV) and the specific diseases categorised thereof, including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with poly-angiitis (EGPA). Chemiluminescence immunoassays (ChLIA) and bead technology have emerged as promising tools for fast, sensitive and accurate autoantibody detection. Applied to PR3- and MPO-ANCA, they could improve limitations in the sensitivity, narrow measuring range and level of quantification seen in other assay formats. Here, we examined the routine performance of ChLIAs using human recombinant PR3 as well as human native MPO antigens.

Methods: The Anti-PR3 ChLIA (IgG) and prototype Anti-Myeloperoxidase ChLIA (IgG) were processed on the RA Analyzer 10 (EUROIMMUN) and the EliA PR3^S and EliA MPO^S on the Phadia250 (Thermo Fisher Scientific), both in accordance with the recommendations by the manufacturers. For a comparative analysis of the routine performance, 675 sera from 615 individuals to be tested for PR3-ANCA, MPO-ANCA or both at the Central Diagnostic Laboratory at Maastricht University Medical Center were measured with the respective assays on both automation systems. The results were compared in respect to the qualitative outcome and numerical correlation.

Results: Of the total 675 samples, 588 and 561 were subjected to PR3-ANCA and MPO-ANCA analysis, respectively. For both ANCA types, all samples found positive with EliAs were also positive in the corresponding ChLIAs. 24 and 26 samples resulted positive for PR3- and MPO-ANCA by ChLIA, respectively, but were below cut-off in the relevant EliA test. Of those, 50.0 % (n=12 for PR3) and 96.2 % (n=25 for MPO) were from individuals in follow-up after AAV diagnosis; in the remaining cases an ANCA involvement was suspected based on symptoms of the patients. The overall concordance between the two assay systems was 95.9 % for PR3-ANCA and 95.4 % for MPO-ANCA detection.

Conclusions: In a routine scenario, the ChLIAs fully covered the PR3- and MPO-ANCA detection by the compared reference test system. Moreover, further positive results in samples found negative by EliA demonstrated enhanced detection rates by both ChLIAs, predominantly in samples from individuals with a known history of AAV. The clinical relevance will be subject to further studies.

Disclosures: YB, CD, AK and WS are employed by EUROIMMUN AG, a manufacturer of diagnostic reagents.

214. Utility of serum complement factors C3 and C4 as biomarkers in Giant Cell Arteritis

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Background: There is a strong unmet need for novel biomarkers in Giant Cell Arteritis (GCA): C-reactive protein (CRP) may be unreliable in case of patients treated with Tocilizumab (TCZ). Several molecules have been proposed, but, to date, none of them has provided sufficiently robust evidence to be used in clinical practice. In this regard, we aimed to assess whether serum complement factors, whose activation has a paramount role in several autoimmune diseases, may be considered a useful biomarker in GCA.

Methods: We retrospectively enrolled all GCA patients from our vasculitis center who underwent C3 and C4 measurement at baseline. All patients were evaluated at 3, 6, 12 and 24 months after first diagnosis, as part of routine follow-up visits. Two assessments after the end of the observational period, in case of further relapses, were also included.

Results: One-hundred and thirty-nine consecutive patients were enrolled. At baseline, mean serum levels of C3 and C4 were within the normal range. Both C3 and C4 values decreased significantly between baseline and the first follow-up evaluation at remission (Table 1). C4 levels showed a stronger predictability for the state of disease compared to C3 using a binary multivariate regression model (C4: ß coefficient 0.71, p=0.005, C3: ß coefficient 0.009, p=0.141). When patients were stratified according to disease activity, C3 and C4 appeared significantly reduced in patients in remission (107.07±19.86; p=0.0006 and 19.86±10.27; p=0.01, respectively) and sustained remission (95.85±18.04, p=0.001; and 15.61±9.75; p=0.006). Moreover, there was a statistically non-significant trend towards lower C3 and C4 serum levels in patients with sustained remission and GC-free remission compared to patients who had a shorter duration of remission and/or needed higher GC doses. In patients in remission, CRP levels correlated strongly with C3 and C4. A correlation of CRP with C3 was also found in active patients at baseline, while C4 levels were not associated with CRP at baseline and at relapse. In a binary regression model CRP and ESR showed significantly

stronger association with the state of disease than C3 and C4. Among the patients who relapsed, a statistically significant difference with remission findings was evidenced for CRP, ESR and C3, but not for C4. In patients treated with TCZ, serum levels of C3 and C4 were statistically significantly decreased compared to baseline. No significant correlation was found between C3 and CRP (r=-0.04, p<0.9), and C4 and CRP (r=0.4, p=0.28). No significant association was found between C3 and C4 and imaging findings.

Conclusions: Serum C3 and C4 do not seem to provide any added value in the diagnosis of GCA, as normal values do not rule out active vasculitis. However, serum levels of C3 and C4 correlate with disease activity. In patients treated with TCZ, C3 and particularly C4 levels are even lower than in the ones on treatment with other immunosuppressants. As the low C4 complement levels found in TCZ-treated patients are not correlated with CRP-levels, C4 should be further evaluated as a potential biomarker in TCZ-treated patients, in whom CRP may be unreliable. Preliminary data[1] have displayed that C4 may increase in refractory or relapsing patients treated with TCZ: this may suggest that the reduction of C4 is related to disease activity and not only to the pharmacological inhibition of IL-6, confirming its potential reliability in such patients.

Disclosures: None.

Table 1. Markers of inflammation and complement factors in different stages of disease

	Baseline (T0)	Remission	*p* value
CRP (mg/l)	52.1±41.3	8.41±11.5	<0.00001**
ESR (mm/h)	57.6±32.4	16.7±15.4	<0.00001**
C3 (mg/dl)	133.0±29.0	107.1±27.1	0.0006**
C4 (mg/dl)	25.9±9.0	19.9±10.3	0.01*
	All remissions	Relapse	*p* value
CRP (mg/l)	8.4±11.5	21.4±28.0	0.02*
ESR (mm/h)	16.7±15.4	28.3±23.6	0.035*
C3 (mg/dl)	107.1±27.1	122.8±16.7	0.031*
C4 (mg/dl)	19.9±10.3	27.3±9.1	0.07
	Before TCZ	During TCZ	*p* value
CRP (mg/l)	44.9±33.1	0.4±0.7	0.00042**
ESR (mm/h)	42.9±36.1	5.0±5.2	0.003**
C3 (mg/dl)	129.4±32.8	83.1±19.7	0.001**

C4 (mg/dl)	21.9±7.2	8.3±3.8	0.000069**

List of abbreviations: CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; TCZ: Tocilizumab; *p<0.05; **p<0.01 (Student T-test).

215. Circular RNA expression profiles and identification of hsa_circ_0028381 as a potential biomarker for ANCA-associated vasculitis

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Background: Growing evidence indicated that dysregulated circRNAs play a vital role in autoimmune diseases. However, their role in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) has never been illustrated. This study aims to determine the expression profiles of circRNA in plasma of AAV patients and explore the potential of circRNA as biomarker of AAV.

Methods: RNA-sequencing (RNA-seq) was performed to identify the circRNAs and mRNAs expression profiles in plasma from 5 AAV patients and 5 healthy controls (HCs). Hsa_circ_0028381, one of the four candidate circRNAs were validated by quantitative reverse-transcription (qRT)-PCR in a validation cohort of 51 AAV patients and 30 HCs and was confirmed to be significantly upregulated. And it was further verified in other connective tissue diseases (CTDs) by qRT-PCR. The receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic value.

Results: RNA expression profiles revealed that 143 circRNAs and 304 mRNAs were aberrantly expressed, among which, 62 circRNAs were upregulated and 81 circRNAs were downregulated in AAV patients compared to HCs. The result of qRT-PCR verification suggested that hsa_circ_0028381 was significantly increased in plasma from AAV patients compared to that in HCs and CTDs. The receiver operating characteristic (ROC) curves analysis showed has_circ_0028381 had a good diagnostic value to distinguish AAV patients from controls (HCs and other CTDs) with area under the curve (AUC) of 0.81. In addition, has_circ_0028381 was associated with renal involvement. Most importantly, increased baseline level of has_circ_0028381 had a predictive value for renal progression to end-stage renal disease (ESRD).

Conclusions: RNA-seq revealed that circRNAs were aberrantly expressed in plasma of AAV patients. Has_circ_0028381 might function as a potential biomarker for AAV diagnosis and renal prognosis.

Disclosures: The authors have no conflicts of interest to disclose.

216. Baseline soluble immune checkpoints predict relapse risk in PR3-ANCA vasculitis following rituximab induction therapy

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Background: We investigated whether soluble immune checkpoints (sICPs) predict treatment-resistance, relapse risk, and risk of infections in patients with anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV).

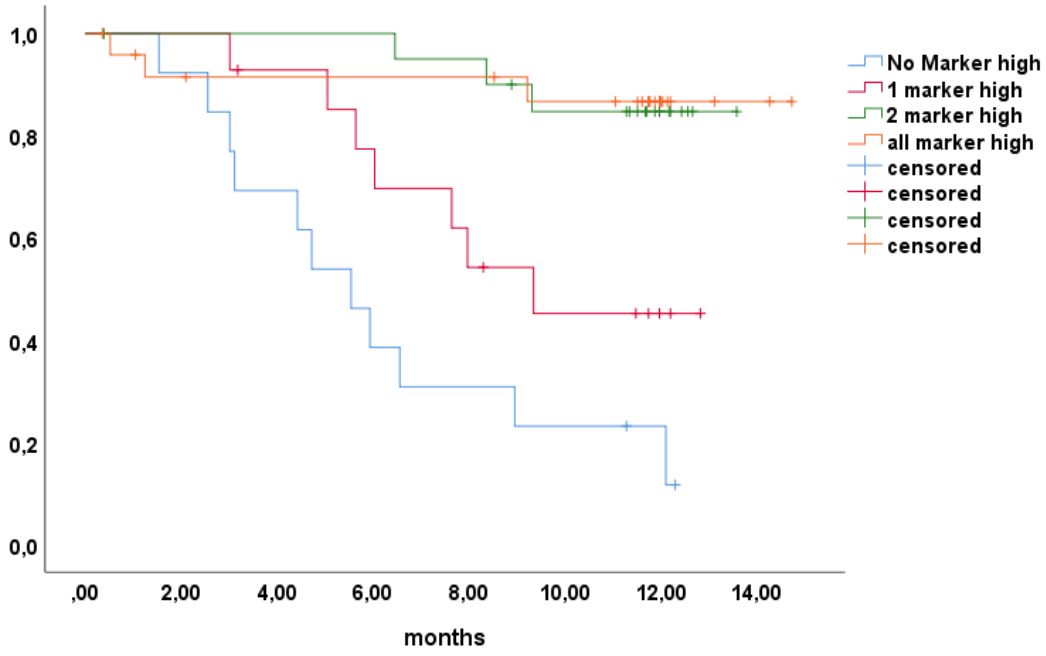
Methods: Plasma levels of sICPs were measured by enzyme-linked immunosorbent assay from samples obtained at baseline and during follow-up from patients with AAV in the RAVE trial and were correlated with selected clinical outcomes. Log rank test was used to evaluate survival benefits. Optimal cut-off values of the marker molecules were calculated using Yeldons J.

Results: Among 95 patients receiving rituximab as induction therapy, lower soluble (s)Lag-3 (< 90 pg/mL) and higher sCD27 (> 3000 pg/mL) were predictive of not achieving remission. Among patients with remission, 32.9% relapsed with a median relapse free survival of 5.64 months. Low baseline values of sTim-3 (< 1200 pg/mL), sCD27 (< 1250 pg/mL), and sBTLA (< 1000 pg/mL) were associated with disease relapse (see Figure 1). In addition, patients with high levels of at least one of these marker were prone to infectious complications. These findings were restricted to patients with proteinase 3 (PR3)-ANCA vasculitis and not observed in patients with myeloperoxidase (MPO)-ANCA vasculitis. Moreover, these relationships do not hold for the group of patients randomised to receive cyclophosphamide/azathioprine.

Conclusions: Rituximab-treated patients achieved remission less frequently when sLag-3 was low and sCD27 was high. Higher expression of sTim-3, sCD27, and sBTLA at baseline was associated with a lower risk of relapse in PR3-ANCA vasculitis following rituximab. These results will require confirmation in future studies, but may contribute to personalized medicine in AAV.

Disclosures: AK received Consultancy Fees from Otsuka, Alexion, Vifor Pharma, UriSalt and Catalyst Biosciences.

Figure 1. Kaplan-Meier curves for the duration of complete remission in rituximab treated patients in months from the time point of complete remission achievement. Relapse defined the event. The combination of those three markers using the predefined cut offs in RTX treated patients.



217. Does introducing a gating policy for ANCA testing result in delayed diagnosis of ANCA-associated Vasculitis?

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Background: ANCA are markers for well-defined types of small-vessel vasculitis. Most diagnostic laboratories test for ANCA by indirect immunofluorescence (IIF), with reflex testing of IIF positives by immunoassay for anti-PR3 and anti- MPO. The 2017 revision of the 1999 international consensus on ANCA testing in GPA and MPA concluded that immunoassays can be used as the primary method for ANCA testing, without the categorical need for IIF and recommended that a gating policy based on clinical indications be used to limit requests for ANCA testing. Potential unintended consequences include delayed diagnosis of vasculitis for cases where gating criteria are not met, loss of essential IIF skills in laboratories, and well as cost. Our laboratory uses an IIF method validated to have a 100% sensitivity for detection of anti-MPO and anti-PR3 with reflex immunoassay testing of IIF positive samples, and we assessed the potential impact of the 2017 revised consensus.
The aims of this audit were to confirm the sensitivity of IIF screening, determine compliance of requests with 2017 gating criteria, and determine if all patients diagnosed with ANCA-associated vasculitis (AAV) would have met gating criteria at the time of diagnosis.

Methods: We tested 250 consecutive serum samples that were negative for ANCA by IIF by immunoassay for PR3 and MPO, and assessed concordance. Indications for testing, where available were reviewed and compared with the gating criteria. We identified all positive PR3 and MPO samples over the past 4 years, assessed the indication for ANCA testing by reviewing medical records and compared the indication with the gating policy in the 2017 consensus. We assessed how many ANCA positive patients were ultimately diagnosed with AAV.

Results: All 250 IIF negative samples tested negative for both MPO and PR3 by ELISA. The clinical indication for 127 of these requests from Beaumont Hospital were available, of which 40 fitted the 2017 gating policy and 87/127 did not. Of 16,958 samples tested for ANCA, between 01/01/2017 to the 31/12/2020, 1,974 (11.6%) were tested for anti-MPO/PR3. 70 new patients were identified (0.4% of total tested; 3.5% of those tested for anti-MPO/PR3). 29 with positive for anti- MPO (Range 3.5 - >134 U; Ref < 3.5U); 38 for anti- PR3 (Range 2.1 – 150U; Ref <2.0U). 3 were dual positive. Indications for testing 33 (47%) patients fitted the gating policy while 37 (53%) did not. 16 patients were diagnosed with AAV; 6 MPO-associated Vasculitis, 7 PR3-associated vasculitis, 1 dual positivity (drug induced) and 2 Eosinophilic granulomatosis with polyangiitis (EGPA), both MPO positive. Of the 16 patients diagnosed with vasculitis, 13 (81%) fitted the gating policy clinical indications while 3 (19%) did not.

Conclusions: This audit demonstrates that initial testing for ANCA with an IIF method with validated sensitivity is not inferior to testing all samples with immunoassays. A sampling exercise showed that 63% of requests for ANCA testing in our centre do not fulfil the clinical indication suggested in the 2017 Consensus. Samples fulfilling the gating criteria accounted for 47% of ANCA positive samples, and 81% of patients ultimately diagnosed with AAV. Use of gating criteria would have delayed diagnosis for 19% of patients with AAV.

Disclosures: None

218. C-Reactive Protein to Albumin Ratio is Associated with Disease Activity in Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis

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Background: C-reactive protein to albumin ratio (CAR) is a composite indicator of inflammation and nutritional status which has been recently recognized as a prognostic marker in vasculitides. Since there are limited data on assessment with CAR in patients with ANCA-

associated vasculitis (AAV), this study aims to investigate CAR and its relationship with disease activity and damage in prevalent ANCA vasculitis patients.

Methods: Fifty-one AAV patients and 42 age and sex-matched controls were enrolled in this cross-sectional study. Birmingham vasculitis score (BVAS) was used to assess vasculitis activity and vasculitis damage index (VDI) to provide information on disease damage. The relationship between clinical features and CAR, BVAS and VDI were also investigated.

Results: Median (25^{th}-75^{th}) patient age was 55 (48-61) years and median duration of disease was 34 (11-72) months. CAR was significantly higher in AAV patients than controls (1.9±2.7 vs 0.7±0.4; p=0.006). The 75^{th} percentile of BVAS was defined as high BVAS (BVAS≥5) and ROC curve analysis showed that CAR≥0.98 predicted BVAS≥5 with 70.0% sensitivity and 68.0% specificity (AUC:0.660, CI: 0.482-0.837, p=0.049). Comparison of clinical, demographic and laboratory data according to C-reactive protein to albumin ratio (CAR) are shown in Table 1. When patients with CAR≥0.98 were compared to those without, BVAS [5.0 (3.5-8.0) vs. 2.0 (0-3.25), p<0.001], BVAS≥5 [16 (64.0%) vs 4 (15.4%) patients, p:0.001], VDI [4.0 (2.0-4.0) vs. 2.0 (1.0-3.0), p=0.006] and CAR [1.32 (1.07-3.78) vs. 0.75 (0.60-0.83), p<0.001] were significantly higher whereas albumin [3.8 (3.1-4.3) vs. 4.1 (3.9-4.4) g/dL, p=0.025] and haemoglobin [12.1 (10.4-13.4) vs. 13.0 (12.5-14.2) g/dL, p=0.008] were significantly lower. Multivariate analysis revealed that BVAS [OR (95% CI):1.313 (1.003-1.719), p=0.047] was an independent factor associated with CAR≥0.98 in patients with AAV. Furthermore, correlation analysis showed that CAR significantly correlated with BVAS (r: 0.466, p=0.001).

Conclusions: In this study, we observed CAR was associated with disease activity in AAV patients and can be used to monitor disease activity in this patient population.

Disclosures: None.

Table 1. Comparison of clinical, demographic and laboratory data according to C-reactive protein to albumin ratio (CAR)

	CAR ≥0.98 n:25	CAR <0.98 n:26	P
Age, years	57.0 (51.5-62.0)	50.5 (46.5-59.3)	0.149
Male, gender, n (%)	14 (56.0%)	11 (42.3%)	0.406
BMI, kg/m^2	28.1 (24.8-32.2)	27.8 (26.0-30.9)	1.000
Smoking, n (%)	4 (16.0%)	3 (11.5%)	0.703
Duration of disease, months	18 (5.0-66.0)	36 (18.8-77.5)	0.124
p-ANCA, n (%)	8 (32.0%)	13(50.0%)	0.305
c-ANCA, n (%)	15 (60.0%)	10(38.5%)	

ANCA negative	2 (8.0%)	3(11.5%)	
Granulomatosis/Microscopic, n	17/8	15/11	0.565
BVAS	5.0 (3.5-8.0)	2.0 (0-3.25)	<0.001
BVAS ≥5	16 (64.0%)	4 (15.4%)	0.001
VDI	4.0 (2.0-4.0)	2.0 (1.0-3.0)	0.006
Glucose, mg/dL	100.0 (88.5-111.0)	88.5 (81.8-97.2)	0.136
Creatinine, mg/dL	1.51 (0.95-2.36)	1.10 (0.84-2.13)	0.136
GFR, ml/min/1.73m^2	45.8 (27.5-73.5)	57.9 (31.2-91.5)	0.294
Albumin, g/dL	3.8 (3.1-4.3)	4.1 (3.9-4.4)	0.025
Calcium, mg/dL	9.3 (8.6-9.8)	9.6 (9.2-9.8)	0.165
Phosphorus, mg/dL	3.6 (2.9-4.7)	3.7 (3.1-3.9)	0.664
Aspartate transaminase, U/L	18 (13-22)	18 (13-20)	0.910
Alanine transaminase, U/L	15 (10-21)	16 (12-20)	0.590
Hemoglobin, g/dL	12.1 (10.4-13.4)	13.0 (12.5-14.2)	0.008
Platelet, x10^3/mL	306 (249-360)	262 (238-301)	0.129
Leukocyte, x10^3/mL	8.2 (7.2-12.3)	6.7 (5.6-9.6)	0.042
CRP, mg/L	5.3 (3.1-13.8)	3.2 (2.6-3.2)	0.001
ESR, mm/h	32.0 (16.3-51.8)	22.5 (12.5-35.5)	0.186
CAR	1.32 (1.07-3.78)	0.75 (0.60-0.83)	<0.001

219. Anti-complement C5a receptor antibodies are decreased in ANCA-associated vasculitis and associated with relapse

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Background: Complement activation has been shown to play an important role in anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) (1,2). Circulating proinflammatory anaphylatoxin C5a concentrations are increased and correlate with disease activity in AAV (3). Interaction of C5a with C5aR represents a proinflammatory amplification loop (1). Binding of C5a to its corresponding G protein-coupled receptor (C5aR/CD88) enhances the influx of neutrophils and their activation, leading to ROS generation and severe necrotizing of vascular walls (3). Blocking of C5aR is protective in a murine model of ANCA-induced necrotizing crescentic glomerulonephritis (4). In humans, recent studies demonstrate efficacy of the C5aR antagonist avacopan as glucocorticoid-sparing agent in AAV (5). The aim of the present study was to examine whether concentrations of anti-C3aR and anti-C5aR antibodies correlate with clinical findings and outcomes in AAV.

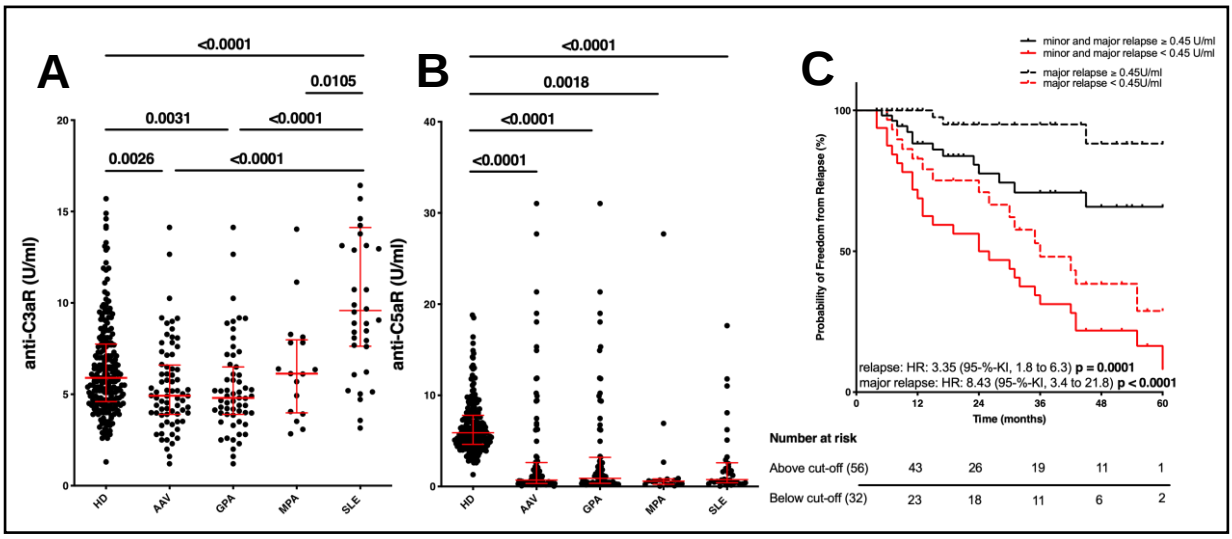
Methods: Sera and plasma of AAV patients [granulomatosis with polyangiitis (GPA), n=82; microscopic polyangiitis (MPA), n=28], systemic lupus erythematosus (SLE, n=36) and healthy donors (HD, n=220) were measured by Elisa for circulating autoantibodies against complement receptors C3a (anti-C3aR), C5a (anti-C5aR) and plasma levels of C3a and C5a. Expression of C3aR and C5aR on T-cells was determined using flow cytometry. Clinical data were assessed at the time of serum sampling and during follow-up for 60 months.

Results: Decreased concentrations of anti-C3aR and anti-C5aR antibodies were found in AAV compared with HD (figure 1a, p=0.0026; figure 1b, p≤0.0001). Whereas both anti-C3aR and anti-C5aR antibodies were decreased in GPA, anti-C3aR antibody levels were similar to HD in MPA (figure 1a, 1b). In particular, newly diagnosed GPA patients with high disease activity displayed the lowest levels of anti-C5aR antibodies (p=0.0007). C5a and anti-C5aR antibody concentration showed a negative correlation in GPA (r= -0.6831, p=0.0127). The frequency of C5aR expressing cells within the total CD4+ and CD8+ T-cell populations was increased in GPA compared to HD (10.76±2.55% *vs*. 3.44±0.68%, p=0.0021 and 9.74±2.10% *vs.* 4.11±0.92%, p=0.0198, respectively). Anti-C5aR antibody concentrations <0.45U/ml were associated with an increased risk for relapse in AAV (fig.1c).

Conclusions: Low concentrations of circulating anti-C5aR antibodies reflect disease activity and are associated with an increased risk for relapse in AAV.

Disclosures: none

Figure 1. Anti-C3aR and anti-C5aR antibody concentrations in AAV. A: Anti-C3aR antibody concentrations compared to HD, MPA, and SLE B: Anti-C5aR antibody concentrations compared to HD, MPA, and SLE. C: Anti-C5aR antibody concentrations <0.45 U/l were associated with a higher relapse rate in AAV.



220. A systematic review and meta-analysis on the value of serial ANCA titer evaluation.

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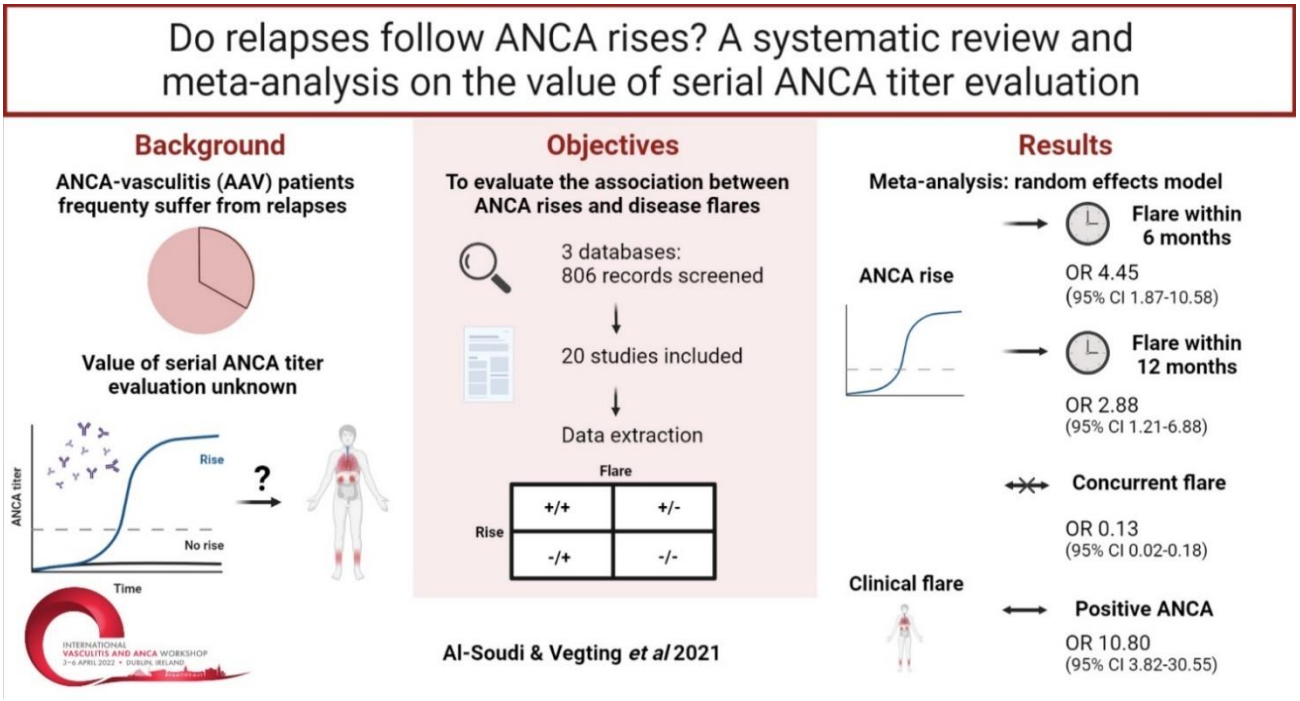
Background: ANCA-vasculitis (AAV) patients frequently suffer from relapses and risk subsequent organ damage. There is much debate on the value of serial ANCA titer evaluation to monitor disease activity. We aimed to evaluate the association between ANCA rises and disease flares at (I) moment of the rise, (II) within 6 months or (III) within a year from the rise.

Methods: 3 databases (MEDLINE, EMBASE and COCHRANE) were searched from 1993 through 2021. We included studies that reported flare incidence within 12 months after an ANCA rise measured by ELISA in peripheral blood of AAV patients in remission. Quality assessment was performed using QUADAS-2. Finally, a meta-analysis was carried out to estimate average OR using a random effects model.

Results*:* 20 unique studies were included. The methodological quality was limited due to risk of selection bias. An ANCA rise often preceded a disease flare within 6 months (OR 4.45, 95% CI 1.87-10.58) and less often within 12 months (OR 2.88, 95% CI 1.21-6.88), while it was not indicative of a concurrent flare (OR 0.13, 95% CI 0.02-0.18). Once a flare is diagnosed, ANCA is significantly more often present than not (OR 10.80, 95% CI 3.82-30.55). As expected based on clinical variability, there was substantial heterogeneity across studies in all analyses (I^2 = 70%-87%).

Conclusions: An ANCA measurement upon clinical suspicion of a disease flare aids diagnosis. Patients with a rise in ANCA are at risk of encountering disease flares in the upcoming 6 or 12 months.

Disclosures: This work was supported by the Dutch Kidney Foundation [Grant number 19OK007 to MH and YV] and ZonMW [VENI grant number 91617058 to PK]



221. Serum soluble CD206 complements urinary soluble CD163 in detecting active ANCA-associated glomerulonephritis

William Jiemy[1,2], Joop P. Aendekerk[3], Inge Strating[2], Gerjan J. Dekkema[2], Jan-Stephan F. Sanders[4], Coen A. Stegeman[4], Mark A. Little[5], Peter Heeringa[2], Pieter van Paassen[3]
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Background: Early detection of active glomerulonephritis (GN) in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is crucial to minimize kidney damage, but accurate biomarkers are currently lacking. Urinary soluble CD163 (usCD163) has been shown as a potent biomarker for active ANCA GN. However, false negative rates can be as high as 29%. Here, we investigated whether serum soluble CD206 (ssCD206; macrophage mannose receptor), complements usCD163 in the detection of active ANCA GN.

Methods: Biopsies from ANCA GN patients were immunohistochemically (IHC) stained for CD206. The percentage of positive cells were analysed with QuPath image analysis software. Colocalization of CD163 and CD206 was assessed by immunofluorescence (IF). For ELISA, three independent cohorts (C1-Maastricht University Medical Center, C2-University Medical Center Groningen & C3-Trinity College Dublin) with available serum, urine, and kidney biopsy samples (C1 only) were included. usCD163/creatinine (ng/mmol) and ssCD206 (ng/ml) were assessed in urine and serum, respectively. The performance of usCD163 and ssCD206 to detect ANCA GN was assessed using receiver operating characteristics (ROC) curves.

Results: IHC revealed elevated numbers of CD206+ macrophages in the kidneys of active ANCA GN patients. CD206+ macrophages are mainly detected in the tubulointerstitial compartments. Albeit to a lower extent, CD206+ macrophages were also found in the glomerulus. CD206+ macrophage infiltration was significantly higher in crescentic class, both in the tubulointerstitial and glomerular compartments. IF showed glomerular presence of CD163+CD206- cells, whereas CD163+CD206+ and CD163-CD206+ cells were mainly found in the tubulointerstitium. For ELISA, patients (C1/C2/C3) with active ANCA GN (n=42/17/47), active non-renal AAV (n=3/3/12) or patients in remission (n=4/8/38) were included. Healthy controls (HCs; n=6) were included for C1. usCD163 was significantly higher in active ANCA GN compared to active non-renal AAV and remission in all cohorts, and healthy control urine in C1 (Kruskal-Wallis, $P<0.001$). ssCD206 was significantly higher in active ANCA GN compared to patients in remission (C2 & C3) and extrarenal AAV (C3) (Kruskal-Wallis, $P\leq0.0006$). usCD163 had a specificity of 93% (C1), 100% (C2) and 96% (C3), whereas sensitivity was 80% (C1), 88% (C2) and 72% (C3). ssCD206 increased the sensitivity to detect active ANCA GN in all cohorts to 83% (C1), 100% (C2) and 89% (C3).

Conclusion: Histological assessment revealed distinct glomerular and tubulointerstitial populations of CD163+ and CD206+ cells in the kidneys of renal active AAV patients. ssCD206 complements usCD163 and reduces false negative rates in the detection of active ANCA GN.

Disclosure: Nothing to disclose.

222. ANCA (+) vasculitis: value of urinary biomarkers in distinguishing active disease

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Background: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis is a chronic relapsing and remitting disease and a cause of rapidly progressive glomerulonephritis. CD163 and calprotectin have been proposed as biomarkers of active renal vasculitis. The objective of this study was to determine if serum and urine (s/u)calprotectin and urine (u)CD163 are disease activity and prognosis biomarkers in ANCA vasculitis.

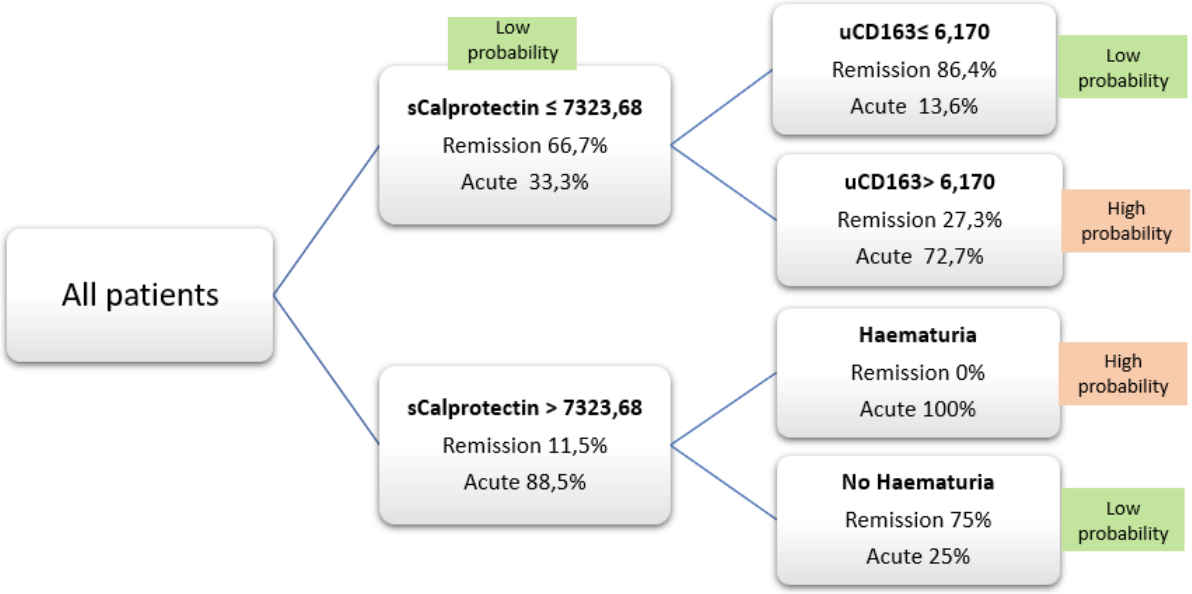
Methods: We included 179 patients diagnosed with ANCA vasculitis (n= 73 acute phase, n=106 in remission) and 4 healthy controls. We collected serum and urine at the time of inclusion. We determined the serum and urinary concentration of calprotectin and urinary CD163 using Enzyme Linked Immunoassay (ELISA). We compared the concentrations of biomarkers between groups using the Mann Whitney U test. We plotted the ROC curve of each biomarker to assess its ability to discriminate disease activity. We elaborated a combining biomarker model using the recursive partition method and we presented the result in the form of a decision tree.

Results: The concentration of sCalprotectin and uCD163 was higher in patients in the acute phase compared to patients in remission ($p<0,0001$ and 0,0013, respectively). We did not find differences regarding the concentration of uCalprotectin. We evaluated the ROC curves of the different biomarkers to determine the detection of disease activity and we observed that sCalprotectin and uCD163 were good biomarkers to discern activity [0,712 (0,62-0,80), $p<0,0001$ and 0,67 (0,57-0,77) $p=0,0014$, respectively] while uCalprotectin was not [0,56 (0,46-0,66) and $p= 0,22$]. The combining biomarker model (fig 1.) that included sCalprotectin, uCD163 and haematuria increased the sensitivity, specificity, and likelihood ratio exhibited by biomarkers separately (88%, 87% and 7.25, respectively).

Conclusions: Our study concludes that in patients with ANCA vasculitis, sCalprotectin and uCD163 could be useful in detecting active kidney disease and helping to monitor response to treatment.

Disclosures: None

Fig 1. Combining biomarker model



223. Autoreactive plasmablasts after B cell depletion with rituximab and relapses in ANCA-associated vasculitis

Alvise Berti[1,2,3], Sophie Hillion[4], Marta Casal Moura[2], Amber M. Hummel[2], Eva Carmona[2], Tobias Peikert[2], Fernando C. Fervenza[5], Cees G.M. Kallenberg[6], Carol A. Langford[7], Peter A. Merkel[8], Paul A. Monach[9], Philip Seo[10], Robert F. Spiera[11], Paul Brunetta[12], E. William St. Clair[13], Kristina M. Harris[14], John H. Stone[15], Guido Grandi[3], Jacques-Olivier Pers[4], Ulrich Specks[2], Divi Cornec[4]

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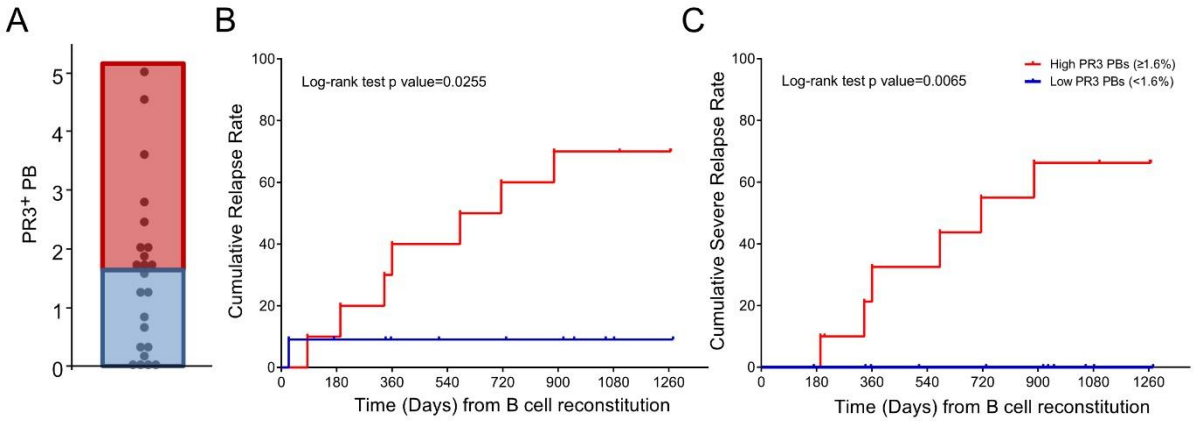
Background: Autoreactive B cells are responsible for ANCA production in ANCA-associated vasculitis (AAV). Rituximab depletes circulating B cells including the autoreactive ones. We

aimed to evaluate changes and associations with relapse of the circulating autoreactive B cell pool following therapeutic B cell depletion in AAV.

Methods: Sequential flow-cytometry was performed on 148 samples of peripheral blood mononuclear cells from 23 patients with proteinase-3 (PR3)-ANCA$^+$ AAV treated with rituximab for remission-induction and monitored off-therapy during long-term follow-up in a prospective clinical trial. PR3 was used as ligand to target autoreactive B cells (PR3$^+$ B cells). B cell recurrence was considered to occur at the time of the first blood sample with ≥10 B cells/μL after rituximab.

Results: At B cell recurrence, autoreactive B cell frequency among B cells was higher than at baseline ($p<0.01$). Frequencies of transitional and naïve subsets were higher, while memory subsets were lower at B cell recurrence than at baseline within both autoreactive and total B cells ($p<0.001$ all comparisons). At B cell recurrence, frequencies of B cells and subsets did not differ between relapsers and non-relapsers. In contrast, the frequency of plasmablasts within the autoreactive B cell pool (CD19$^+$CD27$^+$CD38$^+$PR3$^+$) was higher in relapsers (median [25-75%IQR]; 1.95% [1.315-3.845] vs 0.84% [0.05-1.66], $p=0.022$) and severe relapsers vs non-severe relapsers (2.165% [1.66-4.315] vs 0.84% [0.1-1.74], $p=0.015$). Time-to-relapse and time-to severe-relapse were significantly shorter in patients with circulating PR3$^+$ plasmablasts higher than the median value of the cohort at B cell reconstitution (1.6%, PR3$^+$PB in Figure A; cumulative rate for relapse and severe-relapse represented in Figure B-C). In addition, levels of PR3$^+$ plasmablasts higher than baseline were more likely to be found in patients who relapsed within the following 12 months compared to non-relapsers ($p<0.05$).



Conclusions: The composition of autoreactive B cell pool varies significantly following treatment of AAV with rituximab, and an early enrichment of plasmablasts within the autoreactive pool is associated with future relapses.

Disclosures: PB: employee of Genentech during the conduct of the RAVE trial, received salary and Genentech stock. PM: Consulting: AbbVie, AstraZeneca, Biogen, Boeringher-Ingelheim, BMS, Celgene, ChemoCentryx, CSL Behring, Forbius, Genentech/Roche, Genzyme/Sanofi, GlaxoSmithKline, InflaRx, Insmed, Jannsen, Kiniksa, Kyverna, Magenta, Novartis, Pfizer, Sparrow, Takeda, Talaris. Research Support: AstraZeneca, Boeringher-

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224. Investigating adenosine deaminase 2 activity in ANCA and large vessel vasculitis

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Background: Deficiency of adenosine deaminase 2 (DADA2) manifests broadly, in some leading to vasculitis affecting small, medium, or large vessels with fever, rash, and stroke and in others immunodeficiency and haematological manifestations. In contrast, plasma ADA2 activity is elevated in inflammatory conditions including systemic lupus erythematosus and systemic juvenile idiopathic arthritis with macrophage activation syndrome. The role of ADA2 in the vasculitides is not yet understood. Using two well-characterised cohorts of large vessel and anti-neutrophil cytoplasmic antibody associated (ANCA) vasculitis, we sought to establish the potential role of ADA2 activity and deficiency.

Methods: ADA2 activity was measured in adults with Takayasu arteritis (TA) (n=135), large vessel giant cell arteritis (LV-GCA) (n=44), ANCA vasculitis (n=116, 59 PR3+, 44 MPO+, 13 ANCA negative), intracranial vasculitis (ICV) (n=7) and healthy control (HC) (n=52) subjects, using a published coupled spectrophotometric assay. Plasma from 11 patients with genotyped DADA2 and 10 patients heterozygous for pathogenic variants in ADA2 defined thresholds for deficiency and carrier status respectively. Activity levels above the upper limit of normal (ULN) were defined as >99th percentile of the HC activity. To assess potential associations with TA and ANCA disease status, ADA2 was measured prospectively in matched active and remission samples (TA n=29, ANCA n=15). TA disease activity was determined as active, grumbling or stable and ANCA as active or remission using clinical and radiological features, physician impression, CRP and Indian Takayasu clinical Activity Score (ITAS) for TA and using the Birmingham Vasculitis Activity Score (BVAS) for ANCA. Differences between groups were analysed using non-parametric tests, $P<0.05$ was considered significant.

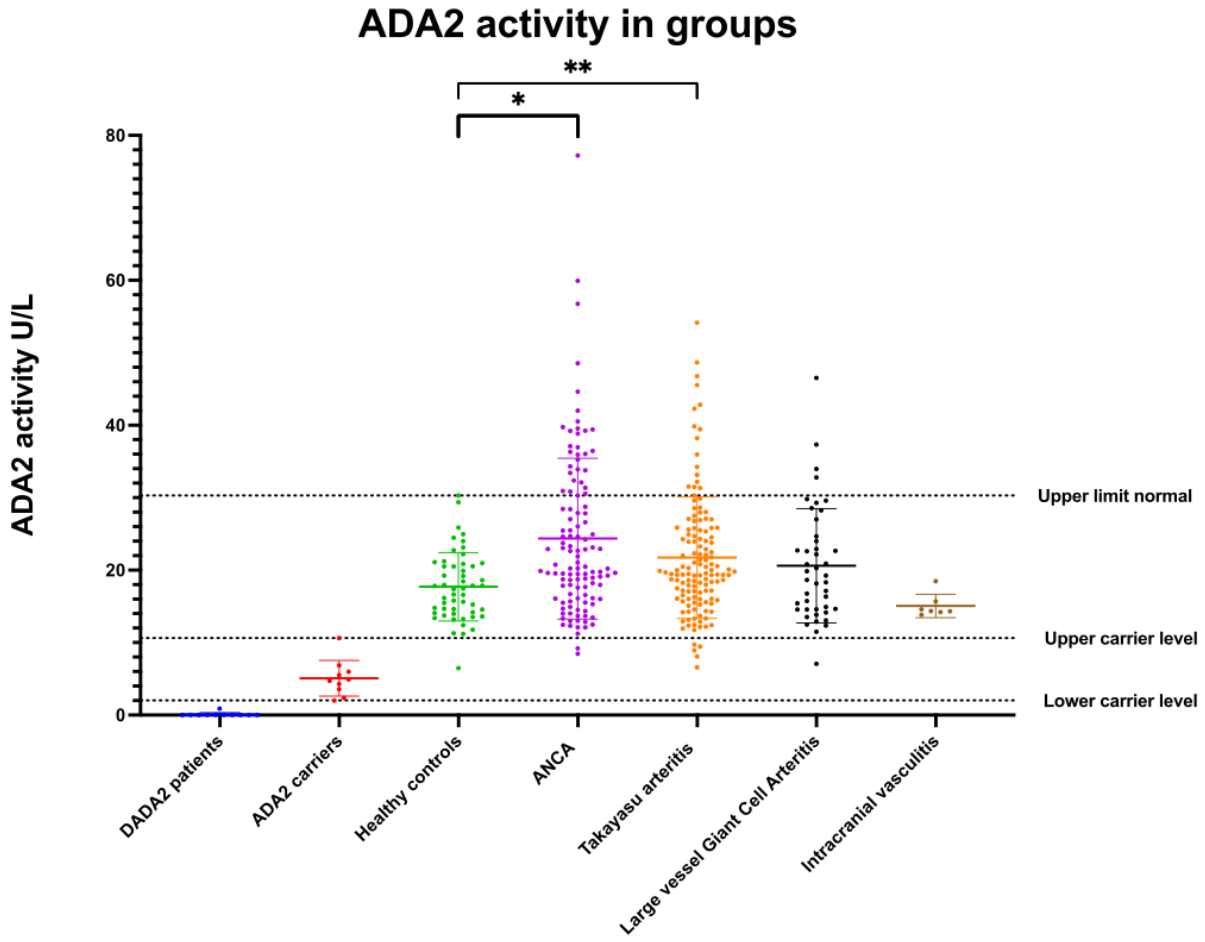
Results: In 302 vasculitis patients tested, none were found to have ADA2 deficiency, while 9 subjects had activity within the carrier range (1 HC (1.9%), 5 TA (3.7%), 1 LV-GCA (2.3%), 2 ANCA (1.7%)). Compared to HC levels (median value 17.43 U/L [14.11 – 20.78]), activity in the TA and ANCA groups were significantly increased (TA 19.68 U/L [6.6 – 54.16], p=0.0113; ANCA 20.62 U/L [8.5 – 77.2], p=0.0002), while LV-GCA and ICV were not significantly different. In 50 cases, activity exceeded the upper limit of normal; 16 TA (11.9%, p=0.0068; 4 active, 2 grumbling, 10 stable), 30 ANCA (25.9%, p<0.0001, 14 active, 16 remission) and 4 LV-GCA (9.1%, p=0.0409). There was no correlation between ADA2 activity and either disease activity score (ITAS and BVAS) or CRP in TA and ANCA patients. Subgroup analysis within the

TA group revealed that ADA2 activity was most prominently elevated in the TA stable group relative to HCs (TA stable 20.54 U/L [8.08 - 48.66], median +17.8%, p= 0.0006), with no significant difference in active or grumbling TA. In ANCA, activity was elevated in both the active and remission groups (active 21.04 U/L [8.48 – 77.22], p= 0.0008, remission 19.88 U/L [12.12 – 47.82], p= 0.0021). Prospective analysis in the TA group demonstrated significant increase in ADA2 activity in remission vs active disease (p=0.024), with activity increasing in 18 (62%) patients achieving remission. No significant change was observed between matched active and remission ANCA samples.

Conclusions: There were no cases of ADA2 deficiency in this cohort. Consistent with other inflammatory conditions, ADA2 activity was elevated in TA and ANCA patients. In TA, increased ADA2 activity was linked to stable disease in both cross-sectional and prospective analyses. In ANCA, ADA2 activity was elevated in both active and remission groups. Future work will aim to understand the mechanism and significance of elevated ADA2 enzymatic activity in vasculitis.

Disclosures: None

Figure 1. ADA2 activity in groups
Upper limit normal - >99th percentile of HC activity; 30.3 U/L. Upper and lower carrier level (2.02 – 10.62 U/L) – determined from 10 patients heterozygous for pathogenic variants in ADA2 *p<0.05 ** p<0.001



225. Fibroblast activation protein is modulated in giant cell arteritis

Shuang Xu[1], William Febry Jiemy[1], Annemieke MH Boots[1], Yannick van Sleen[1], Kornelis SM van der Geest[1], Peter Heeringa[2], Elisabeth Brouwer[1], Maria Sandovici[1]
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Background: Giant cell arteritis (GCA) can present with serious acute complications such as blindness, stroke and aortic aneurysm that are related to both inflammation and remodeling of the vessel wall. GCA frequently overlaps with polymyalgia rheumatica (PMR). The pathogenesis of GCA starts in the adventitia where fibroblasts are the major stromal cell population. Preliminary study [1] reported the migration of adventitial fibroblasts to the intima, contributing to intimal hyperplasia in GCA. Fibroblast activation protein (FAP) is a protease which can be present in a membrane-bound form and a soluble, plasma form. The origin of the plasma FAP is unknown. FAP promotes inflammation and fibrosis in coronary artery disease and rheumatoid arthritis [2-3]. We hypothesized that FAP is involved in GCA vasculopathy due to its pro-inflammatory and pro-fibrotic effect. Objective was to determine FAP plasma levels and FAP protein expression at the site of vascular inflammation in GCA.

Methods: In our prospective cohort of GCA, PMR and healthy elderly (GPS), we measured the plasma FAP levels with ELISA in 62 new-onset, treatment-naïve GCA, 63 new-onset, treatment-naïve PMR patients and 42 age-matched healthy controls (HC). In addition, we measured the plasma FAP levels at follow-up (3-months, 1-year, 1.5-year and treatment-free remission (TFR)). Temporary artery biopsies (TAB) from treatment-naïve GCA patients (n=9) and non-GCA patients (n=9), aorta samples from GCA-related aneurysms (n=9) and atherosclerosis (n=11) were stained for FAP using immunohistochemistry.

Results: Baseline plasma FAP levels were significantly lower in GCA patients than in PMR patients and HC. FAP levels at baseline correlated inversely with C-reactive protein (CRP), interleukin (IL)-6, macrophage-associated protein YKL-40 (Chitinase 3-like 1/CHI3L1) levels and monocyte counts. Plasma FAP levels increased to the level of HC when patients were in treatment-free remission. Increased FAP expression in GCA TAB (adventitia, media, intima) and aorta (media) compared with tissues from non-GCA was documented. FAP was abundantly expressed in fibroblast- and macrophage- rich areas in TAB (figure).

Conclusions: This study describes for the first time the dynamics of circulating FAP levels, in conjunction with an increased expression of FAP in GCA affected arteries. FAP may represent a pathogenic link between the inflammatory and remodeling processes in GCA. As such FAP levels may have utility as a biomarker and should be further investigated as target for therapeutic intervention.

Disclosures: None

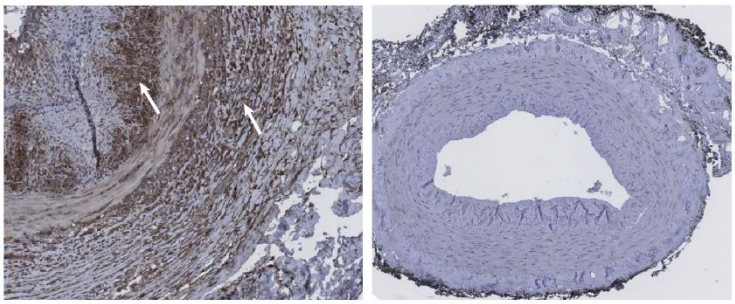

Figure. Immunohistochemical staining of fibroblast activating protein (FAP) in temporal artery. Abundant expression of FAP (brown staining, white arrow) is seen in giant cell arteritis (GCA) as opposed to negative staining in a non-GCA biopsy.

226. Annexin A1 in anti-neutrophil cytoplasmic antibody-mediated vasculitis: a potential biomarker

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Background: In anti-neutrophil cytoplasmic antibody-mediated vasculitis (AAV), uncontrolled systemic inflammation is present with a prominent role for neutrophils. Annexin A1 (AnxA1) is increased by neutrophil-mediated inflammation and plays an important role by reducing neutrophil infiltration and inducing neutrophil apoptosis. Proteomic analysis in AAV patients shows a dysregulation in AnxA1, sustaining a pro-inflammatory state. We hypothesized AnxA1 levels are increased during active AAV reflecting (neutrophil-mediated) inflammation. Furthermore, we hypothesized AnxA1 decreases in response to the dampening effect on inflammation by initiating immunosuppressive therapy. To test these hypotheses, we assessed serum AnxA1 levels in a prospective longitudinal AAV cohort and healthy control patients.

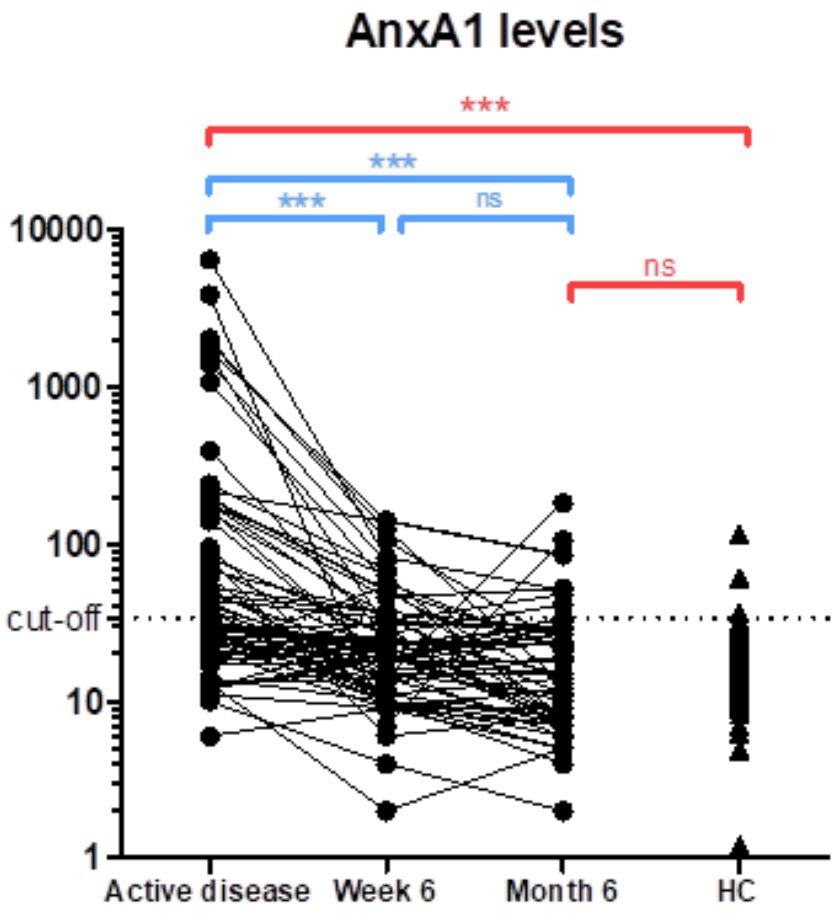
Methods: Patients (*n*=72) were included from the PROMAVAS study, i.e., a prospective longitudinal study including patients presenting with active AAV at Maastricht UMC, between April 2019 and June 2021. Clinical outcome data were obtained from the PROMAVAS clinical database. Longitudinal serum samples were obtained at the time of active disease (*n*=72), and 6 weeks (*n*=61) and 6 months (*n*=61) after initiating therapy. Disease activity was scored using the BVAS. Consenting healthy donors (HC) were recruited to assess normal serum AnxA1 levels. Serum AnxA1 levels, determined by an AnxA1 specific ELISA, are expressed in ng/ml and presented as median [IQR]. Based on the healthy control cohort (*n*=61) the normal range for AnxA1 was set to 0-34 ng/ml.

Results: Seventy-two active AAV patients were included with a mean age of 63 (±13) years and a M:F ratio of 1.8. PR3-, MPO-ANCA or both were detected in 38 (53%), 33 (46%) and 1 (1%), respectively. Renal (*n*=41; 59%) and pulmonary (*n*=33; 47%) involvement were the predominant organs affected. All patients were treated with immunosuppressive therapy (i.e., corticosteroids with either Rituximab [*n*=43; 60%], cyclophosphamide [*n*=16; 22%] or both [*n*=13; 18%]). At 6 months 68 (96%) patients were in remission according to a BVAS of 0. Death occurred in 5 (7%) patients. AAV patients showed higher median levels of AnxA1 compared to HC (38 [24-154] vs. 16 [11-24], respectively, Figure 1, Mann-Whitney U test, $P<0.0001$). At presentation 38 (53%) AAV patients had AnxA1 levels above the cut-off value. This number decreased to 16 (26%) and 10 (16%) at 6 weeks and 6 months, respectively, after initiating therapy. AnxA1 levels at presentation, week 6 and month 6 reduced from 38 [24-154] to 20 [12-35] and 15 [8-30] (ng/ml, Figure 1, Wilcoxon-signed rank, $P<0.001$) respectively. Interestingly, in contrast to active disease, at month 6 AnxA1 levels did not differ from healthy control levels (Figure 1, $P=0.76$). AnxA1 levels did not correlate with CRP. AnxA1 levels did not differ between sex, ANCA specificity, renal or pulmonary involvement.

Conclusions: Serum AnxA1 levels were increased in active AAV patients compared to healthy controls. Furthermore, AnxA1 levels decrease after initiation of immunosuppressive therapy. These results indicate that serum AnxA1 can be helpful in recognizing active AAV and beneficial in assessing treatment response. Further studies are warranted to decipher the role of AnxA1 in dampening inflammation and fibrosis formation in AAV.

Disclosure: none

Figure 1. AnxA1 levels (ng/ml) during active AAV were significantly higher than healthy controls (HC). Levels decreased significantly after initiating immunosuppressive therapy at week 6 and remained low at month 6. At month 6, AAV serum did not differ from HC serum. AnxA1 levels were compared using Mann-Whitney U test (red) and Wilcoxon signed rank test (blue). ns, not significant; *** P<0.0001



227. Urine and Plasma Complement Ba Levels During Flares of Nephritis in Patients with ANCA-Associated Vasculitis

Salem Almaani[1], Huijuan Song[1], Meshora Suthanithra[1], Christopher Toy[1], Anna Levesque[1], Lynn Fussner[1], Alexa Meara[1], Haikady Nagaraja[1], David Cuthbertson[2], Nadir A. Khalidi[3], Curry L. Koening[4], Carol Langford[5], Carol McAlear[6], Larry Moreland[7], Christian Pagnoux[8], Philip Seo[9], Antoine Sreih[6], Kenneth Warrington[10], Paul Monach[11], Peter A. Merkel[6], Brad H. Rovin[1], Daniel J. Birmingham[1]

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Background: The alternative complement pathway has been implicated in the pathogenesis of ANCA-associated vasculitis (AAV). This knowledge has been leveraged therapeutically and incorporated in the management of AAV. However, it is not clear whether activation of complement primarily occurs systemically or in affected organs such as the kidney. This study measured levels of urinary and plasma complement fragment Ba (uBa and pBa respectively) at multiple time points in patients with AAV.

Methods: The complement fragment Ba was measured by ELISA in serial samples of urine (uBa) and plasma (pBa) from 21 AAV patients who developed a renal flare, 19 who developed a non-renal flare, and 20 in long-term remission. Because the timing of visits prior to a flare differed from patient to patient, visit number was used as a time variable, where visit 0 represents a disease flare in the renal flare and non-renal flare groups. uBA levels were corrected for concentration and uBa-to-creatinine ratios (uBa/uCr) were used for analysis. uBa/uCr levels were correlated to markers of disease activity. Changes in Ba levels were modeled using mixed linear effect models. A logistic regression model was fit to predict a renal flare using Ba/Cr ratio at the visit 0 vs. the non-renal flare and long-term remission groups.

Results: Data from 60 patients were used for this analysis; 32 (53%) were male, 56 (93%) were Caucasian, and 34 (74% with antigen-specific testing) had PR3-AAV. uBa levels increased at renal flare ($p<0.001$), but did not increase at non-renal flare ($p=0.956$), and remained stable in long-term remission ($p=0.337$) (Figure 1a). pBa levels were stable over time in all groups (Figure 1b). uBa correlated with renal AAV activity measured as the renal component of the BVAS score ($R^2= 0.33$, $p<0.01$) (Figure 2a), but did not correlate with the overall BVAS score during renal flare ($R^2= 0.13$, $p=0.12$) or non-renal flare ($R^2= 0.10$, $p=0.22$) (Figure 2b,c). The logistic regression model using Ba/Cr ratio to predict a renal flare had an AUC of 0.76. At a Ba/Cr cutoff of 4160 ng/mg, the sensitivity and specificity for detecting a renal flare were 76.2% and 68.4% respectively.

Conclusions: Urine, but not plasma, Ba levels increase at the time of a flare of renal disease in AAV, suggesting intra-renal alternative complement pathway activation. uBa levels increase at the time of a renal flare but remain stable in patients with a non-renal flare or those in remission, suggesting its potential for use as a surveillance biomarker of renal vasculitis.

Disclosures: This work was supported by the Vasculitis Clinical Research Consortium and the Columbus Medical Research Foundation.

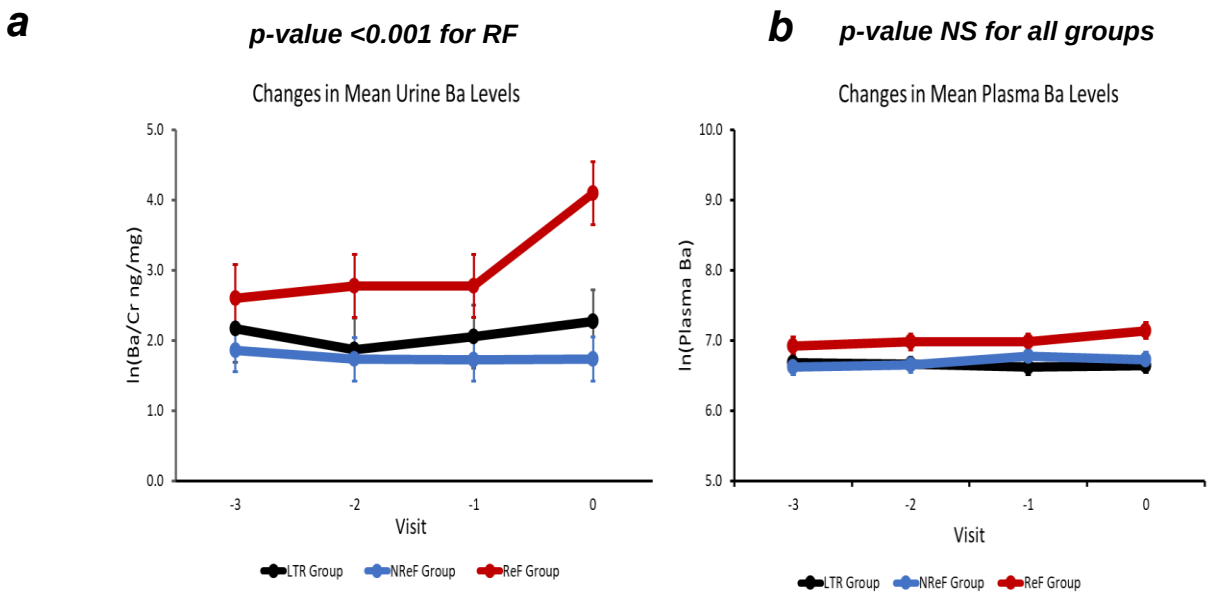

Figure 1. Changes in urine (a) and plasma (b) Ba levels over time. Visit 0 indicates a flare visit in the non-renal flare (NReF) and renal flare (ReF) groups. LTR: long-term remission. NS: not significant. ln: Natural log. Cr: creatinine.

228. Factors Associated with Thrombosis in Behçet Syndrome: A Systematic Review and Meta-Analysis

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Background: Behçet syndrome (BS) is a unique vasculitis that can affect arteries and veins of all sizes. Thrombosis is an important component of vascular involvement in BS. Although several studies were conducted to highlight the mechanism of thromboinflammation in BS, it is still not fully understood. We performed a systematic review and meta-analysis of studies investigating thrombotic, fibrinolytic, and endothelial factors in BS.

Methods: We searched PubMed and EMBASE with the keyword “Behcet*” in four languages (English, German, French and Turkish) from their inception up to April 2020. Titles and/or abstracts of all studies were screened independently by two reviewers (GGO and BY) and conflicts were solved by a third reviewer (GH). Studies comparing BS patients with and without thrombosis and studies comparing BS patients with thrombosis and patients with thrombosis due to other causes were analyzed separately. The pooled odds ratios (OR) with 95%CI were calculated for binary outcomes and standardized mean differences (MD) were calculated for continuous outcomes using RevMan 5.3.

Results: Of 15548 articles, 15052 were excluded due to duplication and inappropriate study design after reviewing titles and abstracts. Full text review of the remaining 388 articles yielded 106 papers meeting our predetermined inclusion criteria. Factors significantly associated with BS thrombosis compared to BS without thrombosis were high frequency of factor V Leiden mutation (15 studies, OR: 2.55, 95% CI 1.66, 3.93), high homocysteine levels (14 studies, MD: 4.27, 95% CI 2.31, 6.22), high protein C levels (5 studies, SMD: 0.80, 95% CI 0.15, 1.45), high VEGF levels (2 studies, SMD: 1.63, 95% CI 0.21, 3.05), high CEC concentrations (2 studies, SMD: 1.00, 95% CI 0.22, 1.77), and high factor 8 levels (4 studies, MD: 17.17, 95% CI 7.79, 26.55). There were no significant differences among the 18 factors assessed in at least 2 studies as shown in the table. Among the other factors assessed in 1 study each, ADMA level (MD: 0.16, 95% CI 0.08, 0.24), anti-C1q level (MD: 9.11, 95% CI 0.51, 17.71), thrombin level (MD:35.90, 95% CI 12.40, 59.40) and TAFI activity (MD:28, 95% CI 4.12, 51.88) were significantly high in patients with BS thrombosis compared to BS without thrombosis. Factors that were associated with BS thrombosis compared to thrombosis due to other causes including JAK-2 mutation, circulating endothelial cells, activated protein C resistance, tPA, and PAI were assessed in 1 study each. Among these, tPA levels (MD: -6.00, 95% CI -10.99, -1.01), APCR (OR: 0.09, 95% CI 0.01, 0.73) and JAK-2 mutations (OR: 0.01, 95% CI 0.00, 0.06) were significantly less in patients with BS thrombosis compared to patients with thrombosis due to other causes.

Conclusions: Several factors were identified that may potentially be associated with thrombosis in BS. However, the cut-offs used for defining the normal level for these factors, time of blood collection (during acute or chronic stage of thrombosis, use of anticoagulants) and the type of thrombosis (arterial, venous, or cerebral sinus) were not uniform across the studies. Studies investigating these factors together, in a large number of patients, and together with appropriate controls are needed to confirm these results.

Disclosures: SNE has received honorariums for presentations from UCB Pharma, Roche, Pfizer, and Merck Sharp Dohme. VH has received grant/research support from Celgene and has served as a speaker for AbbVie, Celgene, Novartis, and UCB Pharma. GH has received grant/research support from Celgene and has served as a speaker for AbbVie, Celgene, Novartis, and UCB Pharma.

Table. Factors that were assessed in the pathogenesis of BS thrombosis in at least 2 studies

Prothrombotic Factor	Number of studies	Number of Behçet's patients		MD/OR (95% CI)
		With thrombosis	Without thrombosis	
Factors with significant results				
Factor V Leiden mutation	15	309	720	OR: 2.55 (1.66 to 3.93)
VEGF	2	27	43	SMD: 1.63 (0.21 to 3.05)
Homocysteine levels (µmol/L)	14	325	536	MD: 4.27 (2.31 to 6.22)
FVIII levels (IU/dL)	4	50	110	MD: 17.17 (7.79 to 6.55)
Protein C level	5	93	260	SMD: 0.80 (0.15 to 1.45)
CEC	2	27	45	SMD: 1.00 (0.22 to 1.77)
Factors with non-significant results				
Antithrombin 3 levels (IU/dL)	3	59	159	MD: 0.54 (-4.56 to 5.63)
Prothrombin mutation	6	125	258	OR: 0.78 (0.14 to 4.27)
Mean platelet volume	6	132	570	SMD: 0.51 (-0.16 to 1.18)
Lupus anticoagulant	4	62	145	OR: 3.33 (0.86 to 12.86)
MTHFR (C677T) mutation	4	78	177	OR: 1.09 (0.53 to 2.21)
MTHFR (A1298C) mutation	2	23	48	OR:1.87 (0.60 to 5.89)
Thrombomodulin	5	92	264	SMD: 0.24 (-0.24 to 0.77)
Anticardiolipin antibodies	4	79	137	OR: 1.88 (0.85 to 4.15)
Protein S level	5	93	260	SMD: 0.15 (-0.38 to 0.68)
Prothrombin fragment 1,2	3	64	156	SMD: 0.41 (-0.12 to 0.95)
Annexin V antibodies	2	53	65	SMD: 0.14 (-0.23 to 0.50)
aTAFI	2	73	121	SMD: -12.40 (-36.4 to 11.6)
Factor VIIa level	2	20	56	SMD: 0.13 (-0.39 to 0.65)
PAI-1 antigen	2	48	86	SMD: 0.11 (-0.47 to 0.70)
tPA	2	48	86	SMD: -0.53 (-1.32 to 0.25)
EPC	2	27	45	SMD: 0.20 (-1.02 to 1.43)
Activated protein C resistance (as ratio)	2	25	18	MD: -0.30 (-0.61 to 0.01)
Activated protein C resistance (yes/no)	3	72	131	OR: 2.32 (0.35 to 15.18)
vWF	3	54	147	SMD: 0.61 (-0.17 to 1.38)

aTAFI: activated thrombin activatable fibrinolysis inhibitor; CEC: circulating endothelial cells; EPC: endothelial progenitor cells; PAI: plasminogen activator inhibitor; tPA: tissue plasminogen activator; vWF: von Willebrand factor; VEGF: vascular endothelial growth factor; MTHFR: methylenetetrahydrofolate reductase; MD: mean difference; OR: odds ratio; SMD: standardized mean difference

229. Profiling the autoantibody repertoire in ANCA associated vasculitis with multiplex antigen arrays to predict relapse

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Background: The difficulty in predicting relapse, and selection of patients in whom immunosuppression may be stopped early, is an important unmet need in management of patients with ANCA vasculitis. Our goal was to characterize the autoantibody repertoires in long-term-remission-off-therapy (LTROT) patients and patients experiencing flares.

Methods: Pooled plasma samples provided by the Rare Kidney Disease (RKD) biobank were tested on a planar array including 42000 antigens representing 19000 unique proteins. Based on the results of this proteome-wide screening, combined with literature review, 346 protein fragments (based on proteins generated in the Human Protein Atlas project) were selected and immobilized on magnetic beads to generate a targeted in-house bead-array. Plasma and serum samples from 43 individuals with AAV in remission were studied using this bespoke array to identify novel autoantibodies capable of distinguishing those who remained in remission from those suffered a relapsing course.

Results: The total number of antigen reactivity were higher in anti-MPO patients, and unaffected by sex or age. Individuals from the relapse cohort showed higher reactivity towards protein fragments representing KCNK14, BMERB1, METTL6 and ATF3 (p-value<0.05).

Conclusions: We have identified several putative candidate autoantibodies that classify those patients with vasculitis at high risk of long-term relapse. These results will be validated in a large independent cohort. .

Disclosures: This project is part of the HEalth data LInkage for ClinicAL benefit (HELICAL) program.

230. NETs and terminal pathway factors as potential biomarkers for complement overactivation assessment in ANCA-associated vasculitis

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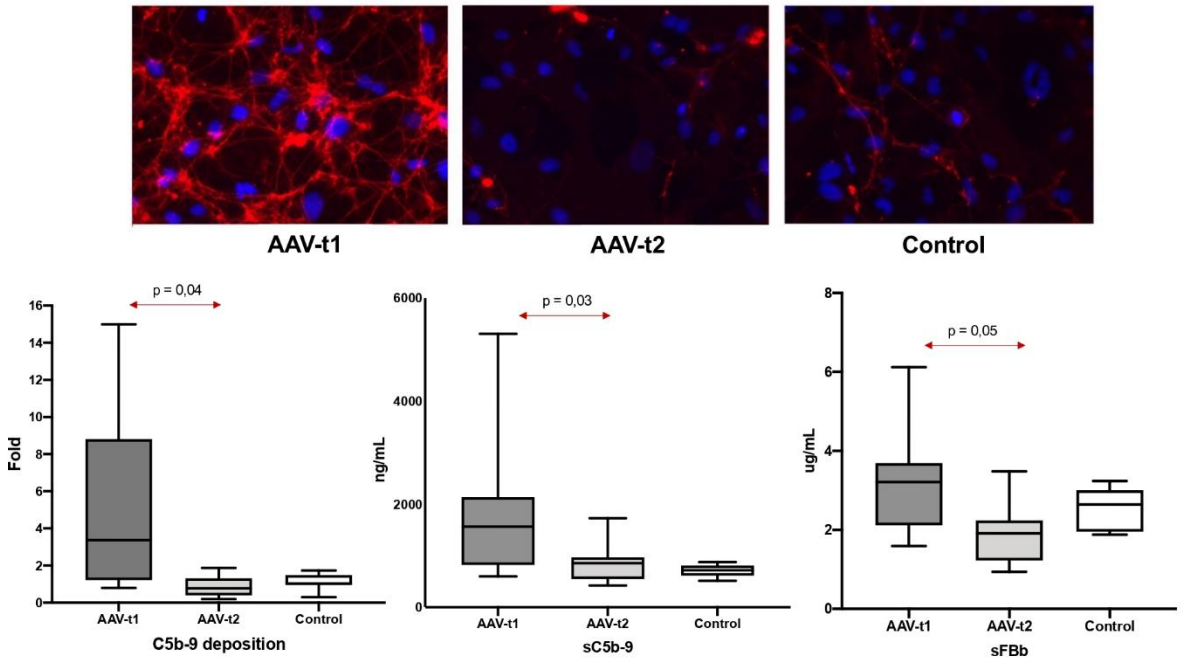
Background: Clinical, *in vitro*, and animal model-derived evidence has demonstrated a critical involvement of the alternative complement pathway (aCP) in the pathogenesis of ANCA-associated vasculitis (AAV). In this regard, neutrophil extracellular traps (NETs) have been suggested to be a key element between ANCA-induced neutrophil activation and aCP. However, the role of the terminal complement pathway (tCP) is less well studied.

Methods: A prospective, observational, multicenter study analyzing first episodes and relapses of patients with AAV, with a minimum follow-up of 6 months, was performed. Blood samples were collected at diagnosis (AAV-t1) and at remission (AAV-t2). Control population consisted of age and sex-matched individuals. Complement activation was assessed by analyzing the complement membrane attack complex (C5b-9) deposition on cultured endothelial cells (HMEC-1), by immunofluorescence, after exposing them to activated plasma (a-plasma: obtained by mixing patient's citrated plasma with healthy subjects' sera pool, 1:1). C5b-9 deposits induced by patients' a-plasma were calculated as percentage of labeled area with respect to the total area analyzed. Results from patient and control samples were expressed as fold increase (mean±SEM) vs. those obtained with the pool of a-plasma from healthy subjects. Plasma levels of tCP and aCP soluble factors, such as sC5b-9 and sFBb (respectively), were also measured (mean±SEM). Circulating NETs were indirectly measured by quantifying circulant dsDNA plasmatic concentration (mean±SEM) as a NET surrogate.

Results: The present results were obtained with samples from 13 AAV-MPO patients who achieved complete remission (38% men, age 63±14 years) and 10 controls (45% men, age 66±6 years). At AAV-t1, there was a statistically significant increase ($p<0.05$) of C5b-9 deposition on HMEC-1 in response to patients' a-plasma (fold increase of 5.3±1.3) compared to control samples (fold increase of 1.2±0.2). Samples obtained at AAV-t2 induced less C5b-9 deposition than at AAV-t1 (fold increase of 0.9±0.2; $p<0.05$), with values similar to controls. Regarding soluble factors, levels of both sC5b-9 and sFBb were significantly increased in AAV-t1 (1882±418 ng/mL and 3.2±0.4 µg/mL, respectively; $p<0.05$) vs. AAV-t2 (852±104 ng/mL and 1.9±0.2 µg/mL, respectively; $p<0.05$). At AAV-t2, levels were similar to controls (708±42 ng/mL for sC5b-9, and 2.4±0.2 µg/mL for sFBb). Circulating NETs were also increased in AAV-t1 (22.2±3.5 µg/mL) compared to both AAV-t2 and controls (13.6±1.1 µg/mL and 13.7±0.3 µg/mL, respectively; $p<0.05$). Moreover, NETs in AAV-t1 presented a significant correlation with sFBb levels, both in AAV-t1 ($r=0,709$; $p<0.05$) and in AAV-t2 ($r=0,585$; $p<0.05$).

Conclusions: There is a relationship between NETs, AAV activity and sFBb, which supports the role of NETs and cAP in AAV pathogenesis. Moreover, differences in C5b-9 deposition between the two stages of the disease suggest that tCP may be dysregulated in AAV. Further characterization of this dysregulation may lead to new diagnostic or disease activity biomarkers, as well as new therapeutic options for the management of patients with AAV.

Disclosures: Dr. Cid reports consulting fees from GSK, Abbvie and Janssen, receiving a grant from Kiniksa, educational activities fees from GSK, Roche and Vifor, and meeting attendance support from Roche and Kiniksa. Dr. Espígol-Frigolé reports consulting fees from Janssen, and meeting attendance support from Roche and Boehringer. The remaining authors have nothing to disclose.



231. The presence of anti-phosphatidylserine/prothrombin complex antibodies in cutaneous vasculitis: possible involvement in the pathogenesis

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Background: We assessed the IgG and IgM prevalence of anti-phosphatidylserine/prothrombin complex (aPS/PT) antibodies (Abs) in patients with vasculitis using a novel commercial ELISA kit. To examine whether aPS/PT Abs were involved in the pathogenesis of cutaneous vasculitis, inbred wild-type rats were intravenously administered with a rat IgM class aPS/PT monoclonal Ab established previously or with rat immunoglobulins as controls. Then, the development of cutaneous vasculitis was determined by histopathological analyses.

Methods: 1) Rats (n=4) were given a subcutaneous injection of 0, 2.5, 25, and 250 µg/ml cell-free histones on the back (300 µl/site). Two hours later, the skin was resected for immunostaining using a rat IgM class aPS/PT monoclonal Ab. Formalin-fixed, paraffin-embedded skin tissues were cut into 4 µm sections, and the sections were allowed to react with 1 µg/ml aPS/PT monoclonal Ab (rat IgM) followed by 2 µg/ml Alexa Fluor 594-conjugated goat anti-rat IgM Ab. 2) Rats (n=19) were given a subcutaneous injection of 250 µg/ml cell-free histones and then divided into four groups: Group A with an intravenous administration of 1.25 µg/g weight of the rat IgM class aPS/PT monoclonal Ab 2 hours after priming by histones (n=5; histone isc with aPS/PT iv), Group B with rat IgM (n=4; histone isc with IgM iv), Group C with rat IgG (n=5; histone isc with IgG iv), and Group D without immunoglobulin administration (n=5; histone isc). One week later, all rats were euthanized for histopathological analyses.

Results: Serum IgM aPS/PT Ab levels were elevated in patients with systemic vasculitis with skin involvement and cutaneous arteritis compared to those in patients with systemic vasculitis without skin involvement and healthy controls. To express PS on the surface of vascular endothelium, these rats were given a subcutaneous injection of cell-free histones in advance. There was no significant difference in the serum levels of IgG aPS/PT Abs between the patients and healthy controls. Correspondingly, inbred wild-type rats intravenously administered with the aPS/PT monoclonal IgM Ab after appropriate priming-subcutaneous histone injection-developed cutaneous vasculitis. Some rats given rat IgM instead of the aPS/PT monoclonal Ab also developed cutaneous vasculitis, whereas vasculitis did not occur in rats given IgG or only priming by histones.

Conclusions: We suggested that IgM aPS/PT Abs could be involved in the pathogenesis of cutaneous vasculitis based on these findings.

Disclosures: The authors declare no conflicts of interest.

232. Complement Activation during Remission in ANCA-Associated Vasculitis

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Background: Experimental and clinical observations have shown that the complement system is crucial for the pathogenesis of ANCA-associated vasculitis (AAV), and the development of new drugs has put emphasis on the complement inhibition. Previous studies have shown that complement activation is common not only during relapse but also during remission, but the origin and importance of this is largely unknown. The aim with this study is to investigate if complement activation during stable remission is an indicator of upcoming relapses and to

study clinical correlates to the activation through the classical, alternative, or terminal pathways.

Methods: During 2015-2018, there were selected 206 plasma samples from 81 patients with GPA or MPA and preserved in -80°C. BVAS at the date of sampling was used to categorize the samples as remission samples, and those were further divided into samples with and without subsequent relapses. C4d is a sub-product of C4, that is a component of the classical and lectin pathways. C3bBbP is a C3 convertase from the alternative pathway, and sTCC (soluble terminal complement complex) is the final component of general complement activation. Sandwich ELISA using monoclonal antibodies specific for those complement activation products were analysed in all samples.

Results: The levels of C4d, C3bBbP and TCC were higher in many, but not all patients with AAV during remission, compared to the levels from healthy controls. TCC was correlated with both C4d and C3BbP, but there was no correlation in between C4d and C3bBbP. While 44 patients had at least one relapse, 37 of the patients had no relapses during the follow-up. There were no significant differences in the levels of complement activation products between samples taken from patients that had at least one subsequent relapse and from patients that had no relapses until the end of the follow-up, which was 3-5 years. Similarly, patients with multiple relapses did not have higher levels of the complement activation products compared to those who had one or those with no relapses. On the other hand, there was a positive correlation between levels of TCC and creatinine, but there was no correlation in between C4d and C3bBbP with creatinine levels. Patients with no or low dose of corticosteroids (<5 mg/day) had higher levels of C4d, which indicates that corticosteroids supress the activation through the classical pathway. There was no correlation in between complement levels and other immunosuppressive drugs.

Conclusions: Complement activation products cannot be used as biomarkers for predicting relapse in AAV, based on the results from this study. Higher levels of TCC are correlated with low GFR, suggesting that organ damage or damage to the vasculature can be reflected in complement activation products. Corticosteroids seem to suppress activation of the classical pathway in AAV, which might be an important mode of action for these agents to prevent relapse.

Disclosures: Anna Blom is the inventor in a patent application that comprises claims for using C4d as a biomarker. The other authors declare no conflicts of interest.

233. Residual Platelets in stored serum and plasma samples Release Small Extracellular Vesicles Ex-vivo

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Background: Small extracellular vesicles (sEV) are membrane bound particles released from cells that act like messengers between them. They are found in biological liquid including blood, and are particularly abundant in systemic disease such as ANCA-associated vasculitis (AAV). SEVs are composed of protein, lipid and RNA cargo and play a crucial role in cell-cell communication. Their composition varies with cell activation or injury, which potentially could be used as a novel and powerful tool to monitor disease activity and predicting relapse in AAV. Isolating pure sEV from human blood is a challenge due to co-purification of plasma proteins and lipoproteins, but we have optimised protocol for doing this (Malys et al). Here we used this method to enable us to characterise proteins expressed on the surface of sEV in human blood samples with the objective of identifying their cellular origin.

Methods: Serum, plasma, and platelet poor plasma (PPP) samples were prepared from blood taken from individual donors. These were then used to purify sEV by DUC, either immediately or after storage for 14 days at either 4°C or - 80°C. Concentration and size were Any measured by nanoparticle tracking analysis (NTA) while vesicle morphology, size and CD9 positivity were evaluated by transmission electron microscopy (TEM). SEV were further analysed by western blotting and MACSPlex – bead-based antigen binding array – in order to profile their protein expression.

Results: There was no difference in the number or diameter of sEV isolated from fresh serum, plasma, and PPP, or from samples stored at -80°C. By contrast, MACSPlex analysis showed that molecules associated with platelets (including CD9, CD63, CD41b, CD42a and P-selectin) were more abundant in sEV preparations purified from fresh serum than fresh plasma, platelet marker abundance also increased in sEV from stored plasma; these changes were greatly attenuated in sEV from PPP. Immuno-EM images from serum and stored plasma samples showed increased CD9 expression. Together, these data suggest that a substantial proportion of sEV detected in serum and stored plasma samples are generated ex-vivo platelets. We confirmed this in experiments in which we deliberately activated platelets by addition of Ca++. TEM from these experiments also identified vesicles with diameters <70nm similar in size to alpha granules released from activated platelets, and below the detection limit of NTA analysis.

Conclusions: We have shown that serum and stored plasma contain similar populations of sEV, substantial portion of which were not present in the circulation but were released from platelets ex-vivo; this phenomenon can be attenuated by purifying sEV from fresh plasma or from PPP. Our findings have obvious implications for the use of sEV as biomarkers.

Disclosures: The authors declare no conflict of interest. This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 813545.

234. Soluble urokinase plasminogen activator receptor is predictive of kidney disease in ANCA-associated vasculitis

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Background: Soluble urokinase plasminogen activator receptor (suPAR) is an emerging biomarker of inflammation and kidney disease. Recent studies with small sample sizes have found elevated suPAR in ANCA-associated vasculitis (AAV), an autoimmune disease featuring both inflammation and kidney disease. suPAR has been shown to correlate with biomarkers of inflammation and renal function in these studies and has been associated with AAV disease activity. However, no study has associated suPAR with the presence and severity of kidney disease in AAV.

Methods: In our study, we enrolled active ANCA-positive patients at diagnosis (n = 229), healthy controls (n = 36) and other kidney disease controls (n = 26). We measured plasma/serum suPAR concentration and assessed whether the level was different in those with AAV with glomerulonephritis (GN) compared to those with only extra-renal vasculitis. We distinguished "minimal" kidney disease (n = 71), with no evidence of GN, from "moderate" (n = 41), with evidence of GN but normal excretory kidney function and "severe" kidney disease (n = 116), which was associated with impaired kidney function.

Results: Median serum creatinine 89 µmol/L, 209 µmol/L and 374 µmol/L in minimal, moderate, and severe kidney disease cohorts. Median BVAS was 16, 15 and 16 and median CRP was 32.5 mg/dL, 23 mg/dL and 38.5 mg/dL, respectively. A plasma/serum suPAR level of 4 ng/mL reflected the 90th centile of healthy control values; 38% of patients with minimal kidney disease had a level higher than this, compared to 62% and 92% of those with moderate and severe kidney disease respectively (Figure 1A). suPAR concentration was positively associated with BVAS, CRP and serum creatinine level. Urine soluble CD163 was moderately correlated with plasma suPAR level (Figure 1B). Moreover, plasma suPAR concentrations were reduced in patients in clinical remission.

Conclusions: Approximately ⅓ of patients with AAV without GN had elevated suPAR concentrations, reflecting the systemic inflammatory state. In those with GN but normal kidney function, approximately ⅔ had an elevated concentration, potentially indicating an association between suPAR release and the pathological development of GN. Most patients with severe

kidney disease had an elevated suPAR level, likely reflecting the known accumulation of this molecule with reduced glomerular filtration rate.

Disclosures: None

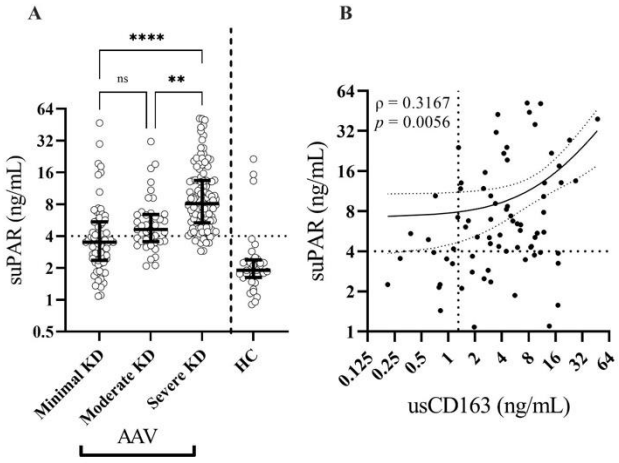

Figure 1. Plasma/serum suPAR concentrations are elevated in AAV patients with kidney disease and correlate with urinary soluble CD163.

(A–B) AAV patient and healthy control (HC) plasma suPAR concentrations were measured by ELISA and incorporated with existing clinical data.

(A) Plasma suPAR concentrations by severity of kidney disease (KD) in AAV patients and healthy controls. Horizontal bars represent median values and error bars depict interquartile range. Statistical tests are Kruskal-Wallis test with Dunn's multiple comparisons tests as depicted. ** $p < 0.01$, **** $p < 0.0001$.

(B) AAV patient plasma suPAR concentrations for versus urinary soluble CD163. Solid line represents linear regression and dashed lines depict 95% confidence bands. Correlations between the two variables was calculated using Spearman correlation (ρ) which generated an associated *p* value

235. Protein profiling to identify biomarkers for disease activity in ANCA-associated vasculitis

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Background: To differentiate between a relapse with increased inflammatory activity and lasting effects of permanent organ damage caused by previous inflammation is a common difficulty in the follow-up of patients with ANCA-associated vasculitis (AAV). Few clinical or molecular biomarkers have been identified and validated to differentiate between these two states.In order to improve clinical diagnostics of patients with AAV, we aimed to identify reliable and easily measurable protein biomarkers of active inflammation in PR3- and MPO-ANCA positive (+) AAV.

Methods: Plasma samples were collected from patients with AAV with active inflammation and no/ minimal ongoing immunosuppression (n = 69), from patients with AAV in remission (n = 45; Birmingham vasculitis activity score = 0, under treatment), disease controls with active

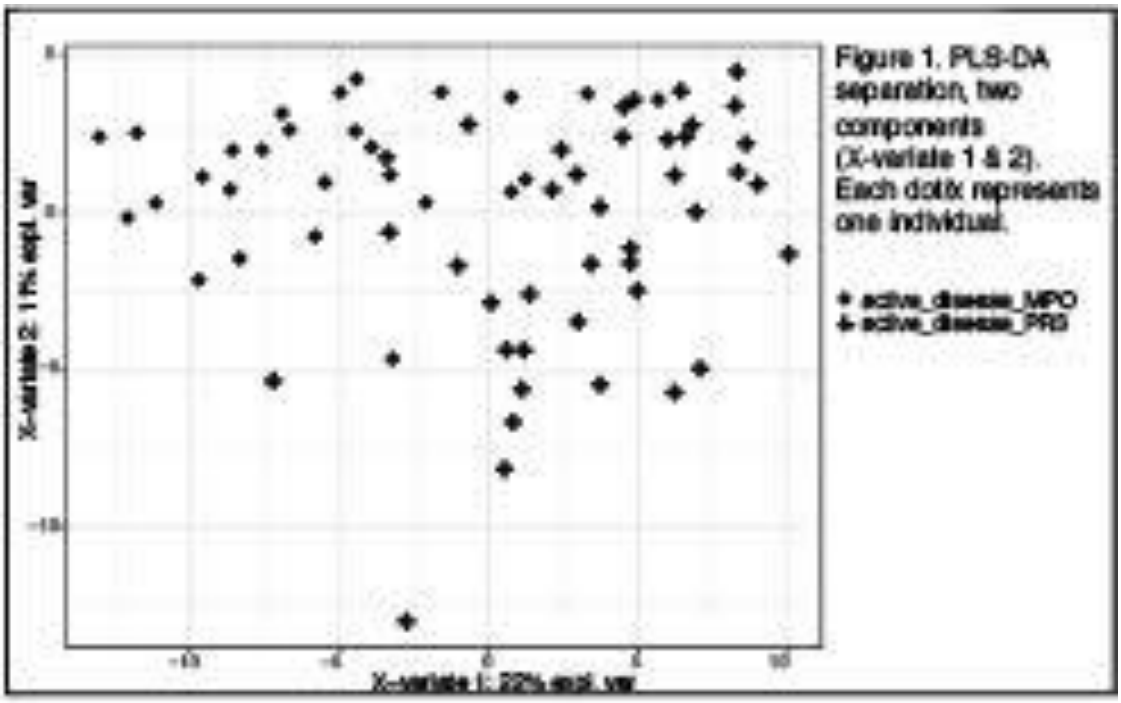
inflammation in SLE (n= 15) and RA (n = 31) and healthy controls (n = 138) at six Swedish rheumatological and/or nephrological centers. All AAV patients were classified into granulomatosis with polyangiitis or microscopic polyangiitis according to the European Medicines Agency algorithm. Data concerning age at inclusion, presence of ANCA and creatinine levels were collected from medical records. Samples were analyzed for the relative levels of 181 proteins associated with inflammation and/or cardiovascular disease, using proximity extension assay (OLINK protein panels). Differential protein expression between groups was analyzed using ANOVA, with age and glomerular filtration rate (CKD-EPI) as covariates and Tukey adjusted P value threshold, and partial least square discriminant analysis (PLS-DA).

Results: In univariate analyses, sets of proteins with levels significantly differentiating from those of healthy controls, were identified for patients with active PR3- and MPO-ANCA+ AAV, respectively. Patients with active PR3/MPO-ANCA+ AAV, SLE and RA showed distinct protein profiles in comparison with healthy controls, and in between the different patient groups. Importantly, the protein profiles differed between PR3- and MPO-ANCA+ patients. Next, protein levels were compared between AAV patients with active disease and patients in remission, divided according to ANCA, revealing significant differences in proteins levels, partially overlapping differences identified in comparison with healthy controls. Comparison between patients with active PR3-ANCA+ AAV and MPO-ANCA+ AAV identified 11 proteins with significantly different levels. PLS-DA multivariate analyses confirmed key proteins within the protein sets that separated the groups, including separation between PR3- and MPO-ANCA+ AAV (Figure 1).

Conclusions: We conclude that altered plasma protein expression in patients with active inflammatory AAV distinguish these individuals from patients in remission, patients with other autoimmune diseases and healthy controls and that analysis of selected proteins may facilitate clinical evaluation of patients' disease state. Differential protein profiles between PR3- and MPO-ANCA+ AAV patients confirm previous indications of different pathophysiology behind these subgroups.

Disclosures: None.

Figure 1.



236. Anti-GBM Epitope specificity at rebound and renal outcome in GOODIDES 1.0

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Background: Anti-glomerular basement membrane (GBM) disease is a small-vessel vasculitis affecting glomerular and/or alveolar capillaries where autoantibodies are deposited along the basement membrane. Renal function at diagnosis and percentage of crescents in non-sclerotic glomeruli are established prognostic factors, but there are reports that autoantibody levels at diagnosis also matters. However, very little is known about autoantibodies produced after start of treatment. The autoantibodies are directed towards the NC1 domain on the α3-chain of collagen IV (NC1(α3)IV) where 2 major epitopes have been identified, denoted Ea and Eb, but their relative contribution to the pathogenesis is unclear. IdeS is a streptococcal enzyme specifically cleaving human IgGs within minutes, and it was used in the GOODIDES-01 trial. The aim of this study was to elucidate the role of rebound of autoantibodies and the relative contribution of autoantibodies with different epitope specificity.

Methods: The GOODIDES-01 trial recruited 15 patients in 5 European countries, all received a single dose of IdeS on top of standard treatment. Patients were followed prospectively for 6 months. In sera, reactivity towards the entire NC1(α3)IV (denoted α3) as well as each of the epitopes Ea and Eb were measured using ELISA. Results are presented in optical density (OD). Descriptive statistics, group comparisons using Mann-Whitney multiple ranks test or a

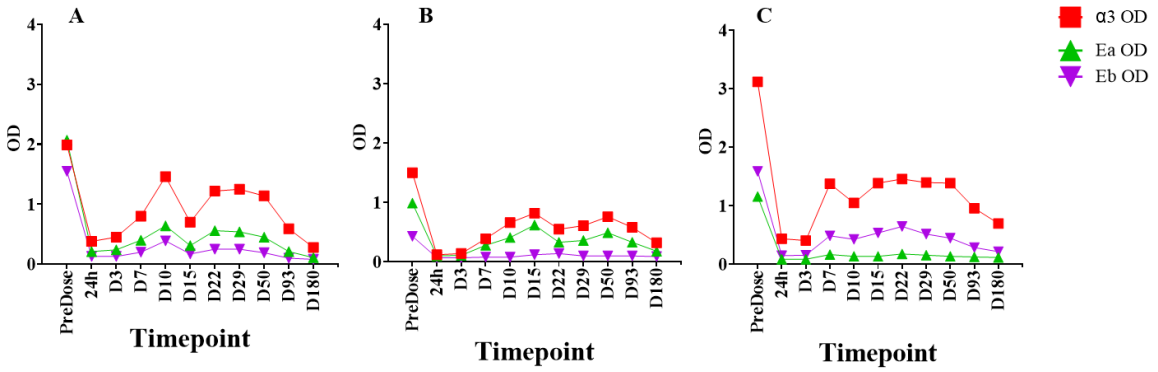
mixed model for analysis of variance with Hólm-Sídak method for correction and graphs were generated using GraphPad Prism version 9.0.

Results: In 4 patients autoantibodies did not rebound, they all displayed renal survival at 6 months. In 4 patients autoantibodies against Ea and Eb were of similar proportion at rebound, 2 of them were still dialysis dependent at 6 months. In 5 patients autoantibodies against the Ea epitope dominated at rebound, 1 of them were dialysis dependent at 6 months. In 2 patients the rebound was dominated by autoantibodies against the Eb epitope, both of them were dialysis dependent at 6 months.

Conclusions: Rebound of autoantibodies was in this study associated with adverse prognosis. Patients with more reactivity toward the Eb epitope at rebound were more often dialysis dependent at 6 months compared to patients with reactivity towards only Ea. This could indicate that autoantibodies towards the Eb epitope are more pathogenic and could be a potential early marker of a less favorable renal prognosis.

Disclosures: Mårten Segelmark has received consultancy fees and research funding from Hansa Pharma.

Figure 1. A-C shows 3 different anti-GBM epitope specificity patterns at rebound in 3 patients from the GOODIDES 1.0 trial.



237. Biomarker and clinical data linkage to determine the minimal mRNA set for vasculitis diagnosis

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Background: Vasculitis is a heterogeneous group of diseases that affect blood vessels of different sizes. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) had an estimated prevalence of 200–400 cases per million people. Symptoms of active disease and flares are difficult to distinguish from permanent damage produced by previous episodes. The imperfect sensitivity of current diagnostic standards highlights the needs for new biomarkers for monitoring disease activity, prediction of flare occurrence, distinguishing the drug-induced and drug-free remission states. Objective: Discriminate the healthy population from patients with active vasculitis using BIOPRED targeted mRNA profiling of circulating immune cells. This targeted sequencing tool allows the precise quantification of 2155 mRNA targets associated with auto-, immune and inflammatory pathways with excellent analytical performance thanks to the elimination of the RNA extraction step.

Methods: Whole blood samples collected in Paxgene® (QIAGEN, Germany) RNA tubes from patients with vasculitis, other diseases and heathy subjects were processed on the HTG EdgeSeq platform using the BIOPRED panel. Clinical, laboratory and BIOPRED data from 118 patients with AAV were compared with data from other cohorts comprising 828 patients suffering from various inflammatory-autoimmune disorders, and healthy volunteers. Differentially expressed mRNAs were screened in three subgroups, and Vasculitis signatures were identified using different multivariate approaches. The area under the receiver operating characteristic (ROC) curves (AUC) and associated confusion matrix were used as a summary of overall marker performance. Clinical covariates included creatinine level, medication exposure anti-MPO/PR3 antibody status.

Results: A population characteristics description was performed considering a timeline constructed based on AAV active and remission status. Different variables were determined based on the input data to make an integrated analysis obtaining the identification of biomarkers for the diagnosis of AAV. An algorithm was developed linking the laboratory values, panel of mRNA biomarkers and clinical data to predict performance of their different combinations to be used as a diagnosis of vasculitis. Finally, functional enrichment of selected mRNAs was conducted to explore the potential biological pathways of the final mRNA set.

Conclusions: Integrative analysis of patient data with mRNA-based blood profiling using machine learning tools contribute to the characterization of vasculitis patients and improved definition of clinical remission in patients with AAV. Further studies are needed to validate and improve our precision medicine tool as a predictor of vasculitis relapse risk based on the BIOPRED mRNA candidates.

Disclosures: None

238. Disease activity and relapse tendency in AAV are reflected by neutrophil and intermediate monocyte frequencies

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Background: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of severe autoimmune conditions involving inflammation of the small-sized blood vessels and includes granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). In this study we investigate the relation between different granulocyte and monocyte subtypes and tendency to relapse in AAV patients.

Methods: Peripheral blood from 105 GPA and MPA patients were collected between year 2011 and 2020 and compared to 126 healthy blood donors (HBD). Circulating eosinophils, basophils, neutrophils and monocytes were analyzed using immuno-phenotyping by multicolor flow cytometry. Monocytes were subdivided into classical ($CD14^{++}$ $CD16^{-}$), non-classical ($CD14^{+}$ $CD16^{+}$) and intermediate ($CD14^{++}$ $CD16^{+}$). Neutrophils were subdivided into $CD16^{++}$ or $CD16^{+}$ as well as $CD177^{+}$ or $CD177^{-}$. Clinical and laboratory data were collected for all patients, including disease activity defined by Birmingham Vasculitis Activity Score 3 (BVAS3), tendency to relapse information and current treatment.

Results: AAV patients have decreased frequency of eosinophils *(p=0,014)*, increased frequency of $CD16^{+}$ *(p=0,0042),* $CD16^{++}$ *(p<0,0001)* and $CD177^{+}$ *(p<0,0001*) neutrophils and $CD14^{++}$ $CD16^{+}$monocytes *(p<0,0001)* compared to HBD*.* Paired data from 23 patients showed lower frequency of $CD14^{++}CD16^{+}$ monocytes and higher concentration (10^{9} /L) of $CD16^{++}$ neutrophils during active disease. AAV patients with tendency to relapse (Ttr) had higher frequency of $CD16^{++}$ and $CD177^{+}$ neutrophils (*p=0,017 and p=0,028, respectively*) compared to non-relapsing AAV patients. Sub-analysis of patients based on diagnosis, showed that different subtypes of neutrophils were increased in GPA patients with Ttr whereas $CD14^{++}CD16^{+}$ monocytes were decreased in MPA patients with Ttr. AAV patients treated with Rituximab during the past twelve months had higher $CD14^{++}CD16^{+}$ (*p=0,027)* and $CD14^{++}CD16^{-}$ *(p=0,026)* monocytes subpopulations.

Conclusions: We detect a skewing of different granulocyte as well as monocyte subpopulations in patients with AAV that seems to be associated with disease activity and tendency to relapse. Moreover, patients on rituximab treatment showed increased frequency of classical and intermediate monocytes. These findings might be used as biomarkers and for relapse prediction.

Disclosures: None

239. Von Willebrand Factor Antigen as disease activity marker in Pediatric Antineutrophil Cytoplasmic Antibody-associated vasculitis

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Background: Von Willebrand Factor (VWF) antigen is released from activated endothelial cells and platelets. It plays a role in vascular inflammation and thrombosis, both important in the pathogenesis of Antineutrophil Cytoplasmic Antibody-associated vasculitis (AAV). Previous work found that VWF correlates with disease activity in childhood-onset primary CNS vasculitis[1]. We sought to determine the relationship between VWF and disease activity over time in children with AAV.

Methods: This is a retrospective cohort study including children diagnosed with granulomatosis with polyangiitis and microscopic polyangiitis according to European league against rheumatism (EULAR)/ Paediatric Rheumatology International Trials Organisation (PRINTO)/ Paediatric Rheumatology European Society (PReS) classification criteria for childhood vasculitis or the Chapel Hill Consensus Conference (CHCC) disease definitions at The Hospital for Sick Children, Toronto, between 2006 and 2019. The primary outcome measure was active disease attributable to vasculitis. How this related to laboratory parameters including platelets, c-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and serial VWF antigen measurements was studied using generalized estimating equations (GEE) analysis to account for repeated measurements within a patient. Repeated measures correlation was used to determine associations of paired observations within a child. Diagnostic performance was evaluated using receiver operating curve (ROC) analysis.

Results: 731 total VWF measurements were collected in 25 GPA and 8 MPA patients. Baseline demographics and disease characteristics are shown in Table 1. VWF antigen levels were higher during active disease (median = 2.03 IU/mL, IQR = [1.35, 2.55]) compared to inactive disease (median = 1.18 IU/mL, IQR = [0.94, 1.53). VWF antigen was the only variable that is significantly associated with active disease (OR 3.01, $p<0.001$, 95CI [2.3, 3.93]). The effect of VWF did not show a substantial difference between the MPA versus GPA. There was a moderate positive correlation between VWF antigen and WBC, and moderate negative correlation with HGB and GFR. The AUC was 0.87 with all (VWF, ESR, CRP, platelets) laboratory parameters included, 0.86 and 0.81 when platelets and VWF were removed, respectively.

Conclusions: Increased VWF antigen levels correlate with active vasculitis in this pediatric-onset AAV cohort, and this may be used as an additional biomarker in childhood ANCA-associated vasculitis.

Disclosures: None

Table 1. Demographics, clinical, and laboratory characteristics

Patient characteristic	N = 33
Age at diagnosis, years	13.1 (11.3, 15.3)
Sex, female	22 (67%)
Diagnosis by clinical manifestation	
GPA	25 (76%)
MPA	8 (24%)
Antibody status	
Anti-PR-3 positive	21 (64%)
Anti-MPO positive	9 (27%)
ANCA negative	3 (9%)
Organ system involvement	
Renal disease	27 (82%)
Dialysis-dependent	3 (9%)
Pulmonary disease	23 (70%)
Pulmonary hemorrhage	8 (24%)
Sinus disease	14 (42%)
Disease duration at study inclusion, months	46 (15, 62)
Study observation period, months	32 (14, 60)
Glomerular Filtration Rate	89 (67, 109)
VWF (reference ranges and units: O: 0.41-1.26 IU/mL. A+B+AB+: 0.61-1.58 IU/mL)	1.56 (1.12, 1.83)[1]
Platelets (reference range and unit: 173 - 361 x10^9/L)	279 (238, 346)[1]
ESR (reference range and unit: 2 - 34 mm/Hr)	19 (13, 28)[1]
CRP hs (reference range and unit: 0.1 - 1.0 mg/L)	6 (3, 10)[1]
HGB (reference range and unit: 112 - 141 g/L)	125 (117, 132)[1]
WBC (reference range and unit: 4.23 - 9.99 x10^9/L)	9.19 (7.08, 10.49)[1]
Treatment for induction of remission	
Cyclophosphamide	21 (64%)
Rituximab	17 (52%)
Dialysis	7 (21%)
Plasma exchange	4 (12%)
Antihypertensive	20 (61%)

Legend: [1]Individuals' mean laboratory values across visits are calculated first, then medians were presented. GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; ANCA = antineutrophil cytoplasmic antibody; PR-3 = proteinase-3; MPO = myeloperoxidaseVWF = von Willebrand factor antigen; MPA = microscopic polyangiitis; CRP = C-reactive protein; ESR = Erythrocyte sedimentation rate; HGB = hemoglobin; WBC = white blood cell count

[1]Cellucci T, Tyrrell PN, Pullenayegum E, Benseler SM. von Willebrand factor antigen--a possible biomarker of disease activity in childhood central nervous system vasculitis? Rheumatology (Oxford). 2012 Oct;51(10):1838-45.

240. Subjectivity in the visual interpretation of ANCA screening by indirect Immunofluorescence testing

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Background: The most commonly used screening test for ANCA is the indirect immunofluorescence (IIF) test with ethanol and formalin-fixed neutrophils. This is followed by separate specific measuring of antibodies to PR3 and MPO. The classic perinuclear ANCA staining pattern (P-ANCA) is characterized by perinuclear staining with nuclear extension and is usually accompanied by anti-MPO. The classic cytoplasmic ANCA pattern (C-ANCA) is characterized by granular, cytoplasmic staining with central or interlobular accentuation and is usually associated with anti-PR3. The P-ANCA pattern attributable to MPO-ANCA is actually an artifact as with formalin-fixed neutrophils, MPO-ANCA produces a C-ANCA pattern. Atypical P-ANCA pattern, which can be defined as perinuclear IIF that does not meet the criteria for classic P-ANCA, are usually associated with inflammatory conditions other than AAV. Although several automated processing and detection systems are available, many laboratories still perform conventional visual interpretation. Studies investigating the comparability of ANCA slide assessments are lacking. We aimed to evaluate interpretation between trained analysts for different ANCA patterns based on the subjectivity of the interpreter and to determine the proportion of samples in which formalin-fixed neutrophil slides are needed for final decision.

Methods: All samples (n=560) referred to the Immunology Laboratory, Department of Rheumatology were simultaneously tested with ethanol- and formalin-fixed neutrophils and determined as either negative, P-ANCA, C-ANCA or atypical P-ANCA patterns by 6 trained analysts and correlated with MPO/PR3-ANCA ELISA results. All of the analysts had >5 years of experience and were competent in reading and interpreting ANCA-IIF testing.

Results: According to the consensus among analysts as well as anti-MPO/PR3 results, there were 455 (81.3%) negative, 14 (2.5%) C-ANCA, 49 (8.8%) P-ANCA and 42 (7.5%) atypical P-ANCA patterns among 560 samples. On average, analysts attributed a negative result to 78% of the samples, which is 3% less compared to the final results. On average, analysts attributed a C-ANCA result to 2.7% of samples, which is the same proportion as the final results. 5/14 samples with C-ANCA patterns were simultaneously positive for anti-PR3. For the latter, all analysts correctly chose the C-ANCA pattern. On average, analysts assigned 9.3% of samples to the P-ANCA result, which is comparable to the proportion of P-ANCA in the final results. 25/49 samples also had anti-MPO antibodies. Among the latter, analysts correctly decided on a P-ANCA pattern in 20/25 P-ANCA MPO + samples. In 5 samples, there was no consensus. The IIF on Ethanol-fixed neutrophils was mostly homogeneous with or without perinuclear rim staining, while formalin-fixed readings were either negative or negative with nuclear staining. On average, analysts assigned atypical P-ANCA result to 7.9%, which is comparable to the

final results. On average 30% of samples had a negative reading on ethanol-fixed slides, concluding that in more than 70% of the samples additional testing on formalin-fixed neutrophils was needed.

Conclusions: Analysts had the most comparable results for negative samples and for samples with C-ANCA pattern, with slightly more variability in P-ANCA and atypical ANCA patterns. Differences were found mainly in samples with low fluorescence intensity and unclear pattern. For routine performance of IIF ANCA it is suggested that samples are tested in both ethanol and formalin-fixed neutrophils and viewed in parallel by two analysts. However, the slides with an unclear pattern should be reviewed by a third one. The final report should further be agreed considering all available data, i.e. anti-MPO/PR3 antibodies and antinuclear antibodies, as detected on Hep-2 slides.

Disclosures: None

Table 1: The proportion of IIF ANCA pattern among tested samples

IIF ANCA pattern	
negative	455/560 (81,3%)
C1	7
C2	4
C3	3
C1,2,3	14/560 (2,5%)
P1	8
P2	13
P3	28
P1,2,3	49/560 (8,8%)
P1/A	15
P2/A	16
P3/A	11
P1,2,3 A	42/560 (7,5%)

Risk Score Prediction

241. Predictors of arthritis, gastrointestinal and renal involvement in adult IgA vasculitis

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Background: IgA vasculitis (IgAV) is not an uncommon vasculitis in adults, yet the disease in adults is still poorly defined. The aim of our study was to determine the predictors of arthritis, gastrointestinal (GI) or renal involvement in adult IgAV.

Methods: Medical records of histologically proven adult IgAV cases diagnosed between January 2013 and September 2021 at our secondary/tertiary rheumatology center were analyzed. The impact of 14 variables (age, gender, current smoking, history of preceding infection, use of new medication prior IgAV, the extent of skin purpura (generalized above the waist vs. localized), skin necroses, constitutional symptoms and the laboratory parameters (erythrocyte sedimentation rate, C reactive protein, haemoglobin, platelets, neutrophil to lymphocyte ratio (NLR) and elevated serum immunoglobulin A (IgA) level) on the presentation of IgAV was evaluated using logistic regression models.

Results: During the 105-month observation period we identified 268 new adult IgAV patients (60.4% males, median (interquartile range) age 64 (47-76) years). Arthritis, GI tract and renal involvement developed in 35 (13.1%), 66 (24.6%) and 110 (41.0%) cases, respectively. Characteristics of IgAV patients are presented in Table 1. In a multivariate logistic regression model increasing age was associated with a lower risk of arthritis (OR 0.98 (95%CI 0.96 – 0.99), p=0.011). Generalized purpura (OR 5.52 (95%CI 2.66 – 11.44), p<0.001), constitutional symptoms (OR 3. 86 (95%CI 1.69 – 8.79, p=0.001) and NLR (OR 1.22 (95% CI 1.09 – 1.37), p=0.001) emerged as risk factors for GI involvement. Increasing age was negatively associated with development of GI disease (OR 0.98 (95%CI 0.96 – 0.99), p=0.006). Elevated serum IgA (OR 2.58 (95%CI 1.49 – 4.47), p<0.001), current smoking (OR 2.46 (1.27 – 4.75), p=0.007) and age (OR 1.02 (95%CI 1.00 – 1.03), p=0.019,) were all associated with an increased risk of glomerulonephritis in our cohort.

Conclusions: Age has an important impact on a clinical presentation of adult IgAV. Purpura above waistline is a strong predictor of GI involvement, whereas active smoking and elevated serum IgA are associated with renal involvement.

Disclosures: Authors have no conflict of interest to declare.

Table 1. Characteristics of IgAV patients

Clinical characteristics	*IgAV cases (268)*	*Clinical characteristics*	*IgAV cases (268)*
Male gender (%)	60.4	Skin necroses (%)	46.3
Age (years)*	64 (48–76)	Generalized purpura[&] (%)	52.2

Symptom duration (day)*	7 (5–21)	Arthritis (%)	13.1
Current smoking (%)	20.9	GI involv. (%)	24.6
New medication (%)	25.4	Severe GI involv. (%)	6.0
Prior infection (%)	30.3	Renal involv. (%)	41.0
Elevated serum IgA (%)	50.0	Severe renal involv. (%)	12.7
Constitutional symptoms	14.2	BVAS-3*	6 (2-13)

Legend: * median (IQR); & purpura above the waistline; GI gastrointestinal; severe GI involvement - bloody diarrhea or ileus or surgical intervention; severe renal involvement - acute renal failure or nephrotic syndrome; BVAS-3 Birmingham Vasculitis Activity Score –3;

242. A systematic review and meta-analysis of models to predict the diagnosis of giant cell arteritis

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Objectives: The diagnosis of giant cell arteritis (GCA) can be difficult in individuals with inconclusive symptoms and inflammatory markers. Temporal artery biopsy (TAB), while often thought of as the gold standard, may miss a proportion of diagnoses. As such, many diagnostic models incorporating various predictors have been developed to assist clinicians in predicting a diagnosis of GCA with varying utility. This systematic review seeks to analyze these models to understand common and stable predictors of a diagnosis of GCA, understand their rigor, and determine how different criteria can alter the diagnosis of GCA.

Methods: We performed a literature from January 1990 to May 2020 for studies that used a model to diagnose giant cell arteritis. Studies with models that had fewer than three variables or 30 people were excluded. Abstract screening, data extraction, and risk of bias were performed by two independent reviewers for each study. Study characteristics, patient characteristics, method of and criteria for diagnosis, and model details were extracted and summarized. Meta-analysis of individual signs and symptoms was performed using generic inverse variance. The PROBAST tool was used to assess risk of bias in each individual study.

Results: We screened 1 446 abstracts and included 34 studies using data from 11 countries. 42 diagnostic models were identified. A total of 13 388 patients, 12 570 TABs, and 3 718 diagnoses of GCA were included. 22 studies required TAB positivity to diagnose GCA, 7 diagnosed using a composite of clinical and investigative findings, and 4 only required clinical findings. Rates of diagnosis of GCA were 25.0%, 39.0%, and 44.9% in each group respectively; Rates of TAB positive diagnoses was 98.2%, 53.7%, and 69.8%. There were 82.9% more diagnoses of GCA when using composite criteria over TAB positivity alone. Jaw claudication and Temporal changes were most associated with a diagnosis of GCA, however there were more predictive of TAB positive GCA than a clinical diagnoses, whereas headache and vision loss were more associated with non-TAB based diagnoses of GCA. 22 studies were at high risk of model bias and 4 were low risk.

Conclusions: Models used to predict a diagnosis of GCA are of variable methodological quality and are largely dependent on using TAB positivity as a gold standard for a diagnosis of GCA. Despite this, predictors of GCA are consistent. Future models should focus on validation and use diagnostic standards that include composite criteria that reflect current practice.

Disclosures: NK – Trial support from Roche, BMS, Sanofi, Abbvie**.** All others - None

Table 1: Meta-odds ratios and 95% confidence intervals of predictors of a diagnosis of GCA, stratified based on including all studies, including studies that diagnosed GCA based on a positive TAB, and studies that diagnosed GCA using clinical and/or composite criteria to diagnose GCA.

Predictor	All models predicting GCA	TAB to diagnose GCA	Clinical/Composite criteria for GCA
Age	1.04 (1.02-1.05)	1.04 (1.01-1.05)	1.04 (1.02-1.05)
Headache	2.96 (1.75-5.02)	2.55 (1.63-4.00)	3.60 (1.78-7.28)
Temporal artery and/or scalp changes	2.60 (1.75-3.85)	2.80 (1.71-4.59)	2.07 (1.35-3.18)
Jaw Claudication	3.73 (2.48-5.63)	4.05 (2.38-6.91)	2.62 (1.89-3.64)
PMR	1.58 (0.68-3.66)	1.53 (0.33-7.08)	1.59 (0.76-3.31)
Vision Loss	2.09 (1.50-2.92)	1.93 (1.23-3.04)	2.51 (1.35-4.69)
ESR (mm/hr)	1.03 (1.01-1.04)	1.03 (1.01-1.05)	1.18 (0.81-1.72)
CRP (mg/dl)	1.36 (1.04-1.78)	1.36 (1.24-1.49)	1.58 (0.63-3.96)
Platelets (10^9/L)	1.01 (1.01-1.01)	0.95 (0.90-1.00)	1.43 (1.07-1.90)

243. RRS and histopathological classification for ESKD prediction and factors associated with eGFR variation in ANCA-glomerulonephritis.

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Background: Recently, - "the Renal Risk Score" (RRS) has been proposed to evaluate the risk of end-stage kidney disease (ESKD) in (ANCA)-associated glomerulonephritis (ANCA-GN). However, few studies have compared the value of RRS and the histopathological classification in the same population. Besides, the factors associated with eGFR recovery after the onset of ANCA-GN have been poorly studied. Thus, the aim of the present study was first to analyze and compare the value for ESKD prediction of RRS and histopathological classification in a large and well phenotyped cohort. Next, we analyzed the factors associated with eGFR variations within the first two years following ANCA-GN diagnosis.

Methods: We used the Maine-Anjou ANCA-associated vasculitis (AAV) registry, which, since January 2000, has gathered data on all consecutive patients diagnosed with ANCA-GN in 4 French Nephrology Centers. All adult patients with kidney biopsy performed at ANCA-GN onset showing pauci-immune crescentic GN and with at least 6 months of follow-up were included. Renal biopsies were reviewed and scored for the purpose of the study. The prognostic value of AAV histopathological classification and of RRS was evaluated in the cohort. Then, factors associated with eGFR variations between ANCA-GN diagnosis and 2 years of follow-up were studied.

Results: Among the 180 patients of the registry, 123 could be included for the analysis of both histopathological classification and RRS predictive values for ESKD ("ESKD prognosis cohort"). Among the 123 patients, 80 had full eGFR data during follow-up and were included in the "eGFR cohort". The initial median eGFR of the ESKD cohort was 17.9 mL/min/1.73 m2, 22.8% required renal replacement therapy at ANCA-GN onset and 33.3% developed ESKD after a median follow-up of 42 months. Twenty-nine patient were classified within focal, 25 within crescentic, 50 within mixed and 19 within sclerotic histopathological classes, while 40 patients were classified in low, 55 in medium and 28 in high RRS classes. The predictive value of RRS for ESKD was greater than histopathological classification. In the eGFR cohort the median eGFR increased from ANCA-GN diagnosis to month 6 and stabilized thereafter. Neither renal histological lesions at ANCA-GN diagnosis nor RSS value were associated with eGFR variation after 2 years. The only factor associated with eGFR variation was eGFR at ANCA-GN diagnosis, with higher eGFR at diagnosis being associated with eGFR loss ($p<0.001$).

Conclusions: This study confirms the better predictive value of RRS as compared to histopathological classification for ESKD prediction. The main determinant of eGFR variation was eGFR at ANCA-GN onset. Thus, the present study suggests that eGFR recovery is poorly dependent of the severity of histological damage at ANCA-GN diagnosis.

Disclosures: The authors declare that they have no conflicts of interest in relation to this abstract.

244. Prediction of Vascular Complications in Takayasu Arteritis by Machine Learning: A Cohort-Based Proof-Of-Concept Study

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Objectives: Vascular complications are common poor prognosis in Takayasu arteritis (TAK). We aimed to develop machine learning (ML) models for prediction of vascular complications in TAK based on prospective data from the East China Takayasu Arteritis (ECTA) cohort.

Methods: Data were collected from the ECTA cohort in which patients were enrolled from January 2009 to August 2020 and followed till February 2021 (n = 517). Predictor variables included 53 baseline features and outcome of interest was incident vascular complications. Data were randomly split into a training (85%) and test (15%) set. Logistic regression (LR), support vector machine, random forest (RF), k-nearest neighbors, XGBoost (XGB), and light gradient boosting machine models were trained using five-fold cross validation, and evaluated on the test set for recall, specificity, precision and area under ROC (AU-ROC) and precision-recall curves (AU-PRC). Permutation score was applied to assess feature importance to the outcome.

Results: Over a median follow-up of 30 (15–44) months, incident vascular complications were observed in 29.0% (150/517) patients. The RF model demonstrated the best overall predictive performance (AU-ROC = 0.84, AU-PRC = 0.63). Both the RF and LR models had the highest specificity (0.98), and the XGB model had the highest recall (0.87). Progressive clinical course was an important feature significantly associated with the outcome for all models.

Conclusions: It demonstrated the feasibility of developing ML models for prediction of vascular complications in TAK. The XGB model could help for early identification of high-risk patients, and RF and LR models could further confirm.

Disclosures: All the authors declared no conflicts of interest.

245. Outcome Prediction - Proposal of a Risk Score in Anti-GBM Disease

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Background: Anti-glomerular basement membrane (GBM) disease is a rare, aggressive vasculitis that typically presents with severe kidney dysfunction and pulmonary haemorrhage. The need for renal replacement therapy (RRT) at presentation is not uncommon and many patients go on to develop end stage kidney disease (ESKD). Clinical and histological variables predicting outcome are needed to individualise therapy and improve outcomes.

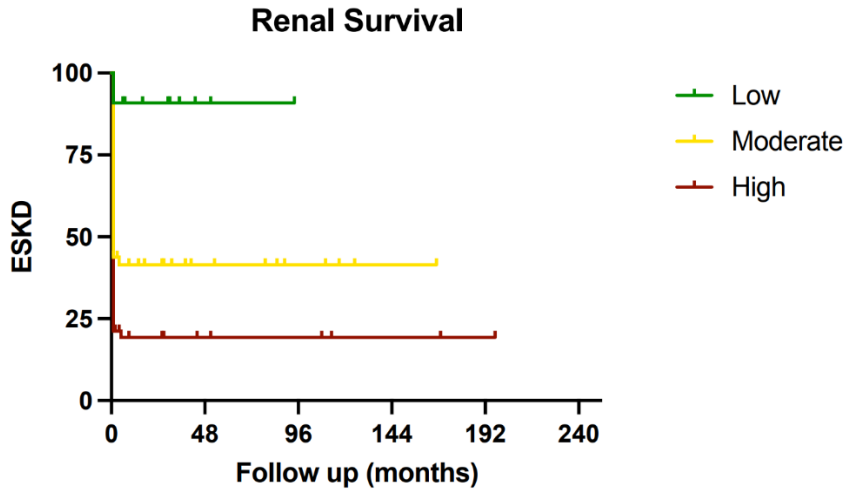
Methods: A retrospective, multicentre, international cohort study collected data from 2005-2021. We investigated the Renal Risk Score (RRS) for its prognostic value in anti-GBM disease and modified its parameter to optimise outcome prediction. We used the published cut-offs for percentage of normal glomeruli, estimated glomerular filtration rate (eGFR), and a simplified cut-off for tubular atrophy and interstitial fibrosis (T0 ≤ mild to moderate, T1 = severe). We assigned points to each parameter and patients to risk groups as previously published. We then adjusted the eGFR cut-off according to patients' outcome (G1 ≤ 7 ml/min/1.73 m^2) and validated the modified RRS in anti-GBM disease.

Results: Of the 137 patients included, median age was 60.5years (IQR 45-71) with a slight female predominance (n=74, 54%). Eighty-two patients (60%) presented with GBM antibodies, 37 (27%) presented with dual GBM and MPO antibodies, and 18 (13%) presented with GBM and PR3 antibodies. The median eGFR at presentation was 6ml/min (IQR 4.75-10) and 83.2% (n=114) required RRT at presentation. The RRS predicted renal survival in anti-GBM disease. None of the patients in the low risk group developed ESKD (n=8, ESKD=0, 0%), half of patients in the moderate risk group developed ESKD (n=26, ESKD=13, 50%), and over 70% of patients from the high risk group developed ESKD (n=91, ESKD=65, 72.2%, p<0.0001), respectively. A regression tree with adapted risk points for patient outcomes further optimised outcome prediction (Figure 1, p<0.0001). Seven of 16 patients in the low-risk group (43.8%), 47 of 58 patients in the moderate risk group (81%) and 49 of 51 patients in the high risk group (96.1%) required RRT at time of presentation (p<0.0001). Four of these seven patients recovered renal function in the low risk group (57.2%), 15 of 47 patients in the moderate risk group (31.9%), and six of 49 patients in the high risk group, respectively (12.2%, p=0.008). None of the patients with the highest score of 11 recovered renal function.

Conclusions: Anti-GBM patients with as little kidney function as an eGFR of 2ml/min on presentation recovered kidney function. The renal risk score accurately predicted the need for renal replacement therapy at presentation, the potential for renal recovery and the development of ESKD. Combining histological features and clinical parameters enhances outcome prediction and utilising the score in clinical practice might aid management in the future.

Disclosures: DG is a consultant to ChemoCentryx and Aurinia Inc. NB and SRB received honoraria from Vifor. The other authors have no other disclosures or competing interests.

Figure 1:



246. Predictive factors of eosinophilic granulomatosis with polyangiitis long term evolution: data from a European cohort

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Background: Eosinophilic granulomatosis with polyangiitis (EGPA) is a small-vessel necrotizing vasculitis characterized by blood and tissue eosinophilia and asthma. Glucocorticoids (GCs) effectively control the disease, but relapses and/or GC-dependence are frequent. Evolving concepts distinguish vasculitis-related symptoms from asthma and/or ENT manifestations. That distinction has become even more important since the development of B-cell and eosinophil-targeted therapies. Our objective was to build models to predict the evolution towards a relapse of vasculitis or towards a GC-dependent asthma and/or ENT manifestations.

Methods: We set up a multicenter European retrospective study including 809 EGPA patients. EGPA diagnosis was made according to ACR and/or MIRRA criteria. We developed a multivariable prediction model using the PMSAMPSIZE algorithm: one model for the vasculitis relapse risk during follow-up (excluding asthma and/or ENT manifestations) and one model for the risk of GC-dependent asthma and/or ENT manifestations at two years of follow-up.

Results: Mean age was 52 (+/- 14.8) years, and median follow-up was of 72 months (IQR 37-115). During follow-up, 228 experienced at least one vasculitis relapse, with a cumulative incidence at 12 years of 41% (CI95% 36-47). At two years of follow-up, 66,4% of patients had GC-dependent asthma and/or ENT manifestations. A model predicting vasculitis relapse included the following variables: older age at EGPA diagnosis (HR 1.07 [IC 95% 0.98-1.18]), GC-dependent asthma before EGPA diagnosis (HR 1.43 [IC 95% 1.16-1.77]), arthralgia (HR 1.32 [IC 95% 1.09-1.61]), myocarditis (HR 1.27 [IC 95% 0.96-1.69]), peripheral neuropathy (HR 1.33 [IC 95% 1.09-1.63]), positive MPO-ANCA (HR 1.37 [IC 95% 1.10-1.72]), C-reactive protein level (HR 1.07 [IC 95% 1.00-1.15]) and lower eosinophils count (HR 0,76 [IC 95% 0,67-0,86]) at baseline. The final model allowed the development of a nomogram and the calculation of a score predicting the vasculitis relapse risk at 5 and 12 years of follow-up. A model

predicting GC-dependent asthma and/or ENT manifestations at two years of follow-up included the following variables: younger age at EGPA diagnosis (OR 0.98 [IC 95% 0.97-0.99]), history of chronic sinusitis before EGPA diagnosis (OR 1.11 [IC 95% 0.70-1.77]), ENT manifestations at baseline (OR 1.65 [IC 95% 1.09-2.47]), peripheral neuropathy (OR 1.36 [IC 95% 1.01-1.84]), the absence of MPO-ANCA (OR 0.68 [IC 95% 0.51-0.92]) and lower eosinophils count (HR 0.45 [IC 95% 0.28-0.72]). The final model allowed the development of nomogram and the calculation of a score predicting GC-dependent asthma and/or ENT manifestations at 2 years.

Conclusion: Through a large retrospective European EGPA cohort, we developed two models for the prediction of vasculitis relapse during follow-up and GC-dependent asthma and/or ENT manifestations at 2 years. These models should be validated in prospective studies, and could be used to guide the use of biotherapies targeting B cells or eosinophils.

Disclosures: nothing to disclose.

247. Predicting the 1-year risk of kidney failure in patients with ANCA-associated vasculitis

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Background: The risk of kidney failure varies substantially amongst patients with anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis. We derived a simple instrument to estimate the 1-year risk of kidney failure in patients with ANCA-associated vasculitis.

Methods: Analysis of individual patient data from 7 international randomized controlled trials conducted by the European Vasculitis Study Group covering the spectrum of severity in ANCA-associated vasculitis. Candidate predictors included age, sex, ANCA type, creatinine, estimated glomerular filtration rate, and use of dialysis. The outcome of interest was kidney failure by 1-year post-enrollment. Candidate predictors were included in iteratively fit logistic regression models with parameters that did not improve fit dropped. Models were internally validated using bootstrapping and externally validated in an 8th randomized controlled trial. Alternative models were compared using discrimination and calibration statistics and decision curve analysis.

Results: Kidney failure occurred in 54 of 786 participants in the derivation data. Serum creatinine, fit with a cubic spline, and need for dialysis at baseline resulted in the simplest, most parsimonious model with a C-statistic of 0.919 and Brier score of 0.050 in the derivation data set and a C-statistic and Brier score of 0.876 and 0.102 respectively in the validation data. A simpler model using only serum creatinine categorized as <200 µmol/L, 200 to 300 µmol/L, >300 to 500 µmol/L and >500 µmol/L or receiving dialysis performed similarly to the best model

for patients up to an 11% risk and discrimination and calibration statistics in the external validation data were similar to the best fitting model (C-statistic 0.830 and Brier score 0.108).

Conclusions: A single serum creatinine is a useful estimator of the risk of kidney failure at one year in patients with ANCA-associated vasculitis. Even simple categorization of serum creatinine can reliably identify patients at low risk of kidney failure adequately.

Disclosures: The authors have no relevant financial disclosures

248. Refined Renal Risk Score for ANCA-associated glomerulonephritis

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Background: Treatment related morbidity and mortality significantly impact outcome in ANCA associated glomerulonephritis (GN). The aim is to optimise kidney and patient survival by personalising medicine according to a reliable risk stratification.

Methods: We conducted a multicentre, international retrospective study investigating patients with biopsy proven ANCA associated GN. We validated and refined the ANCA Renal Risk Score (ARRS) to optimise the outcome prediction for end stage kidney disease (ESKD) and the recovery from acute renal failure at presentation.

Results: Six regional referral centres from the US, England, Turkey and Mexico, and the Irish national registry provided data on 766 patients with ANCA GN. Median age was 63 years (interquartile range 46 - 69), 56.4% of patients were male. 51.3% of patients were anti-myeloperoxidase positive, 42.6% anti-proteinase 3 positive and 6.1% ANCA negative. 17.6% initially required renal replacement therapy, and 57.7% of these patients recovered renal function. During a median follow up of 58 months, 26% of patients developed ESKD. The original risk score correlated with outcome; 12.5%, 24.4%, and 64.3% of patients developed ESKD in the low, moderate and high-risk groups, respectively (p=0.002). The risk score was modified by adjusting cut-offs according to regression tree analyses assigning risk points to create new risk groups. The refined score predicted renal recovery in patients presenting with dialysis dependent acute kidney injury (83.3%, 50%, 33.3%, p=0.02) as well as the development of ESKD during follow up (11.4%, 37%, 66.7%, p=0.0004).

Conclusions: We developed and externally validated a reliable prediction tool enabling personalised medicine in ANCA associated GN. Adjusting the ARRS using real world data from around the globe optimised the risk stratification.

Disclosures: DG is a consultant to ChemoCentryx and Aurinia Inc. NB and SRB received honoraria from Vifor. The other authors have no other disclosures or competing interests.

249. ANCA-associated vasculitis: predictors of progression to end stage renal disease and mortality

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Background: Vasculitis is a process defined by inflammation of any blood vessel with necrosis in variable degrees. ANCA-associated vasculitis (AAV) are characterized by necrotizing inflammation of small blood vessels. Renal involvement is present in the majority of patients with AAV and can be severe, being associated with poor survival and increased risk for progression to end stage renal disease (ESRD). The goals of this study were to describe the predictors for mortality and progression to ESRD in our population, as well as to assess possible prognostic factors at presentation and during follow-up.

Methods: We conducted an observational retrospective study including all the patients diagnosed with AAV with biopsy-proven renal involvement diagnosed in our centre in the last 20 years. We collected information on demographics, clinical presentation, laboratory parameters, treatment, and progression to ESRD or death. Laboratory parameters were assessed at presentation and at 3, 6, 12, 18 and 24 months of follow-up, and included: antibody type (peroxidase 3 [PR3] or myeloperoxidase [MPO]) and titters, serum creatinine, haemoglobin, C-reactive protein, and the presence of urine sample abnormalities (proteinuria, haematuria, leukocyturia).

Results: We included 52 patients, with a median age of 65.1 years (57.9-76.6 years) at presentation and no differences concerning the gender (50% males). Constitutional symptoms were the most frequent clinical picture (82% of the patients) and 32% of the cases presented with upper airway involvement. The majority of patients were positive for MPO antibody (n=49, 83%). ESRD-free survival of our study population was of 76%, 64% and 61%, respectively at 12, 36 and 60 months of follow-up. We observed global mortality rates of 15%, 29% and 37%, at the same timings, irrespectively of treatment or progression to ESRD. The patients that did not progress to ESRD nor death were significantly younger at presentation than their counterparts – 60.0 years, versus 71.1 years (ESRD), versus 76.4 years (death); p=0,008. This group of patients also had more frequent airway involvement (55%, versus 15% [ESRD], versus 20% [death]; p=0,027) and presented with lower creatinine concentration (2.77mg/dL, versus 4.84mg/dL [ESRD], versus 3.37mg/dL [death]; p=0,001). No differences were observed

concerning haemoglobin or C-reactive protein levels, nor the presence of haematuria or leukocyturia at presentation. After adjusting for possible confounders, the independent predictors of progression to ESRD were higher serum creatinine levels (HR 1.164, P=0.031) and ANCA titters >1/640 (HR: 3.326, P=0.049). The independent risk factors for mortality were higher age at diagnosis (HR 1.12 per year, p=0,001) and the presence of MPO (versus PR3; HR 4.34, p=0,043).

Conclusions: The high rate of progression of AAV to ESRD and the high mortality rate that we observed in our study are in accordance with what was previously described in the literature. Since the consequences of a missed or delayed diagnosis of this condition are potentially life threatening, we defend that it is of upmost importance to identify the risk factors for the progression of the disease, in order to better and more efficaciously treat our patients. Hence, our work highlights the importance of classic risk factors, including higher serum creatinine and older age, on the renal and global prognosis of these patients.

Disclosures: None

250. Combined crescentic and chronicity score for prognostic assessment in ANCA-associated vasculitis with glomerulonephritis

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Background: Combining the evaluation of acute inflammatory activity and chronic changes on kidney biopsy is probably optimal for prognostic assessment of renal outcomes in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) with glomerulonephritis (AAV-GN).

Methods: A retrospective cohort study of MPO- or PR3-ANCA positive patients with AAV and active renal disease. We developed a Crescentic Index (CI) corresponding to the ratio between the number of crescents and/or necrosis and the total number of glomeruli and scored as follows: 0 ≤ 25%, 1 = 26-50% and 2 > 50%. Then, we summed the score obtained in the CI combined with the grades obtained in the Mayo Clinic Chronicity Score (MCCS) (1 – minimal, 2 – mild, 3 – moderate and 4 – severe) to evaluate the implications on outcome prediction in AAV-GN.

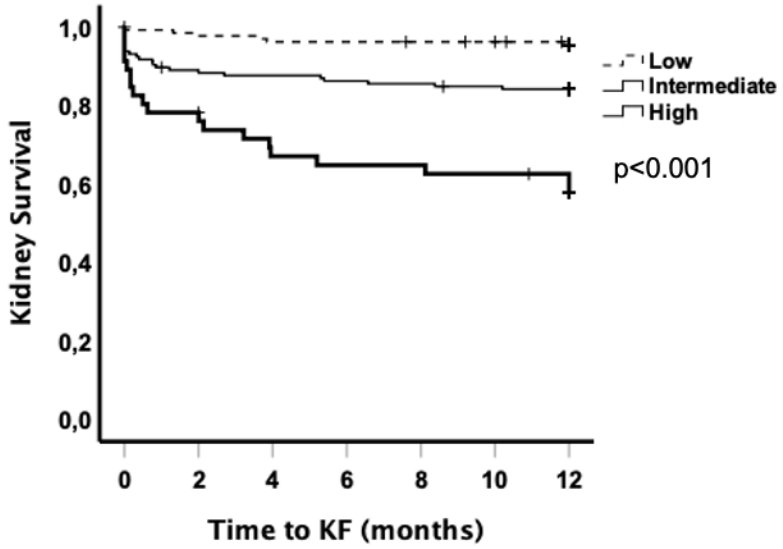
Results: We analyzed 326 patients with kidney biopsies available to score. The biopsies had in median (IQR), 13 glomeruli (9-20), 4 crescents (2-6) and a CI of 28.6% (15.3-47.6). We applied the CI and found that 154 (47.2%) patients scored 0, 106 (32.5%) patients scored 1 and 66 (20.2%) scored 2. After the combination of the scores, the population was classified

according with the risk of progression to kidney failure (KF) in 3 classes as (i) low – 134 (41.1%), (ii) intermediate – 125 (44.8%), and (iii) high – 46 (14.1%). Median eGFR at baseline correlated with the overall risk categories: 40.6 vs. 20.8 vs. 16.2 mL/min/1.73 m^2, p<0.0001. The proportion of patients with severe renal disease at diagnosis was increased in patients classified as high: 89.1% vs. 71.2% vs. 37.3%, p<0.0001. Clinical presentation, severity of the disease estimated by BVAS/WG, ANCA specificity, remission-induction or remission-maintenance treatment did not differ across the 3 categories. Renal recovery was more frequent in patients at low risk of progression: 87.1% vs. 56.3% vs. 36.7%, p<0.0001, whereas kidney failure at 12 months, dialysis, and combined events of KF and/or death at 24 months were more frequent in patients at higher risk (41.3 % vs. 15.8% vs. 4.5%, p<0.0001; 35.7% vs. 12.6.0% vs. 6.0%, p<0.001; 47.8% vs. 21.9% vs. 10.4%, p<0.0001, respectively). The combination of CI with MCCS grades independently predicted the risk of KF at 12 months (HR 2.107,95%CI 1.388-3.199, p<0.0001), particularly increased in patients classified as high risk (HR4.237, 95%CI 1.837-9.774, p=0.001) and in patients with PR3-ANCA (HR1.897, 95%CI 1.072-3.358, p=0.028) independently of eGFR at AAV-GN diagnosis and adjusted for severity of renal involvement and age.

Conclusions: The combined assessment of acute inflammatory activity and chronic changes on kidney histology independently predicted renal outcomes in patients with AAV-GN. The combined score is simple to apply and accurately stratifies the patients according in 3 categories of risk for kidney failure.

Disclosures: Dr. U. Specks has received consulting fees from AstraZeneca, ChemoCentryx and research grants from AstraZeneca, GSK, Bristol Myers Squibb, Genentech. Dr. F.C. Fervenza has received research grants from Roche/Genentech.

Figure 1. Kaplan Meier plots of kidney failure (KF) over 12 months according with the risk group defined by the combination of the CI with the MCCS.



Myocarditis & Cardiovascular Disease

251. Prediction of Subclinical Left Ventricular Dysfunction by Speckle Tracking Echocardiography in Patients with ANCA Associated-Vasculitis

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Background: Although cardiovascular disease is the leading cause of mortality in patients with ANCA-associated vasculitis (AAV), left ventricular function has not been adequately assessed in this patient population. The current study aimed to evaluate left ventricular functions using speckle tracking echocardiography (STE) in patients with AAV.

Methods: Clinical and biochemical characteristics were recorded. All subjects underwent conventional and two-dimensional STE. ROC curve analysis was performed to determine the cut-off value for serum N-Terminal prohormone of brain natriuretic peptide (NT Pro-BNP) that predicted subclinical left ventricular dysfunction. Spearman correlation analysis was used to determine the correlation between left ventricular global longitudinal strain (LV-GLS) and NT Pro-BNP. Data are presented as median (interquartile range).

Results: Thirty-one AAV patients were compared with 21 healthy subjects. Sex and age were similar among the study groups. Seventeen patients (54.8%) were male. Mean patient age was 53 (15) years. Twenty patients (64.5%) had GPA, and 11 (35.5%) patients had an MPA diagnosis. Median disease duration was 36 months (73 months). The frequency of hypertension and serum triglyceride, creatinine, C-reactive protein (CRP) and NT Pro-BNP levels were higher in AAV patients, while LDL and HDL were similar between the two groups. Conventional echocardiographic and speckle tracking measurements are shown in Table 1. While LV-GLS was lower in AAV patients 19.3 (4.5) vs. 21.7 (4.7), p=0.014, interventricular thickness 11 (2) vs. 10 (1) mm, p=0.044 and posterior wall thickness 10 (2) vs. 9 (2) mm, p=0.032 were higher in patients with AAV as compared to healthy controls. Correlation analysis showed that LV-GLS was negatively correlated with NT Pro-BNP ((p =0.005, r=0.401). The cut-off LV-GLS value for left ventricular dysfunction was considered 20% based on the American Society of Echocardiography guidelines. ROC analysis demonstrated that NT-pro BNP > 42.5 pg/ml predicted subclinical left ventricular dysfunction with 87.5% sensitivity and 69.5% specificity (AUC: 0.695, CI:0.544-0.846).

Conclusions: We found that LV-GLS measurements were lower in AAV patients than controls. While STE can be used for detecting subclinical myocardial dysfunction, NT-pro BNP

measurement is a simple method in identifying patients at high risk. This preliminary data suggests conventional echocardiography may underestimate the risk of cardiovascular disease in AAV patients. Subclinical left ventricular dysfunction was detected by STE in patients with AAV who were free of clinically overt cardiovascular disease. LV-GLS was negatively correlated with serum NT Pro-BNP levels.

Disclosures: None. Preliminary data published here: https://onlinelibrary.wiley.com/doi/10.1111/1346-8138.15810

Table 1: Conventional echocardiographic and speckle tracking measurements of the study populations.

	Patients n: 31	Controls n: 21	P
LVEDD (mm)	48.5 (6)	47.0 (9.5)	0.570
LVESD (mm)	31.5 (5)	31.0 (6)	0.834
Ejection Fraction (%)	58.5 (8)	60.0 (8.7)	0.796
Interventricular septum (mm)	11 (2)	10 (1)	0.044
Posterior wall (mm)	10 (2)	9 (2)	0.032
Left Atrial diameter (mm)	33 (7)	31 (5)	0.905
Systolic PAP (mm Hg)	30 (18)	27 (15)	0.564
E (m/s)	0.81 (0.58)	0.91 (0.50)	0.804
A (m/s)	0.86 (0.40)	1.02 (0.40)	0.206
DT (ms)	169 (45)	151 (52)	0.507
E' (cm/s)	11.0 (6)	10.5 (6)	0.781
A' (cm/s)	10 (6)	10 (4)	0.689
E/E'	8.8 (3.4)	8.9 (3.8)	0.992
RV s' (cm/s)	12 (2)	12 (2)	0.492
TAPSE (mm)	23.5 (4)	23.0 (3)	0.928
LV-GLS (%)	19.3 (4.5)	21.7 (4.7)	0.014
RV-GLS (%)	22.2 (5)	21.7 (3.7)	0.572

LVEDD: Left ventricular end diastolic diameter; LVESD: Left ventricular end systolic diameter, PAP: pulmonary artery pressure, DT: deceleration time, RVs': Right ventricular systolic velocity, TAPSE: tricuspid annular plane systolic excursion. LV-GLS: Left ventricular global longitudinal strain, ns: Non significant RV-GLS: Right ventricular global longitudinal strain. Data are presented as median (IQR).

252. Myocardial infarction in ANCA-associated vasculitis- a population-based cohort-study

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Objectives: To determine the incidence rate (IR) and predictors of acute myocardial infarction (MI) in patients with ANCA-associated vasculitis (AAV).

Methods: This population based retrospective cohort study included 325 patients diagnosed with AAV between 1997 and 2016 in a defined population in southern Sweden. To identify patients diagnosed with MI, the AAV cohort was linked to the SWEDEHEART registry, a national quality of care registry including all MI-cases hospitalized at coronary care units in Sweden, and to the Skåne Healthcare register (SHR), a regional diagnosis database. Cases found in SHR but not included in SWEDEHEART were confirmed via case record review. Demographics and clinical data were collected from time of AAV diagnosis. MI events occurring in a period beginning 3 months prior to AAV diagnosis and any time after were considered AAV-related MI. For each patient with AAV, we randomly sampled 10 age and sex-matched controls from the background population. The incidence rate (IR) of AAV- related first MI was calculated dividing cases by sum of person years of follow up. Follow up time was defined as time from diagnosis of AAV (index-date for controls assigned as same as date of AAV-diagnosis in AAV-partner) to first MI-event, death, or end of study in November 2018. The incidence rate ratio (IRR) was calculated by dividing the IR for patients with AAV by the corresponding rate for the controls. Predictors of MI in AAV was studied using Cox-regression model using the following factors in uni- and multivariable analysis: age at AAV diagnosis, disease phenotype, creatinine per 100 µmol/L increase and ENT-involvement.

Results: Thirty-seven patients (11.4%) were diagnosed with a first time AAV-related MI during a follow up time of 2330 person-years. The IR of MI was 1.6/100 person-years (95% CI 1.1-2.1). Compared to official Swedish statistics, the AAV- patients of this cohort were more than five times as likely to suffer a MI compared to the overall adult population. The IR was highest within three months from AAV diagnosis, 10.2/100 person-years (95% CI 3.1-17.2). The IRR of MI was 1.9 (95% CI 1.3-2.8, p=0.001). The highest IRR were obtained for patients with MPO-ANCA+ disease (2.5, 95% CI 1.5-4.3, p=0.0004), and those with BVAS $\geq$15 at time of AAV-diagnosis (2.1, 95% CI 1.3-3.3, p=0.002). Age at AAV diagnosis independently predicted occurrence of MI.

Conclusions: This cohort study shows that patients with AAV are more prone to suffer from MI, particularly within the first period after disease onset. Age was the single independent predictor of MI in AAV-patients.

Disclosures: The authors declare that they have no conflict of interest.

Table: Incidence rate of MI per 100 person years of follow up in 282 patients with AAV compared to 2763 age-, sex- and index-year matched controls from background population

	AAV MI, n	AAV person-years	AAV IR	Controls MI, n	Controls person years	Controls IR	IRR	95% CI	p-value
All	31	1817	1.7	192	21497	0.9	1.9	1.3-2.8	0.001
Female	14	945	1.5	75	10851	0.7	2.1	1.2-3.7	0.013
Male	17	871	1.9	117	10646	1.1	1.7	1.0-2.9	0.037
Age < 65 years	8	1026	0.8	42	11315	0.4	2.1	0.9-4.4	0.086
Age ≥ 65 years	23	791	2.9	150	10182	1.5	1.9	1.2-3.0	0.003
MPO-ANCA+	17	728	2.3	80	8844	0.9	2.5	1.5-4.3	<0.001
PR3-ANCA+	13	921	1.4	104	10870	1.0	1.4	0.8-2.6	0.246
BVAS<15	11	844	1.3	77	9812	0.8	1.6	0.8-3.1	0.164
BVAS ≥15	20	944	2.1	115	11454	1.0	2.1	1.3-3.3	0.002

IR: incidence rate, IRR: incidence rate ratio (Rate in AAV: rate in controls), CI: confidence interval, MPO: myeloperoxidase, PR3: proteinase 3, BVAS: Birmingham vasculitis activity score.

253. Targeting atheroma formation in crescentic glomerulonephritis

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Background: Crescentic glomerulonephritis (CGN) as is frequently found in Antineutrophil Cytoplasmic Antibody (ANCA)- associated vasculitis, represents a severe form of glomerular inflammation characterised by abnormal or excessive glomerular neutrophil and monocyte activation with evidence of release of leukocyte proteases, such myeloperoxidase (MPO), and neutrophil extracellular traps (NETs) inducing kidney damage. Diseases associated with CGN are almost uniformly treated with glucocorticoids (GC), and both disease and treatment can lead to severe morbidity. Recent data suggest that even modest GC doses are associated with markedly increased rates of cardiovascular disease, translating to a significant cause of premature mortality in these patient cohorts. We have previously shown that MPO inhibition attenuates disease severity in preclinical nephrotoxic nephritis. We established a combined preclinical model of non-accelerated nephrotoxic nephritis (NTN) and atheroma to investigate the effect of renal inflammation on atheroma formation. We subsequently, used this model to investigate the effect of MPO inhibition, using the selective MPO inhibitor AZM198, and glucocorticoid therapy on atheroma formation in the presence of nephritis.

Methods: Thirty-seven ApoE$^{-/-}$, 5 C57BL/6 and 5 MPO$^{-/-}$ApoE$^{-/-}$ mice were immunised with sheep nephrotoxic serum mixed 1:1 with Lipopolysaccharide. Six ApoE$^{-/-}$ mice were immunised with saline solution to act as a control. During the first two weeks post immunisation all groups received the same high fat diet. From week 3 until week 10 the ApoE$^{-/-}$ animals were divided in three treatment groups and the following compounds were incorporated in their high fat diet: vehicle control (high fat diet alone), MPO inhibition (AZM198; 500□mol/kg/day) and Prednisolone (5mg/kg/day). Weekly weights, urine protein and urine glucose were recorded. At the beginning of week 11, animals were sacrificed, blood and 16-hour urine were collected, and aortas, hearts and kidneys harvested. Aortas were dissected and stained with Red O and kidney sections were stained for haematoxylin and eosin and Periodic Acid-Schiff stain.

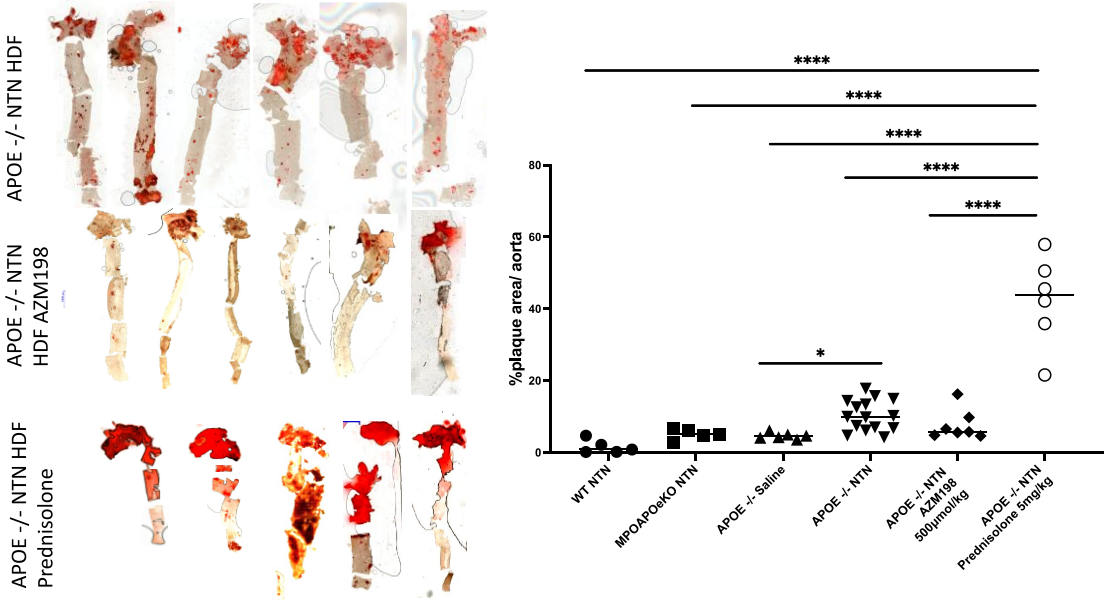
Percentage atheromatous plaque area was quantified using Image J software and histological renal severity was assessed using a red cell cast (0-4) and glomerular thrombosis score (0-4).

Results: ApoE$^{-/-}$ mice with NTN had increased atheroma formation compared to ApoE$^{-/-}$ animals without NTN (p =0.04) (Figure 1). There was no significant difference in plaque area between the vehicle control group and the group treated with MPO inhibition (p=0.87)as well as the MPO deficient (MPO$^{-/-}$ApoE$^{-/-}$ mice) (p=0.46). The animals treated with prednisolone had significant atheroma formation, which was significantly higher than all other groups (p < 0.001). There was significant mortality associated with the prednisolone group compared to both vehicle (p=0.001) and MPO inhibition group (0.01) but no significant difference in mortality between the vehicle group and the MPO inhibition group (p=0.09). There was no significant difference in weekly urine proteinuria (p >0.2) and glycosuria levels (p >0.4) amongst the three treatment groups throughout the study. There was no significant difference in terminal serum creatinine (p>0.16) , blood glucose (p>0.75) and 16- hour proteinuria (p>0.26) as well as histological disease severity amongst the three treatment groups (p>0.28). C57BL/6 animals with NTN did not develop atheroma formation compared to the ApoE$^{-/-}$ mice with NTN (p=0.04).

Conclusions: Renal inflammation significantly accelerates atheroma formation in susceptible animals. Treatment with glucocorticoids led to significant atheroma formation and mortality compared to treatment with myeloperoxidase inhibition.

Disclosures: MA received funding from Medical Research Council Grant MR/P001777/1

Figure 1. Representative images and graph of percentage plaque area of murine aortas from mice with non-accelerated nephrotoxic nephritis or saline control.



254. Myocardial Infarction in Patients with Systemic Vasculitis and Population Controls: Characteristics and Overall Mortality

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Background: The deleterious effect of inflammation combined with glucocorticoid treatment may increase the risk for atherosclerotic events. The aims of this study were to investigate differences in baseline characteristics and survival after incident MI in patients with systemic vasculitis [SV: ANCA-associated vasculitis (AAV) and Giant Cell Arteritis (GCA)] compared to a matched reference “non-vasculitis” population with MI.

Methods: The study cohort consisted of 1527 patients with SV (GCA n=1202; AAV n=325) diagnosed between 1997-2016 in Skåne, southern Sweden. Using a unique personal identification number, the SV cohort was linked to the national SWEDEHEART register which covers every coronary care unit admission in Sweden. All cases with SV diagnosed with acute MI after the onset of SV were identified and, matched with 10 controls (age, sex and year of MI diagnosis). Baseline characteristics were compared between SV-patients and controls. The risk for death at 1, and 3 years after the MI was assessed using a Cox regression model.

Results: A total of 86 patients (6%) were diagnosed with incident MI corresponding to proportions of 7% and 5% among AAV and GCA patients respectively. Table 1 presents the baseline characteristics of patients with SV and reference subjects. A history of MI, in particular, and stroke was less common in patients with SV. Patients with SV presented more often with elevated CRP and had on average lower haemoglobin levels. The frequency of STEMIs was slightly higher in patients with SV but there were no differences in treatment strategy, with equal proportion of patients undergoing angiography and percutaneous coronary intervention with stent implantation among patients with SV and their controls. There were no differences in the 1-year and 3-year mortality, hazard ratio (HR) of 1.16 (95% CI, 0.71-1.89) and 0.98 (95% CI, 0.64-1.49), respectively. Subgroup analyses investigating the 1-year all-cause mortality in AAV and GCA separately showed no outcome differences compared to controls, with HR 1.26 (95% CI, 0.52-3.08) and 1.11 (0.63-1.95) respectively.

Conclusions: In this population-based cohort, patients with systemic vasculitis suffering from myocardial infarction were less likely to have a previous history of cardiovascular events compared to controls. Apart from this, they had a comparable risk profile at presentation, were treated to the same extent with percutaneous coronary intervention and showed no difference in outcome compared to matched controls. One- and 3-year all-cause mortality was not increased in patients with SV after their MI diagnosis. The impact of glucocorticoids and other

anti-inflammatory therapies on the risk of atherothrombosis and related outcomes should be further studied.

Disclosures: Nothing to disclose.

Table 1. Baseline Characteristics of patients with systemic vasculitis and their reference population at the time of myocardial infarction diagnosis.

Variable	Reference	SV	p-value
n of events	776	86	NA
Demographics			
Age, years	76.0 (71.0-82.0)	77.0 (71.0-83.0)	0.65
BMI, kg/m^2	25.8 (23.4-28.8)	25.8 (23.5-27.2)	0.38
Female sex	444 (57.2%)	51 (59.3%)	0.71
Smoking status			
Never smoked	335 (43.2%)	45 (52.3%)	0.18
Ex-smoker	285 (36.7%)	24 (27.9%)	0.18
Current smoker	106 (13.7%)	10 (11.6%)	0.18
Comorbidities			
Diabetes	164 (21.2%)	16 (18.6%)	0.57
Hypertension	403 (52.1%)	46 (53.5%)	0.81
History of MI	261 (33.9%)	15 (17.4%)	<0.01
Stroke	66 (11.2%)	5 (7.6%)	0.37
Medications at baseline			
ACE-I/ARB	296 (38.3%)	26 (30.2%)	0.14
Beta-blockers	341 (44.1%)	35 (40.7%)	0.55
Aspirin	364 (47.0%)	33 (38.4%)	0.13
Statins	253 (32.7%)	27 (31.4%)	0.80
Ca-Inhibitors	141 (18.2%)	20 (23.3%)	0.26
Clopidogrel	59 (7.7%)	4 (4.7%)	0.32
In-hospital characteristics			
SBP, mmHg	150.0 (130.0-167.0)	140.0 (120.0-158.0)	0.02
DBP, mmHg	80.0 (70.0-90.0)	75.0 (65.0-90.0)	0.15
S-Creatinine, umol/L	87.0 (71.0-111.0)	92.0 (73.0-117.0)	0.27
Biomarkers			
Troponin T, ng/L	0.7 (0.3-2.8)	1.2 (0.3-8.1)	0.30
HS-Troponin-T, ng/L	334.0 (128.0-1367.0)	385 (145.0-1554.0)	0.71
CRP, mg/L	5.2 (2.0-16.0)	8 (4.7-49.0)	<0.01
Hemoglobin, g/L	133.0 (120.0-145.0)	126.0 (116.0-139.0)	0.08
Type of MI			
NSTEMI	620 (79.9%)	64 (74.4%)	0.23
STEMI	156 (20.1%)	22 (25.6%)	0.23
Angiography			
Procedures, n	496 (63.9%)	54 (62.8%)	0.84
Stent implanted	285(58%)	32 (59%)	0.85

SV: Systemic Vasculitis; NA: Not applicable; BMI: Body mass index; ACE-I: angiotensin converting enzyme inhibitors; ARB: Angiotensin II receptor blockers; Ca-inhibitors: Calcium channel inhibitors; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HS-Troponin-T: High Sensitive Troponin T; S-: serum; CRP: C-reactive protein; NSTEMI: Non-ST-Elevation Myocardial Infarction; STEMI: ST-Elevation Myocardial Infarction

255. Aneurysmal Disease in Patients with Takayasu Arteritis: a Canadian Perspective

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Background: Takayasu Arteritis (TAK) most often leads to stenotic and occlusive disease. Aneurysmal lesions are rarer, though frequencies vary in literature, likely related to sample size, ethnicity, selection process & imaging modalities used. This study aims to evaluate the frequency, as well as main characteristics, of aneurysmal disease in a Canadian cohort of TAK patients.

Methods: This single-centre study included TAK patients, followed at Mount Sinai's Vasculitis Clinic (Toronto), from its inception in 2002 up to January 2021. Diagnosis of TAK was based on clinical presentation, laboratory measures & imaging studies, and/or satisfied the 1990 ACR classification criteria. Baseline demographics, disease-specific characteristics, medical and endovascular treatments were extracted from medical charts, as well as existing centre (CanVasc) database. Information on vascular territory involvement and type of arterial lesion were recorded using reports from available imaging, including conventional angiography, CTA, MRA, PET-Scan and/or TTE/TEE.

Results: The cohort comprised 74 patients. Aneurysmal disease was found in 23 (31.1%) of them, at any time during their follow-up. Median disease duration, in these 23 patients with aneurysms, was 9 [7-19] years; most were female (87%), of Caucasian (42.9%) or Asian (42.9%) descent (Table 1). Prior hypertension (p = 0.016) was more common in patients with aneurysms, who also reported more fever (p = 0.04), seizure disorders (p = 0.03), but had less vascular symptoms (p = 0.04), such as less limb claudication (p = 0.013), than those without aneurysms. At last follow-up, 22 of these 23 patients had repeat imaging showing persistent and/or new aneurysms (renal aneurysm had regressed in one patient, under medical treatment only). Thoracic aorta aneurysm (n = 13/22 (59.1%)) was the most common, followed by abdominal aorta aneurysm (n = 8/22 (36.4%)). Aorta vasculitis involvement had previously been diagnosed in all of these patients (p = 0.05, for comparison with patients without aneurysms); aortic valve regurgitation was also more frequent (9/23 (39.1%); p = 0.001). Most patients with aneurysms (21/23 (91.3%)) had been treated with glucocorticoids (median duration of 6.1 years [3.7-8.1]). Methotrexate, azathioprine and leflunomide were used in 69.6%, 47.8% & 30.4% of patients, respectively. In patients with aneurysmal disease, infliximab (n = 7/23 (30.4%)) was used more often than in those without (p = 0.04). Tocilizumab was received only by 4/74 patients, all with aneurysmal disease (p = 0.008). At last visit, 65.2% of patients with aneurysms were still on immunosuppressives, compared to 49% without (p = 0.196). Patients with aneurysms suffered more frequent vasculitis relapses (2 [0-4] vs 1 [0-2] in

patients without aneurysms; p = 0.038). Aorta repair was required in 5/23 (21.7%) of patients; no aneurysmal rupture or deaths were recorded.

Conclusions: Aneurysmal disease, most often thoracic, was found in a significant proportion of patients with TAK. Given that aneurysms may carry a risk of rupture, and are associated with a higher rate of relapse, they should be analyzed and reported systematically in TAK studies.

Disclosures: None

TABLE 1
Main Characteristics of TAK Patients, With or Without Aneurysmal Lesions

		With Aneurysm (n = 23)	**Without Aneurysm** (n = 51)	p-value
Demographic Characteristics				
Female, n/N (%)		20/23 (87.0%)	49/51 (96.1%)	0.170
Age at diagnosis (years), mean (SD)		27.9 (10.9)	33.3 (11.9)	0.069
Ethnicity, n/N (%)				0.016
	Caucasian	9/21 (42.9%)	20/48 (41.7%)	
	Asian	9/21 (42.9%)	18/48 (37.5%)	
	Other	3/21 (14.3%)	10/48 (20.8%)	
Follow-up duration (years), median (IQR)		9 (7-19)	12 (7-19)	0.665
Prior Hypertension, n/N (%)		16/23 (69.6%)	20/51 (39.2%)	0.016
Renovascular Hypertension, n/N (%)		8/23 (34.8%)	16/51 (31.4%)	0.772
Clinical Manifestations				
Fever, n/N (%)		7/23 (30.4%)	5/51 (9.8%)	0.040
Headache, n/N (%)		9/23 (39.1%)	16/51 (31.4%)	0.514
Seizure, n/N (%)		4/23 (17.4%)	1/51 (2.0%)	0.030
Vascular symptoms, n/N (%)				
	All/Any	16/23 (69.6%)	46/51 (90.2%)	0.040
	Claudication	12/23 (52.2%)	41/51 (80.4%)	0.013
	Stroke	3/23 (13.0%)	11/51 (21.6%)	0.527
Vessel Involvement				
Stenosis, n/N (%)		21/23 (91.3%)	49/51 (96.1%)	0.584
Arterial Wall Thickening, n/N (%)		21/23 (91.3%)	40/51 (78.4%)	0.322
Aneurysm Anatomy				
At Last Follow-Up, n/N (%)				
	Ascending Aorta	9/69 (13.0%)		
	Aortic Arch	5/69 (7.2%)		
	Descending Aorta	7/71 (9.9%)		
	Abdominal Aorta	8/71 (11.3%)		
	Carotid Artery	6/71 (8.5%)		
	Vertebral Artery	1/66 (1.5%)		
	Subclavian Artery	7/71 (9.9%)		
	Iliac Artery	1/40 (2.5%)		

256. Cardiovascular Burden in Patients with ANCA-Associated and Non-ANCA Associated Vasculitis

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Background: ANCA-associated vasculitis (AAV) comprises a group of rare auto-inflammatory diseases. Patients with AAV are at risk of complications from both their disease and its treatment. Several studies have reported that these patients are at increased risk of cardiovascular complications from accelerated atherosclerosis with an excess cardiovascular (CV) risk of 65%.[1,2]. One such study of 535 participants from four European Vasculitis Society (EUVAS) trials revealed that 14% of patients with GPA or MPA developed CV events within 5 years of diagnosis. It also showed that independent determinants of CV outcome were older age, diastolic hypertension (HTN), and PR3-ANCA (OR 0.39, 95% CI 0.20 to 0.74).[3] HTN and diabetes mellitus (DM) are two of the most reported treatment related complications observed at long-term follow-up. Given that HTN and DM are well-known CV risk factors, it is unsurprising that patients with AAV are at increased risk for CV disease. However, the risk of CV disease is greater in AAV and cannot be explained through traditional CV risk factors alone.[4] ANCA are harmful antibodies that are directly involved in blood vessel damage through neutrophil and complement cascade activation, but it is unclear if they are directly responsible for the higher rate of CV complications in AAV.[5] Therefore, we aimed to compare ANCA-associated and non-ANCA associated vasculitis and their associations with mortality and CV outcomes.

Methods: In this retrospective cohort study, we identified patients with ANCA-associated and non-ANCA-associated vasculitis based on ICD-10 codes, using the Nationwide Inpatient Sample database (NIS) from 2016 to 2019. We included all-cause mortality, atrial fibrillation (Afib), ST-elevation (STEMI) and non-ST elevation myocardial infarction (NSTEMI), heart failure (HF), cerebrovascular accident (CVA), and peripheral arterial disease (PAD) as our outcomes of interest. We implemented logistic regression analysis in the univariable and multivariable models. In the multivariable model, we adjusted all outcomes for potential confounders, including age, sex, ethnicity, obesity, anemia, diabetes, hypertension, renal failure, history of smoking or alcohol abuse, prior history of MI, primary coronary intervention (PCI), or coronary artery bypass grafting (CABG), coagulopathy, liver disease, chronic pulmonary disease, ischemic cardiomyopathy, Elixhauser comorbidity index, hypothyroidism, cancer, history of defibrillator or pacemaker, and long-term use of steroids, anticoagulants, antiplatelet or antithrombotic agents. The analysis was done using the STATA software, version 17.0 (SE).

Results: We identified 141,470 patients with vasculitis, of whom 55,695 (39%) had AAV and 85,775 (61%) had non-ANCA associated vasculitis. Our results showed that patients with AAV had a higher mortality (OR: 1.17; 95%-CI 1.00-1.37; p-value = 0.045) when compared to patients with non-ANCA associated vasculitis even after adjusting for potential confounders. There was no difference in risk of ACS between the two groups (OR: 0.88; 95%-CI 0.75-1.03;

p-value = 0.12). AAV was associated with a lower risk of Afib (OR: 0.74; 95%-CI 0.68-0.81; p-value <0.001), HF (OR: 0.65; 95%-CI 0.60-0.71; p-value < 0.001), CVA (OR: 0.57; 95%-CI 0.51-0.64; p-value < 0.001) and PAD (OR: 0.56; 95%-CI 0.50-0.62; p-value < 0.001) when compared with patients with non-ANCA vasculitis.

Conclusions: Patients with AAV had a higher risk of in-hospital mortality. However, patients with non-ANCA vasculitis had a higher prevalence of Afib, ACS, HF, CVA, and PAD which may be related to their older age and larger vessel involvement. These results suggest that ANCA antibodies alone are not responsible for increased CV disease in this population.

Disclosures: None

Table 1. Comparison of mortality and CV outcomes in patients with AAV vs non-ANCA associated vasculitis

			Univariate analysis		Multivariate Analysis		
Outcomes	ANCA-associated vasculitis	Non-ANCA associated vasculitis	OR with 95% Confidence Interval	P-value	OR with 95% Confidence Interval	P-value	ROC for Multivariate Model
	N= 55695 (39.4%)	N= 85775 (60.6%)	ANCA-associated vs non-ANCA associated vasculitis		ANCA-associated vs non-ANCA associated vasculitis		
Mortality (%)	2495 (4.1)	2730 (3)	1.41 (1.24-1.61)	<0.001	1.17 (1.00-1.37)	0.045	0.77
Afib (%)	7370 (13.2)	15605 (18.2)	0.69 (0.64-0.74)	<0.001	0.74 (0.68-0.81)	<0.001	0.8
ACS: STEMI & NSTEMI (%)	4285 (7.7)	13705 (16)	0.74 (0.64-0.85)	<0.001	0.88 (0.75-1.03)	0.12	0.76
HF (%)	14045 (25.2)	23130 (27)	0.91 (0.86-0.97)	0.002	0.65 (0.60-0.71)	<0.001	0.86
CVA: Stroke &TIA (%)	5845 (10.5)	16620 (19.4)	0.44 (0.40-0.48)	<0.001	0.57 (0.51-0.64)	<0.001	0.7
PAD (%)	1465 (2.63)	3035 (3.54)	0.49 (0.45-0.53)	<0.001	0.56 (0.50-0.62)	<0.001	0.8

257.. Evidence of ultrasound subclinical atherosclerosis in Eosinophilic Granulomatosis with Polyangiitis (EGPA)

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Background: Atherosclerosis is a multifactorial chronic inflammatory process involving the innermost layer of arteries. In addition to traditional risk factors, non-traditional ones, such as systemic inflammation and endothelial activation are determinant in atherosclerosis progression. Patients suffering from anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) display a two-fold incidence of cardiovascular thrombotic events, partially reflecting (o suggesting) the endothelial damage mediated by ANCA and other inflammatory mediators. Intima-media thickness (IMT) has been demonstrated to mirror generalized atherosclerosis and to directly correlate with cardiovascular disease risk. An increased subclinical atherosclerosis (defined as increased IMT and presence of carotid plaques) has been reported in Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA). Eosinophilic Granulomatosis with Polyangiitis (EGPA, formerly known as Churg-Strauss syndrome) is a rare AAV in which eosinophil-mediated manifestations coexist with vasculitic ones. Eosinophils are known to contribute to a prothrombotic state through the release of tissue factor, which initiates coagulation, and cationic proteins which inhibit natural anticoagulant activity and activate platelets. Despite arterial events being more common in EGPA than in normal population, no data exist on subclinical atherosclerosis in these patients. Objective: The present study aims to evaluate accelerated subclinical atherosclerosis in a cohort of EGPA patients by vascular ultrasound assessment of carotid IMT and the presence of carotid plaques.

Methods: Forty EGPA patients and 80 controls matched by age, gender, and major cardiovascular risk factors were included. All participants underwent sonographic IMT measurement and detection of plaque in the common carotid arteries (CCA). IMT was considered increased when exceeding 0.9 mm, while the presence of carotid plaques was defined as an IMT greater than or equal to 1.3 mm. CCA-IMT levels and the presence of carotid plaques were compared between patients and controls. Furthermore, in the patient's group, markers of subclinical atherosclerosis were evaluated according to disease phenotype (vasculitic vs eosinophilic), ANCA-status, disease duration, cumulative steroid dose, and immunosuppressive treatments. Patients were also evaluated according to the number of relapses, Vascular Damage Index (VDI) at ultrasound examination, and Five-Factor Score (FFS) at disease onset, which were considered as an expression of disease severity.

Results: Demographic and clinical characteristics of both EGPA and controls are shown in *Figure 1A*. No differences in terms of traditional cardiovascular risk factors between EGPA

patients and controls. However, CCA-IMT was significantly higher in EGPA compared to controls (median, 1.03 mm vs 0.79 mm; p=0.0002) *(Figure 1B)*. The proportion of subjects with increased CCA-IMT levels was significantly higher among patients than controls (75% vs 37%; p<0.0001) *(Figure 1B)*. Also, the presence of carotid plaques was more frequent among EGPA cases (42.5% vs 13.75%; p<0.0001) *(Figure 1B)*. Within the EGPA cohort, CCA-IMT directly correlated with disease duration (Spearman's rho 0,034) and with corticosteroid cumulative dose (Spearman's rho 0,004). No significant differences were found based on immunosuppressive treatment (steroids alone vs DMARDs plus steroids). Also, no significant differences in CCA-IMT levels nor the presence of carotid plaques were found when patients were stratified according to vasculitis phenotype, ANCA-status, number of relapses, VDI, and FFS. When EGPA patients were divided based on the presence or absence of increased IMT, no differences were found in the prevalence of traditional cardiovascular risk factors (data not shown).

Conclusion: Ultrasound markers of subclinical atherosclerosis are increased in EGPA patients in respect of controls, independently of traditional cardiovascular risk factors. A longer disease duration and a higher cumulative corticosteroid dosage, but not the disease phenotype and severity, seem associated with increased IMT in EGPA patients.

Disclosure: The Authors have declared no conflicts of interest.

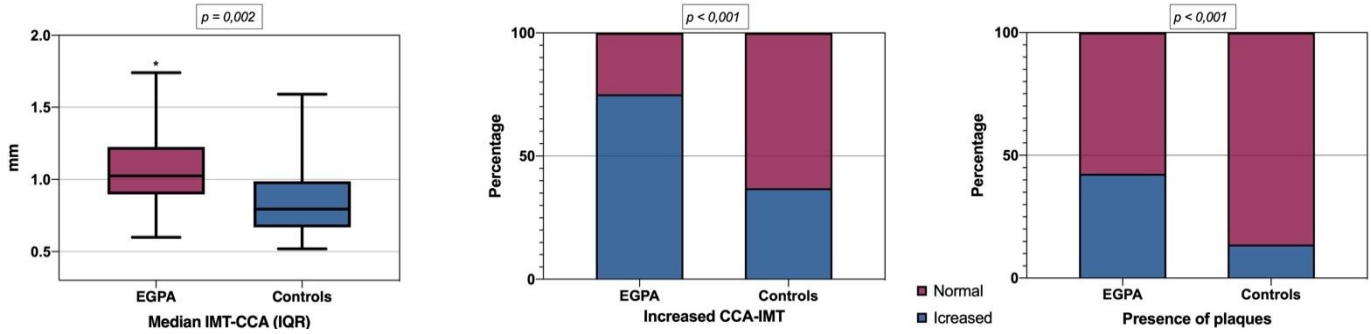
Figure 1. A- Demographic and clinical features of EGPA patients and controls. B- Comparison of mean CCA-IMT and presence of increased IMT and carotid plaques between EGPA patients vs controls.

A.

	EGPA patients (N; % out of 40)	Controls (N;% out of 80)	p-value
Demographic characteristics			
Age at disease onset (median (IQR))	53.0 (43.0 – 62.0)		
Age at sonographic IMT assessment (median (IQR))	59 (48-71)	56.0 (45.0 – 69.0)	0.229
Female sex	24 (60.0)	47 (58.8)	1.000
Smoking habit	7 (17.5)	13 (16.3)	1.000
Comorbidities			
Hypertension	20 (50.0)	35 (43.8)	0.563
Hypercholesterolemia	17 (42.5)	34 (42.5)	1.000
Diabetes	2 (5.0)	5 (6.3)	1.000
Obesity	0	0	-
Atrial fibrillation	4 (10.0)	0	n.a.
Cancer	3 (7.5)	0	n.a.
Disease duration (months)	65 (35-86)		
Disease manifestations			
Asthma	40 (100.0)		
Ear-nose-throat (ENT) involvement	33 (82.5)		
Peripheral nervous system	24 (60.0)		
Heart	13 (32.5)		
Gastrointestinal	8 (20.0)		
Skin	8 (20.0)		

Kidney	2 (5.0)
Articular	1 (2.5)
Ocular	1 (2.5)
ANCA positivity	18 (45.0)

B.



EGPA = eosinophilic granulomatosis with polyangiitis; ANCA= anti-neutrophil cytoplasmic antibodies; CCA = common carotid artery; IMT = intima-media thickness;

258. Cardiac involvement in EGPA: interval CMR Imaging to monitor response to treatment

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Background: Cardiac involvement in EGPA is common and associated with both early and late morbidity and mortality. However, optimum approaches to diagnosis, treatment and follow up are unclear.

Methods: Retrospective review of patients with myocardial involvement in EGPA treated with steroids, rituximab and cyclophosphamide, who underwent interval Cardiac MR imaging to monitor response. Data are presented as median +IQR unless stated otherwise.

Results: *Clinical Presentation:* Six patients (3 male; age 54 years [46-63]) presented between 2016-20. All had history of asthma, and 4 had prior diagnosis of sinusitis/ nasal polyposis. At EGPA diagnosis, peak eosinophil count was 9.9 x10^9/L [5.3-17.0] and all tested patients had negative cytogenetics / molecular diagnostics to exclude haematologic hypereosinophilic syndromes. Median CRP and ESR were 157 mg/L [100-223] and 70 mm/hr [27-79], respectively, and 3 patients were MPO-ANCA positive (median titre 134 iu/mL). The proportion of patients affected by active/new ENT, lung, cutaneous and neurological disease at diagnosis were 4/6, 5/6, 3/6 and 3/6, respectively. All patients had some evidence of kidney involvement (serum creatinine 117 µmol/L [86-191], urinary protein 89 mg/mmol [58-116]). Three patients underwent kidney biopsy, confirming a pauci-immune glomerulonephritis.All patients had cardiac disease presenting with reduced exercise tolerance (4/6), oedema (3/6) and/or chest

pain (1/6). ECG changes were present in 4/6 and abnormal echocardiographic findings were present in 4/6. All had elevated cardiac troponin concentrations (peak 10,762 ng/L [399-64,102) and CMR evidence of myocarditis (see below). *Treatment & Outcome:* Patients were followed for an average of 30 months [14-69]. All received treatment with high-dose steroids, iv cyclophosphamide and rituximab, with azathioprine maintenance. By 3 months all achieved clinical disease remission with improvements in laboratory parameters: median eosinophil count 0.1 $x10^9$/L , CRP 0.75 mg/L, sCr 106 µmol/L, uPCR 16.5 mg/mmol, and MPO-ANCA (median titre 4.9 iu/mL). Serum troponin normalised in all patients. At 12 months, all patients were in sustained remission. *CMR findings:* All patients had baseline and interval CMR imaging (Figure), with 1st follow up scan performed at 3.5 months [3.2. - 3.7]. Average LV function at baseline was 47 EF units (range 25-61 EF units) and at follow-up was 56 EF units (range 36-65). The average change in LV function with treatment was +9 EF units. All cases had evidence of oedema on the initial scan, and this improved in all cases (though remained borderline abnormal in all cases when quantified by T2 mapping). 5/6 cases had late gadolinium enhancement on their scan at presentation and this persisted in every case though with significantly lower burden. Apical thrombus was present in 3/6 cases at baseline but persisted in only 1/6 at follow-up.

Conclusions: Cardiac MRI identifies a range of phenotypes in EGPA including different scar patterns, the presence of apical thrombus, and ongoing disease activity. Although response to treatment is often significant, residual myocardial scarring (and low grade oedema) is common. Further work will elucidate the implications of this convalescent phenotype on disease course and prognosis, and the optimum treatment for cardiac disease in EGPA.

Disclosures: The authors have no relevant financial disclosures

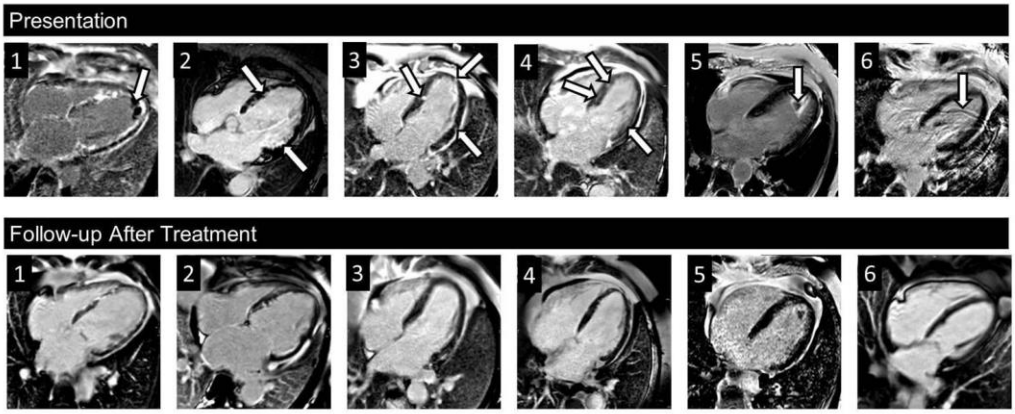

Figure Legend: 4-chamber late gadolinium enhancement cardiac MRI imaging demonstrating the spectrum disease at presentation and following treatment. 1 - extensive subendocardial enhancement throughout the LV involving the RV and including apical LV thrombus. 2 and 3 - multiple small subendocardial areas of enhancement. 4 - mixed pattern with subendocardial and mid-wall enhancement. 5 - apical subendocardial enhancement with embedded thrombus. 6 - no late enhancement (artefact from failure of breath-holding arrowed highlighting the challenges of imaging patients with lung disease). The lower row shows a spectrum of responses including resolution of thrombus (1), persistence of thrombus (5), dramatic reduction in late enhancement (1), partial response (2, 3, 4) and minimal response (5).

ENT and/or Pulmonary Disease

259. Are there any different findings in AAV-related pulmonary involvement in comparison with CTD or IPF

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Background: Patients with ANCA associated vasculitis (AAV) have a wide spectrum of pulmonary involvement from parenchymal necrotizing granuloma formation, trecheobronchial inflammation, pulmonary capillaritis to interstitial lung disease. Pulmonary involvement is relatively common in connective tissue diseases (CTDs). Both rheumatologic disorders and idiopatic pulmonary fibrosis (IPF) might cause the usual interstitial pneumonia (UIP) pattern. However, little is known regarding the clinical and radiologic similarities/ dissimilarities of those diseases. We aimed to evaluate the thoracic computed tomography (CT) findings of patients with AAV, CTDs-related interstitial lung disease (ILD) or IPF.

Methods: Patients whose thoracic CT performed at the time of the diagnosis or relapse of AAV (n=64), at the time of the diagnosis of CTD related ILD (n=55) or IPF (n=52) were included in the analysis. Demographic, clinical and serological data were collected retrospectively. Radiological patterns of pulmonary involvement were evaluated by two expert pumonary radiologists and abnormal thoracic CT findings were classified according to Fleischner Society guidelines. Intra- and inter-observer variation were calculated. Multonominal logistic reggresion was performed to identfy disease specific findings in thoracic CT.

Results: A total of 171 patients were involved and of them 64 patients (57.8% with granulomatosis with polyangiitis, 42.2% with microscopic polyangiitis) in AAV group, 55 patients in CTD related ILD (50.9% with scleroderma, 40.0% with rheumatoid arthritis, 9.1% other or undifferensiye connective tisue disease) group and 52 patients in IPF group. Demographic and thoracic CT findings were summarized in table 1. In univariate analysis according to Fleishner Society definition, patients with AAV had more common pulmonary noduls, cavities, consolidation. However, patients with AAV were less likely to have interlobular septal thickening (ILST), lymph node adenopathy (LAP) and reticulation compared to both CTD related ILD and IPF. In multivariate analysis with multinominal logistic reggresion, the presence of nodul and consolidation and the absence of ILST and mediastinal LAP were independent determinant findings in thoracic CT in patients with AAV in comparison with both CTD related ILD or IPF (Table 2).

Conclusions: The results of this study show that in additon to clinical and labaratory characteristics, some thoracic CT imaging findings like the presence of nodules and

consolidation and the abscence of LAP and ILST may be useful to differentiate pulmonary involvement of AAV from other relatively common rheumatologic conditions and IPF.

Disclosures: None

Table 1. Demographic characteristics and Thoracic CT findings of patients

	AAV patients (n=64)	CTD related ILD (n=55)	IPF (n=52)	p
Characteristics				
Age at diagnosis, yrs, mean (SD)	58.6 (15.0)	61.8 (12.0)	72.4 (9.4)	<0.001
Sex, male, %	70.3	30.9	75	<0.001
Smoking, ever, %	77.8	26.5	62.8	0.29
Chest CT findings according to Fleishner guideline, %				
Ground glass opasity	30.2	38.2	9.6	0.019
Reticulation	19.4	52.7	94.2	<0.001
Interlobular septal thickening	29.0	69.1	98.1	<0.001
Peribronchial thickening	11.3	20.0	3.8	0.27
Honeycombing	14.5	25.5	63.5	<0.001
Bronchiectasis	31.7	47.3	86.5	<0.001
Consolidation	46.8	12.7	5.8	<0.001
Micronodules	6.6	3.6	0	0.06
Nodules	48.4	10.9	3.8	<0.001
Cavities	22.6	0	0	<0.001
Eymphysema	19.4	7.3	19.2	0.91
Mosaic attenuation pattern	6.5	20.0	38.5	<0.001
Mediastinal lymph node adenopathy	26.8	53.7	57.7	0.001
Pleural effusion	15	1.8	0	0.001
Pericardial effusion	6.7	9.1	0	0.14

Table 2. Multinominal logistic regression analysis of ANCA-associated vasculitis compared with both CTD-related ILD and IPF

	AAV vs CTD-related ILD		AAV vs IPF	
	B (CI 95%)	p	B (CI 95%)	p
Interlobular septal thickening	-1.723 (0.052-0.609)	0.006	-4.231 (2.765- 107.681)	0.002
Nodules	3.116 (4.682-108.635)	<0.001	4.744 (12.246-1076.944)	<0.001
Bronchiectasis	0.188 (0.363-4.013)	0.76	-1.728 (0.040-0.789)	0.023
Consolidation	2.475 (3.144- 44.944)	<0.001	2.848 (2.765-107.681)	0.002
Mediastinal lymph node adenopathy	-2.113 (0.030- 0.487)	0.003	-1.867 (0.032- 0.743)	0.020

260. Which one is important in thoracic CT findings; ANCA subtype or subgrups of ANCA-associated vasculitis?

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Objectives: Antineutrophil cyctoplasmic antibody (ANCA) associated vasculitdes (AAV) are a group of systemic vasculitis and associated with ANCA. Myeloperoxidase ANCA (MPO-ANCA) is mostly associated with microscopic polyangiitis (MPA) and proteinase-3 ANCA (Pr3-ANCA) is associated with granulomatosis with polyangiitis (GPA). Pulmonary involvement is one of the most common presentation in AAV. In recent years, the differences of clinical characteristics and organ involvement in ANCA subtype groups (MPO-ANCA and Pr-3 ANCA group) have been subject of research. We aimed to investigate the impact of ANCA subtype or diagnosis of GPA or MPA on thoracic computed tomography (CT) findings in patients with AAV.

Methods: Patients with AAV who had thoracic CT at the time of the diagnosis or relapse (n=116) were studied and patients who had anormal thoracic CT findings (n=64) were involved. Demographic, clinical and serological data were collected retrospectively. Radiological patterns of pulmonary involvement were evaluated by two expert pulmonary radiologists. Intra- or inter-observer variation was calculated. Binary logistic regression was performed to identify ANCA subtype or AAV subtypes related finding in thoracic CT.

Results: Sixty four patients with AAV (57.8% with GPA, 42.2% with MPA, 70.3% male, median [IQR] age at diagnosis 56 [21]) were involved. In patients with MPA, 15 (55.6%) of them MPO-ANCA positive, 3 (11.1%) Pr-3 ANCA positive and 9 (33.3%) were ANCA negative. In patients with GPA, 30 (81.9%) of them Pr-3 positive, 4 (10.8%) MPO-ANCA positive, 3 (8.1%) were ANCA negative. When we analyzed patients according to ANCA subgroups the most common abnormal findings were consolidation (51.5%), nodules (54.5%), cavities (27.3%) and ground glass opacity (27.3%) in Pr3-ANCA positive patients. Interlobular septal thickening (ILST) (55.6%), bronchiectasis (52.6%) and ground glass opacity (47.4%) were common findings in MPO-ANCA positive patients. Bronchiectasis, mosaic attenuation, reticulation, honeycombing and interlobular septal thickening were more common in MPO-ANCA positive group than Pr-3 ANCA positive group. However, the percentage of nodules and cavities were not statically different in MPO-ANCA positive and Pr3-ANCA positive groups (Table). When we performed multivariate analysis by binary logistic regression, honeycombing was the only independent determinant (B:-3.060; CI%95 [0.02-0.881], p=0.041) in ANCA subtype.
Moreover, we analyzed patients in two diagnostic groups (GPA or MPA) we found that nodules (64.9%), consolidation (48.6%) and cavities (37.3) were common in patients with GPA; ILST (42.3%), bronchiectasis (40.7%) and consolidation (40.7%) were common in patients with MPA. Honeycombing was common in MPA group meanwhile nodules and cavities were more

frequent in GPA group (Table). When we performed multivariate analysis by binary logistic regression, there was no independent finding between subgroups of AAV.

Conclusion: Our results showed that if we classified AAV patients according to ANCA subtypes honeycombing was the only independent determinant in favor of MPO-ANCA positive group. However, in subgroups of AAV there was no independent determinant in thoracic CT.

Disclosures: None

Table. Thoracic CT findings according to subtypes of ANCA and subgroup of ANCA-associated vasculitis

Variables, n (%)	MPO-ANCA (+) (n=19)	Pr3-ANCA (+) (n=33)	*p*	MPA (n=27)	GPA (n=37)	*p*
Ground glass opasity	9 (47.4)	9 (27.3)	0.23	10 (37.0)	9 (24.3)	0.29
Reticulation	8 (44.4)	3 (9.1)	0.003	8 (30.8)	4 (10.8)	0.06
Interlobular septal thickening	10 (55.6)	6 (18.2)	0.01	11 (42.3)	7 (18.9)	0.05
Peribronchial thickening	3 (16.7)	3 (9.1)	0.65	3 (11.5)	4 (10.8)	1.0
Honeycombing	7 (36.8)	1 (3.1)	0.001	7 (25.9)	2 (5.6)	0.03
Bronchiectasis	10 (52.6)	6 (18.2)	0.014	11 (40.7)	9 (24.3)	0.18
Consolidation	8 (42.1)	17 (51.5)	0.57	11 (40.7)	18 (48.6)	0.62
Nodules	7 (36.8)	18 (54.5)	0.26	6 (22.2)	24 (64.9)	0.001
Cavities	2 (10.5)	9 (27.3)	0.29	0	14 (37.8)	<0.001
Eymphysema	5 (26.3)	4 (12.1)	0.26	8 (29.6)	4 (10.8)	0.10
Mosaic attenuation pattern	4 (21.1)	0	0.014	3 (11.1)	1 (2.7)	0.30
Lymph node adenopathy	6 (31.6)	7 (22.6)	0.52	6 (23.1)	9 (25.0)	1.0
Pleural effusion	2 (10.5)	3 (9.1)	1.0	6 (22.2)	3 (8.1)	0.15
Pericardial effusion	0	4 (12.1)	0.28	0	4 (10.8)	0.13

261. Interstitial lung disease is associated with an increased mortality in a latin-american anca-associated vasculitis cohort

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Background: To determine if interstitial lung disease (ILD) is associated with an increased mortality in patients with ANCA-associated vasculitis (AAV).

Methods: We included patients from a Latin American AAV cohort (Peru) whose diagnosis was performed between 2014 and 2020. A pulmonologist reviewed all available high resolution computer chest tomographies which allowed dividing the patients into ILD and non-ILD groups. Demographic and clinical features were recorded as well as ANCA-ELISA status and the five-factor score (FFS). Univariate and multivariate Cox proportional hazard models analysis were performed.

Results: Eighty-five patients were included; 57 of them (67.1%) were female. Their mean age was 59.3 (13.1) years. Fifty-five (64.7%) patients had ILD and for most of them the non-usual interstitial pneumonia was the pattern more frequent. During the follow-up, 51 (60.0%) patients died. Patients with AAV-ILD were older and had a lower frequency of ear, nose and throat (ENT) and ocular involvement. However, there were no differences regarding gender and ANCA status between the groups. After adjusting for age, sex, ANCA status and the FFS, ILD was associated with the occurrence of mortality [HR 3.76 (95%CI 1.40-9.59)].

Conclusions: In a Latin American AAV cohort, ILD was associated with an increased mortality after adjusting for relevant confounders. Older age and a lower frequent of ENT and ocular involvement were associated with ILD-AAV.

Disclosures: None

Table

	ILD (n=55)	**Non-ILD (n=30)**	**p value**
Female gender, n (%)	33 (60.0)	24 (80.0)	0.061
Age at diagnosis, mean (SD)	62.7 (12.4)	53.2 (12.2)	<0.001
FFS, n (%)			0.333
0	16 (29.1)	14 (46.7)	
1	26 (47.3)	11 (36.7)	
2	11 (20.0)	5 (16.7)	
3	2 (3.6)	0 (0.0)	

ANCA, n (%)			0.840
Negative	5 (9.1)	2 (6.7)	
MPO	38 (69.1)	20 (66.7)	
PR3	12 (21.8)	8 (26.7)	
Death, n (%)	28 (50.9)	6 (20.0)	0.005
Organ involvement, n (%)			
Renal	39 (70.9)	20 (66.7)	0.685
ENT	7 (12.7)	11 (36.7)	0.010
Ocular	11 (20.0)	12 (40.0)	0.047
Skin	17 (30.9)	4 (13.3)	0.073
Neurological	33 (60.0)	13 (43.3)	0.141
Diagnosis, n (%)			<0.001
EGPA	3 (5.5)	0 (0.0)	
MPA	40 (72.7)	11 (36.7)	
GPA	12 (21.8)	13 (43.3)	
RLV	0 (0.0)	6 (20.0)	

ILD: interstitial lung disease. FFS: five-factor score. ENT: ear, nose, throat. EGPA: eosinophilic granulomatosis with polyangiitis. MPA: microscopic polyangiitis. GPA: granulomatosis with polyangiitis. RLV: renal-limited vasculitis.

262. Clinical characteristics of participants with and without alveolar hemorrhage in the PEXIVAS trial

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Background: Alveolar hemorrhage (AH), a potentially life-threatening manifestation of ANCA-associated vasculitis (AAV), is characterized by bleeding into the distal air spaces of the lungs. Studies describing patients with AH in AAV are typically small and/or retrospective. Presented here are the baseline and outcome data for participants in the PEXIVAS trial with and without AH.

Methods: Clinical data were collected prospectively from 704 participants with AAV at 95 centers in 16 countries in PEXIVAS, a randomized controlled trial comparing 7 sessions of plasma exchange versus none, along with two glucocorticoid regimens. For the present analysis, treatment groups were combined and participants grouped based on presence or absence of AH at enrollment. Baseline characteristics and 1 year outcomes are summarized and compared. Participants with AH were, *a priori*, subcategorized as severe AH if they had an oxygen saturation ≤85% on room air.

Results: Among the 704 participants in PEXIVAS, 191 (27%) had AH and 513 (73%) did not have AH. Participants with AH were younger (mean age 61.1 years with AH vs. 63.9 without

AH, p=0.018), more frequently proteinase 3-ANCA positive (51.5% vs. 36.5%, p<0.001), and less frequently had newly-diagnosed (as opposed to relapsing) AAV (85.8% vs.93.0%, p=0.004). Participants with AH had higher baseline disease severity based on BVAS/WG (median 11 vs. 7, p<0.001) and lower serum creatinine (median 184 vs. 304 µmol/L, p<0.001), but were more frequently dialyzed at enrollment (25.3% vs. 18.0%, p=0.033). Additional baseline characteristics are presented in Table 1. Among the 191 participants with AH, 61 (31.9%) had severe AH, of which 29 (47.5%) required mechanical ventilation. Twenty-three (12.0%) participants with AH at enrollment died in the first year as compared to 34 (6.6%) without AH (p=0.019). Of the 23 deaths in the AH group, 16 (69.6%) occurred in those with severe AH. Among participants who died within 1 year of enrollment, 14 of 23 (60.9%) deaths among participants with AH occurred within 30 days of enrollment versus 11 of the 34 (32.4%) in those without AH (p=0.033). The risk of end-stage kidney disease (ESKD) and serious infections in the first year were similar between participants with and without AH (ESKD 16.0% vs. 13.1%, p=0.341; serious infections 41.4% vs. 39.2%, p=0.599).

Conclusions: Based on the PEXIVAS trial cohort, patients with AAV and AH have a high overall degree of disease severity and differ from those without AH in multiple other ways, including age, ANCA specificity, and use of dialysis, and are more likely to die within 30 days and 1 year. These prospectively-collected data among participants with a wide spectrum of severity of AH provide important insights into the characteristics of this disease manifestation of AAV as will analysis of the impact on AH of the different treatment regimens in the PEXIVAS trial.

Disclosures: Dr. Merkel reports the receiving funds for the following activities: Consulting and Research Support: AbbVie, AstraZeneca, Boeringher-Ingelheim, Bristol-Myers Squibb, ChemoCentryx, Forbius, Genentech/Roche, Genzyme/Sanofi, GlaxoSmithKline, InflaRx, Takeda. Consulting only: CSL Behring, Dynacure, EMDSerono, Jannsen, Kiniksa, Kyverna, Magenta, MiroBio, Neutrolis, Novartis, Pfizer, Sparrow, Talaris. Royalties: UpToDate. Remaining authors: None

Table 1. Baseline characteristics of participants with and without alveolar hemorrhage enrolled in the PEXIVAS trial. P-values are based on crude associations.

Characteristic	**Alveolar Hemorrhage n=191**	**No Alveolar Hemorrhage n=513**	**P-value**
Age, mean years (SD)	61.1 (15.4)	63.9 (13.4)	0.018
Female, n (%)	78 (40.8)	229 (44.6)	0.366
ANCA type, n (%)			
PR3	99 (51.8)	187 (36.5)	<0.001
MPO	92 (48.2)	326 (63.6)	
New diagnosis of AAV, n (%)	164 (85.8)	477 (93.0)	0.004
BVAS-WG, median (25^{th}-75^{th} percentile)	11 (9-13)	7 (6-9)	<0.001
Creatinine, median µmol/L (25^{th}-75^{th} percentile)	184 (115-320)	304 (212-442)	<0.001
Dialysis at baseline, n (%)	48 (25.3)	92 (18.0)	0.033
Randomized to plasma exchange, n (%)	95 (49.7)	257 (50.1)	0.932

Randomized to reduced glucocorticoid, n (%)	96 (50.3)	257 (50.1)	0.969
Immunosuppression, n (%)			
Oral cyclophosphamide	44 (23.0)	197 (38.4)	<0.001
Intravenous cyclophosphamide	107 (56.0)	247 (48.2)	
Rituximab	40 (20.9)	69 (13.4)	
1 Year Outcomes, n (%)			
Death	23 (12.0)	34 (6.6)	0.019
End-stage kidney disease	25 (13.1)	82 (16.0)	0.341
Serious infection	79 (41.4)	201 (39.2)	0.599

263. Diagnosis and clinical features of respiratory involvement in ANCA-associated vasculitis

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Background: Respiratory involvement is a heterogeneous clinical feature in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). This study aims to describe the frequency and characteristics of respiratory involvement in AAV and the risk factors for respiratory relapse.

Methods: We conducted a retrospective study between 2004 and 2019 of all patients over 18 years in Toulouse University Hospital (France) with a diagnosis of microscopic polyangiitis (MPA) or granulomatosis with polyangiitis (GPA). We collected the clinical and paraclinical data (including biological findings, pulmonary function tests, CT imaging, endobronchial lesions and bronchoalveolar lavage fluids). We classified respiratory involvement into four groups: diffuse alveolar haemorrhage (DAH), pulmonary nodules and masses, interstitial lung diseases (ILDs) -excluding DAH- and tracheobronchial involvement. Respiratory and non-respiratory relapses were also noted.

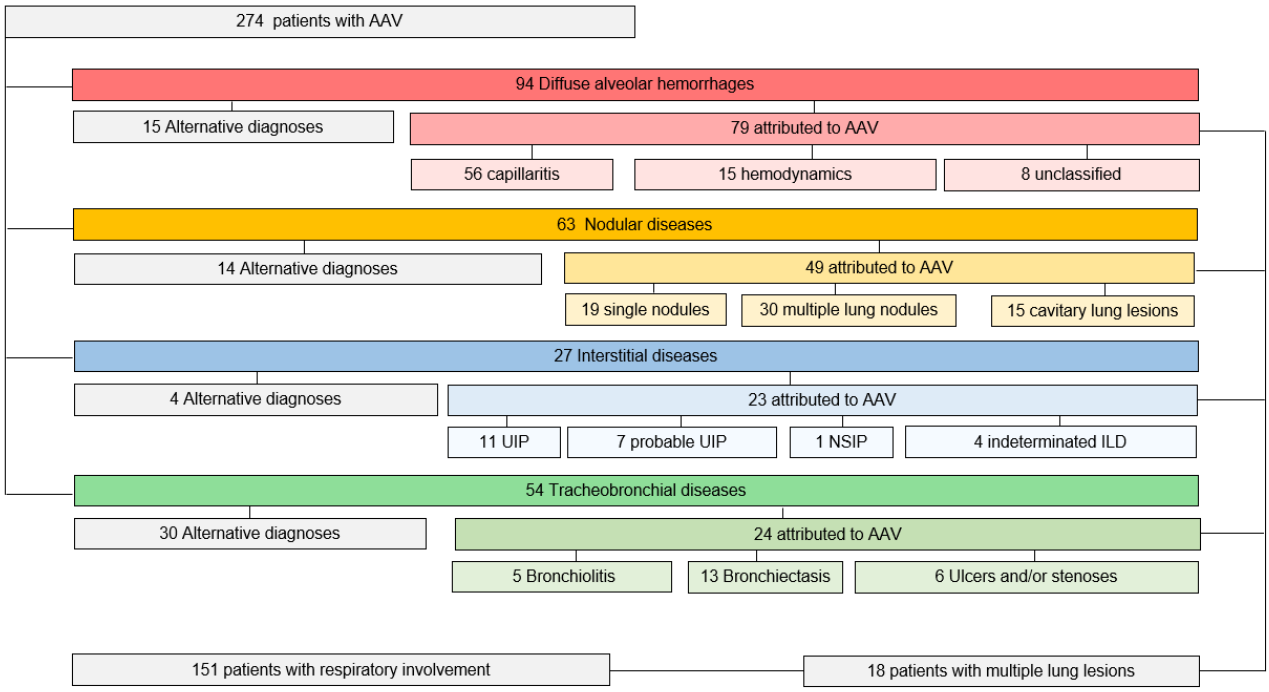
Results: Two hundred and seventy-four patients were included. One hundred fifty-one (55%) had respiratory involvement after excluding differential diagnoses (e.g. pulmonary infections, pre-existing lung diseases). DAH was the most frequent manifestation (52%), followed by nodules and masses (32%), tracheobronchial involvement (16%) and ILDs (15%). Alternative diagnoses to AAV were found in 55% of tracheobronchial presentations, 22% nodules, 16% DAH, and 15% ILDs. The coexistence of multiple lesions concerned 12% of patients.
A total of 86 patients (31%) experienced a relapse within a median of 66 months. Relapse occurred more frequently in anti-PR3 patients (p=0.0007) and those who had not received rituximab as maintenance therapy (p<0.0001). Of the 86 patients, 45 had respiratory relapse. Risk factors for respiratory relapse identified in the multivariate analysis were: initial respiratory involvement (HR 9.6; 95% CI [1.2; 74.6]; p=0.03), cardiovascular involvement (HR 6.4; 95% CI [1.7; 24.3]; p=0.006), mechanical ventilation (HR 21.6; 95% CI [1.9; 247.5]; p=0.014), blood

transfusion (HR 3.6; 95% CI [1.2; 10.7]; p=0.002) and the presence of cavitary lung lesions (HR 5.2; 95% CI [1.7; 15.8]; p=0.004). Rituximab used as induction therapy was a protective factor with a 4-fold lower risk for respiratory relapse (HR 0.23; 95%CI [0.06; 0.86]; p=0.03).

Conclusions: Respiratory involvement occurred in 55% of AAV patients at diagnosis. DAH is the most common, followed by nodular, tracheobronchial and interstitial involvement. Alternative diagnoses to AAV should be considered for lung lesions. Initial respiratory involvement was associated with an increased risk of respiratory relapse. Rituximab used as induction therapy may be associated with a reduced risk of respiratory relapse.

Disclosures: None.

Table.



264. Pulmonary function in patients with ANCA-associated Vasculitis

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Background: Although, pulmonary manifestations occur frequently in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV), empirical evidence of their impact on pulmonary function testing (PFT) is scarce. This project analyzed lung function data from a large cohort of patients with granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) to quantify a possible change in lung function according to each subtype.

Methods: Patients with AAV and least one valid PFT during their medical treatment encompassing the time period from 2008-2018 were identified retrospectively from the database of our vasculitis center in a tertiary university hospital. Patients with significant acute pulmonary comorbidities unrelated to AAV were excluded. The PFT comprised spirometry, plethysmography, and measurement of diffusing capacity including helium dilution technique. Data on forced vital capacity (FVCex), Tiffeneau-Index (rFEV1), total airway resistance (RAWtot), total lung capacity (TLC), residual volume (RV), and transfer factor (TLCO) were recorded. For the analysis these measures were expressed as a percentage of predicted values. First, the mean was compared to the defined standard value of the population (100%). Additionally, there was a comparison between patients with/without pulmonary manifestation in case history. Data were analyzed according to their distribution with t-test or Mann-Whitney-U-test for a significance level of $\alpha = 5\%$.

Results: *Table 1*. In total, 147 AAV-patients (GPA: n=81; MPA: n=37; EGPA: n=29) were included, of which 98 had a history of pulmonary involvement (GPA: n=50; MPA: n=20; EGPA: n=28). The mean age at the time of PFT was 58.5 years. Patients had a median disease duration of 8.5 months. In patients with GPA, FVCex, RV and TLCO were significantly reduced compared to expected normal values of 100% predicted. However, there was no significant difference between patients with or without pulmonary manifestations. In patients with MPA, even stronger reductions of FVCex and TLCO were observed compared to the population. These were accompanied by a decrease of TLC. The restrictive pattern and impairment of CO diffusion capacity was significantly stronger in MPA-patients with pulmonary involvement compared to patients without. In EGPA-patients RAWtot and RV were significantly elevated and TLCO was reduced.

Conclusions: Patients with MPA and interstitial lung disease show a significant restrictive ventilatory defect which is accompanied by a reduction of CO diffusion capacity compared to MPA-patients without pulmonary manifestation. As expected, many patients with eGPA have an obstructive ventilatory pattern which is related to the accompanying asthma. The interpretation of our data is limited by the retrospective design and potential indication bias for

PFT. Pulmonary function testing should be included in future prospective clinical trials in patients with AAV.

Disclosures: The authors declare that there is no conflict of interests as defined by the International Committee of Medical Journal Editors.

Table 1: Pulmonary function test results.
*On the left: comparison with 100% predicted of population. On the right: comparison between patients without (n1, first row) and with (n2, second row) pulmonary manifestation. Depending on the presence of Gaussian distribution bidirectional unpaired t-test or Mann-Whitney-U-test with a significance level of α = 5% were used for statistical analysis. Regarding to this mean value or median (cursive) was quoted. A significant p-Score is marked with *.*

	PFT Variables	n	Mean ± SD or *Median ± IQR*	p-Score „Population“	n1 n2	Mean ± SD or *Median ± IQR*	p-score „Involvement“
GPA	FVCex	77	78,95 ± 15,47	<0,001*	29 48	79,79 ± 15,63 78,44 ± 15,52	0,712
	rFEV1	79	100,32 ± 10,31	0,786	30 49	102,13 ± 10,68 99,20 ± 10,03	0,223
	RAWtot	50	*101,5 ± 80,0*	0,252	18 32	95,0 ± 85,0 101,5 ± 89,0	0,871
	TLC	52	96,60 ± 14,95	0,107	18 34	98,89 ± 15,01 95,38 ± 15,00	0,427
	RV	52	121,46 ± 31,82	<0,001*	18 34	*121,0 ± 30,0* *118,5 ± 39,0*	0,825
	TLCO	62	91,19 ± 22,38	0,003*	24 38	97,00 ± 23,32 87,53 ± 21,26	0,105
MPA	FVCex	34	*64,5 ± 31,0*	<0,001*	15 19	*87,0 ± 23,0* *57,0 ± 11,0*	<0,001*
	rFEV1	35	103,57 ± 13,78	0,135	16 19	*98,5 ± 12,0* *106,0 ± 17,0*	0,230
	RAWtot	22	*131,5 ± 75,0*	0,016*	9 13	*140,0 ± 93,0* *117,0 ± 87,0*	0,102
	TLC	22	85,82 ± 21,20	0,005*	9 13	*106,0 ± 13,0* *73,0 ± 29,0*	0,001*
	RV	22	103,00 ± 31,27	0,657	9 13	*118,0 ± 29,0* *84,0 ± 53,0*	0,025*
	TLCO	29	87,17 ± 29,11	0,025*	16 13	*93,5 ± 28,0* *76,0 ± 42,0*	0,022*
EGPA	FVCex	26	70,96 ± 16,12	<0,001*	8 18	*70,50 ± 34,0* *72,0 ± 27,0*	0,605
	rFEV1	26	96,65 ± 11,08	0,136	8 18	*100,0 ± 17,0* *96,0 ± 13,0*	0,724
	RAWtot	18	*133,5 ± 88,0*	0,024*	7 11	*147,0 ± 67,0* *110,0 ± 110,0*	0,479
	TLC	17	95,47 ± 15,41	0,243	7 10	*92,0 ± 32,0* *98,5 ± 21,0*	0,364
	RV	17	*137,0 ± 49,0*	0,009*	7 10	*104,0 ± 53,0* *141,0 ± 31,0*	0,055
	TLCO	23	*87,0 ± 16,0*	0,014*	8 15	*86,0 ± 24,0* *87,0 ± 15,0*	0,728

265. Isolated subglottic stenosis secondary to GPA: a descriptive cohort study

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Background: Subglottic stenosis (SGS) is a common manifestation of granulomatosis with polyangiitis (GPA) and is defined as narrowing of the airway immediately below the vocal cords. Symptoms include stridor, hoarse voice, and dyspnoea, and may be severe enough to require tracheostomy. Distinguishing 'idiopathic' SGS from 'limited' forms of GPA is challenging, and the role of immunosuppressive therapy is unclear.

Methods: We undertook a retrospective analysis of patients presenting to a single tertiary unit with SGS between 2008 and 2020, and identified those where SGS was an isolated or predominant feature of GPA. Patients were distinguished from 'idiopathic SGS' and defined as 'GPA-SGS' if they had endoscopic evidence of SGS and (i) positive serologic testing for ANCA (by indirect immunofluorescence or antigen-specific assay), and/or (ii) an airway biopsy showing histologic features compatible with GPA (vasculitis, granulomatous inflammation), and/or (iii) they manifested additional features of upper airway GPA (laryngotracheal involvement, septal perforation, sinonasal involvement, nasolacrimal involvement, recurrent otitis media).

Results: We identified 29 patients with GPA-SGS. 69% (n=20) patients were female and the median age at presentation was 46 years (range 16-87) years. The main symptom at presentation was dyspnoea, associated with stridor in 52% (n=15) patients, wheeze in 25% (n=7) and cough in 7% (n=2). Other clinical features included dyspnonia (n=4), epistaxis (n=3), and chronic rhinitis (n=1). The median time for diagnosis from symptom onset was 38.4 months. On bronchoscopy, all had SGS and 28% (n=8) patients had evidence of further tracheal stenosis and 3% (n=1) individual had glottic stenosis. 86% (n=25) patients underwent airway biopsies; these showed active chronic inflammation in all cases, with confirmatory features of *vasculitis* in 3 and granulomatous inflammation in 4. 66% (n=19) had positive ANCA serology: 6 patients had a positive cANCA by IIF (of whom 4 had detectable PR3-ANCA); 13 were pANCA positive by IIF (of whom 4 had detectable MPO-ANCA). 93% (n=27) patients required airway intervention via microlaryngoscopy, and 17% (n=5) needed more complex interventions in the form of laryngotracheal reconstruction. 76% (n=22) patients were treated with systemic immunosuppression. In patients not immunosuppressed this was due to risk of infection (n=3), frailty (n=3), mild symptoms (n=1). In patients who were immunosuppressed, first line treatments were azathioprine (n=10), cyclophosphamide (n=3), MMF (n=2), MTX (n=2), rituximab (n=2) and prednisolone alone (n=3), although choice of immunosuppression varied during follow up. Immunosuppressive treatment was associated with fewer surgical interventions: the average frequency of intervention was 1 procedure per 32.4 months follow-up during periods of immunosuppressive treatment and 1 procedure per 13.4 months during periods of non-treatment.

Conclusions: GPA-SGS shares many features of 'idiopathic' SGS, including female preponderance, age of onset, and potential for very delayed diagnosis. Patients with GPA-SGS often present with severe and life-threatening manifestations. Our experience suggests that immunosuppression may be associated with reduced need for airway interventions in GPA-SGS, though more work is needed to understand the value of specific treatments and the influence of confounding associations in more detail.

Disclosures: None

Neurological and/or Skin Manifestations

266. Neurologic involvement in ANCA-associated vasculitis: Data from multicenter longitudinal observational study

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[1]*Vasculitis Clinical Research Consortium*

Background: The prevalence of neurologic involvement (NI) in ANCA-associated vasculitis (AAV), especially central nervous system (CNS) involvement, is not well characterized. This project aimed to describe the prevalence and types of peripheral nervous system (PNS) NI and CNS NI in AAV, and associations of NI with other manifestation of vasculitis.

Methods: Analysis of patients with AAV [granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), or eosinophilic granulomatosis with polyangiitis (EGPA)] participating in a multicenter longitudinal observational study. Data were from 2006-2021 from patients at least 18 years old at enrollment. Standardized forms were used to document patient demographics, disease type, organ involvement, and ANCA status. Patient subsets were compared according to presence or absence of NI.

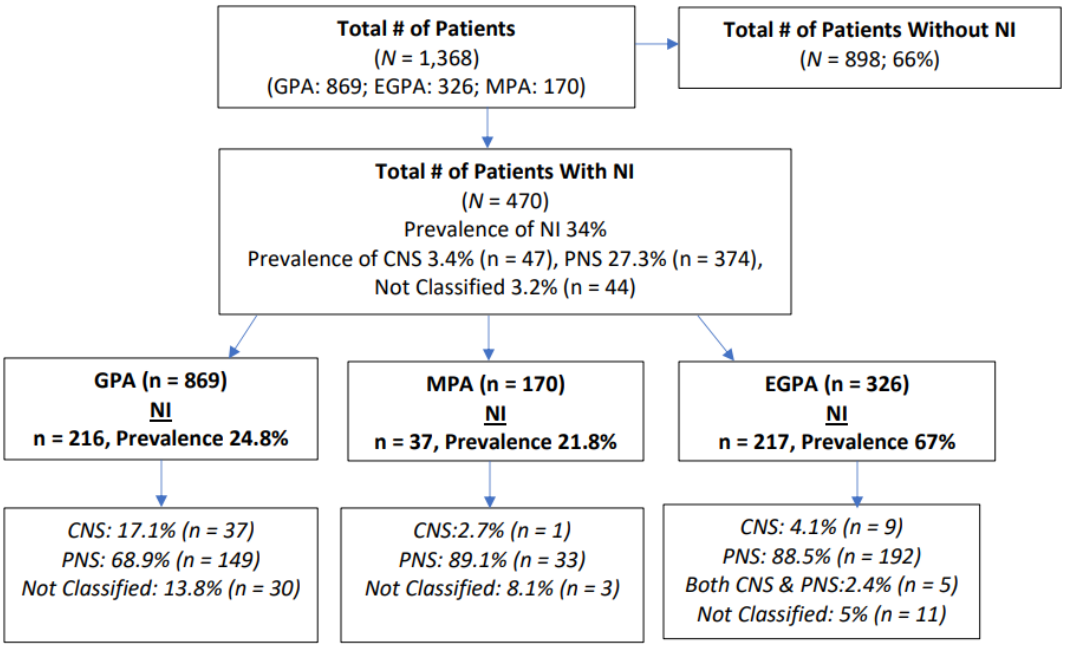
Results: Data from 1368 patients were available: 470 (34%) had NI (Figure) of whom 216 (46%) had GPA, 37 (7.8%) had MPA, and 217 (46.2%) had EGPA. The prevalence of NI was 24.8% (216/869) in GPA, 22% (37/170) in MPA, and 67% (217/326) in EGPA. The prevalence of CNS NI in the total cohort was 47/1368 (3.4%) and the prevalence of PNS NI was 374/1368 (27.3%), with 44 patients (3.2%) having NI that was not classified. GPA was the most common diagnosis in patients with CNS NI (78% compared to 2% in MPA and 19% in EGPA). For PNS NI, EGPA was the most common diagnosis (51% compared to 40% in GPA and 8.8% in MPA). Patient sex and race did not differ between patients with or without NI. Patients with NI were 53% female and 47% male, 88.7% were White, 1.5 % Black, 3.2% Hispanic, and 4.8% Asian.

Mean age at diagnosis of patients with NI was higher than patients without NI (51.4 vs 47.0 years, p <0.001). NI was associated with skin (49.4% vs. 29.5%, p < 0.001), venous thrombosis (12.8% vs. 8.6%, p= 0.016), and cardiovascular (15.5% vs. 7.2%, p < 0.001) involvement. Patients with NI were less likely to have renal (45.6% vs. 55.9%, p < 0.001), and eye (20 % vs. 28%, p < 0.001) involvement. NI was associated with skin and kidney involvement in EGPA, musculoskeletal, skin, kidney, venous thromboses in GPA and constitutional and musculoskeletal symptoms in MPA. Patients with NI were more likely to have P-ANCA pattern (43.1 % vs 31.2 % p =0008) and anti-MPO (44.4% vs 30% p < .0001) than patients with no NI.

Conclusions: NI in AAV is common, occurring in approximately one-third of patients, and was most common in EGPA, compared to GPA or MPA. CNS NI occurs more commonly in GPA. NI is associated with various specific organ systems and P-ANCA/anti MPO positivity. These data are informative for clinicians and patients with AAV, and should raise the awareness of this common manifestation of vasculitis. The relationships of NI with other specific manifestations of disease warrants additional study.

Disclosures: The Vasculitis Clinical Research Consortium was supported in part for this work from The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), The National Center for Advancing Translational Sciences (NCATS), and GlaxoSmithKline

Prevalence of neurologic involvement (NI) in patients with ANCA-associated vasculitis



GPA: Granulomatosis with polyangiitis; MPA: Microscopic polyangiitis; EGPA: Eosinophilic granulomatosis with polyangiitis; CNS: Central Nervous System; PNS: Peripheral Nervous System

267. Differentiating primary central nervous system vasculitis from non-inflammatory intracranial vasculopathy

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Background: The diagnosis of primary CNS vasculitis can be challenging and requires exclusion of other mimics. One of the major differential diagnoses for primary CNS vasculitis includes non-inflammatory vasculopathy and distinguishing the two can be challenging and potentially leading to invasive investigations. In this study, we aimed to investigate distinguishing primary central nervous system (CNS) vasculitis compared to non-inflammatory intracranial vasculopathy using features in clinical presentation and blood and cerebrospinal fluid (CSF) markers.

Methods: We evaluated all cases enrolled in the prospective registry of CNS vasculopathy at a tertiary medical center. Final diagnoses were reviewed and patients with incomplete workup were excluded. Infectious vasculopathy, reversible cerebral vasoconstriction syndrome, autoimmune or inflammatory disease, and cardio-embolic disease were excluded since they may be more readily distinguished from primary CNS vasculitis. Several clinical features on first presentation such as gender, ethnicity, clinical presentation, past medical history, and medications in addition to serum and CSF findings were investigated for their ability to predict the final diagnosis. Logistic regression model was developed and validated using 3-fold cross validation.

Results: Overall, 206 patients were identified who had completed the workup with a final diagnosis. Forty-eight patients with primary CNS vasculitis and 19 patients with non-inflammatory vasculopathies (large vessel atherosclerotic disease, small vessel disease, intracranial dissection, and Moya Moya disease) were included. A logistic regression model was evaluated with top 3 features including race, seizure on presentation, and CSF pleocytosis. The model predicted primary CNS vasculitis in validation cohort with sensitivity 72.2% and specificity 94.7%. Seizure upon presentation and CSF pleocytosis were associated with the diagnosis of CNS vasculitis and African-American race was associated with the diagnosis of non-inflammatory vasculopathy.

Conclusions: Primary CNS vasculitis might be differentiated from non-inflammatory intracranial vasculopathy based on clinical presentation and CSF findings. Larger studies are warranted to validate these observations.

Disclosures: none. Prelimimary data published here: https://acrabstracts.org/abstract/neurologic-involvement-in-anca-associated-vasculitis-data-from-multicenter-longitudinal-observational-study/

Table. Available demographic, clinical features, and laboratory features of patients with CNS vasculitis and noninflammatory vasculopathy including intracranial atherosclerotic disease, small vessel disease, dissection, Moyamoya disease, and unclear non-inflammatory vasculopathy. Statistically significant results are highlighted with *. N=number.

	CNS vasculitis	Non-inflammatory	P value
Gender	N = 48	N = 19	
Male, N (%)	28 (58.3)	8 (42.1)	0.282
Race	N = 48	N = 19	
White, N (%)	43 (89.6)	13 (68.4)	0.063
African American, N (%)	1 (2.1)	4 (21.1)	0.021*
Other, N (%)	4 (8.3)	2 (10.5)	1.000
Past medical history	N = 48	N = 19	
Hyperlipidemia, N (%)	14 (29.2)	9 (47.4)	0.169
Hypertension, N (%)	17 (35.4)	10 (52.6)	0.270
Diabetes mellitus, N (%)	10 (20.8)	4 (21.1)	1.000
Meningitis, N (%)	3 (6.3)	0 (0.0)	0.553
Clinical presentation	N = 48	N = 19	
Headache, N (%)	24 (50.0)	9 (47.4)	1.000
Seizure, N (%)	10 (20.8)	0 (0.0)	0.052
Visual symptoms, N (%)	16 (33.3)	6 (31.6)	1.000
Aphasia or dysarthria, N (%)	24 (50.0)	5 (26.3)	0.103
Focal sensorimotor deficit, N (%)	21 (43.8)	8 (42.1)	1.000
Decreased level of consciousness, N (%)	16 (33.3)	4 (21.1)	0.387
Memory impairment, N (%)	25 (52.1)	6 (31.6)	0.176
Behavioral changes, N (%)	10 (20.8)	3 (15.8)	0.744
Serum	N = 47	N = 19	
Elevated C-reactive protein (> 1.0 mg/dL), N (%)	6 (12.8)	1 (5.3)	0.663
Antinuclear antibodies present, N (%)	3 (6.3)	2 (10.5)	0.621
Vessel wall imaging MRI	N = 24	N = 15	
Vessel wall enhancement on MRI, N (%)	10 (41.7)	10 (66.7)	0.191
CSF	N = 41	N = 19	
Leukocyte count, mononuclear leukocytes per µL median [IQR]	11 [2 – 28]	2 [0.5 – 3.5]	<0.001*
Protein, mg/dL, median [IQR]	66 [43 – 89]	43 [31 – 53.5]	0.004*
Pleocytosis (≥ 5 mononuclear leukocytes per µL) (corrected for RBCs), N (%)	26 (63.4)	1 (5.3)	<0.001*
Elevated protein (>45 mg/dL) (corrected for red blood cells), N (%)	28 (68.3)	7 (36.8)	0.027*

268. Central nervous system involvement in ANCA-associated vasculitis – a retrospective cohort study.

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Background: Both peripheral and central nervous system (CNS) may be involved in patients with ANCA-associated vasculitis (AAV), with peripheral symptoms predominating. CNS involvement is rare symptom of AAV with reported prevalence rate of 7% to 11%.

Methods: The purpose of this study was to describe the clinical presentation of patients with ANCA-associated vasculitis (GPA - granulomatosis with polyangiitis and MPA - microscopic polyangiitis) presenting with CNS involvement treated in one academic center between 1988 and 2021. Medical database of 255 GPA and MPA vasculitis patients were retrospectively reviewed, and demographics, serological, and clinical features of the patients presenting CNS involvement throughout the disease course were recorded. Comparisons of disease characteristics and long-term outcomes were performed between patients with and without CNS involvement.

Results: 27/255 patients (10.5%) had symptoms of CNS involvement associated with the disease. All but one patient had abnormalities confirmed in MRI or CT of the head. Headache (16/28) was the main clinical symptom, followed by vestibular syndrome (11/24), deafness (7/10), motor impairment (9/24) and seizures (4/10). Three patients had psychiatric symptoms and dementia. CNS involvement was characterized by cerebral ischaemic lesions in 19, pachymeningitis in 8, and haemorrhagic lesions in 1 patient. Three patients had thrombosis of brain sinuses and 1 patient had Posterior Reversible Encephalopathy Syndrome (PRES). In 5 of them CNS changes were secondary to infiltrations from skull base. None of our patients had pituitary gland involvement. Two patients had both cerebral and spinal cord pachymeningitis. Lumbar puncture was performed only in one patient. None of the patients had brain biopsy performed. When compared with group without CNS involvement we found only two statistically important differences: patients with CNS involvement were more often cANCA positive and they had more often eye involvement.

Conclusions: CNS involvement is severe complication of AAV. Headaches, cANCA positivity and eye involvement are associated with this complication.

Disclosures: All Authors declare no disclosures.

269. Withdrawn

270. Neurological Manifestations of IgG4 Related Disease: A Descriptive Study

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Background: Neurological manifestations of IgG_4-related disease (IgG_4-RD) is rare compared to other involvements. It may be in four different forms: pachymeningitis, orbital disease, hypophysitis and parenchymal disease. This study is aimed to describe clinical features, diagnostic parameters, and therapeutic management of patients with a neurologic spectrum.

Methods: Patients diagnosed with IgG4-RD from January 2005 – September 2021 were included in the study. Demographic data, clinical features, involved organs, disease course, laboratory parameters, and therapeutic responses were analysed.

Results: Among 99 IgG4-RD patients, 76 patients with regular follow-up visits were included in the study. The female to male ratio was 1:1, and the mean diagnostic age (years) was 47.38 ± 14.9 SD. Median follow-up period was 27.5 months and median serum IgG4 level was 184.75 mg/dL (min 14 - max 765 mg/dL). Neuro-IgG4RD was present in 16 (21%) of the patients (10 had orbital disease, 5 had pachymeningitis, one had hypothalamohypophyseal axis involvement). In the neuro-IgG4RD group, the female to male ratio was 1.3:1 and the mean diagnostic age was 47.5 ± 17.7 SD. Neurological involvement is the presenting symptom in 77% of the patients (n: 13), while in the remaining 23%, it was additive to another organ involvement (n: 3). Median serum IgG4 level was 128.43 mg/dL (min 14 – max 349 mg/dL) in this group. 60% of the patients with the orbital disease were male and the most frequent presenting symptoms were headache, loss of vision, and proptosis. The most frequent radiological findings of orbital disease were thickening of extraocular muscles, staining in the retrobulbar area and compression or inflammation around optic nerve. 80% of the patients with pachymeningitis were male, and the most frequent presenting symptoms were headache and accompanying cranial nerve involvement. In this group, skull base was most affected and the most frequent site of involvement was tentorium cerebelli. Main choice of treatment were corticosteroids in neuro-IgG4RD; but in 43.75% of the patients, rituximab was needed to be added to the treatment (n: 7). In all patients receiving rituximab, neuroradiological findings were either stabilized or regressed.

Conclusions: Neurological involvement was observed in one out of every five patients, either at presentation or during follow-up. Orbital disease and pachymeningitis are the most frequent

neurological manifestations in this cohort. Therapeutic options include corticosteroids and conventional immunosuppressive drugs. Rituximab might be an effective treatment option in resistant cases.

Disclosures: Professor Karadag: Received funding supprot Abbvie, Novartis, Roche, Viela-Bio, R-Pharm outside this study. Received consultancy fees and/or speaker fees from Abbvie, Abdi İbrahim, Amgen, Celltrion, Gilead, Farmanova, Lilly, Pfizer, Roche, UCB

Renal Disease &/or Ocular Disease

271. Withdrawn

272. Ocular Manifestations of ANCA-Associated Vasculitis

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Background: ANCA-associated vasculitides (AAV) are multisystem diseases that can have multiple ophthalmic manifestations. Although there are some data on ocular disease in granulomatosis with polyangiitis (GPA), even less are available for microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). Further, there also few reports differentiating symptoms seen at disease onset versus later in the disease or the ocular complications of AAV.

Methods: Patients with GPA, MPA, or EGPA enrolled in a longitudinal study between April 2006 and April 2021 were included in this study. Data concerning diagnosis, demographics, cranial disease manifestations and their time of onset, treatment, and ocular complications were extracted. Prevalence of ophthalmic manifestations at disease onset and incidence of manifestations over the course of follow up, median time to onset of new manifestations and complications of disease were calculated.

Results: Data from 1389 patients were included for analysis which included 6392.8 patient-years of follow up. There were 852 cases of GPA, 165 cases of MPA, and 372 cases of EGPA; with 258 (30.3%), 7 (4.2%), and 13 (3.5%) ocular manifestations present at baseline, respectively (Table 1). The most common manifestations seen were conjunctivitis/episcleritis

and scleritis; multiple ophthalmic manifestations were seen in 79 (9.3%) of patients with GPA, 3 (1.8%) patients with MPA, and none with EGPA. During follow up, 56 (6.6%) patients with GPA had incident ocular manifestations (of which 53.6% were new manifestations), while such events were rare in MPA (n=1) and EGPA (n=2). Frequent manifestations seen during follow up were conjunctivitis/episcleritis and dacrocystitis/lacrimal duct obstruction. The most common complication seen across all 3 diseases was cataracts, seen in 9.1-15.3% of patients. Non-cataract complications followed a similar pattern to other manifestations: 67 (7.9%) patients with GPA experienced such complications (of whom 31 experienced vision threatening complications) followed by 10 (2.7%) of those with EGPA, and 7 (4.2%) of those with MPA. Optic Neuritis (n=8) and orbital wall destruction (n=12) were only seen in those with GPA; 8 individuals with GPA experienced blindness as well as one with MPA.

Conclusion: Among patients with AAV, ophthalmic manifestations and complications are common in GPA, but rare in MPA and EGPA. Inflammatory eye conditions are the most common ophthalmic manifestation seen, and cataracts are the most common complication. New ophthalmic manifestations after disease onset are rare. These data are informative for clinicians caring for patients with AAV and investigators studying this spectrum of vasculitis.

Disclosures:
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AS – Employed by Bristol-Myers Squibb, Stock options in Alexion. KW – Recipient of research support from Eli Lilly and Kiniksa. PM – Consultant and recipient of research support for AbbVie, AstraZeneca, Boeringher-Ingelheim, Bristol-Myers Squibb, ChemoCentryx, Forbius, Genentech/Roche, Genzyme/Sanofi, GlaxoSmithKline, InflaRx, Consultant for CSL Behring, Dynacure, Eicos, EMDSerono, Forbius, Janssen, Kiniksa, Magneta, Neutrolis, Novartis, Pfizer, Star Therapeutics Takeda, Talaris, Recipient of research support from Sanofi, Receives royalties from UpToDate. NK – Trial support from Roche, BMS, Sanofi, Abbvie

Table 1: Ocular manifestations of AAV at disease onset

Baseline Manifestations	GPA	MPA	EGPA
Total number of patients	**852**	**165**	**372**
Any ocular manifestations	258 (30.3%)	7 (4.2%)	13 (3.5%)
Conjunctivitis or episcleritis	111 (13.0%)	3 (1.8%)	3 (0.8%)
Scleritis	61 (7.2%)	3 (1.8%)	1 (0.3%)
Uveitis	22 (2.6%)	0 (0.0%)	2 (0.5%)
Dacrocystitis and/or lacrimal duct obstruction	36 (4.2%)	0 (0.0%)	0 (0.0%)
Orbital Mass or proptosis	26 (3.1%)	0 (0.0%)	0 (0.0%)
Peripheral ulcerative keratitis	9 (1.1%)	1 (0.6%)	0 (0.0%)
Retinal Changes	10 (1.2%)	3 (1.8%)	5 (1.3%)

273. A long-term retrospective outcome analysis of ANCA-negative pauci-immune glomerulonephritis

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Background: Pauci-immune glomerulonephritis (GN), usually associated with circulating antineutrophil cytoplasm antibodies (ANCA), is one of the most common causes of rapidly progressive glomerulonephritis that results in high incidence of end-stage kidney disease (ESKD). Most of the existing large trials looking at treatment efficacies exclude ANCA-negative patients, and relatively few studies have reported their long-term outcomes. Therefore, we conducted a single-centre retrospective study to examine the long-term overall survival and renal outcome in this cohort of patients.

Methods: All cases of newly diagnosed biopsy-proven pauci-immune GN from 2006 - 2019 were identified through a local histopathology database. Patients with negative anti-myeloperoxidase (MPO) and anti-proteinase-3 (PR3) serology were identified (ANCA-negative group) and comparisons made with the cohort of patients with positive serology (MPO/PR3 positive group). Patients with relapsing ANCA-GN, eosinophilic granulomatosis with polyangiitis, other co-existing glomerulonephritis or missing data on induction therapy or outcome were excluded. Baseline demographics, initial serum creatinine (sCr), estimated glomerular filtration rate (eGFR), systemic involvement and histopathology features including percentage normal glomeruli, and interstitial fibrosis/tubular atrophy score of >25% were collected and compared. Kaplan Meier survival analysis was used to compare overall survival and end-stage kidney disease (ESKD) progression rate between the two groups.

Results: We identified 178 patients of whom 83 were female (47%) and median age was 62 years. Median follow-up was 44 months. Fifteen (8%) were ANCA-negative and 163 (92%) were MPO- and/or PR3-ANCA positive. There were no differences in baseline characteristics such as age, gender and proportion of patients with normal glomeruli <25% on initial histology. However, we observed a significantly higher proportion of patients with renal-limited vasculitis in the ANCA-negative group (67% vs 24% p=0.01) and more severe renal dysfunction at presentation (median sCr 309umol/L vs 204umol/L, p= 0.01). We also demonstrated a higher proportion of patients with an IFTA score of >25% on renal biopsy (53% with >25% IFTA in ANCA-negative cohort vs 27%, p =0.03). The ANCA-negative group were more likely to receive combination immunosuppressive therapy that included plasma exchange (47% vs 23%, p value 0.04). When considering overall survival there was significantly higher mortality (40% vs 16%, p value 0.009) and rate of progression to ESKD (53% vs 18%, p value 0.001) in the ANCA-negative cohort. When we compared patients with renal-limited vasculitis only however, there was no significant difference in either overall survival or rate of progression to ESKD (p=0.85 and 0.84 respectively). We found that ANCA-negative patients with systemic disease did still have significantly higher rates of both progression to ESKD and overall mortality (p=0.002 and p=0.02 respectively).

Conclusions: In our cohort, patients with ANCA-negative pauci-immune GN have poorer renal function and higher IFTA scores on biopsy at presentation perhaps reflecting delayed diagnosis due to a lack of diagnostic serology and the higher proportion of renal-limited disease in this subgroup. Despite intensive immunosuppressive therapy, this study observed overall higher treatment failure rates in ANCA-negative patients, largely in those with systemic disease. This possibly relates to a different underlying disease process. Larger, prospective studies are required to enhance understanding of the disease pathogenesis to allow optimal tailored treatment for these patients.
Disclosures: None. Preliminary data published here: P0383, p.708 https://www.era-online.org/VirtualCongress2020/Accepted_Abstracts_ERAEDTA_2020.pdf

274. Fundus Fluorescein Angiography – a Valuable Adjunct to Diagnosis and Monitoring in Systemic Autoimmune Disease?

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Background: Systemic autoimmune disease (SAD) is often associated with ophthalmic signs and symptoms. Ophthalmic symptoms of retinal vasculitis are often nonspecific. Fundus fluorescein angiography (FFA) can be a useful adjunct in objective assessment and aid in reaching a diagnosis or monitoring response to therapy. FFA features of retinal vasculitis and anterior ischemic optic neuropathy (AION) include retinal arterial leakage and sheathing, peripher§al capillary drop out, reduced venous perfusion, patchy choroidal filling and increased arm to eye time. Here we present a case series illustrating the utility of FFA in monitoring and diagnosing a variety of SAD.

Methods: We retrospectively describe a case series in which FFA was used in the diagnosis and / or monitoring of SAD with visual involvement. All patients were attending the Rheumatology and Ophthalmology department at the Mater Misericordiae University Hospital (MMUH), Dublin between May-October 2021. All data was anonymised and patient consent was granted for their information to be presented and published as an abstract.

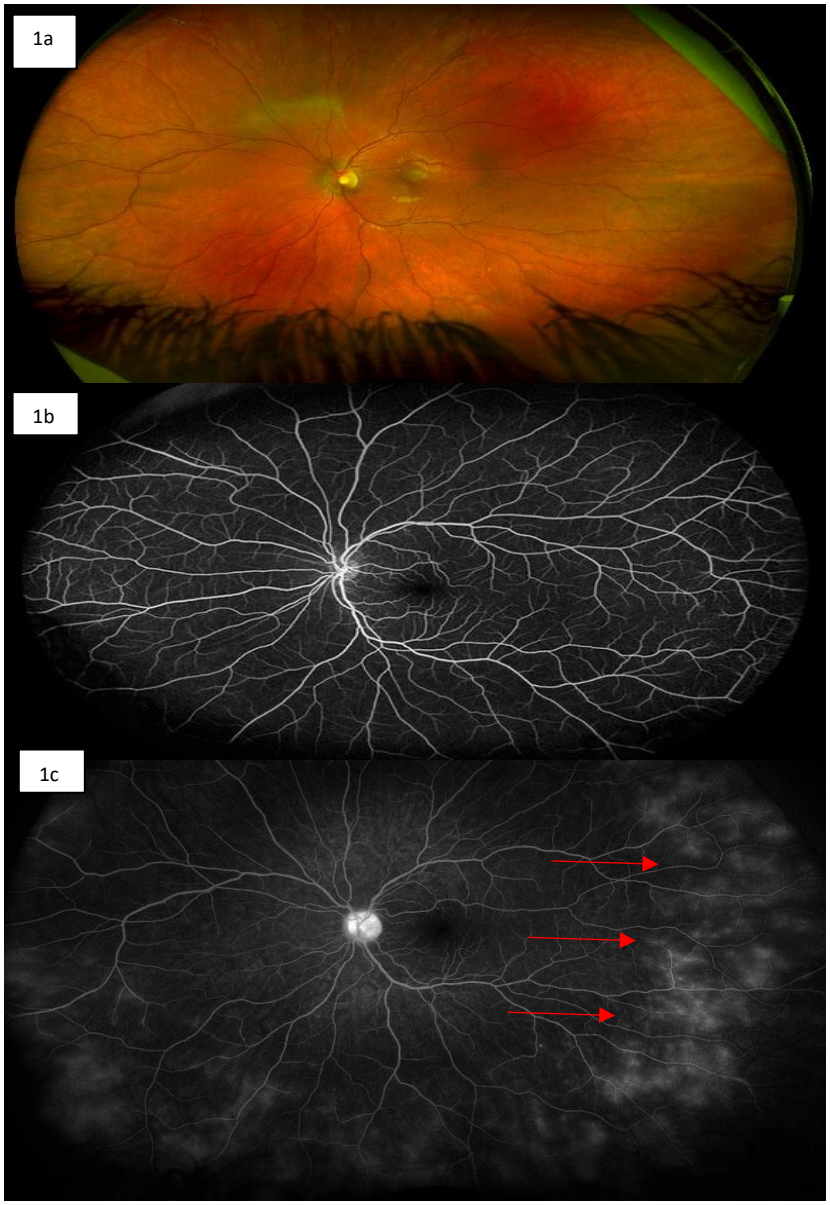
Results: We identified 4 patients with a variety of SAD in whom defining the nature and extent of visual symptoms and retinal vasculitis proved challenging or in whom FFA provided additional diagnostic utility. Case1: 75-year-old female with biopsy proven giant cell arteritis (GCA) diagnosed in 2016 re-presented with recurrence of headache but no other signs or symptoms of active GCA. Inflammatory markers were normal. FFA showed an enlarged foveal avascular zone and patchy choroidal filling suggestive of imminent AION. Given the FFA findings, the patient was treated as a GCA relapse. Her corticosteroid dose was increased with subsequent resolution of her FFA finding. Case 2: 43-year-old female with SLE who presented with acute painless monocular visual loss. MRI brain showed non-specific white matter changes and lumbar puncture was bland. FFA demonstrated loss of capillary bed in the temporal periphery with adjacent abnormal vasculature. These findings were consistent with AION with bilateral posterior segment peripheral ischemia at the level of the capillary beds.

FFA was repeated at 3 months following initiation of immunomodulatory therapy and showed no interval change, indicating stable disease. Case 3: 19-year-old male presented with a 4 day history of headache, bloodshot eyes, photophobia and reduced vision in both eyes. CRP was 105mg/L and ESR 77mm/hr. He had bilateral acute anterior uveitis and was prescribed topical steroids. He complained of bilateral flashing field defects. His retinal exam was normal. FFA showed bilateral occlusion of his capillary beds in the peripheral temporal retina. The FFA confirmed a panuveitis. He subsequently developed inflammatory lower back pain and was diagnosed with axial spondyloarthropathy and commenced on anti-TNF therapy. Case 4: 49-year-old female presented with gradual onset inferior quadrantanopia in the setting of a weak positive MPO-ANCA and no other clinical or laboratory features of systemic vasculitis. Retinal exam revealed inferiorly swollen optic discs. The working differential diagnosis was AION secondary to MPO-ANCA vasculitis vs non-arteritic ischaemic optic neuropathy (NAION) secondary to anatomical anomaly of the optic discs. Monitoring via FFA has shown resolution of disc leakage following steroid treatment inferring an AION and commencement of systemic immunosuppression.

Conclusions: These cases illustrate the potential utility of FFA in the diagnosis and monitoring of patients with SAD and ocular involvement. Ophthalmic symptoms of SAD are often mild, and patients find them difficult to describe. FFA allows detection and monitoring of subclinical or overt manifestations of SAD. FFA also allows delineation of the type and level of vascular bed affected. Further research is needed to validate the utility of FFA in diagnosing and monitoring SAD with eye involvement.

Disclosures: No disclosures

Figure 1. 1a Patient fundus (normal) 1b Normal FFA 1c Patient FFA (abnormal) red arrows to area of leakage



275. **Maintenance of Remission and Risk of Relapse in Myeloperoxidase Positive Antineutrophil Cytoplasmic Antibody-Associated Vasculitis Glomerulonephritis**

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Background: Optimal time of remission-maintenance therapy in patients with MPO-ANCA associated vasculitis (MPO-AAV) is not established. Defining clinical and laboratory parameters to guide safe withdrawal of maintenance therapy is required to mitigate the risk of relapse and unnecessary exposure to immunosuppression.

Methods: A retrospective cohort study of all patients followed at the Mayo Clinic with MPO-AAV (MPA and GPA) and glomerulonephritis (MPO-AAV-GN). Relapse rate, correlation with MPO-ANCA status and remission-maintenance therapies were characterized.

Results: We analyzed 159 patients with active MPO-ANCA-GN. A total of 66 (41.5%) patients had at least 1 relapse. Patients with MPO-ANCA who became persistently negative did not relapse (HR 0.028, [95%CI,0.003–0.272], p=0.002). The reappearance of MPO-ANCA in patients who had turned MPO-ANCA negative was associated with increased risk of relapse (HR 2.386, [95%CI,1.471–3.870], p<0.0001). Immunosuppression was withdrawn in 80 (50.3%) patients; this was less likely to occur in those who received CYC for remission-induction or were persistently MPO-ANCA positive (OR 0.443, [95%CI,0.228–0.861], p=0.016; OR 0.418, [95%CI,0.213–0.820], p=0.011, respectively). Relapse incidence was not different between patients who withdrew remission-maintenance therapy versus those who maintained (40.0% vs. 43.0%, p=0.697), even in persistently MPO-ANCA positive (39.1% vs. 48.8%, p=0.508). ENT involvement (OR 6.095 [95%CI, 1.280–29.010], p=0.023) and MPO-ANCA reappearance (OR 9.248, [95%CI, 3.126–27.361], p<0.0001), were independent predictive factors for relapse after treatment withdrawal.

Conclusion: Our results indicate that patients who turn and remain MPO-ANCA negative during remission are at low risk for subsequent relapse even when remission maintenance therapy is withdrawn. Subsequent reappearance of MPO-ANCA is associated with an increase of the relapse risk. Serial MPO-ANCA determinations provide useful information for clinical decision-making about remission-maintenance treatment in patients with MPO-AAV-GN.

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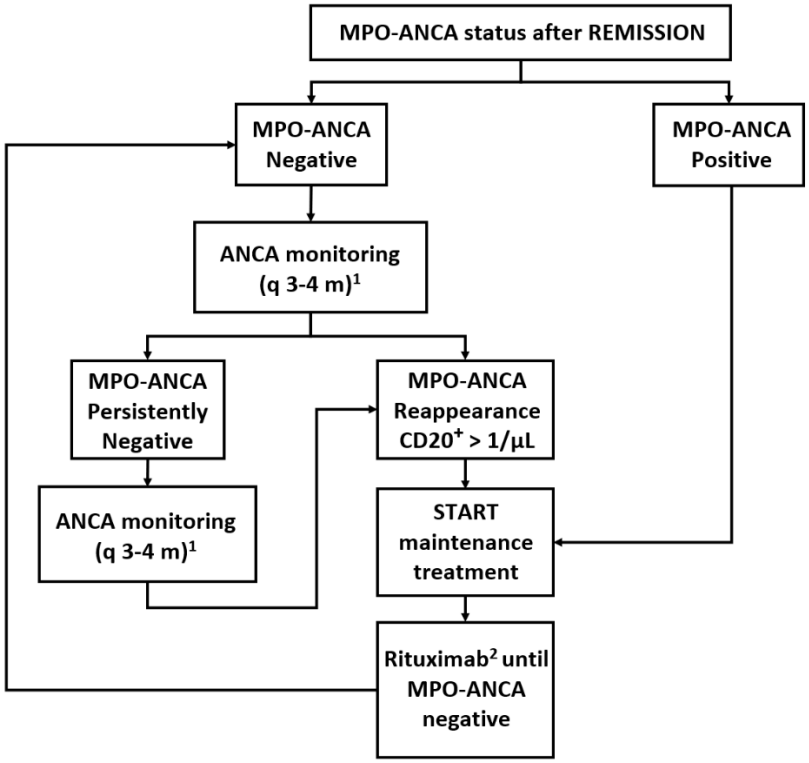
Figure 1. Algorithm for the clinical use of MPO-ANCA status for remission-maintenance guidance in MPO-AAV-GN: proposal for clinical follow-up based on the MPO-ANCA status. [1.] The ideal interval monitoring MPO-ANCA negative with ANCA and B-cell levels is between 3 to 4 months according to the time to MPO-ANCA reappearance and the time to relapse. [2.] In accordance with the most recent guidelines and clinical trials, RTX is favored as the treatment of choice for remission-maintenance.



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276. Interstitial ANCA-associated vasculitis associates with severe kidney injury independent of glomerulonephritis

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Background: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a small vessel vasculitis affecting multiple organ systems, including the kidney. Small vessels in the kidney include small-sized arteries (interlobular artery, afferent and efferent arteriole), capillaries (glomerular and peritubular capillary) and venules. Although crescentic ANCA glomerulonephritis (GN) is a common histological finding reflecting glomerular small vessel vasculitis, it is reasonable that manifestation of AAV could also contribute to interstitial small

vessel vasculitis. Therefore, we here aimed to expand our current knowledge focusing on interstitial vasculitis in ANCA GN by systematic histological scoring of vascular lesions analogous to Banff.

Methods: A total number of 49 kidney biopsies with confirmed renal involvement of AAV at the University Medical Center Göttingen were retrospectively included between 2015 till 2020. A renal pathologist (SH) evaluated all biopsies and was blinded to clinical data collection and analysis.

Results: Since previous studies established that crescentic ANCA GN associates with severe kidney injury and acute deterioration of kidney function in AAV, we first systematically scored interstitial vasculitis in association with requirement of renal replacement therapy (RRT). Among all active and chronic tubulointerstitial lesions analogous to the Banff scoring system, the only association between severe kidney injury requiring RRT was observed for interstitial vasculitis in AAV reflected by peritubular capillaritis (ptc, p=0.0002) and arteritis (v, p=0.0069), affecting 5/49 (10.2%) and 11/49 (22.4%) of renal biopsies, respectively. Since it is known that severe deterioration of kidney function also correlates with crescentic ANCA GN, we next directly compared glomerular and tubulointerstitial lesions. The fraction of normal glomeruli was inversely associated with interstitial fibrosis (ci), total (ti) and inflammation in IFTA (i-IFTA), whereas glomerular crescents were associated with interstitial inflammation (i), tubulitis (t) and total inflammation (ti). In contrast, global glomerular sclerosis associated with less interstitial inflammation (i) but correlated with interstitial fibrosis (ci) and tubular atrophy (ct), confirming established mechansim that chronic glomerular injury leads to tubular atrophy and interstitial fibrosis. Interestingly, no association between interstitial vasculitis (ptc and v correlating with severe kidney injury) and any glomerular lesion in ANCA GN (also correlating with severe kidney injury) was observed, thereby confirming that interstitial vasculitis contributes to severe kidney injury independent of ANCA GN. By contrast, short-term renal recovery from RRT was equal in both groups, suggesting a distinct association with acute decline of kidney function at disease onset.

Conclusions: Taken together, by using the Banff scoring system we here expand our current knowledge of renal interstitial lesions in AAV revealing peritubular capillaritis and arteritis as important histological alterations associated with severe kidney injury in a considerable subset of AAV. Furthermore, our findings that interstitial vasculitis did not correlate with crescentic ANCA GN implicate that the characteristics of each vasculitis manifestation are independent and could further improve our understanding of mechanisms contributing to renal injury. These observations suggest that interstitial vasculitis in AAV may also affect long-term prognosis requiring further investigation.

Disclosures: The authors declare no competing interests.

277. ANCA-associated renal vasculitis: the Northern Irish experience

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Background: We examined the demographic characteristics, treatment and outcomes of ANCA-associated vasculitis (AAV) in Northern Ireland.

Methods: Adult cases of newly diagnosed biopsy-proven pauci-immune glomerulonephritis between 1st January 2011 and 31st August 2019 were identified from central pathology records. Cases were excluded if they were unknown to adult renal services, had less than 1 year follow-up, had relapsed disease (initial diagnosis before 2011) or had AAV in a renal transplant. Data were collected retrospectively using the Northern Ireland Electronic Care Record and the eMed regional renal database.

Results: We identified 123 patients of whom 69 (56%) were male. The median age at diagnosis was 67 years (IQR 59-73). Median follow-up time was 46 months (IQR 23 - 81). Seventy-six (62%) were MPO positive, 45 (36%) were PR3 positive, 2 were ANCA negative and 3 were dual positive with anti-glomerular basement membrane antibodies. The median serum creatinine at diagnosis was 196 umol/l (IQR 149 - 272). The majority of patients (n=90, 73%) had multi-system disease while 33 (27%) patients had renal-limited disease. Most patients (n=88, 73%) received oral cyclophosphamide (CyP) induction with 11 (9%) receiving intravenous CyP, 7 (6%) receiving Rituximab (RTX) and 3 (2%) receiving RTX and CyP. All patients received corticosteroids at induction and 20 patients required plasmapheresis. Complete remission occurred in 117 patients (95%). Median time to remission was 105 days. Relapse requiring admission to hospital or organ/life-threatening disease occurred in 26 patients (21%). The median time to first major relapse was 666 days (IQR 348 – 1123). Fifteen (12%) patients reached end-stage renal disease (ESRD), 5 were dialysis dependent from presentation and the median time to ESRD for the other 10 patients was 309 days (IQR 24 - 914). An additional 8 patients required renal replacement in the study time period but recovered renal function. Complications of treatment were common. The most common was infection requiring intravenous antibiotics or admission with 57 patients (46%) having 1 or more episodes. Of the 114 patients screened for diabetes mellitus (DM), 23 (20%) developed a new diagnosis of Type 2 DM or steroid induced diabetes. Cancer was also common with 11 patients (9%) having 1 or more episodes, the majority being non-melanomatous skin cancer. The median time to first cancer episode was 38 months (IQR 28 – 72). Twenty per cent of patients died during the follow up period. The median time to death was 26 months (IQR 5 – 59) from diagnosis. The cause of death was either unknown/undocumented or infection in the majority of patients (8 and 10 patients respectively).

Conclusions: This retrospective study of AAV in Northern Ireland over the last decade shows that renal and patient survival is comparable to other studies but complication rates were high, particularly the rate of significant infection. However, most patients received oral CyP induction

and conventional prednisolone dosing. More data is required to see whether the use of newer agents (RTX) and lower-dose prednisolone may reduce complication rates.

Disclosures: None

278. Risk of Recurrent Disease in Vasculitis Patients Following Renal Transplantation. Are serological markers of value?

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Background: Vasculitis is an important cause of end stage renal disease (ESRD), and many patients proceed to renal transplantation. However, recurrent disease following transplantation can cause graft failure. The value of serological markers in predicting recurrent disease in this group is unclear. We considered this in vasculitis patients following renal transplantation in Northern Ireland (NI).

Methods: Transplant patients with a primary renal disease of vasculitis, including polyarteritis nodosa, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, and ANCA-associated vasculitis (AAV), were identified using the Northern Ireland Kidney Transplant database. Additional information was collected using the NI Electronic Care Record (NIECR) and regional renal-specific electronic system (eMED). Patients from 2010 to present were identified.

Results: There were 26 transplants in 25 patients. Table 1 summarises relevant patient and donor information. One patient was lost to follow up due to emigration, for the remaining 24 patients the median follow up was 60 months from first transplant. At time of transplant, ANCA titres were detectable in 9 cases and had normalised in 12 (having previously been positive). Titres were unavailable in 5 cases. ANCA titres were checked in 18 cases (73.1%) as part of transplant follow-up. Of these; 4 (22.2%) were persistently positive, 2 (11.1%) fluctuated between positive and negative, 7 (38.9%) went from positive to negative, 3 (16.7%) stayed negative, and in 2 (11.1%) the titre became positive having been negative. Clinically significant recurrent disease was evident in 3 cases (11.5%). The first patient had pauci-immune crescentic glomerulonephritis on graft biopsy (prompted by acute graft dysfunction) at 41 months from transplant, in association with an elevated MPO of 2.6 AI (normal <0.9 AI). This prompted revision of his primary disease diagnosis of IgA nephropathy to AAV. This patient returned to dialysis but received a second transplant with no current evidence of recurrent disease (29 months from time of transplant). MPO has been consistently normal following second transplant. The second patient had focal segmental necrotising glomerulonephritis on biopsy (prompted by haematuria and respiratory symptoms) 47 months from transplant. MPO had been persistently positive, but subsequent to treatment for recurrent disease reduced significantly. Non-visible haematuria resolved and respiratory symptoms settled. Renal function remains excellent however MPO remains positive at low level. The third patient had necrotizing granulomatous inflammation on cutaneous biopsy, consistent with extra-renal manifestation of

GPA, 78 months from transplant. Serology demonstrated a marginally elevated PR3 of 1.3 AI (normal <0.9 AI). PR3 had been significantly elevated prior to transplant but had not been checked in the interim. Renal function remains stable. There was no histological evidence of recurrent disease reported in the remaining 23 cases (88.5%). Neither ANCA positivity nor MPO/PR3 level appeared to be associated with clinical evidence of recurrent disease.

Conclusions: Renal transplantation is appropriate for patients with ESRD due to vasculitis with good outcomes. Recurrent renal disease is uncommon but can lead to graft failure. Serological markers alone are not a reliable marker of disease activity but may be of use when accompanied by other clinical features of recurrent vasculitis.

Disclosures: None.

Table 1. Recipient and donor characteristics

		1978-2009
Number	Patients	25
	Transplants	26
Sex n (%)	Male	13 (52%)
	Female	12 (48%)
Recipient age (yr) median (range)		60 (17-82)
Prior dialysis duration (months) median		22
Donor age (yr) median (range)		55 (30-78)
Donor type	Deceased	12
	Living	14
Cold ischaemic time (mins)		682
Average A-B-DR mismatch		3

279. Outcomes Following Renal Transplantation in Vasculitis Patients

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Background: Vasculitis is a significant cause of end stage renal disease (ESRD) and is not limited to a particular demographic. Renal transplantation is the optimal form of renal replacement therapy (RRT) for suitable patients, and therefore the most appropriate treatment in many with vasculitis. The particular transplant issues related to vasculitis are (i) risk of recurrent disease and (ii) cumulative impact of immunosuppression (typically with pre-transplant burden to manage original disease). We assessed the long-term graft and patient outcomes in vasculitis patients following renal transplantation in Northern Ireland (NI).

Methods: Transplant patients with a primary renal disease of vasculitis, (including polyarteritis nodosa, granulomatosis with polyangiitis and ANCA-associated vasculitis), were identified using the NI Kidney Transplant database. Additional information was collected using the NI

Electronic Care Record (NIECR) and regional renal-specific electronic system (eMED). Patients from 1978 to 2009 were identified and included for further analysis.

Results: There were 24 transplants in 22 patients from 1978 to 2009, two patients were transplanted twice in this period. *Table 1* summarises relevant patient and donor information. All kidneys were gifted from brainstem death donors. One case was excluded from further analysis due to immediate technical failure. Median graft survival was 99 months (range 1 to 238 months), with three grafts still functioning. Graft survival was 87.0% at 1 year, 78.3% at 5 years and 34.8% at 10 years. There were 17 deaths over the follow up period, 15 patients died with a functioning graft and 2 died following transplant failure. Median survival was 114 months (range 10 to 238 months), with four patients still alive. Recipient survival following first transplant was 95.2% at 1 year, 85.7% at 5 years and 52.4% at 10 years. Deaths were predominantly due to complications of cardiovascular disease (9), malignancy (5) and infection (2).

Conclusions: Renal transplantation is appropriate for patients with ESRD due to vasculitis with comparable outcomes to other transplanted patients in this era. Despite this almost half have died within 10 years of transplantation, but without a predominance of malignancy or infection.

Disclosures: None.

Table 1. Recipient and donor characteristics

		1978-2009
Number of	Patients	22
	Transplants	24
Sex n (%)	Male	18 (75%)
	Female	6 (25%)
Recipient age (yr) median (range)		57 (34-67)
Prior dialysis duration (months) median		23
Donor age (yr) median (range)		37 (10-69)
Donor type	Deceased	24
	Living	0
Cold ischaemic time (mins)		1226
Average A-B-DR mismatch		3

Paediatric & Translational Science

280. Urinary IgA and C5a levels are indicators of renal involvement in children with IgA Vasculitis

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Background: Nephritis is a recognised complication in children with IgA Vasculitis (IgAV, previously Henoch-Schönlein Purpura) and accounts for 1-2% of kidney failure. Understanding the pathophysiology of this disease may allow identification of targets for earlier diagnosis and/or treatment. The aim of this cross-sectional study was to assess whether Immunoglobulin A (IgA) and Complement 5a (C5a) could be detected in the urine of children with IgAV and whether they are increased in patients with nephritis.

Methods: Paediatric patients and healthy controls (HC) were recruited as part of the IgA Vasculitis Study (Alder Hey Children's NHS Foundation Trust, Liverpool, REC 17/NE/0390). Urinary IgA and C5a levels were measured using commercially available ELISA kits (Novus Biological) and normalised to creatinine. Patients were grouped into IgAV nephritis (IgAVN) or IgAV with no nephritis (IgAVwoN). Nephritis was defined as a urinary albumin-creatinine ratio (UACR) > 30 mg/mmol at the time of sample collection. Statistical analysis was performed using GraphPad Prism version 8.0. Data is presented as median [range].

Results: A total of 59 children were included in this study (IgAVN n=11, IgAVwoN n=36, HC n=12). Median age was 7.1 years [1.8-17.9] and male to female ratio was 1.9:1. Urinary IgA and urinary C5a levels were both increased in patients with IgAVN (IgA/Cr –2504.5 ug/g [483.0-12437.7]; C5a/Cr – 720.2 ng/g [157.6-7826.3]) compared to IgAVwoN (IgA/Cr – 535.7 ug/g [4.4-8035.5]; C5a/Cr – 121.5 ng/g [9.03-2214.8]; $p < 0.01$) and HC (IgA/Cr – 430.6 ug/g [166.4-1168.6]; C5a/Cr – 55.1 ng/g [15.2-1138.9]: $p < 0.01$). There was no difference between HC and IgAVwoN. There were clear outliers with extremely increased urinary IgA and C5a levels in both IgAVN and IgAVwoN groups (*Figure 1*).

Conclusion: Urinary IgA and C5a can be measured and the concentration appeared to be associated with nephritis in this cohort. These could be useful markers to identify patients who warrant further intervention and/or potential drug targets. Further longitudinal studies are needed to assess their clinical relevance.

Disclosures: None.

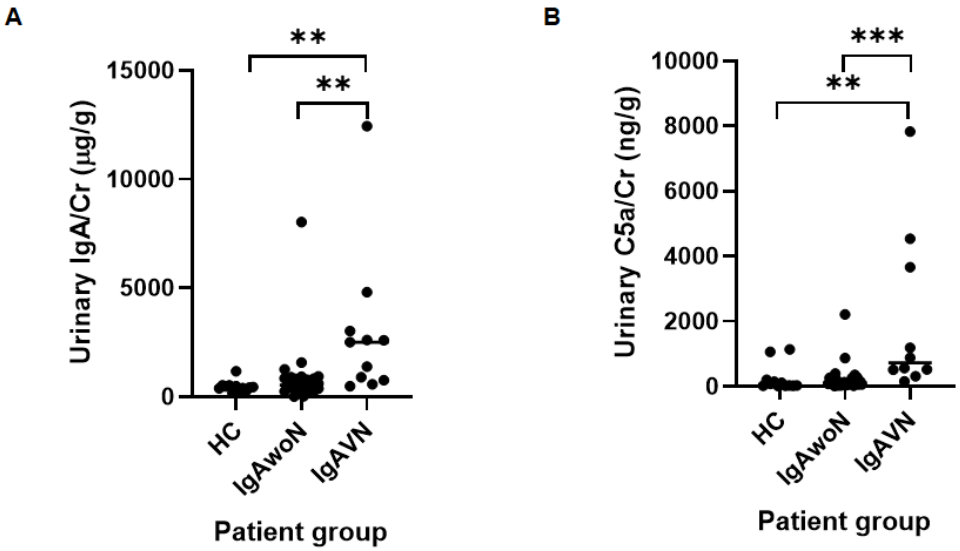

Figure 1: *Urinary IgA/Cr (A) and C5a/Cr (B) levels by patient group with median lines. Asterisks indicate a statistical difference between groups (** - p < 0.01 ; *** - p < 0.001). IgA: immunoglobulin A; C5a: complement 5a; Cr: creatinine; HC: healthy controls; IgAVN: IgA vasculitis nephritis; IgAwoN: IgA vasculitis with no nephritis.*

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281. Proton pump inhibitors suppress IL-1 mediated carditis in a murine model of Kawasaki disease

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Background: Kawasaki disease (KD), is the leading cause of acquired heart disease in childhood, with a portion of children developing coronary artery lesions (CAL) despite standard of care treatment, intravenous immunoglobulin (IVIg). Murine and patient data indicate Interleukin-1 (IL-1) contributes to CALs. Calcium mobilization plays a role in inflammasome activation and is key to the immunobiology of KD. Proton pump inhibitors (PPI), a class of medications used to limit gastric acid secretion, have also been shown to have anti-inflammatory properties. Objective: To determine if PPIs inhibit IL-1 production and resulting CALs in the Lactobacillus casei cell wall extract (LCWE) induced coronary arteritis murine model of KD.

Methods: Human monocyte cell line (THP1) derived macrophages and bone marrow derived macrophages (BMDMs) were stimulated with a TLR1/2 agonist Pam3Cys-Ser-(Lys)4 (Pam3Cys) and LCWE, in the presence or absence of PPIs. IL-1 was measured via ELISA. To exclude toxic effects, viability was tested via flow cytometry and trypan blue exclusion. Presence of caspase-1 was detected within BMDMs and murine heart tissue via Western Blot. Calcium flux was measured via fluorescent imaging plate reader on THP-1 macrophages. In vivo, KD was induced by intraperitoneal LCWE injection. Mice were injected with LCWE alone,

LCWE+PPI, saline or PPI alone. Coronary artery inflammation was blindly scored by a pathologist.

Results: Following stimulation with either Pam3Cys or LCWE, PPIs inhibited BMDM IL-1 production in a dose-dependent manner. Inflammasome activation is prevented by PPI inhibition of signal two. Stimulated macrophages treated with a PPI, in vitro, had a less calcium flux than untreated stimulated macrophages. In vivo, compared to untreated KD diseased mice, those treated with PPI were shown to have significantly reduced coronary artery inflammation based on overall cardiac severity score ($p<0.01$), area of inflammation ($p<0.05$) and elastin breakdown ($p<0.01$)

Conclusions: Our data indicate that PPIs have anti-inflammatory properties: decreasing macrophage IL-1 production in vitro and in an in vivo KD murine model preventing IL-1 induced coronary artery inflammation. The data suggest two novel findings. Firstly, PPIs may inhibit inflammasome activation by preventing intracellular calcium accumulation. Secondly, PPIs have the potential to be a novel inexpensive, oral, and safe adjuvant anti-IL-1 medication to treat KD.

Disclosures: None

282. A Data-Driven Multiomic Approach Identifies Signatures on the Same Spectrum for MIS-C and Kawasaki Disease

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Background: Multisystem inflammatory syndrome in children (MIS-C) has clinical similarities to Kawasaki Disease (KD). Despite multiple studies highlighting the clinical characteristics of MIS-C there remains limited data describing the pathobiology driving MIS-C, and direct comparisons to KD. We aim to characterize children with KD and MIS-C with unsupervised machine-learning approaches.

Methods: Study design: A single center prospective cohort study of consecutive children with MIS-C diagnosis over a 16 month period. Core clinical data/outcomes with standardized set of biospecimens pre-treatment and at serial time-points after discharge were collected. Data from patients with pre-pandemic KD (pKD) were also collected from a partner study. In total, 26 MIS-C patients and 35 pKD patients where included. Analytical procedures/framework: Using plasma samples 71 cytokines/chemokines and soluble receptors were measured via Luminex-based multiplex assays. RNA was extracted, with gene expression focused on interferon (IFN) response genes. Data was processed and used for subsequent dimensionality reduction by cross-validated probabilistic principal component analysis (PPCA). Patient scores on sparsified composite signatures produced by PPCA were then used for clustering by Gaussian Mixture Model clustering (GMMs).

Results: Five composite variables/principal components (PC) describe meaningful clinical and biologic patterns: PC1 (Proinflammatory cytokines), PC2 (IRG and cytopenias), PC3 (endothelial injury and platelet activation), PC4 (viral response) and PC5 (vascular remodeling and low chemotaxins). Five distinct patient clusters identified by GMMs. These clusters had unique genomic signatures and clinical phenotypes and were given the following cluster names: A) Classic KD; B) Interferon (IFN) mediated KD; C) Compensated KD; D) Mild KD and E) KD shock. Cluster A (Classic KD) consists predominantly of typical KD patients. Cluster B (IFN mediated KD) is composed almost evenly of MIS-C and pKD patients. The remaining three clusters were composed of smaller patient numbers. Stratifying patients accordingly to comprehensive clinical and multi-omic data not only correlated with clinical severity but also with response to treatment. In rank order of disease severity, the clusters were: E (KD shock), C (Compensated KD), B (IFN KD), A (Classic KD), and D (Mild KD). Those treated with IVIG alone, treatment response rate matching exactly with the reverse order of disease severity.

Conclusions: Unbiased machine learning approaches using system-wide data, identified unique patient subgroups with distinct genomic and phenotypic signatures in children with post-infectious hyperinflammation. These patient groupings are clinically and biologically meaningful with clear associations with disease activity, treatment response and clinical outcomes. This contrasts with data using classic disease definitions showing shared and overlapping genomic and clinical features between patients with MIS-C and KD, suggesting that KD and MIS-C both fit on the same disease spectrum.

Disclosures: None

Paediatric - Trials & Treatment

283. Treatment with anti-TNF and anti-IL 6 agents in childhood-onset Takayasu arteritis

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Background: Biologics are new treatment alternatives in Takayasu Arteritis (TA), although data in childhood is limited. The aim of this study was to share our experience in seven childhood-onset TA patients who received a TNF-α inhibitor (adalimumab) or the IL-6 receptor inhibitor (tocilizumab) and the effect of switching therapy.

Methods: We retrospectively evaluated the medical treatment records of seven patients with TA, followed between August 2005 and January 2021 at the Pediatric Rheumatology Department of Hacettepe University Faculty of Medicine, Ankara, Turkey. Disease severity was based on the Numano classification. Indian Takayasu Arteritis Score (ITAS) was used to assess disease activity.

Results: The median age of patients was 14 (11-15) years, and 6 were female. All of the patients had severe disease with type III-V involvement according to the Numano classification. All had high acute-phase reactants. The patients initially received only steroids or steroids+CYC. Prednisone was decreased and biological agents were started once the acute phase reactants decreased, and ITAS returned to normal. Initially, four patients received tocilizumab (TCZ), and three patients adalimumab (ADA) (Table I). However, due to the progression of MR angiography findings or persistent elevation in acute-phase reactants, the biological agents were switched from TCZ to ADA in four patients (patient number-pn:1, 2, 3, 4) and from ADA to TCZ in three patients (pn:5, 6, 7). There was no significant difference between median ITAS scores after biological agent change (median ITAS; 0 (0-1) in ADA-TCZ and 0 (0-0.5) in TCZ-ADA, respectively).

Conclusions: In conclusion, both TNF-α and lL-6 inhibitors are effective alternatives in treating patients with childhood-onset TA. However, prospective randomized controlled trials are needed for the comparison of their effectiveness.

Disclosures: None

Table I. Management and outcome of seven children with TA

Patient no.	Treatment pre-biologic	ITAS pre-changes	Biological changes	ITAS post-changes	Outcome
1	Steroid, CYC	4	TCZ---» ADA	0	Under remission without any active complaints.
2	Steroid, CYC	3	TCZ---» ADA	0	She is in remission, but she has 40% vision loss in the left eye.
3	Steroid, CYC, MTX	5	TCZ---» ADA	0	Under remission without any active complaints.
4	Steroid, CYC, MTX	6	TCZ---» ADA	1	She is in remission but has heart failure.
5	Steroid, CYC	4	ADA---» TCZ	1	She is in remission but has 25% vision loss in the left eye and 10% vision loss in the right eye.
6	Steroid, CYC	5	ADA---» TCZ	0	Under remission without any active complaints.
7	Steroid	3	ADA---» TCZ	0	Under remission without any active complaints.

TCZ, Tocilizumab; ADA, Adalimumab; CYC, Cyclophosphamide; MTX, methotrexate; ITAS, Indian Takayasu Arteritis Score

284. Single nucleotide polymorphisms of HMGB1 and AGER and association with clinical features in IgA vasculitis

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Background: IgA vasculitis (IgAV) is the most common childhood vasculitis in which variants of various non-HLA genes can play role in the manifestation of different disease phenotypes. The aim of this research was to investigate single nucleotide polymorphisms (SNPs) of genes HMGB-1 and AGER encoding for high mobility group box-1 (HMGB1) ad receptor for advanced glycation end products (RAGE), in predisposition and clinical features of patients with IgAV.

Methods: HMGB1 and AGER gene polymorphisms were genotyped using a real-time PCR. The presence and frequency of polymorphisms in HMGB1 (rs2249825, rs 1045411, rs1060348, rs1412125, rs41369348) and RAGE (rs1800625, rs1800624, rs2070600, rs3134940) were determined. Clinical data were collected from the database of patients with IgAV from two Croatian tertiary centers for pediatric rheumatology.

Results: 103 pediatric IgAV patients were included, 55 boys and 48 girls, as well as 150 age- and sex-matched healthy controls without any history of autoimmune disease. The median age of IgAV patients was 6.75±3.22 years, and among them 75,5% had joint involvement, 34,3% had gastrointestinal manifestation, while 30,1% patients developed nephritis. The purpuric rash which extended from lower extremities to the trunk, upper extremities and face (generalized rash) was present in 47,1% of patients and 23,5% had at least one relapse. There was no statistically significant association of the analyzed polymorphisms with the IgAV predisposition compared to healthy controls. However, several polymorphisms proved to be linked with a well-defined clinical phenotype. Polymorphisms rs41369348, rs1045411, rs2249825 and rs1412125 were significantly related with the development of generalized purpuric rash, and rs1412125 was also associated with gastrointestinal involvement. Heterozygote carriers of rs1412125 had decreased chance of developing IgAV nephritis (IgAVN) (overdominant model T/T+C/C vs. C/T; OR 0.29, 95% CI 0.10-0.83, p=0.01). Neither of examined polymorphisms of RAGE was associated with clinical phenotypes in IgAV.

Conclusions: We observed that analyzed HMGB1 polymorphisms may be involved in the pathogenesis of IgAV with possible effect on different disease phenotypes and that one genotype of HMGB polymorphism might have a protective role for the development of IgAVN.

Disclosures: None. Preliminary data presented here: https://www.bib.irb.hr/1152410

Paediatric - Clinical Outcomes

285. Differentiating MIS-C from Kawasaki Disease, the second most common vasculitis of childhood

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Background: Some clinical and laboratory features of and multisystem inflammatory syndrome in children (MIS-C) have become a major part of the paediatric rheumatology practice. MIS-C is a cytokine storm syndrome that may mimic Kawasaki disease (KD) or may present as a shock-like syndrome. In the presented study we describe the features that may help distinguish KD from MIS-C based on our clinical experience in pediatric patients.

Methods: We retrospectively evaluated the MIS-C patients with Kawasaki-like symptoms and those with KD, followed between July 2020 and October 2021 at the Pediatric Rheumatology Department of Hacettepe University Faculty of Medicine, Ankara, Turkey. All MIS-C patients met the criteria for MIS-C defined by the Centers for Disease Control and Prevention (CDC) or the World Health Organization (WHO), and all KD patients met the criteria by the American Heart Association (AHA).

Results: The median age of MIS-C patients was older than KD patients. Thirty-one MIS-C patients had positive SARS CoV-2 serology, one had positive PCR and 23 had well-defined exposure to COVID-19. None of the patients with KD had PCR positivity or exposure to COVID-19. Thirty of the MIS-C patients met the criteria for complete KD and the others for incomplete KD. While no difference was found between the median fever duration of the patients, rash ($p = 0.044$), oral mucosal changes ($p = 0.044$), and cervical lymphadenopathy ($p < 0.001$) were more frequent in KD. In contrast, MIS-C patients had more acute gastrointestinal symptoms ($p < 0.001$), acute respiratory symptoms ($p = 0.044$), and low blood pressure ($p = 0.002$). MIS-C patients had significant lymphopenia ($p < 0.001$) and lower platelet counts than KD patients ($p < 0.001$). MIS-C patients often had high ferritin, D-dimer, troponin, and brain natriuretic peptide (BNP) levels ($p < 0.001$). MIS-C patients had significantly decreased left ventricular systolic functions ($p = 0.010$) (Table 1). All patients received intravenous immunoglobulin (IVIG) as initial therapy. While most MIS-C patients were also given corticosteroid therapy, only five KD patients with refractory fever received steroid therapy. The median length of stay in the hospital of the KD and MIS-C patients was 8 (5-9) and 6 (4-7) days, respectively. No death occurred in any of the patients.
Conclusions: As the COVID-19 epidemic continues to spread, there is an urgent need to improve our understanding of this new disease. As in KD, the intense inflammation subsides if properly managed at the early stage of the disease.

Disclosures: None

Table 1. Differences between multisystem inflammatory syndrome in children and Kawasaki disease

	MIS-C patients with Kawasaki-mimic (n=33)	Patients with KD (n=15)	P values
Age, years, median (IQR)	7.6 (4.2-10.1)	3.4 (3.1-6.9)	0.004
Gender, male, n (%)	19 (57.5)	9 (60)	0.875
Clinical symptoms, n (%)			
Days of fever, median (IQR)	5 (5-7)	5.5 (5-7.5)	0.327
Rash, n (%)	25 (75.8)	15 (100)	0.044
Oral mucosal changes, n (%)	25 (75.8)	15 (100)	0.044
Bilateral conjunctival injection, n (%)	32 (96.9)	14 (93.3)	0.532
Erythema and edema of extremities, n (%)	8 (24.2)	5 (33.3)	0.509
Cervical lymphadenopathy, n (%)	14 (42.4)	14 (93.3)	0.001
Acute gastrointestinal symptoms, n (%)	24 (72.7)	2 (13.3)	<0.001
Acute respiratory symptoms, n (%)	8 (24.2)	0	0.044
Low blood pressure, n (%)	15 (45.5)	0	0.002
Laboratory findings, median (IQR)			
White blood cell count (× 103/μL)	9.5 (6.7-13.3)	14.4 (12-16.9)	0.004
Lymphocyte count (× 103/μL)	0.9 (0.67-1.2)	2.1 (1.5-2.8)	<0.001
Platelet count (× 103/uL)	159 (98-182)	370 (308-474)	<0.001
CRP, mg/dL (<0.8)	19.1 (10.7-23.3)	8.2 (7.4-14.9)	0.013
IL-6, pg/mL (<6.4)	66.4 (28.8-178.3)	31.2 (21.3-55.6)	0.059
Alanine aminotransferase, IU/L	30 (22-41)	44 (16-116)	0.344
Ferritin, mg/L (<307)	505 (277-1019)	125 (114-171)	<0.001
D-dimer, mg/L (<0.55)	3.8 (2.2-7.2)	0.8 (0.6-1)	<0.001
Troponin, ng/L (<42.9)	28.3 (8.6-109)	4.1 (2.3-5.1)	<0.001
BNP, pg/mL (<100)	329 (90-1055)	75 (59-86)	0.002
Echocardiographic findings, n (%)			
Coronary dilation/aneurysm	1 (3)	1 (6.7)	0.532
Decreased LV function	11 (33.3)	0	0.010
Myocarditis	3 (9.1)	0	0.542
Pericarditis	2 (6.1)	0	1.000
Treatments, n (%)			
IVIG*	33 (100)	15 (100)	NA
Corticosteroids, IV**	32 (97)	5 (33.3)	<0.001
Anakinra, SC***	16 (48.4)	0	<0.001
Plasma exchange	11 (33.3)	0	0.010

BNP, brain natriuretic peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; F, female; IL, Interleukin; IQR, interquartile range; IV, intravenous; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; M, male; MIS-C, multisystem inflammatory syndrome in children; NA, not assessed; PCR, polymerase chain reaction; po, perioral; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SC, subcutaneous

* IVIG, 2 gr/kg
** Methylprednisolone usually 1-4 mg/kg, in some cases 30 mg/kg
*** Anakinra 2-4 mg/kg

286. Clinical characteristics and outcomes of paediatric patients presenting with digital gangrene to a Rheumatology clinic.

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Background: Digital gangrene involving hands and feet is an uncommon presentation in paediatric patients and in many cases an etiological factor is not identified. Paediatric vasculitides are multisystemic diseases which can have digital gangrene as one of the myriad manifestations that need to be diagnosed and treated early to improve outcomes. This study was carried out to evaluate the clinical features, treatment modalities and outcomes of paediatric patients presenting with digital gangrene/pre-gangrene to a Rheumatology clinic over 2 year follow up.

Methods: This prospective observational cohort study was conducted in the Clinical Immunology and Rheumatology department of a tertiary care teaching and referral hospital in Northern India over a period of 24 months (January 2019-December 2020). Clinical details of paediatric patients (<18 years) with digital gangrene were recorded at 1st visit, 3 months ,6 months and 2 years follow up. Patients with frank sepsis or septic shock/DIC were excluded.

Results: 10 pediatric patients with mean age 14.6 +/- 1.48 years were enrolled. The mean duration of illness was 13.95 +/- 20.4 months. 5 patients had both gangrene and pre-gangrene while 5/10 had only gangrene. Presentation was B/L in 6/10 patients with both hands and feet involved in 3/10. Median no of digits with gangrenous changes were 5(IQR 1-10) while median no of digits with pre-gangrene were 5(IQR 0-12). 5 children showed concomitant bacterial infection of digits requiring antibiotic. Raynauld's preceded gangrene in 3/10. The most frequent organ involvement at presentation apart from gangrene was cutaneous (6/10), musculoskeletal (4/10), PNS (3/10) and GI (3/10). 6 patients had leukocytosis (13220 +/- 6972.9 /mm^3) while thrombocytosis (222+/-174.6 x 10^9/L) was present in 3/10. All 10 patients had elevated ESR (69.1+/-33.9 mm) with elevated CRP (20.9□23.2 mg/dl) in 8/10 patients. Mean ESR (17.6+/-13.7) and CRP (3.84+/-4.22) decreased by >50 % at 3 months in 8/10 patients. At 6 months follow up all patients had normal inflammatory markers except raised ESR in 2 and raised CRP in 1. Persistent APLA positivity (> 40 U) at 12 weeks was documented in 3 patients with LAC being most common. Hypocomplementemia was present in 5 patients with 4 showing low serum C3(normal 90-180) and low C4(10-40) in 5/10. 2/10 patients had low IgA levels while one patient with elevated IgG levels was diagnosed with Juvenile SSc with Autoimmune hepatitis at follow up. Arterial doppler showed vasculitis in 5, ischemic changes in 2, both vasculitis and thrombosis in one patient and normal for 3 patients. Gangrene was attributed to Childhood PAN in 3/10, SLE-APS in 2, SLE/Lupus vasculitis in 1, SLE lupus vasculitis and APS in 1, Juvenile SSc in 2 while 1 patient had Scrub typhus associated vasculitis. 8 patients received oral glucocorticoids as treatment including pulse methylprednisolone for 2 patients and concomitant anticoagulation in 5/10. I.V cyclophosphamide was the preferred steroid sparing drug (7/10). 1 patient of Juvenile SSc received methotrexate while 2 patients didn't receive 2nd line therapy. Child with

SLE/APS/small vessel vasculitis required IVIG for myocarditis. Azathioprine was used as maintenance in 8/10 children. The mean dose of prednisolone at 2 years follow up was 4.375□6.022 mg/d. The median pain score on VAS scale of 0-10 was 8(IQR 5-10). Median no of autoamputated digits at 6 months were 2(IQR 0-6). Surgical amputation was done in 4/10 patients. At 2 years clinical remission was seen in 4/10,4/10 had improvement in symptoms without clinical remission,1 patient had active disease while 1 patient with SLE expired due to cardiogenic shock.

Conclusions: In our cohort of pediatric patients presenting with digital gangrene SLE with APS was most common etiology. Childhood PAN, SLE small vessel vasculitis, juvenile SSc and infection associated vasculitis remain the other important causes. In tropical countries infections are important vasculitis mimics and must be ruled out prior to attributing gangrene to autoimmune disease. Long term clinical outcomes of such patients are good provided early diagnosis and initiation of treatment.

Disclosures: None

287. Characteristics of Pediatric ANCA Associated Vasculitis among Racial/Ethnic Minorities- single center experience from United States

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Background: ANCA-associated vasculitides (AAV) are rare systemic diseases that generally manifest in adulthood and include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Adult studies have demonstrated severe disease and higher damage indices in Hispanics in comparison to Caucasians. There is limited information about the characteristics of AAV in children from racial and ethnic minority groups in the United States. The objective of this study was to study the characteristics of AAV among racial/ethnic minorities in comparison to white children in Central California, United States.

Methods: We performed a retrospective case review of patients less than 18 years of age diagnosed with AAV at a tertiary care children's hospital in Central California in United States from January 1, 2010 to March 31, 2021. Cases were identified from electronic health records using ICD-9 and ICD-10 codes for vasculitis. Records were reviewed for a diagnosis of AAV based on ACR/EULAR classification criteria. Demographic and clinical data including laboratory parameters, treatment, and outcomes were collected. Continuous data were expressed as a median and interquartile range, categorical data as frequency and percentages. Chi-square and Mann-Whitney U tests were used for statistical comparison as appropriate.

Results: Twenty-one cases of pediatric AAV were identified. Overall, 43% were white (n=9), 57% were racial/ethnic minority including Hispanics (9), Asians (2), and other/mixed race (1). The median age at diagnosis was 13 years (IQR 10.4-15.3) in the racial/ethnic minority group, compared to 15.6 years (IQR 14-16.7) in the white cohort (Table 1). 92% were female in the racial/ethnic minority cohort meanwhile, among white patients, 44% were female (p=0.05). The racial/ethnic minority group had higher myeloperoxidase (MPO) positivity (77% versus 11%, p <0.01) meanwhile white patients had a significantly higher frequency of proteinase 3 (PR3) positivity (66.7% versus 16.7%, p <0.01). Trends towards longer length of hospital stay (20 days versus 15 days, p=0.2), higher rates of plasmapheresis (33% versus 11%; p=0.3), requirement for dialysis (50% versus 33%, p=0.7), and higher rates of ICU admission (58% versus 44 %, p =0.7) were noted in racial/ethnic minorities, although it did not reach statistical significance. All patients received treatment with high-dose steroids at diagnosis. Immunosuppressive therapy included cyclophosphamide (42% in racial/ethnic minority cohort and 78% in white cohort), rituximab (33% in racial/ethnic minority cohort and 11% in white cohort), cyclophosphamide and rituximab (17% in racial/ethnic minority cohort and 11% in white cohort). There were no deaths in the white cohort, but 17% mortality (n=2) was reported in the racial/ethnic minority cohort. Causes of death were Aspergillus pneumonia and pulmonary hemorrhage.

Conclusions: Our study compares the characteristics of AAV among children from racial/ethnic minority and white groups in the Central California of United States. We observed more frequent MPO positivity in racial/ethnic minority children. Racial/ethnic minority children with AAV required ICU admission, plasmapheresis, and dialysis more frequently than white children. Racial/ethnic minorities had a longer length of hospital stay and death was more frequently noted. Limitations of our study include its small sample size. This study highlights the need for further research to understand the impact of race/ethnicity on pediatric AAV presentation, disease activity, and outcomes.

Disclosures: None

Table 1: Demographics and clinical characteristics of racial/ethnic minority and white patients with Pediatric ANCA-associated vasculitis

	Racial/Ethnic Minority N=12	***White N =9***	***p-value***
Median age at diagnosis (years, IQR)	13 (10.4-15.3)	15.6 (14-16.7)	0.06
Females (n, %)	11(92%)	4 (44%)	0.05
Anti-PR-3 positive (n, %)	2 (16.7%)	8 (66.7%)	<0.01
Anti-MPO positive (n, %)	11 (92%)	1 (11 %)	<0.01
Creatinine at presentation, mg/dL (median, IQR)	6.6 (0.9-12.1)	1.3 (0.7-2.93)	0.5
Peak creatinine, mg/dL (median, IQR)	7.1 (0.91-12.12)	2.4 (0.7-6.19)	0.6
Hemoglobin, g/dL (median, IQR)	7.4 (5.15-9.4)	9.4 (7.5-11.2)	0.07
ICU admission (n, %)	7 (58%)	4 (44%)	0.7
Dialysis (n, %)	6 (50%)	3 (33%)	0.7
Mortality (n, %)	2 (17 %)	0 (0%)	0.5
Median length of stay (days, IQR)	20 (14-41)	15 (10-28)	0.2
Pulse CS (n, %)	13 (100%)	9 (100%)	1
CS + Cyclophosphamide (n, %)	5 (42%)	7 (78%)	0.1
CS+ Rituximab (n, %)	4 (33%)	1(11%)	0.3
CS+ Cyclophosphamide+ Rituximab (n, %)	2 (17%)	1(11%)	1
Plasmapheresis (n, %)	4 (33%)	1 (11%)	0.3

IQR=Interquartile range, PR-3=Proteinase 3, MPO=Myeloperoxidase CS=corticosteroids

288. The Association between Age of Diagnosis and Disease Characteristics in Patients with ANCA-Associated Vasculitis

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Background: Clinical characteristics often differ between children and adults diagnosed with the same rheumatic condition; however, such comparative data is limited in ANCA-associated vasculitis (AAV). The objective of this study was to examine the relationship between age of diagnosis and disease characteristics in patients with AAV.

Methods: This was a cross-sectional analysis of all patients with granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) enrolled in the Vasculitis Clinical Research Consortium (VCRC) Longitudinal Studies, a physician-entered database, from 2013 to 2021. The sample was divided into four cohorts: children (< 18 years old at diagnosis), young adults (18-40 years old at diagnosis), middle-aged (> 40-65 years old at diagnosis), and older adults (> 65 years old at diagnosis). Patients without a listed age of diagnosis were excluded. Missing or unknown data were not included in the calculations for each variable. Continuous variables were reported with medians and interquartile ranges; categorical variables with frequencies and proportions. Group differences were tested via Kruskal-Wallis test for continuous variables and Fisher's Exact tests for categorical variables. Outcomes included demographics, ANCA type (anti-proteinase 3 (PR3) and anti-myeloperoxidase (MPO)), and clinical characteristics at diagnosis and over time. Sub-analyses were performed within each disease category and ANCA type.

Results: A total of 1377 patients were included for analysis, including 66 children, 322 young adults, 767 middle aged, and 222 older adults (Table 1). Of the 1377 patients, 852 (62%) had GPA, 165 (12%) had MPA, and 357 (26%) had EGPA. 998 (81%) of all patients were ANCA positive with 641 (64%) positive for PR3-ANCA, 346 (35%) positive for MPO-ANCA, and 11 (1%) positive for both. AAV diagnosed in childhood had a female predominance, which then decreased with age. AAV diagnosed in childhood was also more commonly GPA and ANCA positive with PR3-ANCA predominance and less commonly EGPA. Older adults at diagnosis had more MPA and MPO-ANCA. Both at diagnosis and over time, the group diagnosed in childhood experienced more subglottic stenosis and alveolar hemorrhage. The incidence of skin, ocular, nasal, sinus, renal, gastrointestinal, and nervous system manifestations were also different in at least one age group over time.

Conclusions: There is an association between age of diagnosis and certain clinical characteristics in patients with AAV, particularly when diagnosed in childhood. Most notably, children diagnosed with AAV experience more subglottic stenosis and alveolar hemorrhage, among other features. An early female predominance in AAV wanes across age groups. While studies often exclude children, sub-analyses of adults with AAV diagnosed in childhood could provide valuable insight into the unique aspects of childhood-onset AAV across the lifespan, allowing for a more evidence-based approach to care and improved outcomes.

Disclosures: None.

Table 1. Characteristics of patients with ANCA-associated vasculitis stratified by age at diagnosis

Characteristic*	Age at Diagnosis: Child *< 18 years old* n = 66	Young Adult *18-40 years old* n = 322	Middle Aged *< 40-65 years old* n = 767	Older *> 65 years old* n = 222	All n = 1377	*p*-value
	Mean (standard deviation) or n (percentage)					
Age at Diagnosis (years)	13.6 (6.1)	29.6 (6.4)	53.1 (6.7)	71.2 (5.2)	48.6 (16.7)	<0.001
Sex (female)	49 (74.2%)	202 (62.7%)	392 (51.1%)	117 (52.7%)	760 (55.2%)	<0.001
Race						0.092
Asian	2 (3.1%)	19 (6.1%)	33 (4.4%)	8 (3.7%)	62 (4.6%)	
Black/African American	0 (0.0%)	10 (3.2%)	14 (1.9%)	1 (0.5%)	25 (1.9%)	
White	62 (96.9%)	274 (88.1%)	699 (93.0%)	207 (94.5%)	1242 (92.3%)	
Other Race	0 (0.0%)	8 (2.6%)	6 (0.8%)	3 (1.4%)	17 (1.3%)	
Ethnicity						0.208
Hispanic	0 (0.0%)	9 (2.8%)	24 (3.1%)	2 (0.9%)	35 (2.5%)	
Not Hispanic	61 (92.4%)	286 (88.8%)	696 (90.7%)	199 (89.6%)	1242 (90.2%)	
Unknown/Not Reported	5 (7.6%)	27 (8.4%)	47 (6.1%)	21 (9.5%)	100 (7.3%)	
Follow Up Time (years)	4.7 (3.9)	3.9 (3.6)	3.8 (3.6)	2.9 (2.8)	3.7 (3.5)	0.008
Disease Category						<0.001
GPA	55 (83.3%)	226 (70.2%)	468 (61.0%)	104 (46.8%)	853 (61.9%)	
MPA	6 (9.1%)	14 (4.3%)	92 (12.0%)	55 (24.8%)	167 (12.2%)	
EGPA	5 (7.6%)	82 (25.5%)	207 (27.0%)	63 (28.4%)	357 (25.9%)	
ANCA Type (ELISA)						<0.001
PR3-ANCA	46 (71.9%)	175 (62.3%)	341 (49.6%)	79 (38.3%)	641 (51.8%)	
MPO-ANCA	12 (18.8%)	45 (16.0%)	196 (28.5%)	93 (45.1%)	346 (27.9%)	
PR3- and MPO- ANCA	0 (0.0%)	1 (0.4%)	10 (1.5%)	0 (0.0%)	11 (0.9%)	
ANCA-negative	6 (9.4%)	60 (21.4%)	140 (20.4%)	34 (16.5%)	240 (19.4%)	
Clinical Manifestations Ever Identified						
Constitutional	55 (83.3%)	256 (79.5%)	619 (80.7%)	174 (78.4%)	1104 (80.2%)	0.778
Fever	20 (30.3%)	82 (25.5%)	178 (23.2%)	53 (23.9%)	333 (24.2%)	0.564
Musculoskeletal	43 (65.2%)	218 (67.7%)	494 (64.4%)	100 (45.0%)	855 (62.1%)	<0.001
Cutaneous	25 (37.9%)	139 (43.2%)	276 (36.0%)	62 (27.9%)	502 (36.5%)	0.003
Mucous Membranes	7 (10.6%)	39 (12.1%)	68 (8.9%)	17 (7.7%)	131 (9.5%)	0.260
Ocular	22 (33.3%)	103 (32.0%)	188 (24.5%)	28 (12.6%)	341 (24.8%)	<0.001
Ear, Nose, and Throat	57 (86.4%)	281 (87.3%)	622 (81.1%)	162 (73.0%)	1122 (81.5%)	0.001
Nasal Septal Perforation	7 (10.6%)	45 (14.0%)	58 (7.6%)	9 (4.1%)	119 (8.6%)	<0.001
Sinus Involvement	47 (71.2%)	238 (73.9%)	508 (66.2%)	120 (54.1%)	913 (66.3%)	<0.001
Subglottic Stenosis	19 (28.8%)	55 (17.1%)	44 (5.7%)	5 (2.3%)	123 (8.9%)	<0.001
Cardiac	3 (4.5%)	37 (11.5%)	83 (10.8%)	28 (12.6%)	151 (11.0%)	0.319
Gastrointestinal Tract	9 (13.6%)	32 (9.9%)	47 (6.1%)	9 (4.1%)	97 (7.0%)	0.011
Pulmonary	50 (75.8%)	251 (78.0%)	587 (76.5%)	174 (78.4%)	1062 (77.1%)	0.904
Alveolar Hemorrhage	25 (37.9%)	78 (24.2%)	137 (17.9%)	47 (21.2%)	287 (20.8%)	0.001
Intubation	3 (4.5%)	21 (6.5%)	34 (4.4%)	10 (4.5%)	68 (4.9%)	0.536
Renal Disease	43 (65.2%)	135 (41.9%)	398 (51.9%)	121 (54.5%)	697 (50.6%)	<0.001
Dialysis	3 (4.5%)	13 (4.0%)	50 (6.5%)	14 (6.3%)	80 (5.8%)	0.441
Nervous System	12 (18.2%)	88 (27.3%)	288 (37.5%)	94 (42.3%)	482 (35.0%)	<0.001
Venous Thrombosis	6 (9.1%)	25 (7.8%)	89 (11.6%)	22 (9.9%)	142 (10.3%)	0.308

GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; ANCA, anti-neutrophil cytoplasmic antibody; PR3, protease 3; MPO, myeloperoxidase.
*Unknown or Missing responses for each characteristic were not included.

289. Clinical features and treatment of patients with severe skin changes in IgA vasculitis: multicenter study

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Background: Skin changes, which are a mandatory classification criterion of IgA vasculitis (IgAV), are most commonly typical, but approximately 2% of children may experience the most severe changes (hemorrhagic bullae and necroses). The purpose of this research was to determine whether such changes were also associated with a more severe clinical picture and the need for more intensive therapy.

Methods: The study included pediatric patients with the most severe skin manifestations as part of IgAV from 8 international tertiary university medical centers. Patients were diagnosed by EULAR/PRES/PRINTO criteria. Data were analyzed descriptively and using the Fisher test.

Results: A total of 41 patients with the most severe skin changes in IgAV were included in the study, of which 26 (63.4%) were male, with a median (range) age of 8.75 (1.5-17.08) years at the disease onset. Control group consisted of 596 IgAV patients who did not develop bullae and/or necroses. In most patients, IgAV started with skin manifestations (62.5%). The time from the onset of the first symptom to the first bullous/necrotic change was 4.5 (0-180) days, and from the onset of the first purpuric change to the first bullous/necrotic change 3.5 (0-180) days. Total duration of bullous/necrotic changes was 10 (4-780) days. The most prominent trigger of IgAV were infections, present in 57.5% patients. The distribution of bullae and necroses followed the distribution of the purpuric changes, predominantly affecting the lower extremities in 70% of the patients. Sequelae of the skin changes were not present in 75% of the patients, while the rest had scars and pigmentation changes. 40% of these patients developed nephritis, and the most common finding was a combination of hematuria and proteinuria. The patients with severe cutaneous manifestations were older in comparison to other patients with IgAV (mean age 8.75 years vs. 7.17 years, $p = 0.008$) and had statistically more frequently affected kidneys (39% vs. 20.6%, $p = 0.01$), however, no one developed chronic renal disease. All these patients were treated: 75% of them received methylprednisolone with a median (range) cumulative dose of 33 (4-170.46) mg/kg for a median (range) of 17 (3-298) days, while 40% were treated with nonsteroidal anti-inflammatory drugs for 5 (2-30) days. Other drugs were administered sporadically. They were significantly more frequently treated with systemic glucocorticoids (90.2% vs. 37.2%, $p < 0.001$).

Conclusions: Patients with IgAV and the most severe cutaneous manifestations were statistically significantly more likely to develop nephritis and were treated with systemic glucocorticoids.

Disclosures: None.

290. Vasculitis of the young: Treat to target when precision medicine is not possible

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Background: Precision medicine refers to the concept of treating the right patient, with the right drug, at the right time. This is an aspiration for children with vasculitis but is not always possible, even with modern diagnostic molecular approaches. The differential diagnosis of paediatric vasculitis is increasingly broad encompassing chronic infection, malignancy, autoimmunity, an ever-expanding number of monogenetic autoinflammatory diseases, and a plethora of non-inflammatory genetic vasculopathies. Next-generation genetic sequencing has disrupted conventional diagnostic approaches but does not always deliver a precise diagnosis. A pragmatic treat-to-target approach is required to facilitate empiric therapeutic decisions (Box) which improves patient quality of life. We present 2 challenging cases illustrating this approach.

Methods/Results: Patient A: a 19-month-old girl was born in good condition following uneventful pregnancy and delivery. At 4 hours old, she developed a widespread purpuric rash. Thrombocytopenia was noted transiently 70 $x10^9$/L. Clotting, cell counts, bone marrow aspirate, and inflammatory markers were normal. ANCA was negative. Congenital infection and immune deficiency were excluded. Skin biopsy revealed florid leucocytoclastic vasculitis (LCV). Workup for interferonopathy (CT head and peripheral blood interferon gene signature) were normal. Whole exome sequencing did not reveal any genetic diagnosis. Cutaneous vasculitis without other organ involvement persisted throughout infancy, despite unsuccessful therapeutic trials of GC, topical tacrolimus, and oral janus kinase 1/2 inhibitor (baricitinib). Empiric treatment with anakinra to treat chronic cutaneous LCV is currently underway. All other targets in Box have been met, providing reassurance to parents (and doctors), in the face of no precise diagnosis. Patient B: a previously well 9-year-old boy presented to his GP with a painless lump on the volar aspect of his forearm. A second lump appeared soon after. There were no fevers although ESR and CRP were both grossly elevated. USS revealed two saccular aneurysms of the brachial artery distal branches. Emergency treatment with high dose intravenous GC was instituted for presumed large vessel vasculitis (LVV). Non-invasive angiography was not suggestive of LVV, however, revealing multiple saccular, thin-walled, non-enhancing aneurysms of his whole aorta, intrarenal arteries, common iliacs, femorals, and brain. Acute back pain developed, necessitating emergency surgical repair of a large aorto-right iliac artery aneurysm and bilateral nephrectomy. Histology of the arterial wall revealed minimal inflammation, no granuloma, and fibrosis with dystrophic calcification. Immunofluorescence was negative. Histology did not resolve the diagnostic equipoise around LVV versus non-inflammatory genetic vasculopathy. Immunosuppression was paused in the

immediate post-operative phase; dialysis was commenced; and ongoing investigations focusing on whole exome sequencing to explore a non-inflammatory vasculopathy are awaited.

Conclusions: These two cases highlight the diagnostic and therapeutic challenges encountered in paediatric vasculitides and illustrate that a treat-to-target approach can still be utilised for children with imprecise diagnoses. The case for empiric immunomodulation in case A is clear, although this child did not have any organ or life-threatening features, and the treatment target is to resolve cutaneous LCV. In contrast, the case for empiric immunosuppression in case B is less clear-cut, even though life-threatening vasculopathic features are present since non-inflammatory vasculopathy may be a more likely cause than LVV.

Disclosures: None

Table 1

Therapeutic targets for vasculitis without a precise diagnosis
Prevent organ injury or death
Normalise markers of systemic inflammation
Minimise glucocorticoid (GC) toxicity
Minimise burden of immunosuppression: *is this disease really inflammatory*?
Maximise growth
Minimise disruption to education: use oral medicines given at home

291. Case report of acute digital ischaemia in 12-year-old boy with Granulomatosis with Polyangiitis

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Background: Granulomatosis with polyangiitis (GPA) is a rare form of vasculitis involving medium and small arteries, affecting predominantly the upper and lower respiratory tracts, often associated with glomerulonephritis.
GPA is typically characterised by necrotising granulomatous inflammation in the presence of antineutrophil cytoplasmic antibodies (ANCA). Objectives: To report an extremely rare presentation of GPA in a child with acute digital ischemia.

Methods: This 12 year old boy, who has a background of poorly controlled type 1 diabetes and autoimmune hypothyroidism, initially presented to hospital very unwell with diabetic ketoacidosis. Treatment was initiated immediately with good response. On further questioning, he was found to have significant weight loss, chronic cough and hearing loss over the past 3 months. On examination, he was very pale and cachexic. He had a productive cough with reduced air entry and crackles on the right side. There were concerns about hypertonia and

clonus in his lower limbs. Initial blood tests showed microcytic hypochromic anaemia (Hb 82g/L), normal white cell count, thrombocytosis and raised inflammatory markers (CRP 138mg/L and ESR 68 mm/hr). His chest x-ray showed enlargement of the right hilum with consolidation/ atelectasis extending into the middle and lower lobes. MRI scans of head and spine were normal apart from fluid and opacification in all the paranasal sinuses. He was extensively screened for infections including Tuberculosis and was started on intravenous antibiotics. On day 13 of admission, he developed painful bluish discolouration of left hand, particularly his thumb, index and middle fingers. His left radial and brachial pulses were not palpable. He was commenced on heparin infusion. The Doppler scan showed occlusion of both radial and ulnar arteries proximal to the wrist with no clear thrombus visualised. He subsequently had a CT thoracic aorta with contrast which showed proximal left radial artery occlusion and distal left ulnar artery occlusion with no clear evidence of proximal embolic source or evidence of vasculitis. It also showed multiple perihilar masses (lymph nodes) in the right lung and peripheral parenchymal masses in both lungs, suggestive of atypical infection or connective tissue disease. Blood tests continued to show raised inflammatory markers (CRP 107mg/L, ESR 86 mm/hr and platelets 658 10^9/L). The autoantibody profile showed positive ANCA with strongly positive anti PR3 titres (>100 U/mL); rest of the autoantibodies, including ANA, ds DNA and anti-phospholipid antibodies, were negative. He further developed similar ischaemic changes in his right foot, especially the right great toe, with a weakly palpable dorsalis pedis pulse. Doppler scan revealed occlusion / narrowing of the posterior tibial artery 6cm proximal to the ankle. Following advice from the vascular team, he was started on ilioprost infusion to aid re-perfusion of the extremities involved, with good results. Based on clinical and laboratory features of systemic inflammation, evidence of upper airway involvement (bilateral conductive hearing loss and sinusitis noted on MRI scan), parenchymal lesions on CT scan of the chest and strong PR3 positivity, a diagnosis of GPA was made.

Results: Our patient responded well to therapy including multiple pulses of high dose methylprednisolone and cyclophosphamide, with improvement of all organs involved and no further digital ischemia.

Conclusion: Although GPA is very rare in children, it is associated with high morbidity and mortality. Many studies show that the spectrum of paediatric GPA is not vastly different from adults, except for higher gender bias towards female, more constitutional and musculoskeletal symptoms, and higher risk of subglottic stenosis. Although there are a handful of case reports of digital ischaemia in adults with GPA, to our knowledge this is the first case report of acute digital ischaemia in paediatric GPA. Early diagnosis and prompt treatment with a multidisciplinary team approach is paramount for good outcome.

Disclosures: None

292. Central retinal artery occlusion as debut of pediatric ANCA-associated vasculitis: a case report

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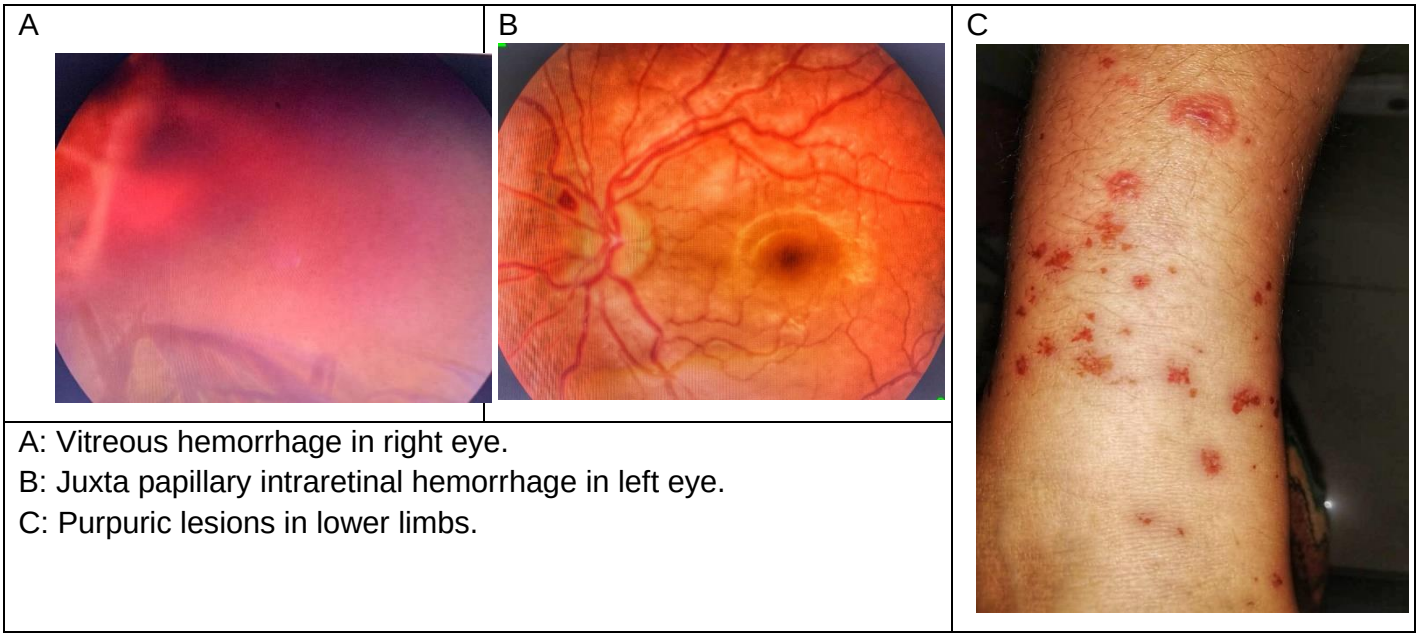
Presentation of case: An eleven-year-old female patient previously healthy presented to us with a 3-month history that begins with bilateral conjunctival injection and headache. After 2 months, other symptoms were associated such as arthralgia, myalgia, and feverish sensation. Finally, in the week before hospital admission, skin lesions with purpuric characteristics were added in the lower limbs, and visual acuity of the right side decreased acutely. The physical examination revealed localized dermatosis at the level of the lower limbs, with brownish crusty lesions and other purpuric lesions, some with a bullous center. In the right eye, total amaurosis was observed, areflectic pupil, photo-motor reflex absent. The ophthalmological examination revealed retinal hemorrhage in the right eye, which made it impossible to visualize the posterior pole, which is why angiofluorescein was performed, which reported absence of perfusion of the central artery of the right retina and ocular ultrasound that reported serous detachment of the right retina. Diagnostic testing: Laboratory tests reveal involvement of multiple systems, increased inflammatory markers (CRP: > 118.6 mg/dl, fibrinogen= 634 mg/dl), C3, C4 in range, ANA and ANTI DNA negative, microhematuria (10-12/field), proteinuria (30 mg/dl), ANCA myeloperoxidase (MPO) positive (>300). Echocardiogram and abdominal ultrasound were normal. An infectious examination was negative for tuberculosis, HIV, CMV, Toxoplasmosis, blood culture. The skin biopsy reported residual changes of leukocytoclastic vasculitis, with thrombosis. In papillary and residual dermis, dilated capillaries were seen, some congestive with thrombi inside, surrounded by lymphocytes, with few neutrophils, and nuclear dust. Renal biopsy was indicated, where 31 glomeruli were observed, some totally sclerosed, others with segmental sclerosis, with fibrinoid necrosis, fibrin exudate and fragments of neutrophil nuclei, corresponding to a focal segmental necrotizing glomerulonephritis, throwing the diagnosis of microscopic polyangiitis.

Discussion and Management: The patient presented with a systemic disease that started with non-specific symptoms. Myalgias, arthralgias, mild fever and finally there were multiple palpable purpuric lesions on the lower limbs, leading to suspicion of inflammatory small vessel disease. Henoch-Schoenlein purpura is the most common systemic small vessel vasculitis in children; however, the sudden decrease in vision in her right eye required further diagnostic testing. The elevations of inflammatory markers but above all hemogram with presence of toxic granulations (15%) lead us to initiate antibiotic therapy. Despite this treatment we observed extension of skin lesions, persistence of inflammatory markers elevated, urinalysis revealed hematuria and proteinuria, so small vessel vasculitis was suggested as a diagnosis, and noting the central retinal artery occlusion (CRAO) that can affect the quality of life of the patient, we started immediate immunosuppressive therapy with methylprednisolone, at 1g/day for three days followed by oral prednisolone. After having renal biopsy results confirming small vessel vasculitis and positive ANCA-MPO, an ANCA-associated vasculitis (AAV) was confirmed. She

also received cyclophosphamide (3 doses currently). Despite the start of corticosteroid therapy, and treatment with cyclophosphamide, there was no improvement in right visual acuity.
Conclusions: AAV is extremely rare in the paediatric population, making diagnosis a real challenge. Total CRAO, due to its rarity, requires a high diagnostic suspicion based on clinical, physical examination and laboratory analysis. Immediate administration of corticosteroids is sometimes necessary, especially when severe complications occur that can negatively impact quality of life such as CRAO.
Disclosures: None

Figure: Clinical manifestations at cutaneous and ocular level



A: Vitreous hemorrhage in right eye.
B: Juxta papillary intraretinal hemorrhage in left eye.
C: Purpuric lesions in lower limbs.

293. Outcomes of kidney transplantation in childhood-onset ANCA-associated vasculitis. A multicentre study

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Background: Kidney failure (KF) is a major complication of ANCA-associated vasculitis (AAV). Kidney transplantation (KTx) has been reported as an effective and safe therapeutic option in

adult patients with AAV and KF while there are limited data for children. We aimed to assess outcomes of KTx in childhood-onset AAV among a large multicentre cohort of patients.

Methods: Patients with AAV onset during childhood (≤18 years) who received KTx because of KF due to vasculitis-related renal involvement were identified in 21 European and Northern American centres and their data collected. We analysed patient and graft survival, rates of AAV relapse, incidence of transplant rejection and of severe infections.

Results: We included 55 patients, of whom 38 (69%) had microscopic polyangiitis (MPA) and 17 (31%) granulomatosis with polyangiitis (GPA). Mean age at diagnosis and at transplantation were respectively 12 (interquartile range, IQR 9-14) and 14 (IQR 12-16) years. Donation was from a living donor in 20 (36%) patients and from a deceased donor in the remainder 35 (64%). At the time of transplantation, all patients had achieved vasculitis remission (BVAS=0) and 14/54 (26%) had positive ANCA. All but one patient received calcineurin inhibitors (84% tacrolimus, 13% cyclosporine), 13 (24%) azathioprine, and 36 (66%) mycophenolate mofetil, while mTOR inhibitors were used in only two patients (3%). The maintenance regimen based on prednisone, mycophenolate mofetil, and tacrolimus was administered to 33 (60%) patients. Further patient characteristics are reported in Table 1. The median follow-up was 54 months (IQR 21-91). Acute rejection was reported by 25 (45%) patients, 12 of whom experienced it during the first 12 months after transplantation, while chronic rejection was established in three (5%). AAV relapse occurred in five patients. Positive ANCA at transplantation was significantly associated with the risk of relapse (29% vs 2%, p=0.02). At last follow-up, 21 (38%) patients had developed graft dysfunction (eGFR <60 ml/min/1.73 m^2) and seven (13%) of them graft failure. Rejection and positive ANCA at the time of transplantation but not the type of AAV, ELISA specificity and donor were significantly associated with the risk of graft dysfunction (Figure 1). Infections occurred in 31 (53%) patients, with 12 (22%) experiencing pyelonephritis, eight (14%) CMV infection, five (9%) EBV viraemia and four (7%) BK virus infection. Neither deaths nor malignancies were reported.

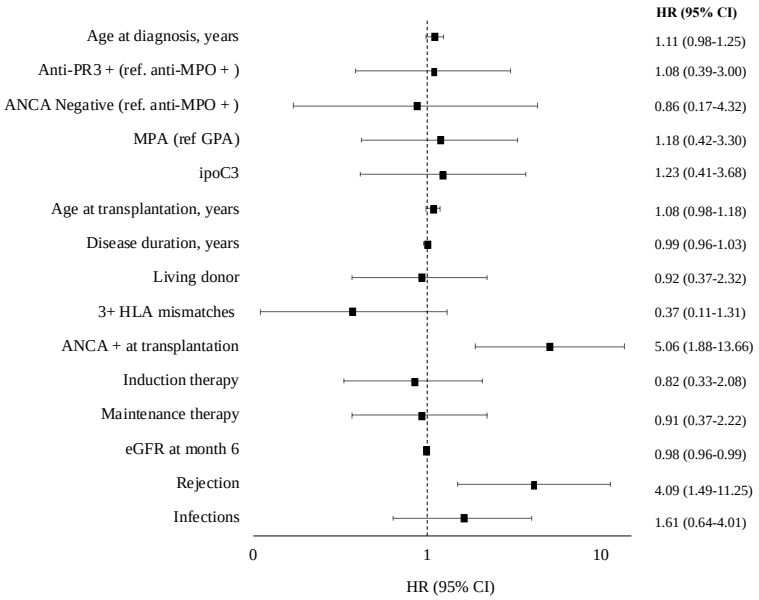
Conclusions: KTx in childhood-onset AAV has good graft and patient survival and few complications. The risk of vasculitis relapse appears low. Positive ANCA at the time of transplantation seem an important risk factor for both AAV relapse and the development of graft dysfunction.

Disclosures: None

Table 1. Characteristics of AAV children with renal transplantation.

	All *n*=55	MPA *n*=38	GPA *n*=17	P value MPA vs GPA
Demographics				
Female, *n (%)*	42 (76)	30 (79)	12 (70)	0.51
Caucasian, *n (%)*	42 (76)	29 (76)	13 (76)	1
Age at diagnosis, median (IQR) – *years* ANCA by ELISA, *n (%)*	12 (9-14)	12 (8-14)	12 (10-14)	0.41
Negative	7 (13)	4 (10)	3 (18)	0.66
PR3-ANCA	17 (31)	7 (18)	10 (59)	0.004
MPO-ANCA	19 (34)	18 (47)	1 (6)	0.004
Missing	11 (20)	9 (24)	2 (12)	
Transplantation				
Age, median (IQR) – *years*	14 (12-17)	14 (11-17)	14 (13-17)	0.80
Living donor, *n (%)*	20 (36)	13 (34)	7 (41)	0.76
Deceased donor, *n (%)*	35 (64)	25 (66)	10 (59)	
Positive ANCA, *n (%)*	14/54 (26)	12/37 (32)	2/17 (12)	0.18
GC + MMF + Tac, *n (%)*	33 (60)	24 (63)	9 (53)	0.55
GC + AZA+ Tac, *n (%)*	13 (24)	7 (18)	6 (35)	0.31
Other, *n (%)*	9 (16)	6 (16)	3 (18)	
Complications, *n (%)*				
Acute rejection,	25 (45)	17 (45)	8 (47)	0.87
Chronic rejection	2 (4)	2 (5)	0	1
AAV relapse	5 (9)	3 (8)	2 (12)	1
Infection	34 (62)	21 (55)	13 (76)	0.23
Malignancy	0	0	0	
Outcome at last follow-up, *n (%)*				
Graft dysfunction	21 (38)	16 (42)	5 (29)	0.55
Graft failure	7 (13)	5 (13)	2 (12)	1
Death	0	0	0	

Figure 1. Forrest Plot illustrating the risk of graft dysfunction.



Clinical Trials - adult

294. Rituximab versus conventional therapeutic strategy for remission induction in EGPA: double-blind, randomized, controlled trial

Benjamin Terrier[1], Grégory Pugnet[1], Claire de Moreuil[1], Bernard Bonnotte[1], Ygal Benhamou[1], Dominique Chauveau[1], Elisabeth Diot[1], Pierre Duffau[1], Nicolas Limal[1], Antoine Néel[1], Geoffrey Urbanski[1], Noémie Jourde-Chiche[1], Nicolas Martin-Silva[1], François Maurier[1], Arsène Mekinian[1], Nicolas Schleinitz[1], Felix Ackermann[1], Anne-Laure Fauchais[1], Antoine Froissart[1], Thomas Le Gallou[1], Yurdagul Uzunhan[1], Jean-François Viallard[1], Alice Berezne[1], Laurent Chiche[1], Bruno Crestani[1], Guillaume Direz[1], Cécile-Audrey Durel[1], Pascal Godmer[1], Jean-Emmanuel Kahn[1], Marc Lambert[1], Mathilde de Menthon[1], Thomas Quemeneur[1],. Léa Jilet[1], Loic Guillevin[1], Hendy Abdoul[1], Xavier Puéchal[1]
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Background: Eosinophilic granulomatosis with polyangiitis (EGPA) is an eosinophilic ANCA-associated vasculitis. Glucocorticoids, alone or in combination with cyclophosphamide in severe forms, induce remission in most patients with EGPA. Rituximab, an anti-CD20 monoclonal antibody depleting B cells, demonstrated efficacy in other ANCA-associated vasculitides. Rituximab might be indicated in the treatment of EGPA.

Methods: This phase 3, comparative, multicenter, randomized, controlled, double-blind and superiority research compared rituximab-based regimen with conventional therapeutic strategies for the induction of remission. Patients with newly diagnosed or relapsing disease were randomized in a 1:1 ratio to receive: the experimental therapeutic strategy based on the use of rituximab, or the conventional therapeutic strategy based on Five-Factor Score (FFS)-assessed disease severity. The primary end point was the rate of patients who achieved remission at day 180 as defined by BVAS=0 and a prednisone dose ≤7.5 mg/day. Secondary end points were duration of remission during the study period, the average daily glucocorticoid dose and safety.

Results: A total of 105 participants underwent randomization (74 with newly diagnosed EGPA, 63 with FFS=0, 59 with negative ANCA), with 52 participants assigned to receive rituximab and 53 to conventional strategy. At day 180, remission was achieved in 33 patients in the rituximab group (63.5%) and in 32 patients in the conventional strategy group (60.4%) (relative risk, 1.05; 95% confidence interval, 0.78 to 1.42, P=0.75). At day 360, remission was achieved in 31 patients in the rituximab group (59.6%) and in 34 patients in the conventional strategy group (64.2%) (relative risk, 1.08; 95% CI, 0.80 to 1.45, P=0.63).
Mean duration of remission was 16.4 (10.37) and 16.2 (11.68) weeks in the rituximab group and the conventional strategy group, respectively. All relapse and major relapse rates were comparable between the two groups. SF-36 was similar between the two groups. However, health assessment questionnaire (HAQ) at day 180 and day 360 (p=0.07 and p=0.09, respectively) and vasculitis damage index (VDI) at day 360 (p=0.07) tended to be better in the rituximab group. There was no significant difference in average daily glucocorticoid dose

between the two arms, with an area under the curve of 4591 mg in the rituximab group and 4453 mg for the conventional strategy group.

Conclusions: In EGPA patients participating to this double-blind randomized controlled trial, rituximab was not superior to conventional therapeutic strategy based on FFS to induce vasculitis remission

Disclosures: None

295. Baricitinib for Relapsing Giant Cell Arteritis: a Prospective Open-Label Single-Institution Study

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Background: Pre-clinical giant cell arteritis (GCA) mouse models have demonstrated effective suppression of arterial wall lesional T-cells through inhibition of Janus kinase 3 (JAK3) and JAK1. However, JAK inhibition in patients with GCA has not been formerly investigated.

Methods: We performed a prospective, open-label, pilot study of baricitinib (4mg/day) in patients with relapsing GCA. The primary outcome was the frequency of adverse events and serious adverse events at week 52. Secondary outcomes included relapse at week 24 and week 52, change in pre-enrollment erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) to week 24 and week 52, and comparison of glucocorticoid dose at enrollment to week 24 and week 52. The study schema is outlined in Figure 1.

Results: 15 patients were enrolled in the study (11, 73% female) with a mean(SD) age at entry 72.4(7.2) years, median(IQR) duration of GCA of 9 (7, 21) months, and median of 1 (1, 2) prior relapse. Treatments prior to study entry included: glucocorticoids (15, 100%); methotrexate (2, 13%); cyclophosphamide (1, 7%); sirukumab (1, 7%). Characteristics at GCA diagnosis and at relapse prior to study entry are listed in Table 1. Four (27%) patients entered the study on prednisone 30mg/day, 6 (40%) at 20 mg/day, and 5 (33%) at 10mg/day. One patient with baseline chronic kidney disease had a decline in renal function below study threshold for continuation and was withdrawn at week 8. The remaining 14 patients completed 52 weeks of baricitinib. At week 52, 14/15 (93%) patients had at least one adverse event recorded with the most frequent events including: infection not requiring antibiotics (n=8), infection requiring antibiotics (n=5), nausea (n=6), leg swelling (n=2), fatigue (n=2), diarrhea (n=1), abdominal pain (n=1). Two patients contracted COVID-19 during the study, both with mild symptoms, neither hospitalized. One patient had a serious adverse event during the study (transient thrombocytopenia attributed to concomitant use of antimicrobial therapy).

Study outcomes are listed in Table 2. ESR and CRP were significantly lower at week 24 and week 52 compared to pre-enrollment values. Patient global assessment at week 0 was also

significantly improved at both week 24 and week 52. Only 1 of 14 (7%) patients relapsed during the study (same patient at week 24 and week 52). The remaining 13 patients achieved steroid discontinuation and remained in disease remission during the duration of the 52-week study. Among patients completing the study, 4/14 (29%) flared during the 12-week follow up period after baricitinib discontinuation.

Conclusion: In this proof of concept study, baricitinib at a dose of 4mg/day appeared both safe and effective in the management of patients with relapsing GCA. Larger randomized clinical trials are needed to determine the utility of JAK inhibition in GCA.

Disclosures: KW received funds from Eli Lilly and Company to assist in the completion of the clinical trial. MK, CS, RG, JJ, EM, AD-G, CW report no financial disclosures of interest related to this study.

Figure 1: Study Schema

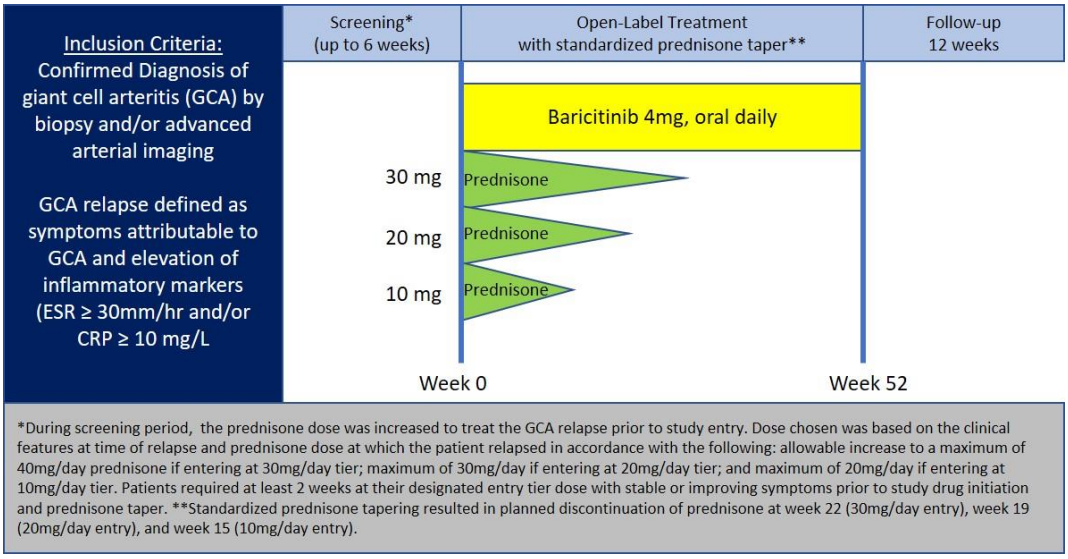

Table 1: Characteristics at giant cell arteritis diagnosis and relapse prior to study entry

Characteristic	GCA diagnosis (N=15)	Relapse prior to study entry (N=15)
Headache	11 (73)	6 (40)
Scalp tenderness	10 (67)	3 (20)
Jaw claudication	7 (47)	1 (7)
Visual Ischemia	4 (27)	0 (0)
Limb claudication	1 (7)	0 (0)

Polymyalgia rheumatica	4 (47)	8 (53)
Constitutional symptoms	11 (73)	8 (53)
New or worse large vessel vasculitis on arterial imaging	5 (33)	4 (27)
Method of diagnosis TAB (+) / Imaging (+) TAB (+) / Imaging (-) or ND TAB (-) or ND / Imaging (+)	 5 (33) 5 (33) 5 (33)	---
TAB, temporal artery biopsy; ND, not done		

Table 2: Study Outcomes

Outcome	Pre-baricitinib relapse	Week 0	Week 24	P-value	Week 52	p-value
Prednisone dose, mg/day**	-	20 (10,30)	0 (0, 0) ¥	<0.001€	0 (0, 0)	<0.001€
ESR, mm/h*	36.1 (19.3)	10.3 (7.6)	21.1 (29.2)	0.005φ	18.4 (29.8)	0.04Ψ
CRP mg/L*	22.8 (7.7)	5.2 (3.7)	7.2 (16.9)	0.006φ	4.0 (3.0)	<0.001Ψ
BVAS**	2 (1, 3)	-	0 (0, 0)	<0.001φ	0 (0, 0)	<0.001Ψ
Patient global assessment*	-	22.4 (21.6)	8.6 (12.9) ¥	0.04€	7.1 (9.1)	<0.007€
Stopped glucocorticoids	-	-	14/14 (100%)	-	13/14 (93%)	-
Relapse on study drug	-	-	1/14 (7%)	-	1/14 (7%)	-
*mean(SD), **median(IQR) φComparison pre-baricitinib relapse value to week 24; Ψcomparison pre-baricitinib relapse value to week 52 ¥Comparison week 0 value to week 24; €comparison week 0 value to week 52						

296. Maintenance of Remission of AAV by Rituximab Based on B-cell Reconstitution vs ANCA Serology (MAINTANCAVAS)

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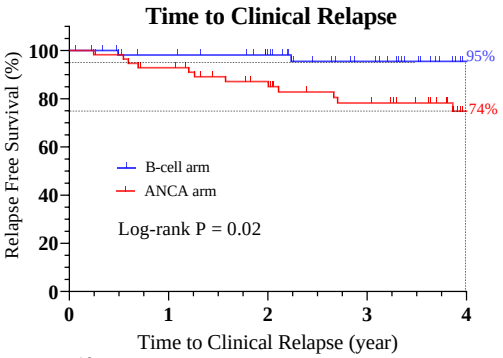
Background: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic autoimmune disease characterized by small vessel inflammation caused by pathogenic autoantibodies to proteinase 3 (PR3) or myeloperoxidase (MPO). Rituximab (RTX), an anti-CD20 monoclonal antibody, is effective at induction and maintenance of remission. However, RTX is associated with adverse events, including hypogammaglobulinemia, infections, and late-onset of neutropenia. The optimal strategy for long-term maintenance of remission remains unknown.

Methods: MAINTANCAVAS is an open-label, single center, randomized, two-arm controlled trial (ClinicalTrials.gov Identifier: NCT02749292) aiming to evaluate maintenance of remission strategies that provide the best relapse-free, long-term survival in patients with AAV. An interim analysis was performed of patients with AAV receiving RTX-induced continuous B cell depletion for a minimum of two years who were enrolled and randomized into one of two arms: intermittent B cell depletion with RTX re-dosing upon (1) B cell return (≥ 10 B cells/mm3) or (2) upon a significant increase in ANCA titer. B cell and ANCA titer were tested every 3 months. Patients were stratified based on ANCA serotype and duration of preceding B cell depletion. Outcome measures of interest include clinical relapse (defined as BVAS-WG ≥ 2), serologic relapse, total rituximab utilization, serious adverse events and death.

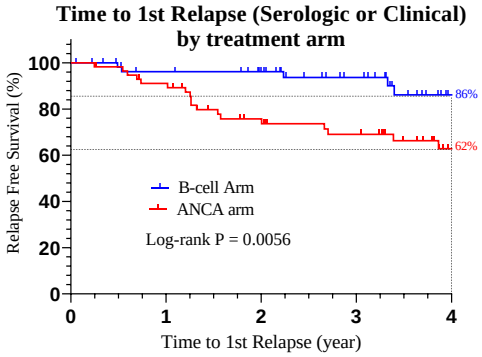
Results: From May 2016 to June 2020, 115 patients (mean age, 60 years; 48% women) were randomized, 58 to the B cell arm and 57 to the ANCA arm. 53 patients were positive for anti-MPO, and 62 for anti-PR3. The two arms had similar baseline characteristics. Relapse-free survival estimates at month 48 were 95% and 74% in the B cell arm and ANCA arm, respectively (hazard ratio of 3.89, CI 1.41 to 10.71 (P = 0.023 by log-rank). The B cell arm had lower number of clinical relapses (3 vs 12 patients, P<0.05), number of major clinical relapses (2 vs 6 patients, P=0.1623) and serologic relapse (3 vs 13 patients, P<0.01) compared to the ANCA arm. However, the B-cell arm had 4.4x higher rituximab utilization (128 vs 29g) and higher number of serious adverse event (29 vs 16 patients, P<0.05) compared to the ANCA arm. Serious infection appears to be the most common complication in both arms (19/30 vs 7/18, B-cell and ANCA arm respectively), but subjects in the B cell arm experienced higher rate of serious infection (18 vs 6 patients, P<0.05). Covid-19 infection was the most common complication in the B cell arm, accounting for 10/19 of all serious infections and 1 death.

Conclusions: Rituximab dosing based on B cell return is highly efficacious at preventing relapses compared to rituximab dosing based on ANCA titer. However, the B cell driven strategy was associated with a higher rate of SAEs and Covid-19 complications. The disease control afforded by B cell guided therapy must be balanced against the risk of serious infections.

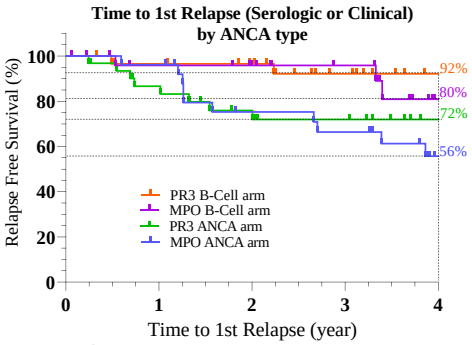
Disclosures: None



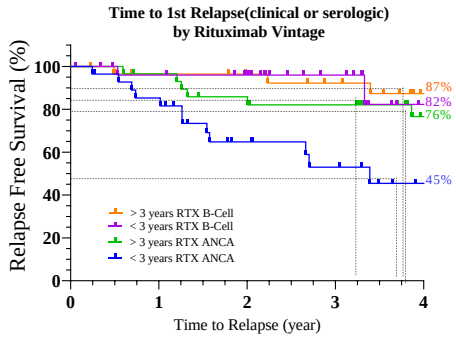
No. at Risk					
ANCA	57	52	43	35	19
B-cell	58	51	44	32	16
Year	0	1	2	3	4



No. at Risk					
ANCA	57	51	37	31	16
B-cell	58	50	44	32	15
Years	0	1	2	3	4



No. at Risk					
PR3 B-Cell	31	28	25	17	9
MPO B-cell	27	23	20	16	6
PR3 ANCA	31	27	20	16	9
MPO ANCA	26	26	18	16	8
Year	0	1	2	3	4



No. at Risk					
> 3years B-Cell	29	26	24	21	14
< 3 years B-Cell	29	25	21	12	2
>3 years ANCA	29	28	24	22	13
< 3 years ANCA	28	24	14	10	4
Year	0	1	2	3	4

297. Patients' Use of Glucocorticoids by Source and Time Period in the ADVOCATE Trial of Avacopan

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Background: ADVOCATE was a Phase 3, randomized, double-blind, controlled clinical study conducted to provide evidence for the efficacy and safety of avacopan as a treatment for patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis. The trial was designed not only to assess the efficacy of avacopan in achieving and sustaining remission, but also to evaluate whether glucocorticoid (GC) use could be safely reduced. This analysis evaluated GC use in the two study groups by source and trial time period.

Methods: Patients were randomized to receive prednisone taper or avacopan on a background of either cyclophosphamide (followed by azathioprine) or rituximab. Efficacy endpoints included the percent of patients achieving disease remission at Week 26 and sustained remission at Week 52. The following information regarding GC use was captured in the electronic case report form: type of GC, dose, unit, route, start date, end date, indication for use. GC doses were converted to prednisone-equivalent doses and cumulative GC dose was calculated for each patient for each study period.

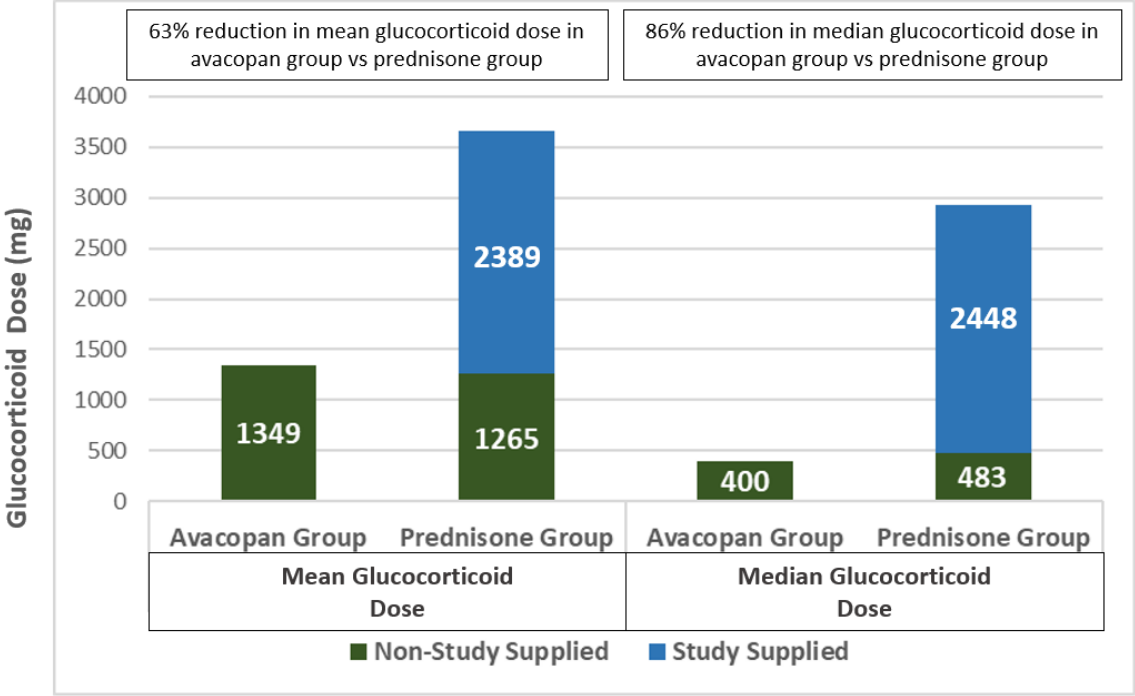
Results: The avacopan group showed superiority to the prednisone group in sustaining remission at Week 52 (66% vs. 55%; P=0.013). There were 4 sources of GC use in the ADVOCATE study. By far the largest source of GC was the protocol-defined prednisone used in the prednisone group but not the avacopan group, constituting two-thirds of the total GC use in this group (total average dose = 2389 mg), which calculates to an average daily dose of 7.8 mg prednisone. Non-study supplied GC use included: GC as pre-medication with rituximab to reduce hypersensitivity reactions, GC taper over 4 weeks if a patient was on GC at randomization, and GC to treat persistent, worsening, or relapsing vasculitis after week 4. The total mean and median GC doses in both arms of the study are illustrated in Figure 1. During the 52-week treatment period, there was a 63% reduction in the mean GC dose and an 86% reduction in the median GC dose in the avacopan group compared to the prednisone group. Most patient-incidence use of GC occurred within the first 4 weeks of the study and was similar between treatment groups. After Week 4, the incidence of non-study supplied GC use dropped substantially and from Week 26 to 52, there was a lower incidence of extra GC use in the avacopan group (27%) compared to the prednisone group (39%).

Conclusions: Given that to date it is not acceptable or feasible to conduct a clinical trial of patients with moderate-severe ANCA-associated vasculitis without allowing GC use, the information presented offers important considerations in the design and implementation of future clinical trials in ANCA-associated vasculitis. In the ADVOCATE trial, the avacopan group had an overall mean reduction of approximately 2500 mg of prednisone-equivalent GC compared to the prednisone group. These data demonstrate the substantial "glucocorticoid-sparing" effect of using avacopan to treat ANCA-associated vasculitis according to the

treatment regimen used in the ADVOVATE trial.

Disclosures: Peter A. Merkel reports receiving consulting and research support from AbbVie, AstraZeneca, Boeringher-Ingelheim, Bristol-Myers Squibb, ChemoCentryx, Forbius, Genentech/Roche, Genzyme/Sanofi, GlaxoSmithKline, InflaRx, Takeda; consulting fees from CSL Behring, Dynacure, EMDSerono, Jannsen, Kiniksa, Kyverna, Magenta, MiroBio, Neutrolis, Novartis, Pfizer, Sparrow, Talaris; royalties from UpToDate. David R.W. Jayne reports receiving consulting fees from AstraZeneca, ChemoCentryx, and Genentech and grant support, paid to the University of Cambridge, and consulting fees from GlaxoSmith-Kline. Pirow Bekker reports receiving consulting fees from and owning stock and stock options in ChemoCentryx

Figure 1. Total mean and median glucocorticoid dose (prednisone-equivalent) by source and treatment group during the 52-week treatment period in the ADVOCATE trial.



298. Effect of Treatment with Avacopan on Patients with ANCA-Associated Vasculitis with Non-Major Manifestations of Disease

Peter Merkel[1], David Jayne, Huibin Yue, Pirow Bekker
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Background: Patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) are affected by a broad range of disease manifestations that range from life- or organ-threatening (severe) to less severe. Although considered less severe (moderate), many such manifestations of AAV result in tissue damage and chronic morbidity. It is often less severe issues, such as rhinosinusitis or arthralgias, that are associated with both relapse in AAV and chronic manifestations.

Methods: ADVOCATE was a Phase 3, randomized, double-blind, controlled study. Patients were included if they had at least one major or three non-major BVAS items, or proteinuria and hematuria. They were randomized to receive a prednisone taper or avacopan with matching placebos on a background of either cyclophosphamide or rituximab. Primary efficacy endpoints were the proportion of patients achieving disease remission [BVAS of 0 and no glucocorticoids (GCs)] at Week 26 and sustained remission at Week 52. This post-hoc analysis examined the outcomes of patients with no major manifestation of AAV at the time of enrollment.

Results: The ADVOCATE trial demonstrated the efficacy of avacopan, an oral selective C5a receptor antagonist, in the treatment of patients with AAV. Remission at Week 26 was achieved in 72% of patients in the avacopan group vs. 70% in the prednisone group, and sustained remission at Week 52 in 66% in the avacopan group and 55% in the prednisone group. The majority (~80%) of patients in this trial had active disease manifestations involving at least one major item on the Birmingham Vasculitis Activity Score (BVAS), including proteinuria and hematuria, at the time of enrollment. Sixty-three of 330 (19%) patients in ADVOCATE had only non-major BVAS items at the time of enrollment: avacopan group, n=32; prednisone group, n=31. Demographics and baseline characteristics are shown in Table 1. Compared to the overall study population, patients with non-major manifestations of disease were 55 years old (vs. 61 in the study population overall); 46% were male (vs. 56% overall); 54% had relapsed AAV (vs. 31% overall); 76% had PR3 AAV (vs. 43% overall); 86% had GPA (vs. 55% overall); 84% received rituximab (vs. 65% overall). Ear, nose, and throat was the most common organ system involved (86%) vs. Renal, 81% overall. The response to treatment among the 63 patients with only non-major manifestations of disease were as follows: in the avacopan group, 24 of 32 (75%) patients achieved remission at Week 26 compared to 17 of 31 (55%) patients in the prednisone group; 22 of 32 (69%) patients in the avacopan group achieved sustained remission at Week 52 compared to 13 of 31 (42%) patients in the prednisone group. Serious adverse events occurred in 7 (22%) of patients in the avacopan group vs. 12 (39%) in the prednisone group, and 4 (13%) in the avacopan group discontinued study medication due to adverse events vs. 7 (23%) in the prednisone group.

Conclusions: In the ADVOCATE trial, a post-hoc, subset analysis, among patients with non-major manifestations of disease at enrollment suggests efficacy and safety with avacopan appears to be consistent with the overall findings of the study.

Disclosures: Peter A. Merkel reports receiving consulting and research support from AbbVie, AstraZeneca, Boeringher-Ingelheim, Bristol-Myers Squibb, ChemoCentryx, Forbius, Genentech/Roche, Genzyme/Sanofi, GlaxoSmithKline, InflaRx, Takeda; consulting fees from CSL Behring, Dynacure, EMDSerono, Jannsen, Kiniksa, Kyverna, Magenta, MiroBio, Neutrolis, Novartis, Pfizer, Sparrow, Talaris; royalties from UpToDate. David R.W. Jayne reports receiving consulting fees from AstraZeneca, ChemoCentryx, and Genentech and grant support, paid to the University of Cambridge, and consulting fees from GlaxoSmith-Kline. Pirow Bekker reports receiving consulting fees from and owning stock and stock options in ChemoCentryx. Huibin Yue reports employment and owning stock and stock options in ChemoCentryx

Table 1. Demographics and Baseline Characteristics of Patients with Non-Major ANCA-Associated Vasculitis in the ADVOCATE Trial

Characteristic	Avacopan (N=32)	Prednisone (N=31)
Age, mean (SD)	56 (15.4)	54 (14.3)
Sex, Male / Female	50% / 50%	42% / 58%
Newly-Diagnosed / Relapsed AAV	44% / 56%	48% / 52%
PR3 / MPO ANCA type	78% / 22%	74% / 26%
GPA / MPA	81% / 20%	90% / 10%
Rituximab / Cyclophosphamide	91% / 9%	77% / 23%
BVAS, mean (SD)	13 (4.1)	13 (5.0)
Active disease manifestations (BVAS categories)		
Ear, Nose, and Throat	88%	84%
General	81%	74%
Chest	66%	48%
Renal	47%	39%

299. Effect of the C5a Receptor Inhibitor Avacopan on Health-Related Quality of Life in ANCA-Associated Vasculitis

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Background: Avacopan, an oral C5a receptor inhibitor, was evaluated in ANCA-associated vasculitis. Efficacy and safety results were reported previously. Health-related quality of life (HRQoL) changes are reported here.

Methods: A 52-week blinded trial (ADVOCATE) randomized 331 patients with ANCA-associated vasculitis 1:1 to either full-dose daily oral prednisone with taper ('Prednisone Standard of Care Group'), or avacopan with no daily oral prednisone ('Avacopan Group'). Both received standard of care (SOC): rituximab induction or cyclophosphamide. Glucocorticoid (GC) exposure including pre-randomization tapering into the blinded treatment period, co-administration with rituximab, and flares was expected and balanced between groups. The total dose of prednisone was ~2500 mg less with avacopan treatment over the entire trial. Primary efficacy endpoints were % patients achieving disease remission at Week 26 and sustained remission at Week 52 using Birmingham Vasculitis Activity Score (BVAS). HRQoL was assessed by Short Form-36 Health Survey version 2 (SF-36), a generic measure of HRQoL that performs well across vasculitis trials, including ANCA-associated vasculitis and giant cell arteritis, and EuroQoL Group 5-Dimensions 5-Levels Questionnaire (EQ-5D-5L).

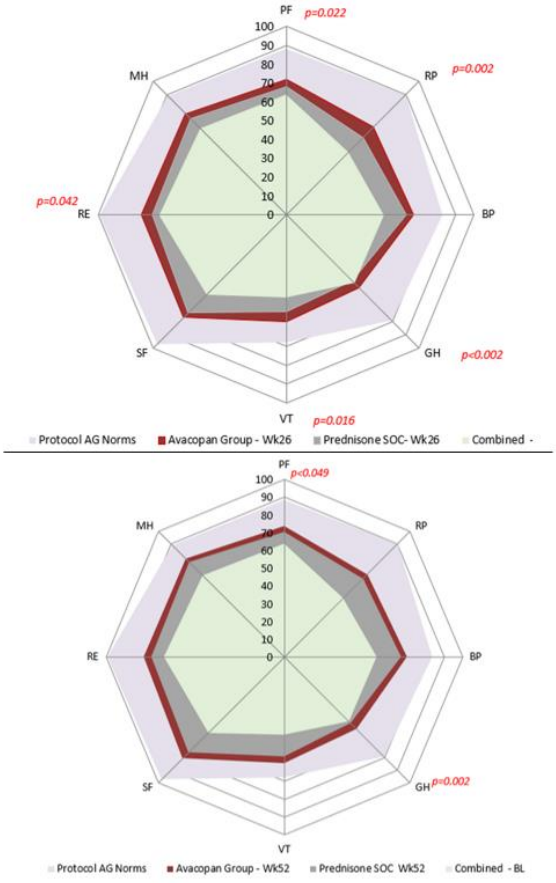
Results: Week 26 improvements in physical component summary (PCS) score with Avacopan Group: 4.5 points vs Prednisone SOC Group: 1.3 points (least squared means, LSM, for all analyses); statistically significant ($p=0.002$) and >minimum clinically important difference (MCID) = 2.5 points[3]. Mental component summary scores (MCS) were: Avacopan Group: 4.9 points; Prednisone SOC Group: 3.3 points, > MCID in both groups. At Week 26 improvements in physical function (PF), role physical (RP), general health (GH), vitality (VT) and role emotional (RE) domains with Avacopan Group were large (3.1 to 16.8 points); statistically significant vs Prednisone SOC Group ($p<0.002$ to $p=0.002$), and >MCID of 5.0 points in 4 domains (Figure 1). This reflects improvements in physical function and activities; also fatigue, energy, emotional role limitations, and general health perceptions. Week 52 improvements with Avacopan Group vs Prednisone SOC Group were maintained or improved. PCS score was 5.0 vs 2.6 points, clinically meaningful, and statistically significant ($p=0.018$). Improvements in PF and GH domains exceeded MCID and were statistically significant ($p<0.049$ and $p<0.002$). The health utility score, SF-6D, based on calculation across all 8 domains of SF-36, indicated broad improvements in patient-reported health status. Improvements at Weeks 26 and 52 were greater with Avacopan Group compared to Prednisone SOC Group; >MID (0.041) and consistent with reported improvements in EQ-5D-5L utility score, which was statistically significant at week 52 ($p=0.009$).

Conclusions: Treatment of ANCA-associated vasculitis with avacopan and a reduced-dose glucocorticoid regimen led to significant improvements in HRQoL compared to SOC. These

findings have important clinical implications for treatment of patients with ANCA-associated vasculitis.

Disclosures: Vibeke Strand reports consultancy with Abbvie, Amgen, Arena, AstraZeneca, Bayer, Biosplice, Bioventus, Blackrock, BMS, Boehringer Ingelheim, Celltrion, ChemoCentryx, EMDSerono, Equilium, Eupraxia, Flexion, Galapagos, Genentech/Roche, Gilead, GSK, Horizon, Ichnos, Inmedix, Janssen, Kiniksa, Kypha, Lilly, Merck, MiMedx, Novartis, Pfizer, Regeneron, Rheos, Samsung, Sandoz, Sanofi, Scipher, Servier, Setpoint, Spherix, Tonix, UCB. Pirow Bekker reports receiving consulting fees from and owning stock and stock options in ChemoCentryx. Huibin Yue reports employment by ChemoCentryx. David R.W. Jayne reports receiving consulting fees from AstraZeneca, ChemoCentryx, and Genentech and grant support, paid to the University of Cambridge, and consulting fees from GlaxoSmith-Kline. Peter A. Merkel reports receiving consulting and research support from AbbVie, AstraZeneca, Boeringher-Ingelheim, Bristol-Myers Squibb, ChemoCentryx, Forbius, Genentech/Roche, Genzyme/Sanofi, GlaxoSmithKline, InflaRx, Takeda and consulting fees from CSL Behring, Dynacure, EMDSerono, Jannsen, Kiniksa, Kyverna, Magenta, MiroBio, Neutrolis, Novartis, Pfizer, Sparrow, Talaris and royalties from UpToDate

Figure 1. Spydergrams of SF-36 Domains vs Age and Gender Matched Norms – Baseline to Week 26 (top) and Week 52 (bottom)



PF: Physical Function; RP: Role Physical; BP: Bodily Pain; GH: General Health; VT: Vitality; SF: Social Function; RE: Role Emotional; MH: Mental Health

300. A Randomized, Double-Blind, Phase II Study of Glucocorticoid Replacement by Vilobelimab in ANCA-Associated Vasculitis

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[1]University of Pennsylvania, Philadelphia, United States of America, [2]University of Tübingen, Kirchheim-Teck, Germany, [3]InflaRx, Jena, Germany, [4]Metronomia Clinical Research, Munich, Germany, [5]University of Cambridge, Cambridge, United Kingdom

Background: Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), subtypes of ANCA-associated vasculitis, are relapsing, remitting potentially life-threatening diseases with severe morbidity from organ damage and therapy-related toxicities. Remission induction utilizes rituximab (RTX) or cyclophosphamide (CYC) and tapering doses of glucocorticoids (GC), followed by either a second course of RTX or other immunosuppressive agents for remission maintenance. There is a strong need for therapies that either replace or markedly decrease the doses of GC used to treat AAV. Vilobelimab (IFX-1) is a monoclonal antibody that specifically binds to the soluble human complement fragment C5a. In pre-clinical studies, vilobelimab was found to bind C5a rapidly and result in near complete blockade of C5a-induced biological effects while not affecting cleavage of C5 or formation of the membrane attack complex.

Methods: The IXCHANGE Trial (NCT03895801), a prospective, randomized, double-blind, double-dummy, active-controlled, 2-part Phase II study, evaluated the efficacy of vilobelimab as a replacement for GC in patients with GPA and MPA. Part 1 of the study compared vilobelimab + reduced-dose GC (RDGC) to standard-dose GC (SDGC) as add-on to standard of care RTX or CYC, while part 2 compared vilobelimab alone to SDGC in the presence of RTX or CYC. After loading doses at 1, 4, and 8 days, patients were given 800 mg vilobelimab every 2 weeks for 16 weeks followed by an 8-week observation period. Primary efficacy evaluated the proportion of subjects achieving clinical response [reduction in Birmingham Vasculitis Activity Score (BVAS) of ≥50% compared to baseline and no worsening in any body system to week 16]. Non-responders were those who received rescue medication prior to the assessment time point or discontinued due to a related adverse event (AE), lack of efficacy or progressive disease. Clinical remission (BVAS=0) was assessed during the treatment period at 4, 8, 12, and 16 weeks. Secondary endpoints among others included safety, estimated glomerular filtration rate (eGFR), and the glucocorticoid toxicity index (GTI).

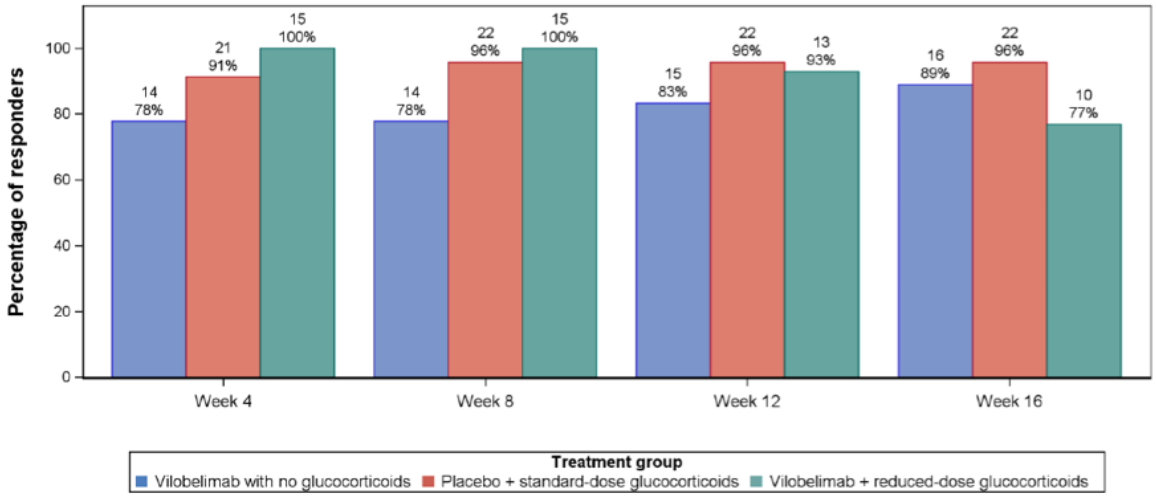
Results: Fifty-one of 57 subjects randomized completed the study. The cumulative mean GC dose received 28 days prior to randomization was comparable in all arms. The mean total cumulative dose of GC from Day 1 (1st dose of IMP) until end of study was 541.9 mg for vilobelimab alone, 3751.3 mg for SDGC, and 1485.8 mg for vilobelimab + RDGC. Clinical response (Figure 1) and clinical remission rates were similar across the three arms (vilobelimab alone vs SDGC vs vilobelimab + RDGC) at week 16: response: 89% *vs* 96% *vs* 77%; remission: 78% *vs* 87% *vs* 77%. The mean (SD) for GTI at week 16 was substantially lower with vilobelimab alone [0.8 (9.0)] when compared to the means for SDGC [44.9 (41.5)] and vilobelimab + RDGC [26.1 (39.2)]. There were no medically meaningful changes in eGFR in any arm. The vilobelimab-only group had the lowest number of reported treatment emergent

AE (TEAE). In total, there were 14 serious TEAE (5, vilobelimab alone; 6, SDGC; and 3, vilobelimab + RDGC). One fatal *pneumocystis jiroveci* pneumonia (PCP) occurred in the vilobelimab alone group and one serious PCP in the SDGC group were reported. Neither patient received prophylactic antibiotics.

Conclusion: Though the IXCHANGE Trial was not powered to demonstrate non-inferiority of vilobelimab alone compared to SDGC, results from the trial suggest that treatment of GPA and MPA with vilobelimab has the potential to induce remission together with RTX and CYC with substantial reduction in the dose and associated toxicity of GC.

Disclosures: P. Merkel: Consulting and Research Support: AbbVie, AstraZeneca, Boeringher-Ingelheim, Bristol-Myers Squibb, ChemoCentryx, Forbius, Genentech/Roche, Genzyme/Sanofi, GlaxoSmithKline, InflaRx, Takeda. Consulting only: CSL Behring, Dynacure, EMDSerono, Jannsen, Kiniksa, Kyverna, Magenta, MiroBio, Neutrolis, Novartis, Pfizer, Sparrow, Talaris. Royalties: UpToDate.B. Hellmich: Consulting: InflaRx. A. Pfaff: Employee of InflaRx. C. Müller: Employee of Metronomia Clinical Research GmbH, a contracted service provider for InflaRx E. Startseva: Employee of InflaRx. D. Jayne: Consulting: from AstraZeneca, ChemoCentryx, Genentech, InflaRx; Consulting and Research Support: GlaxoSmith-Kline

Figure 1: Clinical Response to Treatment in the IXCHANGE Trial of Vilobelimab in ANCA-Associated Vasculitis



301. Effect of Avacopan, a C5a Receptor Inhibitor, on Kidney Function in Patients with ANCA-Associated Vasculitis

David Jayne[1], Peter Merkel, Annette Bruchfeld, Duvuru Geetha, Alexandre Karras, John Niles, Pirow Bekker

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Background: Anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis is a life- or organ-threatening condition in which patients experience severe inflammation of small blood vessels; renal disease is common and confers a high risk for end-stage renal disease and death. Efficacy and safety results from a phase 3 trial evaluating avacopan, an oral selective C5a receptor inhibitor, in patients with ANCA-associated vasculitis have been previously reported. The effect of treatment with avacopan on renal function is detailed here.

Methods: ADVOCATE was a phase 3, randomized, double-blind, controlled clinical study. All patients were randomized to receive prednisone taper or avacopan on a background of either cyclophosphamide (followed by azathioprine) or rituximab. Primary efficacy endpoints were the percent of patients achieving disease remission at Week 26 and sustained remission at Week 52. Secondary objectives included evaluation of kidney function, specifically the change from entry (baseline) through to Week 52 in estimated glomerular filtration rate (eGFR) and urinary albumin:creatinine ratio.

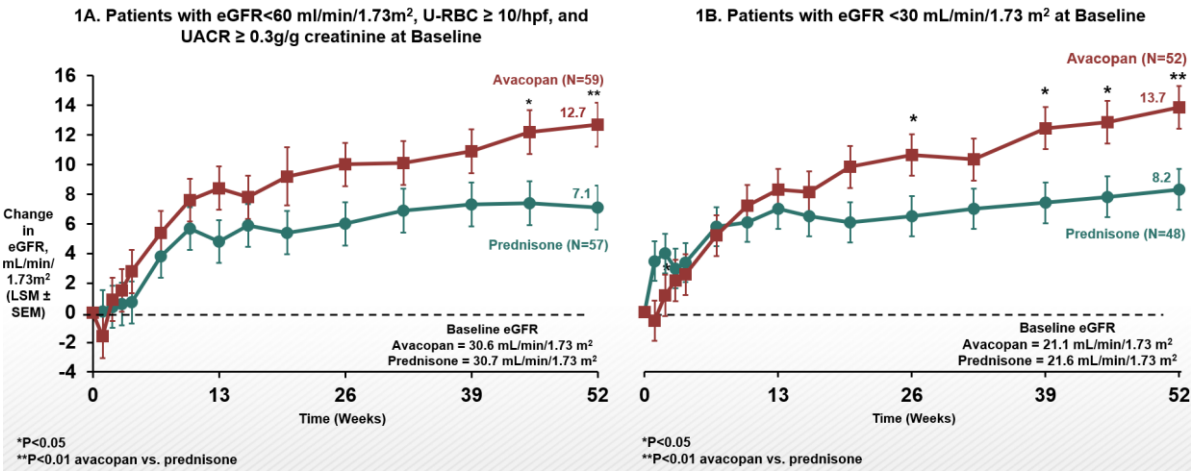
Results: In ADVOCATE, 268/330 (81%) patients had renal disease at baseline. Average eGFR at baseline in patients with renal disease was 44.6 and 45.6 mL/min/1.73 m^2 in the avacopan (n=134) and prednisone (n=134) groups, respectively. eGFR improved more in the avacopan group compared to the prednisone group. At Week 52, the least squares mean (LSM) increase in eGFR in the avacopan and prednisone groups was 7.3 and 4.1 mL/min/1.73 m^2 (p=0.03), respectively.

At Week 52, in patients with baseline eGFR <60 mL/min/1.73 m^2 , U-RBC ≥10/hpf, and U-ACR ≥0.3 g/g the least squares mean (LSM) increase in eGFR was 12.7 (avacopan group) vs. 7.1 mL/min/1.73 m^2 (prednisone group) (p<0.01) (Figure 1A). Improvement in eGFR with avacopan was most prominent in patients with baseline eGFR <30 mL/min/1.73 m^2, for whom by week 52 the least squares mean (LSM) increase in eGFR was 13.7 (avacopan group) vs. 8.2 mL/min/1.73 m^2 (prednisone group) (p<0.01) (Figure 1B). Among patients with Stage 4 chronic kidney disease at baseline: in the avacopan group (n=52), 26 (50%) improved 1 stage and 3 (5.8%) improved 2 stages; in the prednisone group (n=48), 21 (44%) improved 1 stage and 1 (2.1%) improved 2 stages (p=0.32). Avacopan was also associated with more rapid reduction in proteinuria. The largest difference in improvement in urinary albumin:creatine ratio was 40% at 4 weeks of treatment; the LSM±SEM change from baseline was –40±9.5 in the avacopan group compared to 0±9.3 in the prednisone group.

Conclusions: In the ADVOCATE trial, patients with ANCA-associated vasculitis in the avacopan group had greater recovery of kidney function compared to patients in the prednisone group, especially among patients with chronic kidney disease Stage 4 and those with eGFR <60 mL/min/1.73 m^2 and urinary abnormalities at baseline.

Disclosures: David R.W. Jayne reports receiving consulting fees from AstraZeneca, ChemoCentryx, and Genentech and grant support, paid to the University of Cambridge, and consulting fees from GlaxoSmith-Kline. Peter A. Merkel reports receiving consulting and research support from AbbVie, AstraZeneca, Boeringher-Ingelheim, Bristol-Myers Squibb, ChemoCentryx, Forbius, Genentech/Roche, Genzyme/Sanofi, GlaxoSmithKline, InflaRx, Takeda; consulting fees from CSL Behring, Dynacure, EMDSerono, Jannsen, Kiniksa, Kyverna, Magenta, MiroBio, Neutrolis, Novartis, Pfizer, Sparrow, Talaris; royalties from UpToDate. Annette Bruchfeld reports consultancy with Abbvie, AstraZeneca, ChemoCentryx, Merck/MSD, Vifor. Duvuru Geetha reports consultancy with Aurinia, ChemoCentryx. Alexandre Karras reports consultancy with AbbVie, Alnylam, Amgen, AstraZeneca, Gilead, GSK, Novartis, Pfizer, Roche, Vifor. John Niles reports consultancy with ChemoCentryx, Genentech/Roche, InflaRx. Pirow Bekker reports receiving consulting fees from and owning stock and stock options in ChemoCentryx

Figure 1. Change in Renal Function Through Week 52



302. Efficacy of Mycophenolate mofetil for remission maintenance in ANCA associated vasculitis depends on ANCA specificity

Oliver Flossmann[1], Joanne Skinner[1], Thomas Hietra[2], David Jayne[2],
European Vasculitis Society on behalf of [1]Royal Berkshire Hospital Reading, Reading, United Kingdom, [2]University of Cambridge, Cambridge, United Kingdom

Background/ Objectives: Mycophenolate mofetil is an anti-metabolite used for prevention of transplant rejection and treatment of autoimmune disease. Its clinical utility in ANCA associated vasculitis has been assessed for both relapse prevention and induction, as an alternative to cyclophosphamide. The IMPROVE trial[2] aimed to demonstrate that mycophenolate mofetil was superior to azathioprine for the prevention of relapse of ANCA associated vasculitis after cyclophosphamide and steroid induction. The results demonstrated a higher relapse rate in patients treated with mycophenolate mofetil compared to azathioprine but it the association of efficacy with ANCA subtype was not explored.

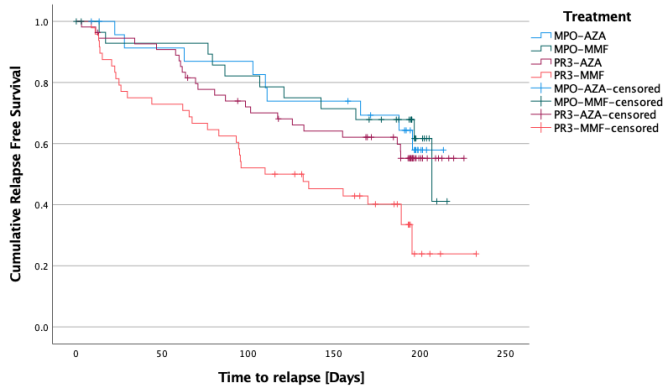
Methods: Eligibility for IMPROVE required a new diagnosis of GPA or MPA with a positive MPO or PR3-ANCA and age ≥ 18 years. A post-hoc analysis of the IMPROVE database was performed to assess differences in relapse free survival between mycophenolate and azathioprine treatment groups according to MPO or PR3-ANCA specificity using the Kaplan-Meier method.

Results: Of 159 patients randomised in the trial 55 (35%) were MPO-ANCA and 103 (65%) PR3-ANCA positive (1 patient was ANCA negative). Patients were randomised to either Mycophenolate mofetil (MPO-ANCA 32, PR3-ANCA 51) or azathioprine (MPO-ANCA 26, PR3-ANCA 57). Patients of either ANCA specificity were well matched in ter of age and entry creatinine.
There was no difference in mean relapse free survival in patients with MPO-ANCA 174.4 days for either treatment group (p=0.97). In patients with PR3-ANCA the mean relapse free survival was 165.6 days for the azathioprine versus 126.8 for the mycophenolate mofetil treatment groups (p=0.01).

Conclusions: This post-hoc analysis found no difference in time to relapse between mycophenolate mofetil and azathioprine for the MPO-ANCA subgroup, but a reduction in time to relapse with mycophenolate mofetil compared to azathioprine for the PR3-ANCA subgroup. These results are consistent with those observed for remission induction in the MYCYC[1] trial and suggest that azathioprine is a preferred relapse prevention treatment for PR3-ANCA vasculitis after cyclophosphamide induction.

Disclosures: None

Figure 1. Kaplan-Meier plot – Relapse Free survival



303. Treating autoantibody mediated vasculitis with the IgG degrading enzyme imlifidase

Mårten Segelmark[1,2,3], Freik Uhlin[3,4 1]
Lund University, Lund, Sweden, [2]Skane University Hosptial, Lund, Sweden, [3]Linköping University, Linköping, Sweden, [4]University Hospital, Linköping, Sweden

Background: Autoantibodies directed to the non-collagenous domain of the alpha 3 chain of Type IV collagen cause small vessel vasculitis affecting capillaries of the kidneys and lungs. With standard treatment chances are slim to salvage renal function if treatment is started late. Imlifidase is the non-proprietary name for the immunoglobulin degrading enzyme of streptococcus pyogenous (IdeS) that *in vivo* can cleave all IgG antibodies both circulating and bound to basement membranes.

Method: We conducted a multi-center (17 sites in five countries) phase 2a open-label study (EuaCT: 2016-004082-39) in 15 adults with anti-GBM antibodies and an eGFR <15 ml/min/1.73m^2. All subjects received a single dose of 0.25 mg/kg of imlifidase on top of standard treatment, but with plasma-exchange only if autoantibodies rebounded. The primary outcome measure was safety and dialysis independency at 6 months.
Results: At inclusion 10 patients were dialysis dependent and 5 had eGFR levels between 7-14 ml/min/1.73m^2. Median age was 61 years (range 19-77), six were women. All kidney biopsies (available from 14) showed crescentic glomerulonephritis with few normal glomeruli (median 9.5%; range 0-35). Six hours after imlifidase infusion, all patients were negative in ELISA for anti-GBM antibodies. There were eight serious adverse events (including one death) reported, but none was assessed as probably or possibly related to the study ug. At six months 10 patients (67%) were dialysis independent, which is significantly higher as compared to 18% in a historical control cohort (p<0.001).

Conclusion: Imlifidase (IdeS) rapidly degraded the autoantibodies in this study, and this was associated with renal recovery in most patients. There was no worrisome safety signal. These promising results encourage further development of this treatment option in this and other conditions where IgG autoantibodies constitute a threat against vital organ function.

Disclosure: Mårten Segelmark has received research funds and consultancy fees and research funding from Hansa Pharma.

304. A randomised, double-blind, controlled, study of rituximab and belimumab combination in AAV (COMBIVAS): study protocol.

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Background: Dual B-cell targeted immunotherapy with B cell depletion (rituximab) and BAFF antagonism (belimumab) may enhance B cell targeting in ANCA-associated vasculitis (AAV) through several mechanis (1).

Study Design: COMBIVAS is a randomized, double blind, placebo-controlled trial designed to evaluate the mechanistic effect of belimumab combined with rituximab in patients with active proteinase 3 (PR3)-AAV. Participants will be randomized 1:1 to receive rituximab plus prednisolone combined with belimumab (combination arm) or placebo (control arm). 30 participants will be evaluated in a per-protocol analysis. Trial duration is two years (12-months treatment, 12- months' follow-up**). Participants:** Participants were recruited from 7 UK sites. Eligibility included age>18 years, severe active AAV (newly diagnosed or relapsing), and positive PR3 ANCA. **Interventions:** Belimumab (200mg) or belimumab placebo was administered subcutaneously on Day 1 and then weekly through to Week 51. Intravenous rituximab 1000mg was administered on Day 8 and Day 22 only. All participants started prednisolone 20 mg/day on Day 1 and followed a tapering regimen aiming for withawal by 3 months.

Outcomes: Primary Outcome: Time to PR3-ANCA negativity; Key Secondary Outcomes: change from baseline in naïve, transitional, memory, activated, plasmablast and plasma cell subsets (B cell flow cytometry) in blood at Months 3, 12, and 24; time to clinical remission; time to relapse, incidence of serious adverse events. Exploratory biomarker assessments - Blood and urine were taken at multiple time points, with key analyses at 3 months (maximal B cell depletion), 12 months (end of treatment), 24 months (B cell reconstitution, end of follow-up). Inguinal lymph node and nasal mucosal biopsies were performed on a subgroup of participants before and three months after initiating treatment for the purpose of exploratory analyses (including single cell RNA sequencing) examining the mechanistic effects of combination B cell depletion within tissues.

Discussion: This experimental medicine study provides a unique opportunity to gain detailed insights into the immunological mechanis of rituximab-belimumab combination therapy across multiple body compartments in the setting of AAV. Trial status - EUACT number: 2017-004645-24; Recruitment completed March 2021. Final study report due 2024.

Disclosures: Rachel Jones has received grants/consultancy fees from GlaxoSmithKline, Vifor Pharma, ChemoCentryx and Roche. David Jayne's disclosures of commercial conflicts for companies with marketed products for 2021 are: Astra-Zeneca, Aurinia, B, Boehringer-Ingelheim, GSK, Janssen, Novartis, Roche/Genentech, Takeda & Vifor.

Vasculitis Therapeutics

305. Human Leukocyte Antigen Association in Azathioprine-induced ug Hypersensitivity Reactions in Patients with Anti-Neutrophil-Cytoplasmic-Antibody Associated Vasculitis.

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Background: ug hypersensitivity reactions (DHRs) account for 6-10% of all ug reactions and may be linked to specific human leukocyte antigen (HLA) genes, particularly class 1 HLA antigens. Azathioprine (AZA) is a therapeutic agent used in the management of Anti-Neutrophil Cytoplasmic Antibody (ANCA) associated vasculitis (AAV). Although infrequent, AZA induced DHRs can be life-threatening and have a reported incidence of up to 9% in AAV patients (1).

Methods: We conducted a retrospective review on a cohort of AAV patients previously treated with, or currently on AZA maintenance therapy. Participants were categorised into those who had experienced AZA DHR and those who were AZA tolerant. High resolution HLA tissue typing was performed in both groups. The primary endpoint was identification of a HLA gene association with AZA DHRs in the context of AAV.

Results: The class I HLA allele, HLA-C*06:02, was solely expressed in AZA DHR patients (33.3%), whilst no patient who tolerated AZA had this allele (0.0%). This yielded a positive predictive value of 100% for HLA-C*06:02 in predicting AZA DHR in AAV patients, negative predictive value of 66.7%, sensitivity of 33.3% and specificity of 100% (Table 1).

Conclusion: HLA-C*06:02, a well-recognised susceptibility allele found in association with psoriasis (2), may predict the development of AZA-induced DHR in patients with AAV. Given the potentially life-threatening nature of such reactions, prospective screening for this HLA marker could be considered, with avoidance of AZA among those with HLA-C*06:02 and caution with AZA in those without the allele. Verification among a larger cohort of patients will be required to confirm this recommendation.

Disclosures: None.

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Table 1. HLA-C*06:02 and azathioprine-induced ug hypersensitivity reaction

	AZA-DHR (N = 15)	AZA-Tolerant (N = 20)	Statistics	Value (95% CI)
HLA-C*06:02 +ve (N = 5)	5	0	Specificity	100.0% (83.1–100.0)
			Sensitivity	33.3% (11.8–61.6)
HLA- C*06:02 –ve (N = 30)	10	20	PPV	100.0%
			NPV	66.7% (58.3–74.1)

Abbreviations: AZA = azathioprine; CI = confidence interval; HLA = human leukocyte antigen; PPV = positive predictive value; NPV = negative predictive value

306. Rituximab in ANCA vasculitis -Is frequent maintenance with rituximab required? Experience from a Tertiary centre

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Background: ANCA associated vasculitis is a systemic disease affecting small and medium sized vessels. Cyclophosphamide based regimens in combination with glucocorticoids have shown promising efficacy with the treatment of ANCA associated vasculitis (AAV). However the risk of infection, malignancy and infertility is known to be associated with cyclophosphamide. Rituximab has been licensed for use in ANCA vasculitis since 2011.In the RAVE trial, Rituximab was found to be non- inferior to cyclophosphamide plus glucocorticoids followed by azathioprine maintenance therapy. Many trials have studied the efficacy of different immunosuppressants in the maintenance of AAV following induction.

In case of persistent disease activity despite induction with cyclophosphamide or rituximab relapses are common in the first 6 months. In MAINRITSAN 3 study, 500 mg of rituximab infused every 6 months for an additional 18 months after an initial 18-month maintenance regimen was effective in reducing relapses. Relapse occurred in 2 out of 50 patients (4%) in the rituximab group versus 12 out of 47 (26%) in the placebo group during the 28-month follow-up. Extended therapy with biannual rituximab infusions over 18 months was associated with a lower incidence of AAV relapse compared to standard maintenance therapy.Here we share a real-world experience of use of Rituximab therapy in ANCA vasculitis from a tertiary care centre. **Objectives:** To study the real -world experience of the use of Rituximab in ANCA vasculitis as an initial therapy or in cases of treatment failure

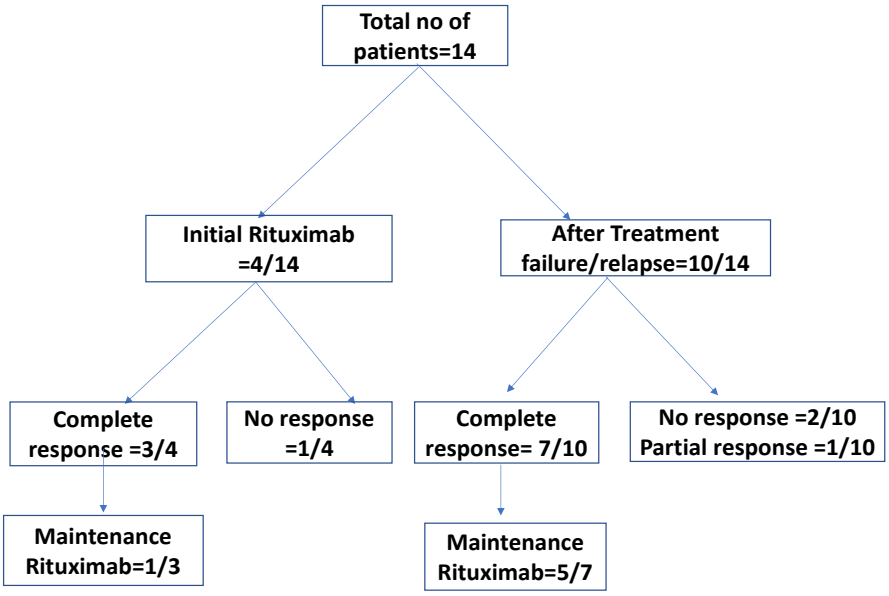
Methods: This is a retrospective descriptive analysis of 14 patients with ANCA associated vasculitis from our institute from 2010 to 2020 who received Rituximab. We studied the case records of these patients and documented the clinical features at presentation, laboratory findings, ANCA status, treatment given as induction and maintenance therapy and during relapse. We assessed the clinical remission after treatment with Rituximab. Criteria for remission was BVAS (Birmingham Vasculitis Activity Score) =0.

Results: Out of 14 patients studied, 7 were females and 7 were males. The Median age of the patients was 35 years and the median duration of follow up was 10.5 years. Fever (71%), malaise (71%), arthritis (85%), pulmonary (92%) and renal (78%) manifestations were most commonly seen in these patients. Subglottic stenosis was seen in 2 out of 14 (14%) of the patients and both were females. 4 out of 14 patients were given Rituximab as initial induction therapy, out of which 3 out of 4 (75%) patients achieved complete clinical remission ,1 out of 3 (33.3%) did not improve.2 of the 3 patients with complete remission had received only single induction therapy with rituximab (2gm) followed by an oral maintenance immunosuppressive therapy and the mean duration of clinical remission in these patients was 5 years. (Figure 1) Rituximab was introduced after the failure of initial induction therapy in 10 out of 14 patients, which included cyclophosphamide, azathioprine, mycophenolate mofetil and methotrexate. 7 out of 10 (70%) patients achieved remission ,1 out of 10 (10%) showed partial response and 2 out of 10(30%) did not show response. Out of the 7 patients who responded, maintenance dose was given in 5 out of 7 patients and 3 out of 5 of them received only single dose of rituximab maintenance therapy (Figure1). The mean duration of clinical remission in these 7 patients from the last dose of rituximab (followed by oral maintenance immune suppression) was 3 years.

Conclusions: From this real world retrospective observation analysis rituximab was effective as initial induction therapy and in cases of relapse/treatment failure. Although it produced complete remission in 70% of these patients,single dose of Rituximab as maintenance therapy was adequate in 35% of them with remission lasting for few years on other immunosuppressive therapy. Rituximab when used as upfront induction agent ,it could be substituted with other immunosuppressants as maintenance agents after induction remission. In resource limited settings ,oral maintenance immunosuppression can be used after successful rituximab induction in severe disease activity or treatment failure or relapse cases.Extended rituximab maintenance therapy may be not be required in all patients. Vigilant close monitoring of disease activity would be absolutely essential . A larger study would be required to corroborate our findings.

Disclosures: None

Figure 1. Flowchart of Rituximab therapy in ANCA patients from our centre



307. Compassionate Use of Avacopan In Difficult-To-Treat ANCA-Associated Vasculitis

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Background/ Objectives: Avacopan is a new, promising treatment for ANCA-associated vasculitis (AAV) and can potentially replace steroids. Compared to steroid tapering, avacopan has demonstrated non-inferiority for treatment response at 26 weeks, superiority for sustaining remission at 52 weeks and a reduction of relapses.[1] Most recently avacopan was approved for the treatment of AAV by the U.S. Food and ug Administration and approval is pending at the European Medicines Agency (EMA).[2] We now report the first clinical experience with avacopan in difficult-to-treat AAV patients in the setting of a compassionate use program.

Methods: We collected disease relevant characteristics for the adult AAV patients who were treated with avacopan in the setting of the compassionate use program at the department of Nephrology of the Leiden University Medical Center. Patients were classified by their reason to start avacopan and clinical remission was based on physician's clinical assessments as reported in the electronic health records. We collected relevant data to assess steroid-related toxicity effects in line with the Glucocorticoid Toxicity Index (GTI) (v2017).[3]

Results: Eight adult AAV patients were treated within the avacopan compassionate use program at our institute. Indications for avacopan were steroid resistance (n=4), steroid dependence (n=2) and high risk of steroid toxicity (n=2). Most patients had relapsing disease (numbers of flares ranging from 0-3) and received multiple previous remission induction therapies (median 2, range 1-6). All patients achieved clinical remission within six months after avacopan was started. Only one patient experienced a major flare, which coincided with a reduction of avacopan dosing to 20mg bd due to delayed supply during the COVID-19 pandemic. Steroid tapering was successful in all patients, with five patients discontinuing prednisone and three patients continuing low doses of prednisolone (2.5-7.5mg/day). After one year of avacopan use, the GTI improved in four patients. In one patient the GTI worsened due to weight gain. Six patients satisfactorily continue avacopan and are persistently in clinical remission. One patient stopped because of a pregnancy wish.

Conclusions: We here provide the first real-life practice observations on the compassionate use of avacopan in difficult-to-treat AAV patients. Avacopan demonstrated added-value in the treatment of our difficult-to-treat AAV cases with respect to improved disease control, reduced steroid dependence and reduced steroid-related toxicity.

Disclosures: The work of YKOT was supported by the Dutch Kidney Foundation (17OKG04) and by the Arthritis Research and Collaboration Hub (ARCH) foundation. ARCH is funded by Dutch Arthritis Foundation (ReumaNederland). YKOT received an unrestricted research grant and consultancy fees from Vifor Pharma.

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308. Withdrawn

309. Real life experience of evaluation and treatment of large Vessel Vasculitis: A Single Centre Experience.

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Background: Giant Cell Arteritis (GCA) is a large vessel vasculitis with overlapping phenotypes including classic cranial arteritis and large-vessel GCA (LV-GCA). Imaging studies of patients with GCA have demonstrated large-vessel involvement is present in up to 83% of

patients[1]. LV-GCA increases the likelihood of aneurys and this is associated with significant mortality. Treatment includes corticosteroids and immunosuppressants such as Methotrexate or Tocilizumab.

Methods: All patients were diagnosed by CT-angiogram or CT-PET from 2011 to 2020. Clinical, biochemical and radiographic data prior to and 6 months following therapy were analysed.

Results: Of 24 patients, 12/24 patients were female. Median age was 64.5 years (IQR 60.8-72). Median time from sympto to diagnosis was 2 months (IQR 1-6.3). Of 24 patients analysed, 18 were diagnosed by CT-PET, 5 by CT angiogram and 1 on thoracic aorta biopsy. The clinical features included: refractory Polymyalgia Rheumatica (45.8%), weight loss (33.3%), chest pain (25%), abdominal pain (20.8%), BP difference >10mmHg (20.8%), fever (16.6%), limb claudication (12.5%), cranial GCA (8.33%), y cough (8.3%) and joint swelling (4.16%). The vessels involved in decreasing order were: Aorta (91.6%), Subclavians (54.16%), both carotids (33.33%), iliacs (29.16%), both axillaries (20.83%), both femorals (16.66%), mesenteric (12.5%), both vertebrals (8.33%) and popliteal (4.16%). 22/24 patients were given prednisolone. Prednisolone was not given in 2 patients for relative contraindications, multifocal motor neuropathy and possible cancer. 23/24 were given additional immunosuppresants including Methotrexate (n=10), Cyclophosphamide (n=7), Mycophenolate (n=3), Leflunomide (n=2) and Tocilizumab (n=1). 6/24 patients required a second agent for progressive or refractory disease. Two patients were given Tocilizumab, One patient Cyclophosphamide and three patients were given Rituximab. At 6 months, mean CRP fell from 108.6 to 4.97mg/L ($p<0.001$), ESR from 70.1 to 15mm/hr ($p<0.001$), Prednisolone dose from 43.9 to 15.7mg ($p<0.001$) (Wilcoxon).18/24 had follow up imaging to date. 16/18 (88.8%) improved or resolved and were treated with Methotrexate (n=6), Cyclophosphamide (n=5), Tocilizumab (n=1), Prednisolone only (n=1), Mycophenolate (n=1), Cyclophosphamide followed by Rituximab (n=1), Mycophenolate/Rituximab combination (n=1). 1/18 imaging was stable (Mycophenolate/Rituximab combination) and 1/18 progressed despite Cyclophosphamide. Two patients died during follow up. One patient developed chronic myelomonocytic leukaemia. The second patient was initially diagnosed with LV-GCA on biopsy after developing aortic dissection whilst being treated for longstanding seronegative rheumatoid arthritis with tocilizumab. Despite Cyclophosphamide therapy she progressed and died from ruptured aortic aneurysm.

Conclusions: We highlight common presentations for large vessel GCA include refractory Polymyalgia Rheumatica and weight loss. We found 91.6% had involvement of the aorta. 88.8% responded at 6 month with initial Prednisolone plus additional immunosuppressant. All GCA patients need close follow up for evolving aortic involvement especially if they are taking Tocilizumab. Tocilizumab therapy can normalise inflammatory markers and may mask progressive underlying vasculitis revealed on histology[2].

Disclosures: The authors have declared no conflicts of interest.

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310. Single centre experience of ANCA associated vasculitis management during COVID-19 Pandemic – Success and Challenges

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Background: To share the experience of delivering ANCA Associated vasculitis (AAV) treatment in a nephrology department in a district general hospital in the UK during Covid 19 pandemic.

Methods: Prior to the pandemic, the chemotherapy was being delivered by two trained nurses who are part of the home therapy team that oversees home dialysis patients and two more staff from home therapy team were trained. They coordinated the pre and post chemotherapy bloods for which the patient usually arranges an outpatient phlebotomy appointment, and the chemotherapy was delivered in a clinic room on the dialysis ward. During COVID, patients needed to be shielded away from the dialysis ward.

Results: The team managed a considerably higher number of patients with AAV during this period compared to the previous year. There were total of 7 new diagnoses in 2018/2019 compared to 15 cases in 2019/2020, which is an increase of 114%. The number of relapsed patients also increased by 3-fold as there were 2 patients in 2018/2019 versus 7 patients in 2019/2020. The arrangements were changed so that the pre and post chemotherapy bloods would be done at home and patients attend for the infusion on to a day case unit where they received the chemotherapy with full adherence to the government social distancing and personal protective equipment guidance. During this period from March 2020 to October 2021, a total of 24 patients received induction treatment with either Cyclophosphamide or Rituximab. Out of these, 5 patients were treated for other pathologies including IgA vasculitis and membranous nephropathy. A total of 14 new patients with a diagnosis of ANCA associated vasculitis started on treatment and 12 patients received IV Cyclophosphamide and 2 patients received IV Rituximab. There were 5 patients with relapse of ANCA associated vasculitis and they were all treated with IV Rituximab. On average each patient receiving IV cyclophosphamide induction therapy requires 19 home visits for phlebotomy during the course of delivering 10 doses. The team also continued their visits for regular blood tests whilst they started on maintenance Azathioprine for first few months; weekly for first months and then two weekly thereafter. For Rituximab, patients require a total of 3 visits for blood tests during the two week induction therapy.

Conclusions: The experience has been very positively accepted by both patients and the nephrology team as it reduced the number of visits the patients attended hospital as well as avoiding the delays caused by patients not being able to attend for their blood tests on time patient felt safer at home and reduced anxiety. It also was felt that it is overall less time consuming for the chemotherapy delivering nurses as they are in full control of when the bloods are taken hence chasing the results appropriately. It also relieved the pressure on phlebotomy team who were operating at much reduced capacity due to limited staffing and to allow for social distancing restrictions. The main challenges of this arrangements were that the Immunosuppression delivery team had to frequently visit the patients at their homes, which may have exposed them to more risk than if the patients attended outpatient phlebotomy. It also adds travel time to the nursing staff's schedule that could have been utilised to achieve another task. This arrangement may also be challenging for centres with large patient numbers. This highlights how the existing community team could be utilised to deliver a safe service during the height of a global pandemic. In summary: 1-Safer immunosuppression delivery during pandemic with upskilling existing staff in a relatively smaller hospital. 2-Reducing hospital visits by average 19 episodes per patient per induction therapy cycle for patients on Cyclophosphamide. 3-Scope for integrating community tea in managing extremely vulnerable group of patients. 4-Scope for outpatient management for relatively stable patients diagnosed with ANCA associated vasculitis or other renal pathologies requiring immunosuppression therapy.

Disclosures – None

311. Safety and efficacy of maintenance therapies for anti-neutrophil cytoplasmic antibody small-vessel vasculitis: A network meta-analysis

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Backgrounds/ Objectives: Over the past two decades, considerable progress has been made in maintaining remission in patients with anti-neutrophil cytoplasmic antibody (ANCA) vasculitis using a variety of medications, including rituximab, azathioprine, mycophenolate, methotrexate, and glucocorticoids. However, although survival has improved amatically over the last decades, relapse rates remain significant for certain patients, stressing the need for advocation of new therapeutic strategies. The aim of this study was to compare the efficacy and safety of different regimens used for maintenance of remission in patients with ANCA-vasculitis.

Methods This network meta-analysis studied adult patients with ANCA-vasculitis in complete remission, who were maintained with various regimens, excluding patients with eosinophilic granulomatosis with polyangiitis, and those who have ended up in end-stage kidney disease. Outcomes of interest included relapse (any/major), relapse-free survival and adverse effects.

PubMed, Scopus, Web of Science, CENTRAL, Clinicaltrials.gov and Google Scholar were systematically searched from inception.

Results: Overall, the meta-analysis was based on 10 reports, describing the outcomes of 7 RCTs including 752 patients with ANCA-vasculitis. Compared to rituximab, relapse-free survival was significantly worse with the use of azathioprine (HR: 2.11, 95% CI: 1.19-3.74), methotrexate (HR: 2.51, 95% CI: 1.24-5.08) and mycophenolate mofetil (HR: 3.57, 95% CI:1.70-7.46). Compared to mycophenolate mofetil, better outcomes were estimated for azathioprine (HR: 0.59, 95% CI: 0.37-0.94), cyclophosphamide (HR: 0.39, 95% CI: 0.20-0.75) and leflunomide (HR: 0.30, 95% CI: 0.11-0.84). Compared to rituximab a higher relapse risk was estimated for azathioprine (OR: 2.15, 95% CI: 1.00-4.59) and mycophenolate mofetil (OR: 4.42, 95% CI: 1.63-11.94). A higher risk of major relapse was calculated for azathioprine (OR: 2.39, 95% CI: 1.10-5.19), methotrexate (OR: 3.18, 95% CI: 1.14-8.89) and mycophenolate mofetil (OR: 5.20, 95% CI: 1.65-16.37) compared to rituximab. The rates of serious adverse effects did not differ significantly among interventions.

Conclusion: Rituximab appears predominant in maintaining remission in patients with ANCA-vasculitis with no cost in adverse events.

Disclosure: None

312. Mycophenolate for the treatment of eye involvement in patients with Behçet Synome

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Background/ Objectives: Mycophenolate has been successfully used in non-infectious inflammatory uveitis. Experience with this agent in uveitis associated with Behçet's synome (BS) is limited. We aimed to report the efficacy and safety of mycophenolate in the treatment of BS uveitis in a tertiary center.

Methods: All patients with panuveitis or posterior uveitis who used mycophenolate for eye involvement between 2016 and 2018 were included. Patient charts were reviewed and data on demographic features, previous immunosuppressives, concomitant therapies, ocular attacks and outcome, and adverse events were extracted. Follow up was ended on October 2021.

Results: We included 12 BS patients (M/W: 8/4, mean age: 35±7 years) treated with mycophenolate during a mean follow-up of 42±19 months (Table). All but 3 patients had bilateral eye involvement. Previous medications were azathioprine (AZA) in 12 patients, cyclosporine-A (Cy-A) in 10, interferon-alpha (INF-α) in 8, infliximab (IFX) in 2, and

adalimumab (ADA) in 1 patient. IFX and INF-α had been discontinued due to adverse events in all patients, AZA in 10/12, and Cy-A in 7/10. Seven patients were prescribed mycophenolate for remission induction. One of these patients had had his first uveitis attack while on AZA treatment due to gastrointestinal involvement. The remaining 6 patients were using other immunosuppressives and experienced relapses that led to mycophenolate use. Mycophenolate mofetil (MMF) was added to a biologic agent in 2 patients (IFX and ADA) and was initiated in combination with IFX in 1 patient. These 3 patients did not experience further ocular attacks and IFX was stopped due to remission in 1 patient. In the fourth patient, MMF was switched to mycophenolate sodium (MPA) due to numbness in hands and feet and MPA was stopped due to arthralgia. This patient did not experience ocular attacks during 5 months of mycophenolate therapy. The remaining 3 patients had further uveitis attacks without decrease in visual acuity 2, 6, and 12 months after MMF initiation, and IFX was added in 2 patients, and ADA in 1 patient. Two of these patients were switched to INF-α due to uveitis relapses. MMF was switched to MPA for diarrhea in 1 patient. Five patients had received MMF for maintenance. One of these was using IFX when MMF was started and these 2 agents were used together. This patient discontinued MMF due to remission 17 months after MMF initiation and is still on IFX monotherapy. The second patient is still on MMF for 39 months without further ocular attacks. ADA, IFX and Cy-A were added in the remaining 3 patients due to ocular attacks 2, 5 and 31 months after MMF initiation. One of these 3 patients stopped IFX and MMF due to remission and is off treatment for 2 years.

Conclusions: Mycophenolate may be an alternative treatment modality in addition to biologics for patients with eye involvement who are intolerant to conventional therapies. Further data is needed to show whether it would be effective when used alone. Mycophenolate was well tolerated in this small series.

Disclosures: Sinem Nihal Esatoglu has received honorariu for presentations from UCB Pharma, Roche, Pfizer, and Merck Sharp Dohme. Gulen Hatemi has received grant/research support from Celgene and has served as a speaker for AbbVie, Celgene, Novartis, and UCB Pharma. Vedat Hamuryudan has received grant/research support from Celgene and has served as a speaker for AbbVie, Celgene, Novartis, and UCB Pharma. No other disclosures were reported.

Table. Demographic, BS manifestations, treatment and outcome of the 12 patients

Age /gender	BS findings	Previous IS therapies	Remission induction or Maintenance therapy	Concomitant biologic	Time to ocular attack (months)	Treatment after ocular attack	At the end of the final follow-up	MMF duration (months)
25/M	O, PP, J, U	AZA, Cy-A	Remission induction	None	2	ADA was added	ADA and MPA[a] were switched to INF due to further ocular attacks	38
42/W	O, G, PP, EN, U, SPR	AZA, Cy-A, INF, IFX	Remission induction	IFX	N/A	N/A	Still on IFX and MMF	72
37/M	O, G, U	AZA, Cy-A, INF, IFX, ADA	Remission induction	ADA	N/A	N/A	Still on ADA and MMF	27
32/M	O, PP, U	AZA	Remission induction	None	12	IFX was added	Still on IFX and MMF	52
33/W	O, G, PP, EN, U,	AZA, Cy-A, INF, ADA, IFX	Remission induction	None	N/A	N/A	MPA[b] was switched to certolizumab and MTX	5
24/M	O, G, PP, U, GI	AZA	Remission induction	IFX	N/A	N/A	Still on MMF and IFX was stopped due to remission	63
37/M	O, G, PP, U, GI	AZA, Cy-A	Remission induction	None	6	IFX was added	IFX and MMF were switched to INF due to further ocular attacks	41
36/W	O, PP, U	AZA, Cy-A, INF	Maintenance	None	2	ADA was added	Still on ADA and MMF	50
36/M	O, G, PP, EN, J, U, DVT, SPR	AZA, Cy-A, INF, IFX	Maintenance	IFX	N/A	N/A	Still on IFX and MMF was stopped due to remission	17
49/W	O, G, PP, EN, U, SPR	AZA, Cy-A, INF	Maintenance	None	N/A	N/A	Still on MMF	39
37/M	O, G, PP, U, DVT, SPR	AZA, INF	Maintenance	None	31	Cy-A was added	Still on MMF and Cy-A	38 d
31/M	O, G, PP, J, U	AZA, Cy-A, INF	Maintenance	None	5	IFX was added	Off treatment for 2 years	38

ADA: adalimumab; AZA: azathioprine; BS: Behçet's syndrome; CyA: cyclosporine-A; DVT: deep vein thrombosis; EN: erythema nodosum; G: genital ulcer; GI: gastrointestinal involvement; IFX: infliximab; INF: interferon alpha; IS: immunosuppressive; J: joint; M: male; MMF: mycophenolate mofetil; MPA: mycophenolate sodium; MTX: methotrexate; N/A: not applicable; O: oral ulcers; PP: papulopustular lesions; SPR: skin pathergy reaction; U: uveitis; W: woman
a MMF was switched to MPA due to numbness in hands and feet, and MPA was stopped due to arthralgia.
b MMF was switched to MPA due to diarrhea.

313. Rituximab as maintenance therapy for ANCA-associated vasculitides: pooled and long-term analysis of the MAINRITSAN trials

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Background: Maintenance therapy after remission induction has been shown to reduce relapse rate in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. The three MAINRITSAN trials have imposed rituximab as gold standard for maintenance treatment. Nevertheless, long-term follow-up of these trials are required to clarify the risk of relapse, as well as rituximab optimal schedule and duration.

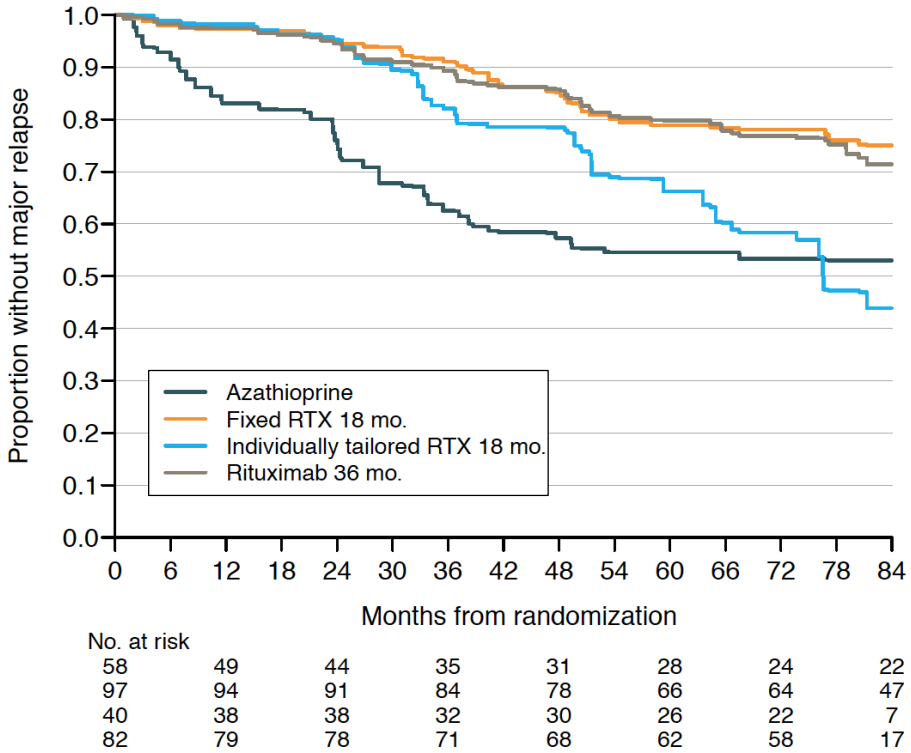
Methods: The MAINRITSAN randomized controlled trials compared fixed 500 mg rituximab infusion at D0, D14, M6, M12, and M18 and azathioprine (MAINRITSAN1); fixed 500 mg rituximab infusion at D0, D14, M6, M12 and M18 (systematic arm) and individually tailored regimen, i.e. when ANCA titer rose and/or circulating CD19+ B lymphocytes reappeared (MAINRITSAN2); and rituximab administered for 18 months to a prolonged treatment with infusions of 500 mg every 6 months of RTX for additional 18 months (MAINRITSAN3) All patients enrolled in these trials were prospectively followed until December 2020 and their data were pooled to analyze relapses and adverse events. Data from the three trials were adjusted for variables identified as associated with relapse to make the data from these studies comparable.

Results: 277 patients were analyzed with a median follow-up of 73 [51-115] months. 203 patients had granulomatosis with polyangiitis (GPA) (73.3%), 196 (70.8%) had newly diagnosed vasculitis, and 255 (92.0%) were ANCA positive, mainly anti-PR3 (n=170, 61.3%). Factors associated with an increased risk of major relapse were the presence of ENT involvement (hazard ratio 2.00; 95% CI 1.23-3.26) and relapsing patients at inclusion (hazard ratio 1.64; 95% CI 1.04-2.58). After adjustment for prognosis factors, rituximab remained superior to azathioprine in preventing both overall (major and/or minor) and major relapses (hazard ratio 0.29; 95% CI 0.17-0.50 and 0.40; 95% CI 0.22-0.71, respectively). In contrast, individually tailored rituximab administration was associated with an increased risk of major relapse compared with systematic administration (hazard ratio 3.00; 95% CI 1.44-6.27). Finally,

prolonged rituximab treatment for 36 months was not associated with a decreased risk of overall or major relapse compared with systematic rituximab administration for 18 months with this extended follow-up update (HR 0.77; 95% CI 0.47-1.26 and 1.16; 95% CI 0.63-2.15, respectively). Long-term follow-up of MAINRITSAN3, by considering the randomization arm in the MAINRITSAN2 trial, showed an increased risk of relapse for patients treated with individually tailored RTX then placebo, compared to patients who received systematic rituximab for 18 months . 68 patients had serious infections during follow-up (24.5%), and prolonged treatment did not increase serious infections rate (hazard ratio 1.14; 95% CI 0.59-2.23).

Conclusion: This pooled and long-term analysis of patients included in the MAINRITSAN trials confir that rituximab is effective in preventing relapses in ANCA-associated vasculitis, especially with 500 mg infusions every 6 months for 18 months, without increasing the risk of serious infection. Individually tailored administration is associated with an increased risk of major relapse. Finally, extending treatment to 36 months does not appear to be associated with a decreased risk of relapse compared with fixed rituximab administration for 18 months after longer follow-up.

Disclosure: The authors have no conflicts of interest to declare.



314. Emergence of New Manifestations During Infliximab Treatment in Behçet Synome

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Background/ Objectives: Infliximab (IFX) is being increasingly used for the treatment of severe manifestations of Behçet synome (BS). However, emergence of new manifestations has also been occasionally reported during IFX treatment. We aimed to assess the frequency of new manifestations in our BS patients treated with IFX.

Methods: A chart review was conducted to identify all BS patients treated with IFX in our clinic between 2004 and 2020. Demographic data, indications for IFX initiation, concomitant treatments, and outcomes were recorded. A new manifestation was defined as the emergence of a new organ involvement or mucocutaneous manifestation developing for the first time during IFX treatment or within 12 weeks after the last infusion of IFX. To better describe our treatment strategies for new manifestations, we categorized new manifestations as major and minor manifestations. Major manifestations included uveitis, vascular involvement other than superficial thrombophlebitis, gastrointestinal, and central nervous system involvement. Minor manifestations included mucocutaneous findings, arthritis, superficial thrombophlebitis, and venous ulcers.

Results: Among our 282 patients who used IFX, 19 (7%) patients had developed a total of 23 new manifestations during a mean follow-up of 20.0±15.3 months. Vascular lesions (11/23, 48%) were the most common new manifestation and 10/23 (43.5%) were major manifestations. Patients with vascular involvement were more likely to develop a new manifestation (12/19, 63%). Initial manifestations that required IFX were in remission at the time of new manifestation in 14/19 patients. IFX treatment was intensified (n=6) and/or glucocorticoids, immunosuppressives, or colchicine were added to IFX (n=21). IFX was switched to another agent for the remaining manifestations (n=8). These treatment modifications led to remission in 17/19 patients.

Conclusions: New manifestations developed during IFX treatment in 7% of our patients with BS. The majority of new manifestations, especially minor manifestations that developed during IFX could be managed by intensifying IFX or glucocorticoids, or adding immunosuppressives or colchicine.

Disclosures: Sinem Nihal Esatoglu has received honorariu for presentations from UCB Pharma, Roche, Pfizer, and Merck Sharp Dohme. Gulen Hatemi has received grant/research support from Celgene and has served as a speaker for AbbVie, Celgene, Novartis, and UCB Pharma. Yesim Ozguler has received honorariu for presentations from UCB Pharma, Novartis, and Pfizer. Emire Seyahi has received honorariu for presentations from Novartis, Pfizer, AbbVie, and Gliead. Ugur Uygunoglu has received advisory board honorariu and speaker fees from F Hoffmann La-Roche, F Hoffmann La-Roche, Bayer, Merck-Serono, Novartis, Teva, and Biogen Idec/Gen Pharma of Turkey. Aksel Siva received honorariu from Bayer-Schering AG, Biogen/Gen Ilac of Turkey, Genzyme, Merck-Serono, and Roche for consulting, fees from Novartis as a consultant and advisory committee member, travel and registration reimbursements from Genzyme, and honorariu from Teva for speaking engagements. Aykut Ferhat Celik has served as a speaker for AbbVie, Takeda, Jansen, and Pfizer, and has received advisory board honorariu from Jansen, AbbVie, and Takeda. Vedat Hamuryudan has received grant/research support from Celgene and has served as a speaker for AbbVie, Celgene, Novartis, and UCB Pharma. No other disclosures were reported.

Table. Demographics, characteristics, new manifestations and treatment of new manifestations of 19 patients

Age at IFX initiation, gender	BS manifestations	Main involvement requiring IFX	Previous drugs	Concomitant drugs	Time to new manifestation (months)	New manifestation	Treatment for 1st new manifestation[c]	Treatment for 2nd new manifestation[c]
16, W	O, EN, U	Uveitis	AZA, CSA, INF, ADA, Anakinra, Canakinumab	None	26	GIS	IFX dose ^	N/A
25, M	O, G, U, IVC	IVC	AZA, INF	AZA, CSA	10	PAT	Pulse MP and CYC	N/A
32, M	O, G, EN, IVC	Budd-Chiari	COL, AZA, CSA, CYC	None	48	Arthritis	MMF	N/A
29, M	O, G, EN, U	Uveitis	COL, AZA, INF	AZA	53	STM	GC was added	N/A
34, M	O, G, EN, DVT, Venous ulcer	Venous ulcer	AZA	None [a] COL[b]	40 and 50	Arthritis[1], STM[2]	COL, GC were added	GC was added
44, W	O, EN, J	Arthritis	COL	None	36	GIS	AZA, GC were added	N/A
35, M	O, G, EN, DVT, Peripheral artery thrombosis	DVT, Peripheral artery thrombosis	COL, AZA, CYC	AZA	32	PAT	Pulse MP and CYC	N/A
21, M	O, G, U, J, DVT, DST	DVT	COL, AZA, CSA, MTX	MMF, GC 20 mg	19	NBS	Pulse MP and ADA	N/A
30, W	O, G, EN, DVT, PAT, DST	PAT-DST-DVT	CYC	GC 2.5 mg	8	Coronary artery thrombosis	Pulse MP and CYC	N/A
42, M	O, G, DVT	Budd-Chiari	COL, CYC	None	19	Arthritis	IFX intervals v	N/A
50, M	O, NBS	NBS	AZA, CYC	None[a] AZA, COL[b]	18 and 30	EN[1], DVT[2]	COL	ADA and GC was added
31, W	O, Budd-Chiari, PAT	Budd-Chiari, PAT	COL, CYC	AZA, GC 5 mg	4	Arthritis	Anakinra	N/A
43, M	O, G, EN, PAT	PAT	COL, AZA, CYC	None	7	Coronary artery	IFX dose ^	N/A

ADA: adalimumab; AZA: azathioprine; COL: colchicine; CSA: cyclosporine-A; CYC: cyclophosphamide; DST: dural sinus thrombosis; DVT: deep vein thrombosis; EN: erythema nodosum; G: genital ulcer; GC: glucocorticoid/prednisolone; GIS: gastrointestinal; IFX: infliximab; INF: interferon alpha; IVC: inferior vena cava; J: joint; M: male; MMF: mycophenolate mofetil; MTX: methotrexate; N/A: not applicable; NBS: Neuro-Behçet syndrome; O: oral ulcers; PAA: pulmonary artery aneurysm; PAT: pulmonary artery thrombosis; Pulse MP: high-dose intravenous methylprednisolone (1 gr for 3 days); STM: superficial thrombophlebitis; U: uveitis; W: woman

[a] Concomitant drugs that were used at the time of first new manifestation

[b] Concomitant drugs that were used at the time of second new manifestation

[c] IFX dose was increased 5 mg/kg to 10 mg/kg in patient 1, 13 and 15. IFX intervals were reduced from 12 weeks to 8 weeks in patient 10, from 6 weeks to 4 weeks in patient 15, and from 8 weeks to 6 weeks in patient 18. None of the patients who had an arterial or venous thrombosis were treated with anticoagulant therapy.

315. Effectiveness of every-other-week tocilizumab maintenance therapy in giant cell arteritis: a prospective single-centre study.

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Background/objectives: Optimal duration of tocilizumab (TCZ) therapy in patients with giant cell arteritis (GCA) is yet to be defined. The GiACTA open-label extension phase showed that 58% of patients treated with a 12-month course of weekly TCZ had a disease flare in the 2 years following therapy suspension[1]. Our aim is to evaluate the efficacy and safety of low-dose TCZ maintenance in patients who achieved remission after one year of standard therapy.

Methods: GCA patients eligible for TCZ according to the 2018 EULAR recommendations[2] and who achieved remission after one year of weekly subcutaneous TCZ were prospectively enrolled. TCZ was administered every-other-week (EOW) for additional 12 months, and eventually suspended. Patients were evaluated 4-monthly during TCZ therapy, and 1 and 6 months after TCZ suspension. In patients with large-vessel (LV) involvement at baseline, PET scan was performed 12 and 24 months after TCZ start. The primary outcome was relapse-free survival at month 6 since TCZ suspension. Relapse-free survival during TCZ therapy and imaging response at PET scan were also evaluated. Adverse events were recorded.

Results: 17 patients were enrolled (12 women, 71%; mean age 71.5±8.7 years). Disease features at diagnosis and TCZ start are listed in Table 1. Reasons for TCZ start were clinical or imaging disease flare (n=9), persistence of disease activity (n=5), and steroid-related adverse events (n=3). At TCZ start, median disease duration was 8 (3-22) months, serum C-reactive protein (CRP) was 13 (6-22) mg/L, daily prednisone (PDN) dose was 25 (15-37.5) mg; 4 patients were already on methotrexate (MTX) which was maintained in 1 of them. Ten patients had LV involvement on PET scan. At TCZ EOW start, no patient was on PDN and 1 patient was on MTX; MTX was added in another patient due to persistence of LV involvement on PET scan. All patients completed the 24-month TCZ course. Two patients (12%) had a polymyalgic flare while on EOW TCZ: one patient at month 1 and one patient at month 6; of note, one of them had a polymyalgic flare also while on weekly TCZ. Both flares were managed with a PDN course with complete clinical remission. No patient had active LV involvement at 24-month PET scan. Adverse events on EOW TCZ were zoster reactivation (n=1) and neutropenia (n=1). At TCZ stop, no patient was on PDN and 2 patients were on MTX. One month after TCZ stop, all patients were in remission. Six months after TCZ stop, 4 patients (24%) experienced a flare, which was successfully managed in all cases with TCZ weekly re-introduction; in 2 patients, a PDN course was also started.

Conclusions: In this proof-of-concept study, low-dose TCZ maintenance in GCA showed excellent disease control, which was maintained in most patients after therapy suspension. Longer follow-up and replication in larger cohorts are required.

Disclosures. AT, SS, LM: none; CC, EB, LD received consultation honoraria from Roche

References.

1.Hellmich B et al. *Ann Rheum Dis*. 2020
2.Stone JH et al. *Lancet Rheumatol*. 2021

Table. Patients' characteristics at giant cell arteritis diagnosis and at study entry

	GCA diagnosis, n=17 n (%)	TCZ start, n=17 n (%)
Headache	16 (94)	5 (29)
Scalp tenderness	11 (65)	5 (29)
Jaw claudication	9 (53)	2 (12)
Ocular ischemic manifestations	3 (17)	0 (0)
Polymyalgia rheumatica	8 (47)	0 (0)
Constitutional symptoms	14 (82)	7 (47)
Active vasculitis on PET	10 (59)	10 (59)
Modality of diagnosis		
Vascular ultrasound	7 (47)	-
Temporal artery biopsy	3 (17)	-
PET	10 (59)	10 (59)

316. Improved relapse-free survival with the Norwich Prednisolone Regimen for Giant Cell Arteritis

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Background/ Objectives: Glucocorticoid therapy is the mainstay treatment for GCA. There is no consensus on the dose of prednisolone to be used. Prednisolone regimens used in clinical trials have reported relapse rates of 66 to 92%. The long-term follow-up of Tocilizumab and prednisolone for 1-year showed a relapse rate of 74% at 2 years. The Norwich Regimen is a bespoke prednisolone plan with an initial dose of 1mg/kg of lean body mass. It delivers 164.64 mg/kg of lean body mass in a logarithmic taper over 100 weeks. It was devised to reduce the risk of relapse and allow patients to be in control of their prednisolone reduction.

Methods: All patients were diagnosed by biopsy, ultrasonography or PET scan and provided with a printed prednisolone plan at diagnosis. All individuals were assessed at approximately 3-6 monthly intervals in addition to suspected relapse, toxicity or other need for course correction. Relapses were confirmed objectively using a modification of the Kerr criteria.

Relapse free survival was recorded at 100 weeks. Patients were given an open invite to contact us in the event of a suspected relapse after coming off prednisolone. A notes review was done to record events at 150 weeks.

Results: 150 consecutive people with objectively diagnosed GCA (mean age 74) since 10/01/2012 have completed 150 weeks since starting prednisolone. ug-free, relapse-free survival at 100 weeks was met by 133/150 (89%). 7 individuals died and 20 relapsed. A further 5 died and 15 relapsed by week 150; 103/150 (69%) survivors were in prednisolone-free remission. Of the 12 deaths – 6 died of cancer, 1 subdural haemorrhage, 1 ischaemic bowel, 1 septicaemia, 1 general decline (aged 93). The cause of death was not available for 2 individuals who died in the community. The median time to relapse for the 35 individuals was 80 weeks (IQR 64,109).

Conclusions: We report the first results of a bespoke prednisolone taper to be used in real life. The Norwich Regimen for the treatment of GCA results in ug-free relapse-free survival of 89% at 100 weeks and 69% at 150 weeks, which is superior to all other reports published so far.

Disclosures: None

317. Efficacy and safety of tofacitinib versus leflunomide treatment in Takayasu arteritis: a prospective study

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Background/ Objectives: Takayasu arteritis (TAK) is a rare large-vessel vasculitis characterized by vascular granulomatous inflammation. Tofacitinib (TOF) is a JAK1/JAK3 signaling pathway inhibitor. In TAK, increasing evidence has suggested that JAK/STAT signaling pathway played an essential role in the pathogenesis of TAK [13, 14]. It has reported that TOF was able to suppress T cells activation and reduce the production of some inflammatory cytokines, such as IFN-γ, IL-17, and IL-21[13]. Thus, this study aimed to compare the effectiveness and safety of TOF with another effective agent, LEF in patients with TAK.

Methods: A total of 67 patients with active disease screened from the prospective East China Takayasu Arteritis (ECTA) cohort were recruited in this study. Among them, 35 patients were treated with glucocorticoids (GCs) and LEF and 32 patients were treated with GCs and TOF.. The primary endpoint was effectiveness rate (ER) at 6 months. The other aspects were also evaluated, including (1) remission rate: complete remission (CR) and partial remission (PR); (2) relapse rate; (3) reduction in inflammatory parameters (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP); (4) vascular imaging changes (vascular improvement,

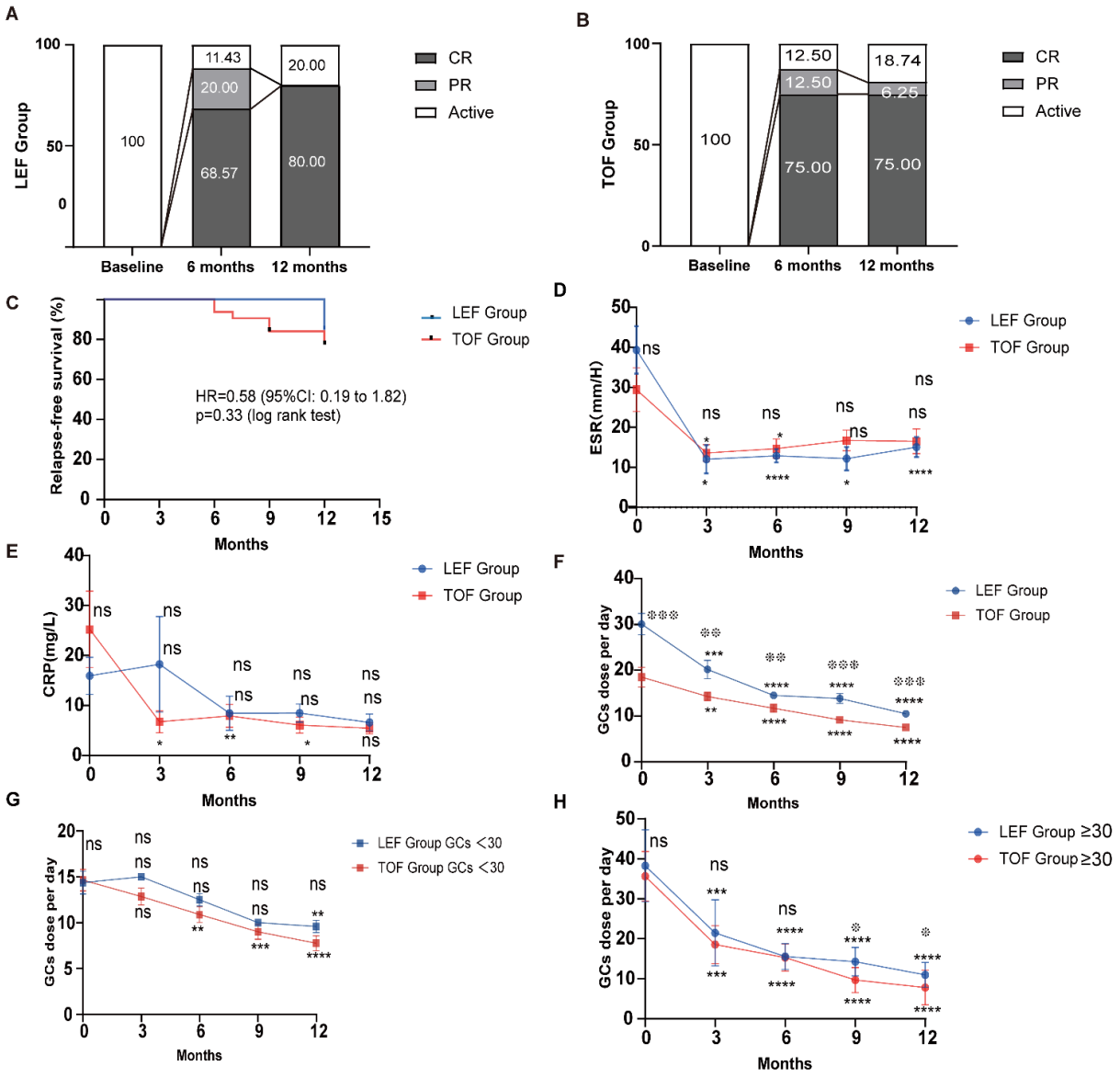
progression or stable vascular lesions); (5) the tapering of GCs dose; (6) side effects. Among them, the rate of relapse and side effects were assessed during a whole period of 12 months. The remaining aspects were all analysed at 6 and 12 months. In addition, treatment effects were also evaluated among naive patients or refractory patients separately between these two groups.

Results: After 6 months' treatment, no difference was observed in ER between two groups (LEF group: 31/35 (88.57%) vs. TOF group: 28/32 (87.50%), p=1.00, Figure1 A-B). Differences of CR rate were also not found between these two groups at 6 months and 12 months (6 months: 24/35 (68.57%) vs. 24/32 (75.00%), p=0.60; 12 months: 28/35 (80.00%) vs. 24/32 (75.00%), p=0.77, Figure1 A-B). During 12 months' treatment, the relapse rate was also comparable between two groups (LEF group: 6 (17.14%) vs. TOF group 7 (21.88%), p=0.76, Figure1 C). However, patients in LEF group achieved longer relapse-free duration than patients in TOF group (11.31±2.83 vs 10.97±1.93 months, p=0.04). ESR and CRP were decreased significantly at 6 (ESR: LEF group: p<0.0001; TOF group: p=0.15; CRP: LEF group: p=0.06; TOF group: p=0.007) and 12 months (ESR: LEF group: p<0.0001; TOF group: p=0.06; CRP: LEF group: p=0.006; TOF group: p=0.14, Figure1 D-E) in both groups compared with their corresponding baseline levels. The proportion of patients with imaging improvement after 12 months' treatment were low in both groups (LEF group: 1 (2.86%) vs. TOF group: 3 (9.38%) p=0.17). After treatment, the doses of GCs were significantly reduced in both groups from the third month onwards compared with their corresponding baseline dose (p<0.05, Figure1F). Among patients with initial GCs dose ≥ 30mg/day, patients in TOF group gained a much lower daily GCs dose than that of LEF group at 9 months and 12 months (p<0.05, Figure1 H). Furthermore, the frequency of side effects was higher in LEF group than that of TOF group (12/35, 34.29%, vs 3/32, 9.38%; p=0.02). Regarding with subgroup analysis, among naive patients, ESR levels were declined more remarkably in LEF group compared with that of TOF group at 6 and 12 months (P<0.05), while the GCs dose was significantly lower in TOF group after 12 months' treatment (p<0.05). No differences were observed in ter of treatment effects among refractory patients between two groups (all p>0.05).

Conclusions: LEF and TOF have comparable treatment effects for patients with TAK. However, TOF is superior to LEF in GCs tapering and safety ile.

Disclosures: None declared.

Figure 1.



318. Long-term efficacy of direct-acting antivirals in patients with HCV-associated cryoglobulinemia

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Background/ Objectives: Direct-acting antivirals (DAAs) have shown their efficacy in patients with HCV-associated cryoglobulinemic vasculitis after short-term follow-up. However, long-term outcomes after HCV eradication are not fully understood.

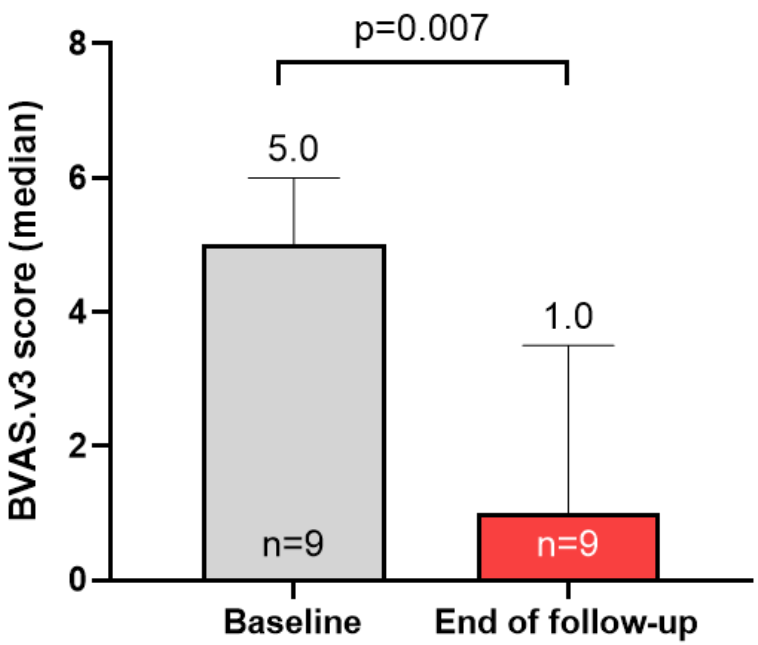
Methods: Patients with HCV- associated cryoglobulinemic vasculitis (HCV-CV) or asymptomatic cryoglobulinemia (AC) treated with DAAs ± ribavirin were retrospectively evaluated. The activity of HCV-CV was assessed by using Birmingham Vasculitis Activity Score version 3 (BVAS.v3). Primary outcomes in all patients were sustained virologic (defined as undetectable HCV-RNA levels 12 weeks after treatment cessation) and immunological (defined as absence of circulating cryoglobulins, rheumatoid factor and normal C4 level) response. In patients with HCV-CV complete (defined by a BVAS.v3 score of 0) and partial (defined as BVAS.v3 score < 50% of the baseline score) response were assessed.

Results: A total of 29 patients [72.4% -females, median baseline age was 53 (48-59) years, 93.1% had cirrhosis, 65.5% had genotype 1b HCV] with HCV - associated cryoglobulinemia were enrolled in this study. Nine (31.1%) of them met the criteria for HCV-CV and 20 (68.9%) patients had asymptomatic cryoglobulinemia. The main manifestations of HCV-CV included skin purpura (89%), arthralgias or arthritis (56%), renal impairment (44%), sensory peripheral neuropathy (44%) and skin ulcers (11%). 3 patients had monoclonal gammopathy. The median duration of follow-up period was 26 (15-36) months after treatment cessation. During the follow-up period all patients achieved SVR12. Median BVAS.v3 score significantly decreased from 5 (at baseline) to 1 point (p=0.007) at the end of follow-up. Complete immunologic response and cryoglobulins elimination was achieved in 10 (34.5%) and 18 (62.1%) of patients, respectively. However, in 11 (37.9%) and 9 (31%) patients cryoglobulinemia and rheumatoid factor persisted, respectively, at the end of follow up. Median rheumatoid factor level decreased from 17.45 IU/ml at baseline to 12.9 IU/ml at the end of follow-up. Complete and partial clinical response were achieved by 3 (33.3%) and 4 (44.4%) patients with HCV-CV, respectively. Two patients (22.3%) were clinical non-responders due to persistence of severe arthralgias, peripheral neuropathy and renal impairment. The HCV-CV skin manifestations were improved in 6 (66.7%) patients with baseline features, joint involvement in 3 (60%) of patients, renal impairment in 3 (75%) of patients and sensory neuropathy only in 1 (25%) patient. Overall, BVAS.v3 score improved in all patients with HCV-CV. One patient had relapse of skin ulcers during follow-up. In this patient cryoglobulins and rheumatoid factor persisted. No patient died or developed severe HCV-CV during follow-up period.

Conclusions: DAAs therapy of patients with HCV-CV and AC was associated with high rates of SVR, elimination of circulating cryoglobulins and clinical improvement in a long-term follow-up analysis. However, most patients did not achieve a complete clinical or immunological response during follow-up period.

Disclosures: The authors declare no conflicts of interest.

Figure 1. Change from baseline in median BVAS.v3 score



319. 2022 EULAR recommendations for the management of ANCA-associated vasculitis (AAV): methods & project update

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Background/ Objectives: The 2008 and 2016 European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of AAV (GPA, MPA and EGPA) [1,2] have provided guidance for management, monitoring, and treatment of AAV in daily practice and are highly cited. The publication of several high-impact research articles in the past 5 years including landmark studies on the role of plasma exchange, standardization of glucocorticoid dosing, use of rituximab for maintenance therapy, C5a receptor targeted therapy and anti-IL5 therapy in EGPA make this an opportune time to update the 2016 guidelines.

Methods: The recommendations will be developed based on an evidence-based approach as outlined in the 2014 EULAR standardized operating procedures[3]. The systematic literature review (SLR) will be restricted to a keyword search of Medline, Embase and the Cochrane

Central databases of topics identified through a Delphi process and those from the 2016 recommendations. Key questions will be framed in the PICO (Population, Intervention, Comparator, Outcome) format. The literature search will be restricted to March 2015 for updated domains but unrestricted for new domains. All types of studies with 10 patients or more will be included. Abstracts of the annual meetings of EULAR, ACR, ERA-EDTA, ASN and the Vasculitis and ANCA Workshops will also be screened, but restricted to randomized controlled clinical trials (RCTs). The number of manuscripts in each category will be described (for example RCTs, prospective versus retrospective studies etc.). The Cochrane revised tool for assessing risk of bias for RCTs (RoB2), ROBINS-1 for observational studies, QUADAS II for studies on accuracy of diagnostic tests and ATAR II for meta-analyses will be used for bias assessment. A summary of findings tables will be created according to the PICO format. When there is need to evaluate treatment modalities, we will consider the need to quantify the treatment effects. When comparing clinical trials, we will give greater weight to outcome measures, which have been validated. Evidence will be categorized based on the GRADE system and the strength of each recommendation will be assigned as per EULAR standardized operating procedures[2]. The recommendations will be developed by a group of experts from several medical disciplines including rheumatology, nephrology and internal medicine, other health care essionals and patient partners from 17 different countries. For recommendation statements, which are not derived from homogenously conducted clinical trials, we will attempt to formulate consensus based clinical recommendations. These will be clearly labelled as arising from an expert opinion approach and these statements will have a default strength of D. The recommendations will be validated independently by a vote amongst the membership of the EUVAS following the Appraisal of Guidelines for Research and Evaluation Version II (AGREE II) instrument. The final set of recommendations will be submitted for the scrutiny of the EULAR clinical affairs committee.

Results: The application to update the recommendations has been approved by EULAR and the SLR is ongoing. Publication of the final recommendations is expected at the end of 2022.

Conclusions: In view of recent fundamental developments affecting key areas of management of AAV, we believe that the 2016 recommendations no longer reflect current standard of management and therefore will now be updated.

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320. Early Biologic Treatment May Prevent Relapses Or New Organ Involvement In Behcet's Patients With High-risk

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Background/ Objectives: Conventional immunosuppressives (cIS) are the choice of treatment for major organ (ocular, vascular, central nervous (CNS) and gastrointestinal (GIS) involvement to prevent relapses and organ damage in patients with Behcet's disease (BD). We aimed to investigate the rate of new major organ involvement in BD patients under cIS treatments during follow-up and to assess the characteristics and treatment protocols of these patients.

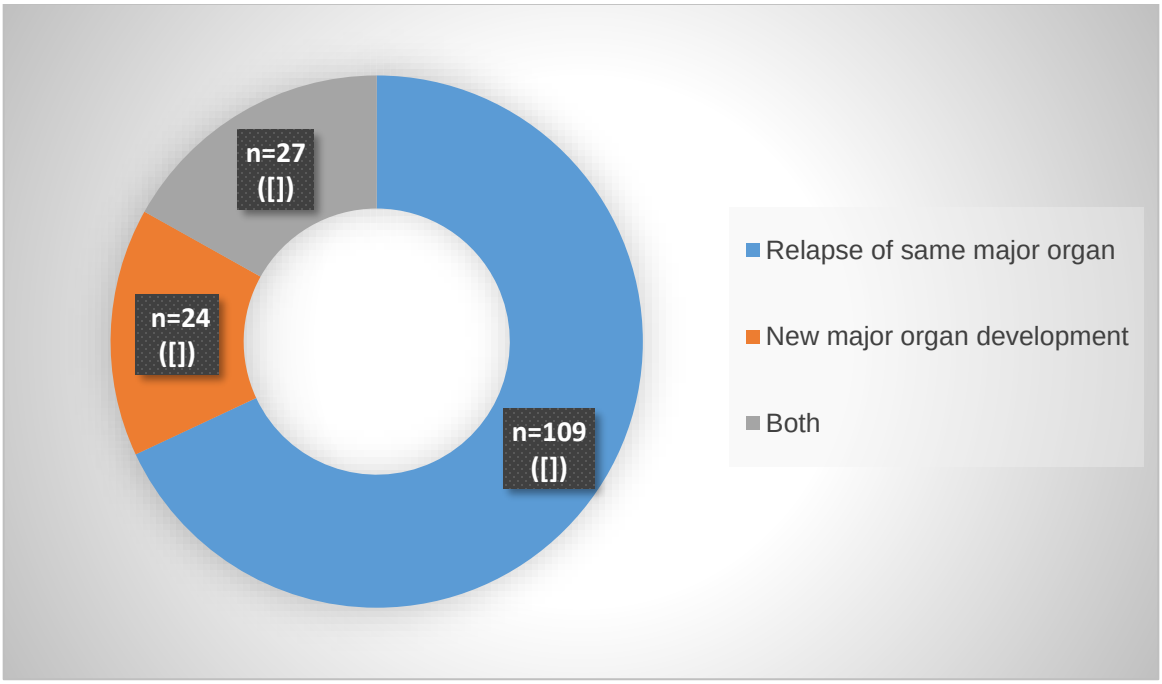
Methods: The files of 1114 patients diagnosed with BD and followed (1992-2019) in the Marmara University Behcet's Clinic were overviewed retrospectively. Patients with follow-up duration less than 6 months were excluded. A total of 806 patients, of whom 56% were male were included in the analysis. Demographic and clinical characteristics, follow-up and treatment data of the patients were recorded from files. Relapse of the same organ and/or new major organ development during the follow-up period of patients receiving cIS was defined as "event under cIS".

Results: Median age at diagnosis was 29 (10-65) years and median follow-up duration was 68 months (6-272). Genital ulcer, erythema nodosum and arthritis/arthralgia were more common in women, whereas papulopustular lesions, vascular and ocular involvement were more common in men ($p<0.005$ for all). Presence of major organ involvement was 56.9% (n=459) and the frequencies of vascular, ocular, CNS and GIS involvement were 29.8%, 33,5%, 9.7%, and 2%, respectively. At diagnosis 232 (50.5%) patients had major organ involvement, whereas it developed in 227 patients during a follow-up of median 3 years (0.5 - 32) after diagnosis. Major organ involvement developed earlier in males compared to females (median 2 years vs 4 years, $p = 0.012$). In patients with a first-degree relative history of BD, major organ involvement also developed earlier, however without reaching significance (median 1 year vs 3 years) ($p= 0,066$). 440 patients had follow-up data under cISs with the follow-up duration of median 65.5 months (6-272). Main reason for cISs use was major organ involvement (86.8%), less frequent reasons were mucocutaneous disease (9.3%) and joint involvement (3.8%). An event under ISs (mainly relapses) occurred in 160 (36.4%) patients with median 23 months after cISs initiation. Majority of events (68%) were relapses of the same major organ (Figure 1). The most commonly used cIS agent was azathioprine (87%). Among patients having an event under cISs, 91% of the relapses and 75% of new major organ involvement developed under azathioprine treatment. In patients with an event under cISs, treatment mostly switched to

other ISs such as cyclophosphamide, interferon-alpha, and high dose corticosteroids. In 22% of patients, azathioprine was switched to tumor necrosis factor (TNF) inhibitors.
Conclusions: In our study, major organ involvement developed in 57% of the 806 BD patients. We observed that disease course was more severe under cIS treatment in male patients diagnosed at a younger age and with the history of familial BD. In one third (36%) of the patients under cIS treatment, a relapse or a new major organ involvement developed despite the cISs use, mainly under azathioprine. TNF-inhibitor use was approved for BD treatment within the last decade in Turkey. Therefore, azathioprine was switched to a TNF inhibitor in only 22%. Our results suggest that earlier and more aggresive treatment of major organ involvement with biologics may be an option in young male patients especially with the history of familial BD, who had the highest risk for severe disease course.

Disclosures: None

Figure 1: Disribution of events under conventional immunosuppressive treatments.



321. Long-term treatment effects of tofacitinib in a cohort of therapy resistant Takayasu patients.

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Background/ Objectives: Takayasu's arteritis (TAK) is a rare systemic large vessel vasculitis that primarily affects the aorta and its main vessel branches, leading to stenosis or aneurysm. There is no explicit therapy option for therapy-resistant patients that have failed on combination therapy consisting of; glucocorticoid steroids (GS) combined with conventional synthetic disease-modifying anti-rheumatic ugs like methotrexate (MTX), azathioprine (AZA), leflunomide (Lef), tumor necrosis factor inhibitor (TNFi) and tocilizumab (TCZ).
Janus kinase inhibitors (JAKi) seem promising in newly published case reports, in a case series of five patients with refractory TAK in addition to a randomized controlled study of biologic naïve TAK patients treated with JAKi compared to MTX (1, 2). All these have a short follow-up without imaging outcome.

Methods: TAK patients who failed on multiple combination therapies were included from MEDUB, an "off-label" treatment data registry at Oslo University Hospital.
Patients started with peroral tofacitinib 5 mg bd, combined with ongoing MTX or Lef in addition to GC. After about 12-24 weeks, tofacitinib was doubled to 10 mg bd if there were insufficient clinical effects. Evaluation of treatment response by; (a) the absence of sympto of vessel inflammation, (b) normalization, or significant reduced C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), (c) absence of progression in vascular imaging MRI or CTA (d) reduced uptake in ^{18}F-FDG PET/CT scan using PETVAS scoring (3), and by (e) reduced GC treatment. Side effects were registered.

Results: The first patient (pt. 1) started with tofacitinib in September 2017. A total of six patients with a mean disease duration of TAK of 6.5 years (0.9-11.5 years) received tofacitinib treatment. All increased tofacitinib from 5 mg bd to 10 mg bd. The average treatment time with tofacitinib is currently 2.7 years (1.1 - 4.0 years), with a total of 16 patients years of tofacitinib treatment. Five patients (5/6 =83%) had a clinical response. In the five patients with clinical response, there was significantly reduced CRP from a mean of 67.6 mg/L to 3.5 mg/L and ESR from 56.4 mm/h to 10 mm/h, respectively. There was no radiographic progression, and a mean PETVAS score fell from a mean value of 15 (range 21-10) to 9.4 (range 15-5) with a mean fall in PETVAS score of 5.6 (range 11-3). The mean dose of GC was reduced from 15.8 to 7.7 mg/daily. There were no severe adverse events registered. All the patients with coexisting autoimmune disease (pt. 1, 2, and 4) responded in their related sympto
Two patients paused the treatment (non-ug-related) and developed severe flare shortly after but went in remission after a restart of tofacitinib.

Conclusions: Tofacitinib was well tolerated and had long-term clinical and steroid-sparing effects in most therapy-resistant TAK patients combined with GC and MTX or Lef. Long-term randomized controlled studies of JAKi in TAK patients are warranted.

Disclosures: None.

322. Infliximab for Vascular Involvement in Behçet's Synome

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Background/ Objectives: Vascular involvement is an important cause of morbidity and mortality in patients with Behçet's synome (BS). TNF inhibitors have been beneficial for the management of mucocutaneous, eye and gastrointestinal involvement of BS. Data on their efficacy in patients with vascular involvement is scarce. We aimed to survey the efficacy and safety of infliximab (IFX) in BS patients with vascular involvement followed in a dedicated tertiary center.

Methods: We reviewed the charts of all BS patients who used IFX for vascular involvement between 2004 and June 2021. A standard form was used for extracting data on demographic and clinical features, type of vascular involvement, concomitant immunosuppressives, duration of IFX use, relapses, adverse events and outcome. The primary endpoint for patients with any vascular involvement was remission defined as lack of new clinical sympto/findings associated with vascular lesion, lack of worsening of the primary vascular lesion, lack of a new vascular lesion on imaging, and CRP<10 mg/dL. For patients with venous ulcers, remission was defined as the complete healing of ulcers. Remission was assessed at month 6 and month 12. Relapse was defined as the development of a new vascular lesion or the recurrence of preexisting vascular lesion/s in patients who were in remission at or after month 6.

Results: Among the 124 patients (102 men, mean age at IFX initiation: 36.5±8.9 years) treated with IFX, 106 (85%) received IFX for remission induction and 84/106 (79%) were refractory to conventional treatments. The main indication for IFX treatment was venous thrombosis in 62 patients (50%), pulmonary artery involvement in 36 (29%), non-pulmonary arterial involvement in 14 (11%), and venous ulcer in 12 (10%) (Table). At the time of IFX initiation, 108 patients (87%) were prescribed concomitant prednisolone and 97 (78%) concomitant immunosuppressives. Remission rate was 73% (90/124) at month 6 and 54% (67/124) at month 12. During IFX treatment, 13/93 (14%) patients experienced 16 relapses after remission had been achieved. Two of these patients had discontinued IFX. The reasons for discontinuation of IFX were remission in 23, adverse events in 14 patients, inefficacy in 12, patient non-compliance in 12, relapse in 2, and others in 7. The adverse events were allergic reactions in 5, tuberculosis, disseminated zona, lung adenocarcinoma, fibromyxoid sarcoma, heart failure, systemic lupus erythematosus, palmoplantar pustulosis, auricular chonitis, and aortic stent graft infection in 1 patient each. Eighteen (78%) of the 23 patients who discontinued IFX due to remission are still in remission while 5 had a relapse after 8, 13, 21, 38, and 79 months. Infliximab was initiated once again in a total of 12 patients. Eight of them discontinued IFX due to allergic reactions (n=3), remission (n=2), non-compliance (n=2), and frequent infection (n=1). At the end of the follow-up, 58 patients were still on IFX including 4 patients who had restarted IFX. Four patients had died and 2 of them were still on IFX treatment at the time of their death. Reasons for death were lung adenocarcinoma (n=1),

sepsis (n=1), and pulmonary hypertension related right heart failure due to pulmonary artery thrombosis (n=2).

Conclusions: IFX see to be effective in BS patients with vascular involvement, even in those who are refractory to immunosuppressives and corticosteroids. No further relapses occurred in 83% (77/93) of the patients during treatment and adverse events leading to discontinuation were observed in 15% (18/124).

Disclosures: Sinem Nihal Esatoglu has received honorariu for presentations from UCB Pharma, Roche, Pfizer, and Merck Sharp Dohme. Gulen Hatemi has received grant/research support from Celgene and has served as a speaker for AbbVie, Celgene, Novartis, and UCB Pharma. Yesim Ozguler has received honorariu for presentations from UCB Pharma, Novartis, and Pfizer. Vedat Hamuryudan has received grant/research support from Celgene and has served as a speaker for AbbVie, Celgene, Novartis, and UCB Pharma. No other disclosures were reported.

Table. The frequency of concomitant immunosuppressive use, duration of infliximab use and outcomes of BS patients with vascular involvement treated with infliximab

	Pulmonary artery involvement (n=36)	Non-pulmonary arterial involvement (n=14)	Venous thrombosis (n=62)	Venous ulcers (n=12)	Overall (n=124)
Treatment for remission induction	24 (67%)	12 (86%)	58 (94%)	12 (100%)	106 (85%)
Number of patients who used concomitant immunosuppressives	26 (72%)	11 (79%)	52 (84%)	8 (67%)	97(78%)
Duration of infliximab use (mean ± SD months)	21 ± 21	23 ± 19	21 ± 21	24.5 ± 20	21 ± 21
Remission rate at month 6	30 (83%)	9 (64%)	50 (81%)	1 (8%)	90 (73%)
Remission rate at month 12[a]	20 (56%)	7 (50%)	38 (61%)	2 (17%)	67 (54%)
Relapse rate throughout duration of infliximab	4 (11%)	3 (21%)	6 (10%)	0	13 (10%)
Number of patients who discontinued infliximab[b]	23 (64%)	6 (43%)	33 (53%)	8 (67%)	70 (56%)
Due to remission	7	0	16	0	23
Due to inefficacy	1	3	4	4	12
Due to relapse	0	1	1	0	2
Due to adverse event	4	2	7	1	14
Due to noncompliance	5	0	4	3	12
Due to other reasons[c]	6	0	1	0	7
Death	2	0	2	0	4

[a] Thirteen patients were not included in this analysis since the duration of IFX use was not yet 12 months.

[b] Remission and relapse rates during the second time IFX was used among the 12 patients who restarted IFX are not included here.[c] Other reasons were preparation for surgical operation (n=2), pregnancy (n=1), willing to get pregnant (n=1), lack of health insurance (n=1), due to prison sentence (n=1), and death (n=1).

323. Imlifidase in ANCA associated Vasculitis

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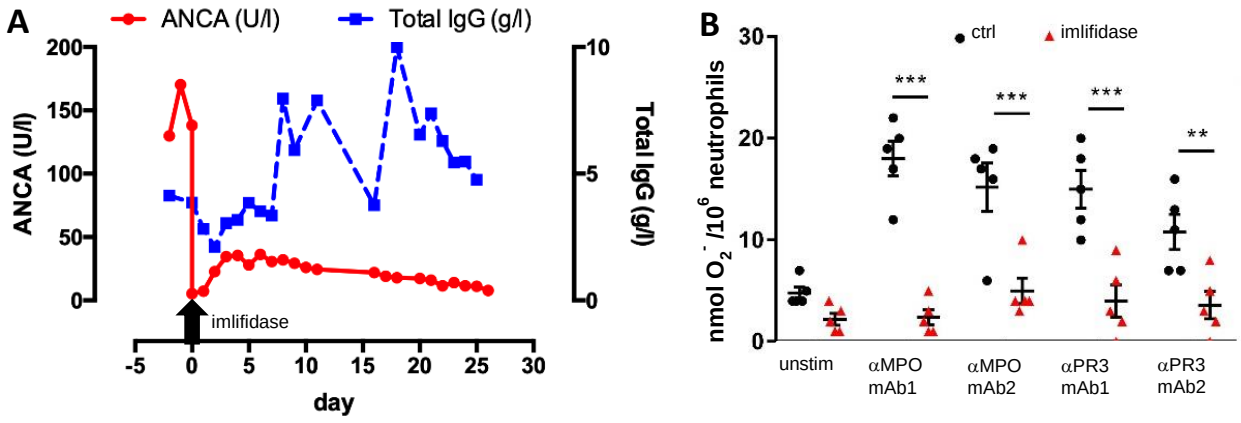
Background/ Objectives: ANCA are IgG directed against the neutrophil antigens myeloperoxidase (MPO) and proteinase 3 (PR3). Through binding and activation of neutrophils they cause severe and irreversible tissue damage. A common and life-threatening manifestation is pulmonary capillaritis presenting as diffuse alveolar hemorrhage (DAH). After PEXIVAS failed to prove significant benefits of plasma exchange (PE) clinicians are left with supportive care and unspecific immunosuppressive regimens which require on average 90 days to induce remission. Imlifidase is an IgG-degrading enzyme derived from Streptococcus pyogenes which rapidly cleaves human IgG into F(ab')2 and Fc fragments. We report on the first use of imlifidase in a 35-year-old male patient with severe refractory DAH due to PR3-ANCA positive granulomatosis with polyangiitis and studied ANCA dynamics and in-vitro effects.

Methods: The patient was treated intravenously with 20 mg of imlifidase. Clinical characteristics were followed closely, ANCA titer dynamics were monitored daily. Inhibitory effect of imlifidase was measured in-vitro. Tumor necrosis factor-α (TNFα)-primed isolated polymorphonuclear leukocytes were stimulated with monoclonal antibody (mAb) against MPO or PR3. Sera were pretreated with either imlifidase or control (ctrl) buffer. Generation of reactive oxygen species (ROS) was measured using superoxide dismutase inhibitable ferricytochrome c reduction.

Results: Hours after administration of imlifidase hemoptysis ceased and lung function improved significantly, enabling rapid weaning from extra-corporal membrane oxygenation (ECMO). This coincided with rapid ANCA seroconversion (Fig. 1A). In-vitro treatment with imlifidase effectively inhibited ANCA-mediated neutrophil activation (Fig. 1B). Unfortunately, the patient succumbed to sepsis after colonic bleeding 26 days after treatment. On post-mortem analysis no evidence of vasculitic organ damage was found.

Conclusions: The patient showed rapid clinical response to imlifidase treatment. This effect was supported by rapid ANCA decrease and astic inhibition of neutrophil activation after ANCA cleavage in-vitro. Thus, imlifidase holds great potential of severe acute ANCA-associated vasculitis. We are currently designing an open label phase II study investigating the ug's potential.

Disclosures: JS, PE and AS are currently designing a phase II clinical study on imlifidase in ANCA associated vasculitis. All other authors disclose no conflicts of interests.



324. Changes of molecular signature in TAK with tofacitinib treatment and their correlation with disease characteristics

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Background/ Objectives: To analyze changes of serum cytokine, chemokine, and growth factor iles in Takayasu arteritis (TAK) patients treated with tofacitinib and explore molecular signatures related with various disease characteristics.

Methods: Seventeen patients with TAK and 12 age-and gender matched healthy controls were recruited in this study. These patients were included from an ongoing prospective TAK cohort treated with glucocorticoids and tofacitinib. Patients' disease activity, disease severity and imaging changes were evaluated at baseline, 6 and 12 months after treatment. Routine inflammatory parameters erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were also collected. Cytokines (PTX3, IL-6, IFN-r, IL-17, TNF-a, YKL40, IL-10), chemokines (IL-16, CCL22, CCL2, CCL5), MMPs (MMP1, MMP2, MMP3), and growth factors (VEGF, FGF, PDGF) were detected in these patients at baseline, 6 and 12 months and healthy controls. Patients' baseline molecules were compared with that of healthy controls and their changes after treatment were analyzed at 6 and 12 months. In addition, correlations among these molecules or between these molecules and ESR or CRP were analyzed. Furthermore, molecule signatures were explored via radar plot to assess their relationship with disease activity, disease severity, and vascular imaging changes.

Results: At baseline, all the patients were in active status according to NIH disease activity criteria, and 10 (58.82%) were assessed as severe disease. After treatment, 1 (5.88%), and 1 (5.88%) patients were in active disease at 6 and 12 months. After 12 months' treatment, 1 (5.88%) patient presented vascular imaging progression, while 6 (35.29%) patients' vascular lesions were improved. Patients' ESR and CRP levels were significantly

reduced at 6 months. (p =0.024, p=0.0467 respectively). In ter of those molecules, patients' cytokines (PTX3, IL-6, IFN-γ), chemokines (IL-16, CCL22, CCL2), growth factor (VEGF) and MMP9 were significantly higher than those of healthy controls (all p<0.05), while FGF was significantly lower in patients with TAK (p=0.02). The correlation analysis showed that PTX3 was correlated with CRP (p=0.01, r=0.60) and IL-6 (p=0.006, r=0.66). After treatment, IL-10 was significantly increased at 6 months compared with its baseline level (p= 0.0069). Levels of TNF-a was decreased at 12m compared with its level at 6 months (p=0.034). IFN-γ also showed an decrease trend at 12 months in contrast to its level at 6 months (p=0.076). The radar plot of molecules in patients with different NIH score demonstrated that PTX3 was closely correlated with disease activity. By comparing these molecular levels at baseline between patients with and without imaging improvment, patients with imaging improvement had relative higher TNFα, ESR and CRP levels (p=0.04, p=0.056, p=0.07 respectively) and relative lower CCL22, FGF and PDGF levels (p=0.056, p=0.06, p=0.08 respectively).

Conclusions: Multiple molecules representative different pathological mechanism participated in the pathogenesis of TAK. Tofaticinib was not sufficient to inhibit the expression of these pathogenic molecules. PTX3 was a prominent marker for disease activity, and CCL22 may have a predictive value for vascular imaging changes.

Disclosures: none

325. Long-Term Rituximab Maintenance Therapy in Granulomatosis with Polyangiitis – A Single-Centre Experience

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Objective: Recent guidelines recommend rituximab for maintenance therapy in severe ANCA-associated vasculitis.(1) Clinical trials have described low rates of relapse with rituximab maintenance therapy.(2,3) Side effects of longstanding rituximab treatment, such as neutropenia and hypogammaglobulinemia, have been a concern and previously not investigated long-term. Here we evaluate the efficacy and tolerance of rituximab maintenance therapy in patients with granulomatosis with polyangiitis (GPA) followed at a single centre.

Methods: All patients with GPA treated with rituximab as maintenance therapy, defined as lasting longer than 6 months from induction, at the Department of Rheumatology at the Uppsala University Hospital in Sweden between the years 2008-2020, were included in this retrospective analysis.

Results: Thirty-two patients (19 female, 59%) were included. The median age at the start of rituximab treatment was 56 years (range 21-81). All patients had a diagnosis of GPA classified according to the EMEA (European Medicines Agency) algorithm, with 31 (97%) being positive for PR3-ANCA. Twenty-six (81%) had pulmonary involvement and 9 (28%) had renal involvement. Information was gathered on a total of 162 patient-years of rituximab therapy;

median treatment duration was 4,6 years (range 0,6-13,4) and median total rituximab dose was 11 gra (range 4-23) at the time of data collection. Of the 32 patients, 21 (66%) received rituximab for control of relapse while 11 (34%) were treated for the initial disease presentation. Twenty-four patients (75%) had previously received cyclophosphamide induction therapy. All patients received induction doses of rituximab (1000 mg at 0 and 2 weeks) before being maintained on 1000 or 500 mg on a fixed schedule every 6 months. One single patient flared during maintenance rituximab therapy. The flare occurred two years after induction and the maintenance dose had just been lowered to 500 mg every 6 months. Of the 15 patients (47%) who had discontinued their rituximab treatment, 2 (13%) flared (both 2 years after their last rituximab dose; they received 4 and 6,5 years of rituximab therapy, respectively), 11 (73%) had not flared (median follow-up time 3 years; they received a median of 3,5 years of rituximab therapy) and 3 (9%) were lost to follow-up. During rituximab maintenance therapy, 18 patients (56%) had at least one infection requiring antibiotics and 3 patients (9%) were hospitalised with an infection (2 for COVID-19 and 1 for pneumonia). Two patients (6%) died during rituximab maintenance therapy, one from COVID-19 and the other of unknown causes. Hypogammaglobulinemia (IgG < 6 g/L) was found in 9 patients (28%) during maintenance treatment; no patients had IgG levels < 3 g/L. Transient mild neutropenia was found in two patients (6%).

Conclusions: Rituximab maintenance therapy for GPA appears to be effective and safe, even long-term. Severe infections were rare and hypogammaglobulinemia was usually mild. Further studies are needed to establish the optimal dosage and duration of rituximab maintenance therapy.

Disclosures: None.

326. RTX-biosimilar (CT-P10) results of a referral vasculitis centre: A real life experience

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Background/Objectives: Biologic agents are breakthrough ugs in the treatment of rheumatic diseases including vasculitis. Rituximab (RTX) becomes one of the standard care in the treatment of ANCA-associated vasculitis (AAV), but high cost limits its use. Biosimilars offer cost-effective treatment options in various diseases due to increasing healthcare expenditures. CTP-10 is the first biosimilar of RTX and has been approved in Europe in all indications held by original RTX (oRTX) with extrapolation. We aimed to describe real life experience in the Vasculitis Centre regarding CTP10 in ter of interchangeability and adverse events.

Methods: Data of Hacettepe University Vasculitis Research Centre was used for this study. Patients receiving oRTX or biosimilar (CT-P10) between October 2020-November 2021 were

included in the study. Demographics, type and duration of disease, concomitant steroid dose, dosage schemes, and cumulative dose of oRTX/CT-P10 were recorded. Reason for interchangeability (substation or switch) was noted. The protocol for RTX infusion, both for oRTX and CTP-10, was standardized and given by the same premedication and dosing intervals. RTX-induced hypogammaglobulinemia was evaluated. Infusion related reactions (IRRs) were assessed during the infusion period according to the Common Terminology Criteria for Adverse Events (CTCAE); grade 1 includes mild sympto that not require intervention, while grade 2 includes moderate sympto that require interruption of the infusion but responds promptly to symptomatic treatment.

Results: Total of 24 (10 female/14 male) patients were included; the median (IQR) age was 57.0 (19) years. Diagnosis were AAV (n=15), IgG4-RD (n=8) and cutaneous polyarteritis nodosa (cPAN, n=1). Fourteen (58.3%) patients used CTP-10 whereas 10 (41.7%) patients were on oRTX. None of the ug changes was due to substitution. All of the switches were made due to the hospital's reimbursement policy which was shown in Table. The most commonly used dosage schemes were 1000 mg once for 6 months or 1000 mg every two weeks for 6 months both for oRTX and CT-P10. IRRs occurred in 42.8% (21.4% at each grade) of patients switched from oRTX to CT-P10 and 22.2% (all of them grade 2) of patients received oRTX. Statistical analysis was not performed due to low numbers.
Commonly observed IRRs were owsiness/weakness and itching/yness/irritation of throat both grade 1 and 2 (Table). RTX-induced hypogammaglobulinemia for IgG and IgM were determined in 2 (15.4%) and 3 (37.5%) patients, respectively.

Conclusions: CT-P10 is an increasingly used biologic agent among our patients with acceptable adverse events. Severe IRR symptom was not seen in any of the patients receiving oRTX or CT-P10. Interchangeability of an originator biologic and use of biosimilar are generally tailored according to emerged scientific evidence as well as local resources.

Disclosures: None

Table. Patients demographics and treatment details (n=25 patients)

Variables*	RTX/CTP-10 (n=14)	RTX/RTX (n=9)	CTP-10/RTX (n=1)
Age, years (IQR)	48.0 (21)	61.0 (19)	-
Sex (M/F)	7/7	6/3	1/0
BMI (kg/m^2), med (IQR)	27.7 (12)	27.7 (18)	-
Smoking status ✓ Ex-smoker ✓ Current smoker	4 (28.6) 1 (7.1)	3 (33.3) 0	1 (100.0) 0
Vasculitis type	8 (57.1)	6 (66.7)	1 (100.0)

✓ GPA ✓ IgG4 related disease ✓ cPAN	5 (35.7) 1 (7.1)	3 (33.3) 0	0 0
Disease duration (years), med (IQR)	3 (4)	5 (7)	-
RTX dosage scheme ✓ 1 g × 2 every 6 months ✓ 1 g every 6 months ✓ 500 mg every 6 months	 6 (42.9) 8 (57.1) 0	 5 (55.6) 4 (44.4) 0	 0 0 1 (100.0)
Cumulative dose of RTX	5 (5.50)	10 (7.63)	-
Concomitant steroid dose (mg/day), med (IQR)	3.8 (3)	10 (22)	-
Previous asthma/ug allergy history	6 (42.9)	3 (33.3)	0
Grade 1 IRRs	3 (21.4)	0	0
Grade 2 IRRs	3 (21.4)	2 (22.2)	0
Hypogammaglobulinemia ✓ Ig G ✓ Ig M	 0 3 (37.5)	 1 (7.7) 0	 1 (7.7) 0

* n (%), if otherwise specified.

327. Retention Rate, Reasons for Discontinuation and Outcome of Infliximab Use in Behçet's Synome

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Background/ Objectives: Infliximab (IFX) plays a key role in the management of severe and refractory manifestations of Behçet's synome (BS). We aimed to assess the retention rate of

IFX, adverse events, causes of discontinuation and outcome after cessation of IFX in a larger group of BS patients who were followed in a tertiary center.

Methods: The charts of BS patients who were prescribed IFX between 2004 and 2020 were reviewed to determine demographic features, reasons for IFX use, previous and concomitant ugs, IFX duration, reasons for cessation of IFX and time to flare following cessation of IFX. Follow-up was censored on March 2021.

Results: A total of 282 patients (220 men, mean age at IFX initiation: 34.5 ± 9.6 years) received IFX for uveitis (n=137), vascular involvement (n=86), parenchymal neurologic involvement (n=40), arthritis (n=12), gastrointestinal involvement (n=10), mucocutaneous involvement (n=6), venous ulcers (n=5), and secondary amyloidosis (n=1). Fifteen patients had more than 1 involvement requiring IFX.During a median follow-up of 52 months (IQR: 30-88), 134 (48%) patients were still receiving IFX for a median period of 36 months (IQR: 13-58) while 142 (50%) patients had discontinued IFX after a median follow-up of 18 months (IQR: 7-30). The remaining 6 patients were lost to follow-up. Reasons for discontinuation were adverse events in 44 (31%), remission in 27 (19%) patients, lack of efficacy in 33 (23%), lack of patient compliance in 31 (22%), pregnancy in 4, and preparation for surgery in 3 patients.

Adverse events (n=44) that required the cessation of IFX were infusion reaction (n=20), infection (n=8), hepatotoxicity (n=4), malignancy (n=4), palmoplantar psoriasis (n=3), lichen planus (n=1), ug induced lupus (n=1), splenic infarction (n=1), a decrease in left ventricular ejection fraction (n=1), and massive hemorrhage due to pulmonary hypertension (n=1).

Among the 27 patients who discontinued IFX due to remission, 5 (20%) had a relapse after 4, 21, 26, 29, 38 and 46 months. The remaining patients did not experience a relapse during a median follow-up of 35 months (IQR: 24-68). At the end of the follow-up, 2 patients had died due to lung adenocarcinoma and 1 with pulmonary artery involvement due to massive hemorrhage during IFX treatment and 3 patients had died 1 year, 3 and 8 years after IFX discontinuation. The causes of death were with right heart failure due to pulmonary hypertension in 1 patient and severe nervous system involvement in 2 patients.

Conclusions: Infliximab see to be effective for the treatment of organ and life-threatening manifestations in the majority of the patients. However, ug retention rate was not optimal, mainly due to adverse events, patient non-compliance, and inefficacy.

Disclosures: Sinem Nihal Esatoglu has received honorariu for presentations from UCB Pharma, Roche, Pfizer, and Merck Sharp Dohme. Gulen Hatemi has received grant/research support from Celgene and has served as a speaker for AbbVie, Celgene, Novartis, and UCB Pharma. Yesim Ozguler has received honorariu for presentations from UCB Pharma, Novartis,

and Pfizer. Emire Seyahi has received honorariu for presentations from Novartis, Pfizer, AbbVie, and Gliead. Vedat Hamuryudan has received grant/research support from Celgene and has served as a speaker for AbbVie, Celgene, Novartis, and UCB Pharma. No other disclosures were reported.

Table 1. Demographic, clinical characteristics and outcome of patients

Characteristic	Systematic review* (n=96)
Male, n, (%)	81/96, (84)
Patients who fulfilled ISG criteria, n/N, (%)	72/80, (90)
Juvenile-onset BS, n/N, (%)	9/49, (18)
Median (IQR) age at BS onset, years	25 (16-33)
Median (IQR) age at BS diagnosis, years	29 (24-35)
Median (IQR) age at AA amyloidosis diagnosis, years	35 (29-44)
Median (IQR) duration since BS to AA amyloidosis diagnosis, years	6 (1-9.25)
Median follow-up duration since AA amyloidosis diagnosis, (months)	20 (4-48)
Patients with a follow up time of less than 1 year (n, %)	29/67 (43)
BS manifestations, n/N, (%)	
Major organ involvement	62/80, (77.5)
Joint involvement	30/71, (42)
Eye involvement	45/77, (58)
Vascular involvement	48/80, (60)
Neurologic involvement	11/71 (15.5)
Gastrointestinal involvement	3/72 (4)
Comorbidities related to AA amyloidosis, n/N, (%)	11/96, (11.5)
Previous medications before AA amyloidosis diagnosis, n/N, (%)	
Colchicine	19/54, (35)
Immunosuppressives	22/54, (41)
Diagnostic tool, n/N, (%)	
Renal biopsy	69/96, (72)
Rectal biopsy	16/96, (17)
Nephrotic proteinuria at AA amyloidosis, n/N, (%)	60/81, (74)
Outcome	
Death	30/72 (42)
ESRD	30/64 (47)

ESRD: end stage renal disease; ISG: International study group criteria; IQR: interquartile range;
* Data on age at BS onset, age at BS diagnosis, age at AA amyloidosis diagnosis, duration since BS diagnosis to AA amyloidosis diagnosis, and follow-up duration since AA amyloidosis were available in 48, 53, 73, 52, and 67 patients, respectively

328. Withdrawn

329. Successful use of cyclosporin A and interleukin-1 blockers in VEXAS synome: a single-centre case series.

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Background/objectives: VEXAS synome is a recently recognized autoinflammatory disease induced by somatic mutations of the UBA1 gene. While the number of diagnosed patients is rapidly increasing, management of VEXAS is still unclear and no successful therapeutic option has been identified yet. Aim of our study is to report the successful use of a combination therapy of cyclosporin A (CsA) and interleukin-1 blockers in 3 VEXAS patients.

Methods: VEXAS patients followed up at our Autoinflammatory Diseases Clinic were identified. VEXAS diagnosis was confirmed by the identification of mutated UBA1 gene (p.Met41Val variant, n=2; p.Met41Thr, n=1). Demographics, disease features and previous treatments were reviewed. Clinical and laboratory responses, defined by change of inflammatory markers and variation of systemic manifestations, were recorded. Dose modification of concomitant steroid therapy was also evaluated.

Results: Three VEXAS patients were identified. All patients were male, with a median age of 69 (IQR, 68-70) years, and were initially treated with high-dose systemic prednisone, with rapid benefit. Two patients were originally diagnosed with adult-onset Still disease and one patient with relapsing polychonitis; median diagnostic delay was 30 (IQR, 29-57) months. Baseline features and previous therapies are summarized in Table 1. In all three cases, disease relapsed after reducing prednisone dose below 20 mg daily. Before combination therapy start, all patients failed monotherapy with 2 biologic or targeted steroid-sparing agents. Combination of canakinumab and CsA was started in one patient who did not tolerate anakinra monotherapy due to extensive cutaneous reaction. Combination of anakinra and CsA was started in one patient who failed canakinumab monotherapy and in one patient who did not tolerate anakinra monotherapy due to extensive cutaneous reaction. Notably, this last patient had a good tolerance to anakinra when administered together with CsA. At combination therapy start, all patients were on prednisone therapy at intermediate dosage. At month 6 after combination therapy start, prednisone was safely reduced to 5 mg daily in all patients. In this time course, no patient experienced a clinical or laboratory flare and no patient needed a temporary increase of steroid therapy. Combination therapy was well-tolerated by all patients. Two patients experienced significant neutropenia (800 and 900 cells/mm^3) but this adverse event was not associated with infectious events and did not require therapy suspension. One case of

upper respiratory tract infection was observed in the patient who did not experience neutropenia.

Conclusions: Interleukin-1 blockers and CsA combination therapy could be an effective steroid-sparing treatment option in VEXAS patients. Treatment-induced neutropenia does not seem to be associated with increased risk of infections. Longer follow-up and replication of these preliminary results in larger cohorts are required.

Disclosures: CC, GC, GDL and LD received honoraria and speaking fees from SOBI and Novartis

Table 1. Clinical, laboratory features and treatment of three VEXAS patients.

Sex Age	Presenting features	Disease-onset, inflammatory markers	Previous treatments & reasons for stop	Combination therapy start, details	Combination therapy start, inflammatory markers	Last evaluation, inflammatory markers
Male 70 years	Fever Erythema nodosum Lung involvement Arthritis	ESR, 120 mm/h CRP, 120 mg/L Ferritin, 1638 ng/mL	1. ANK, adverse event 2. CNK, not effective	ANK 100 mg/d CsA 200 mg/d PDN 30 mg/d	ESR, 59 mm/h CRP, 92 mg/L Ferritin, 623 ng/mL	ESR, 20 mm/h CRP, 1.3 mg/L Ferritin, 445 ng/mL
Male 69 years	Fever Erythema nodosum Lung involvement Polychondritis Arthritis, aphthosis	ESR, 117 mm/h CRP, 161 mg/L Ferritin, 1484 ng/mL	1. ANK, adverse event 2. TCZ, neutropenia	CNK 300 mg q5w CsA 300 mg/d PDN 10 mg/d	ESR, 99 mm/h CRP, 26 mg/L Ferritin, 526 ng/mL	ESR, 51 mm/h CRP, 2.8 mg/L Ferritin, 430 ng/mL
Male 68 years	Fever, arthritis Pyoderma gangrenosum Polychondritis Lung involvement Orbital pseudotumor	ESR, 120 mm/h CRP, 202 mg/L Ferritin, 1680 ng/mL	1. MTX, inefficacy 2. TCZ, neutropenia 3. TOFA, not effective	ANK 100 mg/d CsA 200 mg/d PDN 12.5 mg/d	ESR, 42 mm/h CRP, 31 mg/L Ferritin, 980 ng/mL	ESR, 29 mm/h CRP, 0.8 mg/L Ferritin, 380 ng/mL

Abbreviations. ANK, anakinra; CNK, canakinumab; CRP, C-reactive protein; CsA= cyclosporin A; ESR= erythrocyte sedimentation rate; PDN, prednisone; TOFA, tofacitinib; TCZ, tocilizumab

330. Treatment Efficacy of Biosimilar Rituximab Compared to the originator in Patients with ANCA associated Vasculitis

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Background: Truxima is a biosimilar version of rituximab. It was licensed & launched in the United Kingdom in April 2017. A biosimilar medicine is made to be similar in quality, safety and efficacy to existing licensed “reference” biological medicine and the cost is often significantly lower. A recent systematic review showed comparable long-term efficacy and safety of biosimilar rituximab to the originator ug in treatment of rheumatoid arthritis and non-Hodgkin’s lymphoma. Few data are available regarding the efficacy of biosimilar rituximab in treatment of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). A retrospective study

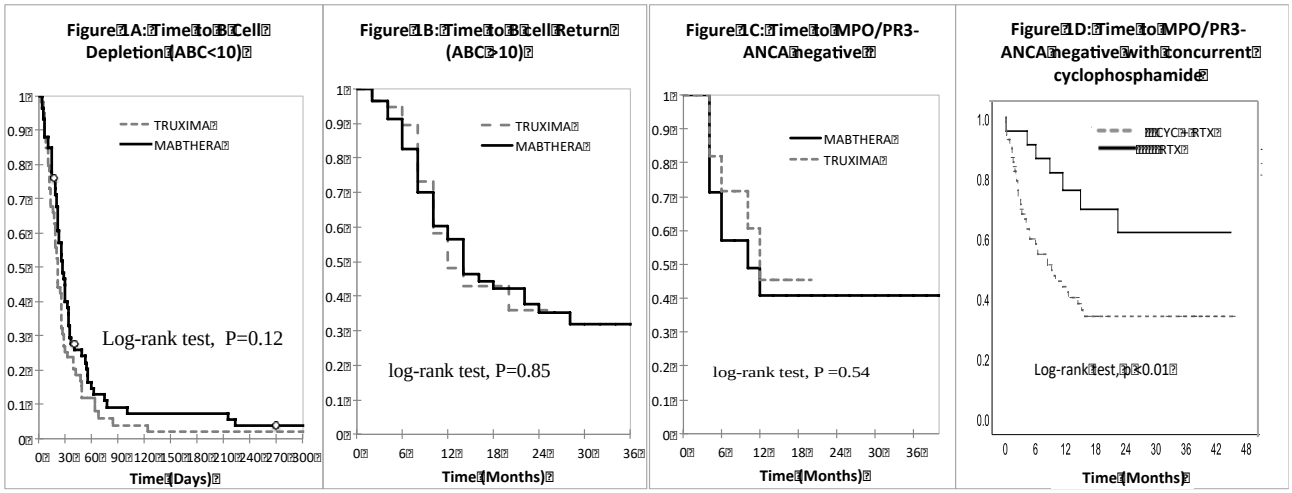
was thus conducted in our centre to examine the efficacy of Truxima when compared to the reference rituximab (MabThera) in the treatment of patients with AAV.

Methods: All patients with new or relapsing AAV who received first ever rituximab therapy between 1/1/2016 and 31/12/2018 were identified via our hospital dispensing database, and stratified into Truxima or MabThera treatment groups depending on the version of rituximab administered. Primary outcomes that were assessed included: time to B cell depletion (defined as absolute B cell count (ABC) □10 cells/μL) and repletion (i.e ABC >10 cells/μL and >20 cells/μL); time to myeloperoxidase (MPO)/proteinase 3(PR3)-ANCA negativity.Secondary outcomes included: overall survival, time to major relapse (defined as relapse requiring further course of rituximab for remission induction); adverse events including episodes of neutropenia, hypogammaglobulinemia and major infusion reactions. Subgroup analysis in patients who received concomitant cyclophosphamide and rituximab or other induction therapy was performed to examine its impact on treatment efficacy and safety.

Results: 59 and 60 patients received Truxima and MabThera, respectively, for treatment of new or relapsing AAV. The baseline characteristic (age, gender, entry estimated Glomerular Filtration Rate, proportion of patients received concomitant cyclophosphamide, ANCA serology, and pattern of organ involvement) of both group were comparable. All patients achieved clinical remission following induction treatment. Using Kaplan Meier analysis and log rank test, no difference was identified in time to B cell depletion or repletion (Figure 1A & 1B), MPO/PR3-ANCA negativity (Figure 1C), overall survival or major relapses requiring further rituximab as induction therapy. Treatment efficacy of Truxima and MabThera did not differ in subgroup analysis. However, we observed that patients who received concurrent cyclophosphamide during induction therapy achieved MPO/PR3-ANCA negativity more rapidly compared to those who did not, irrespective of the version of rituximab received (Figure 1D). No difference in adverse events such as major infusion reactions was seen in either group upon first rituximab exposure. Two patients in each group developed reactions following repeated dosing of rituximab.

Conclusions: Biosimilar rituximab Truxima appears to have comparable B cell depletion kinetics and treatment efficacy compared to the reference ug in our cohort of patients with AAV. Combination of rituximab, regardless of ug type, to cyclophosphamide may lead to more rapid ANCA-negative seroconversion.

Disclosures: None



331. Efficacy and Safety of Biologics in Relapsing and/or Refractory Polyarteritis Nodosa: A European Collaborative Study

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Objectives: To describe the efficacy and safety of biologics for the treatment of relapsing and/or refractory polyarteritis nodosa (PAN) not related to hepatitis B virus (HBV).

Methods: A retrospective European collaborative study was conducted in patients with non-HBV PAN who received biologics for the treatment of refractory and/or relapsing disease.

Results: Fifty patients receiving a total of 60 lines of biologics, including TNF-alpha blockers in 21 cases, rituximab (RTX) in 19 cases, tocilizumab (TCZ) in 11 cases, and other biologics in 10 cases. After a median follow-up of 29 (8-50) months after biologics initiation, complete remission, partial response and treatment failure occurred in 43%, 10% and 43% of patients receiving TNF-alpha blockers, respectively, 55%, 0% and 27% of TCZ recipients, and 32%, 11%, and 58% of RTX recipients. No remission was noted in patients treated with other biologics. Median BVAS opped from 6 (2-15) at baseline to 3.5 (0-12) at 6 months and 2 (0-10) at 12 months in TNF-alpha blockers recipients, from 7 (4-12) to 2.5 (0-19) and 1.5 (0-3) in RTX recipients, and from 7.5 (4-17) to 0 (0-13) and 0 (0) in TCZ recipients, respectively. Median GCs dose decreased from 20 mg/day (3-80) at baseline to 9 (0-25) at 6 months and 5 (0-10) at 12 months in TNF-alpha blockers recipients, from 27 mg/day (0-70) to 9 (0-30) at 6 months and 4 (0-25) at 12 months in RTX recipients, and from 33 mg/day (5-80) to 10 (5-30) at 6 months and 6 (0-15) at 12 months in TCZ recipients. Severe adverse events were observed in 14 (28%) patients, mainly infections, leading to biologics discontinuation in only 3 cases.

Conclusions: These results suggest that TCZ and TNF-alpha blockers may achieve higher rates of remission in relapsing and/or refractory PAN than other biologics. Our data warrant further study to confirm these findings.

Disclosures: None

332. Adding low dose cyclophosphamide to rituximab is associated with sustained remission in ANCA vasculitis patients

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Background: Rituximab (RTX) and cyclophosphamide (CYC) are effective remission-induction therapies in ANCA-associated vasculitis (AAV). High dose CYC is however considered toxic, whereas RTX monotherapy may increase the risk of relapse, depending on the choice of maintenance therapy and baseline disease severity. Particularly with renal

involvement, stable remission will favor prognosis. In this respect, adding low dose CYC to RTX could be superior to RTX alone. We evaluated this premise by retrospectively analyzing our data derived from a pragmatic, clinical approach in patients with severe AAV.

Methods*:* Patients diagnosed with AAV who were treated with RTX for remission-induction in the Maastricht University Medical Centre between March 2007 and January 2019, were screened for eligibility. Remission-induction consisted of either RTX (2x 1000mg two times) or RTX-CYC (2x 1000mg RTX and 2x 15mg/kg CYC intravenously). Corticosteroid tapering was identical in both groups. RTX during the maintenance phase was tailored according to CD19+ B cell repopulation (≥5 cells/ µL) and/or a rise in ANCA level, combined with clinical parameters, without signs of a major relapse. The primary outcome variable was major relapse rate after 2 and 5 years. Secondary outcome variables were clinical data including infections, end stage renal disease, malignancy, and mortality and laboratory parameters including renal function, CRP, MPO- or PR3-ANCA and immunoglobulin levels, and B- and T-cell subsets .

Results: Of the 246 patients with active AAV screened for the study, 28 patients received RTX only and 34 patients received RTX-CYC for remission-induction, both with a subsequent tailored RTX maintenance regimen. All patients were followed for at least 2 years with a median follow-up of 48 months (IQR 24-60). Patient characteristics at baseline are depicted in Figure 1. Biopsy proven renal involvement was more prevalent in the RTX-CYC patients (85.3%) compared to patients treated RTX only (60.7%) (P = 0.028). Baseline serum creatinine and delta serum creatinine after two years did not differ significantly with a median of -6.5 µmol/L (IQR -8.5-14.8) in the RTX only group and -0.5 µmol/L (IQR -30.3-29.5) in the RTX-CYC group (P = 0.737). Relapse rates within 2 years were significantly higher in the RTX only group (n=7 (28.0%) when compared to the RTX-CYC group(n=1 (3.2%); P = 0.015), whereas the number of patients receiving RTX maintenance and the number of infusions did not differ. After 5 years, however, relapse rates were not significantly different. The rate of infections, hypogammaglobulinemia, end stage renal disease, malignancies, and mortality did not differ after 2 and 5 years.

Conclusion*:* Adding low dose CYC to RTX is safe and may favor the prevention of major relapses in patients with severe AAV in the first two years after remission-induction, predominantly with renal involvement. Future prospective studies are needed to examine the role of reconstituted B cells and ANCA levels to better define tailor-made treatment decisions.

Disclosures: None

Table 1. Baseline characteristics.

	RTX only, N = 28	RTX-CYC, N = 34	P-value*
Age in years, median (IQR)	60 (55-69)	63 (48-70)	0.896
Male, n(%)	19 (67.9)	17 (50.0)	0.156
ANCA type, n(%) MPO PR-3 Double positive Other ANCA specificities** Negative	 12 (42.9) 14 (50.0) 1 (3.6) 1 (3.6) 0	 12 (35.3) 21 (61.8) 0 0 1 (2.9)	0.493
Diagnosis, n(%) MPA GPA EGPA	 7 (25.0) 20 (71.4) 1 (3.6)	 8 (23.5) 24 (70.6) 2 (5.9)	1.000
De novo, n(%)	9 (32.1)	12 (35.3)	0.794
BVAS, median (IQR)	12 (7-17)	14 (11-18)	0.164
Renal involvement, n(%) Serum creatinine (µmol/L), median (IQR) Creatinine clearance ≤30 ml/min/1,73m^2, n (%)	17 (60.7) 164 (96-192) 3 (17.6)	29 (85.3) 126 (91-238) 11 (37.9)	0.028 0.499 0.308
Kidney biopsy histopathologic classification, n(%) Not active Focal Crescentic Mixed Sclerotic	 0 6 (54.5) 1 (9.1) 2 (18.2) 2 (18.2)	 1 (4.2) 9 (37.5) 1 (4.2) 5 (20.8) 8 (33.3)	0.791
ANCA renal risk score, n(%) Low risk Moderate risk High risk	 7 (63.6) 3 (27.3) 1 (9.1)	 14 (58.3) 7 (29.2) 3 (12.5)	1.000
Laboratory data, median (IQR) CRP (mg/L) IgG (g/L)	 13 (2-65) 11 (8-15)	 14 (4-66) 9 (5-12)	 0.879 0.251

Abbreviations: RTX = rituximab, CYC = cyclophosphamide, ANCA = anti-neutrophil cytoplasmic antibody, MPO = myeloperoxidase, PR-3 = proteinase 3, MPA = microscopic polyangiitis, GPA = granulomatosis with polyangiitis, EGPA = eosinophilic granulomatosis with polyangiitis, BVAS = Birmingham Vasculitis Activity Score, CRP = C-reactive protein, IgG = immunoglobulin G
* A P-value of 0.05 was considered significant. ** Elastase, cathepsin G, lysozyme, lactoferrin, bactericidal inducing protein, and azurocidin.

333. Treatment of ANCA-associated vasculitis in the elderly: a single-centre UK experience.

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Objective: Despite the high incidence of ANCA-associated vasculitis (AAV) in elderly patients, clinical trials have usually not focused on this patient group and long-term outcome data is lacking. Here, we evaluate the treatment and outcomes in a single-centre cohort of elderly patients with AAV.

Methods: Retrospective data were collected on all hospitalised patients over the age of 74 years who underwent induction treatment for AAV between 2014-2021 at Addenbrookes Hospital (Cambridge, UK). Baseline characteristics and outcomes were assessed, and multivariate Cox models were derived to determine factors associated with infection and mortality.

Results: 85 patients were included with a median follow-up 21 months (IQR 12-44). Sex distribution was equal. Median age was 79 years (range 75–93); the majority of whom (79%) had newly-diagnosed disease, with predominantly MPA (66.6%) and MPO-ANCA (58.8%). Renal involvement was common: median serum creatinine at presentation was 180 µmol/l; 20% were dialysis-dependent. Induction regimen [cyclophosphamide alone (25.8%), rituximab 500mg x2 (low-dose, 22.3%), rituximab 1g x2 (standard dose, 40%) or rituximab-cyclophosphamide combination (11.9%)] was age-dependent with interaction between age and induction regimen for both infection and mortality outcomes. Younger patients tended to receive the rituximab-cyclophosphamide combination, whereas older patients were more likely to receive low-dose rituximab. 76% of the patients received IV methylprednisolone, 47.1% experienced a serious infection at a median of 12 months [IQR 3-29] and 32.9% died with median time to death of 22 months [IQR 11-43]. After including the interaction effect between age and treatment regimen in the adjusted Cox regression models, methylprednisolone use

remained positively associated with increased risk of infection [HR 4.85, CI 1.22-19.2] but negatively associated with mortality [HR 0.23 CI 0.05-0.99]. There was no interaction between methylprednisolone and age or treatment regimen, respectively, in the applied statistical models.

Conclusion: Use of intravenous methylprednisolone was common in our unit and was associated with serious infection. Avoidance of high-dose intravenous corticosteroid may reduce the high rates of infections that complicate contemporary induction regimens for AAV, especially in elderly patients. Lack of power due to small sample size limited the conclusions which could be awn regarding the outcomes related to specific induction regimen. These data will be available later.

Disclosures: None

334. Biologics in Refractory Vasculitis (BIOVAS)-overview of the clinical trial protocol

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Background/ Objectives: Non-ANCA-associated vasculitides (NAAV) have a combined incidence of ~20/million/year. Currently, treatment strategies in NAAV mirror AAV treatments due to similarities in disease pathogenesis and manifestations (Mukhtyar et al. 2009; Mukhtyar et al. 2009a). One third of NAAV patients have refractory disease, and this subgroup experiences the poorest outcomes, the highest ug related toxicity and is most demanding on health resources (Trieste et al. 2012). The BIOVAS trial will investigate efficacy, safety and cost-effectiveness of 3 biologic treatments in refractory NAAV. The trial design concords with the current treatment pathway based on European League Against Rheumatism (EULAR) consensus statements (Mukhtyar 2009)

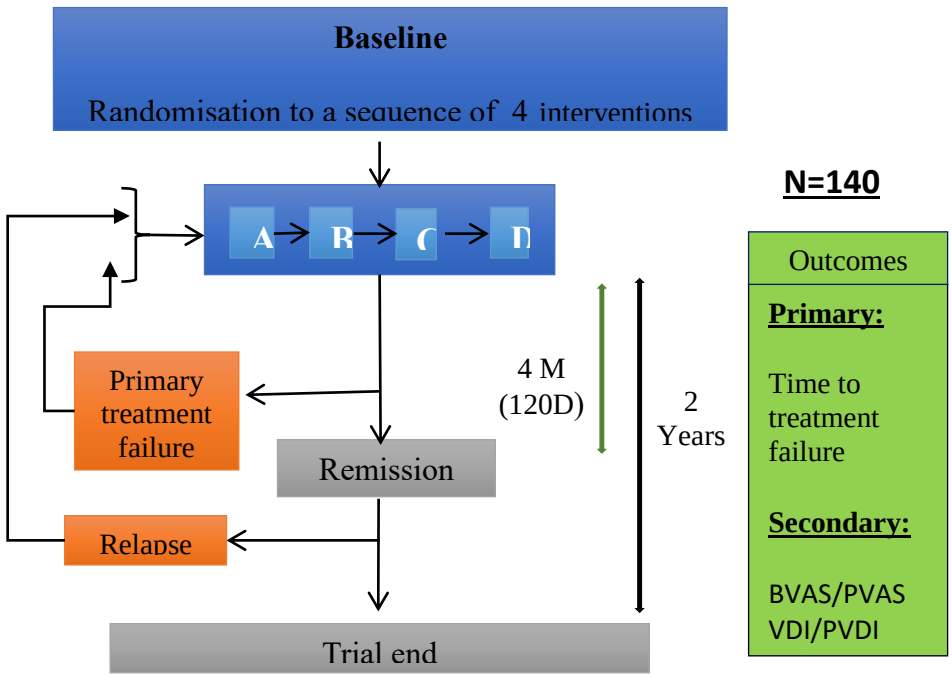
Methods: The BIOVAS trial is a pragmatic, randomised, double-blind, modified-crossover trial in refractory NAAV in adults and chilen. The biologics being studied are: an anti-IL-6 receptor biologic (Tociluzumab), an anti-TNF biologic (Infliximab) and a B-cell depleting biologic (Rituximab). Patients with refractory NAAV aged 5 years or older will be randomised to a randomly generated sequence of 4 blinded interventions: the 3 biologics all administered intravenously as hospital-supplied stock and a placebo administered at the same dosing schedule as one of the three active biologics. Patients initiate first intervention at baseline, and are assessed every 120 days for disease activity and response to treatment. Those who respond continue on the first intervention until failure, severe relapse, or the end of the trial at 2 years. Patients failing to respond to an intervention or experiencing a relapse will be switched to the next intervention in their randomised sequence and continue on the second intervention until relapse, failure to respond or end of trial (figure 1: trial flow diagram). Disease activity

assessment is via a modified BVAS-V3, or PVAS for participants under 16 years of age. Treatment efficacy, and safety outcomes (Serious adverse events and infections) will be analysed. Patient reported outcomes and health resource utility will be recorded, for subsequent health economics analysis. The trial ai to run at multiple centres across the UK and to recruit 140 participants with the following NAAV diseases: GCA, Takayasu's arteritis, Polyarteritis Nodosa (PAN), cutaneous PAN, IgA vasculitis, Cogan's synome, non-infective cryoglobulinaemia, Relapsing polychonitis, and primary angiitis of the central nervous system. The primary end-point is the number of months of response to a specific intervention and each patient will generate 1-4 end-points. A frequentist analysis will compare efficacy of biologics to placebo while Bayesian analyses will explore treatment effects for specific biologics in different vasculitic subgroups. Current status: The trial was activated in June 2021, and to date 1 site is active, with 3 patients randomised. The trial ai to run at multiple centres across the UK and to recruit 140 participants with refractory NAAV.

Conclusions: The BIOVAS trial ai to provide greater evidence for the effectiveness (clinical and cost-effectiveness) of biologic treatments in refractory paediatric and adult patients with NAAV, thereby providing evidence for alternative treatment options to high-dose glucocorticoids.

Disclosures: Maria King (none). David Jayne's disclosures of commercial conflicts for companies with marketed products for 2021 are: Astra-Zeneca, Aurinia, B, Boehringer-Ingelheim, GSK, Janssen, Novartis, Roche/Genentech, Takeda & Vifor. Seerapani Gopaluni-none FUNDING: This study is funded by the National Institute for Health Research (NIHR) HTA programme (project reference 17/83/01). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care

Figure 1: BIOVAS trial flowchart.



335. The effects of plasma exchange in patients with ANCA-associated vasculitis: a systematic review and meta-analysis

Michael Walsh[1], David Collister[2], Linan Zeng[1], Peter Merkel[3], Charles Pusey[4], Gordon Guyatt[1], Chen Au Peh[5], Wladimir Szpirt[6], Toshiko Ito-Hara[7], David Jayne[8]
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Objective: To assess the effects of plasma exchange on important outcomes in anti-neutrophil cytoplasm antibody-associated vasculitis.

Methods: Systematic review and meta-analysis of randomized controlled trials investigating effects of plasma exchange in patients with antineutrophil cytoplasm-antibody associated vasculitis or pauci-immune rapidly progressive glomerulonephritis and at least 12 months follow-up. We searched Medline, EMBASE, and CENTRAL to July 2020. Reviewers independently identified studies, extracted data and assessed the risk of bias using the Cochrane Risk of Bias tool. Meta-analyses were conducted using random effects models to calculate risk ratios and 95% confidence intervals. Quality of evidence was summarized in accordance with GRADE methods. Outcomes were assessed after at least12 months follow-up and included all-cause mortality, end-stage kidney disease, serious infections, disease relapse, serious adverse events, and quality of life.

Results: Nine trials including 1060 participants met eligibility criteria. There were no important effects of plasma exchange on all-cause mortality (relative risk 0.90, 95% CI 0.64 to 1.27; moderate certainty). Data from 7 trials including 999 participants reporting end-stage kidney disease demonstrated that plasma exchange reduced the risk of end-stage kidney disease at 12 months (relative risk 0.62, 95% confidence interval 0.39 to 0.98, moderate certainty) with no evidence of subgroup effects. Data from 4 trials including 908 participants demonstrated plasma exchange increased the risk of serious infections at 12 months (relative risk 1.27, 95% confidence interval 1.08 to 1.49, moderate certainty). The effects of plasma exchange on other outcomes were uncertain and/or considered unimportant to patients. Effects did not vary by degree of kidney function or presence of lung hemorrhage.

Conclusions: For the treatment of antineutrophil cytoplasm-antibody associated vasculitis, plasma exchange has no important effect on mortality, reduces the 12-month risk of end-stage kidney disease but increases the risk of serious infections.

Disclosures: None

336. Plasma exchange and glucocorticoid dosing for patients with ANCA-associated vasculitis: a clinical practice guideline

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Background/Objective: To provide guidance on the role of plasma exchange and the optimal dose of glucocorticoids during remission induction in ANCA-associated vasculitis (AAV) following the publication of the PEXIVAS trial.

Methods: A guideline panel including patients, caregiver, clinicians, content experts, and methodologists produced these recommendations using GRADE and in adherence with standards for trustworthy guidelines. The recommendations are based on systematic reviews. The panel took an individual patient perspective in the development of recommendations.

Results: From the systematic review, plasma exchange had little or no effect on mortality or disease relapse. However, plasma exchange probably reduces the one-year risk of ESKD (graded absolute risk reduction from ~0.4% in those with low risk to ~16.8% in those with high risk) but increases the risk of serious infections (graded from ~2.7% in those with low risk to ~13.5% in those at high risk) at 1 year (moderate to high certainty). The panel agreed the majority (50-90%) of patients with low or low-moderate risk of developing ESKD would consider the har outweigh the benefits, while the majority (50-90%) of those with moderate-high or high risk would consider the benefits outweigh the har For patients with pulmonary hemorrhage without significant kidney involvement, based on indirect evidence, plasma exchange has little or no effect on death (very low certainty) but may have an important increase in serious infections at 1 year (low certainty). The systematic review of different dose regimens of glucocorticoids identified one RCT that enrolled 704 patients. A reduced-dose regimen of glucocorticoid probably reduces the one-year risk of serious infections by ~5.9 % and probably does not increase the risk of ESKD at the follow-up of longer than 1 year (moderate certainty for both outcomes). Based on these data, the panel made a weak recommendation against plasma exchange in patients with low or low-moderate risk of developing end-stage kidney disease (ESKD) (approximate probability ≤ 10% at 1 year), and a weak recommendation in favour of plasma exchange in patients with moderate-high or high risk of developing ESKD (approximate probability > 10% at 1 year). For patients with pulmonary hemorrhage without

impaired kidney function, the panel suggests not using plasma exchange (weak recommendation). The panel made a strong recommendation in favour of a reduced rather than standard-dose regimen of glucocorticoids, which involves a more rapid taper rate and lower cumulative dose during the first 6 months of therapy.

Conclusions: The panel concluded that the majority (50-90%) of fully informed patients with AAV and with low or low-moderate risk of developing ESKD would decline plasma exchange while the majority of patients with moderate-high or high risk would choose to receive plasma exchange. The panel also inferred that the majority of fully informed patients with pulmonary hemorrhage without significant kidney involvement would decline plasma exchange and that all or almost all (at or over 90%) fully informed patients with AAV would choose a reduced-dose regimen of glucocorticoids during the first 6 months of therapy.

Disclosures: None

337. Comparative efficacy and safety of glucocorticoid regimens in patients with ANCA-associated vasculitis: a systematic review

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Background/Objectives: To compare the efficacy and safety of alternative glucocorticoids (GC) regimens as induction therapy for patients with antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis.

Methods: Systematic review of randomized controlled trial (RCTs). Data sources included Medline, Embase, Clinicaltrials.gov and Cochrane Central Register of Controlled Trials up to 10 April 2020. RCTs comparing two (or more) different dose regimens of GC in ANCA-associated vasculitis during induction of remission, regardless of other therapies were eligible. Pairs of reviewers independently screened records, extracted data and assessed risk of bias. Two reviewers rated certainty of evidence using the Grading of Recommendations Assessment, Development, and Evaluation approach.

Results: Of 3912 records identified, full text of two records met the eligibility criteria. Due to the heterogeneity of the populations and dose regimens of glucocorticoids between the two trials, we descriptively presented the two RCTs and did not combine the results using meta-analysis. Compared with the standard-dose regimen, the reduced-dose regimen of GC in both trials may reduce death, risk difference [RD] ranged from -1.7% to -2.1% between the two trials, low certainty), and end-stage kidney disease was not increased (RD ranged from -1.5% to 0.4% between the two trials, moderate certainty). The reduced-dose regimen probably has an important reduction in serious infections at 1 year (RD ranged from -12.8% to -5.9% between the two trials, moderate certainty). The reduced-dose regimen of glucocorticoids probably has

trivial or no effect in disease remission, relapse or health related quality of life (moderate to high certainty).

Conclusions: Reduced-dose regimens vary but compared to regimens considered standard-dose, they may reduce the risk of death serious infections without detrimental effects on the risk of end-stage kidney disease, remission, relapse, or health related quality of life in selected populations.

Disclosures: None

338. Rituximab maintenance therapy in relapsing ANCA-associated vasculitis

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Background/ Objectives: Rituximab (RTX, an anti-CD20 monoclonal antibody) is now used both as an induction and maintenance treatment of ANCA-associated vasculitis (AAV). Several maintenance therapy regimens are used and the optimal treatment management is still discussed. The aim of this study was to review our single-centre experience with the use of RTX in this indication, focused on the long-term prognosis of patients after rituximab withdrawal.

Methods: Maintenance treatment with RTX has been routinely used in all AAV patients with induction RTX treatment (2x1g after 14 days) started after relapse at our department since 2009. RTX was administered preemptively according to the protocol in scheduled intervals (1 gram every 6 months for a total treatment period of 2 years). Basic clinical and laboratory data were evaluated, including examination of humoral and cellular immunity, at 0-3-6 months and then every 6 months.

Results: Rituximab maintenance treatment was initiated in 55 patients with relapsing AAV from January 2009 to December 2018. 34 patients have already completed the therapeutic regimen (28 patients according to the standard protocol, in 6 patients the therapy was extended by 1-2 gra of RTX), 20 patients terminated treatment prematurely (reasons: leaving for renal transplantation or progression to ESKD in 5 patients, insufficient response in 1 patient, stable remission in 8 patients, non-compliance in 2 patients, side effects in 1 patient, new malignancy in 1 patient and death in 2 patients), 1 patient continues the treatment. RTX maintenance therapy was generally well tolerated, with no or only mild side effects, most commonly infectious complications. Hypogammaglobulinaemia below 7 g/l was reported in 33 % of patients, while severe hypogammaglobulinaemia less than 3 g/l was reported in only 2 %. In 34 patients (M / F 18/16, median age 43.5 years, PR3/MPO-ANCA 31/3) who completed the RTX treatment, the median follow-up was 57 (range 12-126) months. The median duration of B

cell depletion after the last RTX dose was 11 months, the median dose of prednisone at the time of the last RTX was 2.5 mg/day and at the end of follow-up 2 mg/day. ANCA levels were mostly (77 % of patients) negative at the end of the scheduled therapy. A total of 17 patients (50 %) developed relapse during subsequent follow-up, the median time to relapse was 20 months after the last RTX dose, with a wide variety. The relapse was treated with RTX re-induction therapy in 82 %, with azathioprine in 12 % and with only corticosteroids in 6 %.

Conclusions: Our study confirmed that RTX is a well-tolerated and effective maintenance treatment for the patients with relapsing AAV. Treatment leads to a long-term stable remission with the opportunity to a dose reduction or discontinuation of corticosteroids, however, despite previous RTX treatment many of the patients still relapse after therapy withawal.

Disclosures: None

339. The effect of upfront methotrexate and 2nd line infliximab on disase activity in Takayasu vasculitis

Birgir Gudbrandsson[1], c. Torhild Garen[1], Oyvind Palm[1]
[1]*Oslo University Hospital, Oslo, Norway*

Background/objectives: Takayasu vasculitis (TAK) is a vasculitis affecting the aorta, its primary branches and less often the coronary and pulmonary arteries(1). The disease course is most often remitting/relapsing or chronic active but some go into longstanding remission on treatment (2, 3). It is known that a large majority of patients with continuous active disease do develop new vascular lesions and have a worse outcome (4, 5). The newly published ACR and EULAR guidelines now recommend an upfront treatment with DMARD followed by TNF or IL-6 inhibitors in resistant cases(6, 7). To our knowledge there is no study that has specifically studied the effect of upfront use of traditional DMARDs or TNF inhibitors as second line treatment on disease activity in TAK, which was the aim of this study.

Methods: Patients were retrieved from a population based cohort database in the South-East Norway(1). Data variables were retrieved from medical chart, laboratory and imaging results (1). All the patients fulfilled either the ACR classification criteria (8) and/or the modified Ishikawa diagnostic criteria for TAK (9). Patients who were immediately started on methotrexate at diagnoses and patients started on infliximab after one DMARD failure were identified. Only patients with at least to follow up visits and imaging were included. Disease activity was assessed using the definition coming from a previous National Institute of Health (NIH) study, which define the clinical status on the basis of 4 elements: 1) systemic features (no other cause identified), 2) elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), 3) features of vascular ischemia or inflammation (such as limb claudication, diminished or absent pulse, bruit, pain over large vessels, asymmetric blood pressure), and 4) new vascular lesion(s) on imaging studies i.e. new stenosis or new dilatation (not previously diagnosed). The active phase was defined as new onset or worsening of 2 or

more of these features. A new lesion in a previously unaffected artery was interpreted as clear sign of active disease. Disease remission was defined as resolution of clinical and laboratory features of active disease and the absence of new vascular lesions on sequential imaging studies. Sustained remission was defined in those who met these conditions for at least six months while on a treatment regimen including prednisone <10 mg/day.
Continuous data are presented as mean with standard deviation or range and categorical data are presented as numbers (percent). The means were compared by independent t-test and the proportions were compared by Chi-square test or Fisher exact as appropriate. The p value of <0.05 was considered significant.

Results: The mean age at disease onset in the total cohort was 30.4 (SD 14) and 33.9 (SD 15) at diagnoses. Follow up time was 11.7 years (SD 11.9). Eighty-six (89%) were female and 19 patients were originated from Asia or Africa (19%). The patients had median 10 visits at our clinic (Oslo University Hospital). During the follow up time 392 and 108 CT angiography, 245 ultrasounds of neck arteries and 198 PET-CT were taken.
Twenty-three patients received Methotrexate (MTXi) immediately at time of diagnoses. They were mean 30.6 (SD 13.9) years old. Seventy-nine percentages were female and 83 % were European Caucasian. The diagnostic delay was mean 16 months (SD 23.4). Seventy percentages had ≤12 month's delay in the diagnoses. The median start dose was 15 mg weekly (range 10-20 mg) and 20 mg at last visit (range 10-20mg). All patients started with parallel Prednisolone therapy, mean 50 mg (range 30-60 mg). The mean treatment duration was 27.6 months (SD 17.5 mts) with total 52 patient years on treatment. At diagnoses the patients had a mean 95 in CRP (SD 88) and 75 in ESR (SD 35). At last visit the CRP had fell to mean 8.7 ($p<0.001$) and ESR to 19 ($p<0.001$). At last visit the mean prednisolone dose was 7.5 mg (SD 4). Nine patients were still taking 10 mg or more prednisolone (39%) and only two were off (8.7%). Twenty-seven patients were started on infliximab (INF) after one DMARD failure. The patients were mean 31.1 (SD 12.7) age old at treatment start, all female and 81% were European Caucasian. A mean 36.2 months (SD 41) went from diagnoses to start of INF treatment. At the start of INF treatment 26 (96.3%) were on Prednisolone and 25 (92.6%) on DMARDs (23 MTX and 2 AZA). Treatment duration was mean 42.4 months (SD 32.6) with total 92 patient years of observation. The start dose was 3 mg/kg in 18 patients and 5 mg/kg in 7 patients every 8th week. Nineteen of 25 (76%) had to increase the initial dose during the treatment time. Maximum dose was 10 mg/kg every 4th week (2 patients). At start of treatment the mean CRP and ESR was 22 (SD 19) and 30 (SD 14) respectively. At las visit the mean CRP had fell to 7 (SD 12) ($p=0.007$) and ESR to 18 (SD 15) ($p=0.001$). Eighty-eight and 69% were still on Prednisolone and DMARDs at last visit. At the start of treatment the mean prednisolone dose was 13.5 mg (SD 8) compared to 8 (SD 8) at last visit ($p=0.02$). In fig 1 one can see the comparison of remission rate and NIH score between MTXi and 2nd line infliximab during follow up.

Conclusions:
In conclusion this retrospective population based observational study provides a novel data on the effectiveness of upfront methotrexate and Infliximab as 2nd line treatment on disease activity during follow up in real life setting. Significantly more patients on infliximab obtained

remission and sustained remission during follow up than patients in the MTXi arm. Based on these results we clinician should probably have a lower threshold to start with infliximab earlier/early in the disease course in TAK patients who do not obtain remission.

Disclosures: none

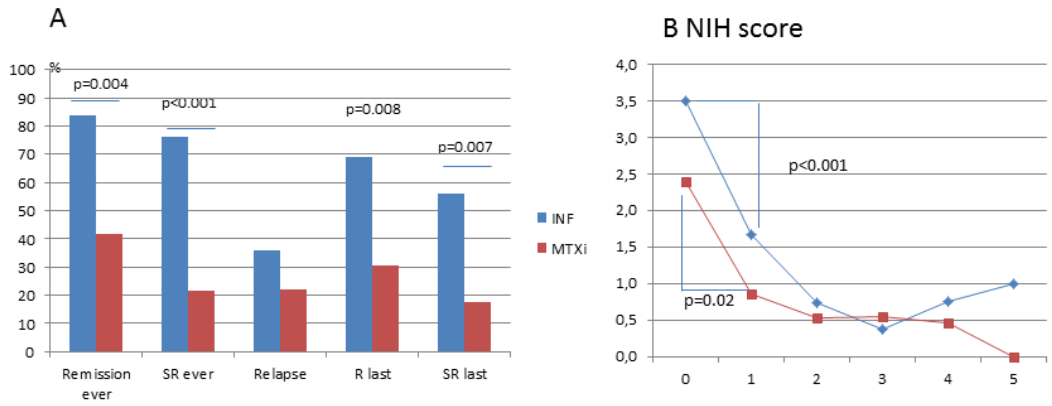

Figure 1. A. Comparison of the effect of Methotrexate and Inflixmab treatment on disease activity. R=remission. SR=sustained remission. B. Mean NIH score during follow up time

340. The effect of upfront methotrexate and 2nd line infliximab on vascular accrual in Takayasu vasculitis

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Background/objectives: Takayasu vasculitis is a vasculitis affecting the aorta, its primary branches and less often the coronary and pulmonary arteries(1). The disease course is most often remitting/relapsing or chronic active but some go into longstanding remission on treatment (2, 3). This has led to that the newly published ACR and EULAR guidelines now recommend an upfront treatment with DMARD followed by TNF or IL-6 inhibitors in resistant cases(4, 5). To our knowledge there is no study that has specifically studied the effect of upfront use of traditional DMARDs or TNF inhibitors as second line treatment focusing on accumulation of vascular damage during follow up, which was the aim of this study.

Methods: Patients were retrieved from a population based cohort database in the South-East Norway(1). Data variables were retrieved from medical chart, laboratory and imaging results (1). All the patients fulfilled either the ACR classification criteria (6) and/or the modified Ishikawa diagnostic criteria for TAK (7). Patients who were immediately started on methotrexate at diagnoses and patients started on infliximab after one DMARD failure were identified. Patients with at least yearly follow up imaging were included. Number of vascular lesions (narrowing/stenosis/occlusion/aneurysm) reported in imaging results at the time of treatment start and during follow up were registrated.

Results: The mean age at disease onset in the total cohort was 30.4 (SD 14) and 33.9 (SD 15) at diagnoses. Follow up time was 11.7 years (SD 11.9). Eighty-six (89%) were female and 19 patients were originated from Asia or Africa (19%). The patients had median 10 visits at our clinic (Oslo University Hospital). During the follow up time 392 and 108 CT angiography, 245 ultrasounds of neck arteries and 198 PET-CT were taken. Twenty-three patients received Methotrexate (MTXi) immediately at time of diagnoses. They were mean 30.6 (SD 13.9) years old. Seventy-nine percentages were female and 83 % were European Caucasian. The diagnostic delay was mean 16 months (SD 23.4). Seventy percentages had ≤12 month's delay in the diagnoses. The median start dose was 15 mg weekly (range 10-20 mg) and 20 mg at last visit (range 10-20mg). All patients started with parallel Prednisolone therapy, mean 50 mg (range 30-60 mg). The mean treatment duration was 27.6 months (SD 17.5 mts) with total 52 patient years on treatment. At the time of MTXi start the patients had total 44 lesions, or mean 1.9 (SD 1.9, range 0-6). Twenty-seven patients were started on infliximab (INF) after one DMARD failure. The patients were mean 31.1 (SD 12.7) age old at treatment start, all female and 81% were European Caucasian. A mean 36.2 months (SD 41) went from diagnoses to start of INF treatment. At the start of INF treatment 26 (96.3%) were on Prednisolone and 25 (92.6%) on DMARDs (23 MTX and 2 AZA). Seventeen of 25 patients (not available in 2) had developed new lesions before INF start. Treatment duration was mean 42.4 months (SD 32.6) with total 92 patient years of observation. The start dose was 3 mg/kg in 18 patients and 5 mg/kg in 7 patients every 8th week. Nineteen of 25 (76%) had to increase the initial dose during the treatment time. Maximum dose was 10 mg/kg every 4th week (2 patients). Eighty-eight and 69% were still on Prednisolone and DMARDs in last visit. The patients had 105 lesions when treatment was started or mean 4.6 (SD 2.9, range 0-12).
During the follow up two patients treated with infliximab (7.4%) developed a total of 2 new vascular lesion compared to 7 patients (30.4%), with total 15 new lesions in the MTXi patients (chi square p=0.04, odd ratio 0.18 (CI 0.03-0.99) (fig 1). The infliximab patients had 2.2 new lesions per 100 patient years compared to 28.8 per 100 patients years in upfront MTX (p<0.001, OR 0.01-0.29)

Conclusions:In conclusion this retrospective study provides novel data on the effectiveness of upfront methotrexate and Infliximab as 2nd line treatment in preventing development of vascular lesions. Despite upfront Methotrexate treatment many patients did develop new lesions within one year. Finding in this study indicate that treatment with Infliximab in addition to prednisolone and Methotrexate is highly effective in preventing development of new lesions and should probably be started earlier in the disease course.

Disclosures: none

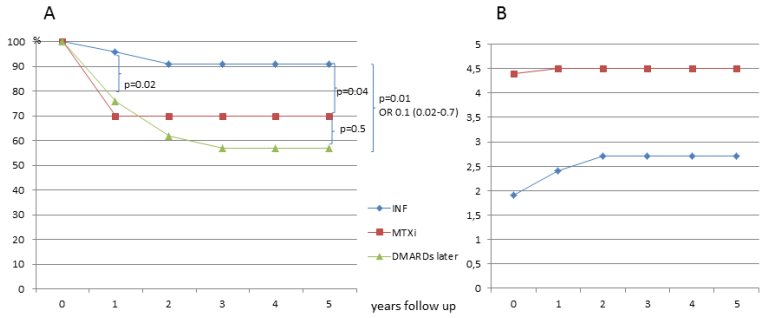

Figure 1 A. Event free time, proportion patients without new vascular lesion on different treatment. INF=infliximab. MTXi= methotrexat treatment startet immediately at time of diagnoses. DMARDs later= includes patients treated with DMARDs at least 6 months after diagnoses. B number of lesion (mean) by follow up years.

341. 2-Mercaptoethane Sodium Sulfonate Prophylaxis in Cyclophosphamide-Treated Patients with ANCA-Associated Vasculitis: Results of an Electronic Survey

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Background/ Objectives: Co-prescribing mesna with CYC for AAV ai to prevent the potential urotoxic effects of CYC. We investigated current clinical practice related to prescribing mesna prophylaxis or not for CYC-treated patients with AAV.

Methods: We searched MEDLINE for publications with the MeSH term “ANCA-associated vasculitis” over a 10-year period. Email adesses of authors were extracted from the online information. These authors were invited by email to participate in an online SurveyMonkey® survey asking about the characteristics of the respondent, their experience with AAV, and their practice in using CYC to treat AAV and in using mesna in CYC-treated patients with AAV and the underlying rationale. We compared 15 response variables to identify factors associated with the use of mesna. Response variables with multiple categories were first analyzed across all categories; if the omnibus test result was significant, additional analyses were used to identify the categories, which were the sources of group separation. Statistical analyses involved Pearson’s chi-square test or Fisher’s exact test. For multiple-response variables, the Rao-Scott correction was applied.

Results: The 139 participants were from 34 countries and were essentially MDs (98%) who mainly worked in rheumatology (50%), nephrology (25%) or internal medicine/immunology (18%). Mesna was given with CYC systematically, never, or on a case-by-case basis by 68%, 19% and 13% of respondents, respectively. As compared with systematic mesna-prescribers, never/occasional mesna-prescribers reported a longer time since receiving their degree (≥ 15 years: 80% vs 50%, P< 0.001), were more frequently based in England/United States (than in France/Germany/Italy) (78% vs 21%, P< 0.001), had longer involvement in care of patients with AAV (≥15 years: 62% vs 37%, P=0.006), had less practice in using intermittent pulse therapy as the exclusive/predominant CYC administration scheme (62% vs 89%, P< 0.001), and, as a rationale underpinning their mesna practice, had less adherence to local operational

procedures (47% vs 73%, P=0.002) or (inter)national management guidelines for AAV (16% vs 49%, P< 0.001).

Conclusions: Practice with regard to prescribing mesna in conjunction with CYC to treat AAV is heterogeneous. Systematic mesna use prevailed over never or occasional use. The decision to prescribe mesna may be based more on circutantial than structural reasons.

Disclosures: None

342. Efficacy of ultra-low dose rituximab for remission maintenance therapy in ANCA-associated vasculitis

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Background: Rituximab (RTX) achieved high remission-induction and sustained maintenance rates for patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). However, RTX is an expensive medication, which may potentially lead to serious side effects. Defining the best dose regimen for maintenance in AAV is still an unmet need. The aim is to compare the effects of ultra-low dose RTX (500 mg or 1000 mg once per year) to standard low dose RTX (500 or 1000 mg twice per year) as remission-maintenance therapy in AAV patients.

Methods: We included AAV patients (classified as GPA and MPA) who successfully achieved disease remission (BVASv3=0) with conventional RTX regimen and have been subsequently treated with RTX for maintenance of remission. All patients received at least two maintenance infusions with 1000 mg or 500 mg, twice per year or once per year. After a period of 18 months, we assessed the effects of ultra-low dose RTX to standard low dose on disease activity (BVAS), damage (VDI), glucocorticoids intake, ANCA status, B-cells depletion, serum IgG levels.

Results: From December 2014 to November 2021, 37 AAV patients (mean age 52, 56.8% female, 97.3% ANCA positive), 28 GPA and 9 MPA, achieved complete disease remission with conventional RTX induction regimen. After 8 [6-13] months, 51.3% patients started maintenance treatment with ultra-low dose RTX (once per year), while 49.7% patients with standard low dose (twice per year), for 18 months. No significant differences at baseline were noted between patients receiving ultra-low dose when compared to those treated with conventional low-dose. At the end of observation period (18 months of follow-up) all patients maintained disease remission (BVASv3=0). Comparing ultra-low dose regimen to low-dose, no differences were noted in negative ANCA rate (50% vs 37 %, p=0.42), ANCA titer (6.8 [0-48] vs 17 [0-47] UI/mL, p=0.55), B-cells depletion rate (88% vs 68%, p=0.15), mean serum IgG (909 vs 821 mg/dL, p=0.32), mean daily glucocorticoid dosage (2 vs 1.5 mg/d, p=0.53) and severe infections rate (11% vs 31%, p=0.28. Patients treated with ultra-low dose had significant lower VDI at the end of observation (4±1.8 vs 2±1.6, p=0.002).

Conclusions: Reduced exposure to RTX was not associated with an impaired efficacy of maintenance therapy in patients with AAV. Remission maintenance with ultra-low dose RTX is safer and more cost-effective option.

Disclosures: None

343. The effects of initial treatment on relapse of ANCA-associated vasculitis in the PEXIVAS trial

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Background: Relapses of granulomatosis with polyangiitis and microscopic polyangiitis, collectively ANCA-associated vasculitis [AAV]), are important health outcomes. We evaluated the effects of plasma exchange (PLEX) and standard- or reduced-dose oral glucocorticoid dosing regimens on relapses in the PEXIVAS trial.

Methods: PEXIVAS was a 2-by-2 factorial randomized controlled trial in patients with severe AAV evaluating the effect of 7 plasma exchanges in 14 days and two regimens of oral glucocorticoids, in addition to standard initial immunosuppression (oral cyclophosphamide, intravenous cyclophosphamide, or rituximab) on the composite outcome of end-stage renal disease or death. In this post-hoc study we evaluated the effects of the randomized treatments on relapses of vasculitis occurring at least 90 days after randomization. Participants were followed for up to 7 years. Analyses were conducted using Cox proportional hazards models adjusted for the randomly assigned treatments and baseline characteristics including initial immunosuppression.

Results: Of the 704 participants in PEXIVAS, 150 (23.3%) experienced at least one relapse. There was no evidence of an interaction between PLEX and glucocorticoid regimen (p=0.41). PLEX did not reduce the risk of relapse (hazard ratio [HR] 0.97, 95% confidence interval [CI] 0.70-1.34). The reduced glucocorticoid regimen did not alter the risk of relapse compared to the standard dose regimen (HR 0.95, 95% CI 0.68-1.32). Compared to intravenous cyclophosphamide, oral cyclophosphamide (HR 0.55, 95% CI 0.36-0.83), but not rituximab (HR 0.75, 95% CI 0.43-1.33) was associated with a reduced risk of relapse. Findings were similar when considering death as a competing risk in sensitivity analyses.

Discussion: In the PEXIVAS trial neither PLEX nor the induction oral glucocorticoid regimen altered the risk of relapse in patients with severe AAV. Treatment with IV cyclophosphamide was associated with a higher risk of relapse.

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MW – Research support from Vifor

344. The effect of different treatment regimens on clinical and 18-F-FDG PET metabolic activity

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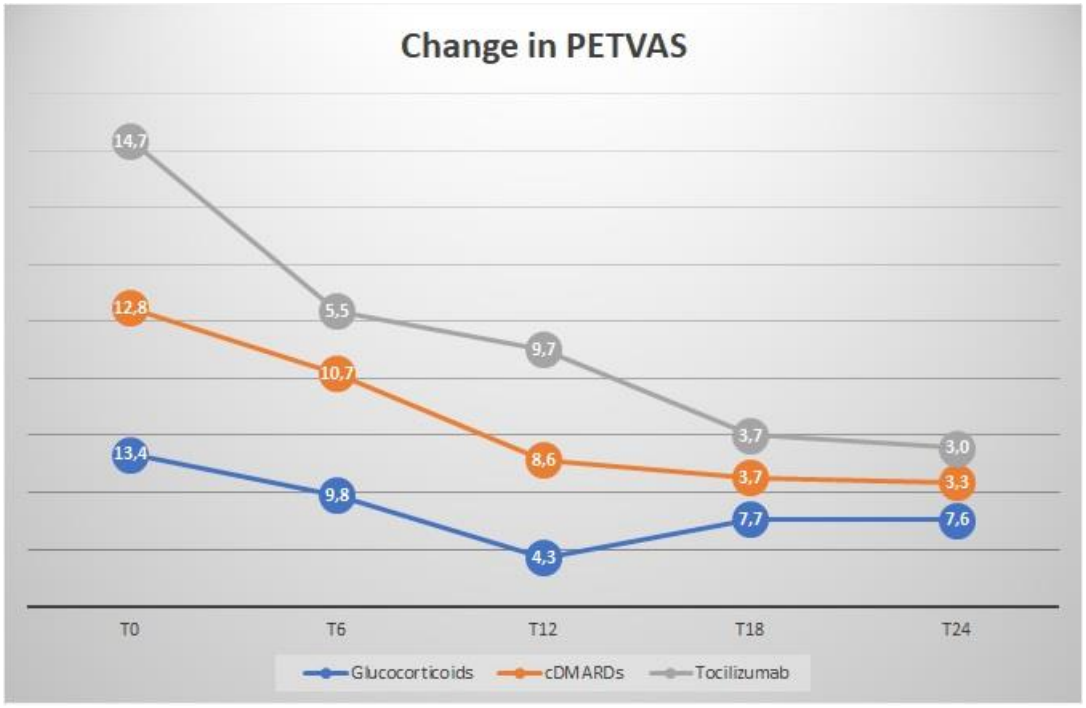
Background: Imaging role in large vessel vasculitis (LVV) patients is tremendously increased in recent years. However, the role of 18-F-FDG PET in evaluating treatment response is still an unmet need. The aim of the present study is to evaluate the effect of different treatment regimens, namely glucocorticoids (GC), conventional disease modifying anti-rheumatic ugs (cDMARDs) and tocilizumab (TCZ), on clinical and metabolic activity.

Methods: Consecutive LVV inpatients and outpatients, classified as giant cell arteritis (GCA), were prospectively enrolled. All patients who underwent to at least 2 consecutive 18-F-FDG PET scan between October 2010 and August 2021. Demographic and clinical data as well as disease activity were assessed before every PET. For each PET scan the vessel's metabolic activity was evaluated using the Meller's grading and the PETVAS score.

Results: The study included 33 patients (age 62 [57-70], 72.7% female) exposed to 51 treatment regimens (n=24 GC, n=16 cDMARDs, n=11 TCZ). A total of 139 18-F-FDG PET scan were conducted (min 2 – max 5). Overall clinical response rate during the follow-up was 70.8% in GC-treated patients, 62.5% in cDMARDs-treated and 90.9% in TCZ-treated (p=0.615). Persistence was comparable among the different treatment regimens (GC 19 [8-27] months vs cDMARDs 13 [7-23] months vs TCZ 18[13-28] months, p=0.439).
All the treatment led to significant reduction of acute phase reactants (GC-treated: ESR 40vs22mmh, p<0.001, ΔESR= -132%, CRP 21vs4.4mg/L, p=0.001, ΔCRP= -129%; cDMARDs-treated: ESR 65vs22mmh,p<0.001, ΔESR= -152%, CRP 49.6vs7.9mg/L, p=0.004, ΔCRP= -118 % and TCZ-treated: ESR 27.5vs9mmh, p=0.155, ΔESR= -141%, CRP 11vs2.5mg/L, p=0.020, ΔCRP= -121%). Significant improvement in PETVAS was observed only in TCZ-treated patients (13vs4, p=0.005, ΔPETVAS= 133%), while the other treatment approaches resulted not significant (GC treated 8vs6, p=0.13, ΔPETVAS= -150%; cDMARDs 12vs6, p=0.086, ΔPETVAS -170%). Daily prednisone dose at last examination was 5 [2.5-10] mg/d in the cDMARDs group vs 2.5 [0-5] mg/d in the TCZ group (p=0.050). Interestingly, at last PET examination a low-grade (Meller 1-2) was observed in 62.5% of GC-treated patients, 43.8% of cDMARDs-treated patients and 63.6% of TCZ-treated patients (p=0.440).

Conclusions: 18-F-FDG PET may be useful in assessing disease activity and monitoring response to therapy. Tocilizumab therapy significantly reduce vessel's metabolic activity over time, when compared to conventional treatment. A persistent low grade uptake during remission is common features in LVV patients, irrespectively of treatment regimens.

Disclosures: None



345. Longitudinal impact (≥ 24months) of Anti-IL5 therapy in Eosinophilic Granulomatosis with Polyangiitis (EGPA)

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Background/ Purpose: In the randomized, placebo-controlled MIRRA trial for relapsing and refractory eosinophilic granulomatosis with polyangiitis (EGPA), adjuvant therapy with 300mg anti-IL5 mAB Mepolizumab [MEPO] for 12 months (M), accrued longer times in remission, reduced steroid exposure and reduced relapse rates[2]. The aim of this study is to analyze the longer term outcomes of 100mg MEPO monthly s/c for a minimum of 24M. Changes to adjuvant immunosuppression and indications for anti-IL5 class switch from MEPO 100mg s/c to Benralizumab (BRZ) or Reslizumab (Res) were assessed.

Methods: In this retrospective descriptive study, 20 EGPA patients received 100mg s/c MEPO every 4 weeks for a minimum of 24M (range 24-43M). Anti-IL5 therapy switched between agents for poor response or intolerance. Time points of assessment included MEPO commencement, 6, 12, 18 and 24 months.

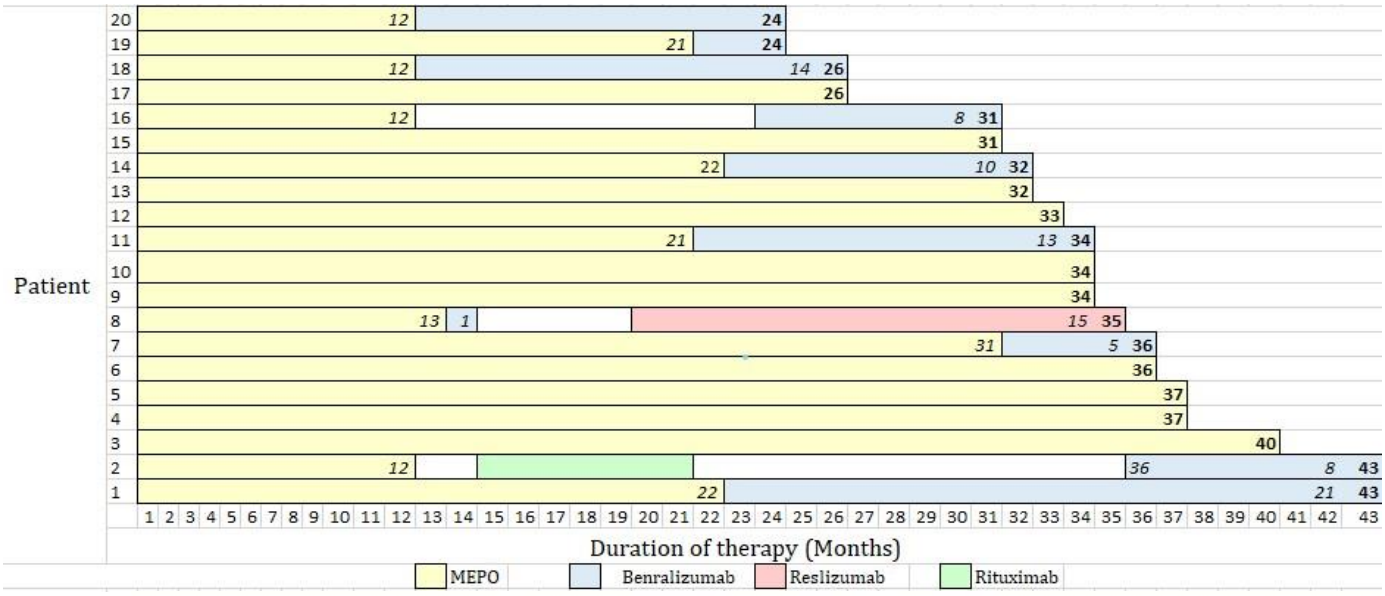
Results: Overall, there was a 50% reduction in steroid usage by 12 months. This continued to reduce to 24M, by which time 2 had withawn steroids and 10 were on

weaning dose ≤ 5mg.The number on adjuvant conventional immunosuppressants (ACIS), reduced over time from 10 at M0 to 4 at M24. Clinical benefits included ANCA serology normalized in all four positive patients by 12 months. Mean eosinophil count reduced from 0.42mg ±0.33 $X10^9$/L at M0 to 0.04±0.03 $X10^9$/L at 12 and 24M. BVAS reduced from median 5 [3-7], to 0 [0-1] by 24M. The change in mean FEV1 over 12 months was from (M0) 2.11±0.66 to (M12) 2.39±0.62 and FVC (M0) 3.42±0.87 to (M12) 3.67±0.93/105.60±20.47 respectively. All 20 EGPA patients receiving anti -IL5 therapy, ranging from 24-43 months remain on therapy. 50% have remained on 100mg s/c MEPO. 10 (50%) have switched to an altenative anti-IL5 agent - 9 switched to benralizumab, 1 initially on benralizumab to reslizumab. 9/10 had achieved partial response prior to switch (reduction in steroids / relapse rate), 1/10 had no response. During the study, 3 patients had a break of therapy, but all resumed anti-IL5 treatment with good response. Hence, all 20 remain on anti-IL5 beyond 24M (range 24 – 43 M).

Conclusion: The relapsing nature of EGPA places a dependency of therapy on steroids. In this study, there was a 50% reduction in steroid dosage by 12 months and steroid requirements continue to decrease to 24 M. By 24 months 2 are steroid free and a further 10 on weaning dose ≤ 5mg. Furthermore, the number on adjuvant conventional immunosuppression reduced over the 24M (n=4 at 24M). This study demonstrates that anti-IL5 therapy serves as a favorable model for steroid and conventional immunosuppressant minimization in EGPA. Clinical benefits of reduction in BVAS, improved pulmonary function tests and reduced serum eosinophilia were recorded.

Disclosures: David Jayne's disclosures of commercial conflicts for companies with marketed products for 2021 are: Astra-Zeneca, Aurinia, BMS, Boehringer-Ingelheim, GSK, Janssen, Novartis, Roche/Genentech,Takeda & Vifor.

Table 1. Anti-IL5 therapy in EGPA [A] Reduction in adjuvant conventional immunosuppression. [B] Duration of anti-IL5 therapy [C] Response to therapy at 24M



Response to therapy by 24 months					
Prednisolone dose	**M0**	**M6**	**M12**	**M18**	**M24**
Mean ±SD	18mg ±10.31	12.26mg ±6.8	9.37mg ± 5.3	9.71mg ±8.1	7.7mg ±7.08
BVAS	**M0**	**M6**	**M12**	**M18**	**M24**
Median ±IQR	5 [3-7]	1.5 [0-2]	1 [0-2]	0.5 [1.25-0]	0 [0 -1]
Eosinophil count N=15		**M0**	**M12**	**M24**	
Mean ±SD		0.42mg ±0.33	0.04±0.039	0.04±0.034	

Adjuvant Conventional Immunosuppression (ACIS)							
Time point (M)	M0	M6	M12	M18	M24	M30	M36
Number of Participants	20	20	20	20	20	16	13
Number on ACIS	10	9	8	7	4	4	4
Number that stopped ACIS	6						
Number starting ACIS	4 (3 subsequently stopped)						
Adjuvant conventional immunotherapy. There is a reduction in ACIS over time							

Non-infections Complications of disease/therapy

346. Arterial stiffness, endothelial dysfunction & impaired fibrinolysis: pathogenic mechanis of cardiovascular risk in ANCA-associated vasculitis

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Background: Cardiovascular disease is a leading cause of morbidity and mortality in anti-neutrophil cytoplasm antibody-associated vasculitis (AAV). Mechanis are poorly understood, and risk-reduction strategies are lacking. AAV is defined by endothelial injury and immune system dysregulation. Endothelin-1 is an endogenous vasoconstrictor that contributes to endothelial function and is regulated by the immune system. The role of endothelin-1 in mediating cardiovascular risk in AAV is unknown. Thus, we assessed endothelial function, endogenous fibrinolysis, arterial stiffness and their relationships to the endothelin and innate immune syste

Methods: In a series of double-blind, randomized case-control forearm plethysmography and crossover systemic interventional studies, we examined arterial stiffness and endothelial function in AAV patients in long-term disease remission and in matched healthy volunteers The primary outcome for the case-control study was the difference in endothelium-dependent vasodilation between health and AAV. The primary outcome for the crossover study was the difference in pulse wave velocity (PWV) between treatment with placebo and selective endothelin-A antagonism. Parallel *in vitro* studies explored mechanism.

Results: *Case-control study:* 32 AAV patients in long-term remission and 32 matched controls were studied. Patients had a mean age of 55□13 years, 23 (72%) were male, 17 (53%) were PR3+ and were a median time from diagnosis of 4 (1-13) years. Compared to health, AAV patients had ~30% reduced endothelium- dependent vasodilation (mean difference: -6.1 mL/100mL of tissue/min, p<0.001) and ~50% reduced acute release of endothelial active tissue plasminogen activator (tPA, mean difference: 29 IU/100mL of tissue/min p<0.001). AAV patients had increased arterial stiffness (PWV: 7.3±1.3 *vs.* 6.4±1.0 m/s, p=0.016). Plasma endothelin-1 was two-fold higher in AAV and independently predicted arterial stiffness and tPA release. *Crossover study:* 24 patients with AAV from the case-control study entered a randomised, double-blind, 3-phase crossover study. Compared to placebo, selective endothelin-A blockade reduced PWV (mean (95% CI) difference: 0.6 (0.4 to 0.8) m/s, *p*<0.001) and increased tPA release in AAV patients. Similar effects were seen with dual endothelin-A/B blockade. *In vitro study:* Patients with AAV had increased platelet activation, more platelet-monocyte aggregates, and altered monocyte endothelin receptor function, leading to reduced endothelin-1 clearance.

Conclusions: AAV patients in long-term disease remission have elevated cardiovascular risk, similar in magnitude to patients with previous myocardial infarction or

advanced kidney disease. Endothelin-1 contributes, and our data support a role for endothelin-blockers to reduce this risk.

Disclosures: None

347. Medication-related emergency department visits and hospitalizations among patients with systemic vasculitis

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Background/ Objectives: Patients with systemic vasculitis take a wide array of medications which place them at particular risk for adverse ug events (ADEs). A knowledge gap exists regarding the contribution of ADEs to emergency department (ED) visits or hospitalizations in vasculitis. Our objective was to determine the rate of ED visits within a cohort of systemic vasculitis patients, and to evaluate the proportion associated with potential ADEs.

Methods: We studied patients enrolled in a longitudinal vasculitis registry between March 2017- February 2020. Data on demographics, disease characteristics, and medications were collected at baseline and annually. Within the cohort, all ED visits and hospitalizations to our centre (from enrolment until December 31, 2020) were identified from medical records. For each ED visit, we recorded reason for ED visit, current medications, and outcomes (diagnosis, disposition). Polypharmacy was defined as taking >5 regular medications concurrently. The primary outcome was the occurrence of an ADE as a primary or secondary reason for the ED visit or hospitalization. Potential ADEs were adjudicated using the 6-point Leape-Bates scale (with scores of 4 representing a probable ADE). Crude event rates of ED visits, hospitalizations, and potential ADE-related ED visits were calculated with 95% confidence intervals, CI.

Results: The cohort comprised 70 patients (24 granulomatosis with polyangiitis, 20 microscopic polyangiitis, 10 eosinophilic granulomatosis with polyangiitis, 4 giant cell arteritis, 5 Behcet's synome, 2 primary angiitis of the CNS, 1 cryoglobulinaemic vasculitis, 4 polyarteritis nodosa). Within the entire cohort, mean disease duration was 7.2 (standard deviation, SD 6.6) years at enrolment. During cohort follow-up (mean of 2.8, SD 0.8, years), 15 ED visits occurred among 11 patients, for a rate of 7.7 visits (95% CI 4.7-12.5) per 100 patient-years. Characteristics of patients with at least 1 ED visit are described in Table 1. At the time of ED presentation, patients took a mean of 8.6 (SD 3.4) regular medications, and all patients took > 5 medications at one or more ED visits. The majority of visits (11/15, 73%) occurred while patients were taking immunosuppressants. Nine of 15 (60%) ED visits required hospital admission (mean length of stay 9, SD 10 days) with the remainder being discharged from the ED. Following chart review, none of the visits were secondary to a vasculitis relapse, and 5

ED visits (33%, 95% CI, 15-58) were associated with potential ADEs (all related to immunosuppressants: 3 infections, 1 probable prion disease, 1 gastrointestinal upset), of which 3 required hospitalization. The rate of potential ADE-related ED visits was 2.6 (95% CI 1.1-6.1) per 100 patient-years.

Conclusions: 1 in 6 patients with established vasculitis (mean disease duration >7 years) visited the ED during cohort follow-up, and one third of these ED visits were potentially ADE-related. Polypharmacy, a known risk factor for ADEs, was extremely common. Further adjudication of medication-related ED visits will help to determine which may have been preventable.

Disclosures: None.

Table 1. Patient characteristics at time of first ED visit during cohort follow-up

Characteristic	N=11
Age, mean (SD)	63.8 (15.2)
Female, n (%)	8 (73)
Diagnosis, n (%)	
Granulomatosis with polyangiitis	3 (27)
Microscopic polyangiitis	4 (36)
Eosinophilic granulomatosis with polyangiitis	1 (9)
Behcet syndrome	1 (9)
Polyarteritis nodosa	1 (9)
Primary angiitis of the CNS	1 (9)
Vasculitis duration, mean years (SD)	6.9 (5.3)
Number of medications, mean (SD)	8.6 (3.4)
Taking > 5 regular medications, n (%)	9 (82)
Current medications for vasculitis, n (%)	
Glucocorticoids	2 (18)
Cyclophosphamide	1 (9)
Rituximab	1 (9)
Azathioprine	3 (27)
Mycophenolate	3 (27)
Methotrexate	1 (9)
Apremilast	1 (9)
Other current medication, n (%)	
Anticonvulsants	5 (45)
Anti-depressants	5 (45)
Anticoagulants	2 (18)
Antiplatelets	3 (27)
Antihypertensives	3 (27)
Antibiotic prophylaxis	2 (18)
Proton pump inhibitor	6 (54)

348. Metabolic synome is associated with increased cardiovascular risk and disease damage in patients with Takayasu

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Objective: Metabolic synome (MetS) is one of the preventable cardiovasculer disease (CVD) risk factors. The aim of this study is to investigate the effect of MetS on CVD and cumulative organ damage in a multi-center, large cohort of TAK patients.
Methods: This is a cross-sectional study involving 192 consecutive TAK patients from 7 tertiary rheumatology centers in Turkey. Clinical data of TAK patients fulfilling the 1990 American College of Rheumatology (ACR) classification criteria were collected from medical records. They were evaluated for risk factors of CVD, disease activity, damage, and MetS at last visits.

Results: Consecutive 192 TAK patients were included in this study. One huned fifty-eight (82%) patients were female, the mean age was 43.3 ± 13 years and mean disease duration was 13.5±9.3 years. MetS was detected in 50 (26%) of patients and CVD was detected in 28 (14.6%). The presence of MetS was detected as an independent risk factor for CVD (p=0.0001). In addition to the mean VDI of the group with MetS was significantly higher than others (4.5±3.3 vs 3.2±2.2, respectively, p=0.004).

Conclusion: The presence of MetS in TAK is an independent risk factor both for increased CVD and disease damage. Awareness and management of MetS can improve disease prognosis in patients with TAK.

Disclosures: None

349. A Systematic Review of AA Amyloidosis Among Patients with Behçet Synome

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Background/ Objectives: Data on patients with Behçet synome (BS) complicated with AA amyloidosis is limited to case reports or case series with a small number of patients. In this study, we aimed to perform a systematic review (SR) of published reports on BS patients with AA amyloidosis.

Methods: PubMed and EMBASE were searched with the keywords "Behcet* AND amyloidosis", without date and language restriction, until May 2020. Two independent reviewers (SNE, GK) performed title/abstract and full text screening and data extraction. A third reviewer (GH) made the final decision in case of disagreement between the two reviewers. Studies that reported patients who were reported by authors as having BS and AA amyloidosis were included. The risk of bias assessment was done using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool.

Results: The systematic literature search yielded 760 articles of which 703 were excluded after title and abstract review. After full-text review, we further excluded 15 duplicate articles and 1 article was added after handsearching the reference lists of the full texts. Finally, we included 43 articles reporting 96 cases. Among these articles, 38 were case reports and 5 were case series reporting between 6 and 14 patients. All patients but 8 were reported from Mediterranean countries. The quality of all articles according to GRADE was very low due to the lack of a control group. The main features of the patients were male predominance (84%), a high frequency of major organ involvement (77.5%) especially vascular involvement (60%), a low frequency of comorbidities predisposing to AA amyloidosis (11.5%), and a very low frequency of gastrointestinal involvement (4%) (Table). All but 8 patients were diagnosed with BS and AA amyloidosis simultaneously. The most common presentation was nephrotic synome. Presenting sympto other than proteinuria were diarrhea (n=2), acute renal failure (n=2), upper gastrointestinal bleeding (n=1), end stage renal disease (ESRD) (n=1), cardiac sympto due to cor pulmonale (n=1), and hypertension (n=1). Renal biopsy (72%) was the most commonly used procedure to diagnose AA amyloidosis. After diagnosing AA amyloidosis, colchicine was initiated in 58 patients, cyclophosphamide in 16, and biologics in 3 (1 anakinra and 2 tocilizumab). In the 67 patients with available data on follow-up, 43% of the patients were followed-up for ≤1 year and median follow-up duration was 20 months (IQR: 4-48). Among the 64 patients with available data, 30 (47%) had developed ESRD. Among the 72 patients with available data on survival status, 30 patients (42%) had died. Ten patients (33%) had died within 6 months, 15 had died after a median follow-up of 48 months (IQR: 24-150), and follow-up duration was not available in the remaining 5 patients including 3 patients whose diagnoses were made by autopsy. Reasons for death were infection (n=7), ESRD (n=6), intractable diarrhea (n=3), pulmonary embolism (n=1), cor pulmonale (n=1), hemorrhage due to pulmonary artery aneurysm (n=1), liver cirrhosis (n=1), gastric cancer (n=1), subarachnoid hemorrhage (n=1), and not reported (n=8).

Conclusions: Male gender and major organ involvement, especially vascular involvement, appear to be risk factors for the development of AA amyloidosis in BS patients. While BS patients complicated with AA amyloidosis have been reported rarely, it is a fatal complication of BS. One third of the patients had died within 6 months after AA amyloidosis diagnosis.

Disclosures: Sinem Nihal Esatoglu has received honorariu for presentations from UCB Pharma, Roche, Pfizer, and Merck Sharp Dohme. Gulen Hatemi has received grant/research support from Celgene and has served as a speaker for AbbVie, Celgene, Novartis, and UCB Pharma. Yesim Ozguler has received honorariu for presentations from UCB Pharma, Novartis, and Pfizer. Emire Seyahi has received honorariu for presentations from Novartis, Pfizer, AbbVie, and Gliead. Vedat Hamuryudan has received grant/research support from Celgene and has served as a speaker for AbbVie, Celgene, Novartis, and UCB Pharma. No other disclosures were reported.

Table 1. Demographic, clinical characteristics and outcome of patients

Characteristic	Systematic review* (n=96)
Male, n, (%)	81/96, (84)
Patients who fulfilled ISG criteria, n/N, (%)	72/80, (90)
Juvenile-onset BS, n/N, (%)	9/49, (18)
Median (IQR) age at BS onset, years	25 (16-33)
Median (IQR) age at BS diagnosis, years	29 (24-35)
Median (IQR) age at AA amyloidosis diagnosis, years	35 (29-44)
Median (IQR) duration since BS to AA amyloidosis diagnosis, years	6 (1-9.25)
Median follow-up duration since AA amyloidosis diagnosis, (months)	20 (4-48)
Patients with a follow up time of less than 1 year (n, %)	29/67 (43)
BS manifestations, n/N, (%)	
Major organ involvement	62/80, (77.5)
Joint involvement	30/71, (42)
Eye involvement	45/77, (58)
Vascular involvement	48/80, (60)
Neurologic involvement	11/71 (15.5)
Gastrointestinal involvement	3/72 (4)
Comorbidities related to AA amyloidosis, n/N, (%)	11/96, (11.5)
Previous medications before AA amyloidosis diagnosis, n/N, (%)	
Colchicine	19/54, (35)
Immunosuppressives	22/54, (41)
Diagnostic tool, n/N, (%)	
Renal biopsy	69/96, (72)
Rectal biopsy	16/96, (17)
Nephrotic proteinuria at AA amyloidosis, n/N, (%)	60/81, (74)
Outcome	
Death	30/72 (42)
ESRD	30/64 (47)

ESRD: end stage renal disease; ISG: International study group criteria; IQR: interquartile range;
* Data on age at BS onset, age at BS diagnosis, age at AA amyloidosis diagnosis, duration since BS diagnosis to AA amyloidosis diagnosis, and follow-up duration since AA amyloidosis were available in 48, 53, 73, 52, and 67 patients, respectively

350. Pneumococcal 13-valent vaccine reactions in patients with Behçet's Synome

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Background: The European League Against Rheumatism (EULAR) recommends pneumococcal 13-valent (PCV13) and 23-valent vaccines in patients with rheumatic diseases (1). Adverse reactions to 23-valent pneumococcal vaccine were previously

reported in patients with Behçet Synome (BS) (2). These were proposed to be associated with the pathergy phenomenon which may be observed in patients with BS.

Objectives: To determine the frequency of adverse reactions to PCV13 in patients with BS who were candidates for TNF inhibitor treatment, together with ankylosing spondylitis (AS) and rheumatoid arthritis (RA) patients as controls.

Methods: All of our patients who are candidates for TNF inhibitor therapy have been offered vaccination with PCV13 since 2016. We surveyed all patients with BS, AS and RA who were vaccinated with PCV13 in our infectious diseases outpatient clinic since 2016. Patients' charts were reviewed and additionally patients were telephoned to identify any adverse local or systemic reactions. Local reactions were defined as redness, swelling, pain, and limitation of arm movement. Systemic reactions were defined as fever, headache, chills, rash, vomiting, joint pain, and muscle pain.

Results: A total of 88 patients with BS, 143 patients with AS and 133 patients with RA had been vaccinated in our infectious diseases outpatient clinic. Among these, 55/88 (62%) patients with BS, 86/143 (60%) patients with AS and all 98/143 (68%) patients with RA could be contacted. Twenty-one of 55 (38%) patients with BS, 18/86 (20%) patients with AS and 27/98 (27%) patients with RA reported at least one local and/or systemic reaction after vaccination. Patients with BS reported more systemic reactions than the other two groups (48%, 12%, 23% respectively). On the other hand local reactions were less common among patients with BS (52%, 88%, 77% respectively). The local reactions were confined to erythema at injection site, pain and difficulty in moving among patients with AS and RA while 2 patients with BS had severe papulopustular skin lesions at injection site, in addition to erythema, pain and difficulty in moving. Both of these patients were pathergy positive at the time of the diagnosis.

Conclusion: Severe papulopustular skin lesions at PCV13 injection site were observed only, but rarely, in patients with BS. Possibility of recall bias due to the retrospective nature of our study and the lack of other vaccines as controls are limitations of our study. Whether the skin lesions are caused by the skin pathergy reaction needs to be studied prospectively, as the pathergy status at diagnosis may be changed by the time these patients become candidates for TNF inhibitor treatment.

Disclosures: Sinem Nihal Esatoglu has received honorariu for presentations from UCB Pharma, Roche, Pfizer, and Merck Sharp Dohme. Gulen Hatemi has received grant/research support from Celgene and has served as a speaker for AbbVie, Celgene, Novartis, and UCB Pharma.

351. Withdrawn

352. Polypharmacy in U.S. Medicare Beneficiaries with Antineutrophil Cytoplasmic Antibody (ANCA) Vasculitis

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Objective: Treatment requirements of antineutrophil cytoplasmic autoantibody vasculitis (AV) and high comorbidity burden among AV patients may lead to higher potential for polypharmacy (i.e., taking ≥5 medications concurrently) and its associated adverse outcomes, including adverse ug events, nonadherence, ug-ug interactions, and higher costs. Medication burden in AV patients has not been well-characterized. In a retrospective cohort study of a national sample of Medicare fee-for-service beneficiaries with AV, we examined prevalence of polypharmacy in the first year after diagnosis overall and among four AV subtypes (microscopic polyangiitis [MPA], granulomatosis with polyangiitis [GPA] without renal involvement, GPA with renal involvement, eosinophilic GPA [EGPA]).

Method: This study used 2015-17 Medicare enrollment data, Part A and Part B medical clai, and Part D prescription ug events to identify incident cases of AV by requiring ≥1 inpatient claim or >1 non-inpatient clai associated with an ICD-10-CM diagnosis code for GPA, MPA, or EGPA in 2016 and no such claim in 1 year prior. Part D records provided data on prescriptions dispensed in outpatient or long-term care settings, while Part B clai provided data on infused medications administered in outpatient settings. We calculated the 91-day period prevalence of polypharmacy (≥5 concurrent medications), by counting the number of unique medications dispensed or administered in the quarter after diagnosis. We further categorized the medication count as high- (≥10 concurrent medications) and moderate- (5 to 9 concurrent medications) polypharmacy. We also calculated the prevalence of polypharmacy for the subsequent three quarters in the first year after diagnosis. We used multinomial logistic regression to compare odds of high and moderate polypharmacy by AV subtype, adjusting for age, sex, race/ethnicity, region of country, and receipt of Medicaid or the Part D low-income subsidy.

Results: We identified 1243 incident cases of AV who remained enrolled in the entire year after diagnosis; 79% were aged ≥65 years, 63% were female, 80% were white, non-Hispanic. A total of 83.8% exhibited polypharmacy in the first quarter (Q1) after diagnosis, followed by 80.5% for Q2, 78.1% for Q3, and 78.8% for Q4. The prevalence of high-level polypharmacy was 40.4% for Q1, 36.0% for Q2, 34.4% for Q3, and 33.6% for Q4. The prevalence of polypharmacy in Q1 among subtypes ranged from 82.09% in GPA without renal involvement to 88.97% in EGPA. The adjusted odds (see Table 1) of high- level polypharmacy in EGPA was higher for all four quarters compared to non-renal GPA, ranging from 1.832 (95% CI: 1.088,

3.082) in Q3 to 2.490 (95% CI: 1.428, 4.341) in Q4; odds of moderate polypharmacy were also higher in Q1 (OR=1.865, 95% CI: 1.018, 3.417). GPA with renal involvement had higher odds of moderate polypharmacy than GPA without renal involvement in Q3 (OR=1.883, 95% CI: 1.231, 2.880) and Q4 (OR=2.144, 95% CI: 1.385, 3.321). MPA patients exhibited no significant differences in polypharmacy across quarters when compared to GPA without renal involvement.

Conclusions: The vast majority of U.S. Medicare beneficiaries with newly diagnosed AV had polypharmacy, with >40% taking 10 or more medications. Polypharmacy was more common in EGPA and GPA with renal involvement, compared to GPA without renal involvement.

Disclosures: None

Table 1. Results of adjusted multinomial logistic regression models for the association between vasculitis disease type and odds of moderate or high polypharmacy, versus no polypharmacy.[1,2]

	Adjusted Multinomial Logistic Regression Results		
	GPA renal OR (95% CI)	MPA OR (95% CI)	EGPA OR (95% CI)
Quarter 1			
Moderate polypharmacy	1.055 (0.668, 1.666)	1.014 (0.645, 1.594)	**1.865 (1.018, 3.417)**
High polypharmacy	1.455 (0.926, 2.285)	1.318 (0.837, 2.076)	**1.918 (1.036, 3.550)**
Quarter 2			
Moderate polypharmacy	1.307 (0.857, 1.994)	0.761 (0.504, 1.149)	1.405 (0.792, 2.493)
High polypharmacy	1.185 (0.757, 1.857)	1.186 (0.781, 1.802)	**2.389 (1.349, 4.231)**
Quarter 3			
Moderate polypharmacy	**1.883 (1.231, 2.880)**	1.443 (0.961, 2.168)	1.357 (0.810, 2.276)
High polypharmacy	1.485 (0.945, 2.333)	1.252 (0.811, 1.932)	**1.832 (1.088, 3.082)**
Quarter 4			
Moderate polypharmacy	**2.144 (1.385, 3.321)**	0.964 (0.644, 1.442)	1.615 (0.933, 2.797)
High polypharmacy	1.589 (0.990, 2.550)	1.315 (0.866, 1.999)	**2.490 (1.428, 4.341)**

[1]Reference category is GPA without renal involvement.
[2]Odds ratios that are statistically significant at the p<0.05 level are shown in bold font.

353. A case of MPO-ANCA vasculitis complicated by haemophagocytic lymphohistiocytosis

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Presentation of Case: A 34 year old white female presented with fever and rigors.
Her history was complex with diagnosis of myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) vasculitis 16 years earlier. At that time, presenting with weight loss, rash, haematoproteinuria and very high titre perinuclear-ANCA and MPO antibodies. In addition, positive speckled anti-nuclear antibody, anti-smith and anti-ribonucleoprotein. Kidney

biopsy showed crescentic nephritis but with immune complexes. She developed pulmonary haemorrhage requiring plasma exchange, IV methylprednisolone and cyclophosphamide. She later experienced atypical sympto including alopecia, angioedema, bilateral hip avascular necrosis, Raynaud's phenomenon and cold-induced urticaria. She stopped mycophenolate maintenance 9 years post-diagnosis until a relapse with haematoproteinuria and pauci-immune focal segmental glomerulonephritis on biopsy, treated with rituximab and azathioprine maintenance, selected due to plans for pregnancy. Her anti-MPO antibody level remained above the maximum lab reported level throughout the entire clinical course.
On this admission she developed persistent pyrexia, 10 days post spinal surgery for disc protrusion. Her clinical status deteriorated, developing headache, abdominal pain, facial swelling and a petechial rash.
Diagnostic Testing: She became pancytopenic. (Haemoglobin: 88g/L; white cell count: 1.7 x10^9/L; absolute neutrophil count: 1.0 x10^9/L; platelets: 12 x10^9/L). CRP: 227mg/L. Fibrinogen 2.8g/L (from 5.5). ESR 35mm/h (from 55). Further testing revealed ferritin 7284ug/L, LDH 933U/L, triglycerides 5.87mmol/L and liver enzyme dysfunction. Serum creatinine: 57mmol/L. Urinary PCR: 194mg/mmol. Blood, urine and sputum cultures were negative. Respiratory viral screen, including COVID-19 PCR, was negative. Parvovirus B19 / EBV / CMV: negative. Abdominal US showed splenomegaly. CT pulmonary angiogram excluded pulmonary embolism or pulmonary vasculitis. MRI spine excluded discitis. Bone marrow aspirate, performed after treatment, was normal.
Differential & Final Diagnosis: Initial diagnosis was infection. However, extensive cultures, screening and imaging did not reveal a source. Other diagnoses considered included vasculitis relapse or systemic lupus erythematosus (SLE) flare given lupoid features historically. The pattern of these features suggested possible SLE/AAV overlap or an underlying genetic immune-dysregulation. The final diagnosis was secondary haemophagocytic lymphohistiocytosis / macrophage activation synome (sHLH/MAS). This hyperinflammatory synome is characterised by fever, splenomegaly and cytopenia and is associated with hyperferritinaemia. HScore[1] was calculated at 257, equating to >99% probability.
Discussion of Management: Our patient received IV methylprednisolone (total 1.5g) and IV immunoglobulin (total 150g) over 3 days, followed by tapering prednisolone. Consideration was given to anakinra but was not required due to rapid response. She subsequently recommenced mycophenolate mofetil maintenance therapy chosen due to features of SLE.
Conclusions: Here we report a case of a patient with atypical MPO-ANCA vasculitis complicated by sHLH/MAS. This association is rare and has been seldom reported in literature. Clinical similarities between infection and autoimmunity can lead to diagnostic delay preventing timely treatment in patients at risk of MAS. This case presents an additional diagnostic challenge with features suggestive of an autoinflammatory disorder suggesting SLE overlap and/or genetic immune dysregulation.

Disclosures: None

354. Safety proile of repeat rituximab treatment in ANCA associated vasculitis: a 10-year single centre study

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Background: Rituximab is a proven effective induction and remission-maintenance treatment in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Hypogammaglobulinemia, infection, and late-onset neutropenia (LON) have been identified as potential adverse events. We conducted a retrospective study to examine the long-term safety ile of repeated rituximab treatment in AAV.

Methods: All patients with AAV treated with rituximab between 1st January 2008 and 31st December 2018 were identified through local dispensary database. Patients were stratified into low (LD) (□4g), medium (MD) (>4g to □8g) and high (HD) (>8g) dose groups according to the cumulative rituximab dose received until 1st October 2019. Baseline characteristics and adverse events including death, opportunistic and serious infections (defined as infections required hospitalization or intravenous antimicrobial), neutropenia (neutrophil count □1.5x10^9/L), hypogammaglobulinemia (IgG level□5.0), and malignancy diagnosed post-rituximab treatment were examined and compared between the groups.

Results: 364 patients (49% male, mean age of 56) received rituximab for AAV treatment. 49% (n=175) had repeated rituximab with 275 treatment courses for relapsing disease and 251 for remission maintenance. 262 (72%), 70 (19%) and 32 (9%) patients were in LD, MD and HD groups, respectively. The median rituximab dose for each group was 2g, 6g and 12g (p<0.001). LD group were older (LD:58-years, MD:50-years, HD:43-years, p<0.001), more likely to have kidney impairment (eGFR<60) (LD:66.4%, MD:38.6%, HD:21.9%, p<0.001) and renal-limited AAV disease compared to MD and HD groups (LD:18%, MD:2.9%, HD:0 p<0.05). Conversely, more ear-nose-throat/ocular limited (40.6% and 12.6%; p<0.05) and PR3-ANCA positive disease (62.5% vs 39.7%, p<0.05) in HD compared to LD group. The median duration of follow up after first rituximab was 47 (IQR:67.2) months. Outcomes (Table1): LD group recorded the highest serious infection rates (LD:14.3/100-Patient-Years (100-PY), MD:8.6/100-PY, HD: 9.2/100-PY, p=0.006). Pneumonia was the leading cause. Herpesvirus (e.g.Herpes Zoster/Herpes Simplex) reactivations were the commonest opportunistic infections across three groups.

Hypogammaglobulinemia incidence was comparable across groups (LD:3.2/100-PY, MD:1.9/100-PY, HD:2.9/100-PY). Age (61 vs 55-years-old, p<0.01), concurrent cyclophosphamide (81% vs 54%, p<0.01) and kidney impairment (75% vs 54%, p<0.01) were risk factors for hypogammaglobulinemia. Neutropenic incidence was higher in LD group (LD:10.1/100-PY, MD:3.0/100-PY, HD:6.8/100-PY, p=0.01). 127/134 neutropenic events were related to concomitant immunosuppressants or illnesses. 5 (LD:3 and HD:2) met definition of rituximab-related-LON. There was no difference in malignancy rate between groups

(LD:1.4/100-PY, MD:2.6/100-PY, HD:0.7/100-PY, p=0.13). The commonest reported new cancers were skin (48%) and breast cancer (14.8%). 58 patients died with comparable mortality rate between LD and MD group (82% survival at 30-month after last rituximab). Conversely, there were no deaths in HD group. Infection was the major cause of death (41.4%).

Conclusions: In this single-centre AAV cohort, repeated rituximab treatment was more common in younger patients and those with ENT involvement. We did not observe an increased incidence of adverse events with increasing cumulative rituximab exposure. This likely reflects both underlying disease features and physician bias in patient selection for repeat treatment. Our data suggests that in selected patients, extended periods of rituximab treatment might be safe.

Disclosures: none

Table 1: Adverse events for each cumulative rituximab dose group

Events following rituximab initiation	All patients (N=364)	LD: ≤4g (N=262)	MD: >4-8g (N=70)	HD: >8g (N=32)	P-value
Serious infection (events, N)	209	145	37	27	
Number of patients (N,%)	122(33.5%)	80 (32.1%)	17 (28.6%)	15 (37.5%)	
Incidence, per 100-PY (95%CI)	12.1 (1.1-1.4]	14.3 (12.2-16.9)	8.6 (6.3-11.9)	9.2 (6.6-14.1)	<0.01
Types of infections (N,%)					
Pneumonia	109 (65%)	72 (49.7%)	26 (70.2%)	11 (40.7%)	
Septicemia/ viraemia	45 (21.5%)	35 (24.1%)	5 (13.5%)	6 (22.2%)	
Gastrointestinal	25 (11.9%)	17 (11.7%)	4 (10.8%)	4 (14.8%)	
Urinary	14 (6.7%)	12 (8.3%)	0	2 (7.4%)	
Skin	9 (4.3%)	5 (3.4%)	1 (2.7%)	2 (7.4%)	
ENT	4 (1.9%)	1 (0.7%)	1 (2.7%)	2 (7.4%)	
Musculoskeletal	3 (1.4%)	3 (2.1%)	0	0	

Opportunistic infection (events, N)	47	31	8	8	
Number of patients (N,%)	43 (11.8%)	30 (11.5%)	7 (10%)	6 (18.8%)	
Incidence, per 100-PY (95%CI)	2.7 (2.1-3.6)	3.2 (2.2-4.5)	1.9 (0.9-3.7)	2.9 (1.2,5.6)	0.42
Events by pathogens (N,%)					
Pneumonitis	3 (6.4%)	2 (6.5%)	1 (12.5%)	1 (12.5%)	
Cytomegalovirus	1 (2.1%)	0	1 (12.5%)	0	
Herpes Simplex Virus	5 (10.6%)	5 (16.1%)	0	0	
Pneumocystis Jirovecii	4 (8.5%)	3 (9.7%)	0	0	
Aspergillus	1 (2.1%)	0	1 (12.5%)	1 (12.5%)	
Mucormycetes	1 (2.1%)128	1 (3.2%)	0	0	
Candida	2 (4.3%	2 (6.5%)	0	0	
Viremia - Cytomegalovirus					
Gastrointestinal	2 (4.3%)	2 (6.5%)	0	0	
Hepatitis C & E	1 (2.1%)	1 (3.2%)	0	0	
Candida					
Skin	1 (2.1%)	1 (3.2%)	0	0	
Varicella Zoster Virus	17 (36.2%)	8 (25.8%)	3 (37.5%)	6 (75%)	
Herpes Zoster Virus^	9 (19.1%)	6 (19.4%)	2 (25.0%)	1 (12.5%)	
Herpes Simplex Virus^					
Hypogammaglobulinemic (events, N)	46	36	8	2	
Number of paptients (N,%)	46 (12.6%)	36 (13.7%)	8 (11.6%)	2 (6.4%)	
Incidence, per 100-PY (95%CI)	2.7 (2.0-3.6)	3.6 (2.5- 4.9)	1.9 (0.8-3.7)	0.7 (0.1-2.6)	0.25
	19 (5.2%)	15 (5.7%)	4 (5.8%)		

Persistent (N,%)	27 (7.4%)	21 (8.0%)	4 (5.8%)	0	
Spontaneous recovery (N,%)	7 (1.9%)	3 (1.1%)	3 (4.3%)	2 (6.5%)	
Relapse (N,%)	7 (1.9%)	4 (1.5%)	2 (2.9%)	1 (3.2%)	
IVIG treatment (N,%)				1 (3.2%)	
Neutropenic (events, N)	134	102	13	19	
Number of patients (N,%)	97 (26.7%)	79 (30.2%)	11 (15.8%)	7 (21.9%)	
Incidence, per 100-PY. (95%CI)	7.8 (6.5, 9.2)	10.1 [8.2, 12.2]	3.0 (1.6, 5.2)	6.8 (4.1, 10.6)	0.01
Late onset neutropenia (N, %)	5 (3.7%)	3 (2.9%)	0	2 (10.5%)	
Other ugs/IST related	118 (88.0%)	88 (86.3%)	13 (100%)	17 (89.5%)	
Concurrent illnesses	8 (5.9%)	8 (7.9%)	0	0	
>12 months post last RTX	3 (2.2%)	3 (2.9%)	0	0	
Malignancies (events, N)	27	14	11	2	
Number of patients (N,%)	24 (6.6%)	14 (5.3%)	9 (12.9%)	1 (3.1%)	
Incidence, per 100-PY (95%CI)	1.6 (1.0-2.3)	1.4 (0.8-2.3)	2.6 (1.3-4.6)	0.7 (0.1-2.6)	0.13
Non melanoma skin cancer	10 (37.0%)	5 (35.7%)	4 (36.4%)	1 (50%)	
Breast	4 (14.8%)	0	4 (36.4%)	0	
Melanoma	3 (11.1%)	1 (7.1%)	1 (9.1%)	1 (50%)	
Urothelial Transitional Cell	3 (11.1%)	2 (14.3%)	1 (9.1%)	0	
Haematological	2 (7.4%)	2 (14.3%)	0	0	
Renal Cell	1 (3.7%)	1 (7.1%)	0	0	
Colorectal	1 (3.7%)	1 (7.1%)	0	0	
Lung	1 (3.7%)	1 (7.1%)	0	0	
Prostate	1 (3.7%)	0	1 (9.1%)	0	

Oesophagus	1 (3.7%)	1 (7.1%)	0	0

^ Infections from reactivation of Herpes Zoster and Herpes Simplex Virus that did not meet criteria for serious infections

355. Retrospective observational study on the long-term safety of Rituximab in ANCA associated Vasculitis (RIVAS)

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Background/ Objectives: To assess the long-term safety of rituximab in a retrospective, secondary use-of-data study in patients with Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA) by (a) estimating the incidence of serious adverse events (SAEs) and (b) comparing those incidence rates between a rituximab-treated cohort and a control cohort treated with other available therapies.

Methods: Patients in both cohorts were followed by review of their medical records from baseline to study end (30 Sept 2018): baseline was defined by the date of first rituximab treatment since 2003 (rituximab cohort) and time of first disease flare/diagnosis since 2003 (controls). Details of all documented SAEs and adverse events of specific interest including infusion related events, hypogammaglobulinemia or neutropenia were recorded every 12-18 months. Primary endpoint (time to first SAE) is presented along with composite endpoints and repeated event analysis using survival models and regression analyses.

Results: Overall, 392 patients (77% with GPA and 23% with MPA) were included in the study (247 rituximab-exposed patients, 145 control patients) with a total of 2,217 patient years (PY, mean study duration 5.7 years). The study population was 52% female and 93% white-British, with a mean ± SD age of 60.9 ± 16.3 years. Rituximab patients received a mean of 7.2 infusion doses (ranging from 1 to 23). Significant baseline imbalances between the two cohorts were found. The rituximab cohort had greater levels of comorbidities, a more complex medication history and longer mean disease duration ± SD at baseline: 54.7 months ±70.9 compared to 33.2 months ± 63.8 (control). A total of 557 events occurred in 164 patients of the rituximab cohort (66.4%) and 185 events in 78 control patients (53.8%). Cohort imbalances will be accounted for by covariate analysis. Estimated incidence rates for infections, cardiovascular events and malignancies will be presented by cohort.

Conclusions: With a long follow-up period and control cohort comparison, the findings of the RIVAS study will provide a good indication on long-term safety of Rituximab in patients with Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA).

Disclosures: David Jayne's disclosures of commercial conflicts for companies with marketed products for 2021 are: Astra-Zeneca, Aurinia, B, Boehringer-Ingelheim, GSK, Janssen, Novartis, Roche/Genentech, Takeda & Vifor.The RIVAS study was funded by Hoffmann la Roche. We also acknowledge Simon Bond & Marianna Nodale of Cambridge Clinical Trials Unit.

356. Withdrawn

Infectious complications of disease / therapy

357. Bronchitis in patients receiving prolonged rituximab for ANCA-associated vasculitis

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Background/ Objectives: Pulmonary complications from B cell depletion with rituximab remain with limited description in the literature. Our objective is to describe the frequency and risk factors for development of cough attributed to bronchitis in patients receiving prolonged rituximab.

Methods: We conducted a single-center retrospective cohort study of 113 adult patients with AAV who had continuous B cell depletion with rituximab for greater than 24 months. The primary outcome measure was an episode of cough measured with an ordinal scale as follows: 0 = no cough; 1 = daily cough, non-productive; 2 = cough with sputum production once daily; 3 = cough with sputum production twice or more daily. Secondary outcome measures included serum immunoglobulin G (IgG) level, sputum culture results, and antibiotic use for bronchitis. Univariate logistic regression analysis was used to assess the odds ratio of developing cough with smoking status, nadir IgG level, length of time on continuous B cell depletion, and lung involvement of AAV as independent variables.

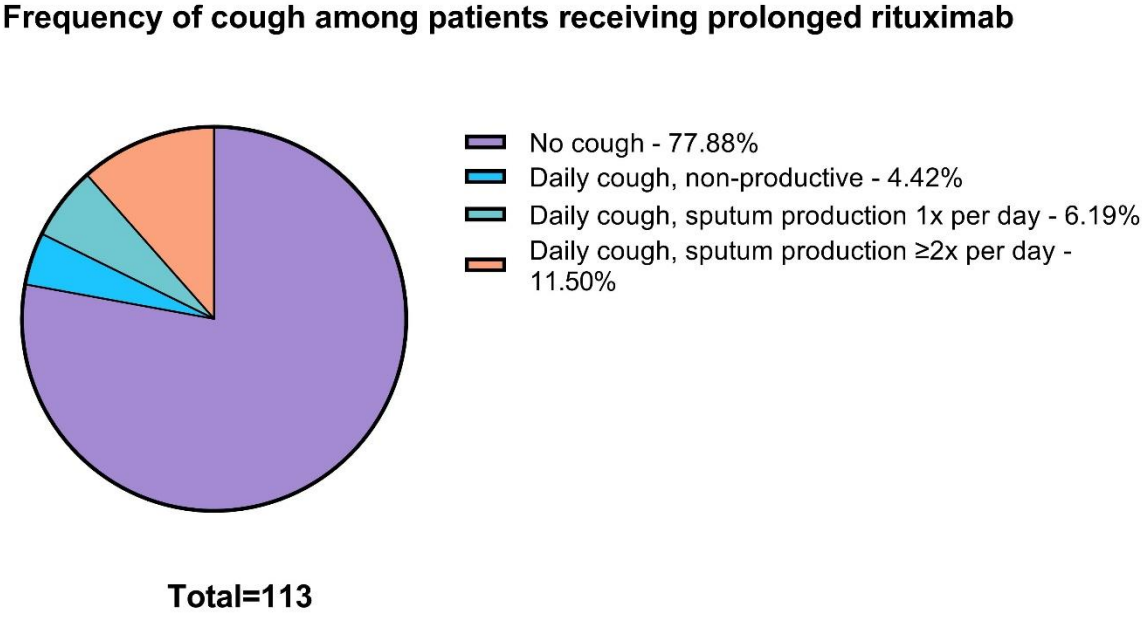
Results: Of the 133 patients, the mean age was 57 years and 47% (n = 53) were female. The median (IQR) duration of continuous B cell depletion was 3.4 years (2.7 – 5.2). The ANCA serotype was PR3 in 62 patients (54.9%), and MPO in 51 patients (45.1%). Fifty-four patients

(47.8%) had lung involvement as part of AAV. Five patients (4.5%) and 43 patients (38.4%) were current and former smokers, respectively, while the remainder never smoked. A y cough was observed in 4.2% of patients (n = 5). A daily cough with sputum production once daily was observed in 6.2% of patients (n = 7). A daily cough with sputum production twice or more daily was observed in 11.5% of patients (n = 13). A specimen for sputum culture was obtained in 25 patients, 12 (48%) of which were positive for a bacterial organism. The most common was Haemophilus influenzae (n = 2). Antibiotics for suspected bacterial bronchitis were used in 19.5% of patients (n = 22). The median nadir IgG level was 675 mg/dL (521 – 798). No patient required intravenous IgG supplementation. In a univariate logistic regression model, the smoking status, nadir IgG level, length of time on continuous B cell depletion, and lung involvement of AAV were not associated with an increased odds of developing a cough.

Conclusions: Cough attributed to bronchitis was observed in approximately one-fifth of patients with AAV on prolonged B cell depletion with rituximab.

Disclosures: None.

Figure 1.



358. Effectiveness of antimicrobial prophylaxis strategies in ANCA vasculitis: a scoping review of current evidence

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Objective: Severe infections associated with use of strong immunosuppressive medication are a leading cause of morbidity and mortality in patients with ANCA vasculitis (AV). Treatment guidelines for AV conditionally recommend prophylaxis against *Pneumocystis jirovecii* pneumonia (PJP) with trimethoprim/sulfamethoxazole (TMP/SMX), but note the lack of robust, high quality evidence directly adessing prophylaxis strategies in AV patients. We conducted this scoping review to map the extent and type of evidence currently available to inform decisions about infection prophylaxis strategies in AV, in order to identify gaps in knowledge and guide the design of future studies.

Method: The Preferred Reporting Ite for Systematic Reviews and Meta-Analysis – extension for Scoping Reviews (PRISMA-ScR) guided our approach. We conducted a comprehensive search of six databases, and reference lists of reviews identified through this search, to identify original research studies published in English between January 1,2000 – July 31, 2020. We included studies that reported the effect of any type of antimicrobial infection prophylaxis strategy (compared to no treatment or another prophylaxis strategy) on infection-related outcomes in AV patients being treated with immunosuppressive medication for remission induction or maintenance. Studies were screened in duplicate for inclusion in two stages (abstract and full-text review) by four researchers using a blinded approach. Data was extracted by two reviewers, with differences resolved via consensus in consultation with a third reviewer.

Results: Nineteen studies met inclusion criteria, including two randomized trials and 17 cohort studies. Sixteen studies were restricted to AV patients only, while three studies included AV patients alongside patients with other for of vasculitis or autoimmune conditions. Most studies included small samples, with seven studies consisting of fewer than 100 patients, and all but two studies with fewer than 200 participants. TMP-SMX was the most commonly assessed prophylactic strategy, and was most often compared to no prophylaxis (8 studies). Eight other studies compared the effect of receiving any prophylaxis with at least one of multiple agents (e.g., TMP-SMX, pentamidine, dapsone, mupirocin, ciloxacin, antifungals, and/or antivirals) to no prophylaxis. Three studies compared use of antiviral agents to no prophylaxis. In the cohort studies, the proportion receiving prophylaxis with the agent(s) studied was highly variable, ranging from 17% to 92%. Studies were also heterogeneous with regard to specific outcomes studied. The most common outcomes included *pneumocystis jirovecii* pneumonia (PJP), serious infections (e.g., requiring hospitalization or intravenous antibiotics), or any infection; other outcomes included specific types of infections (e.g., cytomegalovirus reactivation, herpes zoster, fungal infections), disease relapse, mortality, adverse ug events, and chronic staphylococcus aureus nasal carriage. Most cohort studies included no or very limited control of potential confounding factors.

Conclusion: This scoping review suggests widespread variation in use of recommended and alternative infection prophylaxis strategies in AV. Larger, controlled investigations are critically needed to compare the effectiveness of guideline-recommended TMP-SMX prophylaxis and alternative antibacterial, antiviral, and antifungal strategies, particularly with emerging novel immunosuppressive therapies and approaches to minimize corticosteroid use. Such evidence

is needed to develop more comprehensive and robust recommendations about infection prophylaxis strategies for AV patients, similar to those that exist for other immunocompromised patient populations.

Disclosures: None

359. Pneumocystis jirovecii pneumonia (PJP) among incident cases of giant cell arteritis and polymyalgia rheumatica

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Background: Prophylaxis against pneumocystis jiroveci pneumonia (PJP) has been conditionally recommended for patients with small vessel vasculitis who are receiving moderate doses of glucocorticoids and either rituximab or cyclophosphamide. Patients with giant cell arteritis (GCA) or polymyalgia rheumatica (PMR) also receive moderate-high doses of glucocorticoids after diagnosis and may be at an elevated risk of PJP. The objective of this study was to describe the incidence of PJP among patients on treatment for newly diagnosed GCA or P

Methods: A retrospective cohort study was conducted using data from the TriNetX (Cambridge, MA, USA) electronic health records database, which includes records from multiple United States health organizations. Patients with GCA were identified using validated case-finding algorith (PPV 79%), which required (1) 2 encounters with GCA diagnostic codes (ICD-9-CM 446.5/ICD-10 M31.6 or M31.5) that occurred at least 30 days apart and (2) at least one moderate-high dose prednisone prescription (greater than or equal to 20mg/day of prednisone or one dose of 500mg or greater intravenous methylprednisolone). Patients with Pwere identified using 2 encounters with a Pdiagnostic code (ICD-9-CM 725/ICD-10 M35.3) at least 30 days apart, any dose of prednisone, and not meeting the criteria for GCA. The index date was defined as the first date of moderate-high dose prednisone for GCA and the first date of any prednisone prescription for P PJP infection was defined by any encounter with a diagnostic code for PJP (ICD-9-CM 136.3/ICD-10 B59) or any positive beta-d-glucan test for PJP within 1 year of the index date. Patients who were under 50 years of age at the index date or had any PJP code within the year prior to the index date were excluded. Comorbidities were identified using validated ICD-9/ICD-10 codes, and comorbidity burden was calculated using the Charlson comorbidity index (CCI). Follow up time was calculated with respect to person-years and limited to 1 year after the index date.

Results: We identified 1,450 incident cases of GCA (index-year follow-up time of 1,254 patient-years) and 23,935 incident cases of P(index-year follow-up time 21,448 patient-years). The mean age for GCA was 73.6 (SD 8.2) and the mean age for Pwas 71.9 (SD 8.5). The majority of patients were female (68% GCA, 59% PMR) and reported white (79% GCA, 85% PMR) or black (9% GCA, 6% PMR) race/ethnicity. Common comorbidities at baseline included chronic obstructive pulmonary disease (34% GCA, 24% PMR), diabetes without complication

(28% GCA, 20% PMR), renal disease (20% GCA, 13% PMR), and congestive heart failure (18% GCA, 11% PMR). The mean weighted CCI was 3.2 (SD 2.8) for GCA and 2.6 (2.2) for P A minority of patients received trimethoprim-sulfamethoxazole or dapsone for presumed prophylaxis (14% GCA, 5% PMR). One case of PJP was identified among patients with GCA for an incident-rate of 0.80 cases per 1,000 patient-years. Eight cases of PJP were identified among patients with Pfor an incident-rate of 0.37 cases per 1,000 patient-years. Two of the patients who contracted PJP died within the index year, both of whom had a diagnosis of PMR, did not receive bactrim prophylaxis, and died within 30 days of PJP diagnosis.

Conclusions: In this large analysis of an electronic health records database, PJP was a rare complication in patients with newly diagnosed GCA or P These data do not support routine prescribing of PJP prophylaxis for either group of patients, but additional studies with a better-characterized patient population should be conducted.

Disclosures: Michael Putman is supported by a Rheumatology Research Foundation Scientist Development Grant

Table 1: Demographic and clinical characteristics of included patients, n = 11,668

Characteristic	GCA (n = 1,748)	P(n = 9,920)
Age at Diagnosis, mean (SD)	73.6 (8.2)	71.9 (8.5)
Sex		
Male	462 (32%)	9,869 (41%)
Female	988 (68%)	14,064 (59%)
Race/Ethnicity		
White	1,149 (79%)	20,386 (85%)
Black or African American	128 (9%)	1,318 (6%)
Hispanic or Latino	80 (6%)	382 (2%)
Asian	20 (1.4%)	132 (1%)
Other / NA	73 (5%)	1,719 (7%)
Comorbidities		
Chronic Obstructive Pulmonary Disease	494 (34%)	5,751 (24%)

Diabetes without complication	405 (28%)	4,829 (20%)
Renal Disease	289 (20%)	3,019 (13%)
Congestive Heart Failure	259 (18%)	2,526 (11%)
Liver Disease	130 (9%)	1,355 (6%)
Charlson Comorbidity Index, mean (SD)	3.2 (2.8)	2.6 (2.2)
Medications*		
Tocilizumab	139 (10%)	101 (0%)
Methotrexate	148 (10%)	2,281 (10%)
Trimethoprim-Sulfamethoxazole	189 (13%)	1,148 (5%)
Dapsone	13 (1%)	41 (0%)
* Restricted to medications received during the index-year		

Outcome measures

360. Outcomes in ANCA-associated vasculitis: validating a renal risk score and examining the impact of deprivation

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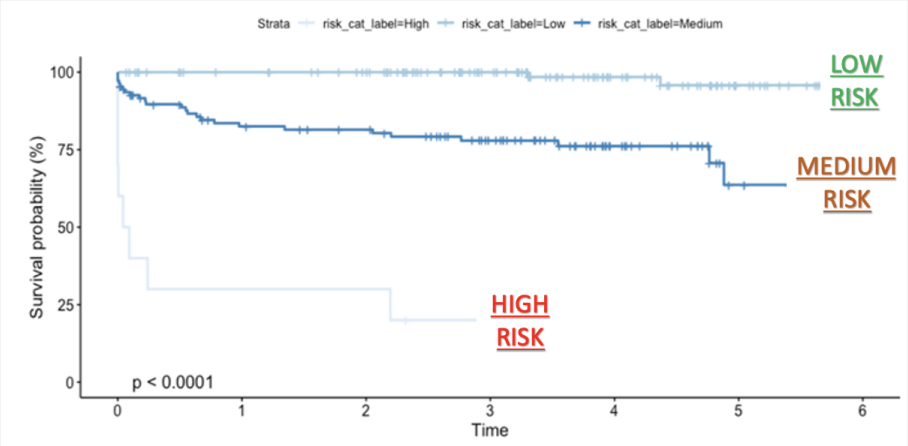
Background/Objectives: Predicting outcomes in ANCA-associated vasculitis (AAV) can be challenging. Using our national cohort of patients who have had AAV confirmed on kidney biopsy, we aimed to validate an ANCA renal risk score (ARRS) which utilises histopathological and biochemical data to predict outcomes[1]. We then used the same cohort to answer an important epidemiological question - whether deprivation is associated with poorer outcomes in AAV.

Methods: The Scottish Renal Biopsy Registry is a complete national dataset of all kidney biopsies performed in Scotland. First kidney biopsies performed between 2014 and 2017 inclusive, with evidence of AAV, were included. Demographic and histological data and

outcomes including relapse, end-stage kidney disease (ESKD) and death were recorded. The ARRS is an aggregate of individual scores incorporating the percentage of normal glomeruli, the percentage of tubular atrophy/interstitial fibrosis and eGFR (CKD-EPI) at time of biopsy. Then, depending upon aggregate score, patients are assigned to a high, medium or low risk group. For deprivation, the validated Scottish Index of Multiple Deprivation (SIMD) was used as a measure of relative socioeconomic deprivation for each patient. Patients were assigned to deprivation quintiles, ranked from 1st (most deprived) to 5th (least deprived). Cox proportional hazard models were created for survival to ESKD, relapse and death and stratified by ARRS group and then SIMD quintile. Statistical analyses were conducted using R software.

Results: There were 241 patients eligible for inclusion: 38 (15.8%) relapsed, 35 (14.5%) progressed to ESKD and 54 (22.4%) died. Mean age at biopsy was 66.7±12.2 years and 52% (n=129) were male; this was similar across the risk groups. Patients were stratified into low (n=123 (50%)), medium (n=112 (46%)) and high (n=11 (5%)) ARRS groups respectively. Within the high-risk group, mean eGFR was lower (high 8.6±6.1 versus low risk 45.7±26.0 ml/min/1.73m2, p<0.001). Proteinuria levels were higher (high 405 (IQR 170-767) versus low risk 81 (IQR 41-155) mg/mmol, p<0.001). Ninety-one (38%) were PR3 antigen positive and PR3 positive patients were over-represented in the high risk compared with the low risk group (70% versus 43% respectively; p=0.006). High risk patients were more likely to receive plasma exchange (80% versus 9%; p<0.001) and/or haemodialysis (70% versus 2%; p<0.001) compared with low risk patients. Relapse was progressively less common with increasing ARRS (low risk: 21.3%; medium risk 11.0%; high risk 0.0%; p=0.038). On Cox proportional hazards analysis, the need for initial kidney replacement therapy (HR 4.6 (95% CI 1.4-14.7); p=0.011) and ARRS (medium risk: HR 9.3 (95% 2.1-42.1) p=0.004; high risk: HR 29.9 (95% CI 3.7 – 239.7) p=0.001) were associated with higher risk of ESKD. High ARRS was associated with a trend towards increased risk of death (HR 1.14 (95% CI 0.99-1.31); p=0.073). There was a trend towards those in the least deprived quintile being older. Otherwise, no significant difference between deprivation quintiles was observed for baseline demographics, presence of pulmonary haemorrhage or treatment modality. After multiple adjustments relative socioeconomic deprivation was not associated with relapse nor ESKD but was associated with an increased risk of death overall (HR 3.44 for most deprived compared to least deprived quintiles [95% CI 1.02-11.57], p=0.046).

Conclusions: A simple RRS, calculated using routinely collected data, can predict progression to ESKD in those with AAV proven on first kidney biopsy. It may also play a role in predicting relapse, with those in the low risk group most likely to relapse. This could be explained by reduced irreversible damage in this group. Furthermore, our analyses did not demonstrate an association with socioeconomic deprivation and worse kidney outcomes for AAV, but was associated with an increased risk of death.



Progression to ESKD by ARRS group

HR 124.8 (unadjusted), 95% CI 26.4 - 590.3, p<0.001.

Mean time to ESKD 371 days.

Disclosures: None.

361. A History of Autoimmune Disease is associated with fewer Relapses in patients with ANCA Vasculitis

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Objectives: To explore the frequency and impact of an autoimmune disease past-medical history (PMH) in the clinical picture and outcomes of patients with antineutrophil cytoplasmic autoantibodies (ANCA) associated vasculitis (AAV). Patients and methods: This was a retrospective study of patients with biopsy-proven AAV, >16 years old, with detailed information about their PMH. Outcomes of interest included remission, treatment resistance, relapse, end-stage kidney disease (ESKD), and death.

Results: 206 patients with biopsy-proven AAV and available information regarding their PMH were studied. 63(30.6%) of them had a history of autoimmune disease prior to AAV diagnosis. The mean age overall was 54.1 years. One huned and five patients (51%) were positive for PR3-ANCA, 101(49%) for MPO-ANCA. Granulomatosis with polyangiitis was diagnosed in 79(38.3%), microscopic polyangiitis in 97(47.1%) and renal-limited vasculitis in 30(14.6%) individuals. Remission rate was similar among patients with and without a PMH of autoimmune disease. Time-to-event analysis indicated that the relapse-free survival was significantly longer in patients with PMH of autoimmune disease (148.2 versus 61.9 months, p-value <0.001). After adjusting for covariates, autoimmune disease history was associated with significantly lower

risk of relapse (HR: 0.33, 95% CI: 0.15-0.72), which remained significant in males, patients ≥60 years old and those with C/PR3-ANCA, kidney and lung involvement.

Conclusions: Patients with a PMH of autoimmune disease, prior to AAV diagnosis, experienced significantly fewer relapses after achievement of remission, compared to patients without such a history, underlining the importance of individualization of maintenance immunosuppressive therapy, given the different etiopathogenetic settings the disease was developed.

Disclosures: None

362. Patient reported outcome measure for Giant Cell Arteritis: Cross-sectional validation study

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Background/Objectives: Giant cell arteritis (GCA) presents in people over the age of 50 with cranial, ocular, and large vessel vasculitis. This study ai to validate a disease-specific patient reported outcome measure (PROM) for patients with GCA, to capture the impact of GCA and its treatment on health-related quality of life.

Methods: This cross-sectional study included UK patients with clinician-confirmed GCA; diagnosed within the last three years or flaring within the last year. Patients completed the 40 candidate PROM ite, the EQ5D-5L, CAT-PROM5 and self-report of disease activity. Rasch and factor analysis were used to determine internal validity and factor structure. Item reductions were based on clinical importance, Rasch model fit, and redundancy. Tests of validity included comparison of the GCA-PROM (i) in participants with ‘active disease’ versus patients ‘in remission’ (known groups validity) and (ii) with EQ5D-5L and CAT-PROM5 scores (convergent validity).

Results: The survey included 428 patients, mean age (SD) of 74.2 (7.2), 285 (67%) female. 327 (76%) cranial GCA, 114 (26.6%) large vessel vasculitis and 142 (33.2%) ocular involvement. Positive diagnostic tests included 167 (39%) temporal artery biopsy, 177 (41.4%) temporal artery ultrasound, and 51 (11.9%) Positron Emission Tomography and Computed Tomography (PET-CT). One huned and eight participants (25%) received second-line immunosuppressants, and 34 (7.9%) anti-IL6 therapy. Active disease was reported in 197

(46%). After the initial analysis (40 ite), ten ite were deleted, and two response categories collapsed to ensure overall fit to the Rasch model. This resulted in a final PROM comprising a 30-item scale with a 4-response category structure. Factor analysis confirmed four factors (domains): Acute sympto (8 ite), Activities of daily living (7 ite), Psychological (7 ite) and Participation (8 ite), all of which individually fitted the Rasch model (X^2 = 25.219, DF=24, p=0.394 including reliability [Person Separation Index, PSI=0.828]), (construct validity). Each domain correlated, at least moderately, with EQ5D-5L and CAT-PROM5 scores (Spearman's Correlation Coefficients 0.44 to 0.78) (convergent validity). The new GCA-PRO discriminated between patients with active disease and remission (known groups validity) (Table 1).

Conclusions: The 30-item GCA-PROM demonstrates internal and external validity in measuring health-related quality of life in people with GCA.

Disclosures: None

Table 1

Domain	Active/Remission	N	Mean	SD	t-stat	p-value
Acute symptoms	Active Disease	188	6.38	4.751	8.743	<0.001
	In remission	176	2.65	3.195		
ADL	Active Disease	190	6.09	5.493	6.819	<0.001
	In remission	178	2.70	3.871		
Psychological	Active Disease	192	8.04	5.057	7.015	<0.001
	In remission	178	4.51	4.588		
Participation	Active Disease	182	6.43	6.613	5.934	<0.001
	In remission	171	2.80	4.656		
Total score	Active Disease	169	26.51	17.749	8.060	<0.001
	In remission	161	12.32	13.917		

363. Renal survival in Anca Vasculitis: Performance of the Anca Renal Risk Score

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Background/Objectives: Berden´s histopathologic glomerulonephritis (GN) classification in ANCA vasculitis is based on glomerular damage [1]. The ANCA renal risk score (ARRS) [2] is a prognostic renal score that takes into account percentage of normal glomeruli (<10/10-25/>25%), percentage of tubular atrophy/interstitial fibrosis (< or > 25%) and glomerular filtration rate (< or > 15 ml/min), with a score from 0-11, and classifies patients into groups at low (0-1 points), medium (2-7 points) or high risk (8-11 points) of end-stage renal disease

(ESRD). Our objective was to evaluate the performance of the ANCA renal risk score in patients with ANCA vasculitis and renal involvement seen at our hospital.

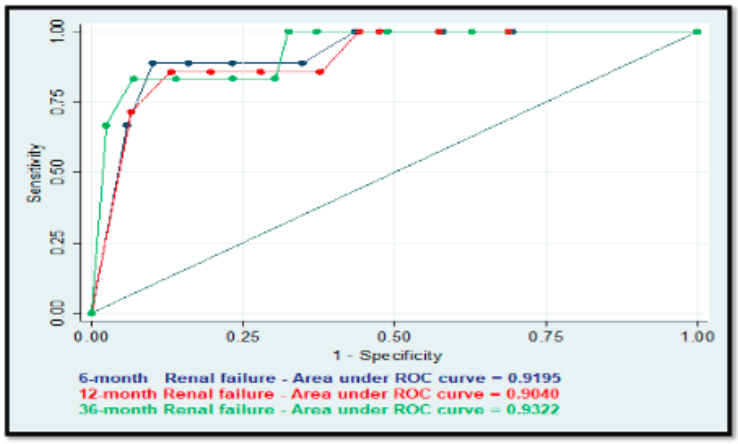
Methods: Observational retrospective study. Patients ≥ 18 years with biopsy-proven ANCA GN were included between 2002 and 2020. Demographic and clinical data were collected from electronic medical records. Renal biopsies were classified according to Berden classification (focal, crescentic, mixed, and sclerotic class). ARRS was calculated at diagnosis. Renal survival, defined as dialysis/transplant-free patients, was evaluated at 6, 12 and 36 months. ROC curves were performed to evaluate the diagnostic accuracy of ARRS. Univariate predictors of renal survival, including the different histological classes and ARRS subgroups, were evaluated using Kaplan-Meier method and Cox proportional hazard model.

Results: Eighty-seven patients with ANCA GN were included: 26 granulomatosis with polyangiitis, 25 microscopic polyangiitis, 4 eosinophilic granulomatosis with polyangiitis and 32 renal-limited vasculitis. Mean age at diagnosis was 65.5 years (SD 16.2), and median follow-up time after renal biopsy was 3.7 years (IQR 1.5-6.5). According to Berden classification, 27 patients had a focal class, 25 crescentic, 22 mixed and 13 sclerotic class in renal biopsy. Sixteen patients (19.5%) died during follow-up. Renal failure was present in 9, 7 and 6 patients at 6, 12 and 36 months respectively, none of whom had a focal class biopsy. Area under ROC curve for ARRS in relation to renal failure at 6, 12 and 36 months was 0.92 (95% CI 0.83-1.00), 0.90 (95% CI 0.79-1.00), and 0.93 (95% CI 0.82-1.00) respectively (figure 1). The best cut-off point in ARSS for predicting renal failure was ≥ 9 with a sensitivity and specificity of 88.9% and 89.9% at 6 months, 85.7% and 86.9% at 12 months, and 83.3% and 93.0% at 36 months. None of the patients with a low or medium ARRS (<8 points) developed ESRD during follow-up. In the univariate analysis, ARRS, as a continuous variable, was associated with renal failure at 6 months (HR 1.75, 95% CI 1.24-2.47, p = 0.001), 12 months (HR 1.82, 95% CI 1.22-2.70, p = 0.003) and 36 months (HR 1.75, 95% CI 1.17-2.62, p = 0.006).

Conclusions: In this cohort of patients with ANCA GN, the ARRS demonstrated a very good discriminatory capacity, sensitivity and specificity to predict renal failure at 6, 12 and 36 months.

Disclosures: none.

Figure 1. ROC curves. Anca renal risk score and renal failure at 6, 12 and 36 months.



364. An International Delphi Exercise to Identify the of Importance for Measuring Response in ANCA-Associated Vasculitis

Kaitlin Quinn[1], Sara Monti[2], Robin Christensen[3], David Jayne[4], Carol A. Langford[5], Georgia E. Lanier[6], Alfred Mahr[7], Christian Pagnoux[8], Beverley Shea[9], Maria Bjork Viðarsdóttir[10], Gunnar Tómasson[11], Peter A. Merkel[12] *[1]National Institutes of Health, NIA, Bethesda, USA, [2]University of Pavia, Pavia , Italy, [3]University of Southern Denmark, Odense University Hospital, , Denmark, [4]University of Cambridge, United Kingdom, [5]Cleveland Clinic, Cleveland, USA, [6]NA, Sherborn, USA, [7]Cantonal Hospital, St. Gallen, Switzerland, [8]Mount Sinai Hospital, University of Toronto, Toronto, Canada, [9]University of Ottawa, Ottawa, Canada, [10]NA, Reykjavik, Iceland, [11]University of Iceland and Landspitali University Hospital, Reykjavik, Iceland, [12]University of Pennsylvania, Philadelphia, USA*

Background/Objectives: ANCA-associated vasculitis (AAV) is characterized by fluctuating levels of disease activity. Randomized controlled trials (RCTs) in AAV have used multiple instruments to define active disease or remission as a dichotomous outcome. However, no formal criteria exist to measure treatment response in AAV. This Delphi exercise aimed to reach consensus about which measures are considered by patients and physicians to be most important when assessing response to treatment in clinical trials in AAV.

Methods: An international 3-round online Delphi exercise was conducted in English. Survey participants included experts in AAV and patients with AAV. Ite in the Delphi were based on a previous systematic literature review of outcome measures in RCTs in AAV, and suggestions from a Steering Committee comprised of vasculitis experts and patients with AAV. Survey participants were asked to rate (on a scale of 1-9) the importance of each item when assessing response to treatment in an RCT in AAV. Ite scored 7-9 by ≥70% participants were considered to be highly important, and ite scored 1-3 by ≥70% participants were considered to be of limited importance.

Results: In total, 265 participants completed three rounds of the Delphi, including 176 physicians with expertise in AAV and 89 patients with AAV. Physicians were from six continents; the majority from Europe [n=81 (46%)] or North America [n=50 (28%)]. Most

physicians specialized in rheumatology [n=105 (60%)] or nephrology [n=50 (28%)]. All physicians were in practice for at least 2 years (two-thirds >10 years) and responsible for managing ≥30 patients with AAV; over half of the physicians managed >75 patients with AAV. Patients with AAV were from four continents, with most located in North America [n=63 (71%)] or Europe [n=23 (26%)] with a diagnosis of GPA [n=72 (81%)] or MPA [n=17 (19%)]. The majority of patients with AAV were female [n=61 (69%)], ages 50-79 years [n=67 (75%)], were diagnosed in the past 10 years [n= 62 (69%)], and were currently on treatment [n=62 (70%)].

The most highly rated ite of response (Table 1) involved disease activity [extent of organ involvement, physician global assessment], mortality [survival], and patient-reported outcomes [patient global assessment and health-related quality of life measures]. Achievement of BVAS ≤1 and BVAS of 0 were highly rated only by physicians. Ite highly rated only by patients included laboratory measures [changes on urinalysis and acute phase reactants], pain, and fatigue. Additional ite related to organ damage and treatment-related adverse events were highly rated by both patients and physicians. There were no ite rated of limited importance by both groups.

Conclusions: In this Delphi exercise, there was consensus between international experts in AAV and patients with AAV on many ite considered important to measure when assessing response to treatment in RCTs in AAV. There were also some ite rated as highly important by only physicians or only patients. These data provide insights into how to evaluate this complex form of vasculitis and will inform the next steps in the development of treatment response criteria in AAV.

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Table 1. Results of the Delphi exercise rating importance of ite to measure when assessing response to treatment in a clinical trial in ANCA-associated vasculitis. The table lists ite rated as highly important by physicians and/or patients after 3 rounds of the Delphi.

		Physicians			Patients		
Category	Delphi Item	N†	Count	%	N†	Count	%
Patient-reported outcomes	Improved fatigue	176	24	14%	89	65	73%
	Improved pain	176	50	28%	89	66	74%
	Improved patient global assessment	182	133	73%	107	77	72%
	Improved HRQoL measures	176	133	76%	89	76	85%
Disease activity	BVAS (any version)						
	BVAS of 0	176	167	95%	89	53	60%
	BVAS ≤1	176	167	95%	89	55	62%
	>50% reduction in BVAS	176	127	72%	89	59	66%
	Kidney function						
	Improved kidney function (eGFR)	181	173	96%	104	86	83%
	No development of ESKD	181	176	97%	104	101	97%
	Ability to discontinue dialysis	176	148	84%	89	56	63%
	Resolution of hematuria on urinalysis	176	75	43%	89	62	70%
	Resolution of proteinuria on urinalysis	176	89	51%	89	65	73%
	Other						
	No new/worse major organ involvement	181	173	96%	103	98	95%
	Improved physician global assessment	181	145	80%	96	77	80%

	No rise in acute phase reactants	176	47	27%	89	63	71%
Mortality	Survival	182	182	100%	113	109	97%
Damage	No new major organ damage	180	170	94%	104	101	97%
	No new non-major organ damage	176	142	81%	89	75	84%
Adverse events	Severe medication-related adverse events	181	171	94%	105	95	91%
	Severe infections	176	172	98%	89	80	90%

HRQoL: health-related quality of life; BVAS: Birmingham Vasculitis Activity Score; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease

†Some participants did not respond to every question accounting for differences in total numbers of responses. The ite approved after round 2 and not included in round 3 had greater responses due to op out of some participants between rounds 2 and 3.

365. Vitamin D status in ANCA-associated vasculitis

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Background/ Objectives: Vitamin D may participate in the pathogenesis of some immune-mediated diseases, although this topic has been minimally examined in ANCA-associated vasculitis (AAV). The aim of this study was to measure the vitamin D status and its association with disease activity in a cohort of patients with AAV.

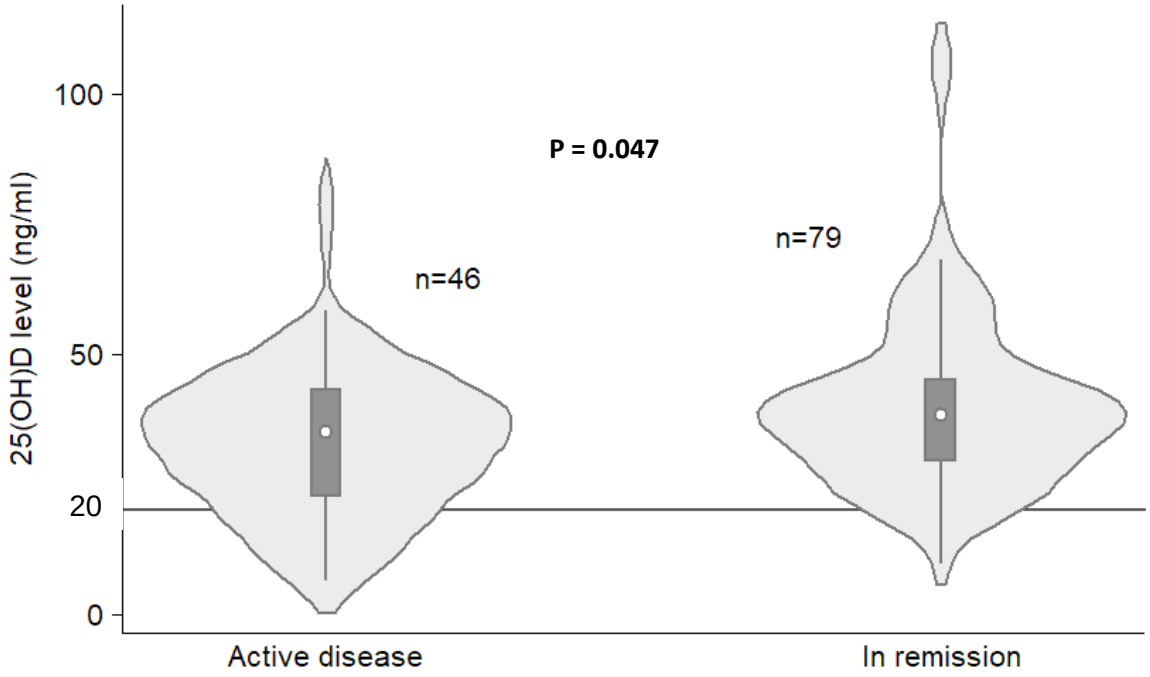
Methods: Vitamin D levels were measured in stored serum samples of 125 randomly selected patients with granulomatosis with polyangiitis (n=50), eosinophilic granulomatosis with polyangiitis (n=50), or microscopic polyangiitis (n=25) enrolled in the Vasculitis Clinical Research Consortium (VCRC) Longitudinal Studies. Sera samples were selected from visits at the time of enrolment, and a subsequent relapse visit for patients who had a relapse during follow-up. Levels of 25-hyoxyvitamin (25[OH]D) were measured using ELISA. Insufficiency was defined as a 25(OH)D level between 20-30 ng/mL (50-75 nmol/L), and deficiency as <20 ng/mL (<50 nmol/L).

Results: Seventy (56%) of the study patients were female, with a mean age at diagnosis of AAV of 51.5+/-16 years; 84 (67.2%) were or had been positive for the presence of ANCA. Main disease manifestations included lung (80%), renal (45.6%) neurologic (42.4%), and/or ears/nose/throat (41.6%) involvement. At their enrollment visit, 79 (63.2%) patients were in remission, the remaining 46 (36.8%) having some disease activity. Mean vitamin D level at enrollment was 37.7+/-16.3 ng/ml; vitamin D deficiency and insufficiency was seen in 13 (10.4%) and 26 (20.8%) patients, respectively (Figure 1). Higher serum levels of vitamin D at enrollment were associated with female sex (p=0.027) and inactive disease (p=0.047) in univariate analysis, but not in multivariate analysis. In both univariate and multivariate analysis deficiency status at enrollment was associated only with active disease (p=0.015). Mean level of 25(OH)D in the 21 patients with a subsequent relapse visit did not differ between baseline and relapse visit (37.8+/-3.6 vs. 38.0+/-9.6 ng/ml, respectively; p=0.92), with deficit in 1 (4.8%) and insufficiency in 3 (14.3%) of the 21 patients at the time of relapse (p=0.28 for comparison to baseline distribution).

Conclusions: Most patients in this cohort of AAV had sufficient 25(OH)D levels. Levels were higher in patients in remission at enrollment, but did not significantly change in patients who had a subsequent relapse. Whether optimization of vitamin D status alters disease manifestations or activity remains to be determined.

Disclosures: The authors declare no disclosures.

Figure 1: 25(OH)D levels for 125 patients with ANCA-associated vasculitis according to disease status. The diamond-shape areas represent the distribution (number of patients) at each level of vitamin D. The box plots in the center of the diamond-shaped areas represent the medians (circles), and interquartiles (upper and lower box lines). Deficiency is defined as <20ng/ml (horizontal bar).



366. Clinical and pathological predictors of relapse in IgG4-related disease

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Objectives: In IgG4-related disease, the relationship between pathological findings and relapse has not been well established. This study aimed to identify the clinical and pathological predictors of disease relapse in IgG4-RD.

Methods: Patients with newly diagnosed IgG4-RD (n = 71) were enrolled between January 2011 and April 2020; all cases were pathologically confirmed. The clinical and pathological features were recorded in a database at baseline and each follow-up visit. Patients were

followed up at least once a month via outpatient clinic examinations and telephone calls. Univariate and multivariate Cox regression analyses and receiver operating curve (ROC) analysis were used to identify the predictors of disease relapse and to assess their predictive value.

Results: Over median follow-up of 26 (range, 6-123) months, 3/71 (4.2%) patients died. Of the remaining 68 patients, 47 (69.1%) patients had achieved clinical remission and 21 (30.9%) had suffered relapse at the last follow-up. The independent predictors of relapse were IgG4 ≥6.5 g/L (OR = 2.84, 95% CI: 1.11-7.23), IgG ≥20.8 g/L (OR = 4.11, 95% CI: 1.53-11.06), IgG4-RD responder index (RI) ≥9 (OR = 3.82, 95% CI: 1.28-11.37), and severe $IgG4^+$ plasma cell infiltration (OR = 6.32, 95% CI: 1.79-22.41). A prognostic score developed using three of the identified predictors (IgG ≥20.8 g/L, IgG4-RD RI ≥9, and severe $IgG4^+$ plasma cell infiltration) showed good value for predicting impending relapse (AUC, 0.806).

Conclusions: In patients with IgG4-RD, IgG4 ≥6.5 g/L, IgG ≥20.8 g/L, IgG4-RD responder index (RI) ≥9, and severe $IgG4^+$ plasma cell infiltration are predictors of relapse.
Keywords: IgG4-related disease; relapse; prognostic factor

Disclosures: None

367. Patient reported outcomes on quality of life in Giant Cell Arteritis and Polymyalgia Rheumatica patients.

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Background/Objectives: Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are often overlapping inflammatory diseases that occur in people older than 50 years. Both diseases can affect the quality of life, due to the burden of vascular inflammation and ischemia-related sympto (GCA), joint sympto (PMR) and systemic sympto (GCA and PMR), in addition to the side-effects of long-term treatment with glucocorticoids. We hypothesized that GCA and Phave both short- and long-term impact on the quality of life. We therefore documented patient reported outcomes (PROs) on the quality of life in GCA and Ppatients for five years.

Methods: We prospectively followed treatment-naïve GCA (n=44) and P(n=40) patients since diagnosis for up to five years. At each visit, PROs were recorded by the Groningen Frailty Indicator (GFI), the Health Assessment Questionnaire-Disability Index (HAQ-DI) and the Short Form (SF)-36. Data were compared with age- and sex-matched healthy controls (HCs) that were also followed for up to five years.

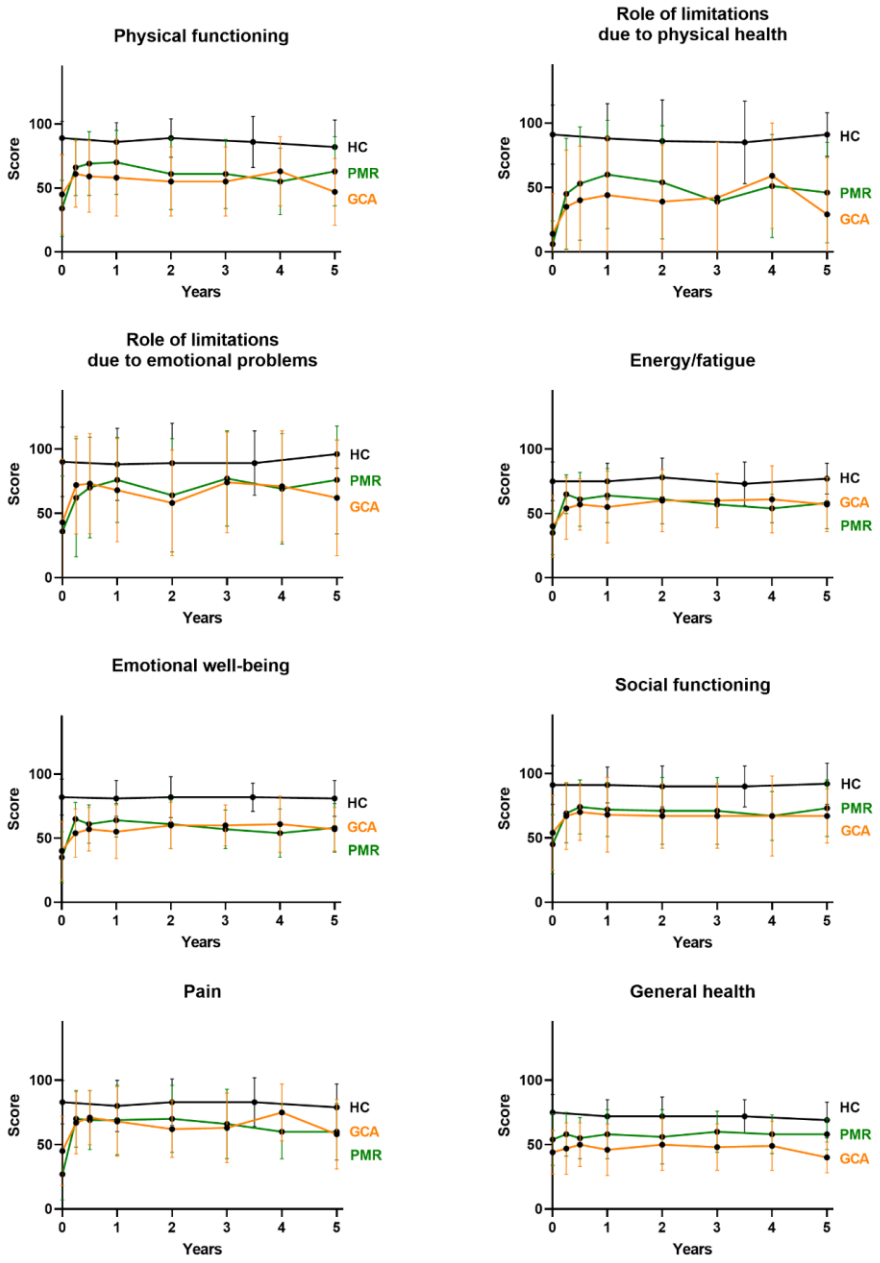
Results: At diagnosis, both GCA and Ppatients reported significantly worse on each PRO compared to HCs. On each of the eight domains of the SF-36, patients scored substantially lower than HCs, with Ppatients scoring slightly worse than GCA patients (Figure 1). Initiation of

GC treatment rapidly improved PROs, however, scores either never recovered to HC values (GFI, SF-36) or increased again after two years (HAQ-DI). SF-36 scores at baseline and during treatment correlated the strongest with patient reported fatigue, rather than physician reported disease activity or levels of acute-phase markers.

Conclusions: GCA and Ppatients experience both short-term and long-term impact on their quality of life, likely caused by both the disease and its treatment. The impact of fatigue in PROs, rather than disease-specific sympto, needs to be emphasized. Future studies should document whether a direct start of additional treatment such as methotrexate or tocilizumab substantially and persistently improve quality of life in these patients.

Disclosures: Van der Geest and Brouwer have received consulting fees, speaking fees, and/or honoraria paid to his institution from Roche (less than $10,000). Brouwer has received consulting fees, speaking fees, and/or honoraria paid to her institution from Roche (less than $10,000). No other disclosures relevant to this article were reported.

Figure 1. Scores of the eight domains of the SF-36 throughout the disease course in GCA and Ppatients. Data are compared to HCs. Scores range from 0-100; a score of 100 indicates the most-healthy outcome.



368. Withdrawn

369. Predictors of Remission and Relapse In Chronic Periaortitis: A Retrospective Study On 115 Patients

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Background/Objectives: to identify predictors of remission and relapse, after the end of treatment, in patients suffering from chronic periaortitis (CP)

Methods: we retrospectively included all consecutive patients: I) with a confirmed diagnosis of CP, II) who had received a glucocorticoid (GC)-based treatment course, alone or combined with other immunosuppressants, for a minimum of 6 and a maximum of 9 months, III) with a follow up of at least 12 months, III) who had undergone at least an imaging examination (CT, or PET-CT) both at baseline and after end of treatment. Logistic univariate and multivariate regression models were used to estimate risk of remission, according to baseline demographic and clinical parameters. Cox univariate and multivariate regression models were used to estimate the risk of relapse, according to demographic and clinical parameters at baseline, at month 4 after treatment initiation and at end of treatment. For Cox regressions, time at risk was set as the time (in months) from disease remission to the first relapse (if any) or to the last available follow-up.
Results: One huned and fifteen patients with a confirmed diagnosis of CP, followed by dedicated outpatient clinics of Parma and Florence University Hospitals, were included. The median follow-up was 33 [17.5-57.7] months. Baseline characteristics are shown in table 1. Every patient received a 6–9-month GC course with/without other immunosuppressive ugs (Methotrexate 19%, mycophenolate mofetil 14%, Rituximab 4%). Remission was reached in 101/115 (87.3%) patients, of whom 42 (42.6%) experienced at least one relapse with a time to first relapse of 14 [8-26] months. Predictors of remission: we found that smoking status and atypical CP localization were negative independent predictors of remission (P=0.049 and P=0.005 respectively), while a positive PET-CT at baseline was an independent positive predictor of remission (table 2a). Predictors of relapse: we found that a positive PET-CT after end of treatment and thoracic vessels involvement were independent predictors of relapse (P=0.003 and P=0.016 respectively, table 2b).

Conclusions: This stratification of patients according to risk of remission and relapse allows for differentiation of treatment choices in different disease subsets, identifying those patients who require a greater load of immunosuppression to achieve remission or avoid relapse.

Disclosures: nothing to disclose

Table 1

Demographic and clinical characteristics of the patients at baseline

Men	40/115 (34.78%)
Age	55 [50-63]
Environmental exposure	
Asbestos	28/100 (28%)
Smoke	89/108 (82.41%)
Pack year	23 [8.25-36.5]
Clinical characteristics	
Idiopathic retroperitoneal fibrosis	105/115 (91.3%)
Perianeurysmal retroperitoneal fibrosis	10/115 (8.7%)
Symptoms	107/115 (93.04%)
Hydronephrosis	78/114 (68.42%)
DVT	19/114 (11.82%)
Established atherosclerotic disease	13/111 (11.71%)
Associated autoimmune disease	38/114 (33.33%)
Fibro-inflammatory disease	19/114 (16.67%)
Laboratory findings	
Erythrocyte sedimentation rate (mm/h)	50 [34-73]
C-reactive protein concentration (mg/L)	13.1 [5.4-33]
Serum creatinine (mg/dL)	1.2 [0.9-2.21]
Hemoglobin (g/dL)	12.4 [10.85-13.3]
Positive ANA test	22/106 (20.75%)
High IgG4	18/92 (19.57%)
IgG4 (mg/dL)	239 [169-299]
Positive quantiferon test	18/80 (22.5%)
Characteristics of CP at CT or MRI	
Typical CP localization	97/115 (84.35%)
Atypical CP localization	18/115 (15.65%)
Thoracic involvement	21/114 (18.42%)
Maximal RPF thickness (mm)	15 [10.28-22]
Characteristics of CP at ^{18}F-FDG	96/115 (83.48)
Grade 0	6/96 (6.25%)
Grade 1	5/96 (5.21%)
Grade 2	30/96 (31.25%)
Grade 3	55/96 (57.29%)

Continuous variables are expressed as median (range) and categorical variables as n (%) or n/N (%). DVT=deep vein thrombosis; ANA=anti-nuclear antibodies, CP=chronic periaortitis; CT=computed tomography; ^{18}F-FDG =positron emission and computed-tomography

Table 2a

	Univariate analysis			Multivariate analysis		
	Estimated OR	IC 95	P	Estimated OR	IC 95	P
Smoking status	0.34	0.12-0.96	0.042	0.34	0.11-0.99	0.049
Atypical vs typical CP localization	0.18	0.05-0.61	0.006	0.11	0.02-0.52	0.005
18F-FDG PET uptake, baseline	16	2.59-98.77	0.003	11.51	1.35-98.20	0.025

Table 2b

	Univariate analysis			Multivariate analysis		
	HR	IC 95	P	HR	IC 95	P
Established atherosclerotic disease	*2.12*	*1.06-4.23*	*0.034*	1.85	0.82-4.21	0.139
Thoracic vessel involvement	*2.02*	*1.02-3.98*	*0.043*	2.61	1.20-5.68	0.016
18F-FDG PET *end of treatment*	*3.09*	*1.44-6.64*	*0.004*	3.47	1.54-7.82	0.003
18F-FDG PET *metabolic Response*	*2.79*	*1.26-6.15*	*0.011*			

370. The Validity And Reliability Of The Turkish Version Of Bodi In A Retrospective Cohort

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Background/ Objectives: Behçet's synome Overall Damage Index (BODI) is a newly developed damage index specific to Behçet synome (BS). We aimed to evaluate validity, reliability and feasibility of the Turkish version of BODI and evaluate its performance for use in retrospective cohort studies for different phenotypes of BS.

Methods: The study included 295 patients with at least 3 BODI scores out of 590 consecutive BS patients who were followed up between January 2015 and August 2017. Turkish version of the BODI form was developed by translating into Turkish and backwards by 2 people. BODI scores were calculated for each year during the follow-up period. The test-retest reliability of BODI was assessed by scoring the same 50 patients at 6-month intervals by the same observer (YYO). Two different observers (YYO- YO) assessed the same 50 patients for inter-observer agreement. The intra-class correlation coefficient (ICC) was used to assess the inter and intra-observer agreement. We also evaluated the median time to fill out the form in patients with different types of involvements.

Results: Of 295 (158 F/137 M) patients, the mean age was 39 (9.9) and the mean follow-up time was 4.3 (1.3) years. Demographic features of BS patients were summarized in the Table. BODI median score was 1 (IQR=0-1). We observed an increased in BODI score in 111 (38%) patients during follow-up. The main reasons for increasing BODI scores were eye, vascular and neurological involvement (Table). The mean ICC for inter-observer agreement was 0.94 (95% CI, 0.89-0.96) and for intra-observer agreement was 1. The median (range) time to complete the form was 2 (1-8) minutes.

Conclusions: This study showed that the Turkish version of BODI was a reliable and feasible instrument that could capture the change over time in damage, and could be used in retrospective cohort studies. Ocular involvement was the most common cause of progressive damage in this cohort.

Disclosures: Gulen Hatemi has received grant/research support from Celgene and has served as a speaker for AbbVie, Celgene, Novartis, and UCB Pharma. Yesim Ozguler has received honorariu for presentations from UCB Pharma, Novartis, and Pfizer. Vedat Hamuryudan has

received grant/research support from Celgene and has served as a speaker for AbbVie, Celgene, Novartis, and UCB Pharma. No other disclosures were reported.

Table. Demographic features and BODI scores of BS patients

Sex	158 F/137 M
Mean age (SD), years	39 (9.9)
Mean age at the time of fulfilling ISG criteria (SD), years	30 (9.2)
Mean disease duration (SD), years	8.8 (5.9)
Mean follow-up time, years	4.3 (1.3)
Clinical features (%)	
Oral ulceration	99.7
Genital ulceration	81.3
Erythema nodosum	57.1
Papulopustular lesions	89.5
Joint involvement	25.2
Pathergy positivity	27.2
Ocular involvement	47.3
Vascular involvement	21.4
Neurologic involvement	3.1
Gastrointestinal involvement	2.7
N of patients with more than 3 BODI scores*(%)	194 (66)
Causes for increase in BODI score(n=111) (%)**	
Ocular involvement	77 (69)
Vascular involvement	17 (15)
Neurological involvement	8 (7)
Gastrointestinal involvement	3 (3)
Mucocutaneous inv.	6 (5)
Cardiovascular inv.	1 (0.9)
Diabetes mellitus	4 (4)
Avascular necrosis	2 (2)
Osteoporosis related fracture	1 (0.9)

*All patients had at least 3 BODI scores,

**Some patients had more than 1 type of involvement

Patient outcomes, preference and attitudes

371. Pulmonary capillaritis and seeking Panakeia

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Background: The Greek goddess Panakeia (Panacea) was the goddess of cures, remedies and panaceas. This is a narrative of the lived experience of having pulmonary capillaritis as noted by a mother. The aim is to share the lived experience of this ultra-rare, alveolar haemorrhaging synome that can be life-threatening. Thereby, hopefully increase awareness of the whole person impact of this disease. This narrative will share the interventions that helped from a lived perspective, of the therapeutic journey and of challenges of having an ultra-rare disease including diagnostic difficulties and the paucity of evidence. In many ways, this is a narrative about seeking Panakeia.

Methods: This is a narrative from the perspective of the mother and primary caregiver who is also a doctor and from the family records kept of results received, interventions and copies of some correspondence received.

Results: Pulmonary capillaritis is an ultra-rare, alveolar haemorrhaging synome that had a ound impact in ter of symptom burden, recurrent hospitalisations and decreased school attendances. Networking with others via social media, looking to the ether of the internet for data and seeking help will be shared. Communication, disbelief and being heard have been important aspects of this journey as a carer. Steroids, cyclophosphamide and more recently, immunomodulatory IV immunoglobulin (IVIg) have been landmark treatments as seen through this lived perspective. Equally the complex side effects of treatment including life-threatening Cryptococcal infection while on immunosuppression occurred.

Conclusions: Living with pulmonary capillaritis has been a very encompassing experience as a family. This included the challenge of diagnosis, the watchful waiting and anticipation of recurrences and acute exacerbations and the juggle of negotiating a complex illness and typical life experiences. Seeking treatment options and possibilities has been a significant part of this jigsaw. Meanwhile as a family we will continue to seek Panakeia.

Disclosure: None.

372. Preferences regarding treatment with plasma exchange for ANCA-associated vasculitis: An extended international patient survey

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Objectives: To elicit patient preferences regarding the use of plasma exchange (PLEX) in ANCA-associated vasculitis (AAV) and its tradeoffs of end stage kidney disease (ESKD) and serious infection.

Methods: Respondents reviewed the estimated one-year risks of ESKD and serious infection in AAV with and without PLEX across 5 serum creatinine categories. For each scenario, participants indicated whether or not they would choose PLEX. Responses were assessed with multilevel multivariable logistic regression models to identify predictors of respondent choice regarding treatment with PLEX.

Results: The 470 respondents from the 13 countries (United States 61.7%, United Kingdom 20.0%, Canada 13.8%, other countries 4.5%) had a mean age of 58.6 (SD 14.3) years, 70.2% female. Respondents were more likely to choose PLEX in scenarios at high risk of ESKD and serious infection (creatinine 350 or 450 µmol/L) compared to lower risk scenarios or the highest risk scenario. However, 145 (30.9%) chose PLEX across all scenarios while 80 (17.0%) declined PLEX across all scenarios. Respondents from the United Kingdom (OR 2.61, 95% CI 1.09-6.22), who received previous dialysis (OR 2.70, 95% CI 1.12-6.52), or received previous PLEX (OR 5.62, 95% CI 2.72-11.61) were more likely to choose PLEX while older respondents (OR 0.98, 95% CI 0.96-0.99 per 1 year increase) were less likely.

Conclusion: Patients with AAV do not express a consistent choice for PLEX based on the benefits and risks it carries for the outcomes of ESKD and serious infection. This inconsistency highlights the need for shared decision-making when considering PLEX in AAV.

Disclosures: None relevant to this work. Preliminary data presented here: https://www.asn-online.org/education/kidneyweek/2021/program-abstract.aspx?controlId=3611478

373. Patient reported outcomes (AAV-PRO) in ANCA-associated vasculitis are independent from disease activity and damage

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Background/ Objectives: The ANCA-associated vasculitis patient-reported outcome (AAV-PRO) measure is a new disease-specific PRO developed and validated to include the patient's perspective into the overall assessment of disease (Robson et al., 2018). As a ile measure the AAV-PRO contains six different domains: Organ-specific sympto (OSS), systemic sympto severity (SSS), treatment side effects (TSE), social and emotional impact (SEI), concerns about the future (CAF), and physical function (PF). Factors that determine the patient's perspective in AAV are yet unclear. The objective of this study was to investigate the

association of disease activity and damage, depression, health-related quality of life, treatment, relapses and different organ manifestations with the patient's AAV-PRO domain scoring.
Methods: AAV-PRO, Beck's depression inventory (BDI), short form 36 (SF-36), Birmingham Vasculitis Activity Index (BVAS) and Vasculitis Damage Index (VDI) were prospectively acquired at baseline (t1) and after 3-6 months (t2). Additionally, patient's data concerning age, sex, disease duration, diagnosis, ANCA-state, therapies, relapses, and organ manifestations were recorded. Data were analyzed by t-tests as well as correlation and regression analyses.

Results: 156 patients with AAV participated. Median AAV-PRO domain scores were higher in patients reporting "active disease" compared to patients reporting "in remission" ($p<0.001$). When the patient cohort was divided based on objective disease activity (BVAS ≥ 1) the results of mean differences were heterogenous. The separate results for each of the six AAV-PRO domains are depicted below (table). OSS was mainly predicted by SF36 'pain' and 'general health' as well as the number of relapses. The strongest predictors of SSS were SF36 'pain' and 'energy/fatigue'. The two of which along with SF36 'emotional well-being' (EWB) were also associated with TSE, however its strongest predictor was the BDI. Especially SEI, but also CAF were chiefly predicted by the BDI and SF36 'EWB'. Overall, the strongest association was seen in the domain PF, which is predominantly predicted by SF36 'physical functioning' ($\square = 0.9$). Patients with longer disease duration showed higher values in TSE, SEI and CAF. No significant relations were seen between the AAV-PRO domains and BVAS, VDI, therapies, organ manifestations as well as sex and age. In the longitudinal comparison (t1/t2) there were no decisive changes of the overall results.

Conclusions: Our data shows convergent validity of all six subdomains of the AAV-PRO with the established questionnaires BDI and SF-36. The degree of predictability varies and depends on the construct of each subdomain. We confirm the formerly reported strong association to the patient's subjective state of disease in a German AAV cohort. None of the AAV-PRO domains are markedly influenced by objective parameters of disease such as BVAS and VDI. Thus, we regard the AAV-PRO as a valuable addition to the overall assessment of AAV patients. It might complement traditional endpoints like activity and damage in future clinical trials. Further investigations of the AAV-PRO in patients with more active vasculitis should be undertaken since most of the patients in our cohort were in stable remission or had low-disease activity.

Disclosures: The authors declare no conflicts of interest.

Table. Baseline characteristics and results of correlation and regression analyses

Basic characteristics		
Diagnosis AAV (total) (N)	156	
GPA	88	
MPA	26	
EGPA	40	
unclassified AAV	2	
Age, years, (median (range))	60 (20-89)	
Female/Male (N)	79/77	
Disease Duration, months (median (range))	56.5 (0-361)	
Disease Activity state (N)		
Remission (BVAS=0)	126	
active disease/relapse (BVAS≥1)	30	
BVAS 1-5	13	
BVAS >5	17	
Patient's self-evaluation of disease state (N)		
In remission	112	
Active disease	43	
Correlation and Regression:	***|r| (p)***	***|β| (p)***
AAV-PRO 'Organ-specific symptoms' (OSS)		
Relapses	0.364 (<0.001)	0.240 (0.019)
SF36 'Pain'	0.376 (<0.001)	0.224 (0.055)
SF36 'General Health' (GH)	0.419 (<0.001)	0.197 (0.174)
BDI	0.380 (<0.001)	0.161 (0.160)
SF36 'Role functioning/ physical' (RFP)	0.364 (<0.001)	0.139 (0.401)
BVAS	0.116 (0.150)	0.046 (0.583)
VDI	0.107 (0.182)	0.008 (0.927)
all other scores	not significant	not significant
AAV-PRO 'Systemic symptoms severity' (SSS)		
SF36 'Pain'	0.654 (<0.001)	0.409 (<0.001)
SF36 'Energy/ Fatigue' (EF)	0.658 (<0.001)	0.314 (0.008)
SF36 'General Health' (GH)	0.633 (<0.001)	0.119 (0.278)
BVAS	0.184 (0.021)	0.072 (0.255)
VDI	0.031 (0.702)	0.088 (0.183)
all other scores	not significant	not significant
AAV-PRO 'Treatment side effects' (TSE)		
BDI	0.522 (<0.001)	0.308 (0.005)
SF36 'Pain'	0.395 (<0.001)	0.196 (0.081)
SF36 'Emotional well-being' (EWB)	0.525 (<0.001)	0.166 (0.216)
SF36 'Energy/ Fatigue' (EF)	0.463 (<0.001)	0.115 (0.431)
BVAS	0.146 (0.069)	0.050 (0.527)
VDI	0.054 (0.506)	0.015 (0.858)
all other scores	not significant	not significant
AAV-PRO 'Social and emotional impact' (SEI)		
BDI	0.759 (<0.001)	0.391 (<0.001)
SF36 'Emotional well-being' (EWB)	0.792 (<0.001)	0.327 (<0.001)
SF36 'Role functioning/ physical' (RFP)	0.649 (<0.001)	0.016 (0.246)
BVAS	0.149 (0.064)	0.004 (0.931)
VDI	0.034 (0.674)	0.064 (0.227)
all other scores	not significant	not significant
AAV-PRO 'Concerns about the future' (CAF)		
SF36 'Emotional well-being' (EWB)	0.706 (<0.001)	0.441 (<0.001)
BDI	0.615 (<0.001)	0.192 (0.035)
SF36 'General Health' (GH)	0.569 (<0.001)	0.147 (0.199)
SF36 'Role functioning/ physical' (RFP)	0.547 (<0.001)	0.141 (0.281)
BVAS	0.079 (0.329)	0.028 (0.675)
VDI	0.108 (0.182)	0.055 (0.422)
all other scores	not significant	not significant
AAV-PRO 'Physical Functioning' (PF)		
SF36 'Physical Functioning' (PF)	0.844 (<0,001)	0.900 (<0.001)
SF36 'Role Functioning/ physical' (RFP)	0.619 (<0,001)	0.270 (0.004)
BVAS	0.288 (<0.001)	0.070 (0.135)
VDI	0.005 (0.948)	0.078 (0.111)
all other scores	not significant	not significant

374. Giant Cell Arteritis patient reported outcome: acceptability as a communication tool in clinical practice

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Background/Objectives: Giant cell arteritis (GCA) presents in people over 50, with headaches, ocular involvement and large vessel vasculitis. A 30-item GCA-specific patient reported outcome measure (GCA PRO) has been developed and validated. In this pilot, the GCA PRO was tested in a clinical setting to explore its feasibility and acceptability to patients and clinicians as a communication tool.

Methods: Patients seen in Rheumatology or Ophthalmology Departments in Bristol and Leeds completed the GCA PRO prior to their consultation. Ite referred to patients' health-related quality of life over the past 7 days. Clinicians were provided with a copy of patients' responses and a summary sheet highlighting overall scores which they referred to during the consultation. After the appointment, patients and clinicians completed short answer questionnaire (SAQ) plus free-text feedback for reporting on the experience of use of the GCA PRO within the consultation.

Results: The GCA PRO was piloted during 16 clinic appointments. 16 patients, mean age (SD) of 74.7 (7.0), 11 (68.8%) female, 7 (43.8%) active disease and 5 (31.3%) with ocular involvement took part. Seven clinicians participated, 5 Rheumatologists and 2 Ophthalmologists. Eighty seven percent of patients agreed that the GCA PRO had helped them to explain their condition; clinicians agreed that the GCA PRO had helped them to understand the patient's condition 88% of the time (Table 1). Clinicians noted that "It was easier for the patient to convey his anxiety and feelings towards the disease and treatment" and that the GCA PRO "indirectly helped via prompting discussion of patient's anxieties and worries", however they were more equivocal on its impact on decision making: "Management plan was informed by sympto, bloods and stage of illness". Patients commented that "It helped us to plan how to manage my GCA based on my answers" and that "The questions seemed relevant and it was helpful to me to be able to think about them before the appointment".

Conclusions: The GCA-PRO was found to be an acceptable tool for use in clinic by patients and clinicians, especially in ter of explaining and understanding the patient's condition.

Disclosures: Nil

Table 1. Patient and clinician feedback summary responses (n=16 appointments)

Question	Patients N (%)	Clinicians N (%)	Response
Helped explain/understand situation	5 (31%)	7 (44%)	Strongly agree
	9 (56%)	7 (44%)	Agree
	2 (13%)	1 (6%)	Neither agree/disagree
	0 (0)	1 (6%)	Disagree
Helped joint decisions	4 (25%)	1 (6%)	Strongly agree
	4 (25%)	7 (44%)	Agree
	7 (44%)	7 (44%)	Neither agree/disagree
	1 (6%)	1 (6%)	Disagree
Would be helpful to repeat over time	2 (13%)	3 (19%)	Strongly agree
	7 (44%)	12(75%)	Agree
	4 (25%)	1 (6%)	Neither agree/disagree
	0 (0)	0 (0)	Disagree
Improved communication	4 (25%)	4 (25%)	Strongly agree
	5 (31%)	7 (44%)	Agree
	5 (31%)	5 (31%)	Neither agree/disagree
	2 (13%)	0 (0)	Disagree

375. Trends in medication interruptions and anxiety during the COVID-19 pandemic among patients with vasculitis

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Background/Objectives: The COVID-19 pandemic has had substantial impact on the care of patients with vasculitis, resulting in frequent interruptions in medication use during the pandemic. This study used longitudinal data to examine changes in anxiety and interruptions in medication use in patients with vasculitis during the COVID-19 pandemic.

Methods: The Vasculitis Patient Powered Research Network online patient registry and partnering organizations invited members to complete a baseline survey (week 0) and then every 2 weeks until week 8, monthly until week 28, with a final survey at week 52. We analyzed patients with vasculitis who completed baseline surveys between March 29 and June 30, 2020 and completed at least one follow-up survey, with follow-up captured through May 2021. Changes over time in the frequency of interruptions in medication use due to COVID-19

concerns (among patients receiving immunosuppressive therapies who did not report a respiratory illness or COVID-19 diagnosis) and changes in PROMIS Anxiety T scores (population mean 50 with standard deviation of 10) were assessed using generalized estimating equation (GEE) models to account for within-person correlations, with models assessing changes in anxiety adjusted for baseline anxiety. Associations between anxiety and interruptions in medication use were also assessed with GEE models, and differences in reasons for interruptions in medication use compared in 2020 and 2021.

Results: A total of 535 patients completed a median of 5 surveys (interquartile range 3-7). The mean age was 57 years, 79% were female, and the most common diagnoses were granulomatosis with polyangiitis, relapsing polychonitis and eosinophilic granulomatosis with polyangiitis (Table 1). Anxiety declined substantially over the course of the study with average PROMIS-Anxiety T-scores changing from 56.8 to 51.7 from March 2020 to May 2021 ($p < 0.001$ for trend). In contrast, interruptions in medication use were more frequent in 2021 versus 2020 (12.1% versus 8.0% [OR 1.59 (95% CI 1.12-2.25)]. However, there were fewer responses to the survey in 2021 vs 2020. Flares did not change significantly from April through December of 2020 ($p = 0.14$ for trend) but increased from December to May of 2021 ($p < 0.001$ for trend). Greater anxiety was associated with more medication interruptions in 2020 but not in 2021 ($p = 0.005$ for interaction). Reasons for interruptions in medication use differed in 2020 and 2021 (Table 1); the most common reason patients noted for an interruption their medication in 2020 was a fear of getting sick (46.6%) in 2020, while the most common reason in 2021 was physician recommendation (58.3%).

Conclusion: Patients with vasculitis had high levels of anxiety at the start of the pandemic, but anxiety decreased close to general population averages by May of 2021. Interruptions in medication use increased in 2021, but were more commonly recommended by physicians and may have been related to interruptions occurring around the time of vaccination. A substantial proportion of interruptions in medication use was not recommended by physicians, however, highlighting the importance of regular communication between the patients and the healthcare team during public health crises to ensure optimal use of mediations.

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Table 1. Baseline Characteristics of Study Participants and Reasons for Medication Interruptions

	All Patients N = 535		
Age, years	56.8 (13.6)		
Female	422 (78.9%)		
White	493 (92.2%)		
MEDICATIONS			
Rituximab	166 (31.0%)		
Methotrexate	88 (16.5%)		
Azathioprine	77 (14.4%)		
Non-rituximab biologic/JAK inhibitor	63 (11.8%)		
Mycophenolate	45 (8.4%)		
Cyclophosphamide	7 (1.3%)		
Glucocorticoids <10 mg/day	176 (32.9%)		
Glucocorticoids ≥10 mg/day	50 (9.4%)		
DISEASE			
Granulomatosis with polyangiitis	220 (41.1%)		
Eosinophilic granulomatosis with polyangiitis	49 (9.2%)		
Relapsing polychonitis	48 (9.0%)		
Microscopic polyangiitis	45 (8.4%)		
ANCA-associated vasculitis-unspecified	45 (8.4%)		
Giant cell arteritis	28 (5.2%)		
Takayasu's arteritis	15 (2.8%)		
Other vasculitis	85 (15.9%)		
PROMIS Anxiety, T-score	57.2 (8.6)		
REASONS FOR MEDICATION INTERRUPTIONS	*2020*	*2021*	*P-VALUE*
	N = 118	N = 24	
Physician told to stop	52 (44.1%)	14 (58.3%)	0.20
Worried about getting sick	55 (46.6%)	6 (25.0%)	0.05
Did not want to visit an infusion center	21 (17.8%)	3 (12.5%)	0.53
Felt too sick	5 (4.2%)	1 (4.2%)	1.00
Heard it was a good idea	4 (3.4%)	1 (4.2%)	0.61
Recommended by friends or family	4 (3.4%)	1 (4.2%)	0.61
Worried about limited supply	2 (1.7%)	0 (0.0%)	1.00
Other reason	18 (15.3%)	5 (20.8%)	0.50

376. Patients' perceptions of glucocorticoid therapy: international development of a Patient Reported Outcome (the Steroid PRO)

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Background/Objectives: Glucocorticoid steroids (GCs) are widely used to treat inflammatory rheumatic diseases. GCs carry a wide range of adverse effects of concern to patients and clinicians. The objective of this study was to explore the impact of GC therapy on health-related quality of life (HRQoL) during treatment for rheumatic diseases, as a basis for development of a Patient-Reported Outcome Measure (PROM) to be used in clinical trials and practice.

Methods: Patients from the UK, USA and Australia who were treated with GCs in the last two years for a rheumatic condition were invited to take part in semi-structured qualitative interviews. A steering committee of patient research partners, clinicians and methodologists devised an initial conceptual framework, which informed interview prompts and cues. Interviews identified physical and psychological sympto and salient aspects of HRQoL in relation to treatment with GCs. Purposive sampling was used to include a range of demographic and disease features. The interview data were organised using NVivo, and inductive analysis identified initial themes and domains. Candidate questionnaire ite were developed and refined using cognitive interviewing, linguistic assessment, and input from patient research partners.

Results: Sixty semi-structured qualitative interviews were conducted (UK n=34, USA n=10, Australia n=16). Mean participant age was 58 years;39 (66.1%) were female. Detailed demographic and GC use information is provided in Table 1. The following initial domains were developed to identify key themes relating to treatment using GCs and their impact on HRQoL: benefits of steroids; physical symptoms; psychological symptoms; psychological impact of steroids; impact of steroids on participation; and impact of steroids on relationships. Forty-one

candidate questionnaire items were developed from the individual themes. These were tested and refined by piloting with patient research partners, iterative rounds of cognitive interviews with patients with a range of rheumatic conditions from the UK, USA and Australia, and a linguistic translatability assessment, to define a draft questionnaire. Conclusions: This international qualitative study underpins the development of candidate items for a treatment-specific PROM for patients with rheumatic diseases. This draft questionnaire is now ready for testing in an online large-scale survey to determine the final scale structure, any item reduction, and measurement properties.

Disclosures: None

Table 1: Demographic and glucocorticoid steroid use summary

Qualitative interviews – Demographics and GC use		UK n=34	Australia n=16	USA n=10	All Sites n=60	
Sex	Male	14	6	1	**21**	**36%**
	Female	20	10	9	**39**	**66%**
Ethnicity	Asian/Asian British	0	2	0	**2**	**3%**
	Black/African/Caribbean/ Black British	1	0	3	**4**	**7%**
	Mixed/Multiple ethnic groups	1	1	0	**2**	**3%**
	White	32	13	6	**51**	**86%**
	Other ethnic group	0	0	1	**1**	**2%**
Age	18-39	5	5	4	**14**	**23%**
	40-59	10	2	3	**15**	**25%**
	60-79	15	8	3	**26**	**43%**
	80+	4	1	0	**5**	**8%**
Mean age		61	56	50	**58**	(SD 17.01)
Rheumatic disease(s)	Systemic vasculitis	13	5	1	**19**	**30%**
	Inflammatory arthritis	14	1	1	**16**	**25%**
	Crystal arthropathy	0	0	2	**2**	**3%**
	Connective tissue disease	4	8	5	**17**	**27%**
	Other	7	2	1	**10**	**16%**
Oral GC dose in last 7 days	>=30mg / day	1	0	1	**2**	**3%**
	>7.5 mg and <30 mg / day	6	4	1	**11**	**18%**
	<=7.5 mg or less / day	14	5	5	**24**	**40%**
	No oral glucocorticoids	13	7	3	**23**	**38%**

377. The impact of glucocorticoid dosing on health-related quality of life in ANCA-associated vasculitis

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Background/Objectives: Glucocorticoids are a mainstay of the treatment of ANCA-associated vasculitis (AAV) but are associated with substantial toxicity. The RITAZAREM trial enrolled

patients with a relapse of AAV to receive rituximab and one of two glucocorticoid regimens in the induction phase, followed by the maintenance phase, where patients were randomized to receive fixed interval, repeat dose rituximab or azathioprine maintenance therapy. The current study aimed to describe the health-related quality of life (HRQoL) in patients with a relapse of AAV treated with one of two different glucocorticoid regimens during the induction phase of the RITAZAREM trial.

Methods: During the induction phase of RITAZAREM, all enrolled patients received rituximab and either lower- or higher-dose glucocorticoids. Glucocorticoid regimens were non-randomized and determined by the treating clinician. HRQoL was assessed using the short form-36 (SF-36), EuroQoL Group 5-Dimensions 5-Level, and Patient-Reported Outcome Measurement Information System (PROMIS) fatigue, pain interference, and physical function questionnaires. All scores were standardized to United States population data. A 10-point patient global assessment (PtGA) scale asked patients to rate their vasculitis disease activity over the previous 28 days. HRQoL outcome measures between glucocorticoid groups were compared using t-tests. A propensity-score weighted model was used to account for potential bias in selection of glucocorticoid regimen, after confirming the absence of endogeneity. Covariates for the treatment selection component were selected based on background knowledge with considerations of baseline imbalances. The treatment selection component included age, sex, relapse severity, baseline physician global assessment, baseline Combined Damage Assessment score, and neurological manifestations, which have previously been shown to impact HRQoL in patients with AAV. Sensitivity analyses for the outcome model incorporated study site geographic region.

Results: Of the 188 patients included in the induction phase of RITAZAREM, 134 (71%) received the lower-dose glucocorticoid regimen and 54 (29%) the higher-dose regimen. Patients who received lower-dose glucocorticoid were more likely to be female (37% vs 54%, p = 0.030), have non-severe relapses (44% vs 19%, p = 0.001), and have previously received rituximab (40% vs 34%, p = 0.036). Lower-dose glucocorticoid was more commonly used in Europe and Australia compared with North America. Average SF-36 physical and mental component scores (PCS, MCS) and PROMIS fatigue, pain interference, and physical function scores were impaired at baseline compared with population norms. All HRQoL scores improved during the induction phase (p <0.001 for all). At Month 4, patients who received lower-dose glucocorticoid, compared with higher-dose, had greater SF-36 physical component scores (mean difference (MD) 5.29 (95% confidence interval (CI) 1.10, 9.48) and less fatigue MD -3.50 (95% CI -6.93, -0.06) (Figure1) in the propensity-score weighted model. Sensitivity analyses did not alter interpretation of results.

Conclusions: Among patients with a relapse of AAV who receive a combination rituximab and glucocorticoids for induction of remission, compared to a higher-dose glucocorticoid regimen, a lower-dose glucocorticoid regimen is associated with greater improvements in physical HRQoL and less fatigue. These results provide support for ongoing efforts to reduce the use of glucocorticoids in patients with AAV.

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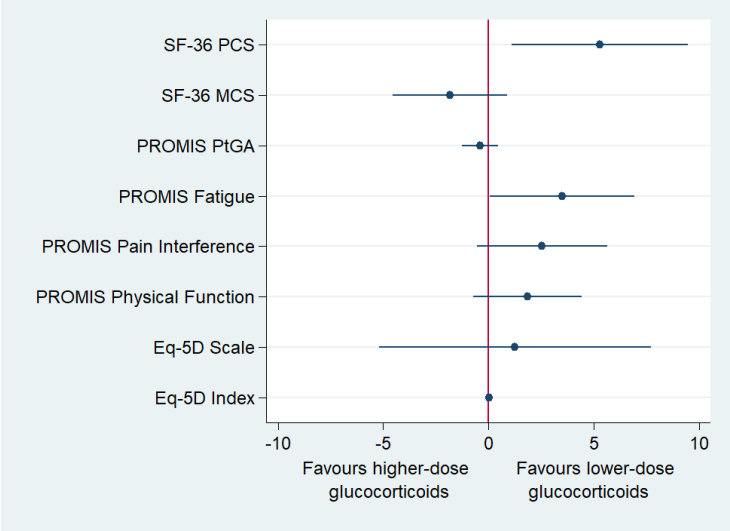
Figure 1. Differences in health-related quality of life measures at Month-4 during the RITAZAREM trial among patients with ANCA-associated vasculitis receiving higher-dose or lower-dose glucocorticoid



SF-36 *short form-36,* PCS *physical component score,* MCS *mental component score*, PROMIS *Patient-Reported Outcome Measurement Information System*, PtGA *patient global assessment*, PROMIS pain *PROMIS pain interference*, PROMIS physical *PROMIS physical function*, Eq-5D *EuroQoL Group 5-Dimensions 5-Level*
Adjusted (propensity score weighted) mean difference and 95% confidence intervals presented.

378. The need for information among patients with AAV differs between groups

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Background/ Objectives: Being diagnosed with ANCA associated vasculitis (AAV) can be a stressful experience that requires an individual to adapt to new situations. Patients that are provided adequate information are better equipped to make well informed decisions regarding their care and thereby stay compliant to the treatment plan. To provide adequate patient-centered information at the appropriate time and to identify those who may need extra support, the information needs to be explored. There have been several studies on the information

needs of various rheumatological patient groups, although very few studies for patients with AAV. The aim of this study was to explore what information patients with AAV need from their rheumatological team.

Methods: Cross-sectional data was collected between 2008 and 2019 from a cohort of patients over 18 years at a Rheumatology Clinic in Sweden. Patients with different forms of AAV (GPA, MPA and EGPA), that were seen by the Rheumatology clinic as primary contact, were included. At inclusion, participants were asked to fill in questionnaires including the Educational Needs Assessment Tool (ENAT) that measures the patient's information needs. The initial question, 'Do you need information right now about something that can help you with your rheumatic disease?' is answered yes/no. ENAT then includes 7 domains (Managing pain, Movement, Feelings, Disease process, Treatments, Self-help measures and Support systems) each containing 4-7 items (4-point Likert scale, 'not at all important = 0' to 'extremely important = 3'). The total sum is divided by the maximum score and gives the percentage response of maximum score (0-100%), 0% meaning no information need and 100% highest information need. The responses are presented as "mean % of the domain score". Independent-sample t-test and one-way ANOVA were used to compare means between groups based on gender, age, social status, disease, disease duration and disease activity.

Results: 178 individuals completed the questionnaire, equally divided by gender. Age ranged from 18-85, median 61, and 33.7% had been diagnosed within 2 years. The mean ENAT total score was 56.8% (range 0-100%). The highest information need was found in the domains 'Disease process' (78.1%), 'Self-help measures' (68.5%) and 'Treatments' (63.6%) whereas lesser need for information was found in the domains 'Managing pain' (47.5%), 'Support systems' (46.5%) and 'Movement' (41.1%). The domain 'Feelings' was scored as moderate (55.5%). Patients who acknowledged a present information need scored significantly overall higher in all the domains. Disease duration and gender were shown to significantly affect the information need where the highest scores were found among females and among those with disease duration < 2 years with significant difference in 3/7 domains (all $p = <0.05$). Age, disease activity, diagnosis and social status did not affect the ENAT scores.

Conclusions: Even though only 38% of participants stated a current need for information, the results indicate that patients with AAV need more information about 'Disease process', 'Self-help measures' and 'Treatments'. Special consideration needs to be taken to females and patients with short disease duration who reported a significantly higher need for information.

Disclosures: None

379. The new player in the assessment of AAV patients: A real life-experience of AAV-PRO

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Background/ Objectives: Even BVAS, BVAS-WG, and VDI are composite indexes has been using for AAV patients, none of them include patients' perspectives related to disease. ANCA-associated vasculitis patient reported outcomes (AAV-PRO) has been published and validated in 2018 (1). Recently, AAV-PRO has been translated into Turkish (2).
This study is aimed to use disease activity and damage indexes along with AAV-Pro and investigate possible correlations of AAV-Pro with BVAS, VDI and patient/ physician global assessments.

Methods: Consecutive AAV patients has been invited to the study during their routine outpatient/inpatient assessment. As a part of their recruitment to the Hacettepe University Vasculitis Research Centre (HUVAC) prospective database starting from October 2014, baseline disease and laboratory characteristics, treatments and BVAS and VDI has been recorded. For the current study, patient and physician global assessment (PtG-VAS and PhysG-VAS) and AAV-PRO (organ-specific symptoms, treatment side effects, social and emotional impact, concerns about the future, physical function, and systemic symptoms) were applied. Disease characteristics and activity parameters with PROs in current visit was compared between PR3- and MPO-positive groups. Pearson correlation analysis was used to investigate possible correlations of AAV-PRO with BVAS, VDI, PtG-VAS, and PhysG-VAS.

Results: A total of 85 AAV patients (54 (63.5%) GPA, 23 (27.1%) EGPA, 5 (5.9%) MPA and 3 (3.5%) renal-limited) were included in the study. 40 (47.1%) of the patients was male and mean age was 51.4 +/- 15.3. Disease duration 61.6 +/- 44.0 months. 43 (50.6%) of patients were PR3 (+). 14 (60.9%) of EGPA patients were ANCA (-). Demographic and clinical characteristics and comparisons between PR3 and MPO AAV patients was shown in Table 1. No difference was found between these groups regarding AAVPro subtypes. BVAS has moderate relationship with AAV-Pro treatment side effects and physical function.
VDI was weakly correlated with all AAV-Pro subtypes. Correlation coefficients were given in Figure separately for BVAS, VDI, PtG-VAS, PhysG-VAS versus AAV-PRO components.

Conclusions: AAV-Pro determines various disease aspects of AAV. MPO(+) and PR3(+) AAV patients were similar in terms of AAVPro subtypes. Even BVAS and VDI could partially reflect AAV-Pro organ-specific symptoms and treatment side effects; those were not correlated to the social and emotional impact and concerns about the future. Implications of all AAV-Pro subtypes will give opportunity to understand all perspectives of AAV.

Disclosures: None

Table 1. Demographic and clinical characteristics and comparisons between PR3 and MPO AAV patients in current visit

	All patients (n=85)	PR3(+) AAV (n=43)	MPO(+) AAV (n=25)	P*
Mean age (years)	51.4 15.3	50.0 15.3	58.2 14.0	0.03
Gender (Male)	47.1	58.1	31.0	0.04
Disease duration (months)	61.6 44.0	70.4 46.9	57.1 38.3	0.23
Constitutional	26/66 (39.4)	13/34 (38.2)	9/18 (50.0)	0.41
Mucocutenous	7/65 (10.8)	5/33 (15.2)	2/18 (11.1)	0.69
Musculoskeletal	27/65 (41.5)	12/34 (35.3)	8/17 (47.1)	0.42
Eye	11/66 (16.7)	7/35 (20.0)	2/16 (12.5)	0.51
Ear-Nose-Throat	28/65 (43.1)	19/35 (54.3)	5/16 (31.3)	0.13
Respiratory	23/63 (36.5)	11/34 (32.4)	4/16 (25.0)	0.60
Cardiac	5/60 (8.3)	2/32 (6.4)	2/16 (12.5)	0.46
Vascular	3/59 (5.1)	0	2/16 (12.5)	0.10
Gastrointestinal	7/60 (11.7)	3/32 (9.4)	1/15 (6.7)	0.76
Renal and Genitourinary	4/61 (4.7)	3/32 (9.4)	1/16 (6.3)	0.71
Nervous	10/60 (16.7)	3/31 (9.7)	2/16 (12.5)	0.77
BVAS	2.9 4.9	2.7 4.5	3.4 6.4	0.59
VDI	2.8 1.6	2.7 1.7	2.9 1.7	0.60
PhysG-VAS	2.6 1.8	2.8 1.8	2.2 2.0	0.24
PtG-VAS	3.6 2.4	3.8 2.4	3.1 2.7	0.32
AAV-PRO (organ-specific symptoms)	16.2 15.0	16.9 15.1	12.6 8.5	0.20
AAV-PRO (systemic symptoms)	26.8 22.2	27.6 22.2	25.5 23.2	0.71
AAV-PRO (treatment side effects)	20.8 17.4	22.4 18.5	18.6 15.8	0.40
AAV-PRO (social and emotional impact)	25.5 22.9	26.4 20.7	20.8 23.1	0.31
AAV-PRO (concerns about the future)	27.5 23.1	30.7 22.6	24.4 23.6	0.28
AAV-PRO (physical function)	17.9 20.8	15.8 17.3	20.8 24.7	0.34

*p value of the comparison PR3 or MPO (+) AAV patients

380. AAV-Pro results in consecutive visits: Is it useful?

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Background/ Objectives: ANCA-associated vasculitis patient reported outcomes (AAV-PRO) has been published and validated in 2018 (1). Recently, AAV-PRO has been translated into Turkish (2). However, data regarding usage of AAVPro in consecutive visits is scarce. This study is aimed to investigate the change in disease activity parameters and AAVPro between two consecutive visits among AAV patients.

Methods: As a part of AAV patients' recruitment to the Hacettepe University Vasculitis Research Centre (HUVAC) prospective database, baseline disease and laboratory characteristics, treatments and BVAS and VDI has been recorded. For our AAVPro study, patient and physician global assessment (PtG-VAS and PhysG-VAS) and AAV-PRO (organ-specific symptoms, treatment side effects, social and emotional impact, concerns about the

future, physical function, and systemic symptoms) were applied to 85 patients. 45 of these patients had consecutive visits. We evaluated the change between two visits in terms of in disease activity, damage indexes along and AAVPROs.

Results: Data of 45 AAV patients (32 (71.1%) GPA, 10 (22.2%) EGPA, 1 (2.2%) MPA and 2 (4.4%) renal-limited) was analyzed. 25 (55.6%) of the patients was male and mean age was 49.9 □ 15.4. Disease duration 56.7 □ 40.6 months. 25 (55.6%) of patients were PR3 (+), and 11 (24.4%) of them MPO (+). Mean duration between two visits was 8.5 □ 6.0 months. BVAS was significantly decreased in the second visit and also Phy-G-VAS seems decreased. However, no statistical difference was found between two visits among all AAVPro subtypes and VDI.

Conclusions: As far as our literature research, this is the first study investigating usefulness of AAV in consecutive visits. We did not find any change in the assessment of AAVPros within 6 months. This result can be explained as AAPro includes both activity and damage parameters. Further studies are required to understand the optimal timing of re-use of AAVPro.

Disclosures: None

Table 1. Demographic and clinical characteristics of patients at each follow-up visit (n=45)

	Visit 1	Visit 2	[redacted]
Constitutional	12/34 (35.3)	8/32 (25.0)	
Mucocutenous	5/33 (15.2)	5/33 (15.2)	
Musculoskeletal	10/34 (29.4)	7/33 (21.2)	
Eye	7/35 (20.0)	2/32 (6.3)	
Ear-Nose-Throat	14/34 (41.2)	15/36 (41.7)	
Respiratory	15/33 (45.5)	9/33 (27.3)	
Cardiac	3/30 (10.0)	3/30 (10.0)	
Vascular	2/29 (6.9)	1/30 (3.3)	
Gastrointestinal	4/31 (12.9)	0	
Renal and Genitourinary	3/32 (9.4)	3/31 (9.7)	
Nervous	6/32 (18.8)	6/33 (18.2)	
			P*
BVAS	3.5 5.8	1.1 2.1	0.035
VDI	2.5 1.6	2.7 1.6	0.10**
PhysG-VAS	2.8 1.8	1.9 1.5	0.064***
PtG-VAS	3.8 2.7	2.9 2.0	0.29***
AAV-PRO (organ-spesific symptoms)	15.0 13.1	13.7 14.7	0.54
AAV-PRO (treatment side effects)	20.6 17.6	17.4 14.0	0.18
AAV-PRO (social and emotional impact)	23.1 21.6	21.6 20.4	0.67
AAV-PRO (concerns about the future)	24.2 22.3	23.3 21.5	0.80
AAV-PRO (physical function)	18.1 20.0	17.8 21.9	0.92
AAV-PRO (systemic symptoms)	22.1 19.7	21.1 19.5	0.75

BVAS: Birmingham Vasculitis Activity Score, VDI: Vasculitis Damage Index, PtG-VAS/PhysG-VAS: Patient/Physician Global VAS. Data were given as n(%) or mean □ standard deviation. *p values of comparing first and second visit disease activity and damage scores.* *n=30 ***n= 25

381. Quality-of-Life Impact of Cutaneous Vasculitis: Findings from the VascSkin study and Vasculitis Patient-Powered Research Network

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Background / Objectives: Cutaneous manifestations of vasculitis can cause itching, pain, and ulceration, and their psychosocial effects may be significant. However, the quality-of-life (QL) impact of skin vasculitis has not been systematically evaluated. This study aimed to assess the QoL of patients with cutaneous manifestations of vasculitis and to determine potential factors affecting patients' experiences. These data may help form the basis of a patient-reported outcome tool for measuring disease severity and response to treatment in clinical studies.

Methods: Utilizing the Vasculitis Patient-Powered Research Network (VPPRN), and incorporating feedback from patient partners, we disseminated an online survey to patients with cutaneous manifestations of vasculitis (all major types) including validated measures of skin-related QoL (Skindex-29) and general health and wellbeing (SF-36).

Results: A total of 234 responses were received. After eliminating duplicates and incomplete responses, 190 remained. Of these, 107 patients had experienced active skin lesions within the preceding 4 weeks and were included for analysis. Skindex-29 survey results were categorized using previously published methods, and SF-36 scores of 50 on a scale of 0-100 were considered "average." The mean QoL impact of skin vasculitis was considered to be severe in every domain of the Skindex-29, including "symptoms," "emotions," "functioning," and "overall," and QoL was below average in 6/8 domains of the SF-36 health survey. Female patients experienced, on average, worse QoL than male patients. QoL impact was greater with increasing disease severity. When analyzed by vasculitis type, cutaneous small vessel vasculitis (CSVV) was determined to have the greatest impact on QoL as assessed by both the Skindex-29 and the SF-36, followed by urticarial vasculitis and IgA vasculitis, and then the remaining types. QoL impact was greatest for those with disease duration of less than 2 years.

Conclusions: Administration of validated skin specific and generic QoL measures to patients with cutaneous manifestations of vasculitis revealed diminished QoL across multiple domains, suggesting skin vasculitis has an important, even severe, impact on health and wellbeing in various types of vasculitis. The negative impact on QoL was notably greater among female patients and those with increased vasculitis disease activity. Interestingly, skin limited CSVV had the greatest impact on QoL, supporting the substantial effect cutaneous vasculitis has on patients' symptoms and self-perception of their health. Future work will examine more closely the role of cutaneous vasculitis in determining overall health related QoL, compare the impact

on QoL of cutaneous vasculitis to that of other skin conditions, and evaluate changes in QoL resulting from successful management of vasculitis involving the skin.

Disclosures: None

382. Utility of the 22-Item Sinonasal Outcome Test Patient-Reported Outcome Instrument in ANCA-Associated Vasculitis

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Background/ Objectives: ANCA-associated vasculitis (AAV) causes sinus symptoms that negatively impact quality of life. The 22-item Sinonasal Outcome Test (SNOT-22) is a patient-reported outcome measure to assess symptoms and quality of life in chronic rhinosinusitis but has not been well-studied in AAV. We compared SNOT-22 scores during remission and active disease in patients with AAV with and without sinus involvement and investigated if SNOT-22 can predict subsequent relapse.

Methods: Subjects with AAV (granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA) and healthy controls were followed longitudinally with data collected on disease activity measures [BVAS/WG, physician global assessment (PGA)], SNOT-22, and treatments. SNOT-22 questions score on a 0-5 scale with higher scores for worse symptoms and include 5 subdomains: rhinologic, extra-nasal rhinologic, ear/facial, psychological, and sleep. Generalized estimating equations evaluated the association between SNOT-22 scores and disease activity. Models were adjusted for concomitant seasonal allergies and use of antibiotics, immunosuppressive drugs, and sinus rinses.

Results: This analysis included data from 159 subjects with AAV (106 GPA, 21 MPA, 32 EGPA) with 747 visits (110 active disease visits, ~3.5 months between visits) and 70 controls. 122 (77%) subjects with AAV had baseline sinonasal involvement. Baseline SNOT-22 scores were higher in AAV vs. controls (mean (SD): 27.5 (1.6) vs. 15.4 (2.1), $p<0.01$) and higher for subjects with AAV with vs. without sinus involvement (mean (SD): 30.3 (20.5) vs. 17.8 (13.2), $p<0.01$). Adjusted SNOT-22 scores were higher during active disease vs. remission for GPA and EGPA, but not MPA (Figure 1A). For all subjects with AAV, higher PGA was associated with higher SNOT-22 ($p<0.01$). In GPA, active disease was associated with higher scores in each SNOT-22 subdomain except sleep. Compared to remission visits, active disease was associated with worse scores in psychological and sleep subdomains for MPA and in rhinologic subdomain for EGPA (Figure 1B). Prior SNOT-22 total scores were not associated with subsequent relapse among all visits, but when limiting visits to those 2 months apart, increase in SNOT-22 score at the prior visit was associated with subsequent relapse (adjusted OR 1.15 per score change of 5, 95% CI: 1.0-1.3, $p=0.03$).

Conclusions: In patients with AAV SNOT-22 scores are higher during active disease vs. remission, particularly among patients with prior sinus involvement. The subdomains impacted most by disease activity differ by disease type. When measured within 2 months, change in SNOT-22 scores at remission are associated with subsequent relapse. SNOT-22 may be an informative patient-reported outcome measure to monitor disease activity in AAV.
Disclosures: None

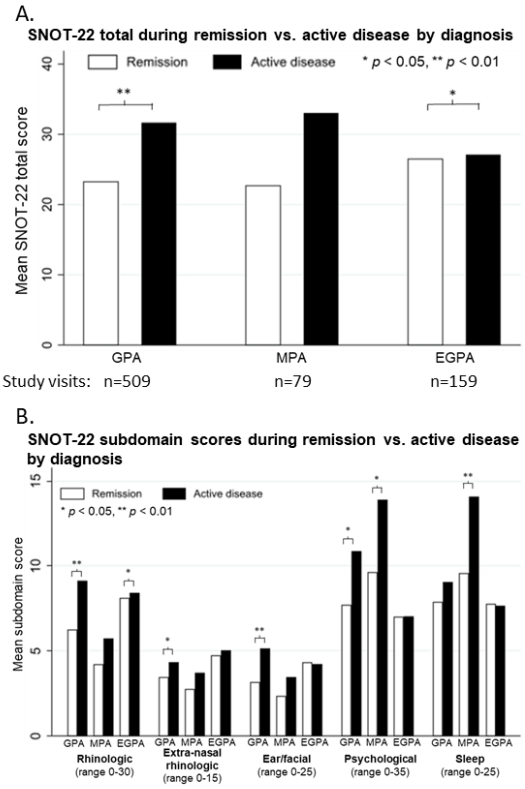

Figure 1. A) SNOT-22 total scores at remission and active disease visits according to diagnosis. Results demonstrate higher scores during active disease for subjects with GPA and EGPA. B) SNOT-22 subdomain scores during remission and active disease. Results demonstrate higher scores during active disease with larger effect on certain subdomains according to diagnosis. Asterisks indicate significant differences in adjusted model. Abbreviations: EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis.

383. Characterization of Symptoms of Nasal Disease in Relapsing Polychondritis Using Patient-Reported Data

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Background: Nasal chondritis is a well-recognized manifestation of relapsing polychondritis (RP), occasionally leading to saddle nose deformity. Early symptoms of nasal chondritis, such as nose pain, are often overlooked. The objective of this study was to characterize nose pain and identify associated symptoms reported by patients with RP.

Methods: Patients with self-reported RP were invited to participate in an online survey. Participants were asked questions about nose pain such as location, onset, duration, frequency, quality, diurnal variation, aggravating and alleviating factors, associated symptoms, and saddle nose deformity. Participants with physician-diagnosed RP, aged ≥ 18 years, and who meet McAdams diagnostic criteria were included in the study. Fisher's exact test was used to compare clinical characteristics between patients with and without nose pain.

Results: A total of 659 subjects were included, of which 484 (73%) were from the United States. The majority (n=548, 83%) identified themselves as Caucasians, and 574 (87%) were female. Mean age was 50 years (interquartile range = 41-58). Many patients (n=430, 65%) reported nose pain. The diagnosis of RP in patients with nose pain was mostly made by rheumatologists (313, 73%) and otolaryngologists (101, 23%). Compared to patients without nose pain, those with nose pain were more likely to report saddle nose deformity, audio vestibular symptoms, joint pain and swelling (Table 1). Treatment with prednisone was reported by 429 (99%) patients, of which 423 (99%) reported symptom relief with prednisone.

In patients with nose pain (n=430), pain was described as stabbing (n=147, 34%), sharp (n=73, 17%), dull (n=73, 17%), or burning (n=46, 10%); a majority (n=313, 73%) reported at least two types of pain and 137 (32%) did not report a pain descriptor. Associated nasal pressure (n=150, 34%), tingling (n=119, 27%), or throbbing (n=61, 14%) was reported. Factors felt to aggravate nose pain were minimal trauma (n=240, 55%), stress (n=210, 48%), and cold exposure (n= 104, 24%); 50% reported more than one aggravating factor. A majority of patients (n=322, 75%) reported the pain lasted for ≥1day. Frequency of reported nasal symptoms were daily (n=65, 15%), weekly (n=73, 17%), monthly (n=83, 19%), and few times/year (n=109, 25%). Onset of pain was mostly reported as variable (n=127, 30%) or gradual (n=138, 32%). The location of nasal pain included bridge (n=252, 58%), sides (n=171, 39%), base (n=146, 34%), or tip (n=134, 31%), with 275 (64%) reporting pain in at least two locations. Many patients reported nose pain during the day (n=262, 60%), some reported nighttime pain (n=169, 39%) and/or pain during sleep (n=108, 25%). The most common symptoms associated with nose pain were redness, swelling, and congestion, each reported by 50% of patients.

Conclusion: Most patients with RP report a wide range of symptoms of nasal disease. The most common nasal complaints are stabbing pain with associated redness, swelling and congestion that lasts longer than a day, pain involving the bridge of the nose and that is

aggravated by minor trauma. Awareness of the complexity of symptoms of nasal disease in RP and a detailed assessment of nasal manifestations could be helpful to clinicians for establishing a diagnosis of RP and monitoring disease activity.

Disclosures: none

Table 1: Comparison of Clinical Manifestations Among Patients with Relapsing Polychondritis Presenting with and without Nose Pain

	Relapsing polychondritis with nose pain n=430	Relapsing polychondritis without nose pain n= 215	P-value
Eye inflammation: n (%)	246 (57)	108 (50)	0.08
Saddle nose deformity: n (%)	69 (16)	20 (9)	0.02
Ear pain, redness, swelling n (%)	397 (92)	189 (88)	0.05
Cauliflower ear/ deformed ear cartilage: n (%)	72 (17)	30 (14)	0.1
Hearing loss: n (%)	134 (31)	54 (25)	0.2
Audiovestibular symptoms*: n (%)	275 (64)	115 (53)	0.004
Airway damage**: n (%)	108 (25)	62 (28)	0.5
Joint pain / swelling: n (%)	369 (86)	165 (77)	0.01

*Audiovestibular symptoms: tinnitus, vertigo

**Airway damage: damage to trachea and/or bronchi

384. Determinants of patient and physician global assessment of disease activity in ANCA-associated vasculitis.

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Objectives: To compare patients' and physician's global assessment of disease activity in ANCA-associated vasculitis and investigate factors influencing the assessment of disease activity.

Methods: Between 2010 and 2020, physicians and patients with ANCA-associated vasculitis in our outpatient clinic assessed a global disease activity score at every visit (numerical rating scale 0 – 10, n=1083). We compared the global disease activity score between physicians and patients. In a multiple linear regression analysis, we examined clinical factors influencing the respective disease activity assessment.

Results: Patients had a mean age of 65 (±15) years and a mean disease duration of 15 years (±7). The median global score of patients' as well as physicians' disease activity assessments was 2 points. The BVAS was recorded 113 times and had a median of 3 points (± 2.9).

Physician-documented disease activity was associated with the level of BVAS (β 0.07, p 0.01), patients' assessments (β 0.18, p 0.001), and patient BMI (β 0.05, p 0.003). In addition, disease activity was rated higher in women (β 0.61, p <0.001). Patients' assessment, was associated with the extent of pain (β 0.36, p <0.001), the physician assessment (β 0.56, p 0.001) and inversely with the BMI (β -0.09, p 0.007).

Conclusion: In our cohort, patients and physicians rated the disease activity equally. Physicians' disease activity assessments correlated with documented vasculitic expressions in the BVAS. In addition, female gender and high BMI were found to influence physician disease activity ratings, whereas pain and low BMI were associated with higher patient disease activity ratings. This study supports the development and interpretation of PROs for disease activity estimation in ANCA-associated vasculitides.

Disclosures: None

385. Health Related Quality of Life Among Patients with Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis

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Background: Anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) is a debilitating disease that can have a significant impact on a patient's quality of life. The aim of this study was to assess the longitudinal quality of life amongst those diagnosed with AAV using the EQ-5D instrument, which allows for calculation of quality-adjusted life years (QALYs.)

Methods: 343 patients with AAV participated in this study, of which 191 (55.7%) were male, resulting in 2746 episodes. The EQ-5D-5L standardised instrument was used to evaluate health related quality of life in the domains of mobility, self-care, usual activities, pain/discomfort, anxiety/depression and to generate a summary index score. Overall health was also rated using a visual analogue scale (0-100). EQ-5D questionnaires were completed during routine nephrology clinic attendances and through a vasculitis patient support smartphone app. We used a mixed-effects model to control for multiple entries relating to individual patients.

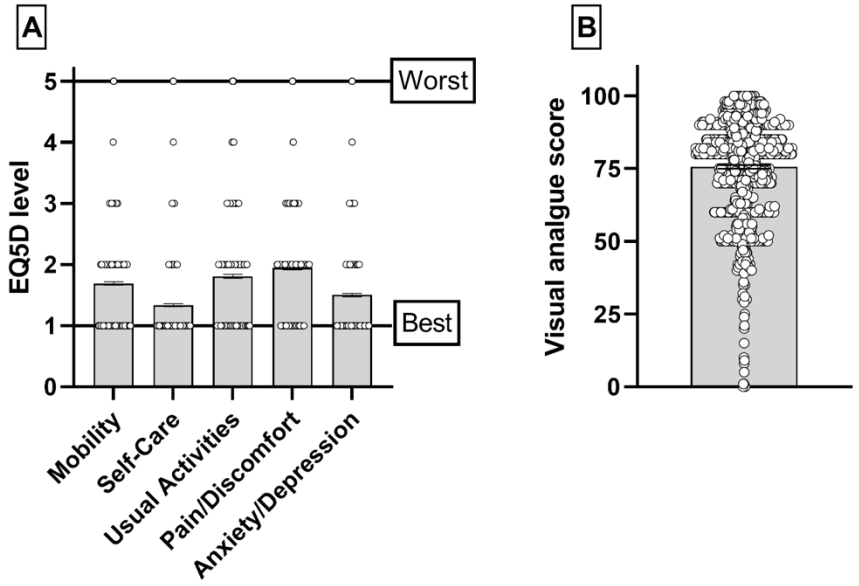
Results: A lower quality of life was seen amongst those with AAV (median index value 0.80, overall population average 0.856). The mean visual analogue scale score was 75.6±17.3 (overall population average 82.8, Fig 1). Patients' pain and discomfort level (mean 1.95) was most affected while self-care (mean 1.33) was least affected (Fig 1). An increase in BVAS

tightly correlated with a reduction in quality of life. The index score decreased with increasing age. Using a median survival rate of 6.16 years for patients with small vessel vasculitis, we calculated the QALYs for this population as 4.9 years.

Conclusions: We have defined for the first time the EQ-5D index value over the full disease course in patients with AAV. Other studies have demonstrated a reduction in quality of life during active disease using the AAV–PRO questionnaire and the Medical Outcomes Study Short Form-36. A decrease in work productivity has also been noted. Previously reported mean index values of 0.72 and 0.76 were lower than our observed values, although both are significantly reduced compared to population norms. In conclusion, this research highlights the negative impact of AAV on patients' lives.

Disclosures: The authors have no conflicts of interest to declare.

Figure 1. (A) Domain specific EQ5D levels and (B) visual analogue score. Both graphs reflect mean and 95% confidence interval.



386. Vasculitis: Effects of Remission Maintenance Therapies on Relapse and Side Effects: Patient Preferences (VERITAS).

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Background: Relapses are common in vasculitis and preventing relapses is a goal of treatment and a focus of research. However, little is known about the degree to which patients

value avoiding relapses and how much risk from treatments for vasculitis patients are willing to accept to avoid a relapse.

Methods: With patient partners, we designed, piloted, and administered a survey called the Vasculitis: Effects of Remission maintenance Therapies on relapse and Side effects: patient preferences (VERITAS). The survey presented scenarios in which the risk of relapse with current treatments was 30% over 5 years followed by a scenario in which additional remission maintenance therapy resulted in either a 5%, 10%, or 15% absolute reduction in the risk of relapse and either a 0% or 5% excess risk of adverse events. Participants were randomly allocated scenarios that either left the additional therapy unnamed or specified it as prednisone. The distribution of minimally important difference (MID) in relapse risk, defined as the lowest ARR at which additional therapy was accepted, was determined for each respondent for each scenario. We used multivariable logistic regression models to calculate estimates of the effect of naming prednisone on the MID for a relapse compared to an unnamed therapy. Given the bimodal response distribution, a MID >5% was used as the outcome for the logistic regression models.

Results: Of 274 respondents, 207 (75.5%) had ANCA-associated vasculitis. 201 (73.3%) participants had usable data for scenarios without, and 205 (74.8%) with, excess AEs. 138 (68.7%) accepted the additional therapy at all ARRs presented (5, 10 and 15%) without excess AEs, while 115 (56.1%) with excess AEs. Conversely, 43 (21.4%) of respondents refused additional therapy for all ARRs presented without excess AEs, and 63 (30.7%) with excess AEs. Naming the additional therapy prednisone clearly increased the benefit needed to accept therapy when no excess AEs were specified (37 [38.5%] respondents had an MID >5% in prednisone scenarios as compared to 26 [24.8%] in unnamed therapy scenarios, p=0.002) but not in scenarios with excess AEs (49 [49%] respondents had an MID >5% in prednisone scenarios as compared to 41 [39.1%] in unnamed therapy scenarios, p=0.11). Similarly, presenting scenarios with excess AEs first increased the benefits required to accept additional therapy compared to when scenarios without excess AEs were presented first (41 [42.3%] respondents had an MID >5% when excess AE scenarios were presented first compared to 22 [21.2%] when no excess AE scenarios were presented first, p<0.001).

Conclusions: In this survey study of patients with vasculitis, most respondents considered ARRs in relapse of at least 5% sufficient to accept additional therapy while less than one-third would not accept additional therapy with an ARR of at least 15%. These results can be used to plan future trials and frame treatment effects for patients.

***Disclosures**:* NK - Advisory board or speakers bureau: Roche; Grants, Research, or Clinical Trials: Roche Clinical Trial (RITAZAREM - AAV). BMS - Clinical Trial (AGATA - GCA and TAK, ABROGATE - GPA), Sanofi - Clinical trial 2020 in GCA and PMR, AbbVie - Clinical Trial 2020-2021 in GCA GSK - Clinical Trial (MIRRA - Mepolizumab in eGPA)

Outcome and morbidity

387. Giant cell arteritis and COVID-19 pandemic

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Background/ Objectives: Patients with giant cell arteritis (GCA) represent a fragile population with an increased infection risk. Older age, male sex, multimorbidity and glucocorticoids (particularly dosages >10 mg prednisolone equivalent) emerged in rheumatic patients as risk factors for severe COVID-19. We aimed to evaluate the frequency and severity of COVID-19 in well-defined GCA cohort.

Methods: We analyzed medical records of histologically and/or by imaging proven GCA patients diagnosed between September 2011 and December 2019 at our secondary/tertiary center and followed during the COVID-19 pandemic between March 2020 and June 2021. Cox hazard regression analysis was used to determine risk factors for death during pandemic.
Results: During the 100-month period, GCA was newly diagnosed in 309 patients, 49 of whom died before March 2020. Of the remaining 260 patients (68.8% females, mean (±SD) age at time of COVID-19 pandemic 77.1 (±8.3) years), SARS-CoV-2 infection was proven in 31 (11.9%) patients (74.2% females, mean (SD) age 75.1 (±9.7 years)). At the time of SARS_Cov2 infection GCA was in a stable remission in 30 patients (7 without therapy, 10 on steroids alone, 8 on leflunomide, 4 steroids + leflunomide, 1 ustekinumab; mean prednisolone dose 4.5mg) and relapsed in one patient 6 weeks prior (prednisolone 30 mg + leflunomide). Twenty-two/31 (71%) patients had mild COVID-19 and were symptomatically treated at home, while nine were hospitalized due to severe infection. Table 1 shows GCA treatment characteristics at the time of mild vs. severe COVID-19.
During pandemic 15/260 (5.8%) GCA patients died, there was one death due to COVID-19. Nevertheless, a 5-year standardized mortality rate (SMR) in GCA compared to general population was lower with the inclusion of pandemic period (1.12 (95 % CI 0.84-1.48), p=0.44), vs. pre-pandemic period (1.32 (95 % CI 0.96-1.76), p=0.078). SMR decreased for 15% (95% CI 4% - 22%, p=0.008). Mortality of GCA patients during pandemic remained at the level of pre-pandemic period. Increasing age (HR 1.11 (95% CI 1.01–1.21), p=0.023) emerged as the only independent risk factor associated with death.

Conclusions: Overall mortality in our GCA cohort was not increased during pandemic. Lower doses of glucocorticoids were not associated with more severe COVID-19.

Disclosures: Authors have no conflict of interest to declare.

Table 1. Comparison between GCA patients with mild vs. severe COVID-19

	Mild COVID-19 (22 pts)	*Severe COVID-19 (9 pts)*	*P value*
Gender	18 (81.8%)	5 (55.6%)	0.185
Age	73.8±9.7	78.3±9.3	0.516
No treatment	2 (9.1%)	5 (55.6%)	0.012
Steroids	12 (54.5%)	3 (33.3%)	0.433
Leflunomide	9 (40.9%)	4 (44.4%)	1.0
Ustekinumab	1	0	1.0

388. SURVIVAL IN GIANT CELL ARTERITIS

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Background/ Objectives: Recent meta-analysis reported no difference in mortality of giant cell arteritis (GCA) at a population level[1]. We aimed to evaluate the survival of GCA patients in Slovenia.

Methods: We included GCA patients diagnosed between Sep/2011 and Dec/2019, and prospectively followed until death or censor date of 24/Jun/2021. Kaplan–Meier analysis, standardized mortality ratio (SMR) using age, gender matched Slovenian population as reference, and Cox hazard regression analysis were used to study survival.

Results: From 309 GCA (65.7% females, median (IQR) age at diagnosis 74.9 (67.7–80.1.7) years), 64 patients died. The one- and five-year survival rate was 92.9% and 83.5%, respectively. Compared to general population, SMR was significantly higher in the first year after GCA diagnosis, whereas later mortality was comparable (Table 1). The most frequent cause of death in GCA was a cardiovascular disease (32.8%), followed by infection (29.7%), and cancer (17.2%). Two patients died due to trauma, two due to complications of gastrointestinal perforation, while suicide, dementia, bleeding, and myopathy were recorded in one patient each. In five patients the cause of death was unknown. Cox hazard regression analysis revealed increasing age (HR 1.12 (95%CI 1.09–1.17), p<0.001) and cerebrovascular events (HR 4.65 (95%CI 2.10–10.29), p<0.001) as predictors of death. Patients with large vessel GCA were not at increased risk of death compared to cranial limited GCA (HR 0.92 (95%CI 0.48–1.74), p=0.792).

Conclusions: GCA patients had an increased risk of death in the first year from diagnosis. Age and stroke emerged as risk factors of death.

Disclosures: Authors have no conflict of interest to declare.

Table 1. Standardized mortality ratios of GCA patients compared to the general population Legend: FU follow up; SMR Standardized mortality ratio; CI confidence interval; * SMR for GCA patients following longer than one year after diagnosis.

Years of FU	Observed deaths	Expected deaths	SMR (95% CI)	P-value	Specific SMR* (95 % CI)	P-value
1	22	11.9	1.85(1.16-2.80)	0.005		
2	33	23.6	1.40(0.96-1.97)	0.066	1.06 (0.53-1.89)	0.980
3	39	33.3	1.17(0.83-1.60)	0.371	0.89 (0.52-1.42)	0.711
4	47	40.6	1.16(0.85-1.54)	0.351	0.98 (0.63-1.44)	0.984
5	51	45.3	1.12(0.84-1.48)	0.443	0.97 (0.65-1.40)	0.951

389. ANCA-negative and myeloperoxidase-ANCA–positive granulomatosis with polyangiitis are distinct subsets.

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Objectives: To investigate whether ANCA-negative and myeloperoxidase (MPO)-ANCA–positive granulomatosis with polyangiitis (GPA) differ from proteinase-3 (PR3)-ANCA–positive GPA.

Methods: Diagnostic characteristics and outcomes of newly diagnosed French Vasculitis Study Group Registry patients with ANCA-negative, MPO-ANCA–positive or PR3-ANCA–positive GPA satisfying ACR criteria and/or Chapel Hill Conference Consensus Nomenclature were compared.

Results: Among 727 GPA, 62 (8.5%) were ANCA-negative, 119 (16.4%) MPO-ANCA–positive and 546 (75.1%) PR3-ANCA–positive. ANCA-negative patients had significantly (P <0.05) more limited disease (17.7% vs 5.8%) and less kidney involvement (35.5% vs 58.9%) than those PR3- or MPO-ANCA–positive, with comparable relapse-free (RFS) and overall survival (OS). MPO-ANCA–positive versus PR3-ANCA–positive and ANCA-negative patients were significantly more often female (52.9% vs 42.1%), older (59.8 vs 51.9 years), with more frequent kidney involvement (65.5% vs 55.2%) and less arthralgias (34.5% vs 55.1%), purpura (8.4% vs 17.1%) or eye involvement (18.5% vs 28.4%); RFS was similar but OS was lower before age adjustment. PR3-positive patients' RFS was significantly lower than for ANCA-negative and MPO-positive groups combined, with OS higher before age adjustment. PR3-ANCA–positivity independently predicted relapse for all GPA forms combined but not when comparing only PR3- vs MPO-ANCA–positive patients.

Conclusions: Based on this large cohort, ANCA-negative vs ANCA-positive patients more frequently had limited disease but similar RFS and OS. MPO-ANCA–positive patients had similar RFS but lower OS due to their older age. PR3-ANCA–positive patients had lower RFS than ANCA-negative and MPO-positive groups, but not lower OS due to effective relapse treatment.

Disclosures: None

390. ANCA trajectory is associated with renal survival and relapse risk in ANCA-associated vasculitis with glomerulonephritis

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Background/ Objectives: Anti-neutrophil cytoplasmic antibody (ANCA) trajectory in ANCA-associated vasculitis with glomerulonephritis (AAV-GN) has been suggested to be associated with AAV relapse. Few studies focused on its association with renal prognosis. Thus, we aimed to investigate the relationship between i) ANCA specificity and evolutive pattern, and ii) renal outcomes.

Methods: This multicentric retrospective study included patients with AAV-GN diagnosed since 01/01/2000. Patients without ANCA at AAV-GN diagnosis and with fewer than 3 ANCA determinations during follow-up (including once between 6-12 then 12-24 months after diagnosis) were excluded. We analyzed eGFR variation over 2 years and the 5-year censored renal and relapse-free survival according to three ANCA patterns (negative, recurrent, persistent) and ANCA specificity (MPO or PR3).

Results: Over a median follow-up of 56 [33-101] months, 19 [13-25] ANCA determinations were performed for the 134 included patients. Patients with a recurrent/persistent ANCA pattern had a lower renal ($p = 0.042$) and relapse-free ($p = 0.041$) survival compared to patients with a negative ANCA pattern. Patients with a recurrent/persistent MPO-ANCA pattern had the worst renal survival ($p = 0.011$) and patients with recurrent/persistent PR3-ANCA pattern had the worst relapse-free survival ($p = 0.022$) compared to other patterns. The negative ANCA pattern was associated with a greater eGFR recovery. In multivariate regression analysis, it was an independent predictor of 2-year eGFR percent variation ($p = 0.003$).

Conclusions: ANCA trajectory after ANCA-GN diagnosis is associated with outcomes. MPO-ANCA recurrence/persistence identifies patients with a lower potential of renal function recovery and a higher risk of ESKD, while PR3-ANCA recurrence/persistence identifies patients with a greater relapse risk. Thus, ANCA trajectory may help identify patients with a

smoldering disease. Further investigations are required to evaluate its usefulness in tailoring immunosuppression.

Disclosures: None

391. Withdrawn

392. Management and Outcomes of ANCA-Associated Vasculitis at a Tertiary Healthcare Facility

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Background/ Objectives: Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis(AAV) is a rare multisystem autoimmune condition with an incidence of 0.4-24 per 1 million person-years. The severity of renal involvement predicts prognosis. Limited data is available on its management and outcomes; thus, we aim to assess this at our tertiary care renal facility.

Methods: Retrospective data were collected using our national renal electronic database (eMED) to identify AAV patients over a period of 5 years. Outcomes included progression to end-stage renal disease(ESRD) or death, chronic kidney disease(CKD), and preservation of renal function.

Results: Thirty-six patients were included in the final study. Cyclophosphamide was used in 24 patients(66.7%), comparatively, rituximab in 7 patients(19.4%) for induction. Seven patients(19.4%) had a documented relapse, 6 patients(85.7%) had Rituximab as induction therapy for relapse. The majority of patients were on azathioprine(61.1%, 57.1% relapse population) as maintenance therapy. Progression to ESRD occurred in 11(30.6%), death in 4(11.1%), established CKD in 15(41.7%), and preservation of renal function in 6(16.7%) patients by the end of the follow-up period.

Conclusions: While Cyclophosphamide remains the choice of induction immunosuppression therapy, we favour Rituximab as an induction agent in the relapse of AAV. Despite aggressive immunosuppression therapy, the incidence of ESRD and death remains high in these patients.

Disclosures: None

393. Clinical characteristics, imaging phenotypes and events free survival in hypertensive Takayasu arteritis population

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Background: Hypertension occurred in 30-80% of Takayasu arteritis (TAK) patients around the world and the occurrence of hypertension might worsen the disease prognosis. This study aimed to investigate the clinical characteristics and imaging phenotypes, as well as their associations with events free survival (EFS) in hypertensive TAK population.

Methods: This current research was based on a prospectively on-going observational cohort-the East China Takayasu Arteritis (ECTA) cohort, centered in Zhongshan Hospital, Fudan University. Totally, 204 hypertensive TAK patients were enrolled between January 2013 and December 2019. Clinical characteristics and imaging phenotypes of each case were evaluated and their associations with the EFS by the end of August 30, 2020 were analyzed.

Results: Severe hypertension accounted for 46.1% of the entire population. Three specific imaging phenotypes were identified: Cluster 1: involvement of the abdominal aorta and/or renal artery (27.5%); Cluster 2: involvement of the ascending aorta, thoracic aorta, and the aortic arch and/or its branches (18.6%); and Cluster 3: combined involvement of Cluster 1 and 2 (53.9%). Clinical characteristics, especially hypertensive severity, differed greatly among three imaging clusters. In all, 187 patients were followed-up for a median of 46 (9-102) months; 127 (67.9%) cases did not experience any events, while 72 events were observed in 60 patients. The overall blood pressure control rate was 50.8%, and the EFS was 67.9% by the end of the follow-up. Multivariate Cox regression indicated that controlled blood pressure (HR=2.13, 95% CI 1.32-3.74), Cluster 1 (HR=0.69, 95% CI 0.48-0.92) and Cluster 3 (HR=0.72, 95% CI 0.43-0.94) imaging phenotype was associated with the EFS. Kaplan–Meier curves showed that patients with controlled blood pressure showed better EFS (p=0.043). Furthermore, patients had controlled blood pressure and Cluster 1 phenotype was set as reference, better EFS was observed in patients with controlled blood pressure and Cluster 2 phenotype (HR=2.21, 95%CI 1.47-4.32), while those had uncontrolled blood pressure and Cluster 1 phenotype (HR= 0.64, 95%CI: 0.52-0.89) and those had uncontrolled blood pressure and Cluster 3 phenotype (HR=0.83, 95%CI: 0.76-0.92) suffered worse EFS. Combined with the above data, we also made a decision tree diagram using three variables: imaging phenotype, blood pressure control status and co-existence of sever AR (shown as Fig 1). Through the diagram, 69.2% patients could be classified into the right prognosis group.

Conclusions: Blood pressure control status and imaging phenotypes showed significant effects on the EFS for hypertensive TAK.

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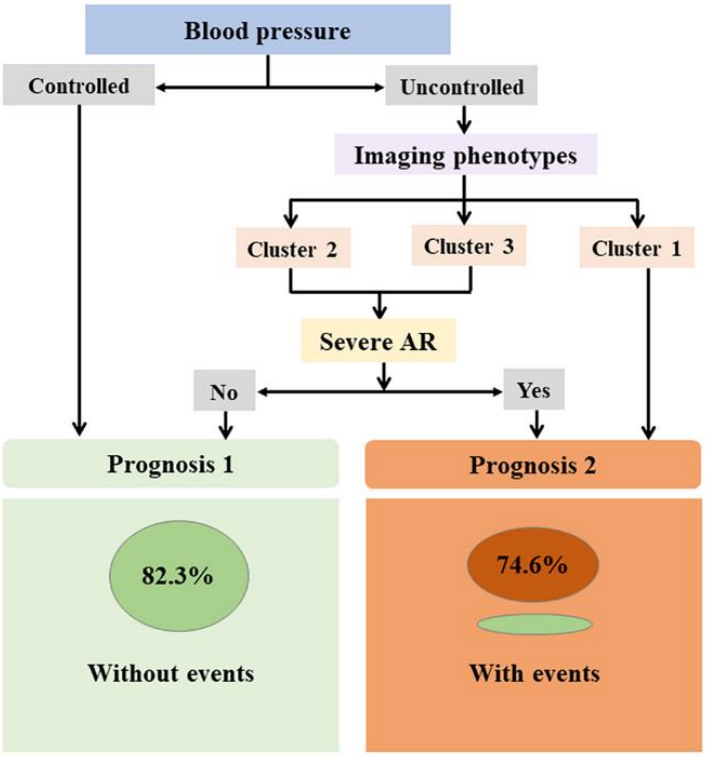
Fig 1. Decision tree for predicting the prognosis of hypertensive Takayasu arteritis. Using three variables including imaging phenotype, blood pressure control status and co-existence of severe AR, a decision tree diagram was established to predict the disease prognosis. Through the diagram, 69.2% patients could be classified into the right prognosis group. AR: aortic regurgitation.



394. Significant disease-related damage occurs early in the course of eosinophilic granulomatosis with polyangiitis

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Background/ Objectives: Following the introduction of effective immunosuppressive treatments, ANCA-associated vasculitides (AAV) have become chronic diseases with a remitting-relapsing course. Therefore, preventing chronic damage accrual during follow-up is critical, as relapses, treatment-related side effects, and comorbidities may significantly affect the long-term outcomes of AAV patients. At present, no study specifically evaluated the burden of damage in patients with eosinophilic granulomatosis with polyangiitis (EGPA). The aim of our work is to describe short-term (6 months) and long-term (5 years) damage accrual in patients with newly diagnosed EGPA.
Methods: Patients diagnosed with EGPA, according to ACR criteria and/or Chapel Hill definitions and regularly followed-up in our vasculitis center for ≥5 years were included. Damage accrual was assessed with the Vasculitis Damage Index (VDI). Short-term and long-

term damage accrual was defined by VDI at 6 months and at 5 years, respectively, and categorized as related to vasculitis or its treatment.
Results: VDI data at 6 months were available for 45 EGPA patients: 24 (53.3%) female, mean age at diagnosis 51.6±13.0 years. ANCA were positive in 17 patients (37.8%), with MPO being the only detected enzyme immunoassay (EIA)-specificity. At 6 months mean VDI was 2.8±1.3; 25/45 (55.6%) and 6/45 patients (13.3%) presented ≥3 and ≥5 items, respectively, whilst only 1 patient (2.2%) showed no items of damage. VDI data at 5 years were available for 32/45 EGPA patients (71.1%): 16 (50%) female, mean age at diagnosis 51.5±13.1 years. MPO-ANCA were positive in 13 patients (40.6%). At 5 years mean VDI was 3.5±1.3, with 26/32 (81.3%) and 7/32 patients (21.9%) presenting ≥3 and ≥5 items, respectively; notably, no patients presented a VDI=0 at 5 years. The most frequent disease-related VDI items at 6 months and at 5 years were asthma, chronic sinusitis, peripheral neuropathy, cardiomyopathy, pulmonary function tests abnormalities and nasal blockage (Figure 1). Osteoporotic fractures, diabetes and systemic hypertension were the most commonly reported treatment-related items at 6 months and at 5 years (Figure 1). Damage accrual progressively rose during the 5-year follow-up (P=0.023), mainly due to disease-related items rather than treatment-related items both at 6 months (disease related VDI 2.6±1.2, treatment-related VDI 0.3±0.6) and at 5 years (disease related VDI 2.9±1.2, treatment-related VDI 0.6±0.7). No significant difference in terms of damage accrual was observed between ANCA-positive and ANCA-negative patients (P >0.5).
Conclusions: In our cohort of EGPA patients damage accrual occurs early, with more than half of the patients displaying ≥3 VDI items already at 6 months. Poor control of previous disease activity, particularly ENT and respiratory manifestations, contributes to progressive damage accrual more than treatment side effects.

Disclosures: None

395. Glucocorticoid-related adverse events in GCA: application of Glucocorticoid Toxicity Index in a large monocentric cohort

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Background/ Objectives: Oral glucocorticoids (GC) are the mainstay of treatment for giant cell arteritis (GCA) but chronic exposure to GC is associated with serious comorbidities. The objective of this study was to determine the GC exposure and risk of GC-related adverse events (AEs) in GCA, validating the Glucocorticoid Toxicity Index (GTI) (1,2) in a cohort of real-world patients.

Methods: 140 consecutive patients with GCA were enrolled in this retrospective monocentric study. All patients were older than 50 years of age, met the 1990 ACR criteria for GCA and/or had the evidence of a large vessel vasculitis at FDG-PET/CT scan. Patients' clinical data were

collected from clinical charts, calculating GC cumulative dose and GTI at baseline and in the following 5 years.

Results: 140 patients were enrolled in the study: median (IQR) age at diagnosis 74 (67-79), Female: 97 (69%), Male: 43 (31%). According to vascular involvement patients were classified in cranial-GCA (C-GCA, n:91), large vessel-GCA (LV-GCA, n:21) and cranial and large vessel-GCA (LV-C-GCA, n:28). Furthermore, 50 (36%) patients were treated with only GC, 44 (31%) with GC+methotrexate (MTX), 46 (33%) with GC+tocilizumab (in 20 cases TCZ was started in the first 3 months after diagnosis: early-TCZ, in 26 cases after 3 months for relapses or AEs: late-TCZ). During the follow up, 57 (41%) patients presented at least one relapse. In the GC group 22 relapses in 18 patients were reported, in MTX group 33 relapses in 25 patients (with 15 relapses before and 18 after MTX start), in early-TCZ group no relapses were reported, in late-TCZ group 21 relapses in 14 patients (with 17 relapses before and 4 after TCZ start) were reported. Median cumulative GC doses after 1 and 5 years were respectively 7.9 (6.3-9.8) gr and 16.5 (13.8-18.9) gr in GC group, 8.7 (5.9-10.0) gr and 16.5 (13.2-20.7) gr in MTX group, 7.1 (5.5-8.0) gr and 13.3 (12.8-13.7) gr in early-TCZ and 7.7 (6.2-11.1) gr and 19.7 (12.2-23.8) gr in late-TCZ. Eighty-eight percent of patients developed at least one GC-AE, with infections and hypertension being the most common reported AEs (42% e 44%, respectively). Median GTI-CWS (Cumulative Worsening Score) after 1 year was 65 (20-137) in GC, 63 (10-95) in MTX, 51 (33-116) in TCZ-early, 44 (0-91) in TCZ-late. Median GTI-CWS after 5 years was 219 (118-240) in GC, 137 (65-206) in MTX, 147 (146-147) in TCZ-early, 200 (121-231) in TCZ-late. A correlation between GTI-CWS and the GC cumulative dose was found (after 5 years r: 0.295, p: 0.026).

Conclusions: Chronic GC treatment is associated with a high risk of developing comorbidities. GTI score demonstrated to be an effective tool to assess GC-related AEs and proved to correlate with GC cumulative dose. TCZ confirmed its efficacy in reducing relapse rate, both in early and late-TCZ groups (3). TCZ showed for the first time in a real-life cohort a GC sparing effect, with a 19% reduction in GC cumulative dose and a 33% reduction in GTI-CWS in 5 years (comparing GC group *vs* early-TCZ group).

Disclosures: none

396. Increased incidence of cancer among patients with eosinophilic granulomatosis with polyangiitis: a multicentre study

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Objectives: No large assessment of the general cancer occurrence in eosinophilic granulomatosis with polyangiitis (EGPA) has been reported. The aim is to investigate the incidence of malignancies in EGPA patients and to examine the effect of immunosuppressive therapy on malignancy risk in these patients.

Methods: The occurrence of cancers was assessed in a cohort of 303 incident EGPA patients (54.8% female, 44% MPO-ANCA positive, 53 [41-61] years old at diagnosis), diagnosed between 1987 and 2019. Demographic, clinical and laboratory data, and the use of immunosuppressive drugs were assessed. Through linkage with Regional Italian Cancer Registries, information about any malignancy occurring before and after EGPA diagnosis was collected. For each patient, the person-years (PY) of follow-up was calculated till the first event: cancer occurrence, last follow-up or death. The PY was stratified by sex, age (in 5-year groups) and calendar-decades (2000-2009 and 2010-2019). Standardized incidence ratios (SIR) between observed and expected numbers (retrieved from the AIRTUM-AIOM database) of cancers were calculated with exact Poisson regression analysis and used as a measure of risk difference.

Results: Thirty patients developed a total of 42 malignancies during a median follow-up of 4.4 [2.1-8.5] years. After excluding patients with a diagnosis of cancer before EGPA onset, 20 first malignancies were observed in 1276 PY observation period. The SIR (95% Poisson CI) malignancy risk was 1.99 (1.22-3.08; p=0.007) for all cancers at all sites, and 1.86 (0.98-2.75; p= 0.025) for all cancers excluding non-melanoma skin cancers. Incidence rates were significantly higher in ANCA positive patients (SIR 2.43 [1.30-4.16]; p=0.007) when compared to ANCA negative, and in those treated with cyclophosphamide (SIR 2.42 [1.11-4.60]; p=0.030) when compared to other immunosuppressive agents. Median latency from EGPA onset and first cancer diagnosis was 5 (2-11) years, with 63.3% of patients developing cancer within 1 and 5 years. Malignancy-free survival at 2, 5, and 10 years of follow-up was 96%, 91%, and 70%, respectively. Of these malignancies, 30% were skin cancers, 25% prostate cancers and 20% breast cancers. Comparing patients who developed malignancies with those who did not, any significant difference was noted regarding sex, ANCA status, age at diagnosis, clinical manifestations, BVAS, FFS, environmental exposure, smoking habit and cancer familiarity. Type of treatment and cumulative doses of cyclophosphamide were not associated with higher incidence of cancers.

Conclusions: EGPA patients have a two-fold risk of overall malignancy than the general population. This cancer excess might be driven by a combination of already known treatment-associated factors and other unknown disease-associated factors, which should be further investigated.

Disclosures: None

397. Long-term Clinical and Radiographic Outcomes in Patients with Isolated Aortitis

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Background/Objectives: Around 2-12% of patients who undergo open thoracic aortic aneurysm repair are incidentally found to have aortitis on pathology. There is no standardized approach to the post-operative care of patients with incidentally-found aortitis nor extensive data on post-operative and long-term outcomes. A better understanding of the risk for recurrent vascular disease and surgical complications in this population could inform clinical surveillance and treatment. This study compared immediate post-operative and long-term outcomes between patients with pathology-diagnosed aortitis and those with non-inflammatory aortic aneurysms after undergoing open thoracic aortic aneurysm repair.
Methods: This is a single-center matched cohort study. Patients with aortitis were identified by histopathology following open thoracic aortic aneurysm repair in the University of Pennsylvania Health System between 2007 and 2017 and lacked any evidence of infection or known prior diagnosis of rheumatic disease. Two comparators who lacked significant inflammation on pathology were matched to each aortitis case by year of surgical repair. Outcomes included length of hospital stay, surgical complications, formation of new vascular abnormalities on CT/MRI imaging, and death. Differences between groups were compared using conditional logistic, Cox proportional hazards, or conditional Poisson regression models accounting for matching.

Results: 162 patients were included: 53 patients with aortitis and 109 matched comparators. Aortitis patients were more likely to be older, female and less likely to have a history of coronary artery disease. 93% of each group had an ascending thoracic aortic aneurysm that was repaired. There was no difference in hospital length of stay, post-operative complications, surgical revision or death between groups. While over 90% of patients in each group followed-up with their cardiothoracic surgeon, only 32% of patients with aortitis saw a rheumatologist in the outpatient setting and 33% received immunosuppressive treatment. On long-term surveillance imaging, no difference was seen in new or worsening aortic aneurysms between groups, but there were significantly more vascular abnormalities in the thoracic aortic branch arteries (carotid, subclavian, brachiocephalic, and celiac arteries) in the aortitis group (39% vs. 11%, $P < 0.01$)(Figure 1).

Conclusions: Among patients who underwent open surgical repair of a thoracic aortic aneurysm, patients with incidentally-discovered aortitis were more likely than non-inflammatory comparators to develop vascular anomalies in major aortic branch arteries. The higher rate of arterial abnormalities in patients with aortitis may reflect ongoing inflammatory changes from an underlying vasculitic process and suggest that more frequent surveillance imaging and involvement of a rheumatologist are needed in the long-term care of these patients.

Disclosures: None

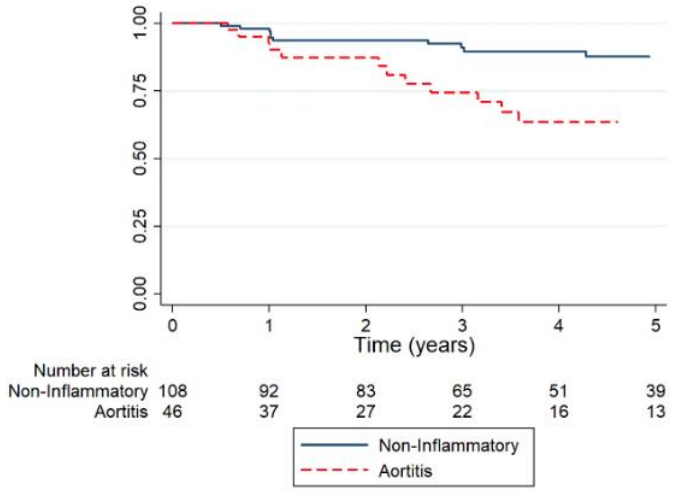

Figure 1. Risk of abnormality in thoracic aortic branch arteries (carotid, subclavian, brachiocephalic, celiac) between patients with isolated aortitis vs non-inflammatory aortic aneurysms. Kaplan-Meier curves depict the proportion free of thoracic aorta branch artery abnormalities over time. Compared to patients with non-inflammatory aortic aneurysms, patients with isolated aortitis are more likely to develop arterial abnormalities involving branch arteries of the thoracic aorta (HR 2.70 [95% CI 1.05 to 6.93], P = 0.03).

398. Ocular Manifestations in a Giant Cell Arteritis Cohort

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Background/Aims: The ophthalmic features of giant cell arteritis involve a spectrum of severity from transient symptoms to bilateral visual loss from anterior ischaemic optic neuropathy or less commonly central retinal or cilioretinal artery occlusion. Data of reported ocular involvement is varied with a range of 10-70%. The variation may be related to the speciality of the unit reporting the data. We run an interdisciplinary service in a tertiary academic unit and report a complete picture of the frequency and nature of ocular involvement in GCA.

Methods: The records of 350 consecutive patients diagnosed objectively on the basis of biopsy or imaging were reviewed. In our centre, the hospital pathway mandates all individuals with suspected GCA with visual symptoms to have a formal ophthalmology assessment including visual acuity, pupil exam and full dilated fundus assessment. We recorded the common signs and symptoms using a structured form which included ophthalmologic symptoms and examination findings along with symptoms commonly associated with GCA - scalp tenderness, headache, jaw claudication, shoulder girdle stiffness, anorexia, night sweats, weight loss, and fever.

Results: From January 2012 to September 2021, 350 individuals were diagnosed with GCA by biopsy, ultrasonography or positron emission tomography. The mean age was 74 ± 7.7 years. 235 (67%) of patients were females. 101 (29%) presenting with GCA had visual symptoms and or signs. 42 of them had mono-ocular and 5 had binocular loss of vision. A summary of the key visual symptoms and signs are shown in table 1. 6 individuals with visual symptoms did not have any symptoms commonly associated with GCA.

Conclusions: We report the frequency of visual involvement in one of the largest cohorts of individuals with GCA. 29% have ocular symptoms. Partial or total field loss occurred in 13% of cases. 2% of patients may be presenting with visual symptoms as the only sign of GCA. Rarely, permanent visual loss may occur without any other manifestation of GCA.

Disclosures: None

Table 1 Visual Symptoms and Signs

Visual Symptoms	101
Blurred Vision	36
Loss of vision	47
Double Vision	27
Ocular Signs	
Right CRAO[1]	1
Left CRAO[1]	10
Right AION[2]	19
Left AION[2]	23
Right extraocular muscle weakness	6
Left extraocular muscle weakness	4

1 Central retinal artery occlusion 2 Anterior ischaemic optic neuropathy

399. Evaluation of Upper Extremity Function, Strength and Endurance in Patients with Takayasu Arteritis

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Objectives: Takayasu Arteritis (TAK) is a large-vessel vasculitis that can cause ischemic symptoms due to stenosis and occlusion of the aorta and its main branches. Arterial ischemia is thought to negatively affect muscle strength, endurance and function. However, functional consequences of arterial ischemia due to subclavian involvement (which is seen in up to 80% of the cases) is unsufficiently assessed. The aim of this study is to quantitatively evaluate upper extremity strength, endurance and function in these patients.

Methods: Patients (n=40, mean age: 45.8±13.4 years) who were classified according to ACR 1990 Criteria for TAK, followed in the Rheumatology Clinics of Marmara University Hospital and age and gender matched healthy volunteers (HC, n=40) were studied. Right and left hand grip strength measurement, arm ergometry and unsupported upper limb exercise (UULEX)

tests were performed in all study participants and Quick-DASH questionnaire in TAK group. The relationship between the parameters evaluating the disease activity and the functional tests were analyzed with Spearman correlation analysis.

Results: The symptom duration was 119.2±66.9 and the follow-up period 99.8±59.0 months in patients with TAK. Both left (TAK: 21 (12-42) kg vs HC: 25.5 (19-41) kg, p=0.001) and right hand grip measurements (TAK: 23 (12-46) kg vs. HC: 27 (18-45) kg, p=0.004) were significantly lower in TAK patients. Mean UULEX test measurements were 127 (48-490) seconds in TAK and 204 (80- 622) seconds in HC (p=0.001). Arm ergometry also resulted in significantly lower duration in patients with TAK (TAK: 355 (33-2100) seconds vs. HC: 1212 (305-2760) seconds, p=<0.001). A positive correlation was found between UULEX and right and left hand grip measurements (respectively r=0.61, p=<0.001; r = 0.47, p=0.002). UULEX test negatively correlated with right and left pain-VAS in TAK patients (r=-0,40, p=0,01; r=-0,43, p=0,006, respectively). The correlation of UULEX with age, BMI, acute phase reactants, ITAS-2010 and TADS were not significant. A negative correlation was present with the Quick-DASH score and right (r=-0.52, p=<0.001) and left (r=-0.42, p=0.006) hand grips, and arm ergometry (r=-0.70, p=<0.001). Quick-DASH score had a positive correlation with disease activity assessed by ITAS2010 (r=0.35, p=0.02). Degree of left subclavian artery involvement also correlated with Quick-DASH score (r=0.35, p=0.02).

Conclusion: In Takayasu's Arteritis, upper extremity strength, endurance and function are shown to be impaired compared to healthy controls. Pain was found to be the most important factor affecting all tests. Functional upper extremity tests and Quick-DASH questionnaire might be useful to assess the impact of arterial ischemia on upper extremity disease-related quality-of-life in patients with TAK, in both clinical trials and daily practice.

Disclosures: None

Table: Upper extremity function, strength and endurance tests in Study Groups

	TAK (n=40)	HC (n=40)	p
Left handgrip (kg, medyan (min-max))	21(12-42)	25,5(19-41)	0.001
Right handgrip (kg, medyan (min-max))	23(12-46)	27(18-45)	0.004
UULEX (sec)	127 (48-490)	204 (80-622)	0.001
Arm ergometry (sec)	355 (33-2100)	1212 (305-2760)	<0.001
Quick-DASH score	32.1 (0-88,6)	-	-

400. Clinical Characteristics of Patients With ANCA-associated Vasculitis in a Scandinavian Cohort

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Background/Objectives: Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), two different ANCA-associated vasculitides (AAV), are characterized by necrotizing vasculitis affecting small blood vessels and the presence of autoantibodies, ANCAs. While the prevalence of AAV is roughly equal between males and females, few studies have investigated whether the clinical presentation of AAV differs between the sexes. Likewise, little is known about the presentation of AAV in patients diagnosed as young adults, in comparison with patients diagnosed with AAV later in life. With the intention to identify clinical tools to improve prediction of outcome in patients with AAV, the aim of this study was to investigate the impact of sex and age at diagnosis on clinical manifestations of GPA/MPA and ANCA specificity.

Methods: In a systematic multicenter study, 1165 patients with AAV attending the clinics of ten different Scandinavian rheumatological and/or nephrological centers, were consecutively enrolled. All patients were adults at the time of inclusion in the study and were classified into GPA or MPA according to the European Medicines Agency algorithm. Clinical data including sex, age, date of diagnosis, ANCA-specificity and any type of engagement of upper airways/ears, lungs, kidneys, eyes, gastrointestinal tract, heart, peripheral nervous system, central nervous system, skin or joints/muscles (ever) were collected from medical records. Disease manifestations were analyzed for associations with diagnosis (GPA/MPA), ANCA-specificity, age at diagnosis, sex and disease duration using simple and multiple logistic regression, with a P value threshold for significance of <0.05.

Results: Of 1165 AAV-patients, 916 had GPA (483 male/ 433 female) and 249 had MPA (98 male/ 151 female), with mean (SD) age at diagnosis of 51 (17.7) and 62 (14.9) for GPA and MPA, respectively. In the whole patient cohort, the age at diagnosis showed a bimodal pattern, with two peaks of incidence with median (range) at 22 (9-31) and 60 (32-91) years of age, respectively. Out of the 180 patients diagnosed before the age of 32, 166 had GPA (92 %); in this group, involvement of upper airways/ears, eyes and the gastrointestinal tract was significantly more common than in GPA patients diagnosed at an older age. Among all patients with GPA, a significantly larger proportion of females than males were younger than 32 years old at diagnosis (21% and 16%, respectively). Among all AAV patients, engagement of upper airways/ears, lungs, skin, eyes, the central nervous system and joints/muscles was significantly more common in GPA than MPA, whereas kidney involvement was significantly more common in MPA. In GPA, involvement of kidneys or lungs was significantly more common in males than in females and, additionally, there was a significantly higher rate of kidney failure in males. In MPA, engagement of upper airways/ears was significantly more common in females than in males. In both GPA and MPA, the presence of PR3-ANCA was significantly more common in males than in females and MPO-ANCA was significantly more common in females than in males.

Conclusion: Our results indicate that GPA and MPA are characterized by different clinical manifestations and ANCA subtypes in males and females, with implications for prediction of

prognosis and clinical decision-making. Moreover, a higher rate of females and increased frequency of upper airway/ear involvement in patients at younger age at diagnosis could suggest specific environmental triggers and pathogenic mechanisms in this subgroup of AAV patients.

Disclosures: None

401. Genotype, Transfusion Dependence and Ear Chondritis Predicts Mortality in VEXAS Syndrome

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Background: VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a newly defined disease cause by myeloid-restricted somatic mutations in blood. Missense mutations at codon 41 of *UBA1* comprise almost all cases of VEXAS and lead to amino acid substitutions of a methionine for either a threonine, valine, or leucine. Median survival and predictors of mortality in VEXAS have not been defined and may be essential to guide management.

Methods: Patients were included if Sanger sequencing confirmed variants at p.Met41 in *UBA1*. Kaplan-Meier was used to estimate median survival. Difference in survival was compared by genotype using the logrank test. Cox proportional hazard regression was used to identify associations between clinical features of disease transfusion dependance, genotype, and mortality. In vitro expression systems were used to study associations between genetic variants and UBA1b isoform expression.

Results: 83 patients were included. Median age at disease onset was 66 years (range 41-80). All patients were male and white. The most common clinically assigned diagnosis was relapsing polychondritis (52%), myelodysplastic syndrome (31%), or Sweet syndrome (22%). The overall mortality was 25%. Median survival from symptom onset was 10 years (Figure 1A). Death was more common in patients with the valine variant (50%) compared to patients with leucine (13%) or threonine (18%) and also had a median survival that was significantly shorter compared to patients with other variants ($p< 0.01$, Figure 1B). In multivariable Cox regression, there were three independent predictors of mortality; patients with the valine variant and

patients who became transfusion dependent had 2.56x (95% CI 1.01-6.47, p=0.01) and 4.47x (95%CI 1.79-11.1, p< 0.01) increased risk of death respectively whereas patients with ear chondritis were less likely to die (HR=0.32, 95% CI 0.12-0.90; p=0.03). Translation of the UBA1b isoform was reduced in p.Met41Val compared to p.Met41Leu or p.Met41Thr.

Conclusion: A relationship between genotype, bone marrow failure, and survival is seen in patients with the VEXAS syndrome. Patients who become transfusion dependent and have a valine amino acid substitution at codon 41 have the highest risk for death. The only clinical symptom associated with mortality was ear chondritis. In vitro expression systems provide a mechanistic basis for the genotype specific mortality. Given the high mortality rate and lack of effective medical treatments, patients with VEXAS should be considered for bone marrow transplantation, with particular focus on patients with risk factors for increased mortality.

Disclosure: None related to this body of work. Preliminary data presented here: https://acrabstracts.org/abstract/genotype-and-transfusion-dependence-predicts-mortality-in-vexas-syndrome-a-newly-described-disease-with-overlap-inflammatory-and-hematologic-features/

402. IgG4-RD and malignancy: Causal relationship or co-occurrence?

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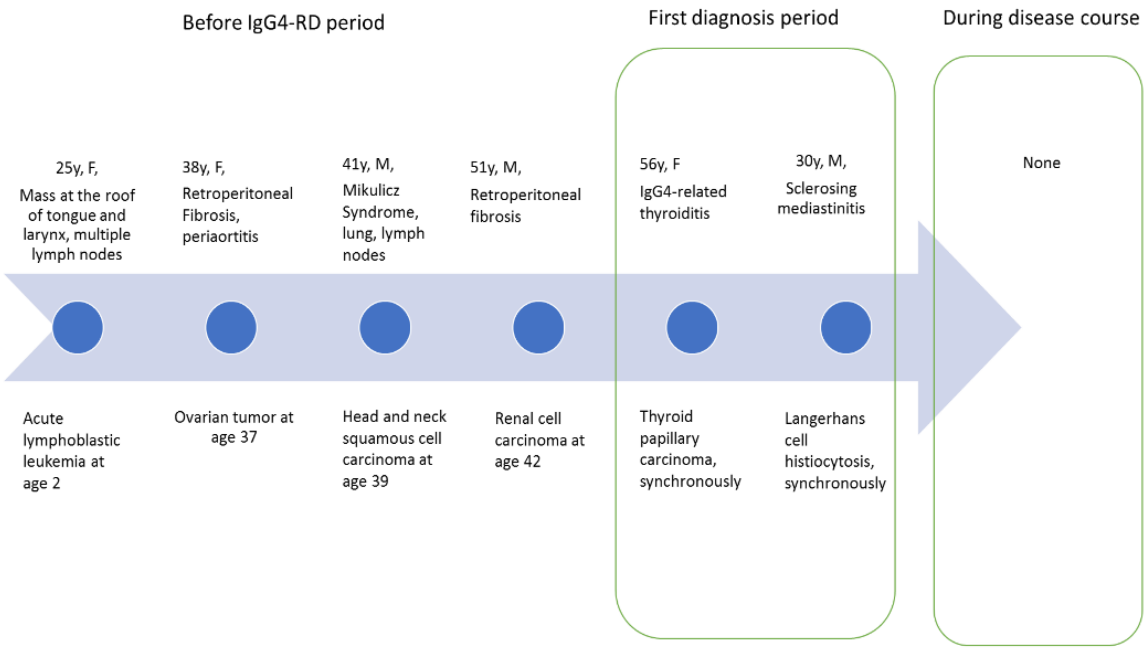
Background/ Objectives: IgG4-related disease (IgG4-RD) is a systemic immune-mediated disease with tumefactive lesions [1]. IgG4-RD sometimes presents with malignancy-like symptoms and may be mistaken for cancer or can be seen together with cancer. However, the data is scarce. In this study, we aimed to evaluate malignancies in a single-centre cohort of IgG4-RD.
Methods: IgG4-RD patients who were referred to our vasculitis centre between Jan 2014 and Jun 2021 and fulfilled the Comprehensive Diagnostic Criteria for IgG4-RD were included in this study [2]. HUVAC database and hospital records were retrospectively evaluated for IgG4-RD patients' age, gender, organ involvements, treatment details and malignancy history.

Results: 97 IgG4-RD patients were assessed for malignancy. Six patients had been diagnosed as having malignancy, and the overall malignancy rate was %6.2. The figure shows the types of cancer and the temporal relationship between cancer and IgG4-RD diagnosis. Three patients have been diagnosed with IgG4-RD and malignancy simultaneously, and in the remainder, the diagnosis of cancer preceded the IgG4-RD by 1, 2, 9 and 23 years. No cases of malignancy were observed after the IgG4-RD diagnosis. Among IgG4-RD patients with a history of cancer four patients (66%) were smokers of former smokers.

Conclusions: IgG4-RD could be related to different types of malignancies. But, the exact mechanism or causal relationship is still unknown. Development of synchronous cancer and IgG4RD at the same anatomic region might be associated with local auto-immunity, chronic local inflammation and cell-cycle dysregulation. Four of our patients having cancer history before IgG4RD diagnosis can be co-incidence or support the idea of IgG4-RD can arise in patients with a history of malignancy. A better understanding of the pathophysiologic relationship between cancer and IgG4-RD will provide better management of these patients.

Disclosures: Professor Karadag: Received funding supprot Abbvie, Novartis, Roche, Viela-Bio, R-Pharm outside this study. Received consultancy fees and/or speaker fees from Abbvie, Abdi İbrahim, Amgen, Celltrion, Gilead, Farmanova, Lilly, Pfizer, Roche, UCB.



403. Glucocorticoid-related damage assessed with glucocorticoid toxicity index (GTI) in patients with Takayasu's arteritis

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Background/ Objectives: Glucocorticoids (GCs) are the mainstay treatment for Takayasu's arteritis (TAK). However, GC-related toxicity still remains a major concern. In this study we

aimed to evaluate GC-associated damage in TAK patients with glucocorticoid toxicity index (GTI) which was developed to assess GC-related toxicity.

Methods: Patients followed in Marmara University Hospital Vasculitis Clinic with a diagnosis of TAK and receiving GC treatment were enrolled in the study. Damage was assessed with GTI under the headings: body mass index (BMI), glucose tolerance, blood pressure, lipids, bone density, steroid myopathy, skin toxicity, neuropsychiatric toxicity, infection, endocrine, gastrointestinal, musculoskeletal, ocular domains. Total GTI score range was defined between −36 and 439.

Results: A total of 57 (F/M: 53/4) TAK patients were included. Mean age was 44.3±12.5 years and cumulative GC dose 11.1±7.2 grams. After mean 82.8±53.8 months of GC treatment, mean GTI score was found to be 51.5±52.4. GTI score was similar between genders (Total GTI: women vs men: 50.2±52.0 vs 37.2±11.7, p=0.88). Total GTI score correlated with age (r=0.32, p=0.014), cumulative GC dose (r=0.34, p=0.017) and duration of GC treatment (r=0.27, p=0.041).

Domain		Points	Patient number with damage item n (%)
BMI	Improvement in BMI	-8	7 (12)
	No change in BMI	0	35 (61)
	Moderate increase in BMI	21	13 (23)
	Major increase in BMI	36	2 (4)
Glucose tolerance	Improvement in glucose tolerance	-8	0 (0)
	No change in glucose tolerance	0	50 (88)
	Worsening in glucose tolerance	32	5 (9)
	Worsening in glucose tolerance despite treatment	44	2 (4)
Blood pressure	Improvement in blood pressure	-10	0 (0)
	No change in blood pressure	0	25 (44)
	Worsening hypertension	19	23 (40)
	Worsening hypertension despite treatment	44	9 (16)
Lipids	Improvement in lipids	-9	4 (7)
	No change in lipids	0	24 (42)
	Worsening hyperlipidaemia	10	28 (49)
	Worsening hyperlipidaemia despite treatment	30	1 (2)
Bone density	Improvement in bone density	-1	0 (0)
	No change in bone density	0	40 (70)
	Decrease in bone density	29	17 (30)
Steroid myopathy	No steroid myopathy	0	51 (89)
	Mild steroid myopathy	9	6 (11)
	Moderate steroid myopathy or greater	63	0 (0)
Skin toxicity	No skin toxicity	0	51 (89)
	Mild skin toxicity	8	6 (11)
	Moderate skin toxicity or greater	26	0 (0)
Neuropsychiatric toxicity	No neuropsychiatric symptoms	0	43 (75)
	Mild neuropsychiatric symptoms	11	14 (25)
	Moderate neuropsychiatric symptoms or greater	74	0 (0)
Infection	No significant infection	0	51 (89)
	Oral/vaginal candidiasis or	19	1 (2)

Conclusions: GC-related toxicity was related to cumulative dose and duration of the GC treatment in our study. GTI is a useful tool to evaluate GC-related toxicity and can be chosen both for clinical studies and routine practice to assess long-term GC-associated damage.

Disclosures: None
Table 1. Damage parameters in TAK patients assessed with GTI

404. Malignancies in patients with AAV treated within the EUVAS trials

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Background/objectives: Patients with AAV are known to have an increased risk for the development of malignancies, which has been largely attributed to immunodeficiency or side effects induced by immunosuppressive treatments. Because there is a considerable latency period for cancer development after exposure to immunosuppressive treatments, little data are available on the incidence of cancer for large cohort of patients with AAV and long follow-up. The aim of this study is to describe the cumulative incidence of cancer in patients with AAV who participated in the EUVAS therapeutic clinical trials from 1995 to 2012.

Methods: 848 patients with AAV from 17 European countries were included in the present study. Information was retrieved from questionnaires sent to the principal investigators of the original RCTs (MEPEX, NORAM, CYCAZAREM, CYCLOPS, IMPROVE, RITUXVAS and MYCYC).

Results: Among the total of 848 patients (median follow-up: 8 years, IQR: 2.2–8.8), 149 patients were diagnosed with 181 malignancies. The 10-year cumulative incidence of cancer was estimated at 20.6%. The median duration of start of AAV therapy-to-time of cancer diagnosis was 4.96 years (IQR: 2.24-8.83). The most common cancer types were skin cancer (37.4%), out of which 6 were melanoma and 62 non-melanoma skin cancer, followed by gastrointestinal cancer (12.6%) and prostatic cancer (9.9%). Patients who developed cancer were significantly older at randomization than those who did not (62±12 vs 57±14 years)

(p<0.001). Considering both remission-induction and remission-maintenance therapies, 94% of the patients received cyclophosphamide, 68.4% azathioprine, 28.2% mycophenolate, 11.4% methotrexate and 10.4% rituximab during the observation period. Six out of the 28 patients, who were treated with rituximab and two pulses of IV cyclophosphamide as induction therapy, developed cancer. Diagnosis of cancer significantly predicted shorter survival (Log rank=9.2, p=0.002).

Conclusions: Our findings, which were derived from a large number of patients with AAV enrolled in clinical trials over the past 25 years, estimates the 10-year cumulative incidence of malignancies following the start of AAV therapy at 20.6%. The development of cancer is tightly associated with decreased survival. Analyses of standardized incidence ratios, using the cancer incidence of the background populations as reference, are underway.

Disclosures: None

405. Characteristics of relapse of individuals with ANCA-associated vasculitis enrolled in the PEXIVAS trial

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Background: Relapses of granulomatosis with polyangiitis and microscopic polyangiitis, collectively ANCA-associated vasculitis (AAV), are common and important events. Few large, international studies describe risk factors for relapse of AAV.

Methods: Relapses occurring in participants with severe AAV enrolled in PEXIVAS, an international, 2-by-2 factorial trial of induction treatments, were studied. The primary outcome of this analysis was relapse occurring at least 90 days after randomization. Candidate predictors included baseline participant and disease characteristics. The association between relapse and the candidate predictors was assessed using time-to-event models incorporating death as a competing event using the Fine and Gray method. All models were adjusted for induction therapies.

Results: Over a median follow-up of 2.93 years, 150 (23.3%) participants experienced at least one relapse (incidence rate 7.4 per 100 patient-years). The median time to relapse was 483.5 days (interquartile range 198-920). The most common manifestations of disease at relapse were renal (58.0%), constitutional (38.7%), and ear/nose/throat (31.3%). Baseline characteristics associated with an increased risk of relapse included: PR3-positive ANCA, skin involvement, and non-hemorrhagic lung involvement (Table 1). Characteristics associated with a lower risk of relapse included female sex and receipt of dialysis.

Discussion: Relapses remain common among patients with severe AAV. Identifying those most at risk of relapses may help plan treatments and monitoring.

Disclosures: PM – Consultant and recipient of research support for AbbVie, AstraZeneca, Boeringher-Ingelheim, Bristol-Myers Squibb, ChemoCentryx, Forbius, Genentech/Roche, Genzyme/Sanofi, GlaxoSmithKline, InflaRx, Consultant for CSL Behring, Dynacure, Eicos, EMDSerono, Forbius, Janssen, Kiniksa, Magneta, Neutrolis, Novartis, Pfizer, Star Therapeutics Takeda, Talaris, Recipient of research support from Sanofi, Receives royalties from UpToDate; NK – Trial support from Roche, BMS, Sanofi, Abbvie; MW – Research support from Vifor

Table 1: Baseline characteristics of participants in PEXIVAS who did not relapse compared to those that did and the sub-hazard ratios for relapse from a Fine and Gray time-to-event model with death treated as a competing risk. Interquartile range (IQR) = 25th to 75th percentile.

	No Relapse N=549	Relapse N=150	Sub Hazard Ratio (95% confidence interval)
Median age, years (IQR)	64 (56-72)	63 (53-71)	1.00 (0.99-1.01)
Female, n (%)	252 (45.4)	56 (37.3)	0.72 (0.51-1.00)
PR3-ANCA positivity, n (%)	201 (36.2)	85 (56.7)	1.67 (1.13-2.45)
Relapsing disease, n (%)	47 (8.6)	16 (10.7)	0.85 (0.49-1.48)
Baseline kidney function			
Median creatinine, µmol/L (IQR)	345 (213-516)	271 (194 to 423)	1.00 (0.999-1.0004)
On dialysis at enrollment, n (%)	123 (22.2)	17 (11.3)	0.50 (0.28-0.88)
Organ systems affected, n (%)			
Constitutional	237 (43.2)	87 (58.0)	1.34 (0.91-1.98)
Skin	45 (8.2)	31 (20.7)	1.87 (1.19-2.94)
Eye/Mucus Membrane	43 (7.8)	28 (18.7)	1.44 (0.93-2.23)
Ears/Nose/Throat	145 (26.4)	54 (36.0)	1.11 (0.76-1.63)
Cardiac	7 (1.3)	3 (2.0)	1.56 (0.38-6.44)
Respiratory*	223 (40.6)	71 (47.3)	1.51 (1.03-2.23)
Nervous	52 (9.5)	10 (6.7)	0.56 (0.29-1.10)
Lung Hemorrhage, n (%)			
No Hemorrhage	403 (72.6)	111 (74.0)	Referent
Non severe hemorrhage	102 (18.4)	28 (18.7)	0.82 (0.52-1.30)
Severe hemorrhage	50 (9.0)	11 (7.4)	0.57 (0.28-1.15)
Enrolment location, n (%)			
North America	194 (35.1)	43 (29.7)	Referent
United Kingdom	140 (25.2)	39 (26.0)	1.95 (0.59-1.55)
Non-UK Europe	136 (24.5)	36 (24.0)	0.92 (0.56-1.52)
Asia-Pacific	84 (15.2)	32 (21.3)	1.43 (0.86-2.38)

*Respiratory system involvement does not include lung hemorrhage or respiratory failure associated with lung hemorrhage.

406. CAUSES OF HOSPITALIZATION IN BEHÇET SYNDROME

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Background/ Objectives: The causes of hospitalization may provide important information on the course of diseases and treatment-related adverse effects. We aimed to determine the

causes and outcome of hospitalizations among patients with Behçet Syndrome (BS) in a dedicated centre.

Methods: We surveyed hospitalization records in our clinic between January 2002 and December 2019 and identified those with a diagnosis of BS. The records of these patients were reviewed for demographic and clinical features, causes of hospitalization and outcome. We divided hospitalization causes into 2 as being BS related (organ involvement or deterioration) and non-BS related (treatment complication or others).

Results: Four-hundred and fourteen BS patients (76% men, mean age 37.4 ±11.6 SD years) were hospitalized for a total of 536 times during 18 years. The median disease duration was 7 (IQR:11) years. Three-hundred and forty-one (64%) patients were using immunosuppressives (IS) with or without corticosteroids (CSs) and 78 (15%) of them were under biologic treatment at the time of hospitalization. The mean duration of hospitalization was 12.7±10.4 SD days. The reasons for hospitalization were directly related to BS in 304 patients (57%) and non-related to BS in 223 (42%). Nine patients were hospitalized for both BS and non-BS related reasons at the same time. The most common reasons were vascular involvement (n=198, 37%) for BS related reasons and infections (n=81, 15%) for non-BS related reasons (Table). Patients hospitalized for BS related causes were younger (34.7±10.6 vs 41.1±12.4, p=0.006), had short mean disease duration (7.1±7.3 vs. 11.6±9.5 years, p<0.001), stayed shorter in the hospital (11.5±8.2 vs 14.1±12.9 days p<0.001) and had less frequent IS±CSs use (59% vs 70%, p=0.01) compared to those with non-BS related hospitalizations. There were no differences between the groups regarding gender distribution (232 M/72 F vs. 166 M/57 F) and use of biologic agents (14% vs 15%). Three patients died during hospitalization. The reasons were malignancy, infection and right heart failure due to pulmonary artery thrombosis and pulmonary hypertension, respectively.

Conclusions: Vascular involvement is the leading cause of hospitalization among BS patients, followed by infections. The predominance of men among hospitalized patients underlines the relatively severe course of BS in men. The retrospective design and inclusion of patients who were hospitalized only in the rheumatology unit are limitations of this study.

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Table-Distributions of BS related and non-BS related reasons of hospitalization		
	BS patients hospitalized with BS related reasons (n of hospitalizations=304)*	BS patients hospitalized with non-BS related reasons (n of hospitalizations=223)*
Causes of hospitalizations (per hospitalization)	Vascular inv. (n=201, 66 %) *Pulmonary artery inv. (n=75, 25 %)* *Deep vein thrombosis (n=42, 14 %)* *Budd-Chiari synd. (n=32, 11%)* *Vena cava inf. thrombosis (n=19, 7 %)* *Peripheral artery inv. (n=18, 6 %)* *Vena cava sup. thrombosis (n=16, 5 %)* *Aorta inv. (n=17, 6%)* *Coronary artery inv. (n=4, 1 %)*	Infection (n=74, 33%) *Pneumonia (n=22, 10%)* *Tuberculosis (n=9, 4%)* *Urinary tract inf (n=8, 4%)* *Gastroenteritis (n=5, 2%)* *Osteomyelitis (n=4, 2%)* *Septic arthritis (n=3, 1%)* *Aspergillosis (n=2, 1%)* *Nocardia (n=1, 0.5 %)* *Salmonella (n=1, 0.5%)* *Others (n=19, 9%)*
	Neurologic inv. (n=61, 20 %) *Parenchymal inv. (n=47, 15%)* *Dural sinus thrombosis (n=14, 5%)*	Drug side effects other than infections (n=37, 17 %) *Interferon (n=10, 5%)* *Azathioprine (n=7, 4%)* *Cyclosporine (n=5, 3%)* *Steroid (n=3, 2%)* *TNF antagonists (n=3, 2%)* *IVIG (n=1, 1%)*
	Gastrointestinal inv. (n=23, 8%)	Additional rheumatologic diseases (n=17, 8%)
	Joint inv. (n=13, 4%)	Renal disease (n=17, 8 %)
	Mucocutaneous inv. (n=13, 4%)	Cardiovascular dis. (n=14, 6%)
	Eye inv. (n=9, 3%)	Avascular necrosis (n=6, 3%)
	Others (n=6, 2%)	Malignancy (n=12, 5%)
		Others (n=47, 21%)
*Some patients were hospitalized more than one times and for both BS related and non-BS related reasons at different time and had more than one type of BS related and/or non-BS related reasons.		

Case Reports & Series

407. A case of propylthiouracil-induced agranulocytosis and antineutrophil antibody-associated vasculitis

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Presentation of Case: This case report presents a patient who experienced agranulocytosis, followed by the onset of ANCA-associated vasculitis, as an adverse effect of propylthiouracil treatment. Even though propylthiouracil is one of the most commonly identified drugs to induce ANCA-associated vascultis, the exact underlying pathogenic mechanism remains to be explained. A 61-year old female patient, previously diagnosed with Graves' disease, presented

to the Department of Endocrinology with a short history of fever, chills and throat pain. The treatment with propylthiouracil was introduced two weeks prior to the admission.

Diagnostic Testing: Initial investigation revealed a low neutrophil count of 0.04×10^9/L and white cell count of 0.51×10^9/L, whilst the red blood line parameters were in range. Biochemistry was normal, with preserved liver and kidney function. Chest radiography identified a basal right sided pneumonia. Elevation of serum level of inflammatory markers was identified, with a severely low TSH level. The course of treatment was further complicated by the occurrence of a generalized annular exanthematous rash and recurrent fever. Further testing was performed, microbiological results came back negative, however immunological findings showed positive ANCAs with MPO positivity.
Differential & Final Diagnosis: Suspicion was raised towards an ANCA positive vasculitis as an adverse effect of propylthiouracil treatment, and was confirmed once the immunological testing came back positive.
Discussion of Management: Propylthiouracil was immediately discontinued, and initial treatment included broad spectrum antibiotics based on empirical experience for community-acquired pneumonia together with graulocyte-colony stimulating factor; Lugol's solution and methylprednisolone were initiated, with a gradual escalation of methylprednisolone dosage, which ultimately led to the resolution of the rash. Primary hypothyroidism was eventually treated surgically.
Conclusions: This case report not only emphasizes the prompt discontinuation of propylthiouracil in drug induced agranulocytosis and ANCA-associated vasculitis, but also sheds a light on the possible mutual pathogenic mechanism which leads to this rare, and sometimes fatal condition.
Disclosures: None

408. Obinutuzumab as Treatment for ANCA-Associated Vasculitis

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Background/Objectives: Rituximab is a standard of care therapy for patients with ANCA-associated vasculitis. When rituximab is contraindicated, or in the case of refractory disease, other treatments are needed. Obinutuzumab is another anti-CD20 antibody for the treatment of hematologic malignancies that may induce a deeper B-cell depletion compared to rituximab. Presented here is a series of three cases of patients with ANCA-associated vasculitis who were treated with obinutuzumab due to their history of anaphylactic reactions to rituximab.

Methods: Case series of three patients with ANCA-associated vasculitis treated with obinutuzumab.

Results: One female patient with microscopic polyangiitis and two male patients with granulomatosis with polyangiitis received obinutuzumab. The treatment was well-tolerated in all patients despite previous anaphylactic reaction to rituximab. Obinutuzumab was effective in i) inducing disease remission, ii) causing total B-cell depletion, and iii) resulting in undetectable serum titers of ANCA. All three patients were retreated with obinutuzumab for maintenance of remission.

Conclusions: Rituximab is the standard of care for treatment of ANCA-associated vasculitis. However, these three cases support the use of obinutuzumab as an alternative to rituximab for treatment of ANCA-associated vasculitis. Obinutuzumab offered the option of giving a chemically dissimilar CD20 depleting agent with the expectation that it would be as efficacious as rituximab for ANCA-associated vasculitis without the risk of an allergic response in these patients and without the need to try a desensitizing regimen for rituximab. Because obinutuzumab is considered to result in a more profound and longer-lasting depletion of total body B cell population, it is theoretically possible that use of this drug might provide better control of vasculitis than rituximab. Prospective studies comparing rituximab to obinutuzumab in ANCA-associated vasculitis patients are warranted.

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Table 1: Clinical Characteristics and Treatment Regimens of Three Patients with ANCA-Associated Vasculitis Treated with Obinutuzumab

	Case 1	Case 2	Case 3
Age	25 years	60 years	44 years
Sex	Male	Female	Male
Disease manifestations	Rhinitis, sinusitis, arthritis, alveolar hemorrhage, skin vasculitis, glomerulonephritis	Pulmonary infiltrates, proteinuria.	Arthritis, skin nodules, abdominal pain, lung nodules, glomerulonephritis, sinusitis
ANCA type	Cytoplasmic ANCA / anti-proteinase 3	Perinuclear-ANCA / anti-myeloperoxidase	Cytoplasmic ANCA / anti-proteinase 3
Previous treatments (in chronologic order)	Glucocorticoids, plasmapheresis, rituximab, azathioprine, oral cyclophosphamide, methotrexate, mycophenolate mofetil, avacopan	Glucocorticoids, plasmapheresis, rituximab, intravenous and oral cyclophosphamide, azathioprine	Glucocorticoids, rituximab, azathioprine, intravenous cyclophosphamide, methotrexate, mycophenolate mofetil, abatacept
Administration of obinutuzumab			
Cycle 1	*February 2020* Day 1: 100 mg Day 2: 900 mg Day 14: 1000 mg	*April 2021* Day 1: 100 mg Day 2: 900 mg Day 14: 1000 mg	*October 2019* Day 1: 1000 mg Day 14: 1000 mg
Cycle 2	*August 2020* Day 1: 1000 mg	*October 2021* Day 1: 1000 mg	*April 2020* Day 1: 500 mg
Cycle 3	*February 2021* Day 1: 1000 mg		*October 2020* Day 1: 500 mg
Cycle 4	*August 2021* Day 1: 1000 mg		*April 2021* Day 1: 500 mg
Cycle 5			*October 2021* Day 1: 500 mg

409. Association of COVID-19 Antigenicity with the Development of Antineutrophilic Cytoplasmic Antibody Vasculitis

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Presentation of Case: We present two cases of antineutrophil cytoplasmic autoantibody (ANCA)–associated vasculitis (AAV). The first was an 86-year-old woman with known bronchiectasis, seronegative inflammatory oligoarthiritis and polymyalgia rheumatic who presented with COVID-19 infection and developed diffuse alveolar hemorrhage with severe hypoxemia. The second case was a previously healthy 60-year-old female who developed dyspnea, weight loss and mononeuropathy with multiple granulomatous pulmonary nodules shortly after COVID-19 vaccination.
Diagnostic Testing: The first case was found to be positive for perinuclear-ANCA and myeloperoxidase (MPO) antibodies. The second case underwent computed tomography-guided lung biopsy which showed acute necrotizing granulomatous inflammation without active infection. She was also strongly positive for proteinase 3 (PR3)-ANCA.

Differential & Final Diagnosis: Case 1 was unable to undergo bronchoscopy due to do-not-intubate status. It was thought that this was truly a new case of vasculitis given that she had previously undergone a workup with negative ANCA antibodies. She was empirically treated with high dose steroids and convalescent plasma with clinical and radiographic improvement. Given the persistently positive antibodies months after hospitalization, she was started on rituximab and then methotrexate which could not be tolerated. Case 2 was diagnosed on granulomatosis with polyangiitis and initiated on prednisone with subsequent rituximab resulting in clinical and radiological improvement.
Discussion of Management: Any inflammatory process can lead to AAV although the causes are vast and can be from infection, genetic predisposition or medication.[1,2] AAV may occur with COVID-19 antigenic exposure, either from infection or immunization, although the risk after vaccination is rare and less common than that associated with other immunizations.[1,3,4]
It was felt to be necessary to wait to administer Rituximab until after the patients had mounted an appropriate antibody response. A prior study did not show worse outcomes for patients with rheumatologic diseases taking immunosuppressants who developed COVID-19 infection, but another study showed more severe disease.[5,6]
Conclusions: Although rare, AAV can be associated with COVID-19 antigenic exposure after infection or immunization. Early diagnosis of AAV is important as immunosuppressive therapy may improve outcomes.
Disclosures: None

410. Unusual Interstitial Lung Changes in Type I Cryoglobulinemic Vasculitis
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Presentation of Case: Type 1 cryoglobulinemic vasculitis is a subtype of cryoglobulinemic vasculitis characterized by precipitated immunoglobulin complexes that circulate in plasma and may occlude medium- and small-sized vessels. Commonly affected organ systems include the skin, kidneys, and peripheral nervous system. Pulmonary system involvement is rare. A 42-year-old man was admitted to hospital in the Spring of 2020 when he presented with purpuric lesions, fingertip ulcerations, arthritis and dry cough. He was found to have type I cryoglobulinemia secondary to paraproteinemia via monoclonal gammopathy of undetermined significance (MGUS), kappa light chain IgG subtype.
Diagnostic Testing: A CT chest at that time was normal. He initially responded to steroids and he was prescribed cyclophosphamide. This was stopped due to profound neutropenia requiring dose reduction and Filagistrim. Steroids were tapered. At review by Hematology, it was felt that intervention was not indicated for his MGUS. During this period of time his cough progressed and he developed dyspnea on exertion. He was then referred for management to a combined Rheumatology & Respirology clinic.
Differential & final Diagnosis: Upon review at the combined clinic he was found to be hypoxic and CXR demonstrated mixed interstitial and airspace disease. His presenting symptoms of fatigue, night sweats, digital ischemia and purpuric lesions had returned. He was reinitiated on prednisone. A follow-up CT revealed continued bibasilar opacities, ground-glass changes, and

septal thickening. COVID-19 screen was negative. Bronchoscopy and bronchoalveolar lavage were negative for alveolar hemorrhage and infection. Surgical lung biopsy revealed organizing pneumonia with fibrosis. At this point an application for Rituximab was made and prednisone was increased to 50 mg with clinical response.
Discussion of Management: A follow-up pulmonary function test revealed improved but persisting moderately-severe restrictive impairment, with significant diffusion impairment (44%). Recent CT has also shown reticulation and traction changes indicative of progression of interstitial lung disease. Currently, he is much improved clinically and has been able to return to work. Over four months, his cutaneous manifestations improved and are now managed with calcium channel blockers.
Conclusion: This case illustrates a unique scenario of interstitial lung changes in the context of type I cryoglobulinemic vasculitis; although pulmonary vasculitis may be associated with diffuse alveolar hemorrhage, interstitial lung changes are not commonly encountered. This case shows an example of interstitial lung changes in context of cryoglobulinemic vasculitis that responded to treatment with high-dose steroids and Rituximab.
Disclosures: SG honorarium Pfizer Sanofi: Clinical Trial AbbVie: Clinical Trial Roche: Educational Grant; Novartis: Advisory Board.

411. Granulomatosis with Polyangiitis presenting with typical features of Giant cell arteritis

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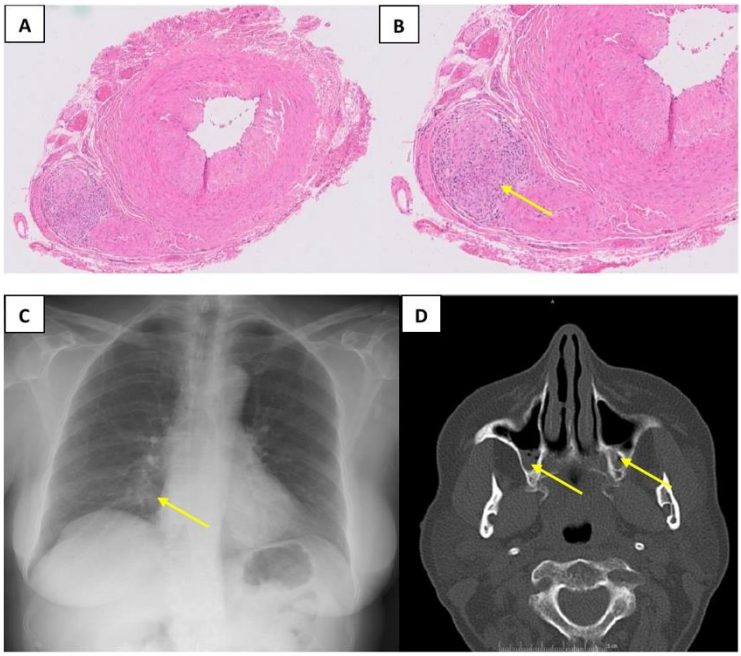
Presentation of Case: A 63-year-old female presented with PMR with CRP 37mg/L and ESR 80mm/hr. Prednisolone 15mg resulted in a marked response. On weaning prednisolone to 10mg she developed headaches, scalp tenderness, jaw claudication and diplopia prompting an increase of prednisolone to 60mg.
Diagnostic testing Temporal artery biopsy was in keeping with GCA (Fig. 1A&B). Her headaches settled, but she developed rhinnorhoea, epistaxis, vasculitic rash and shortness-of-breath. Urinalysis demonstrated no casts. Chest-Xray revealed right-sided consolidation (Fig. 1C) and CT sinuses confirmed mucosal thickening (Fig. 1D). Inflammatory markers remained elevated ESR 39mm/hr and CRP 59mg/L with a normal creatinine 71µmol/L [62-124].
Differentail and final diagnsosis C-ANCA was positive with PR3 114 IU/ml [0-3.1] confirming the diagnosis of GPA. Nasal biopsy demonstrated inflammation without granulomatous changes. She received prednisolone 1mg/Kg and intravenous Cyclophosphamide. Azathioprine maintenance was initiated once she was in remission.
Discossion of management Our case highlights GPA can present with features typical of GCA. This is important as the treatment and prognosis are different with systemic steroids usually sufficient to treat GCA, but GPA requires additional Cyclophosphamide or Rituximab therapy.
Conclusion: Large vessel vasculitis [LVV] can be a feature of GPA and may affect aorta, subclavians or carotid arteries. LVV often presents at the time of initial diagnosis of GPA, but may precede or occur after the GPA diagnosis [1, 2].

Disclosures: None

Figure 1. A – Histological cross-section of temporal artery. B – Granulomatous destruction to a small side branch of artery. C – Chest Xray showing right lower zone patchy consolidation. D - CT scan of sinuses showing bilateral maxillary involvement



412. Critical Role for CTLA4-CD80/86 and PD1-PDL1 pathways in anti-MPO disease immune regulation in vivo.

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Presentation of Case: A 71 year old female developed end stage kidney disease in the context of a pulmonary renal presentation of anti-MPO microscopic polyangiitis (MPA) 5 years prior to presentation. After induction treatment with plasma exchange, iv cyclophosphamide and corticosteroids she remained dialysis dependent. Initially ANCA negative post-induction, her anti-MPO titre fluctuated at a low titre in the intervening years without clinically active disease. Immunosuppression with prednisolone and azathioprine was withdrawn at 2 years and she was active on the deceased donor kidney transplant waiting list. She presented with lower back and hip pain and was evaluated.
Diagnostic Testing: Cross sectional imaging revealed an expansile mass in the right pelvic bone and a 6cm right kidney lesion. A biopsy of the pelvic lesion revealed a clear cell renal cell carcinoma (IMDC Score 3). Serological assays demonstrated a > 4 fold rise in her anti-MPO

titre in the 6 months prior to presentation. Following a multi-disciplinary review that noted the theoretical potential for MPA relapse she was initiated on Ipilinumab (anti-CTLA4) and Nivolumab (Anti-PD1) immunotherapy. Within one week the patient developed malaise, arthralgia, a purpuric lower extremity rash and epistaxis. Her CRP climbed from 20mg/L to 100mg/L.
Differential & Final Diagnosis: The presumptive diagnosis was a rapid relapse of her MPA consequent to dual pathway checkpoint inhibition.
Discussion of Management: Nivolumab and Ipilinumab therapy was withdrawn and the patient was treated with 40mg of prednisolone daily. The rash, epistaxis and systemic symptoms abated within days.
Conclusions: Recent experimental and genetic studies have implicated the role of programmed cell death protein 1 (PD-1), programmed cell death protein-ligand 1 (PDL-1), and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) in the pathogenesis of medium and large vessel vasculitis. This case suggests a key role the PD1-PDL1 and CTLA4-CD80/86 pathways in the down regulating of anti-MPO antibody responses in small vessel vasculitis in vivo. This case highlights the potential for checkpoint inhibition to cause disease relapse but also point to the potential for harnessing these pathways for novel disease modifying therapies in the future.
Disclosures: None

413. A case series on recurrent and persisting IgA vasculitis in children

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Background/ Objectives: Up to 30% of children with IgA vasculitis (IgAV; previously Henoch-Schönlein Purpura) will experience at least one relapse of the disease, sometimes months or even years after the initial presentation. Those cases pose a diagnostic and therapeutic challenge to clinicians due to the lack of consensus on classification and treatment of recurrent and persisting IgAV. The aim of this retrospective case series was to describe a cohort of children diagnosed with either recurrent or persisting IgAV.

Methods: Children with a diagnosis of recurrent or persisting IgAV followed-up within the last 5 years at Alder Hey Children's Hospital (Liverpool, UK) were included in this case series. Recurrent or persisting disease was defined if it had been stated in a clinical letter by a paediatric rheumatologist or nephrologist. Clinical data was retrospectively collected from medical notes. Systematic literature reviews were conducted in line with PRISMA guidance to identify existing definitions for recurrent and persisting IgAV in children.

Results: 13 children met the inclusion criteria. Median age at first presentation was 10.2 years [2.6-15.5], female:male ratio was 1.2:1 and median follow-up was 57.7 months [14.3-165.7]. Recurrent disease was diagnosed in 4 children and persisting in 9. All children presented with a purpuric rash (either recurring or persisting), however the main symptom prompting referral was arthralgia (n=9). 8 children were treated with disease-modifying antirheumatic drugs (DMARDs). The median time from first presentation to diagnosis was 18.4 months [5.3-150.8] and the time from first presentation to treatment (PTT) with DMARDs was 24.1 months [1.8-95.4]. Children with renal involvement were treated more promptly with DMARDs (n=3; PTT – 8.1 months [1.8-24.5]) than those without nephritis (n=5; PTT - 35.3 months [21.6-95.4]). 8 children were admitted at least once over the course of their disease and 10 re-presented at least once to A&E. Further details are shown in *Table 1*. The systematic reviews identified 40 records providing definitions for recurrent (n=31), persisting (n=5) IgAV or both (n=4). 'Recurrent' disease was most commonly defined in the literature as a new onset of purpura alongside any other characteristic signs of IgAV 4 weeks after achieving complete remission and 'persisting' was defined as a typical purpuric rash alongside other symptoms lasting over 1 month.

Conclusions: There is no universally agreed definition of recurring/persisting IgAV and this may contribute to a delay from first presentation to diagnosis and/or treatment. This case series emphasises the need for standardised definitions to enable better management for children with an atypical disease course.

Disclosures: None.

	Persisting	Recurrent	Overall
n (%)	4 (31%)	9 (69%)	13 (100%)
Male/Female	1/3	5/4	6/7
Age at diagnosis[b]	14.1 [7.9-15.5]	9.1 [2.6-15.1]	10.2 [2.6-15.5]
Clinical features at first presentation			
Rash [a]	4 (100%)	9 (100%)	13 (100%)
Gastrointestinal involvement [a]	2 (50%)	5 (56%)	7 (54%)
Joint involvement [a]	3 (75%)	4 (44%)	7 (54%)
Primary reason(s) for referral / presentation			
Rash [a]	3 (75%)	1 (11%)	4 (31%)
Gastrointestinal involvement [a]	1 (25%)	3 (33%)	4 (31%)
Joint involvement [a]	3 (75%)	6 (67%)	9 (69%)
Renal involvement [a]	3 (75%)	1 (11%)	4 (31%)
Persisting proteinuria/haematuria without renal involvement [a]	0 (0%)	3 (33%)	3 (23%)
Time in months between first diagnosis and diagnosis of recurrent/persisting IgAV[b]	21.0 [5.3-29.4]	13.6 [6.9-150.8]	18.4 [5.3-150.8]
Treatment			
Analgesia[a]	4 (100%)	6 (67%)	10 (77%)
Corticosteroids[a]	4 (100%)	3 (33%)	7 (54%)
DMARDs[a,c]	4 (100%)	4 (44%)	8 (62%)
Time in months from first presentation to DMARDs initiation[b]	14.8 [1.8-24.5]	39.0 [23.5-95.4]	24.1 [1.8-95.4]
Time in months from referral to DMARDs initiation[b]	4.3 [1.2-6.1]	24.3 [13.9-41.4]	10.0 [1.2-41.4]
Disease burden			
School attendance affected [a]	3 (75%)	3 (33%)	6 (46%)
Self-conscious of rash and/or frustrated by the disease[a]	3 (75%)	4 (44%)	7 (54%)
Follow up			
Months follow up[b]	42.6 [35.0-71.7]	63.8 [14.3-165.7]	57.7 [14.3-165.7]
Admitted at least once due to recurrent/persisting IgAV[a]	3 (75%)	5 (56%)	8 (62%)
Presented to AE at least once due to recurrent/persisting IgAV[a]	3 (75%)	7 (78%)	10 (77%)
Outcome			
Discharged[a]	1 (25%)	2 (22%)	3 (23%)
Still under follow-up – improved[a]	3 (75%)	3 (33%)	6 (46%)
Still under follow-up – ongoing disease[a]	0 (0%)	4 (44%)	4 (31%)

Table 1: *Clinical characteristics of children diagnosed with recurrent or persisting IgA vasculitis.*
[a]n (%) ; [b]median [range] ; [c]DMARDs used in this cohort: hydroxychloroquine, dapsone, mycophenolate mofetil, azathioprine, infliximab.
IgAV: IgA vasculitis; DMARDs: disease-modifying antirheumatic drugs.

414. ANother CAuse of pituitary dysfunction

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Presentation of Case: A 47year old male was admitted to hospital with profound lethargy, 10kg weight loss, joint pains, shortage of breath, constipation, nasal congestion and headache. Symptoms began in proximity to receiving Covid-19 vaccination. Past medical history included ulcerative colitis on azathioprine, asacol and vedolizumab (the latter stopped due to Covid pandemic). The patient was a keen cyclist and hill walker with a good level of fitness. He had signs of panhypopituitarism with pale soft skin and sparse body hair, tender MCP and PIP joints without synovitis and tenderness on abdominal exam. There was no skin rash, oral or nasal ulceration, nail lesion or digital infarcts.
Diagnostic Testing: Hb 115, Eosinophils 1.32, ESR 59, CRP 7, CK normal
cANCA negative, pANCA 320, PR3 11, MPO 61, RF, CCP, ANA, Extended myositis panel negative, Basal cortisol <3, 30min post Synacthen 31, TFTs T4 14, TSH 0.01, FSH <1, LH <1, Testosterone <0.4, Water deprivation test in keeping with partial cranial diabetes insipidus. CT CAP – active ulcerative colitis, pulmonary embolism. CT/MRI brain – possible pituitary lesion without sufficient features for adenoma. No sinusitis. Colonoscopy – active ulcerative colitis. Nasal biopsy – normal. Colonic biopsy - severe active chronic colitis. Covid negative x5, positive 13/11/21
Differential & Final Diagnosis: Ulcerative colitis related vasculitis, Vasculitis secondary to Asacol, ANCA associated vasculitis affecting pituitary, Vasculitis secondary to Covid-19 vaccine. Final diagnosis has not yet been confirmed.
Discussion of Management: The patient commenced prednisolone 40mg weaning dose of prednisolone, primarily for his flare of ulcerative colitis and was subsequently restarted on vedolizumab/azathioprine. Asacol was withdrawn. There was a dramatic response to oral prednisolone. The patient was struggling to walk on admission and he climbed Slieve Binnian (746m) shortly after discharge. He started hormone replacement, specifically levothyroxine and hydrocortisone. Testosterone and desmopressin were not required as some hormone abnormalities and associated symptoms ie thirst and polyuria improved spontaneously.
He remained well off oral prednisolone and further immunosuppression has not been commenced but as PR3 and MPO persist we are mindful of the possibility of relapse. Anticoagulation for 6 months was given for the pulmonary embolism.
Conclusions: This is an unusual case of ANCA positivity and pituitary dysfunction on a background of ulcerative colitis. There has not been histological confirmation of vasculitis and we have yet to reach a definitive diagnosis but continue to keep the patient under close review.
Disclosures: None

415. Refractory ANCA vasculitis treated with Daratumumab

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Background/Objectives: ANCA-associated vasculitis (AAV) refractory to induction treatment with rituximab and cyclophosphamide is a critical clinical problem with no evidence-based options and high associated morbidity and mortality. One potential reason for treatment failure are ANCA-producing long-lived plasma cells, antibody-secreting cells residing in specialized niches that do not express CD20 and do not proliferate. Daratumumab is an anti-CD38 monoclonal antibody used in multiple myeloma; recent case reports highlight its potential for targeting plasma cells, as they express high levels of CD38. Here we report the first use of Daratumumab in refractory AAV.

Methods: A 57-year-old male patient with MPO-ANCA positive microscopic polyangiitis, crescentic glomerulonephritis, pleuritis and alveolitis had ongoing active disease despite induction treatment with cyclophosphamide and rituximab. Serum creatinine levels increased over time and a repeat kidney biopsy showed active crescentic glomerulonephritis and plasma cell-dominated interstitial infiltrates. Additionally, CT scans showed persistent diffuse alveolar haemorrhage and MPO-ANCA levels remained over the maximum detection limit. He was treated with subcutaneous injections of 1800mg daratumumab once weekly for four weeks. Follow-up included regular clinical visits, as well as laboratory investigations of ANCA titres and blood immune monitoring using mass cytometry.

Results: Daratumumab injections were well-tolerated and no adverse events occurred. Following Daratumumab administration, patient well-being and exercise tolerance improved. Serum creatinine levels, steadily increasing before Daratumumab treatment, decreased from 3.8 mg/dl to 2.2 mg/dl after three months. A follow-up CT scan showed resolution of pleural effusions and alveolitis. MPO-ANCA titers decreased by 24%, approximately as much as vaccine-induced protective antibodies against tetanus toxoid and rubella, indicating the depletion of long-lived plasma cells. Mass cytometry-based immunomonitoring showed an increased proportion of activated neutrophils and T lymphocytes at baseline. Daratumumab treatment induced a stark decrease in CD38 expression on peripheral blood leukocytes, as well as a decrease in natural killer cells.

Conclusions: Daratumumab as a rescue treatment in a patient with refractory AAV induced clinical remission and was not associated with adverse events. This highlights both the fact that long-lived plasma cells are likely responsible for the chronicity of treatment-refractory AAV and that anti-CD38-mediated targeting of plasma cells and other immune cells is a promising new treatment approach in AAV. The safety and efficacy of daratumumab in AAV, however, needs to be established in controlled clinical trials.

Disclosures: None

416. The Vasculitic mimic!

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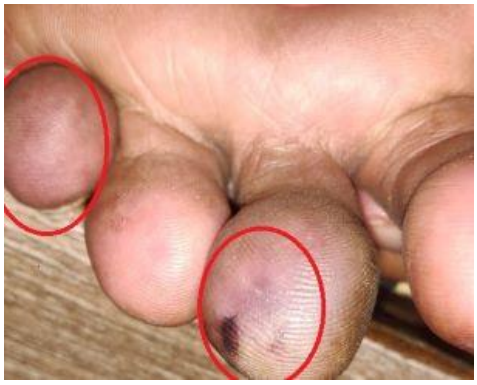
Case presentation: A 60 year old gentleman with no comorbidities presented with history of painful blackish discoloration of second and fourth toe of the left foot since a month. He also complained of pain and swelling in both ankles with early morning stiffness lasting for less than an hour. Pain aggravated on activity. He was on diclofenac for pain almost three times a day. He had history of weight loss of 20 kgs in the last two and a half years, part of which was intentional. There was no history of fever, oral ulcers, headache, skin rashes, sinusitis, cough, hemoptysis, tingling and numbness in the body. The patient had past history of admission for abdominal pain and was diagnosed to have malaria. He was not a known case of diabetes, hypertension, dyslipidemia, ischaemic heart disease. There was no history of alcohol consumption, smoking or drug addiction. There was no history of ayurvedic medication intake. No history of drug intake for migraine.
On examination all his peripheral pulses were well felt. There was blackish discoloration of his left second and fourth toe (Figure 1). His vitals were normal. Abdominal examination showed mild splenomegaly. Rest of his systemic examination was unremarkable.
Diagnostic testing: On evaluation Hemoglobin was 15 g/dl, total WBC count was 22,259 cells/cu mm, Platelets were 9.84 lakh and ESR was 16 mm at end of one hour. Chest x ray, urine examination was normal. There was no proteinuria. ANCA by immunofluoroscence showed 1:10 1+ positive. Anti PR3, Anti MPO were negative. Left lower limb arterial doppler was normal. Serology for HIV, Hepatitis C and HbsAg was negative. His lipid profile, HbA1c was normal. APLA work up was negative. Ultrasound abdomen showed mild splenomegaly.
Discussion of the management: In view of leucocytosis ,thrombocytosis, bilateral ankle arthralgia and gangrene we had clinical suspicion of vasculitis etiology and initiated on pulse doses of 500 mg cyclophosphamide once in two weeks, oral steroids at 0.5mg per kg along with aspirin 75mg per day .We followed him up after three doses of cyclophosphamide .There was significant improvement in pain and discolouration of the toes of the left foot but had persistent thrombocytosis (11.89 lakh cells/cu mm) and leucocytosis ($23*10^3$cells/cu mm) Haematologist opinion was sought who worked up for myeloproliferative neoplasm. He was positive for JAK 2V617H mutation. He was then started on hydroxyurea, aspirin was continued at 75mg per day and steroids was tapered and stopped.
Differential and final diagnosis: The initial subacute presentation of the impending gangrene of the toes with well felt peripheral pulses, no comorbidities /addiction, ankle arthralgia, leucocytosis, thrombocytosis, ANCA positivity with initial response to cyclophosphamide lead us to the possible diagnosis of ANCA vasculitis. The past history of malaria a year back would have explained the mild splenomegaly. In view of persistent thrombocytosis post pulse cyclophosphamide therapy possibility of myeloproliferative neoplasm was considered. The work up showed positive for JAK2 V617H mutation.
Conclusion: Vasculitis are rare heterogenous disorders with myriad manifestations. It is a diagnostic challenge for the treating physicians. Patients can present with a wide spectrum of

manifestations ranging from isolated cutaneous vasculitis to multisystem involvement. It can be mimicked by various diseases of which infections and myeloproliferative diseases are most common. Careful examination, thorough investigations and diligent follow up can help in proper diagnosis. If unrecognised it can lead to untoward consequences.
Disclosures: None
Figure 1. Left foot showing impending gangrene of the second and fourth toe



417. Complete remission of Eosinophilic Angiocentric Fibrosis with Rituximab without glucocorticoids

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Presentation of Case: A 48-year-old Caucasian woman presented with an eight-year history of progressive severe nasal obstruction and occasional rhinorrhoea, left greater than right. Computerized tomography (CT) revealed a large hypodense obstructive mass in the anterior area of the left nasal cavity, associated with an erosion of the nasal septum. The patient underwent a resection of the neoformation and a septoplasty. Histological examination of the resected fragments of septal tissue revealed dense lamellar perivascular fibrosis with focal storiform fibrosis. Tissue infiltration by CD3+ lymphocytes, histiocytes, polyclonal plasmacells and, most of all, numerous eosinophils, was found, especially in the perivascular area. Immunohistochemistry staining showed rare IgG4 positive plasma cells, with a IgG4/IgG ratio lower than 1/40. The fibrotic tissue invaded the underline cartilaginous tissue and septal bone area. No evidence of granulomatous inflammation, necrosis, giant cells, or malignant change were found. After six months the patient reported nasal obstruction recurrence. A magnetic resonance imaging (MRI) confirmed the suspected relapse, showing a new 17x9 mm mass arising from the anterior aspect of the nasal septum. The patient underwent a second resection of the neoformation, and the histological examination was consistent with the first one.
Diagnostic Testing: After the disease relapse, the patient was referred to our Vasculitic Clinic. Serum chemistries, erythrocyte sedimentation rate, C-reactive protein levels, white blood cell

and eosinophil count, serum levels of IgG, IgG4, IgA, IgM, IgE, C3 and C4 were found normal. ANA, ENA, anti-dsDNA, ANCA, IGRA, were negative, as also skin prick allergy test.
Differential & Final Diagnosis: Based on laboratory tests and histological examination, infectious diseases, ANCA-associated vasculitis, sarcoidosis, and neoplastic conditions were excluded. Radiological and histological examination were consistent with a diagnosis of Eosinophilic angiocentric fibrosis (EAF). EAF is a rare entity, characterized by expansive lesions of sinonasal and upper respiratory tract. Its aetiology is unknown but a connection with IgG4- related diseases has been suggested (1).
Discussion of Management: In general, the prognosis of sinonasal tract EAF seems to be indolent and progressive, but in some cases EAF could extend into the adjacent cartilaginous tissue and cause bone destruction, like in our patient. Until now, only isolated case reports on EAF have been published. Multiple surgical resections have been chosen as first-line therapeutic approach in most of these cases, while immunosuppressive therapy and glucocorticoids (GC) seemed to be associated with only limited success (2). Our patient refused to be treated with high dose GC, frightened by possible GC-related adverse effects and by the limited evidence of their efficacy in EAF. Therefore, Rituximab monotherapy was proposed. The patient was treated with Rituximab (RTX) 1,000 mg on days 1 and 15. Three months after the first RTX infusion she repeated an MRI scan and an ENT evaluation, demonstrating no radiological or endoscopic sign of relapse. Based on the efficacy of the induction treatment, RTX 1,000 mg every 6 months was chosen as maintenance therapy. Subsequent MRI scans and ENT evaluations after 10, 18 and 24 months after the first RTX infusion showed persistent disease remission.
Conclusions: EAF is considered a rare, slowly progressive, and benign disease but in some patients can be locally aggressive and relapsing. A systemic treatment might be necessary in these patients and RTX proved to be effective in our patient, even in a monotherapy regiment.
Disclosures: None

418. Fungal infections in Rheumatic diseases-Infection vs flare?- the dangerous mimics!

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Case 1: 30 years old lady developed fever, progressive dyspnoea and painful ulcers Her investigatory report were Hb 10.9 mg/dl, WBC count -10500 platelets- 4.51 lakh cells/cu mm, ESR:112mm/hr, P ANCA: positive, urinalysis: haematuria and proteinuria and 24 hour urine protein: 800 mg. HRCT showed pulmonary infiltrates. Skin biopsy was suggestive of necrotizing vasculitis. A diagnosis of ANCA vasculitis was made and she was initiated on steroids and cyclophosphamide. Patient was steroid dependent for next 9 years. After 9 years into the disease, she developed left sided headache. Over the next 6 months, she developed acute diplopia and mild weakness of the right arm. MRI brain was done which showed right eye pseudo tumour. Repeat ANCA was positive and ESR was 60mm/hr. She was diagnosed as right eye Inflammatory pseudotumor and the dose of steroids was increased. Within a week she was admitted elsewhere with complete right sided hemiplegia with aphasia. With optimal

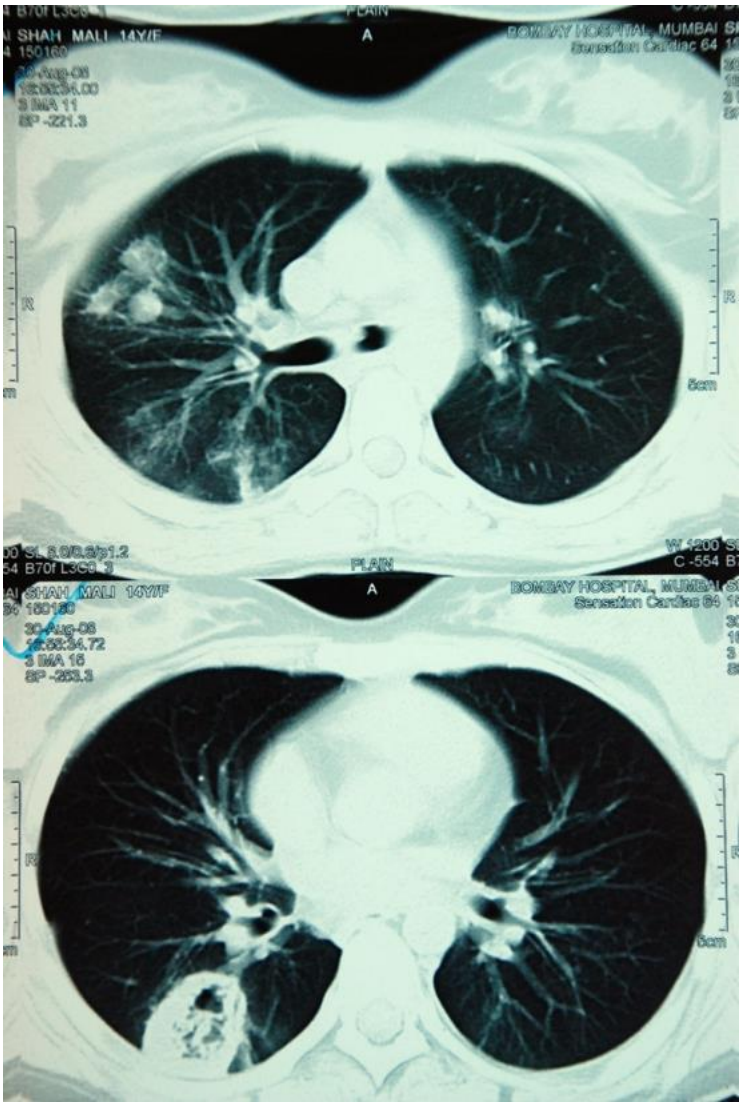
therapy she regained speech but she complained of severe left retro-orbital pain. A diagnosis of vasculitis flare was made and she was treated with pulse methylprednisolone and cyclophosphamide. On examination, weakness status was the same but pain in the left eye persisted. Repeat MRI brain confirmed a soft tissue mass in the left sphenoid sinus with a defect in the lateral wall. Trans-sphenoidal debridement was done and, microbiological examination and histopathology of the debrided tissue confirmed Aspergillus Fumigatus. She improved with voriconazole and repeated trans-sphenoidal debridements

Case 2: 14 years old girl, developed high grade fever (103 degree F) with maculopapular rashes on bilateral upper and lower limbs, painless redness of both eye with no visual impairment, rhinorrhoea with mild epistaxis, intermittent severe abdominal pain, polyarthritis of small joints of right hand , left knee and ankle, dry cough and bluish discolouration of toes all of 2 months duration. She also had unintentional weight loss of 2 kgs. Lab investigations revealed Hb 11 gm%, WBC count 13800cells/cumm, platelets 3.29lakh/cumm, ESR 116 mm, Creatinine 0.8mg/dl. Urine had active sediments and the urine spot protein /creatinine ratio was 0.5. (Up to 0.2). On further evaluation C ANCA was positive. CT thorax showed nodular lesions in the right middle and lower lobe with cavitary lesion in the right posterior lower lobe (Figure 1). CT Paranasal sinus showed bilateral frontal and maxillary sinusitis. Arterial doppler of bilateral lower limb showed occlusion of left distal anterior tibial artery and dorsalis pedis artery on both sides. She underwent biopsy from the nasal cartilage which showed chronic granulomatous inflammation consistent with Granulomatosis Polyangitis. She was initially treated with pulse methylprednisolone and fortnightly intravenous pulse cyclophosphamide therapy and later maintained on azathioprine.After 7 months of therapy, she developed productive cough and dyspnoea with hoarseness of voice. Direct laryngoscopy showed nodular lesions in the vocal cords with erythema. HRCT chest showed right middle lobe consolidation and multiple variable sized nodules at right upper and lower lobe. Blood culture was sterile. Bronchoalveolar fluid showed gram positive cocci with KOH mount showing branched septate mycelial filaments. Ziehl Nielson stain was negative. BAL culture grew Aspergillus species. Serum aspergillus galactomannan was negative.

Discussion: Here we present 2 cases of ANCA vasculitis who were initially treated with immunosuppressive therapy but later developed fungal infections. Fungal infections closely mimic vasculitis. They tend to occur in resistant vasculitis increasing morbidity and mortality. These situations require detailed history and appropriate investigations especially tissue diagnosis. In conclusion in patients with ANCA vasculitis who are adequately immunosuppressed, if there is a purported flare of the disease, care should be taken to rule out infections, especially fungal infections.

Disclosures: None

Figure 1-CT chest showing nodular lesion and cavitary lesion



419. Leucocytoclastic Vasculitis in the setting of COVID-19

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Presentation of Case: A 78-year-old man presented to the Emergency Department with a three-day history of a lower limb rash. The rash was asymptomatic, and he had no other symptoms. Examination revealed a macular purpuric rash on both lower limbs. The remainder of his skin was unremarkable. His past medical history was significant for JAK 2 positive myeloproliferative disorder. His medications included aspirin, hydroxyurea and Ferrograd C. No new recent medications had preceded the onset rash. Three days following presentation, he developed new onset cough and progressive shortness of breath. SARS-CoV-2 PCR was positive. He required oxygen to maintain his lung saturations, but his respiratory involvement improved.

Diagnostic Testing: The patient underwent baseline haematological investigations. Full blood count showed a Haemoglobin of 11.1 and White cell count of 33.96 which were consistent with the baseline in the setting of his known myeloproliferative disorder. Renal function was normal. He had a urine dipstick which was negative for blood and protein. Vasculitic screen was showed a positive ANA of 1:320. ENA and dsDNA were negative. Complement levels, both C3 and C4 were low. ANCA was negative. Skin biopsy demonstrated acute inflammation of capillaries and possibly small venules with leukocytoclasis without evidence of fibrinoid necrosis. Direct immunofluorescence (DIF) showed fibrin positivity, suggestive of vascular injury, but no immune complexes were detected.
Differential & Final Diagnosis: Differential diagnosis on presentation was between cutaneous small vessel vasculitis and capillaritis, with histology favouring the former. Following the detection of SARS-CoV-2, the clinical impression was cutaneous small vessel vasculitis secondary to COVID-19 infection.
Discussion of Management: As the rash was asymptomatic without extracutaneous involvement or clinical features suggestive of medium vessel involvement, an observational approach was taken, and the sole active treatment recommendation was for class 2 compression stockings. He was admitted for respiratory support with oxygen via nasal prongs in the setting of COVID-19. His rash fully resolved aften ten days prior to discharge home.
Conclusion: While the respiratory manifestations of COVID-19 are well established, it has also been associated with dermatological manifestations[1], most commonly urticaria, maculopapular (morbilliform) exanthem, papulovesicular rash, chilblain-like acral pattern, livedo reticularis pattern, and a cutaneous vasculitis[2]. Vasculitis represents 8.2% of skin manifestations of COVID-19 infection[2] and is seen more frequently in elderly patients with COVID-19 infection[3]. Vasculitic manifestations of COVID-19 are associated with more severe illness and higher mortality[3]. Purpuric lesions have been reported as generalised, localised to intertriginous regions or arranged in an acral distribution in COVID-19[2]. The proposed pathogenic mechanisms of cutaneous manifestations of COVID-19 include hyperactive immune responses, complement activation and microvascular injury[1]. Topical corticosteroids have been successfully used for treating mild cases of COVID-19 induced vasculitis. Systemic corticosteroid may be warranted in more severe cases with necrotic-ulcerative lesions[2]. This case underscores the importance of considering COVID-19 infection in patients presents with a cutaneous small vessel vasculitis.
Disclosures: None

420. Anti-SLAMF7 therapy in a case of refractory IgG4-associated sclerosing mesenteritis

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Presentation of Case: A 67-year-old woman was referred to our department due to persistent abdominal pain of the umbilical and hypogastric region and intermittent diarrhoea. Her history was otherwise unremarkable apart from a cholecystectomy 15 years before.
Diagnostic Testing: Chest radiograph, gastroscopy and coloscopy showed normal findings. Abdominal CT imaging disclosed soft-tissues masses encasing the superior mesenteric artery (SMA). Retroperitoneal fibrosis or (peri-)aortitis was not evident. Laboratory testing showed normal values for ESR, CRP, WBC, DBC, creatinine, ALT, AST, ANA, ENA, RF, ANCA, serum-IgG4, and urine analysis. Histopathological findings from a CT-guided biopsy showed a fibro-inflammatory lesion rich in spindle cells with interspersed lymphoplasmacytic infiltrates containing 70 IgG+ and 45 IgG4+ cells per high-power field. The IgG4/IgG ratio was >0.6. Moreover, obliterative phlebitis and storiform fibrosis were found.
Differential & Final Diagnosis: Differential diagnoses of abdominal soft-tissue masses comprise various disorders affecting the mesentery and peritoneum and inflammatory retroperitoneal conditions such as retroperitoneal fibrosis, abdominal aortitis and periaortitis. IgG4-related disease (IgG4-RD) is associated with SM and inflammatory retroperitoneal disorders in 10 – 50% of the cases. No further organ involvement is found in most IgG4-associated SM cases. In our patient, the diagnosis was based on characteristic abdominal imaging and histopathology findings indicative of IgG4-associated SM [2].
Discussion of Management: Following diagnosis, glucocorticoid therapy was started. The patient`s disease however remained refractory to glucocorticoid and subsequent thalidomide, rituximab and cyclophosphamide therapy. Abdominal CT imaging showed a progress of soft-tissue mass-forming lesions obstructing the SMA. Since cytotoxic CD4+SLAMF7+ innate-like T-cells and plasmablasts are considered to be key drivers of IgG4-RD pathology [1], the patient was switched to a course of monoclonal anti-SLAMF7 antibody (elotuzumab) therapy (cumulative dose 6 g i.v. in 12 weeks). We used flow cytometry to follow peripheral blood cell profiles at baseline and subsequently until week 12 under elotuzumab therapy. During this period, we observed a decrease of SLAMF7+ cell frequencies within the circulating neutrophil and monocyte populations and an increase within the lymphocyte population. We found an expansion of SLAMF7 expressing CD4+CD28-CD27- innate-like T-cells and CD4+CD8+ “double-positive” T-cells, which remained unaffected by therapy. An increase in the frequency of CD3-CD56+ NK cells and CD3+CD56+ NKT cells under elotuzumab therapy suggests an immunological response [3]. The patient remained in stable disease for 6 months.
Conclusions: Refractory IgG4-associated SM remains a therapeutic challenge. Elotuzumab could be a therapeutic option in IgG4-RD and is currently tested in a two-part multi-centre clinical trial in the USA (NCT04918147).
Disclosures: None.

421. Giant Cell Arteritis during treatment with Tocilizumab

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Presentation of Cases: We present four cases (table 1) with giant cell arteritis (GCA) presenting for the first time (cases 1 and 2) or relapsing (cases 3 and 4) all with normal ESR and CRP during tocilizumab (TCZ) therapy.
Case 1: 71-year-old female with a 7-year history of steroid-dependent polymyalgia rheumatica (PMR). TCZ was added as a steroid-sparing agent. 19 months later, she developed a new onset GCA with ischemic stroke, confirmed on temporal artery ultrasound (TA-US+) and biopsy. She was treated with steroids, and TCZ was switched to Ustekinumab (UST), which resulted in clinical remission.
Case 2: 70-year-old female with a 14-year history of rheumatoid arthritis (RA) who failed three anti-TNF agents. 11 months following switching to TCZ to control her refractory RA, she developed cranial GCA (TA-US+) treated with high dose steroids. Her TCZ was switched to UST and remained in remission.
Case 3: 62-year-old male with well-controlled RA on Methotrexate (MTX) and Adalimumab (ADA) who developed GCA. He was treated with high dose steroids and switched to UST and remained in remission for over three years. RA subsequently flared, prompting a switch from UST to TCZ. After 2 months he developed a relapse of cranial GCA (TA-US+). He was treated with high dose steroids, and his TCZ was switched to Abatacept (ABA), with RA and GCA remission.
Case 4: 70-year-old female with a history of PMR who developed cranial GCA and large-vessel vasculitis (LVV), which was successfully treated with a high dose steroid and UST. GCA flared 23 months later, prompting a switch to TCZ, resulting in remission. However, after 22 months on TCZ, she had GCA relapse with active LVV (and sacroilitis) on PET-CT, treated with switch of TCZ to ADA.

Diagnostic testing: Normal ESR and CRP in each patient at diagnosis of new/relapsing GCA on TCZ. TA-US, TA biopsy and PET-CT as above.
Differential & Final Diagnosis The final diagnosis was GCA. Differential: primary headache syndromes.
Discussion of Management: T-lymphocytes subsets, both Th1 and Th17, are implicated in the pathogenesis of GCA. They are considered to drive two distinct inflammatory pathways.[1] TCZ inhibits the interleukin-6 receptor, which contributes to Th17 differentiation but not the Th1 cell pathway.[2] TCZ is the first agent licensed for the treatment of GCA.[3] UST blocks both IL-12 and IL-23 activity, which are involved in developing Th1 and Th17 responses, respectively.[4] ABA, a T-cell modulator, also contributes to inhibiting both Th1 and Th17 differentiation. This prompted consideration of these alternative agents in TCZ refractory patients.
Conclusions: These cases demonstrate that GCA may present for the first time or relapse during TCZ treatment. The diagnosis of GCA in this setting is hindered by the normal acute phase reactants typically found in TCZ-treated patients, even in the presence of active rheumatic disease or systemic infection. Patients treated with TCZ (and their primary care providers) should be counselled regarding the unreliability of acute phase markers during TCZ treatment. Vigilance for clinical evidence of relapse should be maintained in TCZ-treated patients and a low threshold imposed for performing radiologic investigations to evaluate disease activity.
Disclosures: None

Table 1. Cases characteristics

	Case 1	Case 2	Case 3	Case 4
Age/ sex	71/ female	70/ female	62/ male	70/ female
GCA event	New GCA	New GCA	Flare of GCA	Flare of GCA and LVV
Time to GCA event on TCZ	19 months	11 months	2 months	22 months
Rheumatic diseases	PMR	Seronegative RA OA	Seropositive RA OA	PMR
Temporal artery Biopsy	Positive	Negative	Negative	positive
Current therapy	UST	UST	ABA	ADA
ESR and CRP at the time of GCA presentation during TCZ therapy	Normal	Normal	Normal	Normal
Prior Biologic therapy	TCZ	ADA ETN RTX TCZ	ADA UST TCZ	UST TCZ

GCA, Giant cell arteritis, PMR, Polymyalgia rheumatica; RA, Rheumatoid arthritis; OA, Osteoarthritis; TCZ, Tocilizumab; UST, Ustekinumab; ABA, Abatacept; ADA, Adalimumab; ENT, Etanercept; RTX, Rituximab

422. Withdrawn

423. Acute Progression of Granulomatous with Polyangiitis in a Pediatric Patient

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Presentation of Case: A healthy 13-year-old female presented with a 3-week history of polyarthralgia and recurrent epistaxis for acute pharyngitis and fatigue, and diagnosed with streptococcus pharyngitis. A few days later she developed acute onset of hemoptysis, dyspnea, and dehydration. She was started on supplemental oxygen for hypoxemia, and transferred to a nearby pediatric hospital, where she was treated for suspected bacterial PNA. She rapidly decompensated requiring intubation for acute respiratory failure. It became difficult to maintain her oxygenation despite maximum ventilator setting, aggressive pulmonary toileting, and the use of nitrous oxide, and she was transferred to a pediatric center with ECMO compatibility. Her hospitalization involved a prolonged ICU stay complicated by pneumothorax requiring chest tubes, ARDS secondary to diffuse alveolar hemorrhage, coagulopathy with the development of an atrial thrombus and an upper extremity DVT, nephritis, anorexia, and deconditioning secondary to paralytic use.
Diagnostic Testing: Initial testing was negative for streptococcus, mononucleosis, and COVID tests, and blood work was otherwise unremarkable. Approximately 4 days later, her blood work was notable for anemia with a drop in hgb from 13.2 to 9.8, elevated inflammatory markers with CRP 14.8 and ESR 82, and a respiratory viral panel that returned positive for rhinovirus/enterovirus infection and a chest x-ray showing bibasilar infiltrates. A Urinalysis showed orange-tinged urine with > 180 RBCs and 11 WBC. Repeat chest imaging was significant for dense interstitial and alveolar opacities suggestive of severe edema, diffuse soft

tissue emphysema along the bilateral chest consistent with pneumomediastinum and pneumopericardium, and extraparenchymal air at the lung apex representing bilateral pneumothoraces (Figure 1). A TEE showed an atrial thrombus. Rheumatological workup revealed positive ANCA with cANCA level to 1:640 and PR3 >150.

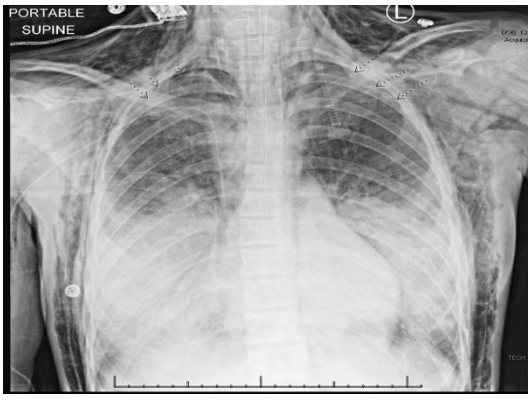
Differentials & Final Diagnosis: Initial differentials included infectious etiologies secondary to a viral respiratory infection and superimposed pneumonia. However, the constellation of symptoms including diffuse alveolar hemorrhage, glomerulonephritis, +ANCA, and +PR3 met criteria for the diagnosis of granulomatous with polyangiitis vasculitis.

Discussion of Management: Treatment included pulse dose solumedrol 1g IV for 5 days, PLEX for 3 doses, 1 dose of Cyclophosphamide, and Rituximab induction with 4 weekly doses based on the RAVE trial[2]. She responded well to therapy, extubated on hospital day 15, and continued on steroid dose of 2mg/kg/day IV. Despite aggressive immunosuppressive therapy, systemic inflammation continued with worsening renal disease progressing to nephrotic range proteinuria. Renal biopsy performed on day 45 of hospitalization was significant for elements of a FSGS with active inflammation prompting treatment with an additional pulse dose of Solumedrol 1g. She was discharged to home on day 49, on a 6-month oral steroid wean and maintenance rituximab.

Conclusion: The triad of upper and lower respiratory tract inflammation and renal disease is characteristic of childhood GPA[1]. Symptoms are commonly indolent and can mimic other disease processes. The average time of diagnosis of GPA vasculitis from symptom onset is approximately 2 months[1]. This case demonstrates a patient with 3 weeks of symptoms prior to presentation of GPA vasculitis with rapid progression to multiorgan system failure. It is important to recognize symptoms early to improve outcomes and minimize morbidity in patients with GPA vasculitis[1].

Disclosures: None

Figure 1. Chest X-ray following transfer to the Pediatric ICU with ECMO capability.



424. Endobronchial Disease in a Patient with ANCA-Associated Vasculitis

Caroline Vo[1,2], Debarati Chakraborty[1], Stephanie Garner[2], Ciaran Scallan[1], Nader Khalidi[2], Gerard Cox[1];

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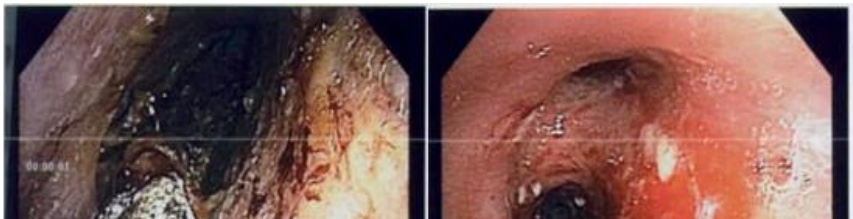
Presentation of Case: A 60-year-old male lifelong non-smoker presented to the emergency room with frontal headaches and diplopia. He also reported progressive fatigue, cough, and hemoptysis. His medical history included asthma and seropositive rheumatoid arthritis treated with golimumab. He also had chronic rhinosinusitis and had undergone three polypectomies.
Diagnostic Testing: A chest computed tomography (CT) demonstrated patchy infiltrates, bilateral upper lobe cavitating lesions and peribronchial nodules. Initial bronchoscopy showed diffuse, severe ulceration of the proximal airways with mucosal bleeding involving the upper lobes, lingula and right middle lobe. The bronchoalveolar lavage (BAL) was bloody, but not sequentially hemorrhagic to indicate diffuse alveolar hemorrhage.
Laboratory examination revealed an elevated proteinase 3 anti-neutrophil cytoplasmic antibodies (> 8 AI) and rheumatoid factor (116 IU/mL). Creatinine peaked during his admission. Urinalysis showed proteinuria and hematuria. His CBC was unremarkable with a normal eosinophil count.
Differential & Final Diagnosis: The differential included infectious trachea-bronchitis and malignancy. Two separate BAL and biopsy samples did not demonstrate infectious etiologies. There was a positive BAL qualitative CMV and HSV polymerase chain reaction, but this was not considered relevant as the patient was not immunocompromised and his clinical presentation was not consistent with a viral pneumonitis. Malignancy was not found on lavage or pathology. Confirmatory testing included a repeat bronchoscopy with examination of nares that showed persistent ulceration, mucosal edema and erythema (Figure 1). Biopsy of the right upper lobe bronchus was revealing for necrotizing granulation inflammation. A subsequent kidney biopsy demonstrated focal segmental proliferative and necrotizing glomerulonephritis, which is consistent with ANCA associated glomerulonephritis. Overall, the patient had a constellation of symptoms consistent with granulomatosis with polyangiitis (GPA). This includes serology (PR3-ANCA positive), pulmonary involvement confirmed on bronchoscopy and CT, nasal polypoid disease, bronchial mucosal inflammation and glomerulonephritis.
Discussion of Management: GPA is a small vessel vasculitis characterized by necrotizing, granulomatous inflammation. A systemic auto-immune disease, GPA predominantly affects the upper respiratory tract, pulmonary parenchyma and kidneys. Endobronchial disease in comparison is relatively rare with mostly case reports or series descriptions, but it carries significant morbidity and mortality. While subglottic stenosis has an incidence of 10%, distal endobronchial disease is reported in only 6% of GPA patients. The presence of endobronchial disease should prompt consideration for both immediate (ex. infectious trachea-bronchitis) and long-term complications (ex. tracheal or bronchial stenosis). Our patient was treated with three doses of IV methyl-prednisolone, followed by high-dose oral prednisone. His high risk of relapse with positive PR3-ANCA was in favor of utilizing rituximab as induction therapy.
Disclosures: None. *These authors contributed equally to this abstract.
Figure 1. A) Anterior nares with ulceration and clots, and B) the right upper lobe bronchus demonstrating erythema, ulceration, and edema with adherent mucous.



425. Withdrawn

426. A case series of distinct phenotypes of Behcets' Disease

Juhi Dixit[1], Kriti Kishor, Dogga Prasanna Kumar, Kunal Chandwar, Digvijay Ekbote, Ankush PM, Abilash Krishnan V;
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Background: Owing to the rarity and heterogenicity , Behcet's disease (BD) remains a diagnostic and management challenge to the internists and rheumatologists alike. Diagnosis is difficult and often of exclusion. Exact prevalence in Indian subcontinent is not known.
Objectives: To study varied clinical manifestations and treatment outcomes of BD presenting to a tertiary care hospital in north India.

Method: Short case series of 4 cases who presented to rheumatology clinic of tertiary care hospital in north India from January 2020 to January 2021. Clinical details, laboratory and radiological findings , treatment details and outcomes were recorded.

Results: First patient was a prototype case and responded well to first line therapies.
In case 2 episodes of syncope pointed towards possible vascular insufficiency which on subsequent evaluation with carotid artery doppler and CT aortography revealed large vessel vasculitis(LVV). Early diagnosis in absence of frank signs of LVV and aggressive treatment altered disease course towards better outcome.
In case 3, large vessel vasculitis with stenotic lesions involving pulmonary arteries and aorta was quite atypical as Bechet's disease is known to have pulmonary artery aneurysm. Presence of other clinical features favored the diagnosis of Bechet's disease over Takayasu.
In case 4, initial presentation with only retinal vasculitis, a drug free remission period of fourteen years followed by orogenital ulcers was quite atypical. Although the patient had accrued damage in the form of bilateral optic atrophy with macular scarring infliximab was given to preserve the residual vision.

Conclusion: Diverse clinical manifestations and atypical presentations make the diagnosis of this not so common variable vessel vasculitis all the more challenging. Delay in diagnosis and management leads to damage accrual with increased morbidity and mortality risk. It is prudent

to have high index of suspicion given early immunosuppressive therapy can favorably alter the disease course.

Disclosures : none

	Case 1	Case 2	Case 3	Case 4
Clinical presentation	Oro genital ulcer Erythema nodosum Right lower limb DVT	Symmetrical polyarthritis (small + large joints) Oro genital ulcers Erythema nodosum Syncope	Dyspnoea on exertion Hemoptysis Oro genital ulcers Polyarthralgia Superficial thrombophlebitis Bilateral posterior uveitis	Orogenital ulcers Bilateral retinal vasculitis Bilateral sensorineural hearing loss
Laboratory investigations	Anemia Thrombocytosis Raised ESR and CRP	Anemia Thrombocytosis Raised ESR and CRP ANA 3+ fine speckled ENA, RF, Anti CCP negative	Anemia Leukocytosis Raised ESR and CRP ANA 2+ fine speckled ENA , APLA, LAC negative	Anemia Raised ESR and CRP ANA, ENA, APLA profile negative
Other relevant investigations	Right lower limb doppler consistent with DVT	Carotid doppler : left carotid stenosis CT aortography : infrarenal abdominal aorta narrowing	CT aortography : stenotic lesions involving aorta and its branches and pulmonary arteries with collaterals	Fundus : bilateral consecutive optic atrophy with macular scarring Pure tone audiometry : bilateral sensorineural hearing loss
Treatment (According to EULAR 2018 recommendations[1])	Low dose oral steroids Azathioprine Colchicine	Oral steroids (1 mg/kg) Pulse cyclophosphamide Azathioprine maintenance	Pulse methylprednisolone 1 gm iv x 3 days Oral prednisolone (1 mg/kg) Pulse cyclophosphamide	Pulse methylprednisolone 1 gm iv x 3 days Oral prednisolone (1 mg/kg) Infliximab 5 mg/kg
Outcome	Improved	Improved	Improved	Improved

427. Withdrawn

428. Sudden blindness in a young female

Juhi Dixit[1], Kriti Kishor[1], Digvijay Ekbote[1], Dogga Prasanna Kumar[1], Kunal Chandwar[1], Abilash Krishnan V[1], Ankush PM[1], Urmila Dhakad[1]
[1]*King George Medical University, Lucknow, India*

Presentation of Case: 15-year-old female presented to Rheumatology clinic with 4-year history of B/L lower limb claudication and recurrent episodes of episodic abdominal pain associated with misophobia. Over the past 2-3 years both her claudication and pain abdomen had worsened restricting her activities of daily living and schooling. Also, there was new onset gradually worsening B/L upper limb claudication making it difficult for her to reach objects above head due to pain. There was history of intermittent anginal chest pain, palpitations, significant loss of weight and appetite. In June 2021 she had 1 episode of sudden onset weakness in left upper and lower limb without facial nerve palsy or seizure that had resolved within few minutes without residual neurological damage. There was no other history suggestive of Connective tissue disorder and no family history of autoimmune disorders, young hypertension / CVA. Personal history was negative for tuberculosis. On evaluation patient was found to have absent pulses in B/L upper limbs with B/L subclavian and carotid bruit and normal B/L lower limb pulses. She was hypertensive with blood pressures of 170/104 & 176/110 in right and left lower limbs respectively. Her cardiovascular, pulmonary, abdomen and CNS examination was normal. Two days later during hospital stay she developed acute onset painless loss of vision bilateral eyes not associated with floaters or restricted eye movements. At the time of episode patient did not have perception of light in both eyes, no signs of ocular inflammation and fundus examination was normal.

Diagnostic Testing: Her blood investigations revealed Hb 9.9 gm%, TLC 8400/mm^3, Platelet count 4,60,000/mm^3, SGOT/SGPT 14/27 IU/dL, Urea/creatinine 23/0.49 mg/dL, HIV/HBsAg/Anti HCV non reactive, ESR 20 mm at 1st hour (<15), CRP 3.26 mg/dL(0-6). Her CT aortography revealed diffuse circumferential mural thickening involving arch of aorta and descending thoracic aorta leading to mild luminal narrowing. Diffuse circumferential mural thickening with severe luminal narrowing was noted for bilateral common carotid and subclavian arteries prior to origin of vertebral arteries. For her ocular complaints MRI brain and FFA was done and was normal.

Differential & Final Diagnosis: In view of her clinical and radiological features she was diagnosed as Takayasu arteritis Type V (ITAS 2010 score 20). Possibility of CVA, CRAO, retinal vasculitis and ocular ischemic syndrome was ruled out in view of normal fundus examination, FFA and MRI brain. A possibility of subclavian steal syndrome was considered due to severe luminal narrowing of first part of bilateral subclavian arteries causing compromised vascular flow to B/L central retinal arteries and amaurosis fugax.

Discussion of Management: She was started on 1 mg/kg oral prednisolone along with anti-hypertensives, methotrexate 10 mg/week and low dose aspirin. Digital subtraction angiography was done along with stenting of right subclavian artery with subsequent resolution of eye symptoms. On follow up she had no recurrence of visual symptoms and right upper limb claudication had improved.

Conclusions: Ocular manifestations in Takayasu arteritis can result from disease activity or as complication of long term steroid use. Our patient had subclavian steal syndrome leading to amaurosis fugax which improved after right subclavian artery stenting. Normal inflammatory markers despite clinically active disease was unusual.

Disclosures: None

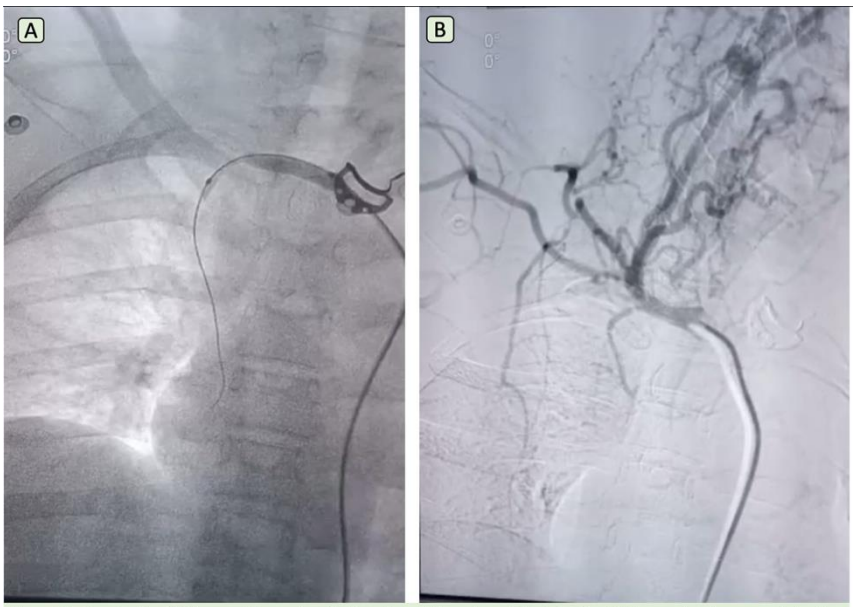

Figure 1 A- Pre stenting DSA image with non visualization of arterial branches , B Post stenting DSA image showing revascularization

429. Severe cytomegalovirus colitis in a patient with systemic vasculitis: a rare complication

Maria Helena Lourenço[1,2], João Borralho[3,4], Inês Silva[1,5], João Vaz Alves[3,5], Rita Sampaio[6], Kamal Mansinho[3,7], Jaime C. Branco[1,2,5];
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Presentation of Case: A 78-year-old woman was admitted to the emergency room due to abdominal pain, nausea and vomiting. She had a previous diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA), with asthma, sinusitis, bullous hemorrhagic vasculitis, symmetric and additive polyarthritis of hands, elbows and tibiotarsal joints, sensorimotor polyneuropathy and peripheral eosinophilia. She was medicated with prednisolone (PDN) 20mg/day (weaning scheme – initial dosage 1mg/kg/day) and cyclophosphamide (2 cycles; CYCLOPS protocol) (previous intolerance to methotrexate), with clinical remission.
Diagnostic Testing: Blood analysis revealed microcytic hypochromic anemia (hemoglobin 10.3 g/dL) and a raised C-reactive protein (8.5 mg/dL). Abdominal computed tomography scan showed colonic thickening, with perforation of the anorectal transition and extraperitoneal air. The patient underwent surgery, during which a bleeding rectal ulcer was detected. Biopsies were performed, followed by a terminal colostomy and a course of broad-spectrum antibiotics.

Differential & Final Diagnosis: Cancer was one of the main differential diagnoses considered, due to the patient' age, symptoms and previous diagnosis (vasculitis may have a tumoral origin). Infectious causes were considered, namely tuberculosis, as the interferon-gamma release assay was positive. However, histological examination of the ulcer showed enlarged cells with thickened nuclear membrane and intranuclear and intracytoplasmic inclusions, typical of cytomegalovirus (CMV) infection and immunohistochemistry was positive to CMV infection. CMV viral load (VL) was 254 IU/mL, compatible with disseminated CMV disease. Two months before, CMV serologies had revealed positive M and G immunoglobulins, with CMV VL <178 IU/mL. No signs or symptoms of other CMV organic disease were documented.
Discussion of Management: Treatment with ganciclovir (5mg/kg 12/12h) was performed for 21 days, after which CMV VL was undetectable. Secondary prophylaxis with valganciclovir 900mg/day was started in conjunction with the vasculitis treatment (PDN 20mg/day), with no CMV disease recurrence. Isoniazid 300mg/day and pyridoxin 40mg/day were also initiated due to latent tuberculosis diagnosis.
Conclusions: EGPA is a vasculitis of small- and medium-sized vessels characterized by lung, paranasal sinus, skin, kidney, nervous system and joints involvement, associated with peripheral eosinophilia. It is a potential life-threatening disease. Immunosuppressive drugs are the mainstay of treatment. Glucocorticoids, cyclophosphamide and rituximab induce remission of the severe forms of disease, but also predispose patients to opportunistic infections. CMV infection is common and usually benign in immunocompetent hosts. However, in

immunocompromised patients, reactivation can occur, carrying poorer outcomes. Colitis is a rare complication mainly reported in patients with human immunodeficiency virus and transplant recipients, with scarce data in ANCA-associated vasculitis (AAV). There is sparse data regarding prophylactic or preemptive treatment of CMV infection in patients with AAV. This case reinforces the need of guidelines concerning surveillance and prophylaxis of CMV infection in these patients.
Disclosures: None.

430. Arthritis as a atypical presenting feature in a case of Takayasu arteritis

Kasturi Hazarika[1], Urmila Dhakad[1];
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Presentation of Case: A 21-year-old girl was on our follow up as a case of polyarticular juvenile idiopathic arthritis (JIA) for the past 6 years. Her complaints of joint pain started when she was around 10 years of age. It was subacute in onset, symmetrical, additive arthritis involving wrists, elbow, knees, and shoulders. There was no history of inflammatory low back ache, no history suggestive of uveitis and no personal or family history of psoriasis. There was history of intermittent fever which wasn't documented and often attributed by the patient to severe pain. She was on methotrexate full dose appropriate to her body weight for the initial two years to which her arthritis had responded well. In the subsequent years methotrexate was tapered and stopped in view of growing intolerance of the patient towards methotrexate and her joint complaints being in remission. After being off medication for around a year and a half, patient visited our tertiary care hospital in view of unrelenting fever of 2 months duration, increased fatiguability and a recently developed pounding sensation in the neck. Patient had documented weight loss of around 5 kgs in the past 2 months. No features suggestive of photosensitivity, Raynaud's phenomenon, or other features suggestive of any underlying connective tissue disease was elicited either in past or present. No history suggestive of recurrent oral and genital ulceration She was found to be hypertensive with unequal blood pressure in both arms and absent lower limb pulses femoral onwards. There was also a wide pulse pressure in both upper limbs. Cardiovascular examination was suggestive of thrill in parasternal, aortic, pulmonary, and bilateral supraclavicular areas. A diastolic decrescendo murmur was observed which was best heard in the aortic area. Bruit were present over bilateral renal angle, over the subclavian, bilateral carotid and over bilateral interscapular areas. Suspecting a large vessel vasculitis, we went ahead with the investigations.
Diagnostic Testing: A hemogram was suggestive of normocytic normochromic anaemia, with thrombocytosis and very high erythrocyte sedimentation rate (ESR) of 115 at the end of first hour by wintergreen method. In retrospect, when we looked into the previous records, a very high ESR with thrombocytosis was also present in her initial presentation six years prior. Radiographs of hands and knees were almost normal given the long history of arthritis. Echocardiogram revealed a left ventricular ejection fraction of 66%, mild aortic regurgitation and mild mitral regurgitation. Computerised tomography (CT) angiography of aorta and its branches revealed significant involvement of the aorta and its branches. There was prominent arch of aorta with narrowing of right brachiocephalic at its origin (Figure 1A). There was long

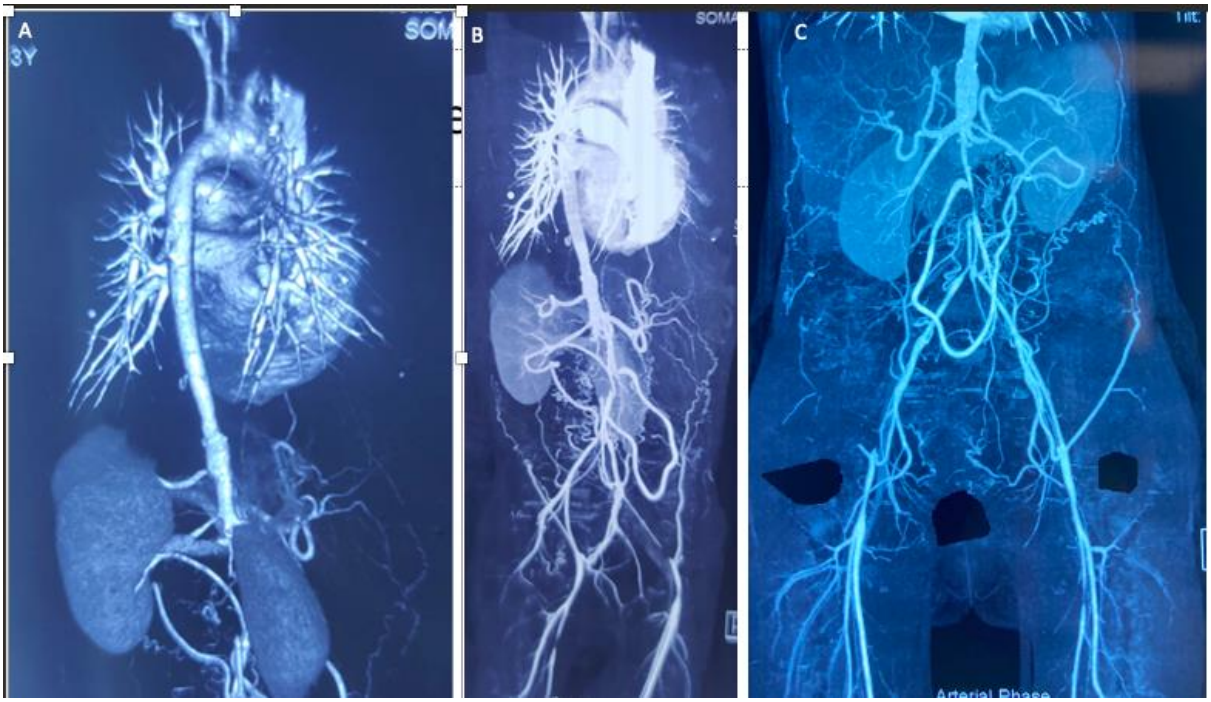
segment narrowing with stenosis of descending thoracic aorta in pre ductal region to supra renal region (Figure 1B). The abdominal aorta was reported to have abrupt narrowing with non-opacification extending from infra renal region to the common iliac artery with opacification of bilateral common iliac artery filled by extensive collaterals (Figure 1C). Anti-nuclear antibody (ANA) test done by indirect immunofluorescence (IIF) was negative.

Differential & Final Diagnosis: To summarize we have a young girl with history of arthritis and on successful treatment with methotrexate, who subsequent to tapering and stopping methotrexate presented with features suggestive of large vessel vasculitis. Our first differential was Takayasu's arteritis. The patient however never complained of typical symptoms of claudication seen in such extensive disease. A possibility of systemic lupus erythematosus (SLE) with the rare feature of large vessel vasculitis was ruled out by the absence of any other clinical or immunologic criteria. Infectious causes of aortitis like tuberculosis were ruled out by a normal chest radiograph, negative Mantoux and a negative quantiferon gold test. She had no history suggestive of recurrent oro-genital ulceration in her entire disease duration of almost ten years making it unlikely to be Behcet disease. Given her young age of onset and characteristic pulse and blood pressure inequality along with characteristic angiographic evidence, our patient fulfilled the American college of rheumatology (ACR) 1990 criteria for Takayasu arteritis.[1]However, the long history of peripheral arthritis preceding the obvious features of vasculitis was very odd in this patient. Joint involvement as a presenting feature of Takayasu arteritis is very rare found only in 6-10% of patients.[2] Whether the use of methotrexate in this patient masked her physical findings of large vessel vasculitis for the past 5-6 years remains unknown. She however never received high dose steroids as recommended for Takayasu arteritis.[3] The grossly wide pulse pressure of in absence of significant aortic regurgitation proven by investigations, may be explained by reduced elasticity of aorta and widespread collaterals.

Discussion of Management: Our patient was on methotrexate for her arthritis and had developed severe intolerance towards it. She was from poor financial background and without any health insurance because of which she could not afford either tocilizumab or anti- tumor necrosis factor inhibitors as conventionally recommended.[3] So we started her on 1mg/kg steroids and pulse cyclophosphamide after counselling and discussion with family members. She was also started on anti-hypertensives and a cardiology consultation was also sought for possible intervention.

Conclusions: A patient presenting with one immunologic feature as arthritis may in distant future evolve into a dangerous and life -threatening disease as vasculitis. Although we may have read of literatures quoting atypical features of diseases, they never strike us unless we encounter them for ourselves. Lastly, the importance of a simple clinical examination as looking for pulse and blood pressure inequality goes a long way in detecting such an atypical presentation.

Disclosures: None



431. An insidious case of an Igg4 related disease mimic

Sharon Cowley[1], Grainne Murphy[1];
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Case presentation: A 57 year old man was referred to inpatient Rheumatology services for consideration of an autoimmune aetiology for a pericardial effusion noted during diagnostic workup for an acute stroke. His past medical history was remarkable for a recent admission with critical limb ischaemia secondary to popliteal aneurysm and thrombosis which required surgical intervention He also had depression, type 2 diabetes and psoriasis. In this early phase of illness he had no additional symptomatology indicative of a connective tissue disease and had no additional symptoms suggestive of vasculitis. Imaging at this time showed no evidence of vascular inflammation, thromboses or new aneurysms.
His medications included apixaban, aspirin and escitalopram. He was an ex-smoker, didn't drink alcohol and worked as a coal merchant. His father had a stroke in his 50s.
Blood abnormalities included a normochromic normocytic anaemia with Hb of 12.6 (13-17g.dl), a monocytosis of 3.04 (0.15 – 1.3 x 10^9), ESR of 52 (0-10mm/hr) and CRP of 28.4(0-5mg/l).
Diagnostic Testing: MRI brain confirmed brainstem stroke. TTE revealed an incidental large pericardial effusion of 2.5cm which evolved into tamponade requiring pericardiocentesis with drainage of 750mls of exudative effusion. Cardiac MRI showed no evidence of pericardial thickening or definitive enhancement. PET scan was completed which did not show any abnormal uptake. Temporal artery biopsy showed no evidence of arteritis.An extensive autoimmune and infectious blood work up was completed. His quantiferon was strongly positive. IgG and IgA were elevated at 19.48(6-16g/l) and 6.59 (0.6-4.0g/l). Igg4 subclass was the upper limit of normal at 0.82 (0.039 – 0.864g/l) with a low C3. While TB cultures from

pericardial fluid were sterile, the infectious diseases service commenced quadruple anti-tuberculous therapy. During follow up he developed a recurrent pericardial effusion necessitating pericardiectomy. Histology showed an acute lymphocytic process with organising fibrinous reaction. He was re-referred to Rheumatology due to severe anterior knee pain which left him wheelchair bound. Knee Xray and MRI were normal. Repeat CT TAP demonstrated pericardial thickening, perinephric fat stranding and subtle mural enhancement of his infra-renal aorta. He was commenced on methotrexate and oral steroid therapy with modest result for presumed Igg4 disease. Leflunomide 20mg OD was added. Symptoms progressed and rituximab was given but he relapsed after a few months of modest benefit. Due to ongoing knee pain a NM bone scan was performed which showed focally intense radiotracer uptake in the proximal left fibula. CT TAP was again repeated which demonstrated an increase in size of the periaortic inflammatory change, now amenable to biopsy. A retroperitoneal soft tissue biopsy revealed a histiocytic neoplasm with BRAF V600E mutation consistent with Erdheim-Chester disease.
Differential Diagnosis: Igg4 disease was strongly considered given the perinephric stranding, borderline Igg4 subclass levels and pericardial involvement. TB, vasculitis and malignancy were also exlcuded. Erdheim-Chester disease was finally diagnosed with classic histology.
Management: Initial management with steroids, methotrexate, leflunomide and subsequently rituximab was justified in the context of a patient with significant systemic symptoms and multiple relapses. Definitive management by haematology was first line treatment with pegylated interferon 135mcg s/c weekly and dexamethasone. He failed this treatment and moved onto second line treatment with vemurafinib 480mg BD. He still uses mobility aids but has had no further disease progression to date.
Conclusions: Erdheim-Chester disease is a very rare multisystem disorder that can present in a similar fashion to many rheumatological diseases including large vessel vasculitis. In patients that fail to respond or follow an atypical clinical course re-imaging and repeated re-evaluation is of critical importance in reaching the diagnosis
Disclosures: None

432. Ischemic Optic Neuropathy Secondary to Varicella Zoster Vasculitis Mimicking Giant Cell Arteritis

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Presentation of Case: An 82-year-old woman presented with sudden onset of a blind spot in her left eye, which she first noticed while watching TV 3 weeks prior and had remained unchanged. She had bilateral optic disc edema and peripapillary haemorrhages, raising concerns for giant cell arteritis (GCA). Her past medical history was relevant for multifocal atrial tachycardia, diverticulitis with sigmoid perforation requiring colostomy, remote history of melanoma, stage 3 chronic kidney disease, lower extremity edema, and viral epiglottis complicated by sepsis a few months prior to her current presentation. Her family history was remarkable for cancer.She had not had any recent onset of a new type of headache, eye pain,

fevers, night sweats, weight loss, jaw pain or claudication, scalp tenderness, or pain, weakness or stiffness in shoulders or hip girdles. Rest of review of systems was negative.The patient's vitals were within normal limits. Her physical exam was unremarkable but for ostomy and 1+ pitting in lower extremities.

Diagnostic Testing: Her labs were within normal limits but for mild anemia with hemoglobin: 11.3 g/dL, erythrocyte sedimentation rate (ESR): 42 mm/hr, BUN: 25.3 mg/dL, creatinine: 1.05 mg/dL, eGFR: 50 mL/min, C-reactive protein (CRP): 16.1 mg/L. Immunological tests were all negative.An electrocardiogram, chest X-ray, chest computerized (CT) angiogram, brain magnetic resonance (MR) imaging (MRI), and neck MR angiogram (MRA) were unrevealing. An MRI of the orbits revealed prominent vessels in the right greater than the left temporal scalp, suggestive of temporal arteritis. A brain MRA revealed a long segment mild-to-moderate stenosis of the proximal basilar artery, and mild asymmetric narrowing of the left middle cerebral artery M2 branches (Figure 1A and 1B). Bilateral temporal artery biopsies revealed arteriosclerosis with local calcifications but no inflammation.

Differential & Final Diagnosis: The presentation in an elderly patient of visual loss and elevated inflammatory markers was concerning for GCA. However, the differential diagnosis was broad and includes non-arteritis ischemic optic neuritis, tumor, demyelinating disease, elevated intracranial pressure due to thrombosis of the cerebral vein and/or sinuses, infectious, other vasculitides or paraneoplastic.Given the suspicion for biopsy-negative GCA with visual involvement, the patient received 1 gram of intravenous (IV) methylprednisolone daily for 3 days and was transitioned to oral prednisone 60 mg orally daily with plan to discuss about tocilizumab initiation during her follow up.A week later, she was evaluated by neuro-ophthalmology. Funduscopic examination demonstrated right optic disc edema and left pallid optic disc with bilateral peripapillary haemorrhages. Despite high dose glucocorticoid treatment, the CRP and ESR remained elevated. A lumbar puncture revealed normal opening pressure, without elevation in CSF protein, but the CSF polymerase chain reaction was positive for varicella-zoster virus (VZV).

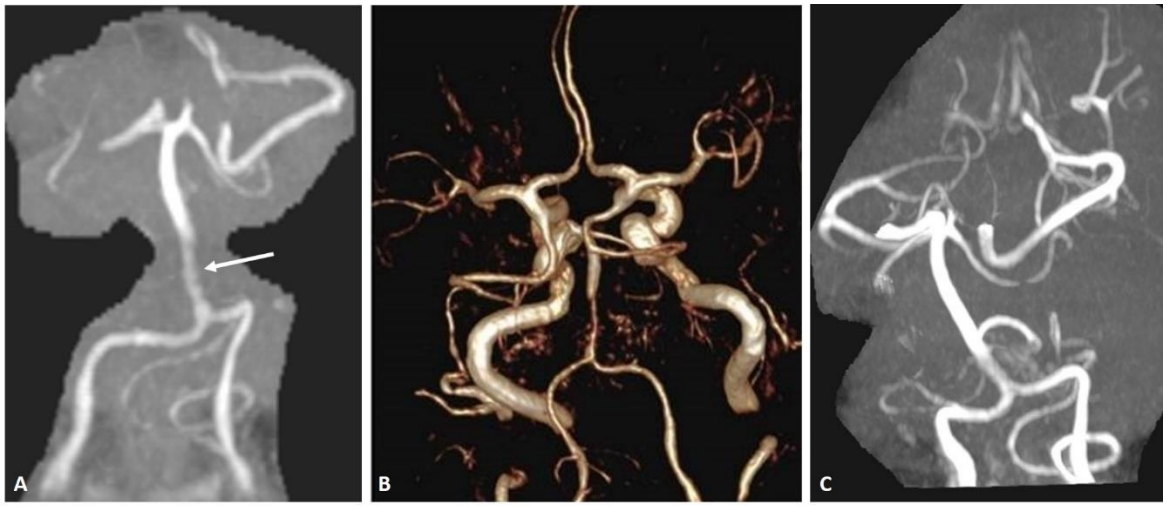
The patient had a prior history of chickenpox in the early teenage years and zoster as an adult 14 years prior, and she had received the shingles vaccine. The final diagnosis was bilateral arteritic ischemic optic neuropathy secondary to VZV infection.

Discussion of Management: She was treated with IV acyclovir for 14 days through a PICC line and her prednisone was rapidly tapered off. Her inflammatory markers quickly normalized. A brain MRA repeated 2 months later showed improvement in the basilar artery stenosis (Figure 1C).

Conclusions: Differentiating GCA from its many mimickers remains a challenge in the clinical practice. In patients with negative temporal artery biopsy, the persistence of elevated inflammatory markers despite high dose steroids, should preclude additional work up for the search of an alternative diagnosis.

Disclosures: The authors have nothing to disclose.

Figure 1.



433. Withdrawn

434. Clinico-pathologic features and outcomes of renal medullary angiitis in ANCA associated vasculitis

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Background: Pauci-immune crescentic and necrotizing glomerulonephritis (GN) is the hallmark of ANCA associated GN, with renal medullary angiitis (RMA) involving vasa recta of the medulla reported infrequently. We sought to describe the clinico-pathologic characteristics and treatment outcomes of RMA in ANCA associated vasculitis (AAV) patients who underwent a diagnostic kidney biopsy.

Methods: A search was conducted in our renal pathology database to identify kidney biopsies in patients with AAV with a diagnosis of angiitis and medullary angiitis for the time period 2000-2021. RMA was defined by the presence of interstitial hemorrhage in the medulla associated with a polymorphonuclear leukocyte infiltrate and karyorrhectic debris. All retrieved cases were examined by a pathologist to confirm that the histologic criteria were met. Demographic, clinical and treatment details were extracted by record review. Descriptive statistics is used to describe the variables of interest.

Results: Among 136 AAV biopsies, we identified 13 (~10%) cases of RMA. The median age was 71 years (range between 17 and 84), 7 (53%) were females, 6 (46%) cases had PR3 ANCA positive serology, and 9 (64%) cases had extra-renal manifestations. The mean (SD) entry eGFR was 16 (10) ml/min/m^2, ESR 98 (33) mm/hr, serum albumin 2.9 (0.5) mg/dL, and proteinuria in 12 patients was 1.8 (1.8) grams. All biopsies included cortex with a mean (SD) of 9 (6) glomeruli, and 6 biopsies with less than 10 glomeruli. Global glomerulosclerosis beyond age adjusted was

noted in 4 cases, and segmental glomerulosclerosis was noted in 2 cases. In 5 biopsies, cellular crescents were noted, and glomerular necrosis was appreciated in 8 biopsies. Majority had moderate to severe interstitial inflammation and mild tubulointerstitial scarring. Granulomatous reaction was noted in one biopsy. Four patients had arteritis involving small renal arteries. Most of the patients (71%) had extensive tubular injury. All patients were treated with pulse methylprednisone and prednisone taper in combination with cyclophosphamide (n=6), rituximab (n=7) and mycophenolate (n=1). During a mean (SD) follow up of 50 (58) months, 1 patient reached ESKD, 1 patient died and the mean (SD) eGFR at last follow up was 45 (21) ml/min/m^2 in the remainder.

Conclusion: RMA was seen in 10% of biopsies in our cohort and clinically presents with severely impaired renal function with elevated inflammatory markers. Acute lesions in the form of crescentic and necrotizing lesions and interstitial inflammation with less chronicity are observed in kidney biopsies with RMA. Despite severe presentation, majority of patients respond to immunosuppression with good recovery of renal function.

Disclosures: None.

435. Withdrawn

436. A giant coronary artery aneurysm in a patient with Behçet's Syndrome

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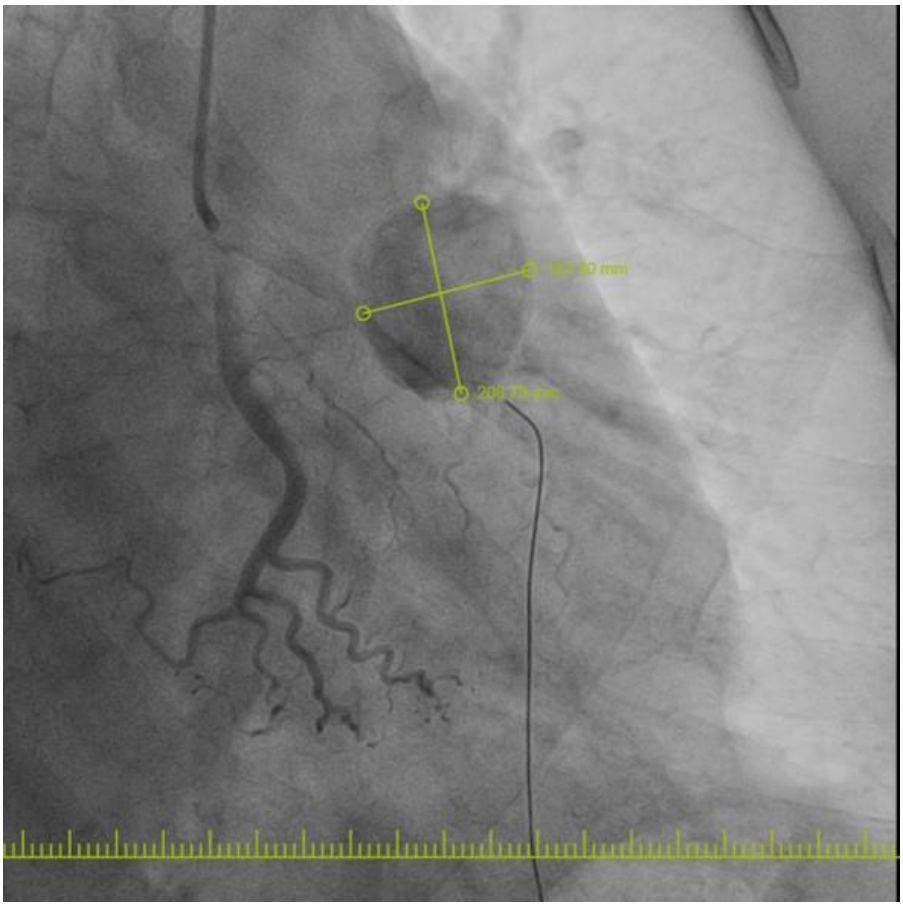
Presentation of Case: A 34-year-old male with a history of low extremity deep vein thrombosis (partially recanalized) was admitted to our clinic for investigating chest pain and extremely high C-reactive protein with suspicion of Behcet's syndrome (BS) diagnosis. He had a history of recurrent oral ulceration and positive HLA-B51 testing but did not report genital ulcers, nodular skin lesion, uveitis, or other BS-associated symptoms.
Diagnostic Testing: Pulmonary chest computed tomographic angiography did not reveal pulmonary artery involvement. Skin pathergy test and uveal examination could not be performed due to the need for urgent percutaneous coronary angiography (CA) for increasing angina pectoris. CA revealed a giant coronary artery aneurysm (CAA) in the left anterior descending artery (Fig.).
Differential & Final Diagnosis: Although the patient did not fulfill BS diagnostic criteria, the patient was diagnosed with a BS-coronary artery involvement that presented with a giant CAA.
Discussion of Management: A coronary artery bypass graft operation was performed after a 3-day course of methylprednisolone (1g/day) and cyclophosphamide (1000 mg i.v.) with a diagnosis of BS-related coronary arteritis.
Conclusions: CAA is a rare condition with a prevalence of 0.3%–4.9% among patients undergoing coronary angiography. Giant coronary artery aneurysm refers to a coronary vessel diameter of >8mm. Underlying inflammatory diseases have been reported in one-sixth of the patients with CAA.Pulmonary or coronary artery involvement should be ruled out by computed tomography or conventional angiography in patients with chest pain with BS. BS-related arterial

aneurysms are prone to rupture and may cause sudden death without proper and early treatment. In addition, disease activity is related to worse outcomes in vascular interventions among patients with BS. Therefore, surgery should be delayed after medical treatment when possible.

Disclosures: None

Figure 2. *Conventional coronary angiography depicts a giant coronary aneurysm*



437. Juvenile systemic lupus erythematosus debut with atypical haematological manifestations and macrophage activation syndrome: case report

Ana Laura Recalde Orrego[1,3], Silvio Apodaca[1,2], Celia Cuellar[1,2], Dolores Lovera[1,2], Natalia Cabrera[4], Antonio Arbo[1,2]

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Presentation of case: A 6-year-old female patient, with painless left submaxillary swelling of 3 weeks evolution. Fever for 1 week (daily peaks up to 38°C), and arthritis (metatarsal joints). Remote history of repeated epistaxis with spontaneous resolution. On hospitalisation, there was evidence of left submaxillary swelling (without local inflammatory signs), ulceration of the jugal

mucosa and ecchymosis. During hospitalisation, the patient remained febrile, with arthritis, mainly elbows and knees and malar erythema. Submaxillary swelling increased in size and became painful, without other inflammatory signs.

Diagnosis testing: Laboratory showed mild anaemia, elevation of inflammatory biomarkers (erythrocyte sedimentation, C-reactive protein, and fibrinogen), blood dyscrasia with decreased prothrombin time and coagulation factor II, and prolonged activated partial thromboplastin time. Occult blood in faeces was positive. Antinuclear antibody (ANA), lupus anticoagulant (aPL) and anticardiolipin IgM were positive. Serum complement C3 and C4 were consumed. During the hospital stay, laboratory results exhibit pancytopenia, hypofibrinogenemia, elevated liver enzymes, elevated acute phase reactants, and hypertriglyceridemia (see table).

Ultrasound showed pleural and pericardiac effusion and heterogeneous hypoechogenic structures (9.2 cm^3 and 5.4 cm^3) in the submaxillary region. Puncture confirmed a haematoma as the cause of the submaxillary swelling. All cultures were negative (blood, urine and punctured haematoma). A bone marrow aspiration was normal.

Differential and Final diagnosis: Initially the submaxillary swelling was considered as an infectious process with poor response to antibiotic therapy, considering other differential diagnosis. The patient persisted with fever, joint pain, and ecchymosis, leading to the hypothesis of an immunological disorder. Because the persistent dyscrasia and anaemia, a haematological disorder was studied. A diagnosis of juvenile systemic lupus erythematosus (jSLE) with atypical haematological presentation was considered (deficiency of coagulation factor II, lupus anticoagulant [aPL] and macrophage activation syndrome [MAS]). Autoimmune haemolytic anaemia, idiopathic thrombocytopenia, antiphospholipid syndrome, and lymphoproliferative processes were ruled out. The poor clinical response under antibiotic treatment during hospitalisation, forced to consider haematological and immunological causes allowing the final diagnosis of jSLE with MAS.

Discussion of Management: Coverage with broad-spectrum antibiotics was started, probabilistically covering community germs (cefotaxime in association with clindamycin) and was extended to resistant germs (vancomycin in association with piperacillin tazobactam). When a diagnosis of jSLE is made she received boluses of methylprednisolone, immunoglobulin, and hydroxychloroquine. Due to dyscrasia she received vitamin K, transfusion of fresh frozen plasma and one transfusion of concentrated red blood cells. The patient had a good response and favourable evolution. Haematological manifestations in LES are frequent, the most common are leukopenia, thrombocytopenia and anaemia, it can be manifested by haemorrhages or thrombosis episodes. MAS can develop during disease flare of jLES, and as at this case, clinical onset.

Conclusion: Atypical haematological manifestation may be the disease onset in jSLE. Epistaxis and blood dyscrasia were the guiding elements for the diagnosis and clinical management of the patient. MAS occurs in jSLE mainly during periods of disease activity as at clinical onset

Disclosures: None

Table 1. Laboratory tests on admission, during hospitalisation and at discharge

	Admission	Inpatient	Discharge	Normal value
Haemoglobin (g/dl)	11.3	8.7	11.2	11.5 – 13.5
White blood cells (/mm^3)	5910	2670	2150	4500 – 10000
Neutrophils	2364	1068	1484	1500 – 8500
Lymphocytes	2719	1522	645	1500 – 6500
Platelets (/mm^3)	387000	279000	189000	140000 – 440000
ESR (mm 1h)	58	125	110	Up to 20
C reactive protein (g/dl)	12	24	12	< 6
Albumin (mg/dl)	4.3	-	-	3.5 - 4.5
Ferritin (ng/ml)	-	> 2000	1140	15 – 150
Fibrinogen (mg/dl)	793	555	519	200 – 400
D-dimer (ug/ml)	-	3,7	0,8	<0,5
LDH (U/L)	-	358	-	240 – 480
Triglycerides (mg/dl)	-	243	-	Up to 150
AST	23	134	20	35
ALT	8	83	21	36
Ig dosage (d/l)				
IgM	-	1.9	-	0,24-2,10
IgG	-	14.4	-	5,04-14,65
IgA	-	1.9	-	0,24-2,10
Autoantibodies				
ANA	-	1/160	-	<1/80
Anti Sm (U/ml)	-	2,2	-	< 12
aCL IgG (U/ml)		19		< 10
aCL IgM (U/ml)		30.4		< 7
Anti Ro (SSA) (U/ml)	-	1,9	-	< 12
Anti La (SSB) (U/ml)	-	2,0	-	<12
Direct coombs test	-	Negative	-	Negative
Rheumatoid factor	-	Negative	-	Negative
Coagulation and complement study				
PT (%)	42	43	100	>70
APTT (seconds)	81	88	33	25 – 45
Factor II (%)	-	6%	-	70 – 120

Factor V (%)	-	80.3	-	70 – 120
Factor VII (%)	-	97.4	-	70 – 120
Lupus anticoagulant	-	1.31	-	0.8 – 1.16
C3 (mg/dl)	-	28	37	90 – 180
C4 (mg/dl)	-	1	5	10 – 40

aCL: anticardiolipin antibody, ALT: alanine amino transferase, ANA: antinuclear antibody, AST: aspartate amino transferase, Ig: immunoglobulin, APTT: activated partial tromboplastine,PT: protombin time, ESR: erythrocyte sedimentation rate, SSA/SSB: Sjogren's syndrome antibody, LDH: lactate dehydrogenase.

438. Severe and high-dose glucocorticoid resistant thrombocytopaenia in IgG4-related (IgG4-RD)

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Presentation of Case: A previously healthy 65 years-old male presented in October 2019 with painless bilateral parotid gland growth, followed by mouth dryness and arthralgias of elbows, ankles, and MCP joints. On physical examination, submandibular and parotid gland enlargement, synovitis on both wrists and left elbow were noticed. Primary Sjögren syndrome (PSS) was suspected, and due to arthritis, prednisone (PDN) started at 10 mg qd. A biopsy of major salivary glands was proposed but refused. He continued with PDN in descent until 2.5 mg qd with improvement. Low C3 and C4 levels, and raised total serum globulins returned to normal. In October 2020 new parotid gland enlargement occurred. January 2021: he had COVID-19 while on PDN 7.5 mg qd with no need for hospitalisation although he had low oxygen saturation. He was treated by another physician with apparently no sequelae and vaccinated later. April 2021: on a follow-up visit, while being asymptomatic, mild leucopaenia (3850/uL) and platelets of 106,000/uL were noticed. Thought to be post-COVID-19 related, he was left untreated; PDN was tapered to 5 mg qd. August 2021: three months previously, he developed large spontaneous ecchymoses, and carpal and PIP arthralgias. Non-palpable purpura and ecchymoses on legs were seen. He had severe thrombocytopaenia (10,210/uL) as single blood cell count abnormality. After haematological consultation, he was prescribed 40 mg qd dexamethasone, but after 5 days platelets went down to 4,000/uL, and was given IV-methylprednisolone 1 g for 3 days. However, he developed pneumonia and required hospitalisation in a social security facility for IV treatment. As inpatient, he was studied by haematologists and rheumatologists. Search for SLE, PAPS, PSS was negative. A bone marrow aspirate showed increased megacariocytes. No vacuoles were seen on bone marrow precursors. IVIG 2 g/kg/day was given for 3 days. He did not develop complications and was discharged 2 weeks later with 37,000 platelets/uL and PDN 40 mg qd. On the latest visit one month after discharge, there were no signs of bleeding, no enlarged salivary glands or lymph nodes. His platelets however remain under 50,000/uL.
Diagnostic Testing: On first evaluation: negative Shirmer´s test, normal ESR, RF, mild fatty liver on abdominal US, normal pancreas. Neck and thoracic CT: posterior cervical lymph nodes, parotid, and submandibular salivary glands enlargement. Low C3 and C4 levels, negative anti-Ro and anti-La, homogeneous 1:640 ANA, serum globulins 3.39 g/dL (upper limit-UL 3), total

IgG 2780.3 mg/dL (UL 1822), normal IgG1 to 3 levels, IgG4 1240 mg/dL (UL 201; 6.16x). Normal serum amylase, lipase, and liver function tests. Baseline platelets: 170,000/uL. During the thrombocytopaenic episode, other causes were reasonably discarded.

Differential & Final Diagnosis: PSS and malignancies have been considered, without supporting evidence. IgG4-RD was suspected based on the exclusion of other maladies. According to the 2019 ACR/EULAR criteria, the patient fits the diagnosis (steps 1 and 2 fulfilled, 30 points).

Discussion of Management: Thrombocytopaenia is an unusual feature of IgG4-RD. Few cases have been described, and some have also had a protracted course in spite of high-dose glucocorticoid and IVIG therapy, with slow recovery of normal platelet counts and the need for additional treatments. To this date, my therapeutic aim points to RTX prescription but he depends on approval by the public health system due to its cost.

Conclusions: An unusual case of thrombocytopaenia in the context of group 3 IgG4-RD is presented without other alternative proven cause. As seen in other reports, return to normal platelet counts can be slow with usual glucocorticoid therapy and may require other pharmacological interventions.

Disclosures

Informed consent was obtained from the patient. Nothing else to disclose.

439. Severe thrombocytopaenia after low-dose rituximab (RTX) for remission maintenance in limited granulomatosis with polyangiitis (GPA)

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Presentation of Case: A 33 years-old female with limited (otorhinolaryngological manifestations) biopsy-proven granulomatosis with polyangiitis since age 15 is presented due to an uncommon serious adverse event. As main damage items, she has had a right mastoidectomy and subglottic stenosis. On remission for the last 10 years with methotrexate (MTX), with a maximum dose of 15 mg/week and during the last 5 years 10 mg/week and nasal mupirocin ointment due to *S. aureus* mucosal colonisation, she desired pregnancy in February 2020. Rituximab (RTX) was proposed as maintenance treatment after which she could proceed with her aim, and MTX was stopped. It was administered at 1 g with all previous necessary tests. The treatment proceeded uneventfully with usual premedication (hydrocortisone, diphenhydramine and chlorpheniramine). Two weeks later she presented vaginal, nasal, and gingival bleeding, and lower limb petechiae.

Diagnostic Testing: Blood cell count at the time of haemorrhagic manifestations: 2,000 platelets/uL, normal red blood cell, and leukocyte counts. Other routine laboratory tests were normal. CD19 and CD20 counts after RTX treatment remained depleted until September 2020 when they started to recover.

Differential & Final Diagnosis: RTX-induced severe thrombocytopaenia was the straightforward diagnosis. No other tests were performed due to the lack of other symptoms and the temporal relation with the first time prescribed RTX dose.

Discussion of Management: She was treated as an inpatient with 1 g IV methylprednisolone (3x on consecutive days) and platelet apheresis, and after four days discharged without complications. She continued with oral prednisone (PDN) with starting dose of 50 mg qd, which was gradually decreased until full stop on April 2020. She remained without treatment for GPA until February 2021 when she had photophobia, and after ophthalmological opinion, she was diagnosed with iridocyclitis. She was given PDN 10 mg qd and MTX was restarted up to 25 mg/week. She has remained in remission with no PDN and MTX 17.5 mg/week. The case presents these interesting points: a) the appearance of severe thrombocytopaenia due to RTX maintenance treatment for GPA, which has seldom been reported despite thrombocytopaenia being known as a potential adverse effect of RTX. Also, RTX is a therapeutic agent in immune-mediated thrombocytopaenia; b) the prolonged remission acquired with 1 g of RTX. She remained symptom-free until 5 months after CD19 and CD20 had recovered; c) the few options available for the safe treatment of GPA patients who desire, especially considering the GPA phenotype for which azathioprine or mycophenolate mofetil does not seem optimal long-term maintenance treatment options. Risk factors known for the development of RTX-induced thrombocytopaenia are basal counts less than 200,000/uL before RTX administration (the patient´s average platelet counts on the year prior to RTX administration was 350,000/uL), high platelet width distribution, haematologic malignancy as primary disease, and concomitant use of fluconazole or ciprofloxacin. None of them are present in this patient.
Conclusions: There is an unmet need for safe and effective treatments in patients who desire pregnancy.
Disclosures: Patient consent was obtained. There is nothing else to disclose.

440. VEXAS syndrome: clinical case series from a Canadian cohort

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Background/Objectives: VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a recently described autoinflammatory condition. It is characterized by vacuolation on bone marrow biopsy and caused by a mutation in the ubiquitin-like modifier activating enzyme 1 (UBA1) gene. The majority of patients in the literature to date have been males over the age of 50. Clinical manifestations include constitutional symptoms, macrocytic anemia, myelodysplastic syndrome, chondritis, and rash. Patients are typically steroid-dependent and prognosis is poor. This case series adds to the literature by describing the clinical features of our patient cohort, presenting one of the first cases of VEXAS syndrome in a female, and featuring the impacts of different therapeutic interventions in these patients.

Methods: Patient recruitment was completed by two rheumatologists in the Division of Rheumatology at two academic centres in Western Canada. The patients in our case series were either genetically confirmed VEXAS syndrome patients who were referred for inclusion in this study or patients with clinical presentations suspicious for VEXAS syndrome who were subsequently confirmed to have the causative UBA1 mutation through genetic testing at the National Institutes of Health.

Results: In our case series we identified 6 patients with VEXAS syndrome. Five patients were male and one patient was female (Turner syndrome). Three *UBA1* variants were seen. A range of initial diagnoses were made prior to the confirmation of VEXAS syndrome in our cohort. Three patients were diagnosed with relapsing polychondritis. The others were diagnosed with erythema nodosum, malignancy, and adult-onset Still's disease vs. vasculitis. Constitutional symptoms, elevated CRP and/or ESR, and macrocytic anemia were seen in all patients. Three patients presented with thrombocytopenia. A positive p-ANCA was noted in one patient, but MPO-ANCA and PR3-ANCA were negative and there were no clinical features suggestive of ANCA-associated vasculitis. Pulmonary capillaritis was noted in one patient who was ANCA negative. Five patients had cutaneous findings. Four of these patients were found to have perivascular lymphocytic infiltration and one patient presented with lupus tumidus. Pulmonary findings were found in four patients and ranged from capillaritis to organizing pneumonia.
All patients who required treatment were responsive to steroids. Most other steroid sparing agents were ineffective with a few exceptions. Some patients experienced partial to good response with IL-6 and IL-1 inhibition but were unable to continue treatment due to side effects. One patient had suppression of symptoms with cyclosporine and low dose prednisone, but eventually had a relapse of her disease. She was switched to etanercept with good effect. One patient is on azathioprine and has been able to taper prednisone to 15 mg daily without a flare of symptoms.

Conclusion: Patients with VEXAS syndrome represent an important cohort of treatment-resistant cases that may mimic other diseases such as relapsing polychondritis or vasculitis. The characteristics of steroid responsiveness and dependence coupled with the presence of constitutional symptoms, macrocytic anaemia, rash, chondritis, and/or pulmonary findings should increase the clinical suspicion of VEXAS syndrome. Moreover, the X-linked nature of this condition does not preclude female patients from being affected. This case series describes one of the few instances of VEXAS syndrome in a woman with Turner syndrome. We suggest the consideration of VEXAS syndrome in individuals with Turner's who are presenting with compatible symptoms.

Disclosures: None.

References

Beck DB, Ferrada MA, Sikora KA, Ombrello AK, Collins JC, Pei W, et al. Somatic Mutations in UBA1 and Severe Adult-Onset Autoinflammatory Disease. N Engl J Med. 2020 Dec 31;383(27):2628–38.

Table 1. Patient demographics and clinical features

Patient	Sex	Age of onset	Disease duration (years)	Initial suspected diagnosis	UBA1 variant	Clinical features	Treatment response
A*	Male	50	11	Relapsing polychondritis	c.122T>C p.Met41Thr	Presented with fever, weight loss, and painful erythematous nodules on the lower extremities. Subsequently developed auricular chondritis, episcleritis, arthralgias, myalgias, macrocytic anemia, lymphopenia, thrombocytopenia, post-operative deep vein thrombosis, organizing pneumonia, and focal fibrotic NSIP. Bone marrow biopsy revealed presence of vacuolated granulocytic and erythroid precursors with no diagnostic evidence of malignancy.	Methotrexate, azathioprine, anakinra, infliximab, rituximab, tofacitinib, baricitinib, and colchicine were trialed with no effect. Patient A had a response to tocilizumab and sarilumab which allowed tapering of prednisone to 7.5 mg daily and 15 mg daily respectively, but was unable to continue therapy due to side effects.
B	Male	67	8	Relapsing polychondritis	c.121A>C p.Met41Leu	Presented with weight loss, persistently elevated CRP, macrocytic anemia, a photodistributive rash with lymphocytic infiltrate on skin biopsy, an episode of suspected auricular chondritis, and known myelodysplastic syndrome. Subsequently developed lymphopenia and arthralgia. Bone marrow biopsy revealed myelodysplastic syndrome and vacuolation of proerythroblasts.	Hydroxychloroquine used for suspected lupus tumidus and stopped due to symptom quiescence for 3 years. Lupus tumidus rash has not returned since stopping hydroxychloroquine. Currently takes no treatments.
C	Male	69	1	Malignancy, not yet specified	c.122T>C p.Met41Thr	Presented with fever, fatigue, weight loss, shortness of breath with CT showing possible interstitial lung disease and PFTs revealing significant restrictive defect, and rash with skin biopsy showing perivascular mixed lymphocytic and neutrophilic inflammation. Subsequently developed macrocytic anemia, pulmonary embolism, and mediastinal/axillary lymphadenopathy. Bone marrow biopsy revealed prominent vacuolation of myeloid and erythroid precursors with no diagnostic evidence of malignancy.	Prednisone 20-50mg needed to keep respiratory and cutaneous symptoms stable. Currently takes prednisone 40mg daily.
D	Male	68	2	Erythema nodosum	c.122 T>C p.Met41Thr	Presented with painful erythematous nodules on his legs, fever, weight loss, night sweats, and normocytic anemia. Subsequently developed macrocytic anemia, lymphopenia, and submandibular/inguinal lymphadenopathy. Bone marrow biopsy revealed vacuolation in granulocytic and erythroid precursors with no evidence of dysplasia or malignancy.	NSAIDs failed to resolve erythema nodosum. Colchicine initially effective but failed to control cutaneous lesions. Hydroxychloroquine trialed with no effect. Azathiprine appears to lower CRP and allow for prednisone tapering. Currently taking prednisone 15mg and azathioprine 125mg daily.
E	Female†	63	4	Relapsing polychondritis	c.122 T>C p.Met41Thr	Presented with fever, night sweats, auricular and nasal chondritis, cough, arthritis, scleritis, and normocytic anemia. Subsequently developed macrocytic anemia, thrombocytopenia, myelodysplastic syndrome, and shortness of breath with CT scan showing bronchiolitis, pulmonary nodules, and mild bronchiectasis. Bone marrow biopsy revealed findings in keeping with myelodysplastic syndrome.	Methotrexate and azathioprine were trialed with no effect and resulted in side effects. Cyclosporine was effective in reducing symptoms, prednisone was tapered to 4mg, but patient was switched to etanercept due to loss of efficacy and side effects. Prednisone maintained at 8mg on etanercept. Azacytidine initiated for treatment of intermediate-risk transfusion-depedent MDS. Currently taking prednisone 8mg daily, etanercept 50mg SC daily, and azacytidine.
F*	Male	73	4	Adult onset Still's disease	c.121A>G p.Met41Val	Presented with rash, intermittent fever, night sweats, weight loss, cough, shortness of breath, and macrocytic anemia. CT chest showed diffuse ground glass opacities and he was eventually diagnosed with cryptogenic organizing pneumonia via lung biopsy. Subsequently developed leukopenia, thrombocytopenia, pulmonary capillaritis, axillary lymphadenopathy, and a nodular rash with skin biopsy showing perivascular lymphoeosinophilic infiltrate.	Rituximab, mycophenalate mofetil were trialed with no effect. Tocilizumab stopped after 2 does due to anaphylactic reaction. Cyclophosphamide initially effective but stopped due to side effects and loss of efficacy. Azathioprine allowed tapering from prednisone 20mg to 15mg but was stopped due to side effects. Anakinra resulted in fever reduction and reduction of prednisone down to 13mg. Prednisone taper below this point resulted in symptom return and anakinra was stopped due to injection site reaction.

*Deceased
†Turner syndrome

441. A Case of Microscopic Polyangiitis after Pfizer-BioNTech SARS-CoV-2 Vaccination in an Elderly Asian Male Patient

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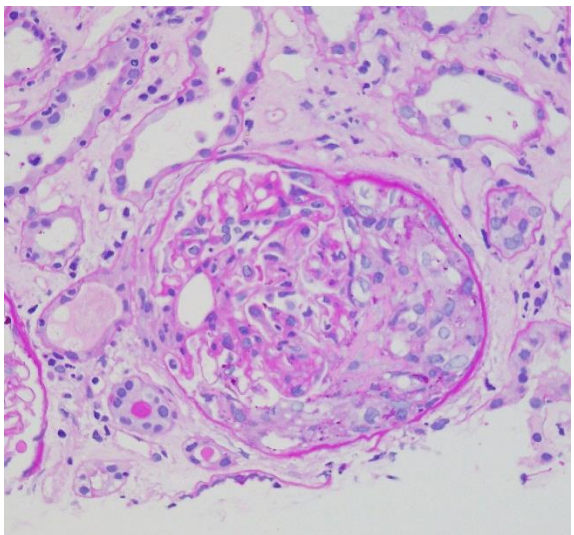
Presentation of Case: An 80-year-old Japanese man with renal insufficiency after Pfizer-BioNTech SARS-CoV-2 vaccine administration was admitted to our hospital. He had no history of decreased kidney function or abnormal urine tests. Three weeks after receiving the second dose of vaccination, he developed malaise. Subsequently, he was diagnosed with high inflammatory response and abnormal renal function and was referred to our hospital. At the time of admission, his blood pressure was 142/95 mmHg, body temperature was 38.9˚C, and SpO_2 was 97%. On physical examination, there was no skin rash or joint pain to suggest collagen or autoimmune diseases.
Diagnostic Testing: His blood tests showed an elevated serum creatinine (Cre) level of 4.52 mg/dL; serum proteinase-3 antineutrophil cytoplasmic antibodies (ANCA) level of <0.5 IU/mL; serum myeloperoxidase-O ANCA level of >134 IU/mL; serum anti-glomerular basement membrane antibody level of <2.0 IU/mL; and C3/C4 of 90/27 mg/dL. Urinalysis showed proteinuria of 1.45 g/gCre and numerous urinary red blood cells. Kidney biopsy revealed severe pauci-immune crescentic necrotizing glomerulonephritis with vasculitis of the renal vessel wall (Fig. 1).
Results: Based on the results of serological and histological examinations, a diagnosis of microscopic polyangiitis was established. He was treated with high-dose oral steroids from day 2 after admission. Rituximab was administered on day 5, and plasma exchange therapy was provided on days 9–11. His condition gradually improved, and he was discharged on day 39. On his 2-month follow-up, his serum Cre level had improved to 2.03 mg/dL.
Discussion: There are some case reports of microscopic polyangiitis after SARS-CoV-2 vaccination from Europe and the United States; however, the association between microscopic polyangiitis and SARS-CoV-2 vaccination is unclear. To our knowledge, this is the first case report from Asia. The number of cases may increase with the increasing vaccination rate against SARS-CoV-2 and the start of the third phase of vaccination. Vasculitis should be differentiated in cases of prolonged fever after vaccination.
Disclosures: None
Figure.1



442. A case of anti-glomerular basement membrane (GBM) antibody-positive tubulointerstitial nephritis.

博士 Wataru Sone[1], Hisayuki Ogura[1], Yoshitada Toyota[1], Keisuke Horikoshi[1], Megumi Oshima[1], Koichi Sato[1]. Shiori Nakagawa[1], Yuta Yamamura[1], Yasutaka Yamamoto[1], Taro Miyagawa[1], Shinji Kitajima[1], Tadashi Toyama[1], Akinori Hara[1], Yasunori Iwata[1], Norihiko Sakai[1], Miho Shimizu[1], Takashi Wada[1]

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Presentation of Case: A 65-year-old woman presented 2 weeks after antibacterial treatment for cystitis, with a severe acute kidney injury. Her serum creatinine level was 1.0 mg/dL two weeks before but had elevated to 2.8 mg/dL at admission. The urinalysis revealed proteinuria of 0.82 g/g Cr, hematuria of more than 100 red blood cells per high-power field (HPF), and a few leukocyte casts. No erythrocyte casts were found. Urine N-acetyl-β-D-glucosaminidase (NAG) and β2-microglobulin levels were 10.5 U/L (normal range, 0.7–11.2 U/L) and 4179 μg/L (<290 μg/L), respectively. Autoimmune serology demonstrated positive for anti-GBM antibodies (51.3 IU/mL). Computed tomography showed no renal enlargement, hydronephrosis, urinary tract abnormality, or alveolar hemorrhage. She was clinically diagnosed with anti-GBM antibody-positive rapidly progressive glomerulonephritis. Plasma exchange was performed for four sessions over consecutive days. She also received one course of steroid pulse therapy (methylprednisolone 500 mg for 3 days) followed by oral prednisolone 40 mg per day. After the initiation of the therapy, the anti-GBM antibody decreased and was finally undetectable (<2.0 U/mL). Her proteinuria became negative and her urine β2-microglobulin level decreased. Serum creatinine improved to 1.59 mg/dL two months after the initiation of the therapy and then became stable, even after oral prednisolone tapered to 15 mg per day.

Diagnostic Testing: A renal biopsy was undertaken 23 days after admission. Light microscopy demonstrated no crescent formation in any of the eight glomeruli. Infiltration of inflammatory cells in the interstitium and tubulitis with rupture of tubular basement membrane was observed. Immunofluorescence demonstrated linear deposition of IgG and IgM on the glomerular capillary wall while no deposition in the tubular basement membrane. Electron microscopy demonstrated no thickening or deposition of the glomerular capillary wall.

Differential & Final Diagnosis: We diagnosed her with atypical anti-GBM antibody-positive nephritis without crescent formation or tubulointerstitial nephritis followed by the production of anti-GBM antibody. The possibility of the existence of crescentic glomerulonephritis could not be ruled out due to the limited number of glomeruli. A few cases of anti-GBM antibody positive-nephritis with atypical histological findings and clinical course has been reported. In these cases, immunofluorescence of renal biopsy demonstrates linear deposition of IgG of the capillary wall without crescent formation. In addition, renal function slowly deteriorates compared to typical anti-GBM antibody type glomerulonephritis. These clinicopathological characteristics were consistent with our case. We also considered the possibility of tubulointerstitial nephritis. Some of the tubular basement membranes contain type IV collagen, as do the glomerular basement membranes. The glomerular and tubular basement membranes share common antigenicity and may exhibit cross-reactivity. We considered that tubulointerstitial nephritis may have caused the production of anti-GBM antibodies.

Discussion of Management: Renal function slowly deteriorates in previously reported cases of atypical anti-GBM antibody nephritis. However, in our case, renal function deteriorated rapidly, and severe tubulitis was found. We treated her in the same way as typical anti-GBM antibody-positive type glomerulonephritis.
Conclusions: We experienced a case of anti-GBM antibody-positive tubulointerstitial nephritis. The patient did not present a typical clinical course and may have developed atypical anti-GBM antibody type nephritis.
Disclosures: None.

443. A path of trial and tribulation to diagnose full-blown ANCA-negative EGPA – a case report.

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Presentation of Case A 71-year old male was admitted with a 3 months history of dyspnea, general weakness and 5 kg weight loss. Adult-onset asthma with accompanying peripheral blood eosinophilia (PBE) was diagnosed and a treatment including montelukast and a short course of low-dose oral prednisolone for one week was started. Five months later, the patient was transferred from a peripheral hospital to our institution with persisting weakness, a further 10 kg of weight loss, bi-pulmonary nodular lesions and mucosal thickening of the maxillary sinuses on CT scan. Further laboratory analyses revealed an increase of PBE from 14.9% to 62%. Tissue specimen obtained from bronchoscopy revealed bronchitis with tissue eosinophilia. Further diagnostics for an underlying cause including (parasitic) infections and systemic autoimmune diseases (ANA, ANCA) were normal. Transthoracic echocardiography and cardiac MRI revealed, multiple intracardiac thrombi (bi-ventricular and pulmonary valve) and an endocardial late enhancement suggesting endocardial fibrosis. A haematologist was consulted and hypereosinophilic syndrome (HES) was suspected. Anticoagulation with s.c. enoxaparine (2 mg/kg weight daily dose) was started. Four days later, the patient presented with dizziness. A cranial CT revealed occipital mass bleeding and the patient was transferred to intensive care unit. No underlying bleeding-cause could be detected in a cranial MRI. Further neurologic assessment then revealed mononeuritis multiplex of the median nerve and lower limbs, suspicious for vasculitis. Biopsy of the sural nerve confirmed a perineural eosinophilic infiltration. A PET-CT scan showed no evidence of underlying malignancy and (large-vessel) vasculitis. In the following days, the patient developed acute kidney injury. Urinalysis revealed proteinuria (700 mg/g PCR) and haematuria. A kidney biopsy was performed without a definite diagnosis. With fulfilment of all 6 of the American College of Rheumatology 1990 classification criteria, diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) was established. An induction treatment with high-dose glucocorticoids and rituximab was started and montelukast was discontinued as a potential trigger of disease.

Diagnostic Testing: Serial laboratory testing, Serial CT scans of trunk and cranium, TTE + cardiac MRI, Bronchoscopy + biopsy, PET-CT scan, Sural nerve biopsy, Kidney biopsy

Differential & Final Diagnosis: Asthma, HES, Montelukast-induced EGPA, Eosinophilic granulomatosis with polyangiitis (EGPA)

Discussion of Management: There was a 9 months delay from onset of symptoms until the final diagnosis was established. The initial diagnosis of asthma is typical, but presence of systemic disease (weakness, weight loss, reduced physical fitness) could have aroused suspicion earlier. Starting anticoagulant treatment without treating the underlying pathology could not stop disease activity and resulted in severe treatment complication. Negative serologic testing for ANCA is frequent in EGPA(1) and significantly complicates diagnosis. Furthermore, EGPA and HES show significant clinical overlap, especially in ANCA-negative patients (2).

Conclusions:

- Diagnosis of EGPA is difficult and often delayed, even if all criteria are fulfilled.
- Early diagnosis and prompt treatment is essential to prevent critical damage.
- An interdisciplinary patient management is mandatory.

Disclosures

PG has received consulting fees from UriSalt (not related with the present work). MR has nothing to disclose in relation with the present work. HN has nothing to disclose in relation with the present work. AK has received consulting fees from UriSalt, Alexion, Vifor Pharma, Otsuka, and Catalyst Biosciences

444. Large vessel involvement in antineutrophil cytoplasmic antibodies associated vasculitis-a rare presentation

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Presentation of Case: A 50year older man presented with a history of fatigue, loss of appetite, loss of weight, on and off fever for the last six months. He also gave a history of central back pain that used to aggravate in a supine position and relieve bending forward. He had intermittent small joint pains without any swelling or early morning stiffness. He was diagnosed with new-onset diabetes and started on oral hypoglycemic agents prior to visiting us. He has had pain and blackish discoloration of the right fourth, fifth toes, and lateral aspect of sole for 10 days. He did not give any history of sinus pain, recurrent nasal or ear discharge, hearing loss, cough, or shortness of breath. There was neither any history of oral ulcers or excess hair loss or photosensitivity or dry mouth or dry eyes. He did not complain of claudication pain. On examination, he was moderately built and moderately nourished. All peripheral pulses felt with normal rate and rhythm. There was no carotidynia, or bruit felt. The examination also revealed gangrene Right fourth and fifth toe and tender erythematous patches over the lateral border of the sole. His Blood pressure was 140/90mm Hg. Musculoskeletal examination revealed tender PIP, MCP joints. Cardiovascular, respiratory, and abdominal examination was normal.
Diagnostic Testing: Blood tests revealed anemia (Hemoglobin-9.5gm/dl),leucocytosis(12,360)and high ESR(80mm) and CRP132 mg/dl).Liver and renal function tests were normal. Urine examination revealed proteinuria and active sediment (2+albumin,6-8 pus cells .6-8 RBC and granular casts).ANCA by immunofluorescence showed a perinuclear pattern(2+). Rheumatoid factor was positive(26 IU, normal<12 IU). Antinuclear and anticardiolipin antibodies were negative. Serum complements were within the normal range. Serum Igg4 levels were normal. Blood and urine cultures were sterile.2D echocardiogram was normal. CT abdomen showed circumferential thickening of the right brachiocephalic artery, bilateral distal common carotid artery, abdominal aorta extending into common iliac artery and internal iliac artery, mild narrowing of left proximal renal and inferior mesenteric artery, right mild hydroureteronephrosis. PET CT also showed the above-mentioned vasculitic changes and avid uptake of the distal thoracic, whole of the abdominal aorta, and left proximal common iliac artery. Renal biopsy showed pauci immune glomerulonephritis(GN) with a focal fibro cellular crescent.
Differential & Final Diagnosis: 50-year-old male with the above clinical picture, the differentials considered are ANCA vasculitis, Takayasu arteritis, IGG4RD, cryoglobulinemic vasculitis, infection, or malignancy-associated vasculitis. There was no evidence of infection (cultures were sterile, procalcitonin normal) and malignancy (PET CT-normal) on evaluation. His C-ANCA was strongly positive, and renal biopsy showed pauci-immune crescentic GN, and therefore we diagnosed him with ANCA vasculitis with aortitis, crescentic GN, and gangrene.
Discussion of Management: Because of severe /organ-threatening involvement, he was treated with pulse methylprednisolone (1000mgx 3 days), followed by oral prednisolone (1mg/kg bd wt)for one month, and then steroids were slowly tapered. Cyclophosphamide

pulses were also prescribed as per the EUVAS protocol. His symptoms improved, and his urine examination showed a decrease in proteinuria and sediment over two months.
Conclusions: ANCA vasculitis must be considered one of the differentials in aortitis cases though it is a rare presentation.
Disclosures: None

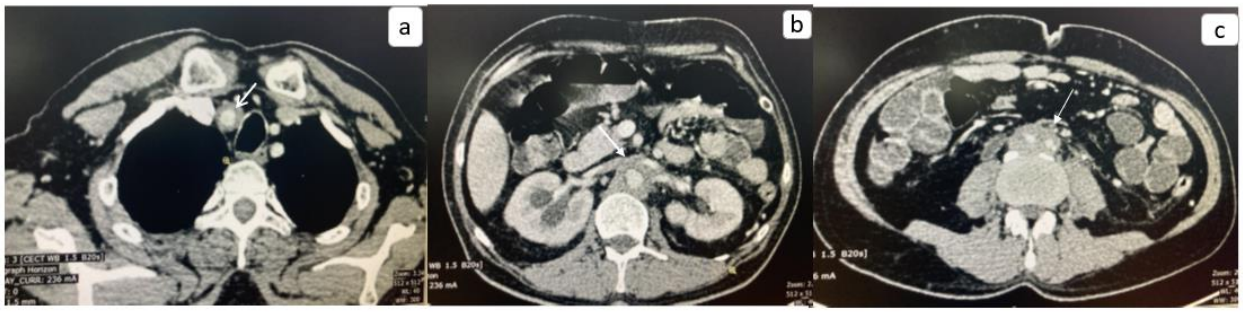

Figure 1. CT chest and abdomen showing circumferential wall thickening(white arrows)of right brachiocephalic artery(a),abdominal aorta(b)and common iliac arteries(c)suggestive of vasculitis

445. An IgG4 related disease mammary manifestation mimicking breast cancer

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Presentation of Case: A fifty-eight-year-old female, with history of IgG4 related vasculitis, under rituximab (375 mg/m^2, weekly for four weeks, every six months), methotrexate (25mg subcutaneous, weekly) and prednisolone (5mg daily) therapy, with low disease activity, presented in the Rheumatology appointment with left breast pain, with a two-week evolution. She denied fever, galactorrhea, and other symptoms. On the physical examination, it was obvious a left nipple inversion, the presence of orange peel like skin surrounding the aureole, a hard painful swelling with no defined limits located within the upper outer quadrant of the left breast and skin redness of the same area. She was empirically medicated with an antibiotic because there was a suspicion of mastitis; no clinical improvement was verified.
Diagnostic Testing: Analitically, there was an increase in sedimentation velocity and C-reactive protein values, 58 mm/h and 4,5 mg/dL respectively. An ultrasound and mamography were requested. The ultrasound raised the hypothesis of breast cancer, reinforced by the findings in the mamography. In the positron emission tomography, it was visible an inflammatory process of the left breast. Simultaneously, the patient underwent a breast biopsy with six fragments for anathomopathology analysis. An intense mixed inflammatory infiltrate, with neutrophil granulocytes and vasculitis lesion, with no malignant neoplasm tissue were identified.
Differential & Final Diagnosis: The subacute and progressive worsening evolution of the breast symptoms caused the main diagnostic hypothesis to be infectious and/or paraneoplastic mastitis, the latter being most likely due to the patient's age. At the same time, there was no history of weight loss, or other symptoms of systemic disease. The performance of breast biopsy allowed the definitive diagnosis of breast vasculitis.

Discussion of Management: The patient then underwent treatment with methylprednisolone 1000mg daily, for 3 days, followed by prednisolone 1mg/kg/day. Concomitantly, the patient repeated the rituximab cycle - 375 mg/m^2, weekly for four weeks, with a favorable clinical and analytical response.
Conclusions: The breast involvement by IgG4 related disease has been described since 2005, under different denominations. However, this appears to be a rare manifestation of a very rare disease. Thus, because of its characteristics, the possibility of breast cancer should always be ruled out.
Disclosures: None

446. In vivo endopeptidase cleavage of ANCA in the GOOD-IDES-01 trial

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Background/ Objectives: IdeS is a streptococcal enzyme which cleaves human IgG of all subclasses within minutes in the circulation but affects no other protein, including IgA and IgM. Plasma exchange is currently used in severe cases of ANCA associated vasculitis (AAV), but efficacy is questionable, maybe due to the limited depletion capacity of this treatment. IdeS has never been used to treat AAV but here we report on the clinical course of patients double positive for ANCA and anti-GBM in the GOOD-IDES-01 trial.

Methods: In the GOOD-IDES-01 (EudraCT number: 2016-004082-39) patients with anti-GBM antibodies were treated with a single dose of IdeS 0.25 mg/kg on top of cyclophosphamide and corticosteroids. Plasma exchange was only given if anti-GBM rebounded after IdeS. The study included 15 patients from 17 sites in 5 European countries. Patients were followed for 6 months with blood and urine samples at clinical visits. ANCA was measured at a central laboratory using the Phadia ELISA assay pre-treatment and at 2 hours, 24 hours, 2 weeks, 3 and 6 months after treatment.

Results: Six patients were double positive for ANCA before treatment with IdeS, 4 for MPO and 2 for PR3. The median age of the double positive patients were 60 years, all but one were male. Two- and 24-hours following administration of IdeS no ANCA was detectable in the circulation in any of the patients. After 2 weeks ANCA had rebounded above the reference level in 2 of the MPO-ANCA positive patients and 1 of the PR3-ANCA positive patients. At 3 and 6 months only 1 PR3-ANCA positive patient remained above the reference range. Renal biopsy showed linear IgG deposits in 4 patients and pauci-immune crescentic glomerulonephritis in 2 patients. At diagnosis, 5 patients were dialysis dependent, at 6 months 3 patients remained on dialysis (1 being the PR3-ANCA positive patient that remained ANCA positive). Both patients with pauci-immune glomerulonephritis that were dialysis dependent at start of treatment could leave dialysis during the study.

Conclusions: Treating ANCA positive patients with IdeS and cyclophosphamide resulted in both rapid and long-term clearance of ANCA in most patients. As all patients in this trial also had anti-GBM antibodies other conclusions are difficult to make, but the positive results from those with pauci-immune findings in the renal biopsy at least does not discourage testing of IdeS in AAV.

Disclosures: Mårten Segelmark has received consultancy fees and research funding from Hansa Pharma.

Table 1. Clinical characteristics of patients in the GOOD-IdeS study who were double positive for Anti-GBM and ANCA. Values are presented as median (range) or percentage (n/N).

	MPO-ANCA	PR3-ANCA
N	4	2
Age	56 years (44-76)	63 (59-67)
Female / Male	1 / 3	0 / 2
S-Anti-GBM at inclusion (U/mL)	38 (11-429)	115 (38-192)
S-ANCA at inclusion (IU/mL)	15 (9-27)	35 (7-62)
Rebound of Anti-GBM	75% (3/4)	100% (2/2)
Rebound of ANCA	50% (2/4)	50% (1/2)
N of PLEX	10 (2-17)	4 (0-9)
Dialysis at start of therapy	75% (3/4)	100% (2/2)
Dialysis at end of study	50% (2/4)	50% (1/2)

447. TNF-α Inhibitors in the Treatment of Neurobehçet Syndrome: A Case Series and Literature Review

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Background/ Objectives: Behçet's syndrome is a systemic inflammatory endothelialopathy which can result in a variable vessel vasculitis. It is characterized by recurrent mucocutaneous ulcers, ocular disease, skin lesions, gastrointestinal involvement, neurologic disease, vascular disease and/or arthritis. Neurobehçet syndrome (NBS) occurs in 5% of cases. NBS is associated with parenchymal or vascular involvement, with parenchymal imaging changes accounting for 75-80% of cases. There is a paucity of evidence supporting treatment of NBS. Our objective was to review the course of three patients with parenchymal NBS who were treated with TNF-α inhibitors (TNFi).

Methods: Three cases of NBS treated with TNFi are presented and a review of the literature was performed.

Results: Case 1. A 28-year-old Chinese male with a prior left midbrain and pons ischemic stroke (February 2020) and right basal ganglia intracerebral hemorrhage (January 2021)

presented to the outpatient rheumatology clinic with new visual symptoms in June 2021. Ophthalmologic evaluation revealed retinal vasculitis with periphlebitis. Cerebrospinal fluid (CSF) revealed increased cells but negative for typical and atypical infection. Further history revealed intermittent oral ulcers since childhood. HLA-B*51 was positive. He was diagnosed with NBS and started on pulse methylprednisolone, azathioprine, and adalimumab. At 4 months, his disease remains in remission, with improvement of ocular inflammation. Repeat CSF analysis demonstrated normalization of cell count and protein. **Case 2.** A 45-year-old Caucasian female with suspected Behçet's syndrome presented to hospital in September 2021 with dyspnea, anemia and diplopia. A few weeks prior, she started azathioprine, which was thought to be the cause of anemia and was held. She described a history of intermittent oral and vaginal ulcers. Physical exam confirmed oral ulcers, ulcerating cutaneous lesions, and cranial nerve 6^{th} palsy. CT PE revealed multiple bilateral pulmonary embolisms. MRI brain revealed cranial nerve VI enhancement and bilateral pontine enhancing lesions. CSF analysis demonstrated elevated protein with normal cell count. HLA-B*51 was negative. She was diagnosed with NBS and started on pulse methylprednisolone and infliximab 5 mg/kg IV. Treatment response is too premature to assess at time of abstract submission. **Case 3**. An 18-year-old South Asian male presented with fever, pharyngitis, and severe headaches in August 2019. Prior history included oral ulcers starting at age 6, followed by onset of erythema nodosum, painful genital ulcers, bilateral uveitis, retinal hemorrhages and epididymitis at age 15. In hospital, CSF analysis revealed elevated WBCs and protein, with negative cultures. MR revealed hyperintensity in the right hippocampal region. HLA-B*51 was positive. He was diagnosed with NBS and started on pulse steroids. Azathioprine was added as an outpatient. With tapering steroids, he experienced recurrent erythema nodosum and epididymitis. Adalimumab was added in December 2019, and azathioprine stopped in December 2020. He remains in remission on adalimumab 40 mg sc every 2 weeks and prednisone 5 mg daily.**Literature Review**: A literature search for treatment of NBS was performed. Full manuscripts describing the use of TNFi for treatment of 2 or more NBS patients were included. Abstracts and case reports were excluded. Eight papers, describing a total of 70 NBS patients were identified. Infliximab was most commonly utilized (61 patients, 87%), with adalimumab described in 9 patients (13%.) TNFi were effective, with 92.8% of patients experiencing complete or partial remission. See Table 1 for details.

Conclusions: NBS is a rare manifestation of an uncommon disease. Parenchymal NBS may be treated with glucocorticoids and azathioprine, however TNFi appear effective in those with severe or refractory disease, and ongoing studies may provide additional insight into their utility.

Disclosures: None

Table 1. Summary of case series evidence for treatment of NBS with TNF-α inhibitors

Reference	# Patients, Study Design	TNFi, Dose	Outcome
Van Laar et al., 2007	2, case series	IFX 3-5 mg/kg q4-12w then ADA 40 mg sc q2w	Complete remission 2/2
Pipitone et al., 2008	8, case series	IFX 5 mg/kg weeks 0, 2, 6 then q6-8w	Clinical improvement: 8 /8 Clinical remission: 7/8 MRI improvement: 5/5
Kikuchi et al., 2008	5, case series	IFX 5 mg/kg weeks 0, 2, 6, 14	Clinical improvement: 3/5
Borhani Haghighi et al., 2011	4, case series	IFX 3 mg/kg (n=2) or 5 mg/kg (n=2)	Clinical response, first month: 4/4 Radiologic response, first month: 4/4
Giardina et al., 2011	5, case series	IFX Dose unknown	Complete remission: 5/5
Vallet et al., 2015	13, case series	IFX 5 mg/kg week 0, 2, 6 then q4-6 weeks (n = 10) or ADA (n = 3) 40 mg sc q2 weeks	Infliximab: response in 9/10 Adalimumab: response in 3/3
Desbois et al., 2015	17, case series	IFX 5 mg/kg (n = 13) or ADA 40 mg (n = 4)	Infliximab: response 12/13 1. Partial response: 8/13 • Complete response: 4 /13 Adalimumab: response 4/4 • Partial response: 3/4 • Complete response: 1/ 4
Zeydan et al., 2016	16, case series	IFX 5 mg/kg weeks 0, 2, 6 then q8w	Response in 15/16
Total	70	61 IFX 9 ADA	Overall: response 65/70 (92.8%) IFX: response 56/61 ADA: response 9/9

Legend: NBS (Neurobehçet syndrome), IFX (infliximab), ADA (adalimumab)

448. Diffuse alveolar haemorrhage secondary to biopsy-proven anti-GBM disease with negative circulating antibodies by standard ELISA

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Presentation of Case: A 21-year old white British female presented to local hospital with acute shortness of breath requiring admission to intensive care for respiratory

support. She had no significant past medical history, was an active smoker and had recently used intranasal cocaine recreationally. She denied haemoptysis, fever or contact with unwell persons. Haemoglobin was found to be 55 g/L with raised CRP and normal creatinine. Urine dip was negative for blood and protein. Chest X-ray and subsequent CT chest showed bilateral lung infiltrates in keeping with possible pulmonary haemorrhage. She was commenced on pulsed Methylprednisolone and transferred to our unit for plasma exchange. Serology including ANA, ANCA, complements and anti-GBM antibody were negative on numerous occasions. Bronchoscopy and subsegmental biopsy confirmed diffuse alveolar haemorrhage with linear alveolar staining for IgG supporting the diagnosis of anti-GBM disease. She received 7 sessions of plasma exchange and 4 doses of intravenous Cyclophosphamide with gradual weaning of corticosteroids. She made an excellent response and was strongly advised to stop smoking.

Diagnostic Testing: Bronchoscopy - diffuse alveolar haemorrhage and linear alveolar staining for IgG with immunoperoxidase and immunofluorescence (fig. 1).

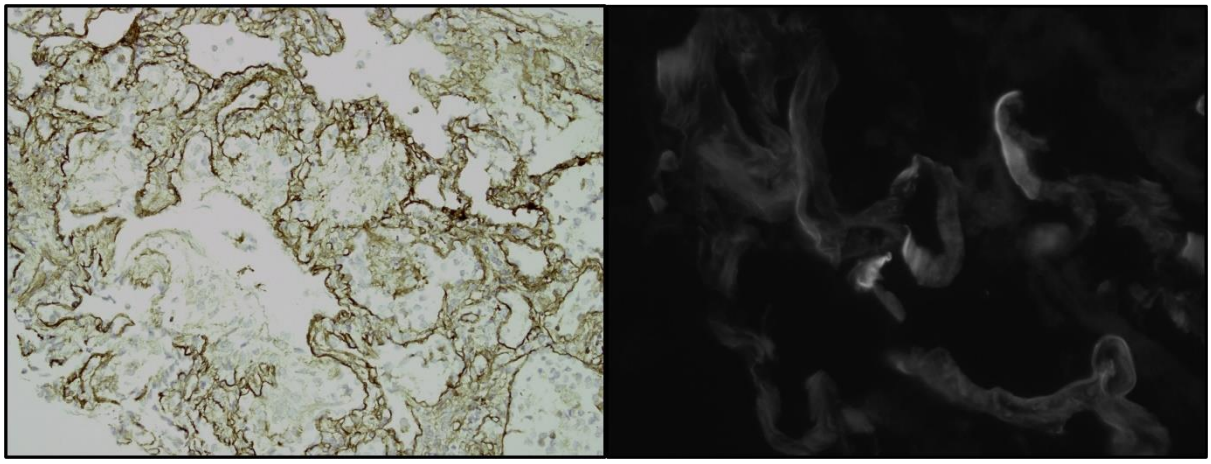
Differential & Final Diagnosis: At presentation, important differentials included crack cocaine lung, atypical pulmonary infections and seronegative pulmonary syndromes including ANCA-associated vasculitis and anti-GBM disease. Bronchoscopy confirmed the diagnosis as anti-GBM disease.

Discussion of Management: We present an unusual case of anti-GBM disease diagnosed by lung biopsy, in the absence of detectable circulating anti-GBM antibodies or urinary abnormalities. In clinical practice, we rely on ELISA to detect circulating anti-GBM antibodies; however, there are reports of renal biopsy proven anti-GBM disease in absence of these antibodies. Lung biopsies are seldom used to diagnose anti-GBM disease where detection of linear IgG staining pattern is less reliable than in glomeruli. There are several possible explanations for negative anti-GBM testing using standard ELISA. The half-life of binding antibodies could be longer than those in circulation thus circulating antibodies could have disappeared when serum sample is collected. Salama *et al*[1] were able to detect circulating antibodies in 2 cases using a biosensor technique despite both ELISA and Western blot being negative. Anti-GBM antibodies are usually IgG1, however other IgG subclasses can be detected. Ohlsson *et al*[2] reported 4 young women with severe alveolar haemorrhage and IgG4 anti-GBM antibodies who showed low or negative result on regular anti-GBM ELISA testing; although in our case lung biopsies were negative for IgG4 staining. Other possibilities include presence of IgA/IgM anti-GBM antibodies or antibodies reacting to an atypical antigen or epitope on type IV collagen.

Conclusions: Anti-GBM disease without circulating autoantibodies is rare but should be considered in patients with unexplained pulmonary haemorrhage. This case emphasizes the importance of obtaining a tissue diagnosis in these settings and that patients can present with isolated lung involvement.

Disclosures: None.

Figure 1. Immunoperoxidase staining (left) and immunofluorescence (right) on lung tissue obtained by subsegmental biopsy showing linear positivity for IgG.



449. The first published GCA case-series in Bahrain, Diagnosis and management

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Background/ Objectives: Giant cell arteritis (GCA) is the most common vasculitis in adulthood with an annual incidence of 1/5,000-1/17,000 adults over 50 years old. It is more frequent in populations of northern European background. Incidence of GCA in Arab population is not common and unknown. To date there is no single publication about GCA diagnosis and management in Bahrain. In Bahrain, the diagnosis in the past was solely dependent on the histopathological findings of unilateral temporal artery biopsy which was rarely done and never positive. In this first case series, 4 cases of GCA patients, diagnosed by using the Clinical diagnostic algorithm for GCA based on the BSR guidelines and their management will be reported.

Methods: Four cases of patients with Giant Cell Arteritis were reviewed who were seen in the Rheumatology clinic in 2021.

Results: this case series is the first of type to be reported in Bahrain. In this series the ratio of men to women was 1:1 with age at diagnosis ranging between 70-82 years. All four cases are Bahrainis in origin with different co-morbidities. The mean time from onset of symptoms to diagnosis was 127 days (range from 60 days to 210 days and Median of 120 days). The common symptoms they had headache 100%, Jaw claudication 100%, scalp tenderness 100%, visual symptoms 75%, and constitutional symptoms in 50% of the cases. ESR was between 25mm/hr to 110mm/hr with mean of 58.5. C-reactive protein was between 12 mg/L to 81 mg/L with mean of 44.5 mg/L. Among the four cases only case number (2) had a unilateral temporal artery biopsy while on prednisone with dose of 60 mg and it was reported as negative. Ultrasound imaging was performed on the four cases, MRI brain on two cases and PET CT scan on one case. All four case received

prednisone 40-60 mg, Methotrexate 20mg/wk in three cases, and Tocilizumab IV 8mg/kg in two cases.

Conclusions: These four cases demonstrate the difficulties faced in diagnosing of GCA in Arabs as it's not a common disease, the challenges faced in diagnosis and the delay in starting the treatment. Unfortunately complete vision loss was in 50% of the cases with partial loss in 25%.

Disclosures: The author has declared no conflicts of interest

450. Systemic P-ANCA vasculitis in a previous unknown antiphospholipid syndrome patient: A case report

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Presentation of Case: A 71-year-old woman presented in the emergency department due to symptomatic anemia (6,7g/dL) and 30% of weight lost in the last 3 months. She had a clinical history of 5 miscarriages, 4 of them in the first trimester in the seventies. No obvious cause was found at that time. She had more recently (in the 5th and 6th decade of life) 3 thrombotic events (arterial and venous) but without thrombophilia investigation at that time. Blood analysis confirmed the anemia and showed an acute kidney injury (blood creatinine of 2.5mg/dL - KDIGO 2) with intrinsic features (leukocyturia, erytrocituria, eosinophiluria). Proteinuria was 1.9g/day. No dysmorphic erythrocites were found.
Diagnostic Testing: The patient was admitted in a medical ward. She had triple positive antiphospholipid antibodies, confirming Antiphospholipid Syndrome as the previous cause of miscarriages and thrombotic events, but without clinical signs of active disease. She was also positive for anti-neutrophil cytoplasmic antibodies (MPO subtype) and, due to the kidney injury, a biopsy was performed, confirming a pauci-imune crescentic glomerulonephritis and some signs of chronic kidney disease. Gastrointestinal neoplasm was excluded by endoscopic studies (due to the anemia) and thorax CT and bronchoscopy showed diffuse alveolar hemorrhage – without clinical signs noticed. Brain CT showed chronic ischemic lesions, mainly on the frontal region and cognitive tests were compatible with moderate dementia.
Differential & Final Diagnosis: The diagnostic testing confirmed a pulmonary-renal disease due to microscopic polyangiitis in a patient with inactive antiphospholipid syndrome with significant damage accrual (miscarriages, kidney disease and ischemic brain lesions)
Discussion of Management: Due to the potencial catasthophic presention the patient was initiated on intravenous immunoglobulins and steroids. After exclusion of other hemorrhage foci, anticoagulation was initiated with acenocoumarol. Rituximab was performed after discharge of the clinical ward with renal and pulmonary clinical response.
Conclusions: The overlap of immune diseases is a clinical challenge and can be a

difficult problem to solve. This case shows a previous unrecognized antiphospholipid syndrome that carried significant damage accrual in a patient with active microscopic polyangiitis that needed significant immunosuppression. We point out the importance of knowing the clinical spectrum of systemic autoimmune diseases, namely vasculitis and the difficult challenges imposed in old patients due to the anticoagulation and immunosuppression issues.
Disclosures: None

451. Pituitary Apoplexy as a Cause of False Positive Temporal Artery Halo Sign

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Presentation of Case: A 75-year-old male with a background of type 2 diabetes mellitus, chronic kidney disease and MPO-ANCA positivity with no evidence of vasculitis, presented with a two-day history of left sided headache and retroorbital pain. Subsequently he developed tunnel vision in his left eye, then the right eye, along with diplopia. C-reactive protein (CRP) was 9mg/l (normal range 0-5) and erythrocyte sedimentation rate (ESR) was 52 mm/hr. He had no jaw claudication or other ischaemic symptoms. He reported 4lb of weight loss and decreased appetite, but no other constitutional symptoms. On examination, he had bitemporal hemianopia, left eye ptosis and mydriasis. Both temporal artery pulses were palpable, but the left temporal artery was tender on palpation. Urinalysis was positive for glucose and ketones with plasma glucose of 16.2 mmol/litre.
Diagnostic Testing: Temporal artery Doppler ultrasound in clinic showed thickening of both temporal arteries (ie positive halo sign) and normal axillary arteries. However subsequent MRI of the head showed an anterior pituitary mass lesion with suprasellar extension and intralesional haemorrhage, compressing the optic chiasm.
Differential & Final Diagnosis: Initial differential diagnosis included giant cell arteritis with atypical presentation, apparently confirmed by the positive halo sign on temporal artery ultrasound. Bitemporal hemianopia with CNIII palsy suggested a lesion of the optic chiasm with possible involvement of the left cavernous sinus. The final diagnosis following MRI was of pituitary apoplexy, histologically confirmed as a gonadotrophinoma.
Discussion of Management: The patient was admitted for management of his hyperglycaemia with ketosis. In view of the acute visual field defect, he was initially treated with high dose glucocorticosteroids for presumed giant cell arteritis while undergoing further diagnostic evaluation. Immunosuppression was discontinued once the pituitary mass was discovered. He underwent transphenoidal resection of the pituitary mass and his headache and diplopia resolved with some improvement of his visual fields.

Conclusions: Vascular ultrasound has been proven a valuable diagnostic test in the evaluation of suspected giant cell arteritis with a specificity of 95% in a recent meta-analysis (Sebastian 2021), although the possibility of a false positive result remains. We are not aware of any previous reports of pituitary apoplexy causing a positive halo sign on temporal artery ultrasound, which we presume in this instance to be a manifestation of increased cavernous sinus pressure. While the combination of headache, acute visual

field defect, diplopia and mildly raised inflammatory markers may raise the strong suspicion of giant cell arteritis, careful evaluation is required to anatomically locate the pathology causing the given ocular involvement, in case a more likely alternative diagnosis becomes apparent.
Disclosures None

452. ANCA-Associated Vasculitis Presenting with Bilateral Renal Infarction

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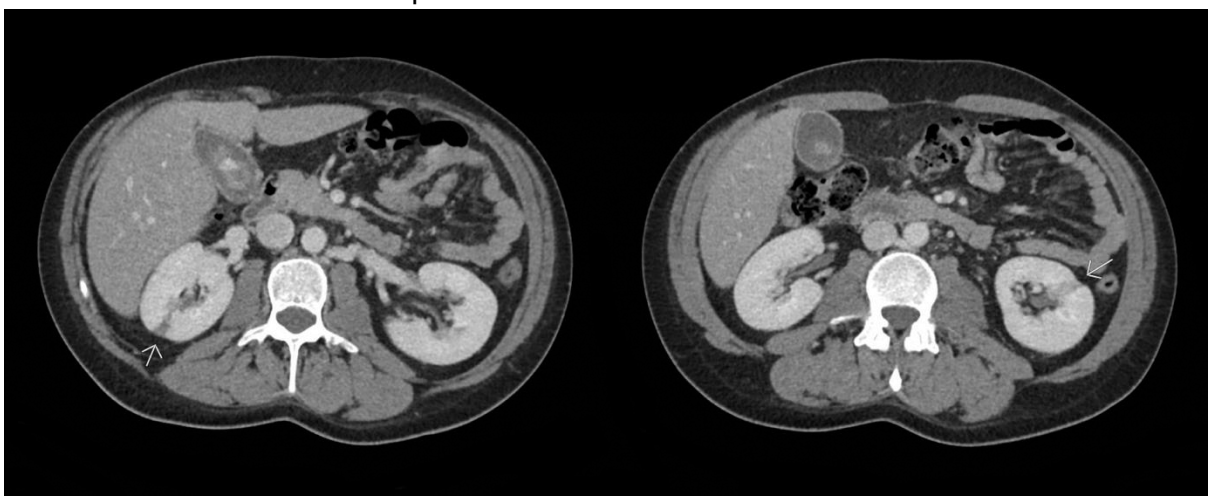
Presentation of Case: A 38-year-old Caucasian male with a background medical history of congenital adrenal hyperplasia and alpha-1 antitrypsin deficiency (Pi*Z genotype) presented with recurrent hospital admissions over several months with unexplained adrenal crises. He had brisk resolution of symptoms with intravenous steroids, however, was quick to relapse when transitioned to his maintenance regimen. His inflammatory markers were persistently elevated with no localising infectious aetiology.
Diagnostic Testing: The peak CRP value was 228 mg/L (0 to 5) with no associated leukocytosis and persistent sterile blood and urine cultures. His creatinine levels were normal and there were no casts on microscopy of urinary sediment. Abdominal CT imaging with contrast revealed wedge-shaped hypoattenuations in both kidneys representing acute renal infarcts (image 1). 24 hr Holter monitor, trans-thoracic and trans-oesophageal echocardiography were unremarkable. A thrombotic screen including anti-phospholipid antibodies, paroxysmal nocturnal haemoglobinuria flowcytometry, myeloma screen, and JAK2 mutation were all reported normal. A positive c-ANCA was identified with associated anti-PR3 17 IU/ml (0-2). A hepatitis viral profile and HIV status were both negative.
Differential & Final Diagnosis: The differential diagnosis, in this case, included a cardiogenic / atherosclerotic embolus, bilateral renal artery injury, or the presence of a hypercoagulable state. These were extensively investigated with a non-revealing workup. A positive c-ANCA with raised anti-PR3 levels was consistent with a final diagnosis of ANCA-associated vasculitis (AAV).
Discussion of Management: This case highlights an uncommon presentation of ANCA-associated vasculitis. Alpha-1 antitrypsin deficiency and associated AAV is described in the literature(1). However, the presentation with bilateral renal infarcts as an isolated phenotype is rare. It was particularly challenging to diagnose this in a patient with congenital adrenal hyperplasia who has been receiving multiple courses of high dose intravenous and oral steroids that likely masked this disease for several months and blunted its clinical expression. Renal biopsy was deemed high risk and a clinical consensus on the diagnosis was reached between nephrology, rheumatology, and immunology. The patient eventually was treated with steroids and Rituximab, induction and maintenance, and has achieved clinical and immunological remission. An interval CT abdomen showed a resolution of the cortical infarcts without the need for systemic anticoagulation.

Conclusions: We describe herein a rare presentation of AAV with bilateral renal infarcts in a patient with alpha-1 antitrypsin deficiency and adrenal insufficiency. This was successfully treated with B-cell depletion without the need for systemic anticoagulation. Vasculitis should be considered in the differential of patients presenting with unexplained organ infarct.
Disclosures: No disclosures

Image 1. Bilateral hypoattenuating wedge-shaped renal lesions consistent with bilateral renal infarctions with normal opacification of the renal arteries and veins.



453. Large vessel vasculitis – a pain in the neck

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Presentation of Case: An 88-year-old female of Pakistani origin presented with a 10-day history of right-sided lateral neck and jaw pain radiating to the right temporal region. She reported associated eye pain, but no visual disturbance, and no jaw or limb claudication, although had experienced intermittent paraesthesia of the hands bilaterally. In the days leading up to admission she had intermittent fever and had received a course of erythromycin for a presumed UTI. She denied malaise, anorexia or night sweats, but reported some minimal weight loss over the previous month. Her medical background included asthma and hypertension only, with no additional cardiovascular risk factors. On examination right sided focal jaw and temporal tenderness was elicited, with a prominently palpable, pulsatile right temporal artery. Heart sounds were normal with no murmurs, no carotid bruits, radial pulses were present and equal and there was no brachial blood pressure discrepancy. Cranial and peripheral nerves were intact.
Diagnostic Testing: Inflammatory blood markers were elevated with ESR >119mm/Hr, CRP 191 mg/L, and platelets 777 x 109/L at their peak. Blood cultures were negative, as was a vasculitic screen including ANCA, immunoglobulins, hepatitis, HIV and syphilis serology. Urine dip demonstrated 1+ erythrocytes only. CT neck with contrast showed no abscess,but noted a poorly opacified left common carotid artery. Subsequent USS of the

carotid arteries demonstrated non-occlusive, hypoechoic atheroma in the right external carotid with 70% stenosis and complete occlusion of the left common carotid by hypoechoic atheroma. CT angiography of the aortic arch and carotids confirmed the USS findings, as well as mural thickening at the origin of the left subclavian artery and the descending aorta. In retrospect mural enhancement of the left carotid artery was evident on initial venous phase CT. CT thorax abdomen pelvis was essentially normal with no evidence of malignancy. Due to isolation requirements, following Covid-19 exposure, transfer off-site for temporal artery ultrasound/PET or temp artery biopsy was not permissible.

Differential & Final Diagnosis: Surgical intervention for carotid artery occlusion was considered unnecessary due to adequate cerebral perfusion and lack of evidence of a cerebral vascular accident. The possibility of infection and incidental atherosclerotic disease was considered, but careful evaluation revealed no focus of infection.

The presentation of cranial symptoms, systemic features, highly elevated inflammatory markers, and CT imaging findings suggested a diagnosis of large vessel vasculitis (LVV).

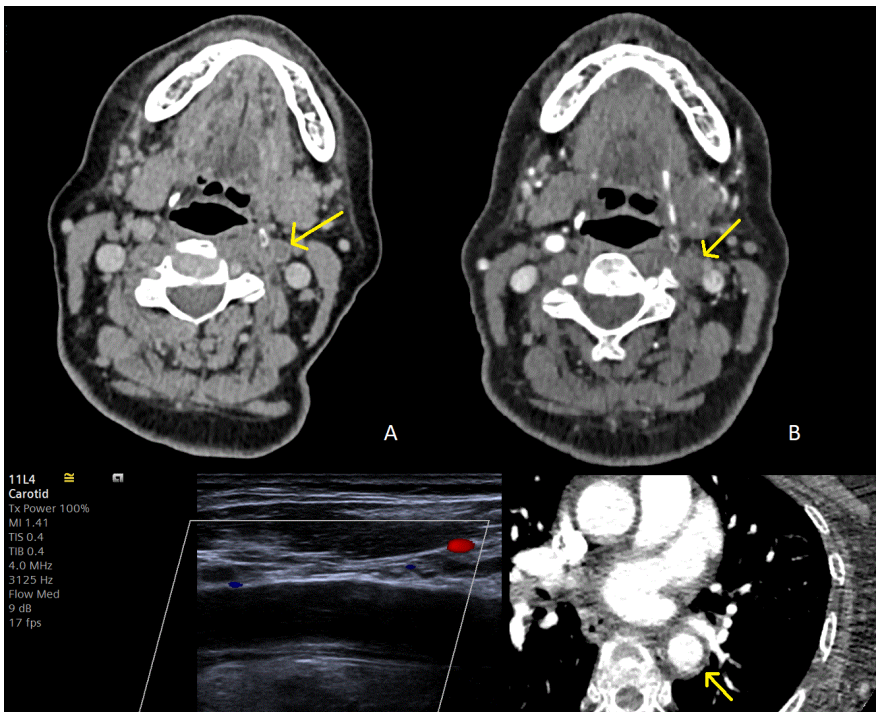
Discussion of Management: Further diagnostic evaluation was desirable but contact isolation requisites and operational pressures would have resulted in significant time delay. Due to the patient's precarious cranial blood supply Prednisolone 40mg once daily was commenced for LVV. Symptoms resolved quickly with a concurrent rapid improvement in serum inflammatory marker levels.

Conclusions: Temporal artery ultrasound and PET CT are considered the imaging of choice for investigation of LVV, however contrast enhanced CT can also demonstrate mural thickening and enhancement consistent with vessel wall inflammation[1].

Carotid artery occlusion has been described in LVV, but our patient uniquely had complete unilateral common carotid occlusion without neurological sequelae. Our case highlighted the validity of alternative imaging methods to establish a diagnosis.

Disclosures: None

Figure 1. A: venous phase CT showing enhancement of occluded left common carotid artery; B: CT angiogram confirming left carotid artery occlusion; C: Duplex ultrasound of left common carotid showing occlusion by hypoechoic matter; D: Mural thickening of descending aorta.



454. Granulomatosis with polyangiitis presenting as compressive cervico-thoracic myelopathy

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Presentation of Case: We present the case of a 64 year old male who presented with a 6 week history of upper back pain and gradual deterioration in his gait, with associated lower limb paraesthesia and leg weakness. His background medical history is significant for a right sided mastoidectomy, in addition to recurrent episodes of sinusitis, with nasal crusting. He also had a history of frequent epistaxis requiring cauterisation. Neurological examination was significant for a spastic paraparesis, with MRC grade 3/5 weakness in lower limb flexors bilaterally, bilateral lower limb hypertonia, sustained clonus, hyperreflexia, and extensor plantar responses. Sensory examination revealed a mid-thoracic sensory level. Other systems examination were normal.
Diagnostic Testing: Routine blood tests revealed normal full blood count, renal and liver indices. Inflammatory markers were elevated: C-reactive protein 43 mg/L (0-5 mg/L) and erythrocyte sedimentation rate 80 mm/hr (0-15 mm/hr). Gadolinium enhanced MRI spine and brain revealed a circumferential enhancing mass-like lesion extending from C5 to T9 with compression of the spinal cord at T2 and T3 levels, with normal brain parenchyma. There was evidence of mild sinusitis in the maxillary sinuses. CT of the thorax, abdomen and pelvis was normal. Urinalysis was normal, as was his urinary protein creatinine ratio, and there was no evidence of red cell casts. ANCA revealed a strongly positive perinuclear pattern (p-ANCA) with a markedly elevated myeloperoxidase (MPO) autoantibody, 117 (0-10 units/mL). Proteinase-3 (PR3) was negative. On identification of spinal cord compromise, the patient underwent urgent neurosurgical evaluation, and surgical exploration. During surgery, direct visualisation revealed the lesion to be solid and mass-like and samples of the tissue excised were sent for pathological analysis. Histopathological studies revealed a dense lymphocytic infiltrate, with fibrinoid necrosis of the blood vessel wall consistent with vasculitis. There was no evidence of granuloma formation.
Differential and Final Diagnosis: A diagnosis of MPO positive, Granulomatosis with polyangiitis, causing compressive myelopathy was made.
Discussion of Management: He was commenced on high dose glucocorticoids which were tapered as per PEXIVAS reduced dose regimen. In tandem, he was commenced on pulsed intravenous cyclophosphamide. Within days of treatment initiation his neurological status improved, and he is currently engaging in rehabilitation. At his most recent review he was walking independently with crutches.
Conclusions: Our case highlights a rare cause of myelopathy but one that should enter the differential diagnosis when assessing a patient presenting with myelopathy, particularly with a mass-like lesion on neuroimaging. It should be treated aggressively and as part of the life threatening organ involvement algorithm.
Disclosures: None.

455. Pregnancy and Takayasu's Arteritis: A case report of management flare of flare while pregnant.

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Presentation of Case: a 35 year old Bahraini female G2P1A0 with a diagnosis of Takayasu's Arteritis since 2011 who was stable on Aspirin and Infliximab infusion prior to pregnancy.
Infliximab was stopped as pregnancy was planned. Patient at week was admitted under the obstetrician care for excessive fatigue and tiredness that started to build up over two weeks, headache that was throbbing in nature diffused with no nausea or vomiting, jaw pain and neck pain with jaw claudication.
Diagnostic Testing: Upon admission her ESR was 73 platelets 501 and CRP 30.
Ultrasound imaging of both carotids has showed bilateral increased wall thickness and bilateral symmetrical common carotid stenosis
Differential & Final Diagnosis: Stroke, Tension headache or pregnancy induced headache or flare of her disease were the main differential diagnosis upon admission.
Discussion of Management: Patient was given Methylprednisone IV for 3 days 1gm OD and Infliximab was started. Her symptoms improved. as discussed with her and her spouse the infusion was kept till day of delivery to eliminate further risk of reactivate. she went into labour spontaneously at week 35 and had normal vaginal delivery and baby was born healthy and needed no medical intervention or help.
Conclusions: Pregnancy with Takayasu's Arteritis poses a stringent challenge to both the Rheumatologist and obstetrician. Close follow up and monitoring is crucial for better outcome for both the mother and the fetus. The guidelines for management for pregnant patients with this disease still remains elusive.
Disclosures: The author has declared no conflicts of interest

Novel online tools & social media

456. Remote clinical management using electronic assessment of patients with vasculitis

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Background/ Objectives: The aim of this project was to develop generalizable digital solutions to help deliver safe, efficient and effective care for patients with long-term rheumatic conditions. We have previously demonstrated that this method is feasible and acceptable to patients with rheumatoid arthritis (RA) and spondyloarthritis (AxSpA). We evaluated the outcomes of remote assessment across a further range of conditions, including vasculitis, connective tissue diseases (CTD) and psoriatic arthritis (PsA).

Methods: We developed a set of online questionnaires using readily available software to conduct a remote assessment in 806 patients awaiting follow-up appointments in rheumatology (delayed as a result of the Covid 19 pandemic). The questionnaire contained measures of disease activity; patient reported outcomes; patient preferences regarding the urgency and type of appointment required; and any other recent problems or changes in medication highlighted by the patient. For vasculitis we designed a self-assessed Birmingham Vasculitis Activity Score (BVAS) and used the published ANCA associated vasculitis patient reported outcome measure (AAVPRO). The information was imported into a bespoke clinical database allowing clinicians to conduct an asynchronous assessment, integrated within our electronic health records (EHR). Report letters were sent to the patient and their general practitioner. EHRs were reviewed in a subset of patients requiring urgent in-person assessments (within 1-month) following remote assessment: disease activity assessments were compared and treatment changes evaluated, using Chi-square test to investigate for significant differences by condition. We defined "stable" disease as patients classified as in remission or partial remission, on or off immunosuppressive therapy.

Results: Table 1 summarises all the patients assessed remotely, by condition, and subsequent follow-up requested. Patients with CTD (9%) or vasculitis (11%) were least likely to require a face to face appointment within 3 months of assessment compared to other conditions (PsA 31%, RA 28%, AxSpa 21%). Agreement between remote and in-person assessment was evaluated in 56 patients (25 RA; 14 PsA; 17 AxSpA). Agreement was present in 21/25 (84%), 9/14 (65%) and 12/17 (71%) of patients with RA, PsA and AxSpA respectively, p=0.35. Treatment changes were made in 21/25(84%), 9/14(65%), 11/17(65%) of patients with RA, PsA and AxSpA respectively, p=0.26).

Conclusions: We have developed and implemented a system of remote clinical management for patients with rheumatic conditions. Following remote assessment only 284/806 (35%) required a subsequent in-person assessment and 351/806 (44%) were stable. Concordance with in-person assessment was highest for patients with RA, but not significantly different to outcomes for PsA and AxSpA. Further work is needed to validate this mode of assessment (compared to in person evaluation) in patients with vasculitis and CTD as well as those declared as having "stable" disease.

Disclosures: Grant from Pfizer Global to develop remote monitoring system for rheumatoid arthritis

	n	Appointment <= 3 months	Face to face (F2F) appointment	F2F <= 3 months	Stable
RA	447	206	167	127	169
CTD	131	20	43	12	86
Vasculitis	90	23	14	10	57
PsA	72	41	33	23	22
AxSpa	66	25	27	14	17
Total	806	315	284	186	351

%	100	39.1	35.2	23	43.5

457. On call work in rheumatology with a focus on vasculitis

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Background/ Objectives: Our aim was to evaluate the impact of vasculitis on a physician led on call service in rheumatology. The objectives were: to measure differences in demand to the service from patients with vasculitis or suspected vasculitis (including GCA) compared to other conditions; to assess the most common concerns requiring urgent attention; to determine changes in the volume of new urgent referrals, suspected flares or non-referral enquiries for patients with suspected or established vasculitis compared to other rheumatological conditions.

Methods: We evaluated data captured by clinicians using a bespoke Microsoft Form, prospectively collected whilst on call, every time a contact was made with primary or secondary care during a 12 month period from October 2020 to October 2021. Calls could be via telephone or urgent email. We compared the on call data for patients with vasculitis with that for RA (using Chi squared testing) and other conditions.

Results: We received 1929 “calls” during the one year study period (1364 telephone vs 565 emails), of whom 1552 had a provisional or actual diagnosis recorded. The two largest groups of conditions for calls were vasculitis (21.3%) and RA (18.5%). More calls were received for suspected new vasculitis than for suspected RA (213 vs 93), whilst more calls were for existing patients with RA vs vasculitis (195 vs 118) ($P<0.00001$). There was no variation in number of calls during periods of high Covid 19 activity (19.8 calls/month for vasculitis or GCA vs 19.2/month for RA) vs low Covid 19 activity (28.9 calls/month for vasculitis or GCA vs 24/month for RA). Most of the calls for vasculitis related to suspected or known GCA (55.9%). Calls for vasculitis took longer to deal with than RA or GCA (mean estimated minutes: 18 vs 13 vs 11.9).

Conclusions: We found significant differences in the reasons for calls between vasculitis (including GCA) and RA, which account for almost 40% of all urgent calls to a rheumatology service. We deliberately included periods of high and low Covid 19 activity, which did not impact on the demands for rheumatology services.

Disclosures: None

	Total calls	Vasculitis (including GCA)	RA	Other
New/re-referral	598	167	81	350
Existing patient	598	118	195	285
Not referred	356	46	12	298

Total	1552	331 (21.3%)	288 (18.5%)	933 (60.1%)

458. Developing a Website Resource through Qualitative Research into Experiences of Systemic Vasculitis and UK healthcare

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Background/ Objectives: People often search online when they have a health-related query. One source of information, support and connection is people's personal experiences of a health condition; this may be particularly welcome where people are trying to make sense of a rare, relapsing and life-changing condition such as systemic vasculitis. However, few websites which feature personal experiences are generated through rigorous research. The international DIPEx (Database of Individual Patients' Experiences) project uses qualitative research methods to develop website resources based on diverse experiences of health conditions. These are available in nine languages across 14 countries. Evaluation indicates people feel better prepared for medical appointments and more confident in taking an active role in their health care (1, 2). As a contribution to the UK database (www.healthtalk.org), we aimed to create a trusted and balanced web resource about people's experiences of systemic vasculitis and UK healthcare. This forms part of the VOICES project (Vasculitis Outcomes In relation to Care ExperienceS), which aims to understand key elements of care delivery associated with health outcomes of prime importance to people with vasculitis.

Methods: Between June 2020 and June 2021, we conducted 32 remote in-depth narrative interviews across the UK with people who have systemic vasculitis. We used Healthtalk methods (Berkshire REC reference number: 12/SC/0495) and recruited via vasculitis charities, social media and NHS services. Interviews were video or audio recorded. We gave each participant the transcript and summary of their interview, with the opportunity to correct, change or remove sections. Further consent enabled use of data for the website. We analysed data thematically, nd developed summaries of topics that were most important to participants' experience with illustrative video, audio or text clips. Patient partners and an advisory panel developed topic lists and carried out sense and sensitivity reviews of topic summaries. The website will be available early 2022.

Results: We interviewed 9 men and 23 women aged between 22 and 81, living in Scotland (n=16), England (n=11), Wales (n=3) and Northern Ireland (n=2). Findings on the website are organised into 28 topic summaries and a 20-minute film montage to support local service improvement, see Figure 1. Contributions convey the complexity and heterogeneity of systemic vasculitis. Themes include wondering what vasculitis will do next, the value of metaphors to describe how vasculitis behaves, making choices about support groups, and the ongoing struggle to explain to family and friends that vasculitis is

lifelong. They also cover experiences of care such as the consequences of missed opportunities to diagnose, perceived gaps in mental health and rehabilitation services, and reflections on care coordination, teams and specialists.
Conclusions: Developing a website resource through rigorous qualitative research as part of an international and established collaboration has created a resource that can be used by people with systemic vasculitis in different ways at different stages to feel connected to others, to compare and contrast experiences, and to think about uncertainties and decisions. The film montage aims to get staff and patients talking together about how they can jointly improve people's experience.

Disclosures:
The VOICES study was funded by Versus Arthritis (grant ref: 22088).

459. Vasculitis Patient Engagement and Impact of Online Patient Support Group Meetings

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Background/ Objectives: Patients living with a rare disease like vasculitis face significant physical and psychosocial challenges. Loneliness is a common feeling among patients with vasculitis and the COVID-19 pandemic has compounded feelings of isolation and loneliness. Online patient support groups are a medium through which individuals with vasculitis can connect and share their experiences. The Vasculitis Foundation established weekly online patient support groups in 2020 for patients with any form of vasculitis. This study was performed to better understand how patients with vasculitis engage in these online support groups and the perceived socio-emotional impact of that engagement.

Methods: An online qualitative survey of the Vasculitis Foundation's (VF) online support groups was sent to all individuals who had attended at least one VF online support group meeting from January 1, 2021 to October 1, 2021. The survey collected participants' demographics, diagnosis and disease state information, and basic information concerning their engagement with the online support groups. The open-ended questions asked participants to describe the main reasons they decided to participate in an online patient support group, why they continue to participate, and what they valued about groups. A total of 57 responses were received with a 100% completion rate. Responses to the closed-ended question were used for descriptive statistical analysis. The open-ended responses were analysed using thematic content analysis with Nvivo 10.0.

Results: Of the respondents, 46 (80.70%) were females. Respondents ranged in age from 18 to over 75 with 33 (57.9%) between the ages of 55 to 74. Respondents represented 10 forms of vasculitis. Eighteen participants were diagnosed less than 1 year ago and 33 (57.9%) were diagnosed less than three years ago. More than half of the respondents have attended at least 5 support group meetings and 37 (66%) attended their first meeting to talk with other patients with vasculitis. The responses to the open-ended questions were conceptualized in the following themes: support and empowering

processes within online vasculitis support groups and support and empowerment outcomes of online vasculitis support groups. Social support was highly valued by VF online support group participants with respondents sharing they came to meet with other patients with vasculitis, gain social support, and that they continue to come to obtain additional social support.

Conclusions: The VF online support groups are an important source of emotional support and connection between patients. The primary reason driving participants to join the group is the desire to communicate with other patients. The COVID-19 pandemic required vasculitis patients to pivot from in person meetings to online support groups. The online groups are successful in addressing the needs of our isolated patients despite their disease state. The online groups provide social support, camaraderie and information to the attendees.

Disclosures: N/A

Table 1. Demographic information and engagement

VARIABLE		TOTAL (N = 57)	% OF TOTAL
Sex			
	Female	46	80.70%
	Male	11	19.30%
Age			
	18 to 24	1	1.75%
	25 to 34	2	3.51%
	35 to 44	2	3.51%
	45 to 54	12	21.05%
	55 to 64	14	24.56%
	65 to 74	19	33.33%
	75 or older	7	12.28%
Race/Ethnicity			
	Asian / Pacific Islander	1	1.75%
	Hispanic	1	1.75%
	White / Caucasian	52	91.23%
	Multiple ethnicity / Other (please specify)	3	5.26%
Disease Type			
Cryoglobulinemic Vasculitis		1	1.75%
Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)		5	8.77%
Giant Cell (Temporal) Arteritis		5	8.77%

Granulomatosis with Polyangiitis (previously called Wegener's Granulomatosis)		22	38.60%
Microscopic Polyangiitis		7	12.28%
Other:		8	14.04%
Polyarteritis Nodosa		2	3.51%
Takayasu's Arteritis		6	10.53%
Urticarial Vasculitis		1	1.75%
Time Since Diagnosis			
	Less than a year ago	18	31.58%
	1 – 3 years ago	15	26.32%
	10 or more years ago	9	15.79%
	4 – 6 years ago	6	10.53%
	6 – 9 years ago	9	15.79%
Disease Activity Level			
Active disease		14	24.56%
Controlled disease activity with medication		25	43.86%
Newly diagnosed, have not started treatment		9	15.79%
Remission (inactive disease; no flaring)		9	15.79%

VARIABLE	TOTAL (N = 57)	% OF TOTAL
Main reason first attended a VF online support group meeting		
To get emotional support	6	10.53%
To learn about resources such as educational webinars, VF events, and research studies, etc.	3	5.26%
To learn more about vasculitis from presenters and guest speakers	4	7.02%
To talk with other patients with vasculitis	38	66.67%
Other (please specify)	6	10.53%

Agree the support groups prepared them to:			
	AGREE Count (% of Total)	DISAGREE Count (% of Total)	NEITHER AGREE OR DISAGREE Count (% of Total)
Better accept my vasculitis diagnosis	39 (73.58%)	4 (7.55%)	10 (18.87%)

Select a vasculitis treatment plan	16 (32%)	6 (12%)	28 (56%)
Better manage my side effects (such as pain, focus, etc.)	33 (62.26%)	4 (7.55%)	16 (30.19%)
Emotionally deal with my vasculitis	42 (79.25%)	3 (5.66%)	8 (15.09%)
To connect with other vasculitis support programs	35 (67.31%)	5 (9.62%)	12 (23.08%)
Communicate better with my loved ones about my vasculitis	38 (71.7%)	7 (13.21%)	8 (15.09%)
Become more productive at work or home	16 (30.19%)	9 (16.98%)	28 (52.83%)
Be more aware of my physical, mental and emotional	43 (81.13%)	3 (5.66%)	7 (13.21%)