Anti-SARS-CoV-2 antibody decay after vaccination and immunogenicity of the booster dose of the BNT162b2 mRNA vaccine in patients with psoriatic arthritis on TNF inhibitors

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ABSTRACT

Objective. *Scanty data on the anti-SARS-CoV-2 IgG level decay after two-dose BNT162b2 vaccination have been published in patients with psoriatic arthritis (PsA) on TNF inhibitors (TNFi). Similarly, no reports on the immunogenicity of a booster dose in such patients have been provided yet.*

We aimed to investigate the IgG level decay after two-dose BNT162b2 vaccination and the immunogenicity and safety of the booster dose in PsA patients on TNFi.

Methods. *Forty patients with classified PsA on TNFi undergoing booster dose with the BNT162b2 mRNA SARS-CoV-2 vaccine (BioNTech/Pfizer) were enrolled. Fifteen days after the third shot, serum IgG levels against SARS-CoV-2 (Abbott®ARCHITECT i2000SR, positivity cut-off 50 AU/mL) were assayed in all patients. Clinimetrics and treatment data were gathered. TNFi treatment was not discontinued. Sera from healthcare professionals were considered as healthy controls for 1:1 propensity score-matching.*

Student's t-test and logistic regression were used for investigating differences in immunogenicity between groups and predictors of antibody response.

Results. *Even though the decay of IgG levels showed similar magnitude between groups, PsA patients had a lower IgG level than matched controls at 4 months after two-dose vaccination (2009.22±4050.22 vs. 6206.59±4968.33 AU/mL, respectively p=0.0006). Booster dose restored IgG levels to a similar extent in both groups (15846.47±12876.48 vs. 20374.46±12797.08 AU/ml p=0.20, respectively). Clinical Disease Activity Index (CDAI) did not change before and after vaccination (6.68±4.38 vs. 4.95±4.20, p=0.19).*

Conclusion. *A BNT162b2 booster dose should be recommended in PsA patients on TNFi as its administration restores anti-SARS-CoV-2 IgG levels similar to healthy individuals.*

Introduction

The humoral response following mRNA SARS-CoV-2 vaccination has been shown for up to 6 months in immunocompetent individuals (1).

Unfortunately, little is known about the decay of anti-SARS-CoV-2 IgG levels in rheumatic patients on biologic agents following complete BNT162b2 vaccination.

It is conceivable that patients with low neutralising antibody levels could be particularly susceptible to breakthrough SARS-CoV-2 infection. Given that, both the US Food and Drug Administration and the European Medicine Agency recommended booster vaccine doses for immunosuppressed individuals (2).

In a recent report, our group investigated the immunogenicity of two-shot BNT162b2 vaccination in a prospective cohort of patients with psoriatic arthritis (PsA) on TNF inhibitors (TNFi), showing no difference in terms of anti-SARS-CoV-2 IgG levels between treated subjects compared to matched controls, despite a trend towards lower immunogenicity among PsA patients (3).

Few longitudinal data exist beyond 3 months reporting the stability of humoral response in immunosuppressed patients with rheumatic and musculoskeletal disease. Additionally, most of the available reports lack of an immunocompetent control group. Most importantly, scanty data exist on the optimal timing for a booster in patients with PsA on TNFi and whether such dose may completely restore the anti-SARS-CoV-2 IgG levels at a similar extent with healthy individuals.

Here, we prospectively investigated the IgG level decay after two-dose BNT162b2 vaccination and the immunogenicity and safety of the booster dose on a homogeneous cohort of PsA patients and matched healthy individuals.

Methods

As previously described, our Institution set up a vaccination campaign during which PsA patients received two shots of the BNT162b2 mRNA vaccine (BioNTech/Pfizer) on April 24th and May 15th and a booster dose on September 14th 2021. Our study included consecutive patients who underwent vaccination during such a campaign. At booster shot and 15 days after, they underwent IgG test against the S1-domain of the spike protein of SARS-CoV-2

Table I. Patient clinical, demographic and laboratory features.

	Last visit before booster dose			15 days from the booster dose		
Patient characteristics	Av.Obs.			Av.Obs		
Age, mean (SD)	31	52.9	(10.8)			
Female, n (%)	31	17	(54.8)			
Disease duration, years, mean (SD)	31	10.7	(9.2)			
Axial, n (%)	31	4	(12.9)			
Psoriasis, n (%)	31	26	(83.9)			
Polyarticular, n (%)	31	17	(54.8)			
PsAID12, mean (SD)	11	2.8	(2.7)			
MMAS-4, median (min-max)	31	0	(0-1)			
DAPSA, mean (SD)	31	8.5	(5.9)			
PASI, mean (SD)	31	0.4	(1)			
CDAI, mean (SD)	31	5.1	(3.9)	31	6.5°	(9.1)
CDAI remission/LDA, n (%)	31	27	(87.1)	31	27 °°	(87.1)
Glucocorticoid, n (%)	31	9	(29)			
Glucocorticoid dose, mean (SD)	9	4.4	(1.8)			
Combotherapy, n (%)	31	15	(48.4)			
Methotrexate, n (%)	31	11	(35.5)			
Methotrexate dose, mg/week, mean (SD)	11	14.8	(3.3)			
Days from MTX discontinuation, median (min-max)	11	4	(1-5)			
Sulfasalazine, n (%)	31	4	(12.9)			
bDMARD treatment 1st line, n (%)	31	5	(16.1)			
bDMARD treatment 2nd line, n (%)	31	24	(77.4)			
bDMARD treatment 3rd line, n (%)	31	2	(6.4)			
Adalimumab, n (%)	31	11	(35.5)			
Infliximab, n (%)	31	8	(25.8)			
Certolizumab, n (%)	31	5	(16.1)			
Etanercept, n (%)	31	5	(16.1)			
Golimumab, n (%)	31	3	(9.6)			
antiSARS-CoV-2 IgG level, AU/ml, mean (SD)	31	2009.2	(4050.2)	31	15846.5*	(12876.5)
Vaccine reactions (PsA patients)						
Arthralgia, n (%)				31	3	(9.6)
24h-fever, n (%)				31	3	(9.6)
Lymphadenopathy, n (%)				31	0	(0)
Matched controls						
Age, mean (SD)	31	51.4	(10.7)			
Female, n (%)	31	15	(48.4)			
antiSARS-CoV-2 IgG level, AU/ml, mean (SD)	31	6206.6	(4968.3)	31	20374.5*	(12797.1)

Av.Obs.: available observations; bDMARD: biologic disease-modifying anti-rheumatic drug; CDAI: Clinical Disease Activity Index; DAPSA: Disease Activity in Psoriatic Arthritis; LDA: Low Disease Activity; PASI: Psoriasis Area Severity Index; MMAS-4: Morisky Medication Adherence Score on 4 Items; MTX: methotrexate; PsAID12: Psoriatic Arthritis Impact of Disease.
° paired t-test, p=0.32; °°McNemar test, p=1; *p=0.0001.

(Abbott®ARCHITECT*i*2000SR, positivity cut-off 50 AU/mL). Blood samples were collected and analysed at the same Institution's laboratory. TNFi treatment and non-MTX csDMARDs were not discontinued throughout the time span of the study. MTX was held the week after each shot in all patients, as previously described (4).

Demographic and clinical characteristics including disease phenotypes, Disease Activity in PsA (DAPSA), Psoriasis Area Severity Index (PASI), Clinical Disease Activity Index (CDAI), Morisky Medication Adherence Score on 4 Items (MMAS-4), and PsA Impact of Disease (PsAID12) (5) were recorded at the last consultation before the booster dose and 15 days after the third shot, as previously reported (3). At the same time, patients were asked for prior COVID-19 and/or related symptoms. We also recorded any vaccine reaction and/or adverse event during the observation period. Sera from 59 healthcare professionals employed at our Institution were gathered 15 days after the second BioNTech/Pfizer vaccine shot from January 2021 to February 2021 and 15 days after the booster shot (administered in December 2021). They were considered healthy controls for 1:1-nearest-neighbour propensity score (PS-)-matching. PS is an epidemiological tool used for the adjustment of non-randomised longitudinal studies. It is a conditional probability of being exposed to a disease given a set of covariates. In brief, this was carried out using the patients' age and gender, with a selected calliper of 0.2, as previously described (3).

We assessed the difference in anti-SARS-CoV-2 IgG levels between groups with Student's t-test. Paired t-test and McNemar test were used to determine the difference between mean CDAI score and remission rate at different time points. Associations of recorded covariates with IgG levels and CDAI scores after vaccination were investigated using linear regression.

This study followed the Declaration of Helsinki and received local Ethics

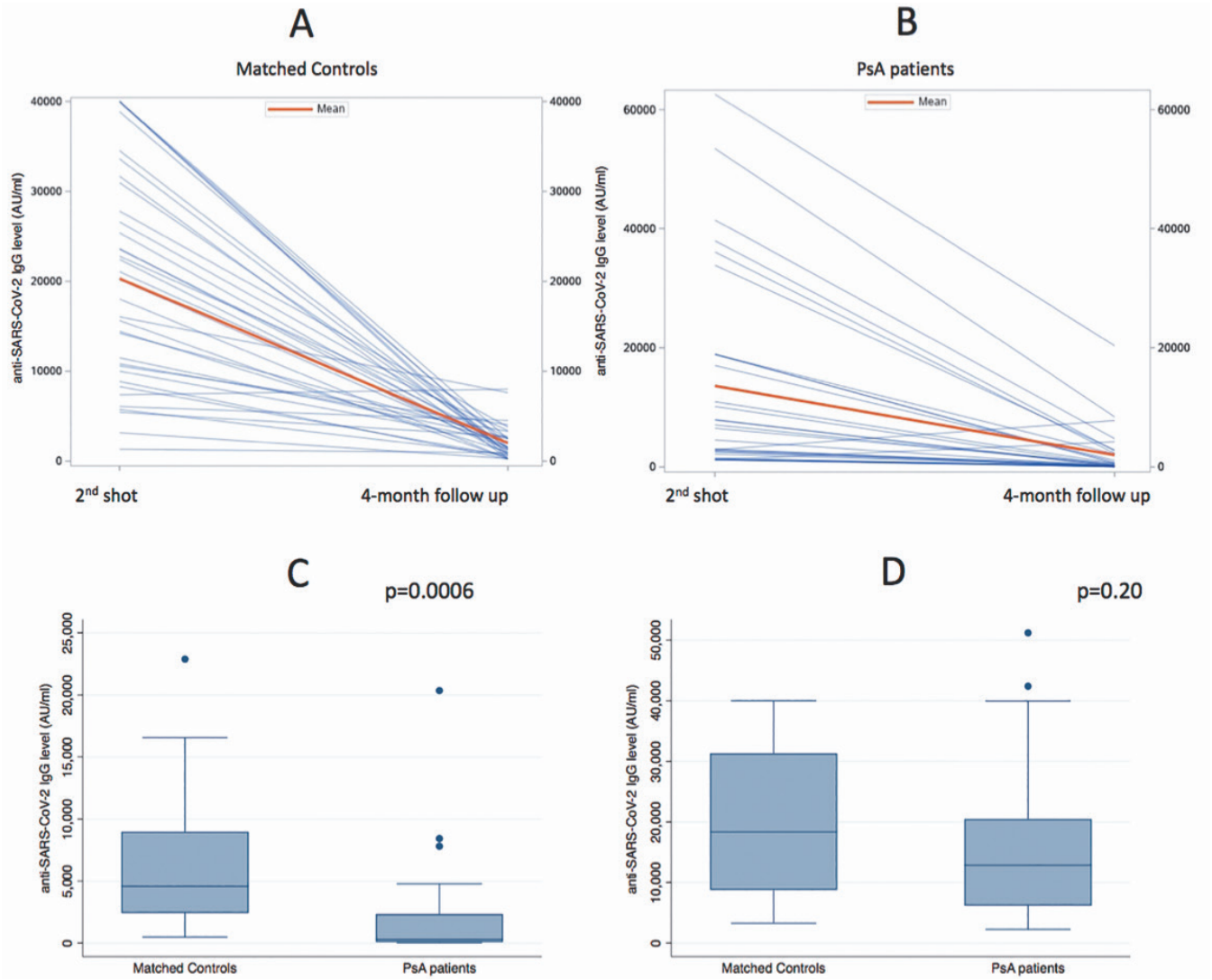

Fig. 1. Anti-SARS-CoV-2 IgG titres of patients with psoriatic arthritis and matched healthy controls.
A-**B**: IgG level decay after two-dose vaccination in psoriatic arthritis patients and matched controls. **C**-**D**: Anti SARS-CoV2 IgG level after booster dose in psoriatic arthritis patients and matched controls.

Committee approval as part of the BIOPURE study (approval no. 5940)

Results

The clinical and laboratory characteristics of the 40 PsA patients and matched controls who underwent initial two-dose vaccination, including anti-SARS-CoV-2 IgG level after the second shot, had been reported elsewhere. At 4 months from the initial two-dose vaccination, IgG testing was carried out in 31/40 PsA patients and 31/40 matched controls, whose characteristics are reported in Table I. At that time, 11/31 patients with PsA (35.5%) were on MTX combotherapy at a mean dose of 14.84±3.34 mg weekly. Patients took the last MTX dose a median of 4 days (min-max 1–5) before vaccination. Overall, 9 out of 31 (29.03%) were on glucocorticoids at a mean dose of 4.4±1.8 prednisone equivalent. All PsA patients had a detectable humoral response with mean (± SD) anti-SARS-CoV-2 IgG level decreasing from 13625.35±16852.36 to 2009.22±4050.22 AU/mL (p=0.0001); similarly, mean serum IgG level in healthy individuals dropped from 18897.58±12593.47 to 6206.59±4968.33 AU/mL (p=0.0001) (Fig. 1A-B). Even though the decay of IgG levels showed similar magnitude between groups (mean Δ change 12690.98±9451.47 *vs.* 11616.12±14160.94, matched controls *vs.* PsA patients, p=0.072, Fig. 1), PsA patients had a significantly lower IgG level than matched controls (*vs.* 2009.22±4050.22 *vs.* 6206.59±4968.33 AU/mL, respectively p=0.0006). In 2 out of 31 PsA patients we observed an increased titre (Fig. 1B); one of them was on MTX combotherapy.

After the booster dose, IgG levels returned similar between groups (20374.46±12797.08 *vs.* 15846.47 ±12876.48 AU/ml, matched controls VS PsA patients, p=0.20). No serious adverse events was recorded. Vaccine reactogenicity is shown in Table I. No disease flare was recorded after booster dose with mean CDAI remaining stable at subsequent assessment (6.68±4.38 *vs.* 4.95 ±4.20, p=0.19, respectively). Neither MTX combotherapy (p=0.22;

95%CI -13394.20–3177.43) nor glucocorticoids (p=0.13; 95%CI -7565.51–1030.71) were associated with booster dose immunogenicity. Similarly, none of the gathered covariates predicted higher post-booster CDAI. No breakthrough COVID-19 was observed.

Discussion

This study assessed the anti-SARS-CoV-2 IgG decay 4 months following two-dose vaccination and the immunogenicity of the booster dose in PsA patients on TNFi.

The need for a booster dose for rheumatic patients has become crucial as immunosuppressed individuals with an impaired humoral response (6) may become particularly susceptible to SARS-CoV-2 variants of concern (7).

Nevertheless, the evidence about the stability of anti-SARS-CoV-2 IgG in patients with inflammatory arthritis on biologic drugs is scarce.

We showed that after 4 months, the antibody levels of PsA patients on TNFi decreased by 6.7 times, leading to a lower humoral response than matched immunocompetent individuals. Our findings are somewhat similar to the results of Frey *et al*., reporting a decrease of 2.8 times from 1 month to 6 months after two-dose vaccination. Of note, participants of the former cohort who had received the mRNA-1273 vaccine were more likely to have a high positive antibody response at 6 months than participants who had received the BNT162b2 vaccine (1). In contrast, our PsA patients received the BNT162b2 mRNA vaccine exclusively.

Notably, we observed increased titres in 2 out of 31 patients. Only one reported MTX use, which might suggest a delayed antibody response in patients on immunosuppressive therapies and is consistent with previous findings (1).

Recent reports showed that the third dose of BNT162b2 is immunogenic in most immunosuppressed individuals, although antibody response may differ based on the type of disease and immunosuppression (8, 9).

To the best of our knowledge, this is the first report showing that booster dose can restore anti-SARS-CoV-2 IgG levels in PsA patients undergoing TNFi throughout vaccination, similar to healthy individuals matched for gender and age. Of note this also happened in patients on low dose steroids and/or MTX combotherapy, albeit the latter had been held the week after each shot. Most importantly, booster dose did not lead to disease flare, with CDAI remaining stable before and after subsequent immunisation. Differently from the immunogenicity of two-dose vaccination, the humoral response of booster dose was associated neither with MTX nor with steroids intake.

Our study has some strengths. First, PS matching on prospectively gathered data, together with homogeneous treatment management, allowed to mitigate bias due to non-randomisation. The timing of sera sampling was the same for all patients; furthermore, to reduce the within-cohort variability, an anti-SARS-CoV-2 IgG assay was run once for all the samples at the same laboratory.

Conversely, as already acknowledged elsewhere (3), we cannot exclude a few patients got asymptomatic SARS-CoV-2 infection at any time before booster dose. Moreover, we did not perform a post-vaccination serum viral neutralising test. Notably, our analysis was not intended nor powered to show the difference between patients assuming or not background MTX mainly for the lack of comparator group continuing treatment. In this regard, the VROOM trial will soon investigate whether holding MTX after vaccine shots might enhance immunogenicity (10). Additionally, since the impairing of vaccine immunogenicity due to steroids and csDMARDs could be arguably dose-dependent, we cannot exclude patients on high-dose glucocorticoids and/or MTX at maximised dose might experience hindered immune response.

In conclusion, although anti-SARS-CoV-2 IgG decay was comparable between groups in terms of absolute values, it led to a significant difference at 4 months from two-dose vaccination. Therefore, a BNT162b2 booster dose should be recommended as its administration is able to restore anti-SARS-CoV-2 IgG levels to a similar extent in both PsA patients on TNFi and healthy individuals. However, further studies are required to assess whether neutralising IgG levels increase as well.

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