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Research Article

Clinical outcomes in severe asthma patients switching biologic therapies: A real-world cohort analysis

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Abstract

Background: Severe asthma is a heterogeneous condition in which biologic therapies targeting type 2 inflammation have substantially improved disease control. However, a proportion of patients fail to achieve a sustained response, necessitating biologic switching in routine clinical practice.

Objective: Evaluate real-world patterns, clinical outcomes, and determinants of biologic switching in patients with severe asthma.

Methods: This 15-year ambispective cohort study evaluated patients with severe asthma treated with biologic therapies between 2009 and 2025. Patients were classified as never-switchers or switchers. Clinical outcomes, exacerbation burden, oral corticosteroid use, lung function, and inflammatory biomarkers were assessed at baseline, 4/6 months, and 12 months. Comparative analyses were performed across cohorts.

Results: Among 345 included patients, 116 (33.6%) underwent biologic switching. Inadequate clinical efficacy was the predominant reason for switching, frequently accompanied by persistent upper-airway comorbidities. Clinical improvement was observed following both initial biologic initiation and subsequent switching; however, patients requiring switching exhibited a higher residual disease burden and rarely achieved the level of disease control observed in stable patients. Early response at 4/6 months was informative for longer-term outcomes, and switching was safe.

Conclusion: In real-world practice, biologic switching represents a common and clinically meaningful strategy in severe asthma. Early treatment response may assist in identifying patients requiring timely reassessment and individualized therapeutic optimization.

Keywords

Biologic therapy, exacerbations, real-world evidence, severe asthma, therapeutic switch

Introduction

Severe asthma (SA) is a complex, heterogeneous condition affecting approximately 3.5–10% of the overall asthma population. Clinically, SA is defined by the requirement for high-dose inhaled corticosteroids (ICS) combined with additional controller therapy or by disease that remains uncontrolled despite such treatment (Frix et al. 2022; Solidoro et al. 2022; Bourdin et al. 2024; Matsumoto et al. 2025).

The introduction of monoclonal antibodies targeting key pathways of type 2 (T2) inflammation has substantially transformed the management of SA, leading to meaningful reductions in exacerbation frequency, improvements in lung function, and decreased reliance on systemic corticosteroids (Papaioannou et al. 2021; Okwuofu et al. 2025). Nevertheless, a significant clinical challenge persists, as approximately 10–25.5% of patients experience either primary or secondary non-response to their initial biologic therapy (Lafarge et al. 2024; Mobayed et al. 2025). Given the frequent overlap in eligibility criteria among available biologics, selection of the initial agent is often complex, and therapeutic switching has become a common strategy to optimize disease control in routine clinical practice (Menzies-Gow et al. 2022b; Caminati et al. 2023).

Real-world evidence consistently indicates that inadequate clinical response represents the predominant reason for biologic switching, whereas adverse events and persistent comorbidities contribute less frequently (Dragonieri et al. 2024; Al Awn et al. 2025; Tran et al. 2025). Patients who require switching often display a distinct clinical phenotype characterized by greater disease severity, increased inflammatory burden, and a higher frequency of exacerbations at baseline (Menzies-Gow et al. 2022b; Matsumoto-Sasaki et al. 2022; Scioscia et al. 2023). Importantly, multiple observational studies have demonstrated that switching between biologic therapies is generally safe and may result in clinically meaningful improvements, particularly when transitioning from anti-immunoglobulin E to anti–interleukin-5 or anti–interleukin-4 receptor therapies (Liu et al. 2021; Caruso et al. 2022; Naumova et al. 2023). These observations are consistent with existing real-world data indicating that biologic switching in severe asthma is more often motivated by insufficient disease control than by tolerability issues. Furthermore, earlier switching, especially within the initial years of biologic exposure, appears to be associated with a greater likelihood of favorable treatment response (Al-Ahmad et al. 2023; Okwuofu et al. 2025).

Despite the proliferation of biologics, no randomized head-to-head trials directly comparing biological agents within the same patient population have been reported in the scientific literature to date, and treatment decisions are often based on guidelines or meta-analyses. Consequently, clinicians lack robust evidence to guide optimal treatment sequencing when initial therapy fails (Couillard et al. 2025; Faria et al. 2025; Lipworth et al. 2025). In addition, key aspects of long-term biologic management remain insufficiently understood, including mechanisms underlying secondary non-response and the potential distortion of inflammatory biomarkers following prior biologic exposure, which may complicate subsequent re-phenotyping and treatment selection (Menzies-Gow et al. 2022b; Mobayed et al. 2025).

The marked heterogeneity of SA and the variability in individual therapeutic responses underscore the need for precision-based management strategies that extend beyond initial biologic selection (Bagnasco et al. 2020; Kuks et al. 2025). While randomized clinical trials provide essential evidence regarding efficacy and safety, they offer limited insight into real-world switching patterns, long-term outcomes, and predictors of sustained response. Consequently, high-quality observational data remain crucial to inform clinical decision-making in everyday practice.

Within this context, longitudinal data for Bulgaria, although available, have never been systematized and analyzed. The first biologic therapy, omalizumab, was approved for reimbursement in 2009 and was the only available biologic therapy for 10 years until benralizumab was approved in 2019, with subsequent introductions of mepolizumab (2018) and dupilumab (2023), as well as tezepelumab (2024), providing clinicians with therapeutic choice. The presence of multiple alternatives has enabled the collection of longitudinal data of a real-world cohort of 345 patients with severe asthma, treated with biologic therapies, including 116 individuals who underwent therapeutic switching. By evaluating clinical outcomes before and after switching, identifying predictors of treatment response, and exploring relevant phenotypic subgroups, this work aims to contribute meaningful real-world evidence to support personalized treatment strategies in severe asthma patients.

Objective

Our aim was to analyze clinical outcomes, phenotypic characteristics, and predictors of therapeutic response in patients with severe asthma treated with biologic therapy, with a special focus on the group switched to another biologic therapy.

Materials and methods

Study design and setting

This was an observational, non-interventional, real-world study of patient health data and clinical outcomes collected during routine follow-up at University Hospital "Alexandrovska," Clinic of Allergology. The study evaluated biologic treatment outcomes in severe asthma and compared never-switchers (treated with one biologic) with switchers (treated with ≥ 2 biologics), including pre- and post-switch effectiveness in routine care.

Under Regulation (EU) 536/2014, this research constitutes a non-interventional clinical study (i.e., a clinical study other than a clinical trial). Treatment initiation and switching were determined by treating physicians as part of standard clinical practice and were not assigned by a study protocol. Participation did not influence prescribing decisions, and the study did not mandate any additional diagnostic or monitoring procedures beyond routine care. The choice of therapy was based on clinical judgment and GINA (Global Initiative for Asthma) Guidelines. The retrospective segment encompassed the years 2009 to 2025, while the prospective segment commenced upon ethical approval in June 2025.

Eligibility criteria

Patients were considered eligible if they:

1. Met the ATS (American Thoracic Society) or ERS (European Respiratory Society) diagnostic criteria for severe asthma;
2. Received at least one biologic therapy in routine practice during the period 2009–2025;
3. Provided informed written consent for the research use of their clinical data if participating in the prospective component of the study;
4. Were ≥ 18 years of age.

For the retrospective component, inclusion was based on the availability of sufficient clinical data in the medical records (i.e., baseline data within the 12 months preceding biologic treatment initiation and follow-up data at 4 or 6 months and, where available, at 12 months.).

Patients were excluded from the final dataset if they:

1. Refused to participate by not providing informed consent for involvement in the prospective segment of the study;
2. Did not meet the ATS/ERS diagnostic criteria for severe asthma;
3. Had clinical records that were incomplete or insufficient for analysis;
4. Participated in randomized interventional clinical trials during the observation period;
5. Had been diagnosed with other chronic respiratory diseases that may confound outcome evaluation, such as COPD with a dominant phenotype.

Management of retrospective and prospective data heterogeneity

Due to the ambispective form of the study, particular measures were instituted to guarantee comparability between retrospective and prospective data. All variables were delineated using standardized clinical criteria and extracted in accordance with a predetermined data collection technique. Only patients with adequately comprehensive and consistent medical records were included in the retrospective data to reduce information bias. In the prospective component, data collection adhered to identical variable definitions and time intervals as defined in the retrospective dataset (baseline, 4/6 months, and 12 months), thus guaranteeing consistency across study periods.

Classification of study participants

Study participants were classified as the following:

- Never-switchers: patients who have received one biologic therapy;
- Switchers: individuals who were subsequently switched at least once to a different biologic therapy (i.e., have received ≥ 2 biologic therapies overall).

Details of participant selection and consent form are provided in Suppl. material 1.

Outcome definitions and response criteria

Clinical outcomes and response/remission definitions were prespecified based on published consensus criteria (Menzies-Gow et al. 2020; Upham et al. 2021; Menzies-Gow et al. 2022a; Canonica et al. 2023; Crimi et al. 2024; Hansen et al. 2024; Scelo et al. 2024; Busse 2025; Pavord et al. 2025; Porsbjerg et al. 2025). Clinical response was characterized by an increase in ACT score of ≥ 3 points and at least one of the following: a ≥ 50% reduction in annual exacerbation rate or a ≥ 50% reduction in oral corticosteroid use. Clinical remission required the simultaneous presence of an absence of exacerbations, complete withdrawal of maintenance oral corticosteroids, well-controlled asthma indicated by an ACT score of ≥ 20 points, and preserved or improved lung function (FEV_1 ≥ 80% predicted or clinically meaningful improvement from baseline). A super-responder was characterized as a patient achieving at least two major criteria (complete elimination of exacerbations, oral corticosteroid withdrawal, or an increase in ACT score of ≥ 6 points) together with at least one minor criterion (≥75% improvement in exacerbation rate, an ACT score of > 19 points, or an increase in FEV_1 of ≥ 500 mL), or all three major criteria, which reflected a robust and sustained response to the biologic therapy. These definitions were uniformly applied across cohorts to guarantee comparability.

Sample size calculation

The study uses a pragmatic real-world cohort consisting of all eligible consenting patients treated at the study center during the study period.

To contextualize sample adequacy, we used Cochran's formula to estimate a proportion with a 95% confidence level and a conservative prevalence of $p = 0.5$ (maximum variance). Under this assumption, the required population size for a ± 5% margin of error is $N = 384$; the achieved

sample (n = 345) corresponds to an approximate margin of error of ± 5.3%. The achieved sample size provides adequate power to detect clinically meaningful changes.

Ethics and data collection

Ethical approval for this non-interventional study was issued by the Institutional Ethics Committee of University Hospital Alexandrovska (Decision No. 9/19.06.2025). The study employed a pragmatic cohort design. The retrospective component encompassed the study of anonymized and aggregated clinical data gathered during standard medical care from 2009 to 2024. The ethics committee permitted the utilization of these data without necessitating individual informed consent, in compliance with national regulations and the explicit stipulations of the Bulgarian Health Law (Art. 86(1)(5)) concerning patient rights and health data protection.

The prospective component of the study began with the issuance of the aforementioned ethics approval in June 2025. Subsequently, all newly enrolled patients submitted written informed consent before participation. The research was conducted in compliance with the Declaration of Helsinki and relevant data protection laws. No treatments were implemented as a direct result of the study protocol, validating the non-interventional design during the prospective phase.

Datasets

The electronic medical record system serves as the principal repository of patient data, consistently utilized in clinical practice at the institution. Clinical information was extracted from the hospital's internal electronic patient record system and complemented by paper-based medical records when required. Extracted data were entered into a structured electronic dataset developed by the research team (Suppl. material 2).

Baseline demographic, clinical, functional, and biomarker characteristics were defined using data collected during the 12 months preceding biologic initiation (index biologic). Follow-up assessments were captured from routine visits at approximately month 4/6 and month 12, where available. For switchers, outcomes were analyzed according to the predefined "pre-switch" and "post-switch" cohorts, enabling evaluation of switching effectiveness in a real-world setting.

Data handling and data protection

Patient-level data were collected by their respective attending physicians and processed in pseudonymized form. Direct identifiers were removed from the dataset in accordance with Regulation (EU) 2016/679 (GDPR). Each participant was assigned a unique study code (e.g., A001 and A002), where the letter indicates the clinical unit and the numeric suffix indicates the sequential entry number. The re-identification key linking study codes to patient identities was stored separately within the treating institution and was accessible only to authorized clinical personnel; statistical analysis was conducted exclusively with the pseudonymized dataset. Data were analyzed and reported only in aggregated form.

Statistical analysis

Due to the observational design of the study, the analyses were predominantly descriptive and exploratory. Statistical analyses were conducted with the R statistical package. Baseline characteristics were summarized for never-switchers and switchers. Three pre-specified comparisons were performed: (1) never-switchers vs. switchers pre-switch, (2) switchers pre- vs. post-switch (paired within individuals), and (3) never-switchers vs. switchers post-switch. Continuous variables were assessed for distributional characteristics and reported as mean ± SD (standard deviation) when approximately normally distributed and median [IQR]. In approximately symmetric distributions, these measures converge; where distributions are skewed, the median [IQR] provides a robust summary. Between-group comparisons used Student t-test (normal) or Mann–Whitney U test (non-normal). Paired pre–post comparisons among switchers used paired t-test. Categorical outcomes were compared using χ^2 test or Fisher's exact test, and paired binary outcomes were evaluated using McNemar's test when applicable. All tests were two-sided, and statistical significance was considered at $p < 0.05$.

Results

Study population

A total of 800 patients were screened, of whom 345 met the eligibility criteria and were included in the final analysis. The study cohort comprised 345 patients with severe asthma, including 229 (66.4%) never-switchers and 116 (33.6%) switchers. Among switchers, 109 patients underwent a single biologic switch, while 7 experienced more than one switch. Data were collected between 2009 and 2025, with a median year of biologic initiation of 2023. Baseline demographic characteristics are summarized in Table 1, and extended patient characteristics are presented in the Suppl. material 3.

At baseline, upper-airway comorbidities were significantly more prevalent among switchers, including nasal polyposis (62.9% vs. 42.8%, $p < 0.001$) and chronic rhinosinusitis (72.4% vs. 41.0%, $p < 0.001$). Switchers also had a higher prevalence of AERD (35.3% vs. 24.0%, p = 0.037) and allergic rhinitis (30.2% vs. 19.7%, p = 0.040), while baseline lung function was comparable between groups (FEV_1% predicted: 50.0 [45.0–55.0] vs. 51.0 [43.0–57.0], p = 0.427). Baseline blood eosinophil counts were lower in switchers pre-switch (median 500 [350–650] vs. 580 [400–860] cells/μL, p = 0.011). Baseline clinical and inflammatory characteristics differed between groups.

Table 1. Baseline demographic, clinical, and treatment characteristics of never-switchers and switchers. Baseline values refer to the time of biologic initiation. Variables with statistically significant between-group differences are shown in bold. FeNO data were available in a limited subset of patients and were therefore not included in comparative statistical testing.

Variable	Never-switcher (n = 229)	Switcher (n = 116)	p-value
Demographics			
Sex			0.294
Female	166 (72.5%)	77 (66.4%)	
Male	63 (27.5%)	39 (33.6%)	
Age at biologic initiation, years	**58.0 [50.0–65.0]**	**52.0 [46.0–59.0]**	**< 0.001**
Age at asthma onset, years	**40.0 [32.0–50.0]**	**38.5 [27.0–47.0]**	**0.027**
Asthma duration, years	**16.0 [9.0–24.0]**	**19.0 [12.0–28.2]**	**0.031**
Body mass index, kg/m^2	26.4 [23.5–30.5]	25.1 [22.7–29.0]	0.061
Smoking status			0.098
Never smoker	205 (89.5%)	109 (94.0%)	
Former smoker	24 (10.5%)	6 (5.2%)	
Baseline disease severity			
Exacerbations per year (baseline)	**3.0 [2.0–4.0]**	**2.0 [2.0–3.0]**	**0.019**
Hospitalizations in prior year (baseline)	**1.0 [1.0–2.0]**	**1.0 [1.0–1.0]**	**0.023**
ACT score (baseline)	10.0 [9.0–12.0]	11.0 [10.0–11.0]	0.450
Biomarkers			
Total IgE, IU/mL	197.0 [96.0–406.0]	173.5 [122.2–374.0]	0.890
Blood eosinophils, %	**7.0 [5.0–10.2]**	**6.1 [4.3–9.0]**	**0.043**
Blood eosinophils, cells/μL	**580 [400–860]**	**500 [350–650]**	**0.010**
FeNO, ppb	34.0 [34.0–34.0]	51.0 [44.2–55.2]	-
Lung function (baseline)			
FEV_1, L, baseline	**1.27 [1.08–1.60]**	**1.39 [1.19–1.68]**	**0.040**
FEV_1, % predicted	51.0 [43.0–57.0]	50.0 [45.0–55.0]	0.427
FVC, L, baseline	1.89 [1.50–2.35]	1.96 [1.62–2.33]	0.266
FVC, % predicted	58.0 [51.0–68.0]	60.0 [54.0–66.2]	0.368
FEV_1/FVC, baseline	0.71 [0.63–0.80]	0.72 [0.65–0.79]	0.585
Clinical characteristics			
Family history of asthma	45 (19.7%)	19 (16.4%)	0.554
Maintenance oral corticosteroids	12 (5.2%)	11 (9.5%)	0.206
Comorbidities			
Nasal polyposis	**98 (42.8%)**	**73 (62.9%)**	**< 0.001**
AERD	**55 (24.0%)**	**41 (35.3%)**	**0.037**
Chronic rhinosinusitis	**94 (41.0%)**	**84 (72.4%)**	**< 0.001**
Allergic rhinitis	**45 (19.7%)**	**35 (30.2%)**	**0.040**
Atopy	102 (44.5%)	47 (40.5%)	0.550
Index biologic therapy			**< 0.001**
Omalizumab	7 (3.1%)	97 (83.6%)	
Benralizumab	179 (78.2%)	12 (10.3%)	
Mepolizumab	27 (11.8%)	5 (4.3%)	
Dupilumab	16 (7.0%)	2 (1.7%)	

Patient flow and switching patterns

Patient transitions by count between biologic therapies are illustrated in Fig. 1A, and switching distribution by year is demonstrated in Fig. 1B. The most frequent switch was from omalizumab to benralizumab (n = 62). The median duration of prior biologic therapy before switching was 4 years (interquartile range [IQR] 2–6; range 1–14), with differences observed between biologic classes. The longest median treatment duration was recorded for omalizumab (Table 2). Switching occurred between 2018 and 2025, peaking in 2023 (n = 35) and 2024 (n = 30); the median switching year was 2023.

Table 2. Duration of previous biologic therapy prior to switching.

Previous biologic	n	Median duration, years [IQR]
Omalizumab	97	5 [2–7]
Benralizumab	15	3 [1–4]
Mepolizumab	8	3 [1.5–4]
Dupilumab	3	1 [1–1]

Reasons for switching

A total of 192 reasons for switching were recorded (Table 3). Primary and secondary reasons were documented in 123 switching events, of which 70 (56.9%) included both a primary and a secondary reason. The most common primary reason for switching was inadequate clinical efficacy or inappropriate initial biologic selection (112/123; 91.1%). The most frequently reported secondary reason was inadequate control of comorbidities, predominantly chronic rhinosinusitis with nasal polyps (CRSwNP) (67/123; 54.5%).

Table 3. Primary and secondary reasons for biologic switching.

Reason for switching	Primary Reason – n (%)	Secondary Reason – n (%)
Low efficacy/inappropriate selection	112 (91.1%)	0 (0%)
Adverse Events (AE)	1 (0.8%)	1 (0.8%)
Inadequate control of comorbidities (CRSwNP)	9 (7.3%)	67 (54.5%)
Missing	1 (0.8%)	53 (43.1%)

A minority of patients required switching due to adverse events (AE). In one patient, the primary reason for switching was a severe local skin reaction at the injection site. In another patient, low back pain was reported as a secondary reason for switching.

Primary longitudinal outcomes

Clinical outcomes were evaluated in never-switchers, switchers prior to first biologic initiation (pre-switch cohort), and switchers following biologic switching (post-switch cohort) at baseline, 4/6 months, and 12 months. Baseline and 12-month outcomes are presented in Table 4, while intermediate 4/6-month outcomes are summarized below to illustrate the early response pattern.

Baseline phenotype

At baseline, cohorts differed in clinical and inflammatory characteristics (Table 4). Asthma control was equally poor at baseline between groups (ACT median 10.0 [9.0–12] in never-switchers vs. 11.0 [10.0–12.0] in switchers prior to the first switch). Baseline blood eosinophil counts were lower in switchers pre-switch compared with never-switchers (median 500 [350–650] vs. 580 [400–860] cells/μL; p = 0.011). Improvements in

Table 4. Changes in clinical outcomes, lung function, biomarkers, and comorbidities over 12 months in never-switchers and switchers before and after biologic therapy. Data are presented as mean ± standard deviation or median [interquartile range], depending on data distribution.

	Never-switcher cohort								Switcher cohort prior to first biologic								Switcher cohort post first biologic							
Variable	**Baseline sample size**	**Paired data available at 12 M**	**Baseline Mean (SD)**	**12 M Mean (SD)**	***p*-value**	**Baseline Median [IQR]**	**12M Median [IQR]**	***p*-value**	**Baseline sample size**	**Paired data available at 12 M**	**Baseline Mean (SD)**	**12 M Mean (SD)**	***p*-value**	**Baseline Median [IQR]**	**12M Median [IQR]**	***p*-value**	**Baseline sample size**	**Paired data available at 12 M**	**Baseline Mean (SD)**	**12 M Mean (SD)**	***p*-value**	**Baseline Median [IQR]**	**12M Median [IQR]**	***p*-value**
ACT	229	143	10.5 ± 2.0	22.8 ± 1.4	***P* < 0.001**	10.0 [9.0–12.0]	23.0 [22.0–24.0]	***P* < 0.001**	116	111	10.6 ± 1.5	18.9 ± 3.2	***P* < 0.001**	11. [10.0–11.0]	20.0 [18.0–20.0]	***P* < 0.001**	123	92	12.2 ± 2.9	21.8 ± 2.0	***P* < 0.001**	12.0 [10.0–14.0]	21.8 ± 2.0	***P* < 0.001**
FEV_1 (L)	229	143	1.36 ± 0.47	2.12 ± 0.81	***P* < 0.001**	1.27 [1.08–1.60]	2.05 [1.50–2.59]	***P* < 0.001**	116	111	1.43 ± 0.39	1.96 ± 0.67	***P* < 0.001**	1.39 [1.19–1.68]	1.86 [1.49–2.30]	***P* < 0.001**	123	92	1.50 ± 0.55	2.07 ± 0.65	***P* < 0.001**	1.37 [1.12–1.69]	2.07 ± 0.65	***P* < 0.001**
FEV_1 (% predicted)	229	144	0.5 ± 0.1	0.8 ± 0.2	***P* < 0.001**	0.5 [0.4–0.6]	0.8 [0.7–0.9]	***P* < 0.001**	116	111	0.5 ± 0.1	0.7 ± 0.1	***P* = 0.0033**	0.5 [0.5–0.6]	0.7 [0.6–0.7]	***P* < 0.001**	123	92	0.5 ± 0.1	0.7 ± 0.2	***P* = 0.016**	0.5 [0.5–0.6]	0.7 ± 0.2	***P* < 0.001**
Exacerbations/ year	229	140	3.2 ± 2.1	0.2 ± 0.5	***P* < 0.001**	3.0 [2.0–4.0]	0.0 [0.0–0.0]	***P* < 0.001**	116	111	2.9 ± 2.1	0.5 ± 1.3	***P* < 0.001**	2.0 [2.0–3.0]	0.0 [0.0–0.0]	***P* < 0.001**	123	92	2.5 ± 2.1	0.2 ± 0.8	***P* < 0.001**	2.0 [1.5–3.0]	0.2 ± 0.8	***P* < 0.001**
Hospitalizations/ year	229	143	1.3 ± 0.9	0.0 ± 0.2	***P* < 0.001**	1.0 [1.0–2.0]	0.0 [0.0–0.0]	***P* < 0.001**	116	111	1.1 ± 0.7	0.2 ± 0.6	***P* < 0.001**	1.0 [1.0–1.0]	0.0 [0.0–0.0]	***P* < 0.001**	123	92	1.2 ± 0.8	0.1 ± 0.4	***P* < 0.001**	1.0 [1.0–2.0]	0.1 ± 0.4	***P* < 0.001**
OCS use (maintenance)	229	143	12/229 (5.2%)	1/143 (0.7%)	***P* < 0.001**	12/229 (5.2%)	1/143 (0.7%)	***P* < 0.001**	116	111	11/116 (9.5%)	8/111 (7.2%)	*P* = 0.69				123	92	13/123 (10.6%)			13/123 (10.6%)		
Total IgE (IU/ mL)	141		345.5 ± 422.1			197.0 [96.0–406.0]			116	111	282.6 ± 234.0						123	92	414.9 ± 312.5			324.0 [195.5–557.0]		
Eosinophils (absolute)	229	143	697 ± 478	69 ± 238	***P* < 0.001**	580 [400–860]	0 [0–10]		116	111	569 ± 363	381 ± 233	***P* < 0.001**	500 [350–650]	390 [270–529]	***P* < 0.001**	123	92	579 ± 512	83 ± 195	***P* < 0.001**	450 [300–780]	83 ± 195	***P* < 0.001**
BDT (mL)	225		369 ± 163			340 [270–420]			116	111	316 ± 75			310 [270–350]			123	92	359 ± 143			320 [270–405]		
Nasal polyposis	229		98/229 (42.8%)			98/229 (42.8%)			116	111	73/116 (62.9%)			73/116 (62.9%)			123	92	78/123 (63.4%)			78/123 (63.4%)		
Chronic rhinosinusitis (CRS)	229		94/229 (41.0%)			94/229 (41.0%)			116	111	84/116 (72.4%)			84/116 (72.4%)			123	92	91/123 (74.0%)			91/123 (74.0%)		
CRSwNP (CRS + nasal polyps)	229		43/229 (18.8%)			43/229 (18.8%)			116	111	57/116 (49.1%)			57/116 (49.1%)			123	92	62/123 (50.4%)			62/123 (50.4%)		

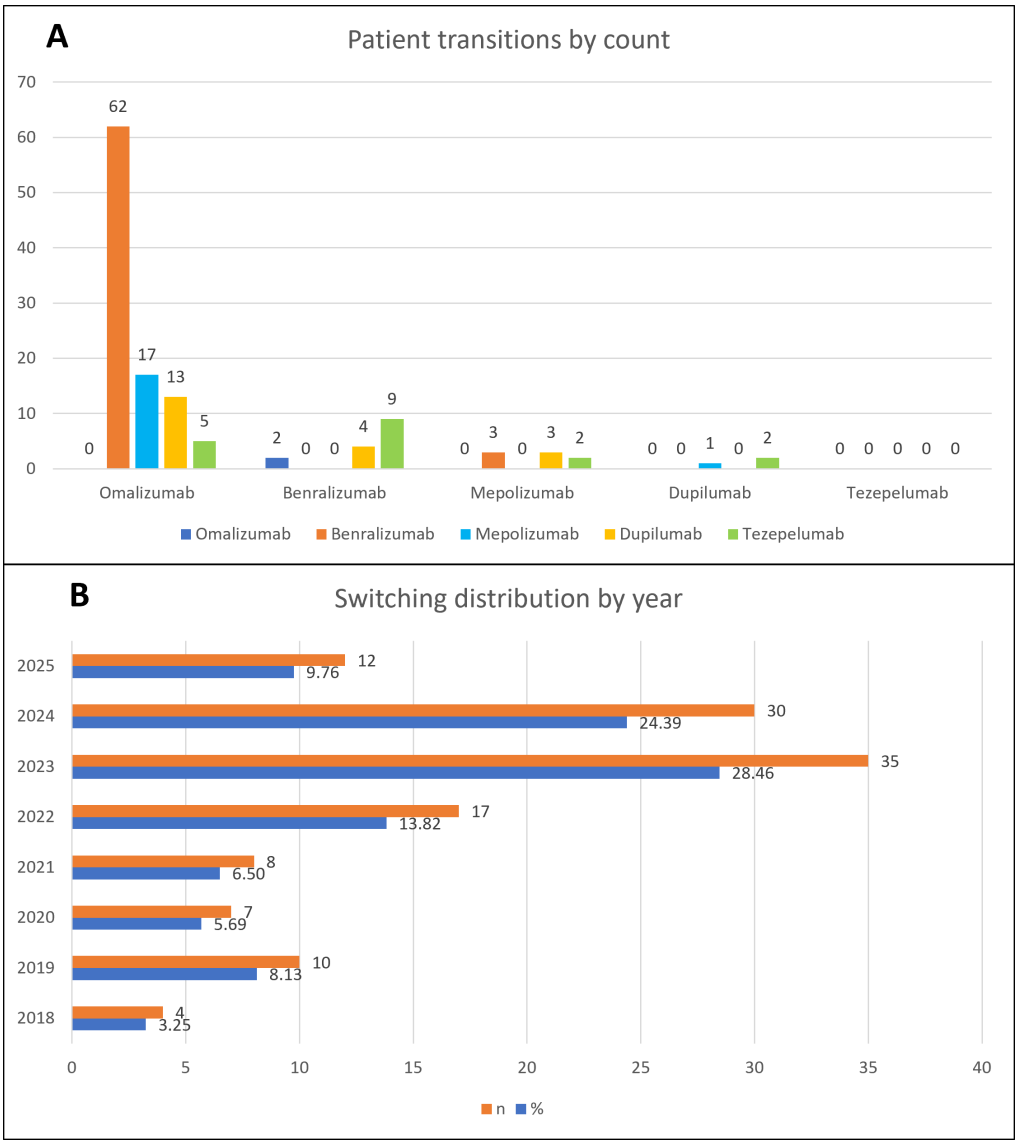

Figure 1. Patient transitions by count (**A**) and by year (**B**). **A.** The horizontal axis shows the initial biologic therapies, while the columns represent the therapy after switching; **B.** The orange columns show the absolute number of transitions within the specified year (vertical axis); the blue columns depict the relative percentage.

asthma control, lung function, exacerbation frequency, and oral corticosteroid use were observed across all groups during follow-up.

Early (4/6-month) trajectory

By 4/6 months, early improvements in symptom control and lung function were evident following biologic initiation and switching. These changes were generally maintained or further improved at 12 months, supporting the clinical utility of early assessment as a predictor of long-term response.

One-year outcomes and comparative trajectories

Never-switchers demonstrated consistent improvement across clinical outcomes, including asthma control, exacerbation rate, hospitalizations, and reduction in oral corticosteroid use, with some variables showing a marked decrease, such as eosinophil absolute count in a large percentage of patients receiving anti-eosinophil therapy (Table 4: Never-switcher cohort). Notably, by month 12, never-switchers had achieved high levels of asthma control (ACT median = 23.0 [22.0–24.0]) and lung function (FEV_1 median = 2.05 [1.50–2.59]). Exacerbation burden declined markedly, with a large proportion of patients reaching zero exacerbations at follow-up. Switchers in the pre-switch cohort improved after the initial index biologic but remained less adequately controlled compared to never-switchers (ACT median = 20.0 [18.0–20.0] vs. 23.0 [22.0–24.0]; $p < 0.0001$). Following the initial switch, significant improvements were observed from pre- to post-switch in both asthma control (ACT median = 20.0 [18.0–20.0] vs. 22.0 [21.0–23.0]; paired $p < 0.0001$) and lung function (FEV_1 = 1.86 [1.49–2.30] pre-switch vs. 2.00 [1.66–2.45] post-switch; paired $p = 0.016$). Despite this improvement, control in switchers

remained significantly inferior to never-switchers at 12 months (ACT $p < 0.0001$).

Eosinophil absolute counts decreased substantially by 12 months, particularly in cohorts receiving anti-eosinophil therapies. Within switchers, eosinophils declined significantly after switching (median 390 [270–529] to 0 [0–100] cells/μL; paired $p < 0.001$), consistent with biomarker response under targeted treatment.

Upper-airway comorbidities and biomarkers

Nasal polyposis, chronic rhinosinusitis, and the combined CRSwNP phenotype were treated as baseline phenotyping variables and were used primarily for between-cohort comparisons. As noted, switchers had a markedly higher upper-airway respiratory comorbidity burden than never-switchers. These comorbidities were not expected to change over follow-up. Accordingly, paired pre–post comparisons within switchers were not interpreted for these variables.

All pairwise comparisons at baseline and 12 months are summarized in Table 5, which reports only *p*-values for clinical variables across time points and cohorts (never vs. pre, never vs. post, and pre vs. post). Detailed statistical outputs for all pairwise comparisons are provided in the Suppl. material 4.

Table 5. Summary of pairwise statistical significance for baseline and 12-month outcomes across switching groups.

Variable	Significance Never vs. Pre	Significance Never vs. Post	Significance Pre vs. Post
ACT baseline	***P* = 0.49**	*P* < 0.001	*P* < 0.001
ACT 12 M	*P* < 0.001	*P* < 0.001	*P* < 0.001
FEV (L) baseline	*P* = 0.189	*P* = 0.011	*P* = 0.025
FEV (L) 12 M	*P* = 0.09	*P* = 0.647	*P* = 0.016
FEV (% predicted) baseline	***P* = 0.442**	*P* = 0.087	*P* = 0.002
FEV (% predicted 12M)	*P* < 0.001	*P* = 0.09	*P* < 0.001
Exacerbation baseline	*P* = 0.133	*P* < 0.001	*P* = 0.065
Exacerbations at 12 M	*P* = 0.012	*P* = 0.749	*P* = 0.048
Hospitalization baseline	*P* = 0.051	*P* = 0.187	*P* = 0.721
Hospitalization at 12 M	*P* < 0.001	*P* = 0.084	*P* = 0.077
OCS use at baseline	*P* = 0.167	*P* = 0.084	-
OCS use at 12 M	*P* = 0.006	*P* = 0.019	*P* = 0.499
Eosinophils baseline	*P* = 0.011	*P* = 0.037	*P* = 0.648
Eosinophils 12 M	*P* < 0.001	*P* = 0.659	*P* < 0.001
Total IgE baseline	*P* = 0.157	*P* = 0.135	*P* < 0.01
BDT (mL) baseline	*P* = 0.001	*P* = 0.585	*P* < 0.001
Nasal polyps baseline	*P* < 0.001	*P* < 0.001	-
Chronic rhinosinusitis baseline	*P* < 0.001	*P* < 0.001	-
CRSwNP baseline	*P* < 0.001	*P* < 0.001	

Discussion

The increasing availability of biologic therapies has introduced new challenges in the management of severe asthma, as clinicians must often select among multiple treatment options without direct comparative evidence and reconsider treatment strategies when adequate disease control is not achieved. This single-center study, conducted in a tertiary referral hospital, may reflect patients with more severe or complex disease characteristics than the overall asthma community. Consequently, the results must be regarded cautiously when extrapolating to wider clinical contexts.

Evidence on biologic switching in severe asthma is derived predominantly from real-world observational studies and a limited number of retrospective or ambispective cohorts, registry analyses, and single-arm switch studies, with substantial heterogeneity in study design, populations, and outcome definitions. Similarly, randomized controlled trials comparing different molecules are not available to date, while network meta-analyses have yet to be published (Crossingham et al. 2022). To our knowledge, this study represents the first national real-world analysis evaluating biologic prescribing patterns, switching frequency, and associated clinical characteristics in patients with severe asthma. We described the underlying reasons for switching and examined the distribution of baseline clinical factors—including nasal polyps, age of asthma onset, and long-term oral corticosteroid use—across different biologic treatment trajectories.

The proportion of patients requiring biologic switching in the present cohort (33.6%) is consistent with real-world European data, although somewhat higher than that reported in large registries. In the Italian ANANKE study (Caruso et al. 2022), approximately 20–25% of patients receiving benralizumab were biologic-experienced, reflecting prior exposure to other monoclonal antibodies, which was consistent with our findings (21.8%). While direct comparison is limited by differences in study design and follow-up duration, the presence of a substantial biologic-experienced population across registries supports the notion that switching represents a frequent and clinically relevant phenomenon in severe asthma management.

Beyond switch frequency, longitudinal comparisons revealed consistent differences between patients who remained on their initial biologic and those who required switching, with switchers exhibiting a persistently higher residual disease burden throughout follow-up. Clinically, the post-switch cohort represents a population with partial or waning treatment response. Accordingly, despite measurable improvement during post-switch follow-up, these patients did not consistently converge to the levels of disease control observed in never-switchers at 4–6 or 12 months. Complete convergence following either initial biologic initiation or subsequent switching was uncommon, underscoring the heterogeneous and multifactorial nature of severe asthma. Importantly, early treatment response at 4–6 months appeared informative for longer-term outcomes, suggesting that early follow-up assessments may help identify patients unlikely to achieve deep disease control with a given biologic and support timely therapeutic reassessment.

Switching biologic therapy was associated with meaningful clinical benefits, including improved asthma control and reductions in exacerbation burden. The largest prospective switch study to date, the OSMO trial, demonstrated significant improvement in asthma outcomes fol-

lowing transition from omalizumab to mepolizumab in patients with uncontrolled severe eosinophilic asthma (Liu et al. 2021). Similar benefits have also been reported in real-world observational studies evaluating switching from anti-IgE to anti–IL-5 or anti–IL-5Rα therapies, including reductions in exacerbations and partial corticosteroid sparing (Carpagnano et al. 2020; Pelaia et al. 2021). However, both published evidence and our real-world data indicate that treatment response following switching is frequently incomplete, with persistent symptoms or continued oral corticosteroid exposure observed in a relevant proportion of patients. This variability likely reflects the biological complexity of severe asthma in routine clinical practice, where overlapping inflammatory pathways and comorbidities may limit the depth of response achievable with single-target therapies.

Switching due to adverse events was uncommon in our cohort, suggesting that safety concerns were not a primary driver of treatment change. Only a small number of patients discontinued therapy because of adverse events, including a severe injection-site reaction in one case and low back pain reported as a secondary reason for switching in another.

Importantly, patients requiring biologic switching were not clinically more severe at baseline but exhibited distinct biological and comorbidity-related characteristics, including enhanced type 2 inflammation and a high burden of upper airway disease. The distinction between biologic-naïve switchers and post-switch patients further emphasizes that switching does not represent a return to baseline disease activity but rather a transitional clinical state shaped by prior biologic exposure. In this context, post-switch patients occupy an intermediate phenotype characterized by partial response or loss of response, which may explain why subsequent improvement does not uniformly translate into full disease normalization. This observation supports the presence of a biologically complex "switcher phenotype," previously described in real-world cohorts, in which overlapping inflammatory mechanisms limit responsiveness to single-target therapies (Numata et al. 2021).

Our results further suggest that switching between biologics with different mechanisms of action, as well as within the same inflammatory pathway, can provide additional therapeutic benefit. In particular, transitions to anti–IL-5Rα therapy have been associated with improved asthma outcomes following inadequate response to anti-IgE or anti–IL-5 agents, although complete normalization remains uncommon (Drick et al. 2020; Kavanagh et al. 2021). These findings indicate that biologic non-response often reflects underlying disease heterogeneity rather than insufficient drug efficacy alone.

More recently, upstream therapies targeting epithelial cytokines have expanded treatment options for biologic-experienced patients. Real-world studies evaluating tezepelumab have demonstrated significant improvement in asthma control and exacerbation frequency after failure of prior biologics, although residual disease activity persists in a subset of patients (Khateeb et al. 2025; Sumi et al. 2025). Our findings are concordant with this emerging evidence and further support the concept of graded biologic responsiveness in severe asthma.

Several limitations should be acknowledged. The combined retrospective data inclusion alongside prospective data collection in a real-world design introduces essential variability in follow-up timing, biomarker availability, and treatment selection, which were determined by routine clinical practice rather than standardized protocols. The timeframe of 2009–2025 was chosen to include therapies based on their approval date. However, this introduces substantial differences in the historical capture of biomarkers due to variability in diagnosis and treatment initiation dates. To diminish heterogeneity, outcomes were assessed by relative changes within individuals (pre–post comparisons) and among distinctly defined cohorts. Nonetheless, residual variability stemming from disparities in historical data availability and clinical practice patterns cannot be entirely eliminated and is recognized as an intrinsic drawback of the real-world approach.

Residual confounding from unmeasured variables cannot be ruled out, and the incomplete availability of biomarker data (e.g., FeNO) represents a limitation of the study. The absence of randomized treatment allocation and direct head-to-head comparisons of biologics restricts the capacity to infer causal conclusions about comparative effectiveness. Nevertheless, this design reflects real-world decision-making and provides clinically relevant insights into treatment trajectories that are not captured in controlled clinical trials.

Finally, large-scale real-world comparative analyses, such as the EU-ADVANTAGE study, have highlighted substantial heterogeneity in biologic effectiveness according to phenotype and prior treatment exposure, reinforcing the need for individualized therapeutic strategies in routine practice (Canonica et al. 2025). Taken together, these observations support a treat-to-target approach, emphasizing early evaluation of response and timely biologic rotation when clinically meaningful improvement is not achieved.

Conclusion

This real-world study confirms that treatment with biologics correlated with significant enhancements in asthma management and reduction in exacerbation frequency.

Approximately one-third of patients required a change in biologic therapy over time, reflecting the heterogeneous and biologically complex nature of the disease.

Although switching resulted in significant improvement in asthma control and exacerbation burden, complete normalization of disease activity, particularly sustained oral corticosteroid independence, was uncommon. Patients requiring switching were not clinically more severe at baseline but demonstrated distinct biological and comorbidity-related features, including enhanced type 2 inflammation and upper airway involvement.

Even though causality cannot be determined due to the observational design of the study, the results indicate that

biologic switching may serve as an effective technique for enhancing illness management in some patients.

These findings underscore the importance of comprehensive phenotyping beyond conventional clinical parameters and support individualized biologic sequencing strategies guided by early treatment response. Future research should focus on predictive models integrating biomarkers, comorbidities, and response dynamics to further advance precision medicine in severe asthma.

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Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

Clinical trials: Ethical approval for the non-interventional study was obtained from the local institutional review board (Clinical Research Ethics Committee of University Hospital Alexandrovska, decision No. 9/19.06.2025).

The authors declared that no experiments on humans or human tissues were performed for the present study.

Informed consent from the humans, donors or donors' representatives: University Hospital 'Alexandrovska', Clinic of Allergology, Sofia.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Artificial Intelligence (AI) use

Regarding the use of AI in the preparation of this manuscript, the authors declare the following:

Description: AI-assisted tools were used to improve the clarity, grammar, and readability of the manuscript. The authors reviewed and edited all content and take full responsibility for the final version of the text.

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Conceptualization, B.K., A.V., and K.T.; methodology, A.V., and M.S.; validation, B.K.; statistical analyses, K.T.; investigation, B.K., A.V., M.N., E.P., and D.N.; resources, B.K., A.V., M.N., E.P., D.N., and M.S.; data curation, B.K., and K.T.; visualization, B.K., and K.T.; ethical review, S.S.; writing – original draft preparation, B.K., and K.T.; writing – review and editing, B.K., A.V., M.N., E.P., D.N., M.S., K.T., and S.S.; supervision, B.K., A.V., and M.S.; project administration, B.K. All authors have read and agreed to the published version of the manuscript.

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Data availability

All essential data are included in the main text and Supplementary Information. Additional data may be provided by the authors upon reasonable request.

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Supplementary material 1

Document of participant selection and consent

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Data type: pdf

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Supplementary material 2

Asthma dataset

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Supplementary material 3

Extended patient characteristics

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Data type: pdf

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Supplementary material 4

Detailed statistical outputs

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