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Article

Keywords:

Posted Date: August 12th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10489207/v1

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Additional Declarations: No competing interests reported.

Biological Therapy Persistence in Severe Asthma: Real-World Evidence Beyond Fixed Follow-Up Analysis

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Abstract

Long-term durability of biological therapy in severe asthma remains insufficiently characterized in real-world clinical practice. Most currently available studies assess treatment effectiveness at predefined follow-up points, potentially overlooking patients who discontinue therapy earlier due to secondary loss of response or insufficient disease control. We performed a retrospective real-world cohort study including 529 patients with severe asthma treated with omalizumab, mepolizumab, or benralizumab to evaluate long-term biologic treatment persistence, defined as time to loss of clinically effective therapy, using a survival-based time-to-relapse model and to identify baseline predictors of long-term treatment persistence. Time-to-relapse was defined as loss of clinically meaningful treatment effectiveness resulting in biologic discontinuation or switching. Patients treated with omalizumab presented lower eosinophilia and earlier disease onset, whereas anti-IL-5/IL-5R therapies were associated with a more pronounced eosinophilic phenotype and greater corticosteroid burden. Among 81 observed relapses, 61.7% occurred between scheduled follow-up visits. The 90th percentile of time-to-relapse was 48 months for mepolizumab, compared with 20 months for benralizumab and 11 months for omalizumab ($p=0.003$). In multivariate analysis, baseline ACQ, FEV1, and peripheral blood eosinophilia emerged as independent predictors of biologic treatment persistence. Biologic treatment persistence may represent a clinically meaningful long-term outcome measure and support the broader application of survival-based methodologies in future real-world studies of severe asthma. Maintenance of biologic therapy in severe asthma could constitute a significant factor for therapy choice; in this context time-to-relapse may

provide a more realistic information than results from conventional fixed follow-up models, biased by patients “vanishing” between check-points.

Introduction

Severe asthma remains one of the greatest contemporary challenges in respiratory medicine due to its heterogeneous immunopathology, high burden of exacerbations, progressive airway remodeling, and substantial healthcare utilization [1-3]. Despite advances in inhaled pharmacotherapy, approximately 3–10% of patients remain uncontrolled despite optimized high-dose inhaled corticosteroid (ICS) and long-acting bronchodilator therapy [1,2]. Severe asthma is associated with impaired quality of life, accelerated decline in lung function, repeated hospitalizations, oral corticosteroid (OCS) dependence, and increased mortality risk [1-4]. The introduction of biological therapies targeting type 2 (T2) inflammation has transformed the therapeutic landscape of severe asthma and advanced precision medicine strategies [2,5-7].

Current biologic therapies target key pathways involved in T2 inflammation, including the IL-5 axis, IL-4/IL-13 signaling, and thymic stromal lymphopoietin (TSLP) [5-8]. Anti-IL-5 and anti-IL-5 receptor agents reduce eosinophilic inflammation, whereas dupilumab inhibits IL-4Rα-dependent signaling shared by IL-4 and IL-13, and tezepelumab blocks the upstream epithelial alarmin TSLP [5-8]. Collectively, these therapies substantially reduce exacerbation frequency, improve asthma control and lung function, and enable reduction or discontinuation of maintenance OCS therapy in selected patients [5-10]. However, despite major therapeutic progress, long-term persistence of biologic therapy in real-world severe asthma populations remains incompletely understood [11-13]. Randomized clinical trials primarily evaluate predefined endpoints at fixed observation timepoints and frequently exclude patients with complex comorbidities, therapy switches, or irregular adherence patterns [11-13]. Analyses restricted to predefined assessment timepoints may fail to adequately capture not only treatment failures themselves but also their exact timing. For example, patients losing treatment response after 13, 17, or 23 months may all be classified similarly in conventional fixed follow-up analyses despite having substantially different durations of successful treatment, or his data can be not included into statistical analysis due to check-point missing data. We refer to this phenomenon as the “real-world vanishing patients”: for example, Biener et al. [14] reported treatment discontinuations before the 6-month assessment that were not included in subsequent efficacy analyses, whereas Gates et al. [15] evaluated outcomes only among patients completing one year of therapy. In both studies great part of the information about treatment failures is lost. The phenomenon may also contribute to overestimation of treatment effectiveness in analyses focusing predominantly on patients reaching predefined follow-up milestones. In contrast, the real routine clinical practice is characterized by dynamic therapeutic trajectories, including discontinuation, requalification, switching between biologics, treatment complications, and variable durability of response [11-13, 16].

Another unresolved issue concerns the determinants of long-term treatment persistence. Although blood eosinophils and fractional exhaled nitric oxide (FeNO) are established biomarkers of type 2 inflammation and predictors of response to selected biologic therapies, their ability to predict long-term treatment persistence remains limited [17-20]. Given the

marked biological and clinical heterogeneity of severe asthma, the durability of biologic therapy is likely influenced by multiple factors extending beyond conventional type 2 biomarkers, including disease chronicity, baseline disease severity, comorbidities, treatment adherence, and broader clinical heterogeneity [11,17,19-21]. Consequently, identifying clinical and biological predictors of long-term treatment persistence remains an important unmet need [11,17,20-22].

Accordingly, the aim of the present study was to evaluate long-term biologic treatment persistence in severe asthma using a Kaplan–Meier time-to-relapse approach, to identify its clinical and biological predictors, and to explore whether a survival-based analytical framework may provide a more complete information about real-world treatment persistence than conventional fixed follow-up methodologies [23-25].

Material and Methods

Study design

We conducted a retrospective real-world cohort study including all adult patients (≥ 18 years) with uncontrolled severe asthma who received biologic therapy at the Department of Internal Medicine, Asthma and Allergy, Medical University of Lodz, Poland, at the Department of Internal Medicine, Pulmonology, Allergology, Clinical Immunology and Rare Diseases and at the Department of Internal Medicine, Infectious Diseases and Allergology of Military Institute of Medicine – National Research Institute, Warsaw, Poland, between January 1st 2018 and August 30, 2025 (n=529, figure 1). Baseline data corresponded to each patient's status on the day of qualification for biologic treatment, whereas follow-up assessments included the Asthma Control Questionnaire (ACQ), Mini Asthma Quality of Life Questionnaire (MiniAQLQ), Global Evaluation of Treatment Effectiveness (GETE), and forced expiratory volume in one second (FEV1), obtained at 6 months, 12 months, and annually thereafter, in accordance with the time requirements imposed by the recommendations of the Therapeutic Program B.44 for the Treatment of Severe Asthma in Poland.

End points

The primary endpoint was biologic treatment persistence, assessed using a time-to-relapse approach. Complete observation (relapse event) was defined as biologic treatment discontinuation resulting from loss of clinically meaningful treatment effectiveness. The event date corresponded to the date of treatment discontinuation. Relapse was defined as biologic treatment discontinuation resulting from loss of clinically meaningful treatment effectiveness and reported into the medical files by physician (one main choice): deterioration of GETE below a good or excellent response, treatment ineffectiveness, lack of clinically meaningful improvement in ACQ or MiniAQLQ, failure to achieve or maintain ≥ 50% reduction in exacerbation frequency compared with the pre-treatment period, or adverse events. Censored observations included ongoing treatment, transfer to another healthcare provider, planned treatment discontinuation, discontinuation for reasons unrelated to treatment effectiveness or patient's death. To characterize long-term treatment persistence, the 90th percentile of the time-to-relapse distribution, expressed in full months. The secondary endpoint was to identify clinical and biological factors associated with treatment persistence in comparable groups of

patients: with baseline peripheral blood eosinophil counts between 0.15 and 0.40 G/L. Additional information regarding methodology is provided in Supplementary Material.

Statistical analysis

Statistical analyses were performed using Statistica 13 PL. Figures were prepared using Statistica 13 PL and GIMP 2.10.38. Continuous variables were compared using the Mann–Whitney U test or the Kruskal–Wallis test with Dunn's post hoc test, as appropriate. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test. Time-to-relapse was estimated using the Kaplan–Meier method and compared using the log-rank test. Multivariable analyses were performed using the Cox proportional hazards model. A two-sided p value < 0.05 was considered statistically significant.

Ethics statement

Ethics approval and consent to participate: This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was reviewed by the Bioethics Committee of the Medical University of Lodz, Poland (Resolution No. RNN/58/25/KE, February 11, 2025). The Committee determined that the study was a non-interventional questionnaire-based survey and did not constitute a medical experiment under applicable Polish regulations. Accordingly, the requirement for informed consent was waived by the Bioethics Committee of the Medical University of Lodz. Consequently, formal ethics committee approval was not required.

Results

General study groups characteristics

Baseline characteristics differed significantly between biologic treatment groups (Table 1). Peripheral blood eosinophil counts ranged from 0.01 to 2.70 G/L and differed significantly across treatment groups ($p<0.001$). Total IgE concentrations were significantly lower in the benralizumab than in the mepolizumab and omalizumab groups (respectively, median 120 IU/ml vs 230 IU/ml and 248 IU/ml, $p=0.002$). Patients treated with omalizumab were diagnosed with severe asthma at a younger age than those receiving mepolizumab or benralizumab (median: 51.0 vs. 57.0 and 59.0 years, respectively; $p<0.001$). They also had the longest disease duration (median 18.0 vs. 13.0 and 15.0 years, respectively; $p=0.032$).

Markers of disease severity also differed between treatment groups. Chronic OCS use during the 6 months preceding qualification date was more frequent among patients treated with benralizumab (n=54; 24.0%) and mepolizumab (n=35; 16.9%) than among those receiving omalizumab (n=7; 8.6%; $p=0.007$). Similarly, previous biologic exposure was more common in the benralizumab and mepolizumab groups (11% in both groups) than in the omalizumab group (1.1%; $p=0.009$). No statistically significant differences were observed for the remaining baseline characteristics.

Biologic treatment persistence – primary endpoint

N=141 therapies were discontinued during the observation time (reasons for therapies ending are presented in supplementary tab. S1). Although ACQ levels did not changed statistically significantly in time, treatment failures were noted in all observation time with no predilection to occurring in the check-points (fig. 2). In the overall study population, mepolizumab was associated with the longest treatment persistence. The 90th percentile of time-to-relapse was 48 months for mepolizumab, compared with 20 months for benralizumab and 11 months for omalizumab (p=0.003; Figure 3). Similar trends were observed in analyses stratified according to baseline blood eosinophil count. Among patients with baseline eosinophilia ≤ 0.40 G/L the longest treatment persistence was observed in the mepolizumab group (90th percentile 35 months), whereas the corresponding value was 5 months for both benralizumab and omalizumab (p=0.301, Figure 4). Among patients with baseline eosinophilia >0.4 G/l, the 90th percentile of treatment persistence was 48 months for mepolizumab and 23 months for benralizumab (p=0.050). Median time-to-relapse was not reached in any Kaplan-Meier analyses because the duration of follow-up was insufficient for 50% of patients to experience the event.

Factors associated with biologic treatment persistence - secondary endpoint.

In univariate Cox regression analysis for the overall study population higher baseline ACQ score was independently associated with shorter treatment persistence (HR=1.416; 95% CI 1.096–1.828; p=0.008). Conversely, higher baseline FEV1 (HR=0.988; 95% CI 0.977–1.000; p=0.043), higher baseline blood eosinophil count expressed in G/l (HR=0.432; 95% CI 0.199–1.938; p=0.043), and absence of previous life-threatening asthma-related events (HR=0.529; 95% CI 0.292–0.958; p=0.036) were independently associated with longer treatment persistence. Compared with benralizumab, treatment with mepolizumab was associated with longer treatment persistence (HR=0.467; 95% CI 0.265–0.820; p=0.002), whereas treatment with omalizumab was not statistically significantly longer (tab. 2).

Severe asthma duration, baseline ACQ, life-threatening asthma-related event and mAb used were used to calculate Cox models for time-to-relapse in patients stratified according to baseline blood eosinophil counts (0.15-0.40 G/L and >0.40 G/L). There was no independent factor influencing time-to-relapse among patients with baseline blood eosinophil counts of 0.15–0.40 G/L (Supplementary Table 6). In patients with baseline peripheral eosinophil counts >0.40 G/L higher baseline ACQ score (HR=1.61; 95%CI 1.113-2.337; multivariate p=0.12;) was associated with shorter treatment persistence, whereas absence of a previous asthma-related life-threatening event (HR=0.37; 95%CI 0.169-0.807; p=0.013;) and treatment with mepolizumab compared with benralizumab (HR=0.48; 95%CI 0.245-0.920; p=0.027) were associated with longer treatment persistence (Supplementary Table 7).

Discussion

A key aspect of our study is the illustration of the “real-world vanishing patient” phenomenon in the analysis of biologic treatment persistence. In our cohort, 50 of 81 observed relapses occurred between scheduled follow-up visits, *ergo* 61.7% of treatment failures would vanish from the standard analysis. Before this publication, Mummler et al. explicitly distinguished long-term responders from non-responders, illustrating how analyses restricted to predefined

follow-up milestones or responder populations may preferentially reflect favourable outcomes [26]. We believe that this problem deserves more attention, including thorough scientific studies. Also, not only the way of researching, but also reporting the treatment persistence in severe asthma has not yet been fully developed. We propose 90th percentile of time-to-relapse function as a simple measurement, easy to convey to the patient as well as to compare e.g. when speaking about treatment centers experiences. Potentially, treatment stability may constitute a key feature for monoclonal antibody assignment, right next to its effectiveness expressed e.g. as the percentage of clinical remissions achieved on the treatment. Another very important, yet not still unexplored issue is the duration of remission after it has been achieved. This also cannot be evaluated with ignorance of time as a critical element of several asthma data landscape.

Our findings support the concept that biologic treatment persistence may represent a clinically meaningful endpoint reflecting long-term disease stability rather than solely short-term treatment effectiveness. Our data suggests, that the discussion about what is long-term observation time in severe asthma shall be opened. In general, according to our research, we could assume 90% of patients is being treated successfully for 24 months and 81% for 48 months (fig. 2). This indicates that 2-year observation may be too short to notice numerous effects of starting a specific treatment. In the design of our study we proposed 3 years as long period of time in the context of severe asthma biological therapy, but it would be optimally to achieve median time-to-relapse. It seems that the longer the observation time, the more precise and reliable data can be obtained.

One of the main findings of the present study was the observation of significant differences in treatment persistence between the analyzed biologic therapies ($p = 0.003$). Important baseline differences were presented between treatment groups. Patients receiving omalizumab had lower baseline blood eosinophil counts, were diagnosed with severe asthma at a younger age, and less frequently required chronic OCS treatment, whereas patients treated with anti-IL-5/IL-5R therapies had higher baseline blood eosinophil counts, greater systemic corticosteroid exposure and more frequent previous biologic use. Our results additionally suggest that long-term biologic treatment persistence may be influenced by baseline disease severity. In the mepolizumab subgroup, lower baseline FEV1 was associated with shorter treatment persistence (HR 0.968; $p = 0.018$). Similarly, in the benralizumab cohort, poorer baseline asthma control measured by ACQ was associated with shorter treatment persistence (HR 1.611; $p = 0.013$), whereas lower BMI was associated with longer treatment persistence (HR 0.909; $p = 0.009$). These findings suggest that patients with poorer symptom control and higher body weight may be less likely to maintain a sustained long-term treatment response. The association between higher BMI and reduced treatment persistence is also consistent with growing evidence that obesity-related asthma represents a partially distinct biological phenotype involving systemic inflammation, metabolic dysregulation, altered airway mechanics, and corticosteroid resistance. Consequently, excess body weight may contribute to reduced long-term effectiveness of biologic therapies in a subset of patients despite adequate suppression of type 2 inflammation. These findings further illustrate the heterogeneity of severe asthma and suggest that treatment persistence may be influenced by differences in disease phenotype and patient characteristics. Although longer treatment persistence was observed in the mepolizumab cohort,

the study was not designed to compare biologic efficacy directly. Therefore, the observed differences should be interpreted cautiously and may reflect differences in patient selection, disease characteristics, treatment era, and other factors not fully captured by the available clinical variables rather than superiority of a specific biologic agent. An important observation of the present study is that baseline asthma control (ACQ), FEV1, and peripheral blood eosinophilia remained independent predictors of treatment persistence in multivariate analysis, which is in line with current literature and constitute an argument for the further exploration of Kaplan-Maier based methodology.

Similar persistence-based approaches have been widely adopted in rheumatology and dermatology, where drug survival is considered an integrated measure of long-term effectiveness, safety, and treatment acceptability. Most currently available real-world studies in severe asthma evaluate treatment response at predefined observation points, typically 6 or 12 months after treatment initiation. However, severe asthma is characterized by dynamic therapeutic trajectories involving secondary loss of response, biologic switching, treatment interruption, remission, and fluctuating disease activity. Consequently, analyses based exclusively on fixed follow-up assessments may not fully capture long-term treatment persistence in routine clinical practice.

The present study also supports the growing concept that severe asthma progression cannot be explained exclusively by eosinophilic inflammation. Despite effective T2-targeted therapies, a proportion of patients still experience secondary loss of response or insufficient long-term disease stabilization [11-14,20,27-29]. This observation suggests that mechanisms beyond type 2 inflammation contribute to long-term treatment outcomes in severe asthma. Consequently, biologic treatment persistence may reflect not only suppression of eosinophilic inflammation but also the cumulative impact of other disease-related factors, including structural airway changes and mechanisms less responsive to currently available biologic therapies [15,17,20,22,24].

Limitations

This study has several limitations related to its retrospective real-world design, including potential selection bias, missing data, and non-standardized follow-up intervals. Important baseline differences were present between treatment groups, particularly regarding baseline eosinophil counts, IgE concentration, disease duration, and OCS exposure. These differences may reflect variation in disease phenotypes and could have influenced treatment persistence independently of the biologic effects of the individual therapies [17-20].

Dupilumab and tezepelumab were excluded due to insufficient long-term follow-up, limiting generalizability to newer biologics. Additionally, relapse was defined according to routine clinical decisions leading to treatment discontinuation or biologic switching. Consequently, treatment persistence may be influenced by organizational, reimbursement-related, or patient-dependent factors and should not be interpreted exclusively as a direct measure of biologic efficacy [11-13,20-22].`

Although the Kaplan-Meier time-to-relapse approach was applied to reduce the methodological impact of the "real-world vanishing patients" phenomenon, censoring in severe asthma cohorts may still be partially informative because treatment discontinuation can result from complex clinical trajectories, including biologic switching, adverse events, or remission. In addition, several subgroup analyses were based on a relatively small number of relapse events, which may have limited the precision and stability of selected Cox regression estimates and should be considered when interpreting subgroup-specific predictors [24,25].

Finally, the study did not include molecular or airway tissue biomarkers, limiting insight into the biological mechanisms associated with long-term treatment persistence. Prospective multicenter studies integrating clinical, molecular, and immunological data are needed to validate the proposed analytical framework and further explore factors associated with long-term biologic treatment persistence in severe asthma [11,17-20,27-29].

Conclusion

The present study provides real-world evidence demonstrating that biologic treatment persistence in severe asthma differs between therapeutic groups. These findings suggest that long-term treatment persistence reflects both treatment effectiveness and the underlying heterogeneity of severe asthma, while also being influenced by patient-related and healthcare-system factors may constitute a useful parameter to describe and compare biological therapies [11-13,20-22,29].

The most original and clinically relevant contribution of the present work is the introduction of the "real-world vanishing patients" concept. We demonstrate that a substantial proportion of treatment failures occurres between scheduled follow-up visits and that conventional fixed follow-up analyses may fail to adequately capture both treatment failures and their exact timing.

Collectively, our results support the concept that biologic treatment persistence may represent a clinically meaningful long-term outcome measure in severe asthma. The proposed methodology may improve interpretation of future real-world evidence studies and contribute to the development of more informative longitudinal outcome measures [11,20,29].

Finally, prospective multicenter studies are needed to validate the proposed analytical framework and determine its potential role in future real-world evaluations of long-term biologic treatment persistence in severe asthma [11,20,29].

Conflict of interest

The authors declare that they have no conflicts of interest related to this work. All authors have completed the ICMJE Disclosure Form and declare that they have no financial or non-financial competing interests that could have influenced the work reported in this manuscript.

Additional information

The statistical analysis was performed by **Dr Alicja Majos, MD, PhD**, Department of Internal Medicine, Asthma and Allergy, Medical University of Lodz, Poland, who is a co-author of this

manuscript. Therefore, the statistical contribution is appropriately reflected in the authorship in accordance with the ICMJE recommendations.

Funding

This research was funded exclusively by the statutory (institutional) funds of the Medical University of Lodz, Poland. No external funding from governmental agencies, commercial entities, or non-profit organizations was received for this study.

Human Ethics and Consent to Participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and applicable national regulations. The study protocol was reviewed by the Bioethics Committee of the Medical University of Lodz, Poland (Resolution No. RNN/58/25/KE, February 11, 2025). The Committee concluded that the project was a retrospective, non-interventional study based on routinely collected clinical data and did not constitute a medical experiment under Polish law; therefore, formal ethics committee approval was not required.

All patient data were fully anonymized prior to analysis, and no interventions beyond routine clinical practice were performed. The study was conducted in accordance with institutional regulations and applicable data protection requirements.

Consent to Publish

Not applicable.

This manuscript does not contain any individual person's data, images, or other information that could identify study participants. All data were analyzed and reported in an anonymized and aggregated form.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available because they contain pseudonymized clinical data that are subject to institutional and legal restrictions regarding patient confidentiality. De-identified data may be made available by the corresponding author upon reasonable request, subject to approval by the participating institutions and applicable data protection regulations.

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Table 1. General study groups characteristics.

	omalizumab				mepolizumab				benralizumab				p
	n	median	min-max	IQR	n	median	min-max	IQR	n	median	min-max	IQR	
EOS [G/L]	44	0.16	0.01-0.69	0.07-0.25	206	0.61	0.19-2.70	0.47-0.84	225	0,59	0.16-2.68	0.44-0.87	<0.001
FEV1%	98	68.50	24.00-124.00	46.00-86.00	205	67.00	20.00-131.00	50.00-77.00	221	64,00	22.00-125.00	52.00-76.00	0.325
ACQ	98	3.40	1.50-5.40	2.70-4.00	206	3.10	1.50-5.40	2.60-3.80	225	3,30	1.60-5.80	2.90-4.00	0.056
OCS dose	98	2.00	0.00-40.00	0.00-5.00	206	1.00	0.00-35.00	0.00-5.00	224	1,10	0.00-60.00	0.00-5.00	0.638
tIgE [IU/ml]	87	248.00	2.00-4463.00	99.00-535.00	68	230.00	1.20-2181.00	79.50-458.50	83	120,00	2.00-2500.00	32.00-331.00	0.002
BMI [kg/m2]	93	28.04	15.57-52.98	24.22-31.64	200	27.35	17.99-46.10	24.49-30.82	212	27,40	15.00-48.89	24.84-32.00	0.647
age at severe asthma diagnosis [years]	98	51.00	18.00-78.00	43.00-61.00	206	57.00	21.00-88.00	48.00-68.00	225	59,00	22.00-92.00	47.00-67.00	<0.001
SA duration [years]	98	18.00	0.00-65.00	10.00-30.00	206	13.00	0.00-71.00	6.00-24.00	224	15,00	0.00-62.00	7.00-27.00	0.032
AER	98	3.00	2.00-9.00	22.00-4.00	206	3.00	2.00-	2.00-3.00	225	3,00	2.00-12.00	2.00-4.00	0.482

			10.00	
	N; %	N; %	N; %	
chronic OCS				0.007
No	N=74; 91.36%	N=171; 83.01%	N=171; 76,00%	
Yes	N=7; 8.64%	N=35; 16.99%	N=54; 24,00%	
sex				0.308
Female	N=67; 68.37%	N=129; 63%	N=156; 69%	
Male	N=31; 32.63%	N=77; 37%	N=69; 31%	
emergency				0.373
No	N-64; 65.32%	N=148; 72%	N=167; 74%	
Yes	N=34; 34.69%	N=58; 28%	N=58; 26%	
mAb number				0.009
1	N=97; 98.98%	N=184; 89%	N=200; 89%	
≥2	N=1; 1.02%	N=22; 11%	N=25; 11%	
life-threatening event				0.269
No	N=86; 87.76%	N=192; 93%	N=203; 90%	
Yes	N=12; 12.24%	N=14; 7%	N=22; 10%	

Abbreviations: mAb – monoclonal antibody; EOS – blood eosinophil count; ACQ – Asthma Control Questionnaire; OCS – oral corticosteroids dose presented as median mg of prednisone per day in last six months; Emergency – asthma-related hospitalization within 6 months preceding baseline; chronic OCS – ongoing oral corticosteroid treatment during the 6 months preceding baseline; AER – annual asthma exacerbation rate; mAb number indicates whether the biologic was first-line (1) or subsequent (≥2) therapy; min-max – minimum-maximum; IQR – interquartile range. Post-hoc tests are presented in Supplementary Table S1. EOS, FEV1%, OCS dose, tIgE, BMI, ACQ, chronic OCS refers to their baseline values (at the qualification for mAb therapy).

Table 2. Univariate Cox proportional hazard regression analysis of predictors of biologic treatment persistence in the overall study population.

Variable	Effect level	P	HR	HR 95%CI
EOS [G/L]		0.034	0.432	0.199-0.938
FEV1%		0.043	0.988	0.977-1.000
ACQ		0.008	1.416	1.096-1,828
OCS dose		0.635	1.007	0.980-1.034
tIgE [IU/ml]		0.512	1.000	0.999-1.001
BMI [kg/m2]		0.441	0.982	0.939-1.028
age at severe asthma diagnosis [years]		0.345	0.992	0.976-1.008
SA duration [years]		0.081	1.013	0.998-1.027
AER		0.592	1.034	0.915-1.170
chronic OCS	No (vs Yes)	0.899	0.965	0.556-1.674
sex	Female (vs Male)	0.629	1.122	0.703-1.790
emergency	Yes (vs No)	0.988	1.365	0.863-2.159
mAb number	1 (vs ≥2)	0.530	0.800	0.400-1.603
Life-threatening event	No (vs Yes)	0.036	0.529	0.292-0.958
Biologic therapy	omalizumab (vs benralizumab)	0.054	1.225	0,727-2,063
Biologic therapy	mepolizumab (vs benralizumab)	0.007	0.446	0,249 - 0,799

Abbreviations: mAb – monoclonal antibody; EOS – blood eosinophil count; ACQ – Asthma Control Questionnaire; OCS – oral corticosteroids dose presented as median mg of prednisone per day in last six months; Emergency – asthma-related hospitalization within 6 months preceding baseline; chronic OCS – ongoing oral corticosteroid treatment during the 6 months preceding baseline; AER – annual asthma exacerbation rate; mAb number indicates whether the biologic was first-line (1) or subsequent (≥2) therapy; min-max – minimum-maximum; IQR – interquartile range. HR – hazard ratio; CI – confidence interval. EOS, FEV1%, OCS dose,

tIgE, BMI, ACQ, chronic OCS refers to their baseline values (at the qualification for mAb therapy).

Fig. 1. Flowchart of patient selection and study population derivation.

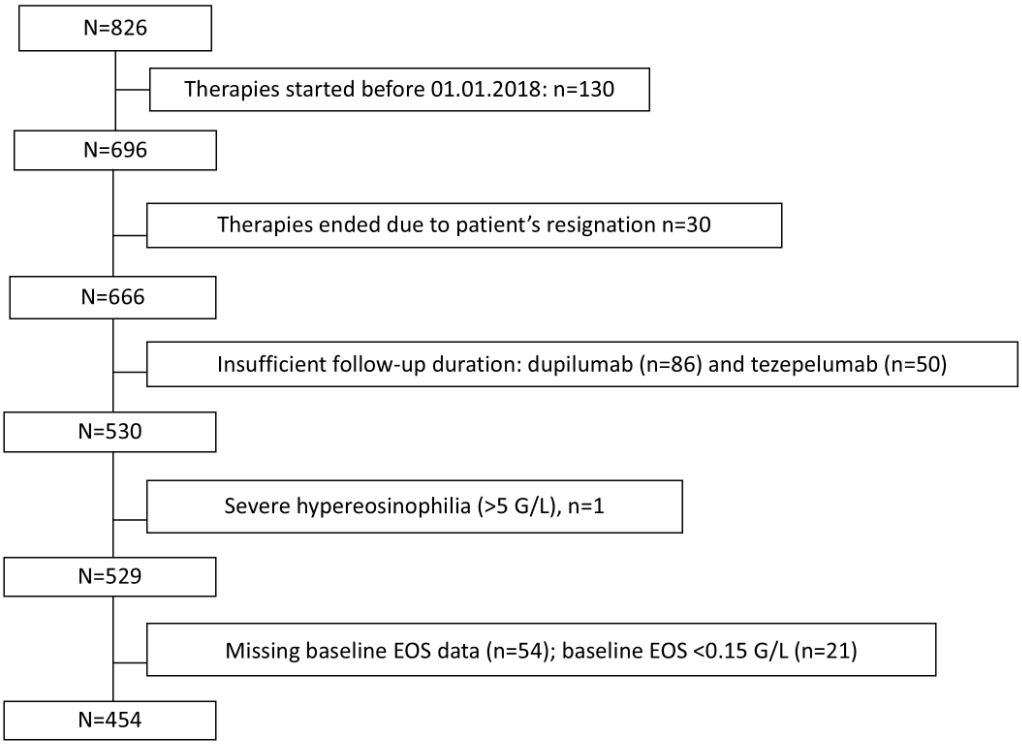


Fig. 2. Distribution of treatment relapses during follow-up and illustration of the "real-world vanishing patient" phenomenon. The figure presents ACQ (median, minimum-maximum) at the follow-up visits distribution (at 6 months, 12 months, and annually thereafter) in time-to-relapse context – despite relapses, mean ACQ does not change significantly.

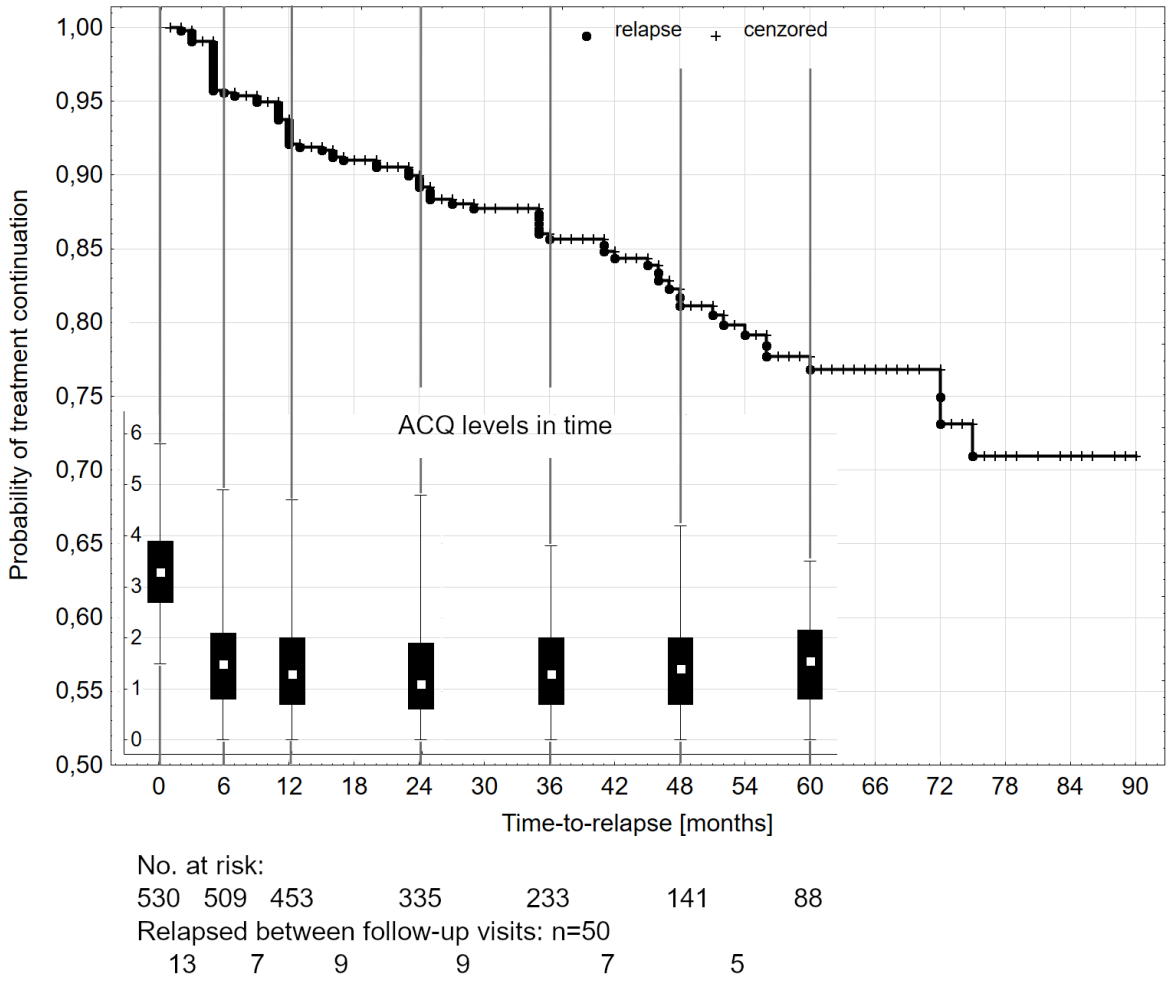
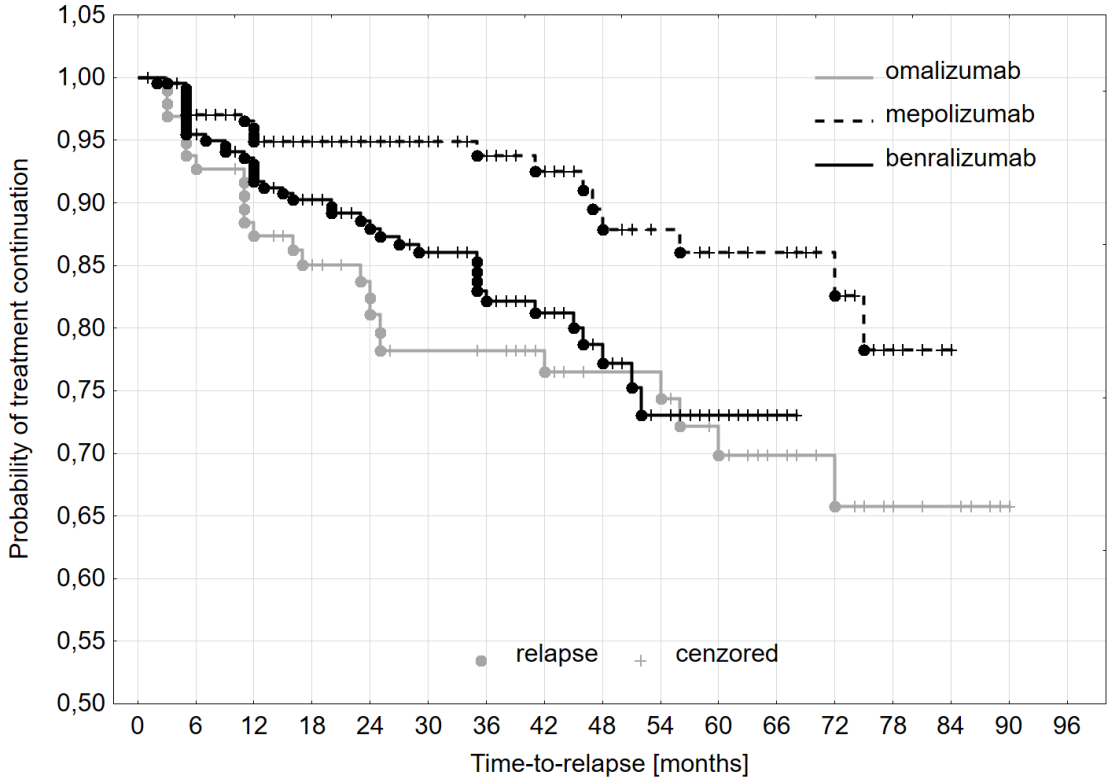


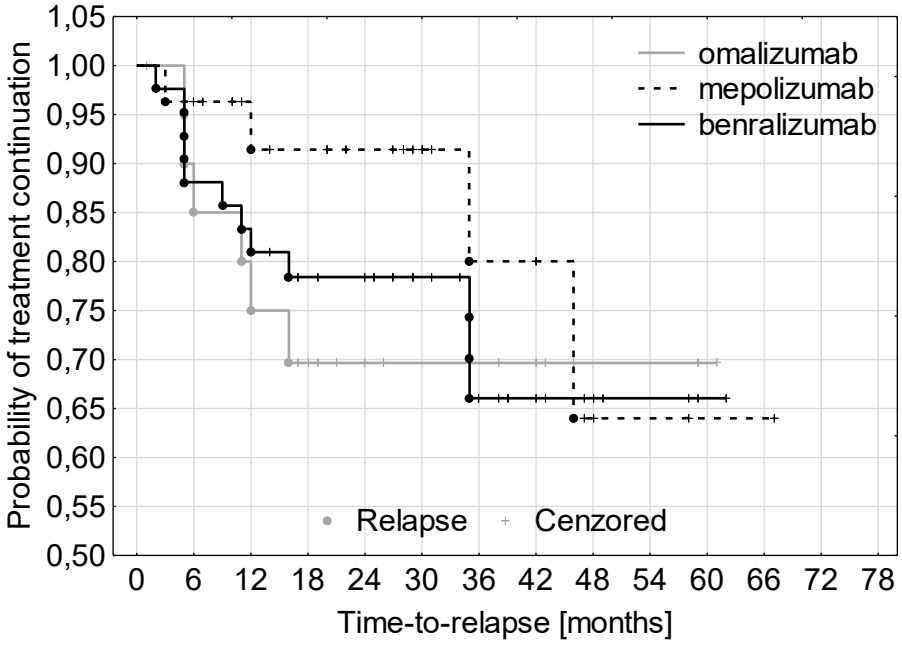
Figure 3. Kaplan-Meier analysis of time-to-relapse according to biologic therapy. Treatment persistence differed significantly between omalizumab, mepolizumab, and benralizumab (respectively, n=98; n=206 and n=225; p = 0.003).



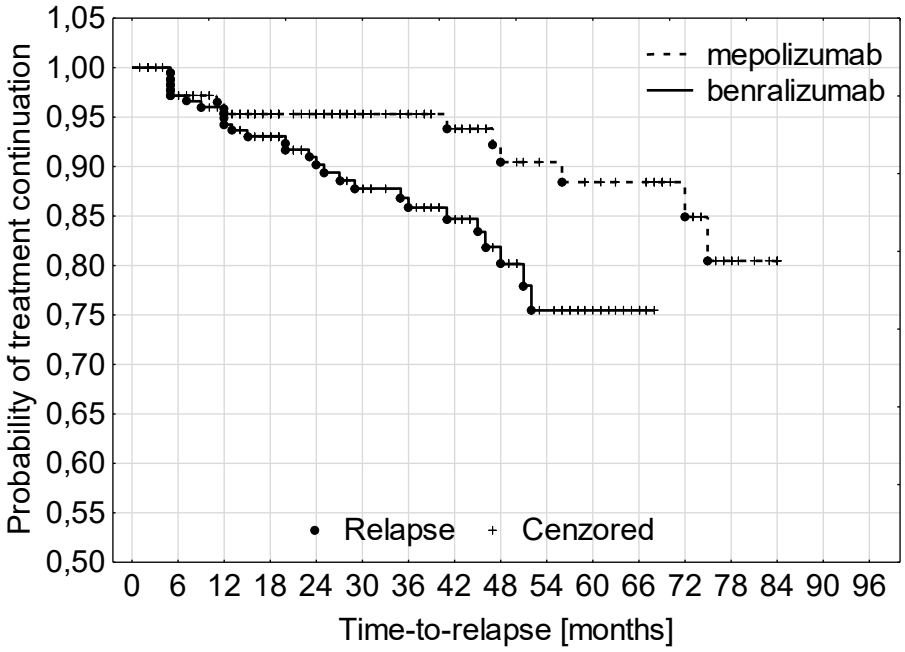
No. at risk:							
omalizumab	98	89	79	57	51	37	29
mepolizumab	206	192	170	118	81	56	41
benralizumab	225	206	193	141	96	48	15

Fig. 4. Kaplan-Meier analysis of biologic treatment persistence according to baseline blood eosinophil count (population with known and comparable baseline blood eosinophilia, n = 454). A. patients with baseline blood eosinophilia 0.15-0.40 G/l. B. patients with baseline blood eosinophilia >0.40 G/l. Differences between treatment groups were not significant in patients with eosinophilia 0.15–0.40 G/L (p = 0.301), whereas significant separation of curves was observed in patients with eosinophilia >0.40 G/L (p = 0.049).

A.



B.



Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- V3.2Supplementary.RealWorldEvidenceBeyondFixedFollowUpAnalysis.docx