ANNALS OF MEDICINE
2024, VOL. 56, NO. 1, 2317356
https://doi.org/10.1080/07853890.2024.2317356

RESEARCH ARTICLE

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Clinical characteristics of complete responders versus non-complete responders to omalizumab, benralizumab and mepolizumab in patients with severe asthma: a long-term retrospective analysis

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ABSTRACT

Background: Some patients with severe asthma may benefit from treatment with biologics, but evidence has been mostly collected from randomized controlled trials (RCTs), in which patients' characteristics are different from those encountered in asthma patients in the real-world setting. The aim of this study was to describe the clinical features of complete responders versus non-complete responders to long-term treatment with biologics in patients with severe asthma attended in routine daily practice.

Methods: Data of a cohort of 90 patients with severe asthma who were treated with biologics (omalizumab, benralizumab, and mepolizumab) for at least 12 months and were followed up to March 2022. Data recorded included clinical characteristics and effectiveness of treatment (exacerbation, Asthma Control Test [ACT] score, lung function, use of maintenance oral corticosteroids [mOCS]), FeNO, and blood eosinophils at baseline, at 12 months, and at the end of follow-up. Complete response is considered if, in addition to not presenting exacerbations or the use of mOCS, the ACT score was >20 and, the FEV_1 >80% predicted.

Results: An improvement in all asthma control parameters was observed after 12 months of treatment and a mean follow-up of 55 months. After 12 months of treatment 27.2% of patients met the criteria of complete response and this percentage even increased to 35.3% at the end of follow-up. Long-term complete response was associated to better lung function with mepolizumab and omalizumab treatment and to less previous exacerbations in the benralizumab group. The main cause of not achieving a complete response was the persistence of an airflow obstructive pattern.

Conclusions: This study shows that omalizumab, benralizumab, and mepolizumab improved the clinical outcomes of patients with severe asthma in a clinic environment with similar effect sizes to RCTs in the long term follow-up. Airflow obstruction, however, was a predictor of a non-complete response to biologics.

KEY MESSAGES

- Treatment with anti-IgE and anti-IL-5 biologics significantly improved clinical outcomes in severe asthma patients.
- The rate of complete responders of 27.2% at 12 months even increased to 35.3% at the end of a mean follow-up of 55 months.
- The persistence of an airflow obstructive pattern was the main cause of the failure to achieve complete response.

ARTICLE HISTORY

Received 23 August 2023
Revised 21 January 2024
Accepted 6 February 2024

KEYWORDS

Severe asthma; biologics; omalizumab; benralizumab; mepolizumab; retrospective analysis

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Introduction

Severe uncontrolled asthma is defined as asthma that is poorly controlled despite adherence with optimized treatment with high-dose inhaled corticosteroids combined with long-acting β_2-agonists and/or other controller medication in the previous year, or with oral glucocorticoids for at least 6 months over the same period. Uncontrolled asthma is defined as at least one of the following: poor symptom control, frequent severe exacerbations, serious exacerbations, and airflow limitation [1]. In a study carried out in pneumology and allergy units in Spain, the prevalence of uncontrolled severe persistent asthma according to clinical judgement was 3.9% [2], but the prevalence would be higher based on definitions of clinical guidelines [1].

Asthma is a common heterogeneous complex disease in both children and adults. Phenotypic heterogeneity is a feature of severe asthma and multiple clinical phenotypes have been described, including subtyping asthma based on methods such as unsupervised clustering approaches [3–5]. Type 2-high eosinophilic airway inflammation is present in around 50% of adults with asthma, but corticosteroid withdrawal studies often reveal eosinophilic airway inflammation suggesting that its prevalence might be underestimated [6]. Atopy is present in 50–60% of adults and children with asthma, although it is more common among children and adults with severe asthma and childhood-onset versus late-onset disease [7,8]. On the other hand, non-eosinophilic asthma has been described in adults and children but is poorly understood [9]. The allergic-dependent and allergic-independent mechanisms that drive eosinophilic inflammation and non-eosinophilic asthma often co-exist, leading to mixed granulocytic inflammation or changes in the inflammatory profile over time.

The goal of asthma treatment is to achieve good asthma control and to minimize symptom burden and the risk of exacerbations. Anti-inflammatory and bronchodilator treatments are the mainstay of asthma management and are used in a stepwise approach. Pharmacological treatment is based on a cycle of assessment and re-evaluation of symptom control, risk factors, comorbidities, side-effects, and patient satisfaction by means of shared decisions [10]. In severe asthma, the concept of phenotype-specific interventions toward precision medicine is increasingly important, with a need to optimize the balance between safety, efficacy, and cost for each therapeutic option. Indeed, new biological therapies for the treatment of severe asthma, combined with advancements in biomarkers, have opened up exciting opportunities for more targeted and personalized interventions. Five biologicals have been approved so far for the treatment of severe eosinophilic asthma. In a systematic review of the efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab, and reslizumab) for severe eosinophilic asthma, there was high certainty that all approved biologicals reduce the rate of severe asthma exacerbations and for benralizumab, dupilumab and mepolizumab for reducing oral corticosteroids [11]. All evaluated biologicals probably improve asthma control, health-related quality of life, and forced expiratory volume in one second (FEV_1) [11].

One of the main current questions in the treatment of severe uncontrolled type 2-high eosinophilic asthma is to assess whether the efficacy of these biological agents demonstrated in the controlled settings of pivotal trials persists in routine clinical practice, where patients may have more diverse characteristics, and to determine the baseline characteristics associated with response to treatment with biologics. In the last two years, numerous studies in real-world settings included in a systematic review and meta-analysis reported by Charles et al. [12] and in a comprehensive narrative review of Nagase et al. [13] have provided robust evidence of the effectiveness and safety of omalizumab, benralizumab, mepolizumab, and reslizumab in daily practice, confirming the results obtained in pivotal clinical trials. These data showed real-life effectiveness across racial and social backgrounds in different countries [12,13]. In the case of omalizumab, available since 2008, there is evidence that its effectiveness is maintained in the long-term (approximately 5 years) resulting in continued benefit in terms of improved symptoms control and reduced risk of exacerbations [14]. Recently, in the International Congress 2023 of the European Respiratory Society, Riccardi et al. [15] presented a head-to-head comparison between biologics in a real-world study of 104 patients over a maximum of 4 years of biologic therapy. This study showed nocturnal awakenings reduction in benralizumab vs. omalizumab/mepolizumab, increase in Delta FVC % post-bronchodilation in dupilumab vs. other biologics, and reduction of neutrophils in benralizumab/dupilumab vs. omalizumab, with all differences being statistically significant. However, more data from head-to-head comparisons of biologics in patients with severe asthma are needed. On the other hand, different questions regarding the characteristics of responders and non-responders, predictors of response, implications for efficacy such as whether a complete response may be expected in all patients and when it appears whether it is maintained in the long-term, and

residual disease after blocking the T2 pathway are still matters of debate.

The aim of this study was to describe the clinical features of complete responders versus non-complete responders to long-term treatment with omalizumab, benralizumab, and mepolizumab in patients with severe asthma attended in a real-world setting.

Methods

Design and participants

This was a single-center retrospective study of adult patients with severe asthma attended at the Severe Asthma Unit of an acute tertiary care hospital in Badalona (Barcelona, Spain) who started treatment with biologics, having maintained it for at least 6 months and with a follow-up of at least 12 months after the initiation of treatment. In March 2022, a review of the electronic medical records database of the Severe Asthma Unit was performed in order to select the study population. Eligible criteria were 18 years of age or older, diagnosis of severe asthma according to guidelines of the Global Initiative for Asthma (GINA) [16] established at least 1 year before inclusion in the study, and having being followed regularly at the Severe Asthma Unit at minimum intervals of every 6 months, and for 12 months before indication of treatment with biologics. Treatment with biological agents had been indicated by the specialist in charge in patients with severe asthma requiring treatment with high dose inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy.

The study was approved by the Clinical Research Ethics Committee of Hospital Universitari Germans Trias i Pujol (Badalona, Spain) (code As-Biol-2022-01 [PI-22-293], approval January 13, 2023). Written informed consent had been obtained from all participants when they had been initially attended at the Severe Asthma Unit.

Study procedures

Data were retrospectively collected from the patients' medical records. We assessed outcomes in all patients with severe asthma under ongoing treatment with biologics at our specialized Severe Asthma Unit in March 2022. Data at three time points were recorded: baseline (visit 0) before starting treatment with biologics, at 12 months after initiation of biological therapy (visit 1), and at the last follow-up assessment in March 2022 (visit 3). Study variables included age, gender, bio-naïve or switch to another biological agent, atopy (defined by a positive prick test), comorbidities, smoking status, duration of biological treatment, serum total IgE level, peripheral blood eosinophil count, exacerbations, the Asthma Control Test (ACT) score [17] (an ACT score ≥20 indicates well-controlled asthma), lung function, fractional exhaled nitric oxide (FeNO), and use of systemic corticosteroids. Clinical response to treatment was defined as ≥50% reduction in the annualized exacerbation rate or in maintenance oral corticosteroids (mOCS) and super response as zero exacerbations and no mOCS for asthma [18]. A complete response was considered if, in addition to not presenting exacerbations or the use of corticosteroids, the patient had an ACT score >20 and an FEV_1 > 80% predicted according to the consensus document of the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) [19]. Complete response was also defined according to these criteria considering an increase in FEV_1 ><200 mL instead of an FEV_1 >80% predicted. Exacerbation was defined according to ATS/ERS criteria [1] as acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing, and chest tightness, or some combination of these symptoms that require the use of systemic corticosteroids (tablets, suspension, or injection), or an increase from a stable maintenance dose, for at least 3 days or a hospitalization or emergency department visit because of asthma, requiring systemic corticosteroids.

Standards indications for each biologic according to the 2023 Spanish Guideline on the Management of Asthma [20] are as follows: (1) Omalizumab: severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to perennial aeroallergens and with reduced lung function (FEV_1 < 80%) as well as frequent symptoms during the day or awakenings at night and who have had multiple documented severe asthma exacerbations, despite using daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist and a total IgE between 70 and 1500 KU/L; and (2) Benralizumab and mepolizumab: uncontrolled severe asthma with an eosinophilic phenotype. The predictive biomarker which has showed a higher efficacy has been an eosinophilia >150 eosinophils/μL in peripheral blood and a determination of >300 eosinophils/μL in any moment of the last 12 months.

Statistical analysis

Categorical variables are expressed as frequencies and percentages, and continuous variables as mean and standard deviation (SD). The chi-square test of the Fisher's

exact test were used for the comparison of categorical variables, and the Student's *t* test, the Wilcoxon signed-rank test, the Mann-Whitney *U* test, the Kruskal-Wallis test or the analysis of variance (ANOVA) were used for the comparison of continuous variables according to conditions of application. A logistic regression analysis was performed to assess independent variables significantly associated with complete response to each individual biological agent at the end of follow-up. Odds ratio, 95% confidence intervals (CI) and the area under the receiver operating characteristics (ROC) curves (AUC) were calculated. Statistical significance was set at $p < .05$. The Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM Corporate, Armonk, NY, USA) was used for the analysis of data.

Results

Study patients and baseline data

A total of 97 adult patients diagnosed with severe asthma met the inclusion criteria and were treated with biologics. However, 7 patients were excluded, 4 of them treated with dupilumab because the treatment duration was less than 6 months, and 3 treated with reslizumab due to being a very small number of patients and not comparable with the other groups. Therefore, the study population included 90 patients, 44 of which received omalizumab, 24 benralizumab, and 22 mepolizumab. The mean follow-up was 55 months (omalizumab 86 months, benralizumab 22 months, mepolizumab 27 months).

The baseline characteristics of all patients and grouped according to the administered biological agent are shown in Table 1. A total of 73.3% of patients were women, with a mean age of 55.3 years. Also, 17.8% of patients were on mOCS, with a mean daily dose of 2.39 mg (and wide SD of 8.5 mg/day), the mean ACT score was 14.4, FEV_1 67.1% predicted, and had suffered from an average of 3.43 asthma exacerbation episodes in the previous year. The mean blood eosinophil count was 607 cells/μL, total serum IgE 495 kU/L, and FeNO 48.5 ppb. FeNO was measured in 63 patients (70%), 29 (65.9%) in the omalizumab group, 19 (79.2%) in the benralizumab group, and 15 (68.2%) in the mepolizumab group. Eighty patients were bio-naïve and 10 (11.1%) switched therapy.

In the comparison of baseline data between the three biological agents, there were statistically significant differences between patients treated with omalizumab and those treated with either benralizumab or mepolizumab (Table 1). Omalizumab-treated patients were significantly younger, with longer duration of disease, higher percentages of food allergy and family history of atopy, higher total IgE values, lower ACT score, higher mean FEV_1, and less treatment switching.

Clinical and complete response at 12 months

Clinical response after 12 months of treatment with biologics was evaluated in 87 patients as 3 patients (benralizumab, $n = 2$; mepolizumab, $n = 1$) were excluded because a duration of treatment of at least 12 months was not achieved. In the overall study population, there were statistically significant improvements in all parameters as compared with baseline (Table 2). The anti-IL-5 compounds benralizumab and mepolizumab produced a significant decrease of blood eosinophils, which was not observed in the omalizumab group. The significant decrease in FeNO values observed in the overall study population was not maintained in any of the biologics groups, but all remaining improvements found in the remaining variables in the overall study patients were also found in each group of biologics except for the use of mOCS (Table 2).

Complete response based on the SEPAR criteria [15] at 12 months was analyzed in 81 patients (omalizumab, $n = 41$; benralizumab, $n = 19$; mepolizumab, $n = 19$). In the remaining 9 patients, the duration of treatment was less than 12 months in 3, and data of some variables recorded at baseline could not be retrieved at 12 months in 6. Complete response was achieved in 22 patients, with a rate of 27,2%. The rates of complete response in the groups of biologics were 34.1% in the omalizumab group (14 patients), 10.5% in the benralizumab group (2 patients), and 31.6% in the mepolizumab group (6 patients). In the evaluation of complete vs. non-complete responders at 12 months of follow-up (Table 3), complete responders showed a lower blood eosinophil count (293 [262] vs. 664 [1147] cells/μL; $p = .001$) and higher FEV_1 (2.35 [0.97] vs. 1.81 [0.66] L; $p = .028$). Statistically significant differences between complete responders and non-responders were also found in FEV_1 L values in the omalizumab group, blood eosinophil count in the benralizumab group, and FEV_1% in the mepolizumab group.

When the criterion of an increase of $FEV_1 > 200$ mL was also considered, the rates of complete responders were 46.8% in the overall study population, 51.2% in the omalizumab group, and 42.1% in both the benralizumab and mepolizumab groups.

Clinical and complete response at the end of follow-up

Clinical response at the end of follow-up was evaluated in the entire study population of 90 patients (omalizumab 44, benralizumab 24, and mepolizumab 22). All

Table 1. Baseline data of the overall study population and according to biological agent.

Variables	All patients ($n=90$)	Biological agent: Omalizumab ($n=44$)	Benralizumab ($n=24$)	Mepolizumab ($n=22$)	p value
Women, *n* (%)	66 (73.3)	31 (70.5)	16 (66.7)	19 (86.4	.267
Age, years, mean (SD)	55.3 (15.0)	49.5 (20.0)	63.8 (11.0)	58.1 (12.5)	.001
Age at diagnosis, years, mean (SD)	50.7 (16.5)	42.4 (16.4)	61.3 (11.2)	55.9 (11.8)	<.001
Duration of treatment, months, mean (SD)	55 (49.3)	86.6 (53.2)	22.1 (11.4)	27.7 (16.1)	<.001
Obesity, BMI ≥ 30 kg/m^2, *n* (%)	6 (6.7)	2 (4.5)	4 (16.7)	0	.057
Never smokers, *n* (%)	68 (75.6)	11 (25.0)	6 (25.0)	5 (22.7)	.856
Rhinosinusitis, *n* (%)	25 (27.8)	15 (34.1)	3 (12.5)	7 (31.8)	.146
Nasal polyposis, *n* (%)	23 (25.6)	10 (22.7)	6 (25.0)	7 (31.8)	.725
Bronchiectasis, *n* (%)	19 (21.1)	9 (20.5)	4 (16.7)	6 (27.3)	.671
Anxiety, *n* (%)	21 (23.3)	10 (22.7)	6 (25.0)	5 (22.7)	.970
Food allergy, *n* (%)	10 (11.1)	8 (18.2)	1 (4.2)	0	.036
Atopic dermatitis, *n* (%)	3 (3.3)	2 (4.5)	1 (4.2)	0	.603
Family history of atopy, *n* (%)	59 (65.6)	42 (95.5)	11 (45.8)	6 (27.3)	<.001
Gastroesophageal reflux disease, *n* (%)	13 (14.4)	4 (9.1)	3 (12.5)	6 (27.3)	.134
Obstructive sleep apnea, *n* (%)	12 (13.3)	5 (11.4)	5 (20.8)	2 (9.1)	.436
Aspirin-exacerbated respiratory disease, *n* (%)	10 (11.1)	4 (9.1)	3 (12.5)	3 (13.6)	.831
Eosinophilic granulomatosis with polyangiitis, *n* (%)	5 (5.5)	0	2 (8.3)	3 (13.6)	.058
Allergic bronchopulmonary aspergillosis, *n* (%)	5 (5.5)	4 (9.1)	1 (4.2)	0	.351
Blood eosinophil count, cells/μL, mean (SD)	607 (1058)	669 (1507)	596 (404)	506 (404)	.845
FeNO, ppb, mean (SD)	48.5 (46.2)	44.6 (45.0)	48.1 (58.0)	56.6 (31.0)	.721
Total serum IgE, kU/L, mean (SD)	495 (724)	713 (899)	329 (419)	239 (401)	.026
Systemic oral corticosteroids, mg, mean (SD)	2.39 (8.5)	1.30 (6.1)	4.59 (13.0)	2.27 (5.0)	.329
Systemic oral corticosteroids, *n* (%)	16 (17.8)	4 (9.1)	6 (25.0)	6 (27.3)	.106
Exacerbations in the previous year, mean (SD)	3.43 (2.63)	3.75 (3.1)	3.25 (1.98)	3 (2.2)	.513
ACT score, mean (SD)	14.4 (5.4)	12.4 (4.9)	17 (5.2)	14.4 (5.3)	.001
FVC, %, mean (SD)	77.6 (17)	75.7 (17)	74.7 (15.5)	84.1 (31)	.129
FEV_1, L, mean (SD)	1.96 (0.76)	2.17 (0.91)	1.68 (0.54)	1.90 (0.51)	.039
FEV_1, %, mean (SD)	67.1 (25.6)	66.6 (23.5)	63.1 (20.7)	72.4 (18.3)	.346
Biologic switch, *n* (%)	10 (11.1)	1 (2.3)	5 (20.8)	4 (18.2)	.013

SD: standard deviation; BMI: body mass index; FeNO: fractional exhaled nitric oxide; ACT: Asthma Control Test; FVC: forced vital capacity; FVE_1: forced expiratory volume in one second.

Table 2. Clinical response at 12 months of follow-up.

	All study patients ($n=87$)			Omalizumab ($n=44$)			Benralizumab ($n=22$)			Mepolizumab ($n=21$)		
Variables	Baseline	12 months	p value	Baseline	12 months	p value	Baseline	12 months	p value	Baseline	12 months	p value
Blood eosinophils, cells/μL, mean (SD)	648 (1126)	132 (179)	<.001	735 (1625)	236 (214)	.078	628 (416)	48 (22)	<.001	506 (248)	83 (69)	<.001
FeNO, ppb, mean (SD)	49 (47)	36 (36)	.040	44 (45)	36 (44)	.387	53 (61)	29 (32)	.176	57 (33)	43 (24)	.122
FVC, %, mean (SD)	77 (18)	88 (14)	<.001	75.7 (7.3)	85.7 (17)	<.001	74 (16.5)	89.2 (12)	<.001	81.8 (19)	91.7 (14)	<.001
FEV_1, %, mean (SD)	66.6 (22)	77.5 (19)	<.001	66.7 (23.5)	76 (19)	<.001	61 (20)	76-7 (19)	<.001	69.5 (18)	79.6 (18)	<.001
FEV_1, L, mean (SD)	1.97 (0.78)	2.23 (0.78)	<.001	2.17 (0.9)	2.39 (0.86)	.001	1.67 (0.6)	2.08 (0.7)	.004	1.81 (0.49)	2.04 (0.5)	.012
FEV_1 < 80% predicted, % patients	74.4	53.8	<.001	70	57.5	.180	89.5	68.4	.125	68.4	31.6	.016
Exacerbations over 1 year, mean (SD)	3.4 (2.6)	0.29 (0.87)	<.001	3.75 (3.1)	0.23 (0.57)	<.001	3.09 (1.9)	0.36 (0.85)	<.001	3.05 (2.27)	0.33 (0.73)	<.001
No exacerbations, % patients	16.1	82.8	<.001	15.9	84.1	<.001	13.6	81.8	< .001	19	81	<.001
OCS, mg/day, mean (SD)	2.47 (8.6)	0.26 (0.96)	<.001	1.3 (6.2)	0.14 (0.67)	.219	5.02 (14)	0.12 (0.55)	.131	2.38 (5)	0.67 (1.6)	.059
OCS, % patients	18.4	6.9	.006	9.1	4.5	.625	27.3	4.5	.063	28.6	14.3	.250
ACT score, mean (SD)	13.9 (5.3)	21.7 (4.7)	<.001	12.3 (5.0)	21.3 (5)	<.001	16.7 (5)	22.1 (4.3)	.006	13.9 (5)	21.9 (4.6)	<.001
ACT score >20, % patients	17.2	73.4	<.001	7.1	75	<.001	33.3	72.2	.016	16.7	72.2	.002

SD: standard deviation; FeNO: fractional exhaled nitric oxide; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; OCS: oral corticosteroids; ACT: Asthma Control Test.

patients in the study had remained on the same original biologics throughout the follow-up period. As shown in Table 3, there was a statistically significant improvement in blood eosinophils, FeNO, pulmonary function, reduction of exacerbations and mOCS, as well as better control of asthma. In the analysis of clinical response in the different groups of biologics, significant decreases in blood eosinophilia were found in the groups of the anti-IL-5 drugs, improvement in pulmonary function in all groups except in mepolizumab-treated patients, decreases in FeNO in the omalizumab group only, and reductions in the rate of exacerbations and improvement in the control of asthma in all three groups of biologics (Table 4).

Complete response based on the SEPAR criteria [15] at the end of follow-up was analyzed in 85 patients

Table 3. Complete response (FEV_1 > 80%) at 12 months of follow-up (visit 2) and related factors.

	All study patients ($n = 79$)			Omalizumab ($n = 41$)			Benralizumab ($n = 19$)			Mepolizumab ($n = 19$)		
Variables	Non-responders	Responders	*p* value	Non-responders	Responders	*p* value	Non-responders	Responders	*p* value	Non-responders	Responders	*p* value
Blood eosinophils, cells/μL, mean (SD)	664 (1147)	293 (262)	.001	713 (1647)	270 (319)	.058	670 (372)	150 (212)	**.044**	530 (266)	390 (125)	.371
FeNO, ppb, mean (SD)	52 (49)	49 (41)	.892	47.6 (47)	46.9 (50)	.617	55.3 (62)	13 (13)	.232	54.3 (33)	58.3 (12)	.624
FVC, %, mean (SD)	74.9 (18)	83.2 (17)	.060	73.3 (18)	83.5 (14)	.090	74.4 (15)	79.5 (33)	.894	78.8 (19)	88.3 (18)	.357
FEV_1, %, mean (SD)	63.5 (21)	73.5 (21)	.064	64.3 (25)	74.1 (20)	.219	61.3 (19)	58 (38)	1	63.9 (16))	81. 7(17)	**.035**
FEV_1, L, mean (SD)	1.81 (0.66)	2.35 (0.97)	.028	1.97 (0.77)	2.73 (1.1)	**.033**	1.65 (0.59)	1.58 (0.4)	.690	1.66 (0.38)	2.11 (0.57)	.075
Exacerbations over 1 year, mean (SD)	3.4 (2.7)	3.6 (2.7)	.802	3.9 (3.3)	3.6 (2.9)	.890	3.4 (1.8)	3 (1.4)	.733	2.5 (1.9)	3.9 (2.8)	.081
No exacerbations, % patients	16.1	13	.733	18.5	14.3	.733	5.9	0	.725	30.8	0	.126
OCS, mg/day, mean (SD)	2.37 (7.2)	3.22 (12.6)	.523	2.11 (7.8)	0	.135	2.3 (9.4)	30 (42)	.210	3.54 (6.2)	0.67 (1.6)	.416
OCS, % patients	21.4	13	.388	14.8	0	.130	23.5	50	.421	38.5	16.7	.342
ACT score, mean (SD)	14.4 (5.7)	13.1 (4.6)	.512	12.5 (5.2)	11.8 (4.8)	.809	16.9 (5.5)	14.5 (6.3)	.502	14.2 (5.6)	14.2 (4.1)	.959
ACT score > 20, % patients	22.2	5.9	.133	10.5	0	.312	40	0	.266	16.7	20	.870
Age, years, mean (SD)	56.6 (15.9)	50.8 (15.3)	.188	51.1 (17)	44.6 (15)	.322	64.6 (11)	64.5 (8)	.947	57.1 (14.1)	60.5 (11.1)	.598
Women, %	76.8	65.2	.290	77.8	57.1	.168	64.7	50	.683	92.3	83.3	.554
Treatment duration, months, mean (SD)	54.2 (48)	61.1 (51.2)	.493	83.5 (54)	83.7 (54)	.891	24.1 (10)	15 (4)	.206	32.9 (17)	24.8 (9.6)	.404
Age at diagnosis, years, mean (SD)	52.1 (16.7)	45.8 (16.6)	.102	44.1 (17)	37.8 (15)	.187	62.6 (12)	63(8)	.894	54.6 (14.3)	58.8 (12.1)	.568
Rhinosinusitis, % patients	23.2	39.1	.152	25.9	42.9	.269	6	50	.054	38.5	33.3	.829
Nasal polyposis, % patients	25	34.8	.378	22.2	28.6	.653	29.4	50	.554	23.1	50	.241
AERD, % patients	14.3	8.7	.497	11.1	7.1	.685	17.6	0	.517	15.4	16.7	.943
EGPA, number/total patients	2/56	3/23	.116	0/27	0/14		1/17	1/2		2/13	1/6	.943
ABPA, number/total patients	3/56	2/23	.580	2/27	2/14	.877	1/17	0/2	1	0/13	0/6	.381
Bronchiectasis, % patients	25	8.7	.101	25.9	7.1	.150	17.6	0	.517	30.8	16.7	.516
Anxiety, % patients	23.2	13	.307	25.9	7.1	.150	23.5	0	.440	23.1	16.7	.750
Obstructive sleep apnea, % patients	12.5	17.4	.568	11.1	14.3	.768	17.6	50	.288	7.7	16.7	.554
Obesity BMI ≥30 kg/m^2, % patients	7.1	4.3	.643	3.7	0	.659	17.6	50	.386	0	0	1
GERD, % patients	12.5	26.1	.139	7.4	14.3	.482	11.8	50	.161	23.1	50	.241
Never-smokers, % patients	73.2	78.3	.764	70.4	78.6	.712	70.6	100	.372	84.6	66.7	.372
Food allergy, % patients	10.7	13	.767	18.5	21.4	.824	5.9	0	.725	0	0	1
Atopic dermatitis, % patients	3.6	4.3	.870	3.7	7.1	.628	5.9	0	.725	0	0	1
Atopia, % patients	62.5	69.6	.551	92.6	100	.296	35.3	0	.310	30.8	33.3	.911
Bologic switch, number/total patients	7/56	1/23	.460	1/27	0/14	.466	3/17	0/2	.517	3/13	1/6	.533
Total serum IgE, kU/L, mean (SD)	482 (791)	474 (590)	.410	847 (1160)	555 (600)	.163	308 (290)	176 (318)	.081	281 (502)	182 (152)	.726

SD: standard deviation; FeNO: fractional exhaled nitric oxide; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; OCS: oral corticosteroids; ACT: Asthma Control Test; AERD: aspirin-exacerbated respiratory disease; EGPA: eosinophilic granulomatosis with polyangiitis; ABPA: allergic bronchopulmonary aspergillosis; GERD: gastroesophageal reflux disease.

Table 4. Clinical response at the end of follow-up.

	All study patients ($n=90$)			Omalizumab ($n=44$)			Benralizumab ($n=24$)			Mepolizumab ($n=22$)		
Variables	Baseline	End of follow-up	p value	Baseline	End of follow-up	p value	Baseline	End of follow-up	p value	Baseline	End of follow-up	p value
Blood eosinophils, cells/μL, mean (SD)	647 (1168)	127 (139)	<.001	733 (1642)	214 (128)	.072	626 (444)	53 (23)	<.001	502 (253)	91.2 (120)	<.001
FeNO, ppb, mean (SD)	49 (47)	33 (33)	.012	44.4 (46)	25.8 (29)	.005	50.6 (58)	36.5 (43)	.448	58 (33)	42 (19)	.091
FVC, %, mean (SD)	77.5 (17)	89.6 (15)	<.001	75.7 (17)	89.3 (13)	<.001	74.3 (16)	91.8 (18)	<.001	84.5 (18.5)	87.5 (16)	.300
FEV_1, %, mean (SD)	66.7 (22)	77.2 (20)	<.001	66.6 (23)	78.8 (18.9)	<.001	62.3 (21)	78.1 (22)	<.001	71.8 (18.5)	73.2 (21)	.627
FEV_1, L, mean (SD)	1.95 (0.77)	2.18 (0.85)	<.001	2.17 (0.91)	2.41 (0.96)	<.001	1.68 (0.54)	2.1 (0.7)	.001	1.78 (0.47)	1.80 (0.80)	.903
FEV_1 < 80% predicted, % patients	72.8	50.6	<.001	70	50	.021	86.4	59.1	.031	63.2	42.1	.125
Exacerbations over 1 year, mean (SD)	3.43 (2.6)	0.33 (0.79)	<.001	3.75 (3.1)	0.39 (0.89)	<.001	3.25 (1.98)	0.25 (0.73)	<.001	3 (2.2)	0.32 (0.6)	<.001
No exacerbations, % patients	15.6	81.1	<.001	15.9	79.5	.008	12.5	87.5	<.001	18.2	77.3	.001
OCS, mg/day, mean (SD)	2.39 (8.5)	0.12 (0.6)	.014	1.3 (6)	0.14 (0.67)	.219	4.59 (14)	0.11 (0.5)	.131	2.27 (4.9)	0.09 (0.4)	.054
OCS, % patients	17.8	4.4	.002	9.1	4.5	.625	25	4.2	.063	27.3	4.5	.063
ACT score, mean (SD)	14.4 (5.4)	21.8 (4.8)	<.001	12.4 (5)	21.4 (5)	<.001	17.1 (5)	21.9 (5)	.002	14.4 (5)	22.3 (4)	<.001
ACT score > 20, % patients	19.4	73.1	<.001	7.1	71.4	<.001	35	75	.008	21.1	73.7	.006

SD: standard deviation; FeNO: fractional exhaled nitric oxide; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; OCS: oral corticosteroids; ACT: Asthma Control Test.

(omalizumab 43, benralizumab 23, and mepolizumab 19). In 5 patients excluded from the analysis, data of some variables recorded at baseline could not be retrieved at the end of follow-up. Complete response was achieved in 30 patients, with a rate of 35.3%.

The rates of complete response in the groups of biologics were 30.2% in the omalizumab group (13 patients), 30.4% in the benralizumab group (7 patients), and 52.6% in the mepolizumab group (10 patients).

As shown in Table 5, in the overall study population, complete responders vs. non-complete responders had a significantly better pulmonary function in the three parameters of FVC %, FEV_1L and FEV_1%. Also, the percentage of patients with nasal polyposis and gastroesophageal reflux disease was higher among complete responders. In the omalizumab group, significant differences between complete responders and non-responders were found in FEV_1 L and FEV_1%, and lower percentages of women and patients with bronchiectasis. In the benralizumab group, significant differences in exacerbations over 1 year and the percentage of women were observed. In the mepolizumab group, significant differences in FEV_1%, duration of treatment, and percentage of patients with eosinophilic granulomatosis with polyangiitis were found.

When the criterion of an increase of FEV_1 > 200 mL was also considered, the rates of complete responders were 43.5% in the overall study population, 34.9% in the omalizumab group, and 52.2% in the benralizumab, and 52.6% in the mepolizumab groups.

The complete response rates in the different groups are shown in Figure 1.

Predictors of complete response

In the logistic regression analysis, variables independently associated with complete response at the end of follow-up were FEV_1 (in L) for treatment with omalizumab (OR = 5.47, 95% CI 1.67–17.87, $p=.005$; AUC of the model = 0.840, 95% CI 0.70–0.98, $p=.002$), less previous exacerbations for treatment with benralizumab (OR = 0.45, 95% CI 0.21–0.96, $p=.038$; AUC of the model = 0.826, 95% CI 0.65–1, $p=.015$), and FEV_1 (in %) for treatment with mepolizumab (OR = 1.09, 95% CI 1.01–1.18, $p=.024$; AUC of the model = 0.867, 95% CI 0.69–1, $p=.007$).

Causes of non-response

As shown in Table 6, the main cause of non-control or failure to achieve a complete response in the overall population treated with biologics was the presence of an obstructive airway pattern at 12 months (32.5% of cases) and at the end of follow-up (34.5%), followed by poor symptom control (ACT score >20) (26.6% and 26.9%). In contrast, exacerbations (≥1 episode) and treatment with mOCS were less frequent causes of non-response. Similar findings were found in the

Table 5. Complete response (FEV_1 > 80%) at the end of follow-up and related factors.

	All study patients (n = 85)			Omalizumab (n = 43)			Benralizumab (n = 23)			Mepolizumab (n = 19)		
Variables	Non-responders	Responders	p value	Non-responders	Responders	p value	Non-responders	Responders	p value	Non-responders	Responders	p value
Blood eosinophils, cells/µL, mean (SD)	640 (1168)	376 (272)	.165	657 (1564)	299 (354)	.124	644 (466)	529 (243)	.788	577 (259)	353 (132)	.080
FeNO, ppb, mean (SD)	51.5 (54)	47.4 (32)	.586	49.2 (511)	38.3 (32)	.962	49.5 (69)	52.7 (32)	.190	61.3 (32.3)	54.4 (34)	.902
FVC, %, mean (SD)	73.7 (18)	85.5 (15)	**.003**	73.6 (18.5)	82.1 (13.5)	.128	71.5 (15)	83.4 (16)	.240	77.9 (20)	90.4 (15)	.156
FEV_1, %, mean (SD)	60.3 (21)	79.6 (18)	**.000**	61.8 (24)	79.9 (17)	**.012**	57.4 (17)	75.7 (25)	.124	60.4 (15)	82.1 (15)	**.006**
FEV_1, L, mean (SD)	1.74 (0.6)	2.3 1 (0.9)	**.004**	1.88 (0.70)	3.03 (0.97)	**.001**	1.58 (0.57)	1.81 (0.45)	.385	1.57 (0.25)	1.95 (0.54)	.146
Exacerbations over 1 year, mean (SD)	3.78 (2.6)	3.07 (2.6)	.234	4.0 (3)	3.44 (3.4)	.348	4 (1.8)	2(1.3)	**.012**	2.6 (2)	3.60 (2.4)	.356
No exacerbations, % patients	12.7	16.7	.618	13.3	23.1	.427	6.3	14.3	.529	22.2	10	.466
OCS, mg/day, mean (SD)	3.55 (11)	0.7 (1.9)	.064	1.9 (7.4)	0	.172	6.4 (17)	1.9 (3)	.737	4.7 (7.1)	0.8 (1.69)	.315
OCS, % patients	21.8	13.3	.339	13.3	0	.167	25	28.6	.858	44.4	20	.252
ACT score, mean (SD)	14.8 (5.6)	13.7 (5.1)	.435	13.1 (5.2)	10.9 (4.3)	.295	16.4 (6)	17.7 (2.8)	.741	16.4 (5)	13.8 (5.6)	.542
ACT score > 20, % patients	21.4	16.7	.640	10	0	.326	35.7	33.3	.919	25	22.2	.893
Age, years, mean (SD)	55.3 (16)	55.2 (15)	.984	51.5 (17)	44 (15)	.243	63.1 (13)	65 (5.6)	.815	54. 1(14)	63 (11)	.156
Women, %	76.4	73.3	.757	80	46.2	**.026**	56.3	100	**.036**	100	90	.330
Treatment duration, months, mean (SD)	57.5 (48)	52 (51)	.624	83.1 (50.7)	88.7 (58)	.751	19.8 (8.9)	29 (14.5)	.082	39 (17)	20.5 (10)	**.050**
Age at diagnosis, years, mean (SD)	50.5 (17)	51 (17)	.896	44.5 (17)	36.5 (15)	.193	61.4 (13)	63 (6)	.814	51 (14)	61.4 (11)	.094
Rhinosinusitis, % patients	29.1	26.7	.812	33.3	38.5	.746	12.5	0	.328	44.4	30	.511
Nasal polyposis, % patients	16.4	40	.016	20	30.8	.443	12.5	57.1	.025	11.1	40	.153
AERD, % patients	7.3	20	.082	10	7.7	.811	0	42.9	.005	11.1	20	.596
EGPA, number/total patients	57.5 (48)	52 (51)	.624	83.1 (50.7)	88.7 (58)	.751	19.8 (8.9)	29 (14.5)	.082	39 (17)	20.5 (10)	**.050**
ABPA, number/total patients	2/55	4/30	.095	2/30	2/13	.366	0/10	2/13	.729	0/9	0/10	1
Bronchiectasis, % patients	27.3	10	.063	30	0	**.026**	12.5	28.6	.349	44.4	10	.089
Anxiety, % patients	23.6	20	.701	23.3	15.4	.556	18.8	28.6	.599	33.3	20	.510
Obstructive sleep apnea, % patients	9.1	23.3	.072	6.7	23.1	.123	12.5	42.9	.104	11.1	10	.937
Obesity BMI ≥30 kg/m^2, % patients	3.6	10	.233	0	7.7	.124	12.5	28.6	.349	0/9	0/10	1
GERD, % patients	9.1	26.7	**.031**	6.7	15.4	.366	6.3	28.6	.144	22.2	40	.405
Never-smokers, % patients	70.9	80	.513	73.3	76.9	.799	62.5	100	.059	77.8	70	.622
Food allergy, % patients	9.1	13.3	.544	16.7	23.1	.620	0	14.3	.122	0/9	0/10	1
Atopic dermatitis, % patients	3.6	3.3	.942	6.7	0	.340	0	14.3	.122	0	0	1
Atopia, % patients	69.1	63.3	.589	93.3	100	.340	43.8	42.9	.968	33.3	30	.876
Bologic switch, number/total patients	4/55	4/30	.492	1/30	0/13	.505	2/16	2/7	.349	1/9	2/10	.622
Total serum IgE, kU/L, mean (SD)	556 (884)	384 (419)	.591	685 (1093)	708 (527)	.303	259 (266)	521 (717)	.882	382 (583)	138 (140)	.270

SD: standard deviation; FeNO: fractional exhaled nitric oxide; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; OCS: oral corticosteroids; ACT: Asthma Control Test; AERD: aspirin-exacerbated respiratory disease; EGPA: eosinophilic granulomatosis with polyangiitis; ABPA: allergic bronchopulmonary aspergillosis; GERD: gastroesophageal reflux disease.

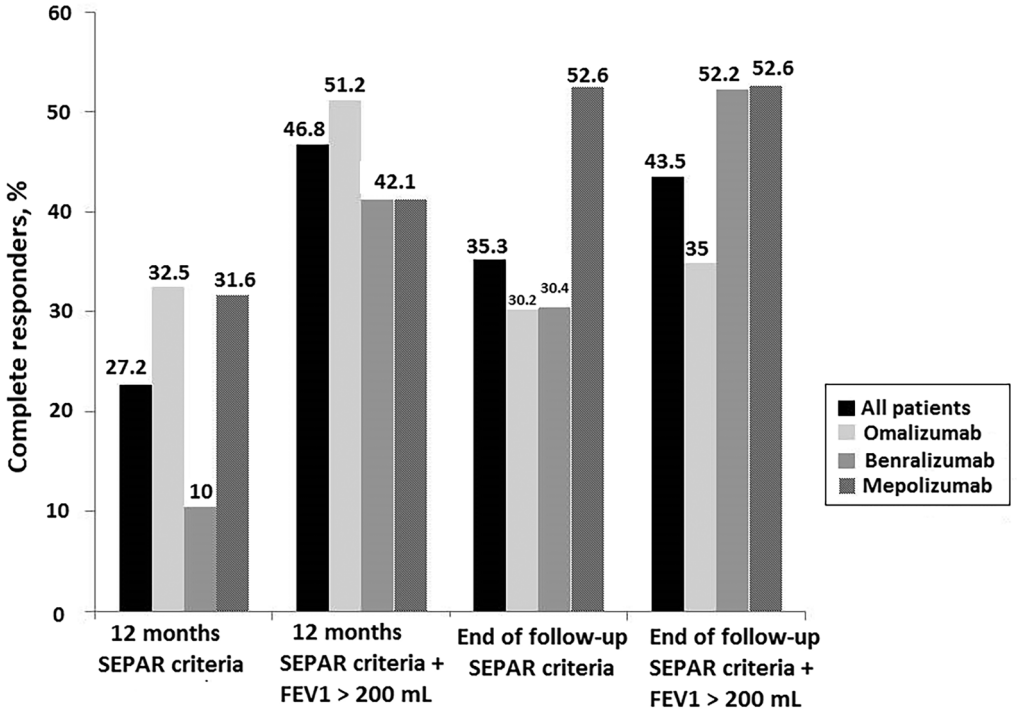

Figure 1. Percentages of severe asthma patients with complete response to treatment with biologics. SEPAR criteria: no exacerbations, no use of corticosteroids, ACT score >20, and an FEV_1 >80% predicted (SEPAR: Spanish Society of Pneumology and Thoracic Surgery [15]).

Table 6. Causes of non-response to treatment with biologics in patients with severe asthma.

	All patients ($n=90$)			Omalizumab ($n=44$)			Benralizumab ($n=24$)			Mepolizumab ($n=22$)		
Variables	Baseline	12 months	End of follow-up	Baseline	12 months	End of follow-up	Baseline	12 months	End of follow-up	Baseline	12 months	End of follow-up
FEV_1 < 80% predicted, %	72.1	32.5	34.5	70	32.6	32.6	87.5	38.9	31.8	59.1	26.3	42
Exacerbations ≥ 1, %	83.9	17.2	18.9	84.1	15.9	20.5	86.4	18.2	12.5	81	19	18.2
ACT score < 20, %	73.4	26.6	26.9	92.9	25	28.6	66.7	27.8	25	83.3	28.6	26.3
mOCS, %	18.4	6.9	4.4	9.1	4.5	4.5	27.3	4.5	4.2	28.6	14.3	4.5

FEV_1: forced expiratory volume in one second; ACT: Asthma Control Test; mOCS: maintenance with oral corticosteroids. Data as percentage of patients.

individual groups of biologics. The obstructive pattern as a major cause of non- asthma control at 12 months and at the end of follow-up remained even when expanding the SEPAR criteria [19] and taking into account improvements in FEV1 > 200 mL despite FEV_1 not reaching >80% of the predicted value.

Discussion

In this real-life retrospective study based on data of 90 patients with severe asthma treated with biologics, omalizumab, benralizumab and mepolizumab, we evaluated the complete response rate after 12 months of therapy and in the long-term at the end of the follow-up in March 2022, as well as the clinical characteristics of the patients associated with response. The present results add evidence of the efficacy of biologics in the management of difficult-to-treat asthma with a persistent improvement at 12 months and in the long term.

The baseline characteristics of patients treated with the anti-IL-5 drugs were similar in terms of asthma severity, comorbidities, demographic characteristics, asthma control, and biomarker levels. However, patients in the omalizumab group were younger, had a higher prevalence of atopy, and a longer duration of treatment. This may have been expected since omalizumab is targeted towards a specific immunophenotype, particularly for severe allergic asthma, and it was the first available biological therapy for the treatment of severe eosinophilic asthma (SEA). Moreover, patients treated with omalizumab had significantly worse

asthma control as measured by the ACT, were on fewer mOCS, and had higher FEV_1 values (in L). These differences in baseline characteristics and asthma control suggest that the populations being treated with omalizumab and anti-IL-5 drugs might have distinct clinical profiles and potentially different underlying mechanisms of asthma non-control.

Biologics have been shown to be effective in randomized controlled trials (RCTs). However, it has been recognized that only a minority of patients with severe asthma would also be eligible for inclusion within an RCT for its baseline characteristics [21]. In a recent systematic review that evaluated the real-world efficacy of biological therapies for severe asthma [12], the baseline characteristics of patients included in the review were similar of those observed in our population, with a mean age of 55.3 years, 73.3% were women, and 75.6% were never smokers.

This present results show an improvement in all asthma control parameters (ACT; exacerbations, FEV_1%, mOCS) after 12 months of treatment in the overall study population. These data are similar to those reported for key clinical parameters in real-world clinical studies and systematic reviews, in which mepolizumab, benralizumab, and omalizumab were effective therapies for asthma. The effects observed in real-world studies are similar to those seen in the active group of equivalent RCTs [12,22–24]. When analyzing the response after 12 months in each group of biologics, these differences were maintained except for mOCS. In all groups, there was a decrease in mOCS especially in patients treated with mepolizumab, but differences did not reach statistical significance probably due to dispersion of the variables and the limited sample size.

There was a statistically significant reduction in the rate of asthma exacerbation episodes in all study groups, as well as a significant increase in the percentage of patients who did not experience any exacerbation. On the other hand, taking into account the decrease in the percentage of patients on mOCS, we found that almost two out of three patients who completed 12 months of biological therapy regardless of which of the three therapies analyzed could be considered as super responders as they did not present exacerbations or used systemic corticosteroids [18].

Interestingly, the reduction of asthma exacerbations, improvement in ACT score, and the reduction of mOCS were observed in all groups of biological drugs at the end of follow-up. It should be noted that in our study the follow-up is long term, superior to other studies using mepolizumab [22] or benralizumab [23] in the real-world setting, except in the case of omalizumab for which long-term data at 9 years have been reported [25].

Of note, improvement in pulmonary function observed at 12 months in the mepolizumab group was not sustained at the end of follow-up. In a systematic review and meta-analysis of licensed biological therapies for severe asthma, FEV_1 change was assessed following the treatment with mepolizumab and benralizumab and there was low certainty of the evidence of an increase in FEV_1 after treatment with these two agents [12]. Real-world trials appear to demonstrate that benralizumab has an effect on FEV_1 which is above the minimal clinically important difference (MCID), while mepolizumab causes a statistically significant change which is below the MCID [11]. It is possible that this effect on FEV_1 below the MCID and a better FEV_1 (both in % and L) at baseline for mepolizumab as compared with benralizumab may account for the loss of improvement of pulmonary function in the long term.

In patients treated with omalizumab, there was a significant reduction of FeNO at the end of follow-up. The ability of omalizumab to improve clinical parameters in real life such as the reduction of exacerbations and T2 inflammatory biomarkers in severe allergic asthma (e.g. FeNO) is well documented [26]. Also, FeNO is a useful biomarker to identify patients who may benefit with omalizumab treatment [27]. The present findings confirm the decrease of FeNO associated with omalizumab therapy, which was maintained at the end of follow-up with even reduced values as compared with data at 12 months.

Relevant data of the study is the rate of complete response achieved at 12 months, which was maintained and even increased at the end of follow-up. In addition, when improvement in FEV_1 >200 mL rather than FEV_1 normalization (FEV_1 > 80% predicted) was added to SEPAR criteria [19], an additional increase in the rate of complete responders was found both at 12 months (19.6% for the overall study patients, 18.7% for omalizumab, 31.6% for benralizumab, and 10.5% for mepolizumab) and at the end of follow-up (8.2% for the overall study patients, 4.7% for omalizumab, and 21.8% for benralizumab). Increases in FEV_1 are also included in multidimensional scales, such as EXACTO [28] or FEOS [29] that have been proposed to assess the response to biologics and to assist clinical-decision making.

In the present population of severe asthma patients under treatment with biologics, robust predictors of clinical response were better lung function and fewer previous exacerbations. Clinical asthma remission is characterized by a high level of disease control, including the absence of symptoms and exacerbations, no need of

mOCS, and normalization or optimization of lung function with or without ongoing treatment [30]. Recently, it has been agreed that to consider asthma remission, clinical improvement should be sustained (present for 12 months) and should include three of more criteria, such as absence of significant symptoms by validated instrument, lung function optimization/stabilization, patient/provider agreement regarding remission, and no use of systemic corticosteroids [31,32]. Complete asthma remission requires normalization or stabilization of any underlying pathology in addition to symptomatic remission, therefore, confirmation of complete asthma remission involves evaluation of inflammatory and more complex pathophysiological biomarkers besides asthma control variables.

Persistence of an obstructive pulmonary pattern despite improvement in FEV_1 as compared with baseline was the main cause of failure to achieve a long-term complete response. In a previous study of our group in adults with severe eosinophilic asthma, airway obstruction (FEV1 < 80% predicted) was the main reason of uncontrolled asthma [33]. These findings are consistent with data reported in other cohort studies in the real-world setting, in which exacerbations (the main variable in RCTs with biological drugs in asthma patients) was not the main cause of non-response [34–36]. In our previous study in severe eosinophilic asthma, persistent airflow obstruction was the main factor associated with poor asthma control, although none of the patients were treated with biologics [33]. In light of the present results, which have to be interpreted considering the limitations of a retrospective analysis and the small sample size, improvement of pulmonary function and probably lung remodeling seems to remain an unmet need to achieve clinical remission in severe asthma patients under therapy with biologics. Although previous studies have not targeted treatment-induced remission, in our opinion long-term clinical remission could be included as a therapeutic goal in studies of asthma treatments. Information on patients with complete response and its maintenance in the long-term is important to improve personalized care. Also, it would have been interesting to assess differences in clinical background data between late and early responders for each drug. However, the reduced number of patients due to the small sample size related to the single-center nature of the study would be an important limitation for the analysis of differences between early and late responders stratified by treatment group.

The overall results of the present study regarding benralizumab and mepolizumab, with reduction of exacerbations, better asthma control, decrease in mOCS, and reduction of eosinophils are comparable to those analyzed in a systematic review and meta-analysis examining biologicals in real-world settings [12]. Omalizumab included in our study was not assessed in the systematic review [12], whereas treatment with dupilumab and reslizumab was not evaluated in our study. In our opinion, the strength of this study is to demonstrate that efficacy in terms of asthma control is maintained and even increases in the long term (in the case of anti-IL-5, longer term than studies or systematic reviews published to date) [12]. This may have an impact on the speed at which a change in biological therapy is considered. It is necessary to balance very well not to sustain biological therapies with partial or no response for a long time, but also not to rush and change the therapy before having achieved the maximum expected response. Another strong point of the study is to demonstrate that the main cause of non-complete response is pulmonary obstruction.

In this study, we have not investigated the clinical benefits of switching biologics, although improvements in non-responder asthmatics switching from mepolizumab to benralizumab [23,37,38] and from mepolizumab to dupilumab [39,40] have been reported. Also, a further important issue refers to the discontinuation of biologics, although there are no criteria for remission in biologics-free patients. Recently, Nagase et al. [13] have proposed an algorithm for withdrawal of biologics comprising an absence of asthma symptoms, no asthma exacerbations, no use of oral corticosteroids, normalized spirometry, suppressed T2 inflammation, and control of comorbidities, although more research is needed to validate these suggested criteria.

Conclusion

Treatment with omalizumab, benralizumab, and mepolizumab improved clinical outcomes in patients with severe asthma in a real-world clinical setting. After 12 months of treatment 27.2% of patients met the criteria of complete response and this percentage even increased to 35.3% at the end of a mean follow-up of 55 months. The main cause of failure to achieve response to biologics was the persistence of an airflow obstructive pattern.

Acknowledgments

The authors thank Marta Pulido, MD, for editing the manuscript and editorial assistance.

Authors contributions

M.B. and C.M. designed the study, reviewed the literature, analyzed the results and drafted the manuscript. I.G.-O., M. M.-C., J.N., C.P., L.P., P.C., G.C.P., L.C., A.R., J.A. and A.R.

participated in data collection. All authors reviewed and approved the final draft. The authors decline the use of artificial intelligence, language models, machine learning or similar technologies to create content or assist with writing or editing the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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Data availability statement

Study data are available from the authors (M.B. and C.M.) upon request.

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