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Article

Long-Term Eosinophil Depletion: A Real-World Perspective on Safety and Durability of Benralizumab Treatment in Severe Eosinophilic Asthma Running Header: Benralizumab Long-Term Safety and Efficacy

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Abstract: Background/Objectives: Benralizumab is an anti-IL-5 receptor alpha monoclonal antibody that induces near-complete depletion of eosinophils. This study aimed to evaluate the long-term safety and effectiveness of benralizumab in patients with severe eosinophilic asthma (SEA) over a 48-month period. **Methods:** This was a single-arm, retrospective, observational, multicenter study involving 123 SEA patients treated with benralizumab at a dosage of 30 mg every 4 weeks for the first three doses and then every 8 weeks. The safety endpoints focused on the frequency and nature of adverse events and the likelihood that they were induced by benralizumab. The efficacy endpoints focused on lung function, asthma exacerbations and control, and oral corticosteroid use. **Results:** Benralizumab, consistent with its mechanism of action, led to rapid and nearly complete depletion of eosinophils. In total, 26 adverse events (21.1%) were observed, with 1.6% related to the treatment and 0.8% categorized as serious (vagal hypotension). Bronchitis was the most common unrelated adverse event (15.4%), occurring between months 36 and 38. Of note, benralizumab maintained its effectiveness over the 48-month period, resulting in significant improvements in lung function and reductions in oral corticosteroid use and exacerbation frequency. **Conclusions:** Benralizumab demonstrated a favorable safety profile comparable to previously published studies with perdurable effectiveness in controlling SEA and reducing oral corticosteroid use. Finally, this study provides evidence that near-complete eosinophil depletion does not increase long-term safety risks and supports benralizumab as a reliable treatment option for SEA patients.

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Keywords: severe eosinophilic asthma; biological therapy; benralizumab; eosinophil depletion; long term benralizumab safety; long term benralizumab effectiveness; real-world study

1. Introduction

Severe eosinophilic asthma (SEA) is characterized by extensive eosinophilic inflammation triggered by the signaling of interleukin (IL)-5 through the IL-5 receptor alpha (IL-5Rα) [Perez-de-Llano L, 2020; Maio S, 2018; Lee JJ, 2012; Klion AD, 2020; Jacobsen EA, 2021; Dunican EM, 2017]. Since increasing blood eosinophil (Eos) counts correlate with asthma severity, leading to a higher risk of exacerbations, poor asthma control, and declining lung function [Bumbacea D, 2004; Price DB, 2015], the depletion of Eos is the primary therapeutic goal [Jackson DJ and Ian DP, 2023]. Two anti-IL-5 monoclonal antibodies (mepolizumab and reslizumab) and an anti-IL-5 receptor antibody (benralizumab) have been approved as add-on maintenance therapy for SEA [Benralizumab SPC]. Mepolizumab reduces Eos by approximately 83–86% [Ortega HG, 2014], while benralizumab causes direct, rapid, nearly complete depletion of Eos from the peripheral blood and lungs [Ghazi A, 2012]. Pharmacovigilance data on the clinical use of biological therapies in asthma confirm the safety of these treatments. Adverse events (AEs) are primarily injection-site reactions, nasopharyngitis, headaches and hypersensitivity, while the association with malignancies, effects on the cardiovascular system, alopecia and autoimmune conditions have not been verified and requires further evaluation [Cutroneo PM, 2024].

Benralizumab has demonstrated efficacy and safety in SEA patients, as shown in several clinical trials, real-world studies, and pharmacovigilance data [Bleecker, 2016; FitzGerald, 2016, Pini L, 2024]. The SIROCCO and CALIMA clinical trials showed the safety and efficacy of benralizumab versus placebo [Bleecker, 2016; FitzGerald, 2016], while the ZONDA and PONENTE clinical trials and the PROMISE and ANANKE real-life study also demonstrated the effectiveness of benralizumab in reducing the need for oral corticosteroids (OCS) [Nair P, 2017; Kavanagh JE, 2020; Vultaggio A, 2023; Menzies-Gow A, 2022; Schleich F, 2023]. The XALOC-1 real-world study assessed benralizumab's effectiveness in 1002 adults with SEA during a 48-week follow-up, showing that the treatment reduced exacerbations, OCS use and improved symptom control and lung functions [Jackson DJ, 2024]. Accordingly, the use of benralizumab has been recommended as an alternative noncorticosteroid treatment for acute exacerbations of SEA [Ramakrishnan S, 2020]. The ANDHI clinical trial showed the beneficial impact of benralizumab on health-related quality of life, exacerbation rate, lung function, and nasal polyposis symptoms [Harrison TW, 2021]. Compared with mepolizumab, benralizumab resulted in greater improvements in lung function and exacerbation frequency [Langton D, 2023] while also showing a faster onset of action [Moran AM, 2020].

Regarding the safety of benralizumab, the frequency of AEs during SIROCCO or CALIMA was comparable to that observed in the placebo arm, with no predisposition to other opportunistic infections [Kuang FL, 2019; FitzGerald JM, 2016] or malignancies [Jackson DJ, 2020]. The results from BORA and MELTEMI extension studies confirmed the sustained efficacy of benralizumab and its long-term safety. The MELTEMI study identified no new safety concerns for up to 5 years. The most common AEs in all groups were upper respiratory tract infections, headaches, and bronchitis [Busse WW, 2019; Korn S, 2021].

This work aimed to provide real-world evidence on the safety of benralizumab in SEA patients over a treatment duration extending to 48 months. For this purpose, the ability of benralizumab to deplete Eos, the incidence of AEs, and the impact on lung function and asthma control were evaluated.

2. Patients and Methods

2.1. Ethical Considerations

 doi:10.20944/preprints202411.2259.v1

The study protocol was approved by the Ethics Committee Marca, protocol number 1321/CE 4 May 2023, and was conducted in accordance with the Declaration of Helsinki, as well as all applicable local laws and regulations concerning the privacy and security of personal information, including the General Data Protection Regulation (GDPR) (EU) 2016/679. Informed consent was obtained from all patients enrolled in the study.

2.2. Study Design and Study Intervention

This is a real-world, single-arm, retrospective observational multicenter study (Montebelluna, Cittadella, Treviso, Dolo, Verona, Vicenza, Rovigo, Mestre, Belluno, Modena, Brescia) to evaluate the safety and effectiveness of benralizumab 30 mg every 4 weeks for the first three doses, followed by every 8 weeks thereafter.

2.3. Patients

Patients were diagnosed according to the European Respiratory Society (ERS) and the American Thoracic Society (ATS) guidelines for severe, uncontrolled asthma receiving treatment with medium- or high-dosage inhaled corticosteroids (ICS) plus long-acting β2-agonists (LABAs) bronchodilators [Chung KF, 2014].

Benralizumab was prescribed to adult patients in accordance with Italian clinical practice, based on the eligibility and reimbursement criteria established by the Italian regulatory drug agency (Agenzia Italiana del Farmaco, AIFA). To be eligible for benralizumab treatment, patients must have had a blood Eos count ≥300 cells/μL in the absence of OCS treatment, measured at any time before benralizumab initiation. In addition to this criterion, patients were required to meet one of the following conditions: (1) at least two exacerbations in the previous 12 months despite maximum-dose inhaled therapy, treated with systemic steroid or requiring hospitalization; (2) continuous OCS treatment received during the previous year in addition to maximal inhaled therapy [Piano Terapeutico AIFA per la Prescrizione SSN di Fasenra (Benralizumab) Nell'asma Grave Eosinofilico Refrattario]. Patients were recruited from the centers of Montebelluna, Treviso, Cittadella, Dolo, Belluno, Mestre, Vicenza, Verona, Rovigo, Brescia, and Modena between January 2019 and March 2024, and they received benralizumab subcutaneously at a dose of 30 mg, with the first three doses administered every 4 weeks and every 8 weeks thereafter.

2.4. Data Collection

Demographic and disease data were collected from medical records based on assessments conducted during physicians' routine clinical practice. Demographic variables included age, sex, body mass index (BMI), current and past smoking status, the age at diagnosis and when the therapy started. Disease information comprised the presence of allergic rhinitis, chronic rhinosinusitis with nasal polyps (CRSwNP), bronchiectasis, atopy, hypersensitivity to acetylsalicylic acid (ASA) and nonsteroidal anti-inflammatory drug (NSAID), gastroesophageal reflux disease (GERD), and eosinophilic granulomatosis with polyangiitis (EGPA). Data on the severity of asthma included Eos count, asthma control test (ACT) score, pre-bronchodilator forced expiratory volume in 1 second (pre-BD FEV_1), pre-bronchodilator forced vital capacity (pre-BD FVC), pre-bronchodilator forced expiratory flow (pre-BD FEF), fractional exhaled nitric oxide (FeNO), which is a non-invasive biomarker for allergic and/or eosinophilic airway inflammation in patients with asthma, and the dosage of OCS. Additionally, data on cardiovascular, metabolic, and/or neuropsychiatric comorbidities were collected.

2.5. Analysis of Safety and Efficacy Endpoints

The long-term safety and tolerability endpoints included the occurrence of AEs, serious AEs (SAEs), hypersensitivity and immunogenicity. SAEs are those events that are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, or cause death, disability or

 doi:10.20944/preprints202411.2259.v1

incapacity. The number and percentage of AEs and the likelihood that they were caused by benralizumab therapy were determined.

Long-term effectiveness endpoints included the depletion of blood Eos and the consequent improvement in lung function, analyzed through FEV_1 and FVC. Effectiveness was also evaluated by analyzing the level of asthma control using the Asthma Control Questionnaire 6 (ACQ-6) and ACT. Additionally, the frequency of relapses and hospitalizations, the daily dosage of OCS (expressed as prednisone-equivalent mg), and the proportion of patients discontinuing OCS usage were analyzed.

2.6. Statistical Analysis

A descriptive statistical analysis was first performed to explore patients' characteristics at baseline. Percentages and frequency rates were used for categorical variables, and medians with interquartile ranges were used for continuous variables. Differences in the sample distribution of safety outcomes at various follow-up time points were assessed using the chi-squared test and Fisher's exact test, as appropriate. Respiratory function parameters were modeled using a linear mixed-effects model for longitudinal data with subject-specific random effects to estimate changes in the target outcomes for patients over the follow-up period.

Statistical analyses were performed using R v4.3. $p<0.05$ was considered significant.

3. Results

3.1. Characteristics of the Population Enrolled in the Study

In total, 123 patients were enrolled in the study; 69 (56.1%) were female. The median age at diagnosis was 43.5 years, and the median age at which they started treatment with benralizumab was 61 years. The median BMI was 26.0, and 67.5% of patients did not smoke. The pre-BD FEV_1 and FeNO values were 71.61 and 59.72, respectively; the ACT score was 15.04, and the Eos count was 646.54 cells/mm^3. Overall, 33.3% of patients had allergic rhinitis, 56.9% had CRSwNP, 36.6% had GERD, and 5.7% had EGPA; bronchiectasis was present in 26.0%, atopy in 41.5%, hypersensitivity to ASA/NSAIDs in 12.2%. Additionally, 40.7%, 27.6%, and 8.1% had cardiovascular, metabolic, or neuropsychiatric comorbidities, respectively (Table 1).

Table 1. Baseline characteristics of the whole sample.

Baseline characteristics	Overall (N=123), median (IQR)/mean (SD)/n (%)
Age at diagnosis (years)	43.5 (30.5–55.6)
Starting therapy age (years)	61.0 (54.0–70.0)
BMI (units)	26.0 (23.2–29.8)
Smoking status (N=122)	
ex	36 (29.3%)
no	83 (67.5%)
yes	3 (2.4%)
Pre-BD FEV_1 (% pred.)	71.61 (21.75)
Pre-BD FVC (% pred.)	93.41 (22.28)
Pre-BD FEV_1/FVC (% pred.)	62.19 (12.60)
Pre-BD FEF% (% pred.)	15.04 (4.68)
ACT score	59.72 (52.52)
FeNO (ppb)	646.54 (636.95)
Eosinophils (cells/mm^3)	7.46 (8.29)
Allergic rhinitis	41 (33.3%)
CRSwNP	70 (56.9%)
Bronchiectasis (n=119)	32 (26.0%)
Atopy (n=122)	51 (41.5%)
ASA NSAID hypersensitivity	15 (12.2%)
GERD	45 (36.6%)
EGPA (n=122)	7 (5.7%)
Cardiovascular comorbidities	50 (40.7%)
Metabolic comorbidities	34 (27.6%)
Neuropsychiatric comorbidities (n=122)	10 (8.1%)

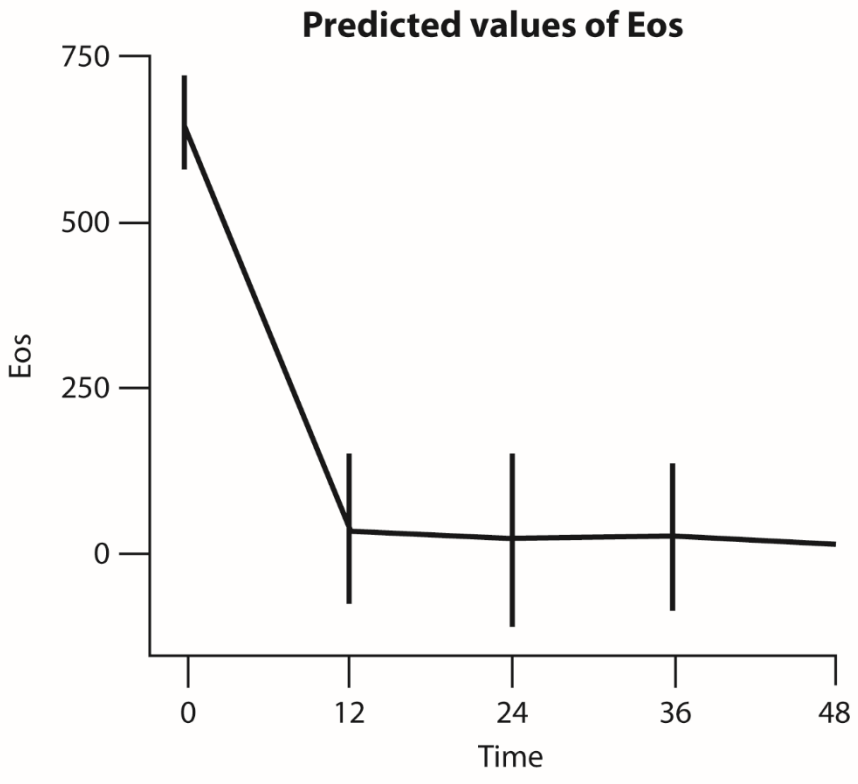
 doi:10.20944/preprints202411.2259.v1

ACT: asthma control test; ASA: acetylsalicylic acid; BMI: body mass index; CRSwNP: chronic rhinosinusitis with nasal polyps; EGPA: eosinophilic granulomatosis with polyangiitis; GERD: gastroesophageal reflux disease; NSAID: nonsteroidal anti-inflammatory drug; Pre-BD FEF: pre-bronchodilator forced expiratory flow; pre-BD FEV_1: pre-bronchodilator forced expiratory volume in 1 second; pre-BD FVC: pre-bronchodilator forced vital capacity; FeNO: fractional exhaled nitric oxide; OCS: oral corticosteroid.

3.2. Safety Outcomes of Depleting Eosinophils with Benralizumab

Benralizumab significantly decreased the eosinophils (Eos) count, confirming its effectiveness in inhibiting IL-5Rα and inducing Eos apoptosis. Eos depletion was nearly complete at 36 months ($p<0.001$) and maintained through 48 months ($p<0.001$, Figure 1).

During the 48-month follow-up period, adverse events (AEs) occurred in 26 patients (21.1%), being that only two patients (1.6%) developed AEs related to benralizumab treatment. The two drug-related reactions occurred at baseline or near administration time and included nausea (1, 0.8%) and urticaria (1, 0.8%). A reaction potentially related to the therapy was vagal hypotension (1, 0.8%); however, its association with benralizumab use was not confirmed. None of the patients who experienced these AEs discontinued benralizumab treatment. Most infections reported as unrelated AEs were bronchitis (n=4/26, 15.4%) cases that developed between 36 and 38 months. No differences were found in the risk of developing AEs based on sex ($p=0.259$), age ($p=0.192$), BMI ($p=0.846$), smoking status ($p=0.662$), allergic rhinitis ($p=0.825$), CRSwNP ($p=0.791$) or bronchiectasis ($p=0.658$; Table 2).



Tab

Figure 1. Analysis of eosinophil count. Graphical representation of Eos predicted values. The bars indicate 95% CI. Eos: Eosinophil.

Table 2. Adverse events reported during the 48-month follow-up following benralizumab treatment and stratified by follow-up time and causality assessment.

 doi:10.20944/preprints202411.2259.v1

Adverse events	Baseline, n (%)	Month 12, n (%)	Month 24, n (%)	Month 36, n (%)	Month 48, n (%)	Overall, n (%)
Related						
Nausea	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
Urticaria	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
Likely						
Vagal hypotension	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
Not related						
Altered coagulative diathesis	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
Bronchitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.6%)	2 (1.6%)	4 (3.3%)
Asthma exacerbation	0 (0.0%)	3 (2.4%)	4 (3.3%)	2 (1.6%)	5 (4.1%)	14 (11.4%)
Influenza	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (0.8%)
Polyarthritis	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
Pneumonia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	2 (1.6%)

3.3. Comparison of Safety Data from Clinical Trials and Pharmacovigilance

Comparing our data with those of clinical trials, it emerged that in this long-term real-world study, only 21.1% of patients experienced AEs, a significantly lower rate than the 62–75% observed in the clinical trials. In this work, the SAE incidence was also much lower, with only 0.8% of patients reporting SAEs (vagal hypotension) compared with the frequency of 2–13.3% observed in the clinical trials. Bronchitis was more common in this study (15.4%) and was identified as an AE unrelated to benralizumab therapy (Table 3). Additionally, no cases of malignancies were observed over the 48-month period in this real-world study.

Table 3. Comparison of the safety profile of benralizumab observed in this study with previous clinical trials in SEA patients.

Study	Design	Population	Duration	Key safety findings	Types of adverse events
SIROCCO [Beecker ER, 2016]	Phase III, randomized, double-blind, placebo-controlled	1,205 patients	48 weeks (12 months)	AEs: 71–73% in benralizumab vs 78% in placebo. SAEs: 12–13% (benralizumab) vs 14% (placebo) Low discontinuation due to AEs (2%)	Common AEs: headaches (7–9%), nasopharyngitis (12%), upper respiratory tract infections (8–11%) Infusion-related reactions: rare (2–4%)
CALIMA [Fitzgerald JM, 2016]	Phase III, randomized, double-blind, placebo-controlled	1,306 patients	56 weeks (13 months)	AEs: 74–75% in benralizumab vs 78% in placebo Drug-related AE: 12–13% vs 8% in placebo SAEs: 9–10% (benralizumab) vs 14% (placebo)	Common AEs: nasopharyngitis (18–21%), headaches (8%), upper respiratory infections (7–8%) Infusion-related reactions: low incidence (2–3%)

 doi:10.20944/preprints202411.2259.v1

				Similar rates of AEs between groups	
ZONDA [Nair P, 2017]	Phase III, randomized, double-blind, placebo-controlled	220 patients requiring chronic OCS	28 weeks (7 months)	AEs: 68–75% in benralizumab vs 83% in placebo SAEs: 10% (benralizumab) vs 19% (placebo) No increase in AEs during OCS reduction	Common AEs: nasopharyngitis (17%), worsening asthma (13%), and bronchitis (10%)
ANDHI [Harrison TW, 2021]	Phase IIIb, open-label, observational	660 patients	24–32 weeks (6–8 months)	AEs: 62% in benralizumab SAEs: 8% in benralizumab Long-term safety was confirmed with no new signals	Common AEs: similar to SIROCCO and CALIMA Most frequent: infection-related AEs and headaches
MELTEMI [Korn S, 2021]	Open-label extension study (2+ years of treatment)	1,025 patients previously treated with benralizumab in prior trials	2 years	AEs: 64.6–84.6% in the benralizumab group vs 45.9–87.7% in the placebo SAEs: 2.4–13.3% (benralizumab) vs 4.5–14.2% in placebo Safety profile consistent, confirming long-term safety	Common AEs: nasopharyngitis (11.1–19.3%), headaches (5–12.6%), upper respiratory infections (1.6–8.9%), and bronchitis (3.6–9.2%) Infection-related AEs similar to previous studies
ANANKE [Vultaggio A, 2023]	Observational retrospective	162 patients	96 weeks	No new safety concerns reported	Not specifically reported
XALOC -1 [Jackson DJ, 2024]	Observational real-world study	1,002 patients (380 biologic-experienced)	48 weeks (12 months)	No new safety concerns reported. Not specifically detailed, but consistent with prior studies in safety profile.	Not specifically reported
Long-term eosinophil depletion: a real-life perspective on safety and durability of benralizumab treatment in severe	Long-term real-world study	123 patients previously treated with benralizumab	48 months (4 years)	AEs: 21.1% (26 total); only 1.6% related to treatment SAEs: 0.8% due to vagal hypotension, leading to discontinuation	Common AEs: bronchitis (15.4%), mostly between 36 and 38 months Related to infusion: nausea (0.8%) and urticaria (0.8%)

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eosinophilic asthma				Bronchitis in 15.4% of infections, unrelated to treatment	SAE: vagal hypotension (0.8%), leading to discontinuation

AE: adverse event; OCS: oral corticosteroid; SAE: serious adverse event.

Comparison with the pharmacovigilance data and spontaneous reporting on benralizumab highlights some key findings. Across different datasets, the most frequently reported AEs were nasopharyngitis, headaches, and, as reported here, bronchitis. The rate of SAEs in pharmacovigilance databases is higher than that reported in this study, ranging from 11.5% to 18%, with rare but notable risks such as anaphylaxis, vagal hypotension, and EGPA. Across all datasets and as observed in this study, infection risks were noted but not significantly increased. The frequency of malignancies was less than 1% in all datasets and 0% in this real-life study. Finally, discontinuation due to AEs was low in all datasets and 0% in this study (Table 4).

Table 4. Safety profile of benralizumab vs pharmacovigilance databases.

Category	**WHO Pharmacovigilance Database [Cutroneo PM, 2024]**	**Spanish Pharmacovigilance Database [Boada-Fernández-Del-Campo C, 2024]**	**Post-marketing surveillance and spontaneous AE reporting [Jackson DJ, 2020]**	Long-term eosinophil depletion: a real-life perspective on safety and durability of benralizumab treatment in severe eosinophilic asthma
Total cases reported	Over 5,512 individual case safety reports (ICSRs)	588 reports in Spain	~36,680 patient-years (post-marketing exposure globally)	26 cases (21.1% of patients)
SAEs	SAEs in 29.5% and 1.3% of cases were life-threatening	18% of total cases categorized as serious	~11.5% (SIROCCO/CALIMA trials) and 16.9% in long-term studies (up to 2 years)	0.8%: vagal hypotension
Common AEs	General disorders (e.g., malaise, fatigue), injection-site reactions, nasopharyngitis, headaches and hypersensitivity	Headaches (14.6%), pharyngitis (16.15%), fatigue (55 cases), pneumonia	Nasopharyngitis (16%), headaches (8.1%), bronchitis (7.9%)	Bronchitis (15.4%), nausea (0.8%), urticaria (0.8%)
Malignancies	Very low malignancy risk (<1%) noted in long-term data	Not emphasized	0.8% malignancy risk during 2-year trials (BORA)	No malignancies reported
Immune system reactions	Eosinophilic granulomatosis with polyangiitis (EGPA) risk noted	Anaphylaxis and hypersensitivity reactions noted	Hypersensitivity reactions (e.g., injection-site reactions) included in labeling	Vagal hypotension (0.8%)

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Discontinuation rates	Not specifically reported	Not reported	~2% discontinuation due to AEs (SIROCCO/CALIMA trials), mostly mild reactions	None
Death reports	~3.2% related to serious adverse events	No specific death reports linked directly to benralizumab therapy	Deaths related to severe asthma complications in ~0.3% of long-term trial participants (BORA)	None

3.4. Effectiveness Endpoints

In parallel with the highly efficient depletion of Eos, lung function improved considerably, as shown by the levels of pre-BD FEV_1, pre-BD FVC, and pre-BD FEV_1/FVC, which significantly increased at 36 months ($p<0.001$) and were maintained at 48 months ($p<0.001$, Figure 2).

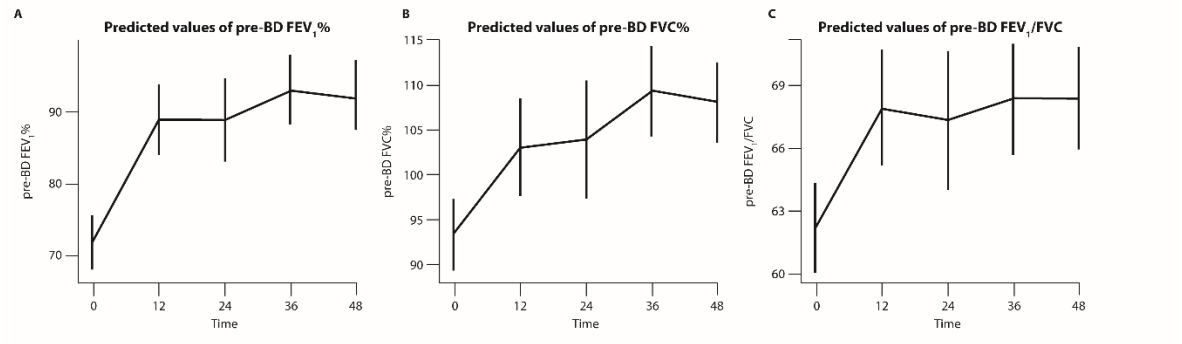

Figure 2. Graphical representation of lung function measured through pre-BD FEV_1, pre-BD FVC and pre-BD FEV_1/FVC. The pre-BD FEV_1 **(A),** pre-BD FVC% **(B)** and pre-BD FEV_1/FVC **(C)** were all significantly increased after treatment with benralizumab compared with baseline.

ACT values increased significantly, and improvements were maintained at 36 and 48 months ($p<0.001$, Figure 3A). ACQ scores were significantly lower at 36 months ($p<0.01$; Figure 3B). These data show that Eos depletion by benralizumab achieves continuous improvement in asthma control and maintains a good safety profile in the long term.

No statistical differences were observed for RV% (Figure 4A), while FeNO decreased significantly (Figure 4B).

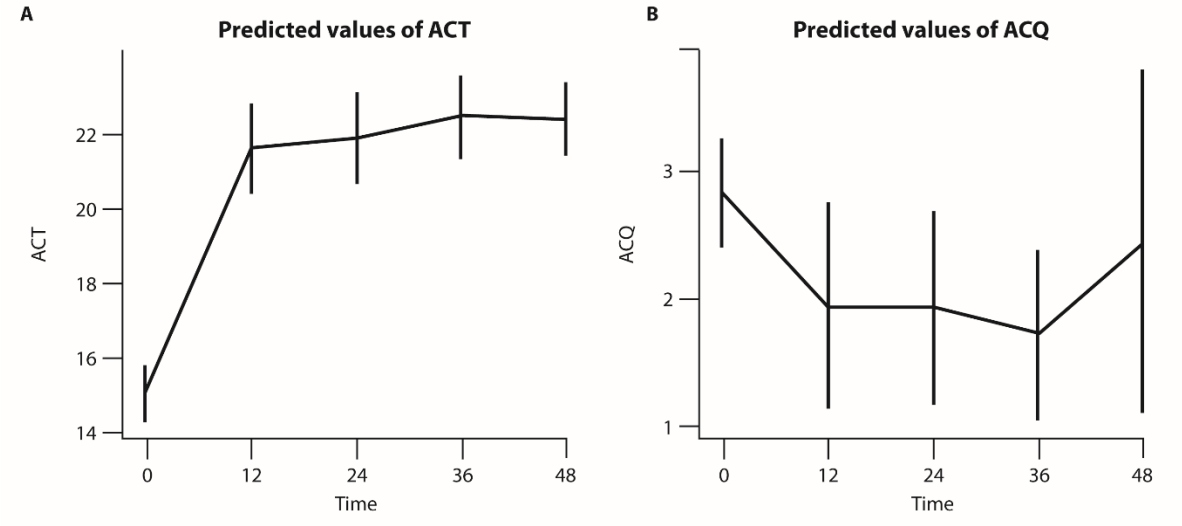

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Figure 3. Graphical representation of predicted values of ACT and ACQ scores over the follow-up period. ACT values significantly increased **(A)** while a significant decrease in ACQ was observed **(B)** upon treatment with benralizumab.

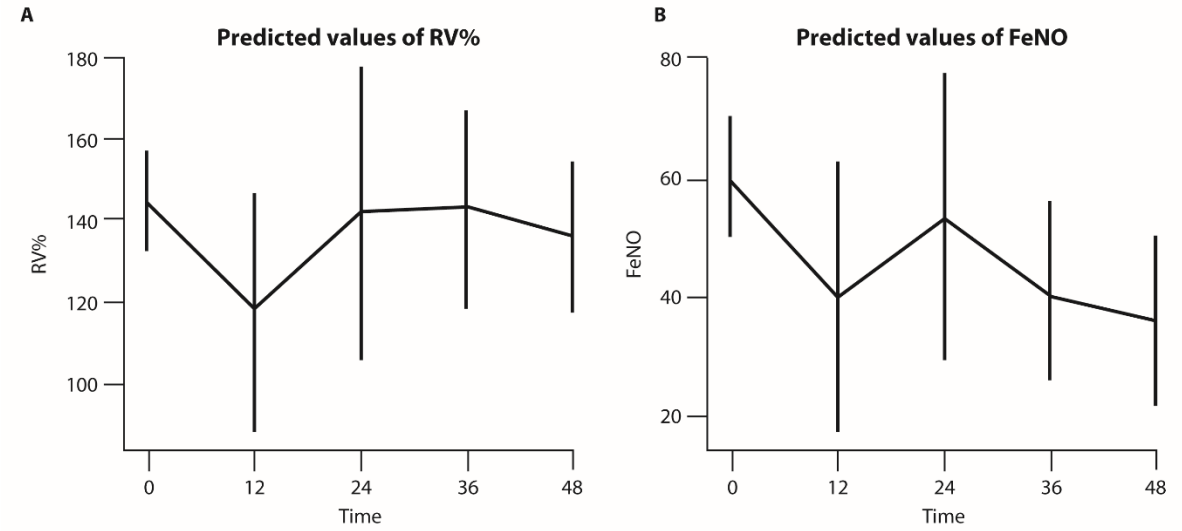

Figure 4. Graphical representation of RV% and FeNO predicted values. RV% did not decrease significantly **(A)** while a significant decrease in FeNO values was observed **(B)** upon treatment with benralizumab.

Treatment with benralizumab reduced the number of hospitalizations, which occurred at baseline (before starting treatment) at a frequency of one hospitalization per year in 15.5% of patients and two hospitalizations per year in 2.1% of patients. At 48 months, these rates were 4.5% (one hospitalization) and 0.0% (two hospitalizations, Figure 5A). Additionally, the dosage of ICS decreased from over 1,000 µg fluticasone in 33.3% of patients at baseline to 10.4% at 48 months, while the percentage of patients using a dosage <500 µg increased from 6.5% at baseline to 22.4% at 48 months (p=0.007, Figure 5B).

The number of hospitalizations decreased significantly at 36 and 48 months (p<0.001, Figure 6A). The dosage of OCS was reduced in 25/44 (56.8%) of patients, with a mean dosage reduction of 98% at 36 months (p<0.001), and in 42/67 (62.7%) of patients, with a mean reduction of 96% at 48 months (p<0.001, Figure 6B).

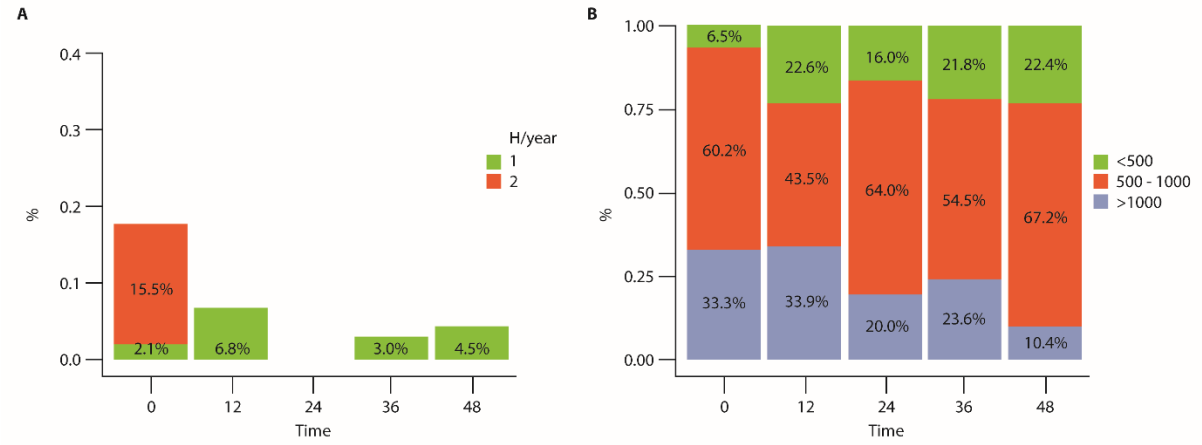

Figure 5. Analysis of hospitalizations and dosage of ICS at each time point of the follow-up period (in months). The number of hospitalizations **(A)** and ICS dosage **(B)** significantly decreased compared with baseline upon treatment with benralizumab.

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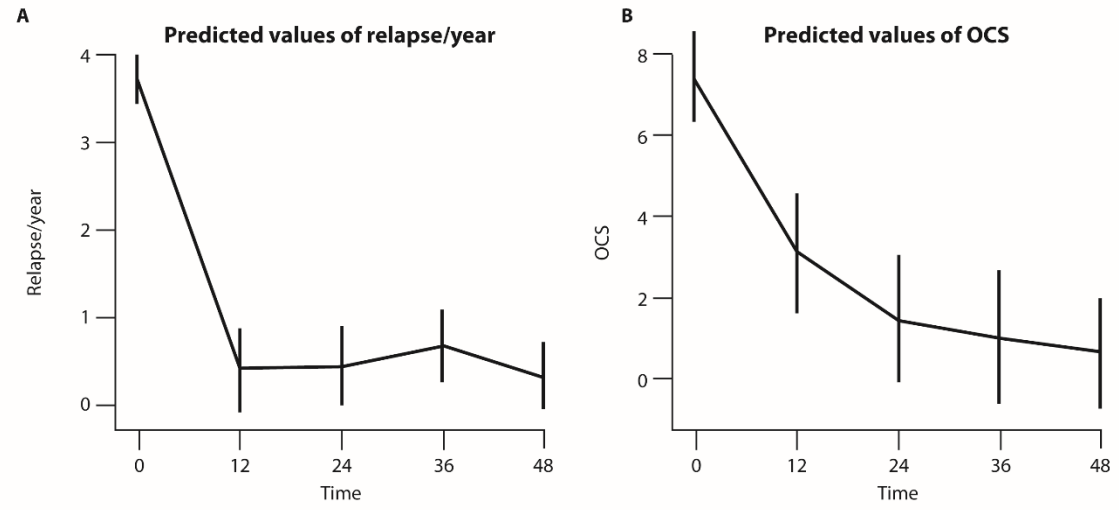

Figure 6. Number of predicted relapses per year and predicted OCS dosage at each time point of the follow-up period (in months). Benralizumab significantly decreased the number of relapses (A) and OCS dosage (B) compared with baseline.

4. Discussion

SEA has a difficult-to-treat profile, and its control remains elusive despite the use of high-dose ICS combined with LABA bronchodilators [Hekking PW, 2015]. Traditional therapy to prevent exacerbations consists of OCS, which, although effective, is associated with significant AEs [Price DB, 2018]. Given the challenges in managing SEA, new biological agents have been developed over the past few decades to specifically target the eosinophilic inflammatory pathway. Biological drugs represent a major advancement in precision medicine for treating SEA, and their pharmacology is essential for selecting the most appropriate therapy for each patient, ensuring the right drug is matched to the individual's specific condition [Couillard S, 2024]. Therapies that deplete Eos have been approved for the treatment of SEA and include the anti-IL-5Rα monoclonal antibody benralizumab [RCP Benralizumab]. However, concerns have been raised about the safety of benralizumab therapy because of the role of peripheral tissue Eos in host defense against helminths [Park YM, 2010; Wen T, 2016], as well as viral, bacterial, and fungal pathogens [Rodrigo-Munoz JM, 2021; Ondari E, 2021; Figueiredo RT, 2018; Marichal T, 2017] and their infiltration in several types of tumors [Sakkal S, 2016; Jackson DJ, 2020]. The safety profile of benralizumab has been periodically reviewed, and no major concerns have been reported to date [Korn S, 2021]. To gain further insights into the safety of benralizumab, this study collected and analyzed real-world data over a 48-month follow-up, which to our knowledge is the longest real-world evidence available in the literature. In this study population, benralizumab induced sustained Eos depletion, showing a good safety profile for up to 4 years. A total of 21.1% of patients reported AEs, while drug-related non-SAEs occurred in a small percentage (1.6%) and included nausea and urticaria. Only 0.8% of patients displayed an SAE, likely related to benralizumab treatment, which consisted of vagal hypotension. None of the AEs led to discontinuation of treatment. No differences were found in AE development based on sex, age, BMI, smoking status, or comorbidities such as allergic rhinitis or bronchiectasis. Overall, the safety profile of benralizumab remains favorable, with consistent findings across spontaneous reports, clinical trials, and long-term follow-up studies. Compared with the MELTEMI clinical trial, this work showed a lower rate of AEs, particularly those related to benralizumab, which could be attributed to differences between real-world and controlled trial environments.

At the same time, by depleting Eos, benralizumab induced long-term disease control, improved lung function, and significantly reduced exacerbations, hospitalizations, and the OCS dosage required. Furthermore, a significant reduction in FeNO was observed, which could be due, as

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previously suggested [Contoli M, 2022], to the strong depletion of basophils and Eos induced by benralizumab.

Although benralizumab achieves almost complete Eos depletion, whereas mepolizumab causes only about 50% depletion, the literature reports a lower frequency of serious side effects in SEA patients treated with either of these two drugs compared with placebo or other treatments [Akenroye A, 2022]. Therefore, no increase in safety issues has been detected for benralizumab in comparison with mepolizumab to date. Moreover, the significant decrease in the need and dosage of OCS induced by benralizumab highlights the potential of this therapy to spare patients from AEs associated with corticosteroids.

We acknowledge that this study has some limitations, such as the small size of the population included and the retrospective nature that does not allow comparison with the placebo arm. Nonetheless, the long-term follow-up and the correlation between benralizumab therapy and the occurrence of AEs allowed us to report significant safety and efficacy real-world data.

This real-world study confirms pharmacovigilance data and the results of clinical trials, showing a good safety profile of benralizumab, similar to that evidenced by numerous real-world data. Benralizumab-induced Eos depletion did not lead to an increase in AEs or SAEs compared with other biological therapies for asthma, such as mepolizumab. The rapid Eos depletion induced by benralizumab resulted in highly effective management of SEA, allowing swift reduction or discontinuation of OCS. In conclusion, these data support the use of benralizumab as a safe and effective treatment for SEA, even in the long term.

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Ethics and consent: The study protocol was approved by the Ethics Committee Marca (protocol number 1321/CE 4 May 2023) and was conducted in accordance with the rules of the Declaration of Helsinki, as well as all applicable local law requirements and regulations concerning the privacy and security of personal information, including the General Data Protection Regulation (GDPR) (EU) 2016/679. Informed consent was obtained from all patients enrolled in the study for the processing of personal data.

Data availability statement: The data supporting this study's findings are available from the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

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