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ORIGINAL RESEARCH

Clinical Remission in Patients with Severe Eosinophilic Asthma – A Single-Arm Observational Study with Benralizumab

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Purpose: To evaluate clinical remission rates and its individual components in patients with severe eosinophilic asthma treated with benralizumab, and to explore predictors of clinical remission using subgroup analyses by blood eosinophils, prior exacerbations, and previous biologic treatment.

Patients and Methods: Data from a prospective, observational, non-interventional study (BEEPS, NCT03907137) of patients with severe eosinophilic asthma (SEA) in Switzerland were analysed post-hoc. Benralizumab 30 mg was administered at weeks 0 (baseline), 4, and 8, followed by an 8-weekly regimen until week 56. Clinical remission was defined as meeting all four of the following criteria: Asthma Control Questionnaire (ACQ-5) scores < 1.5 or ≤ 0.75, no oral corticosteroid (OCS) use, no exacerbations, and a stable lung function. Patients were categorised into three pre-planned subgroups: (1) Blood eosinophils at baseline: 300–400 cells/μL and > 400 cells/μL; (2) exacerbations in the last 12 months: <4 and ≥4 exacerbations; (3) prior biologic treatment: naïve and experienced patients.

Results: At baseline, no patients met all four criteria for clinical remission. After 56 weeks of benralizumab treatment, 58.1% of patients achieved all criteria when using ACQ-5 < 1.5, and 51.6% did so with ACQ-5 ≤ 0.75. Throughout the study, each individual remission criterion improved consistently over time. Across all subgroups, asthma symptoms and annualized exacerbation rates (AER) continuously decreased over the course of treatment.

Conclusion: More than 50% of patients with SEA achieved clinical remission on treatment with benralizumab. Furthermore, benralizumab demonstrated consistent clinical efficacy across all patient subgroups, providing deeper insight into the characteristics and needs of these specific populations.

Keywords: clinical remission, asthma symptom control, exacerbation reduction, OCS reduction, stratification by subgroups

Introduction

The concept of remission in severe asthma as an achievable treatment goal emerged after the introduction of targeted biologic therapies. Extensive, and still ongoing, discussions within both the clinical and research community have led to multiple proposed definitions.[1–3] Finally, in the GINA 2024 report, a new section on remission was introduced:[4] "Clinical remission" refers to the absence of asthma symptoms, exacerbations and oral corticosteroid (OCS) use, as well as a stable or improved lung function over a defined prolonged period. "Complete or pathophysiological remission" additionally includes normalization of airway hyperresponsiveness and/or inflammatory biomarkers (eg reduced eosinophils or fractional exhaled nitric oxide (FeNO)). Both remission concepts were described for patients on- as well as off-asthma treatment. The framework of clinical remission on treatment is consistent with the established goal of asthma

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management to achieve the best possible long-term asthma outcomes for each patient.[5] From a long-term perspective, asthma remission means well-controlled symptoms combined with minimized risks of related mortality, exacerbations, persistent airflow limitation and side effects of treatment. For patients with severe, uncontrolled asthma, various biologic therapies, such as monoclonal antibodies against immunoglobulin E (IgE), interleukin-5 or −5-receptor (IL5/5R), interleukin-4-receptor (IL4Rα), or thymic stromal lymphopoietin (TSLP), are currently available. The treatment selection is influenced by the biomarkers of type 2 inflammation (blood eosinophils, FeNO and total IgE) as well as by comorbidities such as chronic rhinosinusitis with nasal polyps, atopic dermatitis, and allergies.[5] With the introduction of biologics, achieving clinical remission in severe uncontrolled asthma might become a realistic treatment goal.

Asthma is a prevalent condition and severe asthma may affect up to 10%. A recent study in Switzerland showed that in 2023 less than 15% of patients living with severe asthma were treated with biologics.[6] Severe eosinophilic asthma (SEA) is a very common phenotype found in up to 84% of patients with severe asthma.[7–9] These patients frequently experience dyspnea, wheezing, nocturnal awakenings, and exacerbations, and have a reduced quality of life.[10,11] Frequent exacerbations contribute to morbidity and cause a substantial burden of asthma as these attacks often lead to emergency room visits or hospitalizations. Especially patients with eosinophilic asthma are prone to repetitive exacerbations, which represent a major risk factor for a poor prognosis including increased mortality.[12] Thus, a reduction of exacerbations alongside with a reduction in OCS use, often causing serious side effects, are key elements on the path to disease remission.

Benralizumab, an anti-IL-5Rα monoclonal antibody that depletes eosinophils by antibody-dependent cell-mediated cytotoxicity, targets the key driver of type 2 airway inflammation in SEA and has shown early, sustained improvements of symptoms, exacerbations, OCS use, and lung function, making clinical remission an achievable goal.[12–17] Building on prior Swiss real-world findings,[18] this post-hoc analysis quantifies remission rates and its components in a cohort of SEA patients who initiated benralizumab treatment. To better understand the predictors of clinical remission, subgroup analyses based on baseline blood eosinophil count, prior exacerbation rates, and previous biologic use were performed.

Materials and Methods

Study Design and Procedures

A detailed description of this single-arm, non-interventional, observational, prospective study was published recently by Stolz et al 2024[18] Adult patients with SEA according to the American Thoracic Society (ATS) and the European Respiratory Society (ERS) guidelines[19,20] were enrolled if they fulfilled the Swiss label of benralizumab (high-dose inhaled corticosteroids/long-acting β2-agonists (ICS/LABA) as maintenance treatment, ≥2 exacerbations in the last 12 months, blood eosinophil count of ≥ 300 cells/μL). Fixed-dose benralizumab 30 mg subcutaneously (s.c.) was administered at weeks 0 (baseline), 4, and 8, followed by an 8-weekly regimen until week 56. Main exclusion criteria were chronic obstructive pulmonary disease (COPD), pregnancy and lactation. During routine scheduled clinical visits, data were collected from medical records, examination results, and patient-reported outcomes (PRO) questionnaires. After the first benralizumab dose at baseline, early treatment response was evaluated at additional study visits at weeks 1 and 2.

Outcome Measures and Efficacy Assessments

Individual components of clinical remission were assessed separately as well as a combined four-item composite endpoint defined as clinical remission: asthma symptom control determined by an ACQ score either <1.5 or ≤0.75, no exacerbations, no use of maintenance OCS (mOCS), and stable or improved lung function defined as an improvement of prebronchodilator forced expiratory volume in one second (FEV_1) versus baseline including a decline ≤10%.

The proportion of patients achieving clinical remission and its single components were evaluated at week 16 and at week 56 versus baseline.

For the subgroup analyses, patients were categorised into three pre-planned baseline groups in order to achieve a better understanding of the efficacy of benralizumab across different clinical characteristics and biomarkers:

1. Baseline blood eosinophil count: 300–400 cells/μL and > 400 cells/μL
2. Exacerbations in the last 12 months: <4 exacerbations and ≥4 exacerbations
3. Prior biologic treatment: naïve patients and biologic experienced patients

For the analyses, a change in the overall score in ACQ-5 compared to baseline over the course of the study (weeks 1, 2, 4, 8, 16 and 56) was assessed. Additionally, changes from baseline in ACQ-5 score were evaluated by the minimally clinically important difference (MCID) and by changes in asthma control status. A mean score of ≤0.75 indicates well-controlled asthma, scores between 0.75 and ≤1.5 indicate partially controlled asthma, and scores > 1.5 indicate not well-controlled asthma. A score improvement of ≥0.5 is considered as MCID.[21–23]

Also, the AER during the study was evaluated for all subgroups. In this study, exacerbations were defined as worsening of asthma leading to (1) use of systemic corticosteroids, or temporary increase in stable OCS dosage for ≥3 days, or a single injection of corticosteroids; (2) emergency department or visit to an urgent care centre (<24h) resulting in administration of systemic corticosteroids; or (3) hospitalization (≥24h).

Statistical Analyses

All outcomes used descriptive summaries and estimates with nominal 95% confidence intervals (CI). The analyses were performed in the full analysis set (FAS) including all enrolled patients who received at least one dose of benralizumab, irrespective of their protocol adherence and continued participation in the study according to the Intention-to-Treat (ITT) principle. Patients who withdrew from the study were included up to the date of their study participation.

For the assessment of individual components of remission, the denominator was the number of patients with available data at the specified visit, and for composite endpoints the denominator was the number of patients with data of selected components at the specified visit. Due to the single-arm, observational study design adjusted causal modelling to account for potential confounders (eg. changes in background controller therapy and adherence, seasonal variation in exacerbations, healthcare utilization, and comorbidities such as chronic rhinosinusitis with nasal polyps or allergy) was not performed, and no missing data imputation was undertaken. Analyses were conducted as complete-cases. To mitigate confounding, predefined eligibility criteria aligned with the Swiss label were applied, a standardized fixed-dose regimen was used, and consistent data collection schedules were implemented.

Ethics

This study complies with the Declaration of Helsinki and Swiss regulations. The lead ethics review and approval were provided by the Cantonal Ethics Committee Zurich (reference number 2019–00144) on the basis of the Principal Investigator's affiliation at Cantonal Hospital Graubünden, Chur. In accordance with Swiss multicenter governance, the Research Ethics Committees corresponding to co-investigators' affiliations were formally notified following the lead decision and each granted site-level approval to conduct the study. Signed and dated patient informed consent was obtained before any specific procedure for the observational study was performed according to GCP guidelines.

Results

Patient Demographics and Asthma Status at Baseline

This observational study included 73 patients with SEA who received at least one dose of benralizumab. Demographic data and clinical characteristics (Table 1) were described in detail by Stolz et al 2024[18] Briefly, at baseline patients had a mean age of 53.8 years with a mean duration of asthma of 19.3 years. The mean blood eosinophil count was 685 cells/μL, with a mean ACQ-5 score of 2.76 (standard deviation (SD) 1.26). The majority of patients (82.2%) presented with not well-controlled asthma (ACQ-5 > 1.5), and a mean AER of 3.65 (95% CI: 3.18; 4.18) in the 12 months prior to study entry.

All patients had received various combinations of asthma maintenance therapy for the last 12 months prior to inclusion.[18] At baseline, most frequently ICS/LABA was used by 80.8% of patients, followed by long-acting muscarinic antagonists (LAMA) (52.1%), short-acting β_2-agonists (SABA) (46.6%), and ICS (32.9%), as well as mOCS and

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Table 1 Baseline Demographics and Clinical Characteristics of Patients in Full Analysis Set (FAS) and Post-Hoc Analyses per Subgroup

Parameter	FAS	Eosinophils*		Prior Exacerbations		Pre-Treatment	
		>400 Cells/μL	300-400 Cells/μL	<4 Exacerbations	≥4 Exacerbations	Biologic Naïve	Biologic Experienced
Number of patients — n	73	52	20	46	27	53	20
Female sex — n (%)	45 (61.6%)	30 (57.7%)	14 (70.0%)	27 (58.7%)	18 (66.7%)	31 (58.5%)	14 (70.0%)
Age [years] — mean (min; max)	53.8 (19; 83)	54.9 (19; 83)	50.8 (23; 76)	54.7 (19; 83)	52.3 (19; 76)	53.2 (19; 81)	55.4 (27; 83)
ACQ-5 score — mean (SD)	2.76 (1.26)	2.80 (1.29)	2.66 (1.24)	2.71 (1.38)	2.85 (1.05)	2.70 (1.17)	2.93 (1.51)
Proportion of patients with — n (%)							
Well-controlled asthma (ACQ-5 ≤ 0.75)	3 (4.1%)	2 (3.8%)	1 (5.0%)	3 (6.5%)	0 (0.0%)	2 (3.8%)	1 (5.0%)
Partially controlled asthma (ACQ-5 > 0.75 and ≤ 1.5)	10 (13.7%)	8 (15.4%)	2 (10.0%)	7 (15.2%)	3 (11.1%)	8 (15.1%)	2 (10.0%)
Not well-controlled asthma (ACQ-5 > 1.5)	60 (82.2%)	42 (80.8%)	17 (85.0%)	36 (78.3%)	24 (88.9%)	43 (81.1%)	17 (85.0%)
FEV_1 [L] (prebronchodilator) – mean (SD)	1.99 (0.78)	2.03 (0.80)	1.89 (0.76)	1.97 (0.81)	2.02 (0.75)	2.12 (0.78)	1.63 (0.69)
Biomarkers (last available)							
Blood eosinophils [cells/μL] — mean (SD)	685.0 (580.2)	823.8 (637.5)	344.4 (37.9)	709.9 (671.2)	642.6 (386.6)	730.7 (653.7)	564.0 (291.4)
Blood eosinophils [cells/μL] —median (min; max)	600.0 (280; 4800)	650.0 (430; 4800)	330.0 (300; 400)	600.0 (300; 4800)	550.0 (280; 2150)	600 (280; 4800)	490 (300; 1370)
Total IgE [IU/mL] — mean (SD)	346.1 (745.2)	349.0 (782.2)	352.9 (696.5)	405.7 (873.1)	253.2 (485.7)	347.0 (824.8)	344.0 (529.6)
Total IgE [IU/mL] — median (min; max)	85.0 (2; 4475)	81.0 (2; 4475)	95.5 (8; 2930)	67.0 (2; 4475)	96.0 (17; 2150)	81.0 (2; 4475)	125.0 (8; 1970)
FeNO [ppb] — mean (SD)	53.1 (45.0)	58.5 (47.4)	40.5 (37.1)	56.9 (48.9)	45.8 (36.4)	58.4 (48.0)	39.9 (34.3)
FeNO [ppb] — median (min; max)	37.0 (6; 202)	42.0 (6; 202)	29.0 (10; 150)	40.0 (6; 202)	35.0 (7; 153)	42.0 (7; 202)	32.0 (6; 123)
Annualised exacerbation rate —mean (95% CI)	3.65 (3.18; 4.18)	3.73 (3.16; 4.41)	3.40 (2.67; 4.34)	2.37 (1.97; 2.86)	5.82 (4.96; 6.83)	3.63 (3.13; 4.20)	3.70 (2.71; 5.05)
History of positive allergy test							
Positive	35 (47.9%)	24 (46.2%)	10 (50.0%)	21 (45.7%)	14 (51.9%)	30 (56.6%)	5 (25.0%)
Negative	23 (31.5%)	17 (32.7%)	6 (30.0%)	13 (28.3%)	10 (37.0%)	14 (26.4%)	9 (45.0%)
Unknown	15 (20.5%)	11 (21.2%)	4 (20.0%)	12 (26.1%)	3 (11.1%)	9 (17.0%)	6 (30.0%)

Notes: *One patient was excluded from the subgroup analysis due to an eosinophil count of 280 cells/μL.

Abbreviations: ACQ-5, asthma control questionnaire; CI, confidence interval; FAS, full analysis set; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in one second; IgE, immunoglobulin E; SD, standard deviation.

leukotriene receptor antagonists (LTRA) (each 27.4%), respectively. Prior to the study, 27.4% of patients have been exposed to biologics.[18]

Clinical Remission on Benralizumab

At baseline, none of the patients fulfilled all criteria of the three-item composite endpoint of clinical remission, consisting of ACQ-5 score of <1.5 combined with the absence of exacerbations and mOCS use. Over the course of the study, all individual remission criteria including lung function showed consistent improvements (Figure 1).

The proportion of patients achieving a partial control of asthma symptoms (ACQ-5 < 1.5) increased from 17.8% (13 out of 73) at baseline to 71.8% (28 out of 39) after 56 weeks. Similarly, the proportion of patients with well-controlled asthma symptoms (ACQ-5 ≤ 0.75) increased from 4.1% (3 out of 73) at baseline to 56.4% (22 out of 39) at the end of the study (Figure 2).

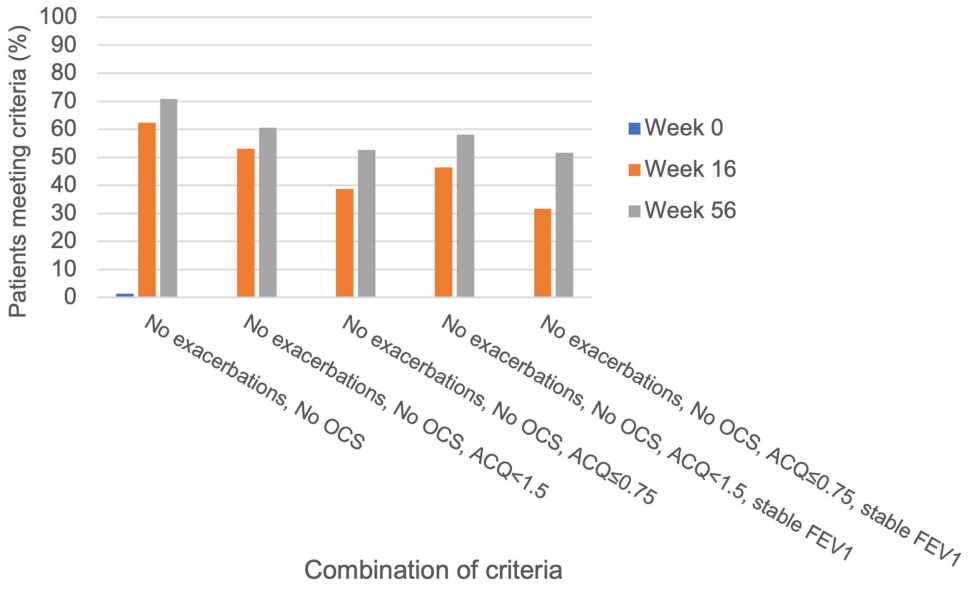

Figure 1 Patients achieving combined components of clinical remission during the course of the study (FAS). Stable FEV_1 defined as improvement of prebronchodilator FEV_1 or as decline ≤ 10% versus baseline.

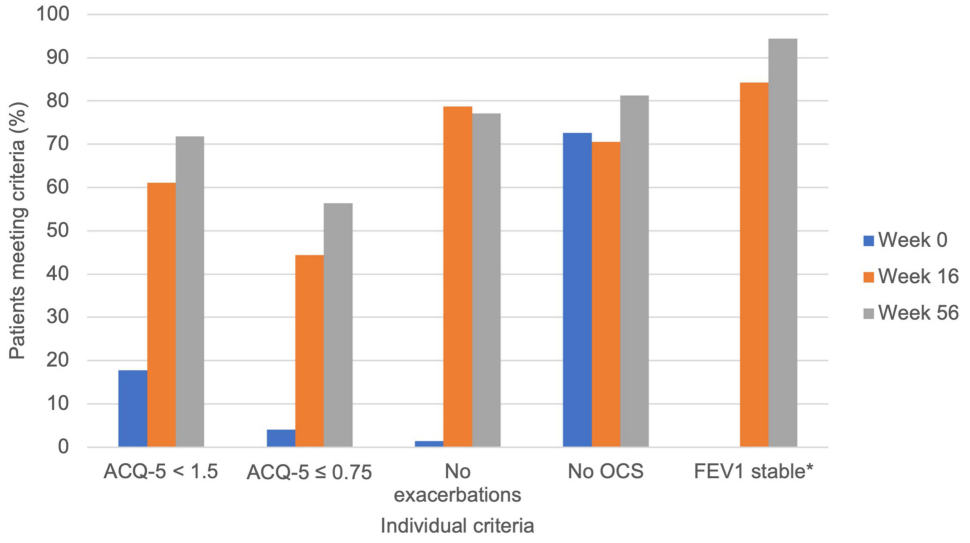

Figure 2 Patients achieving individual components of clinical remission during the course of the study (FAS). *Stable FEV_1 defined as improvement of prebronchodilator FEV_1 or as decline ≤ 10% versus baseline.

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Over the duration of the study, more than three quarters of patients did not experience any exacerbation: 78.7% at week 16 and 77.1% at week 56, respectively, compared to one patient (1.4%) at baseline (Figure 2).

At baseline, 72.6% of patients did not receive any mOCS treatment (53 out of 73). This proportion of patients free of mOCS increased to 81.3% (39 out of 48) throughout the study period (Figure 2).

Compared to baseline, most patients achieved a stable or improved FEV_1 with 84.3% (43 out of 51) at week 16 and 94.4% (34 out of 36) at week 56, respectively (Figure 2).

The proportion of patients who were free of exacerbations and mOCS use increased from 1.4% (1 out of 73) at baseline to 62.3% (38 out of 61) at week 16, and further to 70.8% (34 out of 48) after 56 weeks of benralizumab treatment (Figure 1). When asthma symptom control was added as third criterion of clinical remission, more than half of the patients achieved the three-item composite endpoint at week 56: 60.5% (23 out of 38) of patients with an ACQ-5 < 1.5, and 52.6% (20 out of 38) with an ACQ-5 ≤ 0.75, respectively (Figure 1). When stable or improved FEV_1 was included as fourth criterion, 46.3% of patients (19 out of 41) achieved complete remission with an ACQ-5 < 1.5 at week 16 increasing to 58.1% (18 out of 31) at week 56. Using the stricter threshold of an ACQ-5 ≤ 0.75, 31.7% of patients (13 out of 41) met all four remission criteria at week 16 rising to 51.6% (16 out of 31) at week 56 (Figure 1).

Subgroup Analyses Based on Blood Eosinophil Count

Data from 52 patients with a blood eosinophil count of >400 cells/µL (mean value 823.8 cells/µL) were compared to patients (n=20) with a blood eosinophil count of 300–400 cells/µL (mean value 344.4 cells/µL) at baseline (Table 1). Aside from blood eosinophil differences, clinical characteristics of the subgroup eosinophils >400 showed slightly higher values of ACQ-5, FeNO and AER than in the 300–400 subgroup (Table 1). Additionally, these patients also had a longer duration of asthma (mean 21.5 years) than in the lower eosinophil subgroup (mean 13.3 years). During the study, mean values of ACQ-5 scores decreased consistently in both subgroups.

In the subgroup eosinophils > 400, the mean ACQ-5 score declined from 2.80 (SD 1.29) at baseline to 1.01 (SD 1.14) after 56 weeks of benralizumab treatment (Figure 3). Correspondingly, the proportion of patients with not well-controlled asthma (ACQ-5 > 1.5) decreased from 80.8% (42 out of 52) at baseline to 25.8% (8 out of 31) at week 56. Vice versa, well-controlled asthma (ACQ ≤ 0.75) increased from 3.8% (2 out of 52) to 64.5% (20 out of 31) at the end of the study.

Throughout the study, 71.2% of patients (n=37) were free of exacerbation, 17.3% (n=9) reported one or two such episodes, and 6 patients (11.5%) had ≥3 exacerbations. As a result, the mean AER decreased from 3.73 at baseline (95% CI: 3.16, 4.41) to 0.78 at week 56 (95% CI: 0.42, 1.44) corresponding to a relative reduction of 79.2% (Figure 4).

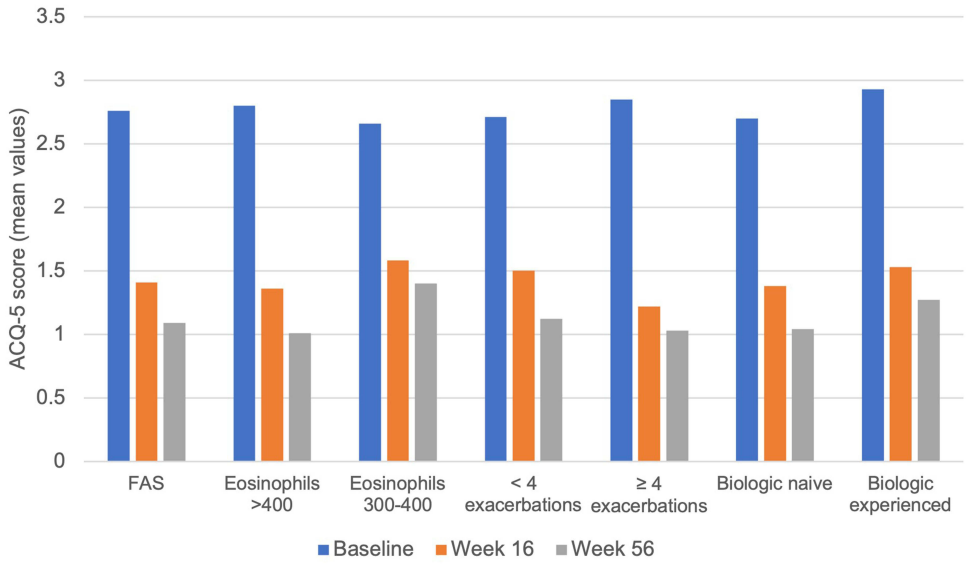

Figure 3 ACQ-5 scores in full analysis set (FAS) and subgroup analyses over the course of the study. Mean absolute values of ACQ-5 scores (unpaired data) at baseline, week 16 and week 56.

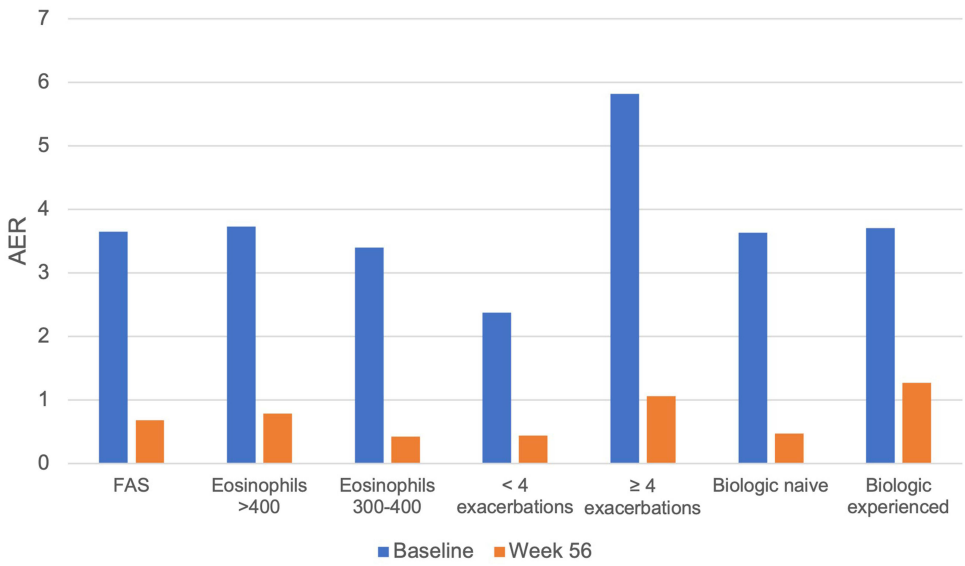

Figure 4 Annual exacerbation rates (AER) in full analysis set (FAS) and subgroup analyses. AER at baseline and at week 56 (negative binomial generalized linear model).

Similar results were obtained in the smaller subgroup eosinophils 300–400. The mean ACQ-5 score decreased from 2.66 (SD 1.24) at baseline to 1.40 (SD 1.12) at week 56 (Figure 3). The proportion of patients with not well-controlled asthma decreased from 85.0% (17 out of 20) at baseline to 37.5% (3 out of 8) at week 56 while the proportion with well-controlled asthma increased from 5.0% (1 out of 20) at baseline to 25.0% (2 out of 8) at the end of the study.

Regarding exacerbations, 80.0% of patients (n=16) in this subgroup remained exacerbation-free during the study, while 20.0% (n=4) reported one or two episodes. The mean AER decreased from 3.40 (95% CI: 2.67, 4.34) at baseline to 0.42 (95% CI: 0.13, 1.35) at week 56 resulting in a relative reduction of 87.7% (Figure 4).

Subgroup Analyses Based on Rate of Prior Exacerbations

Data from 46 patients with <4 exacerbations in the last 12 months prior to the study (mean AER 2.37) were compared with 27 patients who had experienced ≥4 exacerbations (mean AER 5.82) (Table 1). At baseline, the subgroup of frequent exacerbators reported a slightly higher ACQ-5 score but lower FeNO and IgE values compared to the subgroup with <4 exacerbations (Table 1). Throughout the study, mean ACQ-5 scores continuously declined in both subgroups.

In the subgroup < 4 exacerbations, the mean ACQ-5 score decreased from 2.71 (SD 1.38) at baseline to 1.12 (SD 1.21) at week 56 (Figure 3). The low proportion of patients (6.5%, 3 out of 46) with well-controlled asthma at baseline increased to 59.3% (16 out of 27) at the end of the study. Conversely, the high proportion of patients with not well-controlled asthma decreased from 78.3% (36 out of 46) at baseline to 25.9% (7 out of 27) after 56 weeks of treatment with benralizumab.

Throughout the study, 76.1% of patients (n=35) were free of any exacerbations, 15.2% (n=7) reported one episode, and four patients (8.7%) had 2–3 exacerbations. The mean AER declined from 2.37 (95% CI: 1.97, 2.86) at baseline to 0.44 (95% CI: 0.23, 0.86) at week 56 corresponding to a relative reduction of 81.3% (Figure 4).

The subgroup ≥ 4 exacerbations revealed similar results, with the mean ACQ-5 score at baseline (2.85, SD 1.05) decreasing to 1.03 (SD 0.97) at week 56. At baseline, nearly all patients (88.9%, 24 out of 27) had not well-controlled asthma and this proportion decreased to 33.3% (4 out of 12) after 56 weeks of benralizumab treatment. Conversely, none of the patients (0%) had well-controlled asthma at baseline, whereas 50.0% (6 out of 12) reached this status at the end of the study.

Regarding exacerbations, 70.4% of patients (n=19) remained exacerbation-free during the treatment period, 11.1% (n=3) experienced one exacerbation, and five patients (18.5%) reported ≥3. The mean AER decreased from 5.82 (95%

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CI: 4.96, 6.83) at baseline to 1.06 (95% CI: 0.44, 2.55) during treatment corresponding to a relative reduction of 81.8% (Figure 4).

Subgroup Analyses Based on Prior Treatment with Biologics

Based on prior treatment, data from biologic naïve patients (n=53) were analysed separately from data of biologic experienced patients (n=20) (Table 1). Before the study, mepolizumab (n=13), omalizumab (n=6) and dupilumab (n=2) had been used as biologic pretreatments. At baseline, the naïve subgroup reported higher values of eosinophils, FeNO and allergies compared to the other subgroup (Table 1). During the study, mean ACQ-5 scores declined consistently in both subgroups.

In the subgroup naïve treatment, the mean ACQ-5 score decreased from 2.70 (SD 1.17) at baseline to 1.04 (SD 1.18) after 56 weeks of benralizumab (Figure 3). At baseline, 81.1% of patients (43 out of 53) presented with not well-controlled asthma. After 56 weeks of treatment with benralizumab, fewer than one quarter of patients (23.3%, 7 out of 30) reported this level of asthma symptoms. Correspondingly, the proportion of patients with well-controlled asthma increased from 3.8% (2 out of 53) at baseline to 60.0% (18 out of 30) at the end of the study.

Throughout the study, 77.4% of patients (n=41) were free of any exacerbation, 17.0% (n=9) reported one or two such episodes, and 3 patients (5.7%) had 3 exacerbations. Thus, the mean AER at baseline decreased from 3.63 (95% CI: 3.13, 4.20) to 0.47 (95% CI: 0.24, 0.90) at week 56 representing a relative reduction of 87.1% (Figure 4).

Similar results were observed in the smaller subgroup biologic experienced. The mean ACQ-5 score at baseline (2.93, SD 1.51) decreased to 1.27 (SD 0.99) at week 56. At baseline, almost all patients (85.0%, 17 out of 20) had not well-controlled asthma and this proportion declined to less than half (44.4%, 4 out of 9) at the end of the study. Similarly, the low proportion of patients with well-controlled asthma increased from 5.0% (1 out of 20) at baseline to 44.4% (4 out of 9).

Throughout the study, 65.0% of patients (n=13) remained free of exacerbations, four patients (20.0%) reported one or two exacerbations, and three patients (15.0%) had ≥3 episodes. Accordingly, the mean AER decreased from 3.70 (95% CI: 2.71, 5.05) at baseline to 1.27 (95% CI: 0.49, 3.25) representing a relative reduction of 65.8% (Figure 4).

Discussion

In the real-life study of 73 patients with SEA treated with benralizumab for 56 weeks, we found that 58.1% of patients achieved clinical remission defined by absence of exacerbations, no need for mOCS, stable or improved lung function and an ACQ-5 score <1.5. With the stricter threshold of an ACQ-5 score ≤0.75, 51.6% of patients reached clinical remission. Similar remission rates were measured when patients were stratified by blood eosinophil counts, prior exacerbation rates or the prior use of biologics.

At baseline, the majority of patients (82.2%) had presented with not well-controlled asthma (ACQ-5 > 1.5, mean 2.76), a mean AER of 3.65, and a mean mOCS dose of 26.6 mg/day (SD 15.0). As early as week 16 after initiation of benralizumab, a clinical improvement was observed and all four remission criteria were met by 46.3% (ACQ-5 < 1.5) and by 31.7% of patients (ACQ-5 ≤ 0.75), respectively.

These results on the four-item remission endpoint are consistent with the early and sustained response to benralizumab seen in the analyses of the individual remission components in the overall study population published previously.[18]

ICS and OCS have long been considered the gold standard asthma therapy. They are effective but non-specific anti-inflammatory medications, and OCS are associated with a variety of adverse effects contributing substantially to the burden of disease. In recent years, several targeted biologic treatments have been developed and adopted by national and international guidelines and recommendations for the treatment of severe asthma in addition to inhaled medication.[5] Phenotyping, based mainly on blood eosinophils, FeNO and IgE/allergy status, enables a more precise, targeted approach to address the underlying mechanisms of inflammation in individual patients. With this treat-to-target strategy, the concept of remission can generally be applied to all asthma patients regardless of disease severity or treatment. Remission could be established as an aspirational goal and implemented into international guidelines, making a paradigm shift from the traditional treat-to-failure strategy.[5,12] Notably, remission as long-term goal of asthma therapy

was adopted into the German guideline in 2023, aiming for a sustainable prevention of symptoms instead of the previous treatment of symptoms.[3]

Our real-world remission data is in line with a pooled post-hoc analysis of randomized controlled trials (RCTs) of patients with SEA treated with benralizumab for 12 months.[12] In that analysis, 83% of patients achieved ≥2 and 49% achieved ≥3 remission components out of a four-item composite endpoint consisting of ACQ-6 scores <1.5 or ≤0.75, no OCS use, no exacerbations, and an increase of pre-bronchodilator FEV_1 of ≥100 mL. The individual criteria used in these RCT analyses were similar to our approach except the six-item questionnaire ACQ-6 which additionally evaluates rescue medication use. Furthermore, lung function remission in the RCTs was defined as an increase of $FEV_1 \geq 100$ mL, whereas in our study it was defined as an improvement of prebronchodilator FEV_1 from baseline but also allowing a decline of ≤10%. Importantly, no consensus definition of FEV_1 improvement has yet been established, current guidelines do not provide a specific threshold, and a recently published paper calls for a globally standardised definition of remission.[5,24]

Our study is part of the prospective, real-world XALOC-2 program with benralizumab, which also includes SEA patients in Belgium, Canada, and Germany. At week 56, 42% of patients met the three-item remission criteria (asthma symptom control ACQ < 1.5, no exacerbations, no mOCS) which aligns well with the results of our study in Switzerland.[25]

XALOC-1, a large retrospective real-world study program in Canada, Italy, Portugal, Spain, and UK included patients with SEA treated with benralizumab over 96 weeks. In this study, clinical remission was defined as well-controlled asthma symptoms (ACQ-6 ≤ 0.75 or Asthma Control Test (ACT) score ≥ 20), absence of exacerbations and no OCS use, but without including any lung function criterion.[26] Remission was shown to be a realistic and sustainable goal as 39% of patients met the three-item composite endpoint at week 48 and 31% at week 96, respectively.

Taken together, evidence from both RCTs and real-world studies demonstrates that achieving clinical remission with benralizumab is a realistic goal for patients with SEA.[27]

A real-world effectiveness study with mepolizumab, an anti-IL5 monoclonal antibody, reported that 30% of patients fulfilled the four-item remission criteria (no exacerbations, no OCS use, ACT score ≥ 20, $FEV_1 \geq 80\%$) after one year.[28] In the current study, the number of patients achieving the four-item composite remission after 56 weeks was 51.6%. Differences in outcomes might be attributed to different definitions of remission criteria, particularly for asthma symptom control which has a strong impact on remission rates.[24] Additionally, the heterogeneous disease severity of included patients precludes a direct comparison between the available biologics, and corresponding head-to-head trials are still lacking.[12,29,30] Recently, a systematic review reported pooled clinical remission rates of 38% with a three-item and 30% with a four-item definition, respectively, in patients with severe asthma treated with biologics.[31]

Our subgroup analyses stratified by baseline blood eosinophil counts, prior exacerbation rates, or the effect of pretreatment with biologics, confirmed the results obtained from the remission analyses of the total study population. At baseline, patients in all subgroups were characterized by a high burden of disease with elevated ACQ-5 scores ranging from 2.66 to 2.93 and AER between 2.37 and 5.82. After treatment with benralizumab, both asthma symptoms and AER considerably decreased, with consistent improvements across all subgroups. The present subgroup results also demonstrate the early (1–2 weeks) and sustained (week 56) improvement in ACQ-5 scores observed in the total population (data not shown).[18] Regarding exacerbations, AER were reduced to 0.42 and 1.27 by the end of the study. Particularly noteworthy were the frequent exacerbators who entered the study with a mean AER of 5.82 and achieved an impressive reduction to 1.06 (81.8% relative reduction) by week 56. Preventing exacerbations, and thereby OCS bursts, reduces cumulative OCS dose minimizing the risk for OCS associated serious long-term adverse side effects. Despite being recommended only "as last resort" treatment, many patients continue to receive mOCS as also seen in our cohort.[5] With benralizumab treatment, the proportion of patients free of mOCS progressively increased over the course of the study.

The likelihood of clinical remission may be associated with baseline type 2 inflammation, particularly blood eosinophil counts, as well as with a history of recurrent exacerbations and a better lung function. However, subgroup analysis in our study demonstrated that clinical remission can be achieved with benralizumab irrespective of these baseline characteristics. These findings support the use of benralizumab in addition to standard of care as a remission-oriented, treat-to-target approach in SEA. Adopting simple remission criteria (ACQ-5, exacerbation history, mOCS

exposure, pre-bronchodilator FEV_1), measured longitudinally at defined intervals, can facilitate remission evaluation in the clinical setting. Furthermore, our results highlight the need for standardized remission definitions and prospective trials investigating other predictors of durable remission in SEA.

General limitations of our real-world study have been discussed previously by Stolz et al (2024).[18] Due to the study design and the small sample size in certain subgroups no statistical hypothesis testing was performed. Hence, findings of the current subgroup analyses should be regarded as exploratory. Nevertheless, statistically significant and clinically meaningful improvement in mean ACQ-5 scores were observed consistently in all subgroups.

Poor symptom control contributes substantially to the burden of disease in asthma and increases the risk of recurrent exacerbations with emergency room visits and hospitalizations. High relapse rates of asthma exacerbations of around 20% within 18 months after discharge from the emergency department were recently reported in a Swiss retrospective observational study,[32] highlighting the high socioeconomic burden of asthma due to loss in productivity and increasing healthcare costs.[15,33] The majority of patients in our study were in working age (mean age 53.8 years, the youngest being 19 years) and reported frequent symptoms and exacerbations at baseline that most likely impaired their productivity and increased absences from work or school. Importantly, more than half of the patients achieved clinical remission on treatment with benralizumab, presumably with a meaningful favourable socioeconomic impact.

Conclusion

Benralizumab is effective for achieving clinical remission in severe eosinophilic asthma irrespective of baseline characteristics, including blood eosinophil count, history of recurrent exacerbations and lung function. More than half of the included patients met all four remission criteria at week 56 with consistent improvements across symptoms, exacerbation rate, mOCS use, and lung function. These findings support the use of benralizumab for treating and inducing remission in diverse patient populations.

Data Sharing Statement

No data from this study, aside from what is published here, will be made available.

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