CHEST

XALOC-1

Clinical Remission Over 2 Years With Benralizumab in Severe Eosinophilic Asthma

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BACKGROUND: Long-term real-world data on clinical remission in patients with severe eosinophilic asthma (SEA) receiving biologics are lacking. We describe clinical remission over 2 years in patients with SEA receiving benralizumab.

RESEARCH QUESTION: Is long-term clinical remission a viable goal for patients with SEA receiving benralizumab?

STUDY DESIGN AND METHODS: XALOC-1 is a multinational, retrospective, real-world program in adults with SEA who received benralizumab for ≤ 96 weeks. Percentages of patients meeting the components and composite of clinical remission (no exacerbations, no maintenance oral corticosteroid use, and well-controlled asthma [Asthma Control Test score ≥ 20 or 6-item Asthma Control Questionnaire score ≤ 0.75]) were assessed at weeks 0, 48, and 96. The association between key baseline demographics, clinical characteristics, and clinical remission status was assessed at weeks 48 and 96 using multivariable logistic regression analysis.

RESULTS: Of 1,070 patients, 0.4%, 39%, and 31% met the 3-component clinical remission criteria at weeks 0, 48, and 96, respectively. In biologic-naive and biologic-experienced patients, remission occurred in 43% and 32% (week 48), and 36% and 23% (week 96), of patients, respectively. Lower maintenance oral corticosteroid dose (OR, 0.51; 95% CI, 0.34-0.76), lower BMI (OR, 0.56; 95% CI, 0.36-0.86), and higher peak eosinophil count (OR, 1.68; 95% CI, 1.05-2.69) at baseline were positively associated with meeting criteria for clinical remission at week 96.

INTERPRETATION: Our results indicate that clinical remission is a realistic goal, sustainable up to 2 years in around one-third of patients with SEA receiving benralizumab. In this study, remission was more likely in patients with lower baseline disease burden, suggesting that further research is warranted regarding whether earlier initiation of a biologic may be beneficial.

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KEY WORDS: benralizumab; biologics; clinical remission; real world; severe eosinophilic asthma

ABBREVIATIONS: ACT = Asthma Control Test; ACQ-6 = 6-item Asthma Control Questionnaire; AER = annualized exacerbation rate; BD = bronchodilator; BEC = blood eosinophil count; FENO = fractional exhaled nitric oxide; MCID = minimal clinically important difference; mOCS = maintenance oral corticosteroid; OCS = oral corticosteroid; RCT = randomized controlled trial; SEA = severe eosinophilic asthma

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Take-Home Points

Study Question: Is clinical remission a viable and sustainable goal for patients with severe eosinophilic asthma receiving treatment with benralizumab?

Results: The components and composite of clinical remission (no exacerbations, no maintenance oral corticosteroid use, and well-controlled asthma [Asthma Control Test score ≥ 20 or 6-item Asthma Control Questionnaire score ≤ 0.75]) were met by 1.1% (8 of 738), 45% (171 of 379), and 38% (118 of 314) of patients at weeks 0, 48, and 96, respectively. Among patients who met criteria at week 96, 59% had sustained remission from week 48.

Interpretation: Our results show that clinical remission is a realistic and sustainable goal in around one-third of patients with severe eosinophilic asthma receiving benralizumab. In this study, patients with lower baseline disease burden were more likely to achieve clinical remission, emphasizing the importance of early treatment intervention; further research in this area is warranted to determine if earlier initiation of a biologic may be beneficial.

Most patients with severe asthma have an eosinophilic phenotype characterized by eosinophilic airway inflammation and blood eosinophilia.[1] Benralizumab is a humanized monoclonal antibody that binds to the alpha subunit of IL-5 receptor alpha on eosinophils, eosinophilic precursors, and basophils. It induces rapid and near-complete depletion of peripheral blood and tissue eosinophils through enhanced antibody-dependent cell-mediated cytotoxicity.[2,3] Phase 3 randomized controlled trials (RCTs) of benralizumab in patients with severe eosinophilic asthma (SEA) have demonstrated significantly reduced exacerbation rates, improved lung function and asthma symptoms, and reduced daily oral corticosteroid (OCS) use vs placebo.[4-6] Twelve-month data from the real-world XALOC-1 study program demonstrated that patients with SEA receiving benralizumab experienced substantial improvements in clinical outcomes, irrespective of previous biologic use or key baseline characteristics on which treatment decisions are often based.[7]

Although treatment goals have traditionally focused on symptom control, the approval of biologics has transformed the SEA treatment landscape, with international guidelines now including clinical remission as an aspirational goal.[8] The key components of remission in asthma (defined using a modified Delphi survey) are the following: ≥ 12 months without significant symptoms by a validated instrument, no OCS use for asthma, patient/provider agreement regarding remission, and lung function optimization/stabilization.[9] Historically, symptom control validation measures and cutoffs have varied between studies[10-13]; however, consensus has been established for asthma symptom control within the broader framework of clinical remission.[14] Experts from an asthma work group recommend that clinical remission should be characterized by consistently low symptom burden (eg, Asthma Control Test [ACT] score > 20, Asthma Impairment and Risk Questionnaire score < 2, Asthma Control Questionnaire score < 0.75) on all assessments over a 12-month period, with at least 2 measurements within that time frame. Additionally clinical remission should be distinguished from good asthma control by setting more rigorous criteria and recognizing the ability to taper inhaled corticosteroids (particularly in patients receiving monoclonal antibody therapy) as an aspirational marker of remission.[14]

In this integrated analysis of 1,070 patients from XALOC-1, we describe patients with SEA who achieve clinical remission, with or without prior biologic experience, and by key baseline characteristics, over 2 years of benralizumab therapy. This is the largest real-world study to date of patients with SEA receiving benralizumab, including, uniquely, a long follow-up of a large population of biologic-experienced patients who are often underrepresented in clinical trials.

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Study Design and Methods

XALOC-1 is a single-arm, multinational, retrospective, observational real-world program composed of 5 national studies investigating adults (≥ 18 years of age) with SEA who received benralizumab for up to 96 weeks: Canada (Various Outcomes Associated With Long-term Treatment in Patients Switching to Benralizumab [VOLTS]), Italy (Characterization of Italian Severe Uncontrolled Asthmatic Patients Key Features When Receiving Benralizumab in a Real-Life Setting: the Observational Retrospective [ANANKE]), Portugal (Benralizumab Study: Retrospective, Observational Study in Portuguese Hospitals to Describe Patient Characteristics, Treatment Patterns and Outcomes [BETREAT]), Spain (Observational Retrospective Study to Characterise and Assess Clinical Outcomes of Patients Receiving Benralizumab After Marketing Approval in Spain [ORBE II]), and the United Kingdom (Benralizumab Patient Access Programme [BPAP]) (2018-2023). The program was designed to assess the effectiveness of benralizumab, its patterns of use, and the characteristics of patients treated with benralizumab as part of a patient access program or routine care. Methodology has been published previously.[7]

All studies were performed in accordance with the Declaration of Helsinki, good pharmacoepidemiology practice, and the International Conference on Harmonization guideline for good clinical practice and applicable legislation on noninterventional and/or observational studies. Ethical approval was provided by an institutional review board and/or independent ethics committee for each site. Specific details for all studies are included in the Supplementary material. All patients provided informed consent.

Baseline was defined as the 12-month period before the index date (first administration of benralizumab). The follow-up period was from the index date up to 96 ± 4 weeks (2 years, hereafter referred to as week 96). A separate analysis was conducted with a follow-up period of 48 ± 4 weeks (1 year, hereafter week 48) (e-Fig 1). Patients could have been lost to follow-up, discontinued benralizumab, and/or switched to other biologic(s) after benralizumab initiation. Clinical outcome data were censored at week 96, or at loss to follow-up, death, or switching biologic, whichever occurred earlier.

This integrated analysis included adults with SEA, as defined in each national study, receiving benralizumab and with ≥ 3 months of follow-up data available after index date, as described previously.[7] Patients receiving any biologic for asthma in a clinical trial at the time of enrollment were ineligible. Previous routine treatment with mepolizumab, omalizumab, and reslizumab was permitted. No dupilumab- and tezepelumab-experienced patients were included (these biologics were not approved for SEA at the time of XALOC-1 initiation).

Patients were categorized as biologic-naive (no biologic treatment for SEA during baseline period) or biologic-experienced (≥ 1 biologic treatment for SEA during baseline period). Biologic-experienced patients were further stratified by previous omalizumab or mepolizumab use (no stratification by previous reslizumab use due to small sample size). Additional subgroups were defined based on key baseline clinical characteristics (e-Table 1).

Clinical remission was defined by a 3-component composite of no exacerbations, no maintenance oral corticosteroid (mOCS) use, and well-controlled asthma (ACT score ≥ 20 or 6-item Asthma Control Questionnaire [ACQ-6] score ≤ 0.75)[14]; improvement in lung function was not included because data on FEV_1 were limited (only 15% [162 of 1,070] and 4% [43 of 1,070] of patients had data at weeks 48 and 96, respectively). Each component of clinical remission (no asthma exacerbations, no mOCS use, well-controlled asthma) was assessed at weeks 0 (before index date), 48, and 96. Exacerbations at week 0 reflect the baseline period, exacerbations at week 48 reflect the period from baseline to week 48, and exacerbations at week 96 reflect the period from baseline to week 96. To achieve clinical remission at week 96, patients were required to have no exacerbations from baseline to week 96. For inclusion in the 3-component and individual component clinical remission analyses, patients were required to have follow-up data (for all 3 components or for each individual component, respectively), up to each respective timepoint, regardless of benralizumab continuation. A less stringent definition of clinical remission was also applied using different cutoffs for asthma control (ACT score ≥ 16 or ACQ-6 score < 1.5).

Outcomes measured at baseline and weeks 16, 24, 48, 72, and 96 were annualized exacerbation rate (AER), number of asthma exacerbations, mOCS use, mOCS daily dose, patient-reported asthma symptom control scores (ACT [Canada, Italy, Portugal, Spain] and ACQ-6 [Canada, United Kingdom]), prebronchodilator (BD) and post-BD FEV_1, inhaled corticosteroid use, and blood

eosinophil count (BEC). Definitions of asthma exacerbations, asthma symptom control, and minimal clinically important difference (MCID) in ACT and ACQ-6 scores, and BEC are provided in e-Table 1. Reasons for discontinuation of previous biologic were captured for the baseline period, and benralizumab treatment patterns (duration, adherence, discontinuation, and reasons for discontinuation) were captured over the 96-week follow-up period. Reasons for discontinuation were classified as lack of efficacy, adverse event (detail not available), or other.

Descriptive statistics, including mean, median, SD, range for continuous variables, and percentage of patients for categorical variables, are presented for baseline demographics and clinical characteristics; only nonmissing values are presented. The proportion of patients meeting the 3-component clinical remission criteria (and each individual criterion) is presented as number and percentage at weeks 0, 48, and 96, overall (all patients), by previous biologic use, and by key baseline characteristic (e-Table 1).

Logistic regressions (e-Appendix 1) were used to assess the association between key baseline demographics, clinical characteristics, and clinical remission status (no exacerbations, no mOCS use, and asthma symptom control [ACT score $\geq$ 16 or ACQ-6 score $<$ 1.5]) at weeks 48 and 96. Significance was determined using log-likelihood ratios. Results are presented as ORs with 95% CIs and *P* values to examine the association for each of the listed characteristics adjusted for each characteristic in the model. Comparisons were 2-sided with significance considered at α level .05.

Longitudinal mixed models with repeated measures were used to summarize continuous end points over time with estimated means and corresponding 95% CIs for change from baseline in ACT and ACQ-6 scores, pre- and post-BD FEV_1, and peak BEC. The percentage of patients achieving MCID in ACT and ACQ-6 scores was calculated using binomial Clopper-Pearson exact 95% CIs. For inclusion in the analysis of asthma exacerbation, including AER at week 96, patients must have received $\geq$ 1 benralizumab injection after week 48 and either discontinued before week 96 or completed $\geq$ 92 weeks of follow-up from the index date. The AERs and corresponding 95% CIs and *P* values were calculated for the baseline and follow-up periods using generalized linear regression with a negative binomial distribution. An assessment of the differences between those who completed the study and those who dropped out is described in e-Appendix 1.

Results

Patients

A total of 1,070 patients were eligible for inclusion in this integrated analysis. Mean age $\pm$ SD at the index date was 55.2 $\pm$ 13.7 years, and 58.7% of patients were female (Table 1). Clinical characteristics were broadly similar between biologic-naive and biologic-experienced patients, and 55% of patients (585 of 1,070) were receiving mOCS. There were no notable differences in demographic and clinical characteristics: between countries (beyond a range in the baseline AER of 1.7-5.3) (e-Table 2), between all patients and those included in the clinical remission analysis at weeks 48 and 96 (e-Table 3), or between all patients and those included in the exacerbation analysis at week 96 (e-Table 4).

Most patients (62% [662 of 1,070]) were biologic-naive and 38% (404 of 1,070) were biologic-experienced (Table 1). Of those who were biologic-experienced, 44% (176 of 404) had received omalizumab, 63% (253 of 404) had received mepolizumab, and 8.2% (33 of 404) had received reslizumab. The median time between the last dose of a previous biologic and first dose of benralizumab was 46 days (interquartile range, 1-328) for omalizumab (n = 160), 56 days (interquartile range, 18-154) for mepolizumab (n = 248), and 57 days (interquartile range, 43-154) for reslizumab (n = 33). Additional data regarding previous biologic use and reasons for discontinuation across all previous biologics are reported in the supplementary results.

Persistence of Treatment

Overall, 51% of patients (542 of 1,070) had 96 weeks of follow-up data, of whom 78% (424 of 542) were still receiving benralizumab at 96 weeks (79% [256 of 324] of biologic-naive and 77% [166 of 216] of biologic-experienced patients; 2 patients were missing previous biologic experience data) (e-Fig 2). Treatment duration and discontinuation are reported in e-Figure 3. Additional data regarding those with and without 96 weeks of follow-up data are reported in e-Table 5.

TABLE 1] Baseline Demographics and Disease Characteristics, Overall (All Patients) and According to Patients' Previous Biologic Experience

Characteristic	All Patients (N = 1,070)	Biologic-Naive Patients (n = 662)	Biologic-Experienced Patients		
			All Biologic-Experienced Patients (n = 404)[a]	Omalizumab-Experienced Patients (n = 176)	Mepolizumab-Experienced Patients (n = 253)
Age at the index date, y	55.2 [13.7]	56.5 [13.6]	53.1 [13.7]	53.5 [13.5]	52.0 [14.2]
Age at asthma diagnosis					
Years	(n = 703) 37.8 [18.3]	(n = 457) 38.4 [18.8]	(n = 244) 36.8 [17.1]	(n = 100) 34.5 [16.2]	(n = 153) 36.6 [17.9]
< 18 y[b]	114 (11)	74 (11)	39 (9.7)	21 (12)	26 (10)
≥ 18 y[b]	589 (55)	383 (58)	205 (51)	79 (45)	127 (50)
Sex, female[b]	628 (59)	395 (60)	231 (57)	101 (57)	141 (56)
BMI, kg/m^2,[c]	(n = 968) 29.3 [7.0]	(n = 599) 28.8 [6.6]	(n = 366) 30.2 [7.3]	(n = 151) 29.5 [6.7]	(n = 236) 31.0 [7.7]
Smoking history[b]					
Never smoked	630 (59)	388 (59)	239 (59)	101 (57)	146 (58)
Currently smokes	39 (3.6)	28 (4.2)	11 (2.7)	4 (2.3)	7 (2.8)
Previously smoked	329 (31)	209 (32)	119 (30)	50 (28)	82 (32)
Positive atopic status[b, d]	470 (44)	267 (40)	203 (50)	101 (57)	123 (49)
Concomitant CRSwNP[b, d]	331 (31)	196 (30)	135 (33)	48 (27)	91 (36)
Concomitant allergic rhinitis	(n = 871) 186 (21.4)	(n = 524) 104 (19.8)	(n = 343) 81 (23.6)	N/A	N/A
mOCS use at the index date[e]	585 (55)	351 (53)	232 (57.4)	88 (50.0)	161 (63.6)
Daily mOCS dosage, mg/d[e]	15.9 [13.2]	16.1 [13.3]	15.5 [12.9]	14.6 [13.0]	16.9 [14.0]
Daily mOCS dosage, mg/d[e]	10 (5-25)	10 (5-25)	10 (5-20)	10 (5-20)	10 (5-25)
Pre-BD FEV_1, L[d]	(n = 421) 1.9 [0.8]	(n = 294) 2.0 [0.8]	(n = 127) 1.9 [0.8]	N/A	N/A
Post-BD FEV_1, L[d]	(n = 440) 2.0 [0.8]	(n = 285) 2.0 [0.8]	(n = 155) 1.9 [0.8]	(n = 47) 2.0 [0.9]	(n = 106) 1.8 [0.8]
AER during 12-mo baseline period, mean (95% CI)[f]	(n = 636) 3.8 (3.5-4.0)	(n = 372) 3.9 (3.6-4.3)	(n = 262) 3.5 (3.1-4.0)	(n = 100) 3.0 (2.5-3.6)	(n = 177) 3.5 (3.0-4.0)

(Continued)

TABLE 1] *(Continued)*

Characteristic	All Patients (N = 1,070)	Biologic-Naive Patients (n = 662)	Biologic-Experienced Patients		
			All Biologic-Experienced Patients (n = 404)[a]	Omalizumab-Experienced Patients (n = 176)	Mepolizumab-Experienced Patients (n = 253)
Peak BEC during baseline period, cells/μL	(n = 1,034) 500 (300-850)	(n = 648) 600 (400-950)	(n = 383) 400 (190-700)	(n = 167) 490 (300-720)	(n = 239) 300 (100-680)
Total serum IgE, International Units/mL[d]	(n = 616) 161 (56.7-466)	(n = 429) 125 (48.0-387)	(n = 184) 309 (96.1-616)	N/A	N/A
FENO, ppb[d]	(n = 507) 55.9 [49.2]	(n = 298) 52.4 [47.7]	(n = 209) 60.8 [50.9]	N/A	N/A
ACQ-6 score[c]	(n = 389) 3.0 [1.5]	(n = 208) 3.0 [1.4]	(n = 180) 2.9 [1.5]	(n = 51) 3.0 [1.4]	(n = 146) 3.0 [1.5]
ACT score[c]	(n = 350) 14.3 [5.0]	(n = 239) 14.2 [4.9]	(n = 111) 14.4 [5.3]	(n = 62) 15.4 [5.3]	(n = 48) 13.5 [5.4]

Data are presented as mean [SD], No. (%), median (interquartile range), or as otherwise indicated. The index date was the day of benralizumab treatment initiation. The baseline period was the 12 mo before the index date. Of the 1,070 patients, 305 (29%) were from Canada, 216 (20%) were from Italy, 74 (7%) were from Portugal, 199 (19%) were from Spain, and 276 (26%) were from the United Kingdom. ACQ-6 = 6-item Asthma Control Questionnaire; ACT = Asthma Control Test; AER = annualized exacerbation rate; BD = bronchodilator; BEC = blood eosinophil count; CRSwNP = chronic rhinosinusitis with nasal polyposis; FENO = fractional exhaled nitric oxide; mOCS = maintenance oral corticosteroid; N/A = not available; ppb = parts per billion.

[a]Data on biologic-experience status were missing for 4 patients (0.4%); previous biologic therapies included omalizumab (n = 176), mepolizumab (n = 253), and reslizumab (n = 33) (333 [82%] had only used 1 previous biologic therapy and 61 [15%] had used > 1 previous biologic therapy; no patients with a history of dupilumab were included because this treatment was not available at the time of program initiation).

[b]Percentage of total number of patients, which includes missing 367 (34%) for age at asthma diagnosis, 1 (0.1%) for sex, 72 (6.7%) for smoking history, 7 (0.7%) for mOCS use (missing or unknown) in the 12-mo baseline period, 300 (37%) for atopic status, and 7 (0.7%) for CRSwNP.

[c]The most recent measurement in the baseline period.

[d]Based on medical records available at the index date.

[e]mOCS dose was calculated as the patient's mean daily dosage over the past 30 d on or before the index date. Note that an mOCS dose > 100 mg was excluded from this descriptive summary for 1 biologic-naive patient.

[f]Based on the study population for the analysis of asthma exacerbation.

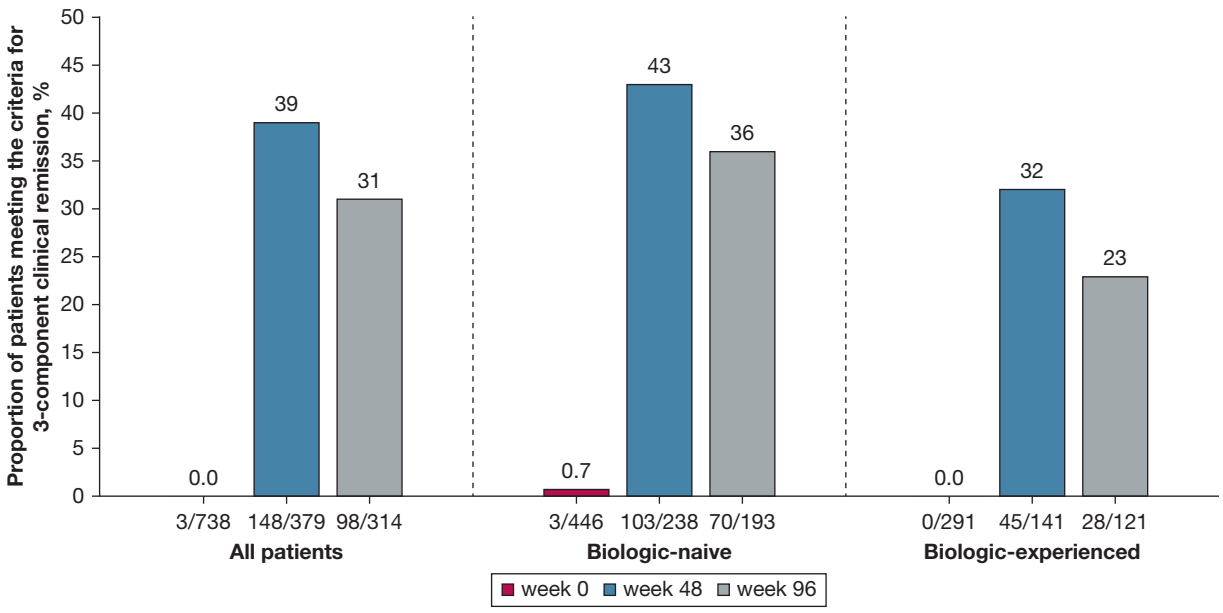


Figure 1 – *Percentage of patients achieving 3-component clinical remission overall at weeks 0, 48, and 96, overall (all patients) and according to patients' previous biologic experience. Previous biologic therapies included omalizumab (n = 176), mepolizumab (n = 253), and reslizumab (n = 33) (333 [82%] had only used 1 previous biologic therapy and 61 [15%] had used > 1 previous biologic therapy; data on previous biologic use were missing for 10 patients [2.5%]). The 3-component clinical remission was defined as no exacerbations, no maintenance oral corticosteroid use, and well-controlled asthma (Asthma Control Test score ≥ 20 or 6-item Asthma Control Questionnaire score ≤ 0.75).*

Clinical Remission

The criteria for 3-component clinical remission were met in 0.4% (3 of 738), 39% (148 of 379), and 31% (98 of 314) of patients at weeks 0, 48, and 96, respectively (Fig 1). Remission was more likely in biologic-naive compared with biologic-experienced patients (week 48: 43% [103 of 238] and 32% [45 of 141]; week 96: 36% [70 of 193] and 23% [28 of 121], respectively).

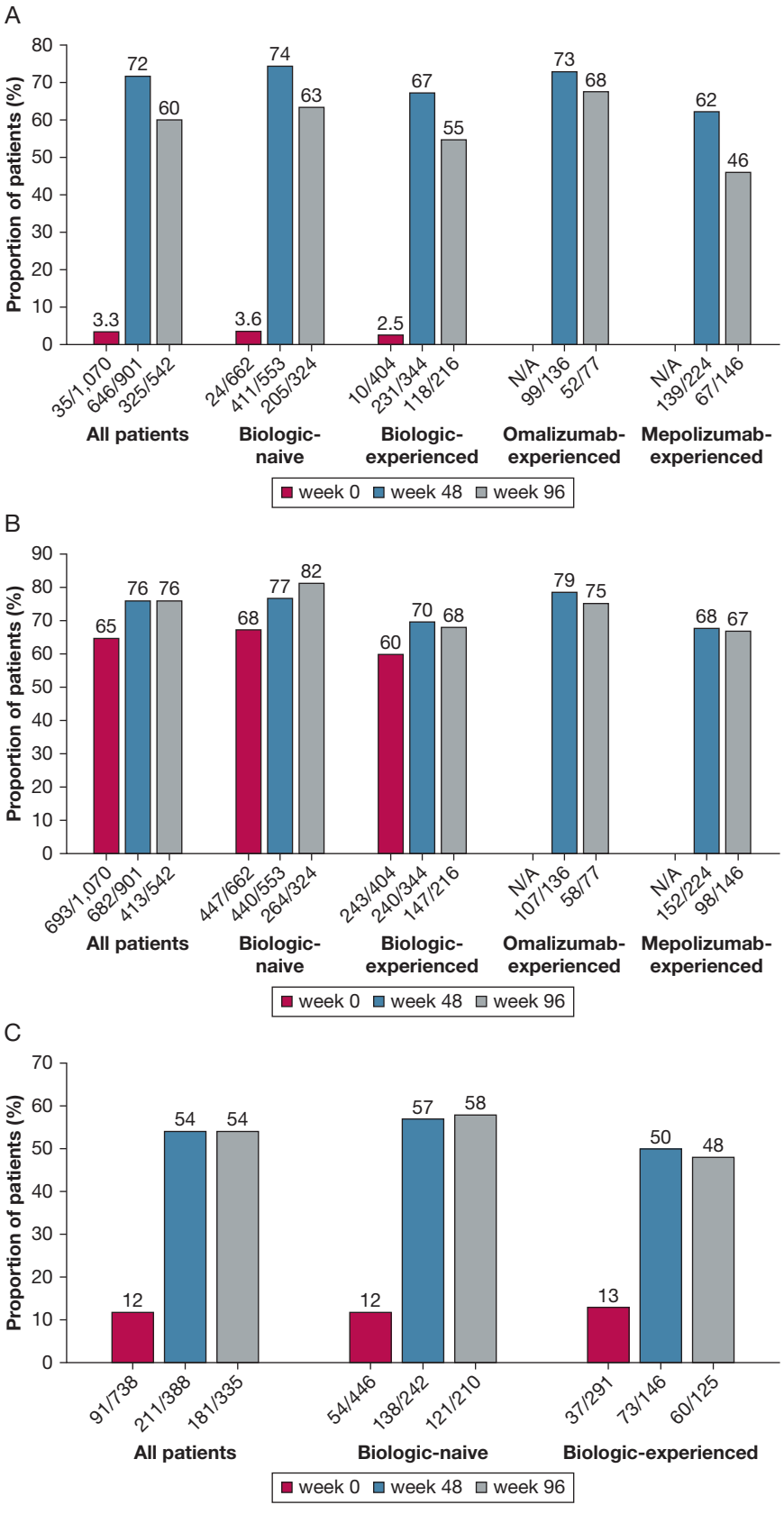
When using the less stringent cutoffs for asthma symptom control (ACT score ≥ 16 or ACQ-6 score < 1.5), the 3-component clinical remission criteria were met in 1.1% (8 of 738), 45% (171 of 379), and 38% (118 of 314) of patients at weeks 0, 48, and 96, respectively (e-Fig 4). Additional data using these criteria are reported in the supplementary results.

At weeks 48 and 96, 3-component clinical remission (using the less stringent cutoffs for asthma symptom control; ACT score ≥ 16 or ACQ-6 score < 1.5) was met more often in patients with lower BMI, concomitant chronic rhinosinusitis with nasal polyps, negative atopic status, higher predicted pre-BD FEV_1, and higher peak BEC at baseline (e-Figs 5, 6). The percentage of patients meeting the 3-component remission criteria (using ACT score ≥ 16 or ACQ-6 score < 1.5) by fractional exhaled nitric oxide (F_{ENO}) level and atopic status are presented in e-Figures 7 and 8.

Clinical Remission: Individual Components

Overall, 3.3% of patients (35 of 1,070) were exacerbation free at week 0, 72% (646 of 901) were exacerbation free at week 48, and 60% (325 of 542) were exacerbation free at week 96 (Fig 2A). A higher percentage of biologic-naive than biologic-experienced patients were exacerbation free at weeks 48 and 96 (74% [411 of 553] vs 63% [205 of 324], and 67% [231 of 344] vs 55% [118 of 216], respectively) (Fig 2A). At week 0, 65% of patients (693 of 1,070) had no mOCS use; this increased to 76% (682 of 901) and 76% (413 of 542) at weeks 48 and 96, respectively (Fig 2B). Use of mOCS was greater for biologic-naive than biologic-experienced patients at weeks 48 (77% [440 of 553] vs 70% [240 of 344]) and 96 (81% [264 of 324]) vs 68% [147 of 216]). Well-controlled asthma (ACT score ≥ 20 or ACQ-6 score ≤ 0.75) was reported in 12% (91 of 738), 54% (211 of 388), and 54% (181 of 335) of patients at weeks 0, 48, and 96, respectively (Fig 2C). More biologic-naive compared with biologic-experienced patients reported well-controlled asthma at weeks 48 (57% [138 of 242] vs 50% [73 of 146], respectively) and 96 (58% [121 of 210] vs 48% [60 of 125], respectively). Achievement of asthma symptom control using the less stringent cutoffs for ACT and Asthma Control Questionnaire (ACT score ≥ 16 or ACQ-6 score < 1.5) is presented in e-Figure 9.

Figure 2 – *A-C, Percentage of patients with (A) no exacerbations, (B) no maintenance oral corticosteroid use, and (C) well-controlled asthma at weeks 0, 48, and 96, overall (all patients) and according to patients' previous biologic experience. Previous biologic therapies included omalizumab (n = 176), mepolizumab (n = 253), and reslizumab (n = 33) (333 [82%] had only used 1 previous biologic therapy and 61 [15%] had used > 1 previous biologic therapy; data on previous biologic use were missing for 10 patients [2.5%]). Well-controlled asthma was defined as Asthma Control Test score ≥ 20 or 6-item Asthma Control Questionnaire score ≤ 0.75. N/A = not available.*



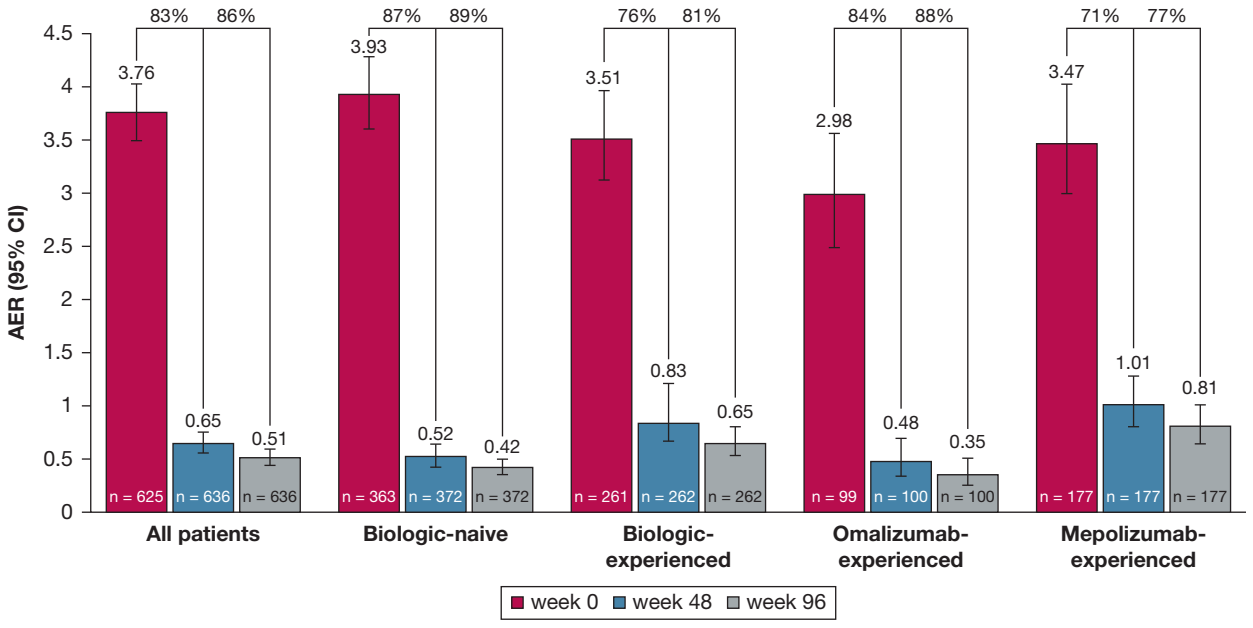


Figure 3 – *Mean AER (95% CI) at baseline, week 48, and week 96, and mean reduction from baseline, overall (all patients) and according to patients' previous biologic experience.* P < *.001 for all mean reductions from baseline. Previous biologic therapies included omalizumab (n = 176), mepolizumab (n = 253), and reslizumab (n = 33) (333 [82%] had only used 1 previous biologic therapy and 61 [15%] had used > 1 previous biologic therapy; data on previous biologic use were missing for 10 patients [2.5%]). AER and corresponding 95% CIs were calculated for the 12-mo baseline period and 96-wk follow-up period using generalized linear regression with a negative binomial distribution. Data included patients treated with ≥ 1 benralizumab injection after week 48 who either discontinued before week 96 or completed ≥ 92 wk of postindex follow-up. Relative risk reduction (%) (95% CI and* P *value) at weeks 48 and 96, compared with the 12-mo baseline period, was calculated using a generalized estimating equations model for repeated measures, using a logit link function including period (baseline period, follow-up period) and age (continuous) as covariates with a negative binomial distribution. AER = annualized exacerbation rate.*

Characteristics Associated With Clinical Remission

Multivariable analyses examining the association between prespecified baseline demographics and key clinical characteristics, and clinical remission (using the less stringent cutoffs for asthma symptom control; ACT score ≥ 16 or ACQ-6 score < 1.5) at weeks 48 and 96 are presented in e-Figure 10. At week 96, lower mOCS dose (OR, 0.51; 95% CI, 0.34- 0.76), lower BMI (OR, 0.56; 95% CI, 0.36-0.86), and higher peak BEC (OR, 1.68; 95% CI, 1.05-2.69]) at baseline were positively associated with meeting the less stringent criteria for remission (e-Fig 10B). Results were similar at week 48 (e-Fig 10A) with the addition of better asthma control (ACT score ≥ 16 or ACQ-6 score < 1.5; OR, 2.41; 95% CI, 1.07-5.41).

Long-Term Clinical Outcomes

Relative reduction in AER from baseline to weeks 48 and 96 was 83% (95% CI, 80-85) and 86% (95% CI, 84-88), respectively (both $P < .001$) (e-Tables 6, 7; Fig 3). The mean percentage change in daily mOCS dose from the index date to week 96 among patients using mOCS at the index date (n = 374, 35%) was −51%. At week 96, 73% of patients had improvements matching or exceeding the MCID of 3 units for the ACT score or −0.5 units for the ACQ-6 score (e-Fig 11). Additional data on asthma exacerbation, maintenance asthma medication, mOCS use, patient-reported asthma symptom control, lung function outcomes, and near-complete depletion of peak BEC in the overall population, by biologic status, and by key baseline clinical characteristics are presented in e-Figures 12-14 and e-Tables 8-10.

Discussion

To our knowledge, XALOC-1 is the largest real-world program of biologic-experienced and biologic-naive patients with SEA initiating benralizumab to date, addressing the underrepresentation of biologic-experienced patients in clinical trials.[7] This integrated analysis of data from 5 national studies demonstrated that 3-component clinical remission is a realistic and sustainable goal up to 2 years for around one-third of patients with SEA receiving benralizumab. The remission criteria were met in just over one-third of patients at week 48. Patients with lower mOCS dose,

lower BMI, and higher BEC at baseline were more likely to achieve remission at week 96.

The remission data are consistent with previous studies in patients with SEA receiving biologics; for example, a pooled post hoc analysis of 1,123 patients from pivotal phase 3 RCTs of benralizumab (A Multicentre, Randomised, Double-Blind, Parallel Group, Placebo-Controlled, Phase III Efficacy and Safety Study of Benralizumab Added to High-Dose Inhaled Corticosteroid Plus Long-acting β_2 Agonist in Patients With Uncontrolled Asthma [SIROCCO] and A Multicentre, Randomised, Double-Blind, Parallel Group, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Benralizumab in Asthmatic Adults and Adolescents Inadequately Controlled on Inhaled Corticosteroid Plus Long-Acting β_2 Agonist [CALIMA]) using similar 3-component remission criteria (no exacerbations, no mOCS use, and ACQ-6 score $<$ 1.5) found after 12 months of treatment that 39% (213 of 544) and 27% (154 of 579) of patients met remission when receiving benralizumab and placebo, respectively.[15] Post hoc analysis of A Multicentre, Double-Blind, Randomized, Parallel Group, Phase 3 Safety Extension Study to Evaluate the Safety and Tolerability of Benralizumab in Asthmatic Adults and Adolescents on Inhaled Corticosteroid Plus Long-Acting β_2 Agonist (BORA) RCT in patients treated with benralizumab for 24 months found that 32% met the 3-component criteria for remission (no exacerbations, no mOCS use, $\leq$ 10% FEV_1 decrease from the predecessor baseline, and ACQ-6 score $<$ 1.5) after 12 months, of which 73% sustained remission up to 24 months. Of those who did not meet the criteria for remission in the first 12 months of treatment, 26% met the criteria at month 24.[16] Real-world data on clinical remission in patients with SEA receiving benralizumab are variable and the definition of remission is inconsistent between studies.[17-19] In a post hoc analysis of the 18-month Multicenter, Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Phase 3b Study to Evaluate the Safety and Efficacy of Benralizumab 30 mg sc in Patients With Severe Asthma Uncontrolled on Standard of Care Treatment (ANDHI-In Practice) and 12-month Multicenter, Open-Label, Phase 3b Efficacy and Safety Study of Benralizumab 30 mg Administered Subcutaneously to Reduce Oral Corticosteroid Use in Adult Patients With Severe Eosinophilic Asthma on High Dose Inhaled Corticosteroid Plus Long-Acting β_2 Agonist and Chronic Oral Corticosteroid Therapy [PONENTE] trials, 29% (19 of 66) and 26% (81 of 312) of patients met clinical remission, respectively.[20] The proportion of patients meeting 3-component remission criteria in our analysis was also consistent with a post hoc analysis of the Real World Effectiveness and Safety of Mepolizumab (REDES) study, in which 3-component remission criteria (no exacerbations, no mOCS use, and ACT score $\geq$ 20) were met by 37% of patients (96 of 260) after 1 year of mepolizumab therapy.[13]

Despite the lack of efficacy with previous treatments, around one-quarter of biologic-experienced patients met the criteria for 3-component clinical remission after 96 weeks of benralizumab therapy. In addition, there were substantial improvements in long-term asthma clinical outcomes with reduction of asthma exacerbations, reduction in daily mOCS use, and improvements in asthma symptom control, irrespective of previous biologic use and key clinical characteristics important to therapeutic decision-making in clinical practice. This aligns with the results of the XALOC-1 12-month analysis.[7] This may reflect differences in the mechanism of action of benralizumab compared with other biologics and the associated variation in BEC reduction. Mepolizumab and reslizumab target IL-5, a key cytokine for eosinophil maturation, activation, and survival, preventing its interaction with eosinophils.[21] However, regardless of their high affinity for IL-5, mepolizumab and reslizumab do not completely deplete eosinophils in the blood and sputum,[22] which may still place patients at risk of asthma exacerbations and reduced symptom control. Conversely, benralizumab binds to IL-5 receptor alpha present on eosinophils, eosinophilic precursors, and basophils, tagging them for natural killer cell-induced apoptosis, independent of the cytokines involved. Accordingly, data suggest that eosinophil depletion is greater with benralizumab than other anti-IL-5 treatments.[3,23] Mechanistically, our data indicate that inadequate suppression of eosinophils with anti-IL-5 therapies is a clinically relevant issue for some patients with SEA. In an observational study of mepolizumab in patients with SEA, despite IL-5 blockade, 48% (n = 28) experienced eosinophilic exacerbations characterized by a sputum eosinophil count of $\geq$ 2%, which, compared with those exacerbations where the sputum eosinophil count was $<$ 2%, were associated with increased FENO, lower FEV_1 percent predicted, and increased BEC.[24] Conversely, in patients who experienced exacerbations while on benralizumab (58%, n = 91), median blood (0×10^9/L; interquartile range, 0-0) and sputum (0%; interquartile range, 0-0) eosinophil levels were depleted. Although eosinophils remained suppressed on

benralizumab, exacerbations were characterized by elevated FENO, sputum neutrophils, and C-reactive protein levels.[25] These observations underscore the rationale for treatment with benralizumab in a broad group of patients suboptimally controlled on alternative biologics. In the observational Biologic Treatment Responders in Severe Asthma Patients (FULL BEAM) analysis from the International Severe Asthma Registry, 20% of patients achieved 4-domain clinical remission within 1 of year of initiating biologic treatment. Patients with less severe asthma impairment and a shorter asthma duration had a greater chance of achieving remission. This highlights the importance of early initiation of a biologic in patients with severe asthma targeting clinical remission.[26]

When using the less stringent cutoffs for asthma symptom control (ACT score $\geq$ 16 or ACQ-6 score $<$ 1.5), lower mOCS dose, lower BMI, better asthma symptom control at week 48, and higher BEC at baseline were positively associated with remission at weeks 48 and 96. Because patients receiving mOCS tend to have more symptomatic disease, the association between higher mOCS use at baseline and lower rates of remission is unsurprising. Similarly, the higher proportion of patients with asthma symptom control meeting remission criteria is expected. These findings are consistent with previous real-world studies with comparable remission definitions in patients with SEA receiving treatments that target the IL-5 pathway. In the real-world observational REDES study, higher BEC, better lung function, and lower mOCS requirements at baseline were positively associated with remission at week 52.[27] Furthermore, an observational prospective study in patients receiving dupilumab showed obesity was associated with a negative OR for achieving remission.[28] Together, these findings suggest that patients with a lower disease burden before treatment were more likely to meet clinical remission during follow-up, warranting further research on the benefits of earlier treatment initiation. The relationship between BMI and clinical remission status was expected, given higher BMIs are often linked to worse ACT and ACQ-6 scores regardless of asthma severity.[29] Moreover, breathlessness in adolescents with obesity has been shown to be driven by physical deconditioning regardless of asthma diagnosis.[30]

A substantial reduction in AER and mOCS use, and clinically meaningful improvements in patient-reported asthma symptom control, lung function outcomes and treatment patterns were consistent with the 12-month integrated analysis.[7] This suggests clinical outcomes for patients with SEA receiving benralizumab are improved and maintained for up to 2 years in the real-world setting, irrespective of previous biologic use and key baseline clinical characteristics used by clinicians in their daily therapeutic decision-making.

One limitation of this analysis, typical for studies using medical chart data, is the absence of a control arm. The study was also confined to data from routine clinical practice, resulting in limited lung function data availability. The available lung function data were likely from patients with severe disease who are more frequently subjected to lung function tests and may not be representative of the overall cohort. Consequently, lung function was not included in the remission composite. Data were further limited by the COVID-19 pandemic, which overlapped with the data collection period. Additionally, some patients were missing complete data for the 3 clinical remission components, and the availability of these data varied by timepoint. The absence of data on participants' race and ethnicity may limit the generalizability of the results, particularly given the varied outcomes observed among racial and ethnic minority groups across the 5 countries. Reliance on medical chart data introduced the potential for misclassification or inconsistencies in coding, within and between practices, and over time. Additionally, the possibility of residual effects from the previous biologic treatment cannot be entirely excluded; however, the median times between the last dose of the previous biologic and first dose of benralizumab were similar to the half-lives of the previous biologic used.[31] Finally, approximately one-half of eligible patients had follow-up data to week 96. Although demographics and clinical characteristics were similar between those with and without 96 weeks of follow-up data, patients with longer follow-up data experienced more baseline exacerbations, had increased use of mOCS, and were less likely to have a history of smoking. This highlights the potential role of survival bias in this real-world observational study because these patients are more likely to respond well to benralizumab and, therefore, are more likely to have remained on treatment and in the study.

The expansive patient enrollment in the XALOC-1 program amplifies the generalizability of its findings, enabling detailed subgroup analyses that overcome limitations in previous retrospective studies. These studies were constrained by smaller patient cohorts, limited numbers of patients with prior biologic experience, shorter follow-up, and data collection confined to a single center.[21,32-34] Moreover, the real-

world setting of XALOC-1 offers an inclusive and diverse patient population compared with the more selective demographics in RCTs. This scale and diversity not only support benralizumab's effectiveness observed in smaller cohorts, but also uniquely demonstrate its effectiveness in biologic-experienced patients and across key baseline clinical subgroups.

Interpretation

This real-world international study of 1,070 patients with SEA, including > 400 biologic-experienced patients who switched biologic treatment, demonstrated that meeting and sustaining 3-component clinical remission for up to 2 years is a realistic, sustainable goal for around one-third of patients with SEA receiving benralizumab. Outcomes were maintained irrespective of previous biologic use and key baseline characteristics that clinicians typically consider in their therapeutic decision-making. Patients with lower disease burden were more likely to achieve clinical remission, reinforcing the importance of early treatment intervention. Further research is thus warranted regarding whether earlier initiation of a biologic may be beneficial.

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Additional information: The e-Appendix, e-Figures, and e-Tables are available online under "Supplementary Data."

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