Received: 10 January 2024 | Accepted: 9 May 2024

DOI: 10.1111/resp.14767

ORIGINAL ARTICLE

Official Journal of the Asian Pacific Society of Respirology
Respirology
APSR
WILEY

Sustained remission induced by 2 years of treatment with benralizumab in patients with severe eosinophilic asthma and nasal polyposis

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Associate Editor: Giorgio Piacentini;
Senior Editor: Fanny Ko

Abstract

Background and Objective: Several randomized controlled trials (RCTs) have shown that benralizumab is characterized by a good profile of efficacy and safety, thereby being potentially able to elicit clinical remission on-treatment of severe eosinophilic asthma (SEA). The main goal of this multicentre observational study was to verify the effectiveness of benralizumab in inducing a sustained remission on-treatment of SEA in patients with or without comorbid chronic rhinosinusitis with nasal polyps (CRSwNP).

Methods: Throughout 2 years of treatment with benralizumab, a four-component evaluation of sustained remission of SEA was performed, including the assessment of SEA exacerbations, use of oral corticosteroids (OCSs), symptom control and lung function.

Results: The present study recruited 164 patients suffering from SEA. After 24 months of add-on biological therapy with benralizumab, 69 (42.1%) achieved the

important target of sustained remission on-treatment (exacerbation rate = 0, OCS dose = 0, pre-bronchodilator FEV_1 ≥80% pred., ACT score ≥ 20). During the same period, a persistent improvement of CRSwNP (SNOT-22 < 30, NP recurrence = 0) was observed in 33 (40.2%) out of 82 subjects with concomitant NP. The latter comorbidity and post-bronchodilator reversibility of airflow limitation were two independent predictors of sustained remission on-treatment (OR = 2.32, $p < 0.05$ and OR = 5.59, $p < 0.01$, respectively).

Conclusion: Taken together, the results of this real-life clinical investigation indicate that benralizumab can induce a sustained remission on-treatment of SEA, especially in those patients with comorbid CRSwNP and reversible airflow limitation.

KEYWORDS

benralizumab, chronic rhinosinusitis with nasal polyps, reversible airflow limitation, severe eosinophilic asthma, sustained remission

INTRODUCTION

Severe refractory asthma is characterized by poor symptom control and recurrent exacerbations in spite of optimized high-dose inhaled therapies, and often requires the addition of oral corticosteroids (OCSs).[1,2] Among the different pathologic traits shaping severe refractory asthma, blood eosinophilia and airway eosinophilic inflammation occur very frequently.[3,4] In this regard, it is well-known that interleukin-5 (IL-5) is the main cytokine responsible for differentiation, activation and survival of eosinophils.[5] The IL-5 pathway can be targeted by the anti-IL-5 humanized monoclonal antibodies reslizumab and mepolizumab, as well as by the anti-IL-5 receptor (IL-5Rα) antibody benralizumab.[6,7]

Several randomized controlled trials (RCTs) have proven that benralizumab is a very effective and safe drug for the add-on biological treatment of severe eosinophilic asthma (SEA). In particular, both SIROCCO and CALIMA studies showed that benralizumab significantly decreased the number of asthma exacerbations and improved symptom control and lung function.[8,9] The RCT ZONDA and the open-label, single-arm PONENTE study demonstrated that benralizumab was able to lower the daily intake of OCS.[10,11] The good profile of long-term efficacy and safety of benralizumab clearly emerged from the results of the BORA phase 3 extension trial, further corroborated by the open-label MELTEMI extension study.[12,13] The excellent therapeutic impact of benralizumab on SEA patients has also been confirmed in real-life observational studies. In this regard, the multinational XALOC program includes both retrospective (XALOC-1) and prospective (XALOC-2) collections of real-world observational data.[14,15] Indeed, real-life investigations make it possible to include many patients, who could not be enrolled in RCTs because of their rigid inclusion/exclusion criteria. Therefore, real-world patient populations are more heterogeneous than those recruited in RCTs, thus better reflecting the wider and more complex scenario of asthmatic sub-phenotypes which are eligible to be treated with benralizumab.

Although benralizumab has not yet been approved as biologic treatment for nasal polyposis (NP), some preliminary results from RCTs and real-world observations suggest it can be therapeutically effective in this condition. According to the phase 3b ANDHI trial, benralizumab induced rapid and persistent improvements in both asthma outcomes and SNOT-22 (sino-nasal outcome test-22) score.[16] Moreover, recent real-life observations suggest that in patients with SEA and NP benralizumab can also improve objective measures of NP severity such as endoscopic nasal polyp score and Lund Mackey CT (computed tomography) score.[17–19]

Within the above context, we present the results of our real-life, multicentre, retrospective and observational study about the therapeutic effects of benralizumab on the upper and lower airways of patients with SEA over 2 years of treatment. In particular, during this period of biologic treatment we focused our attention on benralizumab effectiveness referring to the induction of a sustained clinical remission on-treatment of severe asthma.[20,21]

SUMMARY AT A GLANCE

This real-life study recruited 164 patients with SEA. After 24 months of benralizumab treatment, 42.1% achieved sustained remission. During the same period, CRSwNP improvement was observed in 40.2% out of 82 subjects with concomitant nasal polyps. The latter comorbidity and reversibility of airflow limitation were independent predictors of sustained remission.

METHODS

Study design

In the present retrospective, multicentre and observational study, between September 2019 and March 2023 each centre enrolled consecutive SEA patients undergoing add-on biologic therapy with benralizumab, who had not been previously treated with other monoclonal antibodies. The following 13 centres

participated in this real-life investigation: Respiratory Medicine Section, University 'Aldo Moro', Bari, Italy; Allergology and Clinical Immunology, University 'Aldo Moro', Bari, Italy; Allergy and Respiratory Medicine, University of Catania, Italy; Respiratory Disease Unit, University 'Magna Graecia' of Catanzaro, Italy; Allergology and Clinical Immunology Unit, University of Foggia, Italy; Respiratory Disease Unit, University of Foggia, Italy; Allergy and Clinical Immunology Unit, University of Messina; Allergology and Immunology Unit, University 'Federico II' of Naples, Naples, Italy; Pulmonology Unit, 'Monaldi' University Hospital, Naples, Italy; Pulmonology Unit, University of Palermo, Italy; Allergology and Pulmonology Unit, Provincial Outpatient Center of Palermo, Italy; Respiratory Disease Unit, University of Salerno, Italy; Division of Allergy and Clinical Immunology, University of Salerno. This observational study met the standards of Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki. The study design was approved by the ethics committee of Calabria Region, Italy (Catanzaro, Italy; document n. 113—16 April, 2020). All recruited patients signed a written informed consent.

Benralizumab effects in patients with SEA were evaluated after 6, 12, 18 and 24 months. We also considered the rate of subjects who reached the criteria for sustained clinical remission on-treatment of severe asthma after 24 months of biological therapy.[21] We chose to use the four-component assessment of remission because it relies on both clinical and functional parameters, which together provide the best tool to evaluate an asthmatic patient's response to biologic therapy. Moreover, we detected the percentage of patients with SEA and CRSwNP who had a positive response to anti-IL-5Rα treatment in terms of nasal symptoms and nasal polyp recurrence.[22]

Patient population

We recruited adult patients (over the age of 18 years) with ongoing symptoms of asthma, who needed high dosages of fixed combinations of inhaled corticosteroids (ICS) and long-acting β_2-adrenergic agonists (LABA), often with addition of a long-acting muscarinic receptor antagonist (LAMA). The American Thoracic Society (ATS) and European Respiratory Society (ERS) criteria for severe uncontrolled asthma were satisfied by all enrolled patients.[1] The requirements for inclusion were those mandatory for the prescription of benralizumab in Italy (blood eosinophil count ≥300 cells/μL at baseline, and at least one of the following two items: (i) a minimum of two exacerbations during the prior year despite GINA step 5 treatment; (ii) maintenance OCS therapy during the last year).[23] Moreover, we included only biologic-naïve patients, thus excluding all asthmatics who had been already treated with any other monoclonal antibody. Benralizumab was injected subcutaneously at a dose of 30 mg once every 4 weeks for three doses, and thereafter once every 8 weeks.

Data collection and evaluation

A shared registry was utilized by the research sites to collect clinical, functional and biological data. Enrollment occurred in a sequential manner. At 6, 12, 18 and 24 months of treatment we evaluated the number of asthma exacerbations during the last year, the use of short-acting β_2-adrenergic agonists (SABA) as rescue medication, the number of emergency department (ED) visits, the number of hospitalizations, the daily OCS dosage (prednisone mg/day), ACT score,[24] the score of asthma quality of life questionnaire (AQLQ),[25] SNOT-22 score,[26] endoscopic nasal polyp recurrence, lung function, blood eosinophil and basophil counts, as well as fractional exhaled nitric oxide (FeNO). Asthma exacerbations were diagnosed according to GINA guidelines.[23] Functional data included pre-bronchodilator FEV_1, forced vital capacity (FVC) and forced expiratory flow between 25 and 75 percent of FVC ($FEF_{25\%-75\%}$). Sustained clinical remission on-treatment was defined during a 24-month follow-up period for each outcome as follows: (i) exacerbation rate = 0; (ii) OCS dose = 0; (iii) ACT score ≥ 20; (iv) pre-bronchodilator FEV_1 ≥80% pred.

The eventual coexistence of CRSwNP was ascertained on the basis of symptoms (nasal congestion, nasal discharge, facial pain/pressure and reduction/loss of smell for a minimum of 12 weeks), and NP presence was confirmed through sinus CT scan and nasal endoscopy.[27] We decided to use both CT scan and nasal endoscopy because these two methods are not completely overlapping; hence, when used together they can provide useful and complementary information. The eventual occurrence of NP relapse was assessed by nasal endoscopy in every patient. Subjects with CRSwNP were considered to be responders to benralizumab when they reached, after 2 years of biological therapy, the following outcomes: (i) SNOT-22 < 30; (ii) NP relapses = 0. In order to evaluate treatment safety, we monitored the eventual occurrence of adverse events, and we also performed laboratory measurements since the first benralizumab injection throughout the 24-month study period. Adverse events associated with benralizumab therapy, which eventually resulted in mortality, hospitalization, considerable or persistent impairment or a major disruption of one's capability to accomplish daily activities were classified as serious adverse events. We also evaluated drug safety and tolerability through a monthly telephone call, investigating whether patients had experienced any unwanted side effect.

Statistical analysis

Skewed data distributions were reported as median values with interquartile range (IQR), and normally distributed data were expressed as mean ± standard deviation (SD). The selection of parametric or non-parametric tests was based on data normality. The Anderson-Darling and Kolmogorov–Smirnov tests were used to determine if data had a normal distribution. Student *t*-test, Mann–Whitney *U*-test, Dunnett's

multiple comparison test and Friedman test were used to compare variables, when appropriate. To compare categorical variables, the Fisher exact test was used.

The overall study population was stratified according to either achievement or non-achievement of sustained clinical remission on-treatment. Moreover, we carried out a multivariate logistic regression analysis to define the adjusted OR of variables predicting the chance of sustained remission on-treatment. In the multivariate analysis, all baseline characteristics that differed between the two groups (sustained remission: yes/no) were included. A p-value less than 0.05 (two-tailed) was considered as statistically significant. Statistical analyses and figures were performed using Prism Version 10.1.0 software (GraphPad Software Inc., San Diego, CA, USA).

RESULTS

Clinical, functional and biological effects of benralizumab at 6, 12, 18 and 24 months

The present study recruited 164 patients, of whom 102 (62.2%) were women and 62 (37.8%) were males. The mean age of participants was 54.4 ± 12.5 years, and their median BMI was 25.2 kg/m^2 (22.9–28.1). The median asthma duration was 20.0 (11.0–30.0) years, and 89 (54.3%) subjects were characterized at baseline by a positive bronchodilator reversibility test. The average baseline FEV_1 was 68.9 ± 21.6% of the predicted value. Among the enrolled patients, 82 (50.0%) had CRSwNP and 84 (51.2%) had positive skin prick tests for perennial and/or seasonal allergens. Table 1 provides an overview of baseline patient characteristics.

When compared to baseline, after anti-IL-5Rα therapy the percentage of patients free of exacerbations changed from 4.9% ($p < 0.0001$) to 80.5% at 6 months ($p < 0.0001$), to 76.2% at 12 months ($p < 0.0001$), to 74.4% at 18 months ($p < 0.0001$) and to 73.8% at 24 months ($p < 0.0001$), respectively (Figure S1A in the Supporting Information).

Daily SABA inhalations, used as necessary rescue medication, dropped from 1.0 (0.0–2.0) to 0.0 (0.0–0.0) after 24 months ($p < 0.0001$), as well as after 6, 12 and 18 months (Figure S1B in the Supporting Information). Moreover, during the same period, the recruited asthmatic subjects did not require ED visits and/or hospitalizations (Figure S1C in the Supporting Information). With respect to baseline, after treatment with benralizumab the percentage of patients free of OCS use changed from 25.0% ($p < 0.0001$) to 82.3% at 6 months ($p < 0.0001$), to 92.7% at 12 months ($p < 0.0001$), to 90.2% at 18 months ($p < 0.0001$) and to 89.6% at 24 months ($p < 0.0001$), respectively (Figure S1D in the Supporting Information).

ACT score improved considerably from a baseline value of 14.3 ± 4.3 to 22.5 ± 2.2 ($p < 0.0001$) after receiving benralizumab for 24 months (Figure 1A). ACT score overcame the critical threshold of 20 points already after 6 months (21.4 ± 3.2; $p < 0.0001$), 12 months (21.7 ± 2.7; $p < 0.0001$) and 18 months (22.1 ± 2.5; $p < 0.0001$) of anti-IL-5Rα add-on therapy. Furthermore, after 2 years of benralizumab treatment, AQLQ score significantly increased from a baseline value of 3.4 ± 1.3 to 6.0 ± 0.9 ($p < 0.0001$) (Figure 1B). This positive effect was also evident at the previous time-points of 6 months (5.8 ± 1.1; $p < 0.0001$), 12 months (5.9 ± 1.0; $p < 0.0001$) and 18 months (6.0 ± 1.0; $p < 0.0001$), respectively. In patients with concomitant NP, benralizumab was able to progressively lower SNOT-22 score from 55.8 ± 23.2 to 43.7 ± 20.8 at 6 months ($p < 0.0001$), to 40.8 ± 21.8 at 12 months ($p < 0.0001$), to 37.5 ± 21.0 at 18 months ($p < 0.0001$) and to 36.4 ± 21.3 at 24 months ($p < 0.0001$), respectively (Figure 1C). Moreover, as assessed by nasal endoscopy, in this subgroup of subjects the number of NP relapses decreased from 1.0 (1.0–2.0) to 0.0 (0.0–1.0) ($p < 0.001$) at 6 months, 0.0 (0.0–1.0) ($p < 0.0001$) at 12 months, 0.0 (0.0–0.0) ($p < 0.001$) at 18 months and 0.0 (0.0–0.0) ($p < 0.0001$) at 24 months after starting benralizumab therapy (Figure 1D). In particular, the eventual occurrence of NP relapse was assessed by nasal endoscopy in every patient.

The above relevant and sustained clinical effects of benralizumab were paralleled by marked improvements of lung function. Indeed, after 24 months of add-on biological treatment with benralizumab we detected a significant increase of pre-bronchodilator FEV_1 from the baseline level of 1.9 L (1.4–2.4) to 2.3 L (1.8–2.9) ($p < 0.0001$) (Figure S2A in the Supporting Information). Pre-bronchodilator FEV_1 values were 2.2 L (1.6–2.8) ($p < 0.0001$) at 6 months, 2.2 L (1.7–2.8) ($p < 0.0001$) at 12 months and 2.3 L (1.8–2.8) ($p < 0.0001$) at 18 months, respectively. During the same period, FVC enhanced from a baseline value of 2.8 L (2.3–3.5) to 3.0 L (2.5–3.8) ($p < 0.01$) at 6 months, 3.0 L (2.3–3.7) ($p < 0.05$) at 12 months, 3.1 L (2.6–3.7) ($p < 0.01$) at 18 months and 3.2 L (2.6–3.7) ($p < 0.01$) at 24 months (Figure S2B in the Supporting Information), respectively. Moreover, $FEF_{25\%-75\%}$ increased from a baseline value of 37.5% pred. (24.5–57.8) to 62.0% pred. (47.5–78.5) ($p < 0.0001$) after 24 months of add-on biological therapy with benralizumab (Figure S2C in the Supporting Information). Notably, $FEF_{25\%-75\%}$ already raised to 58.0% pred. (43.0–70.0) ($p < 0.0001$) at 6 months, 58.0% pred. (43.0–70.0) ($p < 0.0001$) at 12 months, and 60.0% pred. (44.0–70.0) ($p < 0.0001$) at 18 months, respectively.

After starting anti-IL-5Rα therapy, blood eosinophil levels, expressed as geometric mean (± geometric SD), lowered from a baseline value of 625.5 ± 1.9 cells/μL, to 0.0 ± 13.2 cells/μL at 6 months ($p < 0.0001$), to 0.0 ± 11.6 cells/μL at 12 months ($p < 0.0001$), to 0.0 ± 12.0 cells/μL at 18 months ($p < 0.0001$) and to 0.0 ± 13.8 cells/μL at 24 months ($p < 0.0001$), respectively (Figure 2A). Furthermore, blood basophil count decreased after 2 years from baseline 40.0 cells/μL (20.0–90.0) to 0.0 cells/μL (0.0–16.0), and this cell depletion was already evident at 6, 12 and 18 months (Figure 2-B), respectively. In addition, FeNO level decreased from baseline 41.0 ppb (27.0–59.0) to 22.0 ppb (12.5–30.0) ($p < 0.001$) at 24 months, and also this effect of benralizumab was already detectable after 6, 12 and 18 months (Figure 2C).

TABLE 1 Baseline patient characteristics, stratified on the basis of who achieved and who did not achieve sustained clinical remission.

Characteristic	Total population $N = 164$	Patients who achieved sustained CR $N = 69$	Patients who did not achieve sustained CR $N = 95$	p
Female gender, *N* (%)	102 (62.20)	42 (60.87)	60 (63.16)	0.8706
Male gender, *N* (%)	62 (37.80)	27 (39.13)	35 (36.84)	0.8706
Age, mean value (SD), years	54.36 (12.55)	53.67 (12.58)	54.86 (12.57)	0.5483
BMI, median value (IQR), kg/m^2	25.21 (22.93–28.10)	24.92 (22.88–28.06)	26.08 (22.94–28.60)	0.4358
Smoking habit, *N* (%)	47 (28.66)	15 (21.74)	32 (33.68)	0.1161
Duration of asthma, median value (IQR), years	20.00 (11.00–30.00)	18.00 (10.25–26.75)	21.00 (14.00–30.50)	0.0343
Age of asthma onset, median value (IQR), years	34.00 (20.00–42.50)	36.00 (23.25–45.75)	32.00 (18.50–42.00)	0.1792
ACT score, mean value (SD), points	14.28 (4.30)	14.48 (4.41)	14.11 (4.27)	0.6020
FEV_1, mean value (SD), % predicted	68.95 (21.61)	76.36 (22.21)	63.17 (19.36)	0.0001
FVC, mean value (SD), % predicted	84.00 (20.41)	90.34 (20.32)	79.07 (19.19)	0.0006
$FEF_{25\%-75\%}$, median value (IQR), % predicted	37.50 (24.50–57.80)	42.50 (31.00–61.25)	33.00 (23.75–45.38)	0.0061
Positive bronchodilator reversibility test, *N* (%)	89 (54.27)	44 (63.77)	45 (47.37)	0.0406
Use of maintenance OCS, *N* (%)	123 (75.00)	51 (73.91)	72 (75.79)	0.8557
Use of LAMA, *N* (%)	110 (67.07)	48 (69.56)	62 (65.26)	0.6157
Blood eosinophils, geometric mean, (GSD), cells/μL	625.5 (1.95)	697.2 (1.93)	563.1 (2.04)	0.3909
FeNO, median value, (IQR), ppb	40.50 (26.25–59.00)	35.00 (24.00–55.25)	45.00 (34.75–63.00)	0.0966
IgE, median value, (IQR), IU/mL	103.0 (52.00–341.0)	112.0 (41.55–341.5)	98.36 (60.00–330.0)	0.8265
Atopy, *N* (%)	84 (51.22)	33 (47.83)	51 (53.68)	0.5275
CRSwNP, *N* (%)	82 (50.00)	45 (65.22)	37 (38.95)	0.0015
Gastro-oesophageal reflux disease, *N* (%)	63 (38.41)	29 (42.03)	34 (35.79)	0.4222
Bronchiectasis, *N* (%)	31 (18.90)	15 (21.74)	16 (16.84)	0.5450
NERD, *N* (%)	21 (12.80)	9 (13.04)	12 (12.63)	>0.9999
Osteoporosis, *N* (%)	21 (12.80)	8 (11.59)	13 (13.68)	0.8144
Anxiety, *N* (%)	19 (11.59)	9 (13.04)	10 (10.53)	0.6299
Atopic dermatitis, *N* (%)	10 (6.10)	2 (2.90)	8 (8.42)	0.1940
Obstructive sleep apnoea syndrome, *N* (%)	9 (5.49)	2 (2.90)	7 (7.37)	0.3053
EGPA, *N* (%)	6 (3.66)	2 (2.90)	4 (4.21)	>0.9999

Abbreviations: ACT, asthma control test; CR, clinical remission; CRSwNP, chronic rhinosinusitis with nasal polyps; EGPA, eosinophilic granulomatosis with polyangiitis; $FEF_{25\%-75\%}$, forced mid-expiratory flow between 25% and 75% of forced vital capacity; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GSD, geometric standard deviation; IQR, interquartile range; LAMA, long-acting muscarinic receptor antagonist; NERD, nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease; OCS, oral corticosteroids.

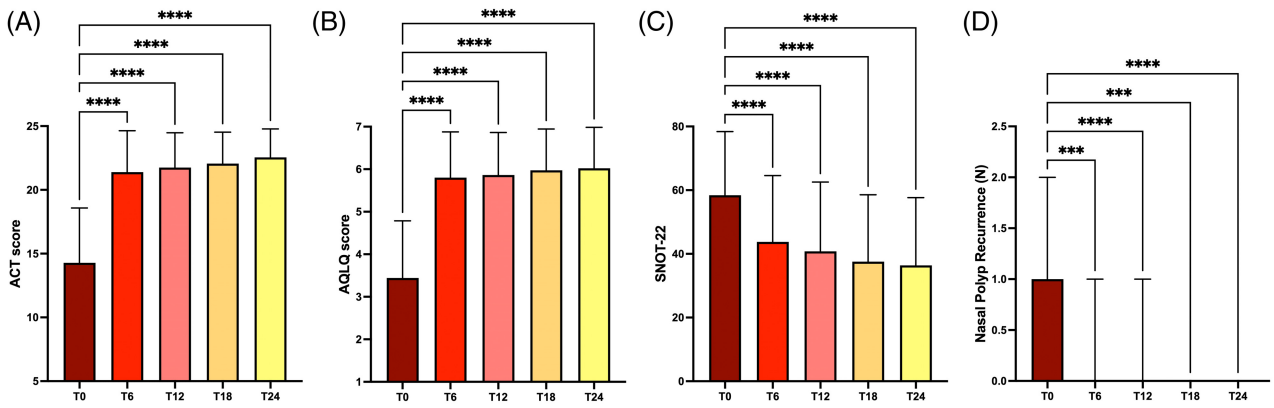

FIGURE 1 Effects of benralizumab on ACT score (A), AQLQ score (B), SNOT-22 score (C) and nasal polyp recurrence (D), recorded at baseline (T0), as well as at 6 (T6), 12 (T12), 18 (T18) and 24 (T24) months after the first drug dose (***$p < 0.001$; ****$p < 0.0001$).

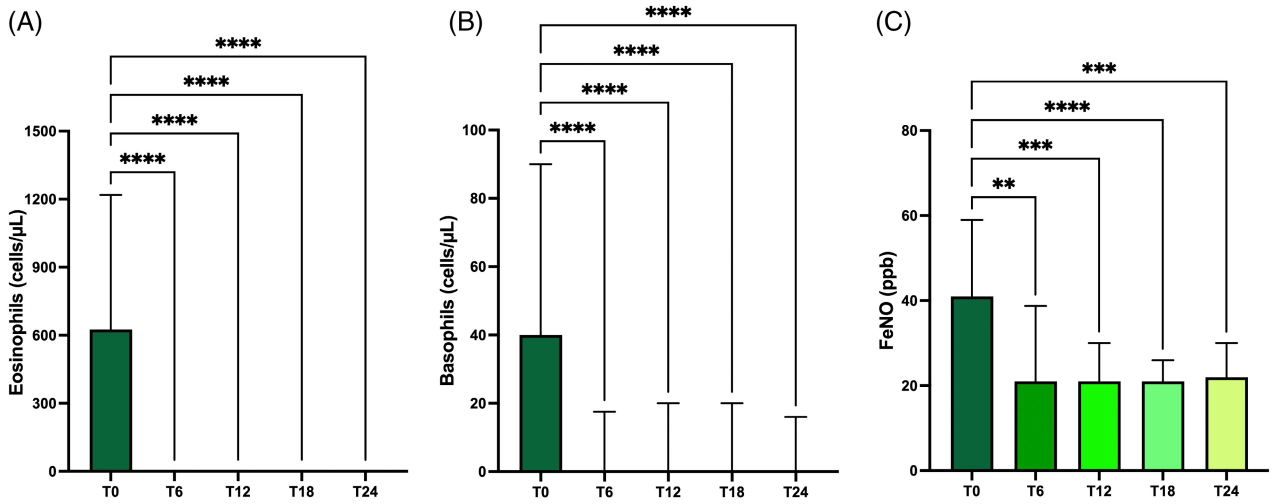

FIGURE 2 Effects of benralizumab on peripheral blood counts of eosinophils (A) and basophils (B), and on FeNO levels (C), recorded at baseline (T0), as well as at 6 (T6), 12 (T12), 18 (T18) and 24 (T24) months after the first drug dose (**$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$).

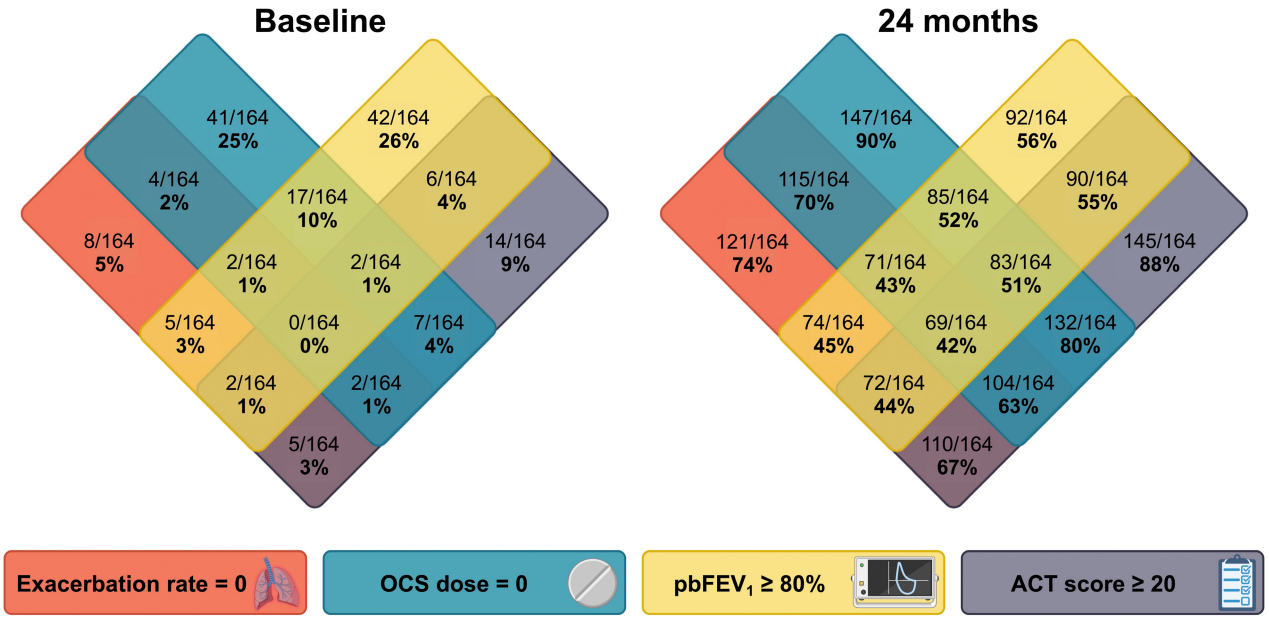

FIGURE 3 Numbers and percentages of patients with SEA satisfying one or multiple requirements of the four-component assessment of sustained remission on-treatment, recorded at baseline (left panel) and after 24 months (right panel) of add-on biologic treatment with benralizumab. In the central-lower part of each panel the absolute number (baseline: 0/164; 24 months: 69/164) and the relative percentage (baseline: 0%; 24 months: 42%) of patients who achieved all four criteria of remission on-treatment are indicated. In addition, the absolute numbers and percentages of patients referring to each of the four components of remission are illustrated using different colours.

Sustained clinical remission on-treatment of severe asthma induced by benralizumab

When considering the 164 patients included in our present real-life study, after 2 years of treatment with benralizumab 69 (42.1%) fulfilled the 4-component definition of sustained clinical remission of severe asthma (exacerbation rate = 0, OCS dose = 0, pre-bronchodilator FEV_1 ≥80%, ACT score ≥20). At baseline no patient satisfied all these four criteria (Figure 3). In particular, among those enrolled 8 (4.9%), 41 (25.0%), 42 (25.6%) and 14 (8.5%) met the requirements referring to zero exacerbations, zero OCS, pre-bronchodilator FEV_1 ≥80% and ACT score ≥20, respectively. After 2 years of treatment with benralizumab, 121 (73.8%) patients were exacerbation-free, 147 (89.6%) were OCS-free, 94 (57.3%) had a pre-bronchodilator FEV_1 ≥80% and 145 (88.4%) reached an ACT score ≥20 (Figure 3).

When compared to patients who did not achieve the four criteria of clinical remission on-treatment at 24 months of therapy with benralizumab, those who reached such goals were characterized by a shorter duration of asthma, that is, 18.0 years (10.2–26.7) versus 21.0 years (14.0–30.5) ($p < 0.05$),

TABLE 2 Logistic regression predicting chance of sustained clinical remission.

Variable	Code	β	Adj. OR	95% CI	p
Duration of asthma	Years	−0.022	0.978	0.947–1.009	0.1756
FEV_1	% predicted	0.041	1.042	0.996–1.094	0.0768
FVC	% predicted	−0.008	0.992	0.954–1.029	0.6728
$FEF_{25\%–75\%}$	% predicted	0.008	1.008	0.976–1.040	0.5965
Positive bronchodilator reversibility test	0: No (ref.)/1: Yes	1.721	5.591	2.053–17.21	0.0014
CRSwNP	0: No (ref.)/1: Yes	0.842	2.321	1.023–5.423	0.0467

Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; $FEF_{25\%–75\%}$, forced mid-expiratory flow between 25% and 75% of forced vital capacity; FEV_1, forced expiratory volume in one second; and FVC, forced vital capacity.

TABLE 3 Baseline patient characteristics, stratified on the basis of CRSwNP response to benralizumab.

Characteristic	CRSwNP population N = 82	CRSwNP responders N = 33	CRSwNP non-responders N = 49	p
Female gender, *N* (%)	48 (58.54)	19 (57.58)	29 (59.18)	>0.9999
Male gender, *N* (%)	34 (41.46)	14 (42.42)	20 (40.82)	>0.9999
Age, mean value (SD), years	53.55 (13.82)	52.15 (14.97)	54.49 (13.06)	0.4558
BMI, median value (IQR), kg/m^2	25.00 (22.93–28.15)	24.92 (23.33–28.56)	25.12 (22.75–28.07)	0.9436
Smoking habit, *N* (%)	27 (32.93)	8 (24.24)	19 (38.78)	0.2318
SNOT-22 score, mean value (SD), points	57.42 (21.76)	43.80 (22.26)	67.44 (15.10)	<0.0001
Use of maintenance OCS, *N* (%)	60 (73.17)	27 (81.82)	33 (67.35)	0.2049
Blood eosinophils, geometric mean, (GSD), cells/μL	611.6 (2.21)	692.9 (2.28)	564.7 (2.2)	0.4219
FeNO, median value, (IQR), ppb	37.50 (26.25–54.50)	34.00 (18.50–50.25)	42.00 (29.00–55.50)	0.2537
IgE, median value, (IQR), IU/mL	190.0 (71.00–359.8)	103.0 (30.30–550.0)	195.9 (88.10–348.0)	0.1734
Atopy, *N* (%)	44 (53.66)	16 (48.48)	28 (57.14)	0.5020
NERD, *N* (%)	15 (45.45)	3 (9.09)	12 (24.49)	0.0894
Obstructive sleep apnoea syndrome, *N* (%)	7 (21.21)	0 (0.00)	7 (14.29)	0.0380

Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; FeNO, fractional exhaled nitric oxide; GSD, geometric standard deviation; IQR, interquartile range; NERD, nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease; OCS, oral corticosteroids; and SNOT-22, sino-nasal outcome test-22.

higher FEV_1 (76.4 ± 22.2% pred. vs. 63.2 ± 19.4% pred.) ($p < 0.0001$), greater FVC (90.3 ± 20.3% pred. vs. 79.1 ± 19.2% pred.) ($p < 0.001$) and better $FEF_{25\%–75\%}$, namely 42.5% pred. (31.0–61.2) vs. 33.0% pred. (23.7–45.4) ($p < 0.01$). Moreover, patients who satisfied the four requirements of sustained clinical remission on-treatment more frequently manifested a reversible airflow limitation (63.8% vs. 47.4%) ($p < 0.05$) and comorbid CRSwNP (65.2% vs. 38.9%) ($p < 0.01$) (Table 1). Multivariate logistic regression analysis proved that positive bronchodilator reversibility test (OR = 5.59; $p < 0.01$) and CRSwNP (OR = 2.32; $p < 0.05$) were independent predictors of sustained clinical remission on-treatment (Table 2).

Sustained improvement of CRSwNP

When considering the 82 SEA patients with concomitant NP, after 24 months of treatment with benralizumab a persistent improvement of CRSwNP (SNOT-22 <30, NP recurrence = 0) was observed in 33 (40.2%) subjects. At baseline no participant satisfied both criteria; 4 (4.9%) had SNOT-22 < 30, and 17 (20.7%) did not experience relapses of nasal polyposis. After 2 years of benralizumab therapy, 45 (54.9%) patients had a SNOT-22 < 30, and 59 (71.9%) did not manifest NP relapses.

In regard to the 82 patients with SEA and comorbid NP, 24 (29.4%) met the aforementioned criteria for sustained clinical remission on-treatment of severe asthma and sustained improvement of CRSwNP. Among the 69 patients who experienced a sustained clinical remission on-treatment of severe asthma, 45 (65.2%) had NP and 24 (53.3%) of them achieved a sustained improvement of CRSwNP. When considering the 95 patients who did not achieve clinical remission of severe asthma, 37 (38.9%) had NP and among these 9 (24.3%) fulfilled the requirements indicative of a sustained therapeutic response of their CRSwNP.

In comparison to patients who did not exhibit a sustained clinical response to benralizumab with regard to the items referring to CRSwNP, subjects who reached the two criteria indicative of a positive therapeutic outcome in relation to NP improvement, were characterized by lower baseline SNOT-22 values (43.8 ± 22.3 vs. 67.4 ± 15.1) ($p < 0.0001$) and the

absence of obstructive sleep apnoea syndrome (0.0% vs. 14.3%) ($p < 0.05$) (Table 3).

Long-term safety profile of benralizumab

Add-on biological therapy with benralizumab was well tolerated; no serious adverse event occurred throughout the 24-month follow-up, and no patient discontinued treatment because of a severe reaction at injection site, anaphylaxis or change in laboratory parameters. After the first drug administration, only nine patients complained of mild fever and chills, which resolved spontaneously without requiring any pharmacologic treatment.

DISCUSSION

The results of this real-life, multicentre and retrospective study convincingly suggest that a sustained clinical remission on-treatment of SEA, based on a composite multicomponent evaluation, is a suitable goal which can be achieved by a relevant percentage of patients treated for 2 years with benralizumab. Such data are interesting because they have been recorded within a real-world context, which makes it possible for many subjects with SEA to be treated with anti-eosinophilic biologic drugs. About 80% of this asthmatic population would not have been eligible for recruitment into the original phase 3 trials of benralizumab because of their rigid enrollment criteria, despite the potential of these patients to benefit from treatment with the biologic.[21,28] Moreover, our present observational investigation showed that benralizumab was also effective as biologic therapy of CRSwNP. In this regard, it is noteworthy that CRSwNP and post-bronchodilator reversibility of airflow limitation were independent predictive factors of sustained clinical remission on-treatment of SEA.

In particular, after 2 years of treatment with benralizumab the median number of AAER fell from 4 to 0, and for the large majority of patients benralizumab therapy obviated the need for ED attendances or hospital admissions and enabled a complete wean off corticosteroid therapy. In regard to the OCS sparing action of benralizumab, our results are superior to those reported by the PONENTE trial.[11] This finding could be explained by our faster rhythm of OCS tapering, which reflects the habitual behaviour adopted by us in daily clinical practice. None of our patients experienced clinical manifestations of adrenal insufficiency such as anorexia, nausea, weakness, drowsiness and/or fever. Furthermore, the requirement for rescue medication also markedly decreased, as shown by the drastic reduction of SABA use. These results were associated with a significant increase of ACT score, which by 6 months had overcome the critical threshold of 20, and this positive outcome persisted throughout the 2 years of benralizumab treatment. During all this period, we also noticed the parallel improvement of AQLQ score, documented by its long-lasting increment. Clinical amelioration induced by benralizumab extended to the upper airways of those SEA patients who also complained of CRSwNP, whose improvement was expressed by a persistent reduction of SNOT-22 score, as well as by the complete prevention of NP recurrence. With regard to lung function, the very positive therapeutic impact of benralizumab was proven by the significant and enduring increases of FEV_1, FVC and $FEF_{25\%-75\%}$.

The above mentioned clinical and functional effects of benralizumab can be reasonably explained by the powerful anti-eosinophilic action of this biologic drug. Indeed, we detected a sharp and persistent fall of blood eosinophil count, which dropped from the baseline geometric mean of 625.5 cells/μL to 0.0 cells/μL across all the timepoints of our study. In fact, when blood eosinophil counts are higher than 300–400 cells/μL, asthmatic patients are subjected to a greater risk of disease exacerbations.[29,30] After initiating treatment with benralizumab, and throughout the study period, we did not detect any patient having more than 100 eosinophils/μL of blood. Eosinophil depletion elicited by benralizumab was also likely responsible for the relevant improvement of lung function observed during the overall 2-year duration of our real-world investigation. Previous studies have shown that elevated blood eosinophil numbers are associated with airflow obstruction.[4] In conjunction with eosinophil depletion induced by benralizumab, we detected higher FEV_1 increases (350, 310, 450 and 430 mL at 6, 12, 18 and 24 months of treatment, respectively) than those reported by several RCTs such as CALIMA, SIROCCO and BISE, whose authors measured maximal FEV_1 increments consisting of 125, 159 and 80 mL, respectively.[8,9,31] However, our real-life results suggest that a sustained clinical remission on-treatment of severe asthma was achieved by a relevant percentage of patients treated with benralizumab, regardless of their baseline blood eosinophil count, which was anyway higher than 300 cells/μL in all of them. Indeed, by comparatively evaluating patients who did or did not satisfy the criteria of sustained clinical remission on-treatment with benralizumab, we did not detect any statistically significant difference with respect to the initial number of blood eosinophils.

In addition to depleting blood eosinophils, according to our results benralizumab also zeroed blood basophil counts throughout all study timepoints. Moreover, in the majority of our patients (57.5%) benralizumab lowered FeNO, another important biomarker of type 2 inflammation, below the critical value of 23 ppb.[32] Elevated FeNO measures coexist with increased risks of asthma exacerbations, airflow obstruction and accelerated lung function decline.[32]

Taken together, our results show that after 2 years of treatment with benralizumab, 69 out of 164 (42.1%) SEA patients reached the target of sustained clinical remission on-treatment, based on four criteria comprising absence of exacerbations, complete interruption of OCS therapy, ACT score of at least 20 and pre-bronchodilator FEV_1 of at least 80% pred.[20,21] Our multivariate logistic regression analysis documented that post-bronchodilator reversibility of airflow

limitation was an independent predictor of sustained remission on-treatment for our patients with severe type 2 eosinophilic asthma. This correlation suggests that better therapeutic results in terms of sustained remission of SEA could be obtained by patients undergoing treatment with benralizumab at an earlier stage of their disease, when it is possible that airway remodelling has not yet advanced towards fixed, non-reversible airflow obstruction. In fact, when compared to subjects who did not achieve sustained remission on-treatment, our SEA patients who centred met target were characterized by a less impaired lung function and a shorter duration of their asthma. The latter findings are consistent with recent real-life observations referring to asthmatic patients treated with biologic therapies and included within the Danish Severe Asthma Register.[33]

Half (82 out of 164) of our SEA patients also complained of CRSwNP. During 2 years of treatment with benralizumab, at all study timepoints (6, 12, 18 and 24 months) these subjects experienced significant reductions of SNOT-22 score, as well as a complete prevention of NP recurrence. Such a positive therapeutic action of benralizumab is undoubtably due to the common pathogenic mechanisms shared by SEA and NP, both of which are largely caused by airway eosinophilic infiltration.[34] Using multivariate logistic regression analysis to evaluate our results, we found that CRSwNP was another independent predictor of SEA sustained remission on-treatment. In other words, the occurrence in the same patient of both SEA and CRSwNP predicts an overall better therapeutic response to benralizumab. Because a large majority of our patients were characterized by late-onset eosinophilic asthma, it is reasonable to argue that a close association exists between this particular phenotype/endotype and CRSwNP in regard to clinical remission on-treatment with benralizumab. Such a co-relationship is consistent with previous observations, showing that patients with severe adult-onset asthma and eosinophilic airway inflammation often have also NP.[35]

According to our results, the powerful effectiveness of benralizumab was associated with an excellent pattern of safety and tolerability. Nine out of 164 patients experienced a transient and self-resolving reaction to the first injection of treatment with mild fever and chills.

Similar to other real-life studies, also ours has some limitations, such as the retrospective design and the lack of a placebo arm. Therefore, benralizumab efficacy was evaluated in comparison with baseline, pre-treatment clinical and functional measures. In consideration of the multicentre nature of this real-world investigation, another potential limitation can depend on the relatively confined geographical area including all participating centres, located in Southern Italy. Hence, our analysis could have missed eventual interesting information arising from heterogeneous populations settled worldwide.

In conclusion, we herein demonstrate that a 2-year on-treatment sustained remission is a feasible goal for SEA patients under ongoing add-on biologic therapy with benralizumab, especially if they have comorbid CRSwNP and reversible airflow limitation. Our global assessment was based on a four-component evaluation, including three important clinical outcomes (prevention of asthma exacerbations, OCS elimination and better symptom control) to which we have added data on lung function improvement. It is thus very likely that an affordable sustained remission on-treatment of SEA can be successfully induced by benralizumab because of its efficacy in dampening type 2 eosinophilic inflammation of airways.

AUTHOR CONTRIBUTIONS

Corrado Pelaia: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); software (equal); supervision (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Claudia Crimi:** Conceptualization (equal); data curation (equal); project administration (equal); supervision (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Alida Benfante:** Conceptualization (equal); data curation (equal); methodology (equal); supervision (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Maria Filomena Caiaffa:** Conceptualization (equal); data curation (equal); methodology (equal); supervision (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Raffaele Campisi:** Conceptualization (equal); data curation (equal); methodology (equal); supervision (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Claudio Candia:** Conceptualization (equal); data curation (equal); methodology (equal); supervision (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Giovanna Elisiana Carpagnano:** Conceptualization (equal); data curation (equal); methodology (equal); supervision (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Isabella Carrieri:** Conceptualization (equal); data curation (equal); methodology (equal); supervision (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Maria D'Amato:** Conceptualization (equal); data curation (equal); methodology (equal); supervision (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Aikaterini Detoraki:** Conceptualization (equal); data curation (equal); methodology (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Maria Pia Foschino Barbaro:** Conceptualization (equal); data curation (equal); methodology (equal); supervision (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Nicola Lombardo:** Conceptualization (equal); data curation (equal); methodology (equal); supervision (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Luigi Macchia:** Conceptualization (equal); data curation (equal); methodology (equal); supervision (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Angelantonio Maglio:** Conceptualization (equal); data curation (equal); methodology (equal); supervision (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Elena Minenna:**

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FUNDING INFORMATION

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

HUMAN ETHICS APPROVAL DECLARATION

This observational study met the standards of Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki. The study design was approved by the ethics committee of Calabria Region, Italy (document n. 113—16 April, 2020). All recruited patients signed a written informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Pelaia C, Crimi C, Benfante A, Caiaffa MF, Campisi R, Candia C, et al. Sustained remission induced by 2 years of treatment with benralizumab in patients with severe eosinophilic asthma and nasal polyposis. Respirology. 2024;29(10):869–79. https://doi.org/10.1111/resp.14767