Original Article

Benralizumab Effectiveness in Severe Eosinophilic Asthma with and without Chronic Rhinosinusitis with Nasal Polyps: A Real-World Multicenter Study

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What is already known about this topic? Benralizumab was shown to be effective in patients with severe eosinophilic asthma in clinical trials. However, real-world data in patients with the copresence of chronic rhinosinusitis with nasal polyps are lacking.

What does this article add to our knowledge? This study represents the largest real-world evidence so far, assessing the effectiveness of benralizumab in patients with severe eosinophilic asthma with or without chronic rhinosinusitis with nasal polyps on clinical, functional, laboratory parameters, and nasal symptoms.

How does this study impact current management guidelines? Benralizumab showed rapid effectiveness in the management of severe eosinophilic asthma in everyday clinical practice. Nasal polyposis could be considered a treatable trait because affected patients experienced improvements in nasal symptoms, asthma control, and respiratory function.

BACKGROUND: Chronic rhinosinusitis with nasal polyps (CRSwNP) affects around 60% of patients with severe eosinophilic asthma (SEA). Benralizumab was recently approved for SEA add-on treatment.

OBJECTIVE: To assess the real-world effectiveness of benralizumab in SEA with or without CRSwNP.

METHODS: We conducted a multicenter observational study, including patients with SEA treated with benralizumab for 24 weeks in 12 Italian specialized facilities. Asthma exacerbations, Asthma Control Test (ACT), lung function, oral corticosteroid (OCS) dosage, and eosinophil and basophil count in peripheral blood were recorded at baseline and after 4, 12, and 24 weeks. The 22-item Sino-Nasal Outcome Test (SNOT-22) and Lund-Mackay scores were assessed at baseline and after 24 weeks in SEA + CRSwNP.

RESULTS: A total of 137 patients with late-onset SEA were included; 57.7% (79 of 137) showed the copresence of CRSwNP. Overall, severe asthma exacerbations decreased from 4 (3-6) to 0 (0-2) ($P < .0001$) after 24 weeks of treatment, and significant improvements were observed as early as 4 weeks in ACT score, OCS dosage, forced expiratory volume in the 1st second (FEV_1)%, FEV_1 (L), forced vital capacity (FVC)%, FEV_1/FVC%

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Abbreviations used
ACT- Asthma Control Test
ADCC- Antibody-dependent cell-mediated cytotoxicity
AER- Annualized exacerbation rate
CRSwNP- Chronic rhinosinusitis with nasal polyps
CT- Computed tomography
ERS/ATS- European Respiratory Society/American Thoracic Society
FEF_{25-75}- Forced expiratory flow between 25% and 75% of FVC
FeNO- Fractional exhaled nitric oxide
FEV_1- Forced expiratory volume in the 1st second
FESS- Functional endoscopic sinus surgery
FVC- Forced vital capacity
ICC- Intraclass correlation coefficient
MCID- Minimal clinically important difference
OCS- Oral corticosteroids (prednisone)
SEA- Severe eosinophilic asthma
SNOT-22- 22-Item Sino-Nasal Outcome Test

($P < .0001$), and forced expiratory flow between 25% and 75% of FVC (FEF_{25-75})% ($P = .0022$). Eosinophils and basophils in peripheral blood were rapidly depleted. In patients with SEA+CRSwNP, SNOT-22 decreased from 46 (39.5-64.5) to 32 (19-46) ($P < .0001$). Furthermore, in comparison with SEA, they showed enhanced responses with regard to ACT minimal clinically important difference ($P = .0387$), FEV_1% ($P = .017$), FEV_1 (L) ($P = .02$), and FEF_{25-75}% ($P = .0362$).

CONCLUSIONS: These real-world data suggest that benralizumab can represent a valid add-on therapeutic option for patients with SEA, especially with comorbid CRSwNP. **© 2021 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2021;9:4371-80)**

Key words: *Benralizumab; Chronic rhinosinusitis; IL-5; Nasal polyps; Real-world; Severe asthma*

Severe asthma is a heterogeneous disease with a high impact on patients' quality of life due to frequent exacerbations and persistent symptoms, often refractory to high-dose maintenance regimens.[1,2] Furthermore, several comorbidities are associated with severe asthma, and their recognition and treatment are crucial for improving disease control.[3,4] Chronic rhinosinusitis with nasal polyposis (CRSwNP) affects around 40% to 60% of severe eosinophilic asthma (SEA)[5-8] with a high impact on symptoms control and exacerbations' risk,[9] contributing substantially to the socioeconomic burden of the disease, due to the need of repeated functional endoscopic sinus surgery (FESS).[10]

SEA and CRSwNP often share common pathogenesis,[11] sustained by IL-4, IL-5, IL-13, and type 2 inflammatory cells.[12] Benralizumab, a recently approved humanized IgG1k monoclonal antibody, binds IL-5Rα expressed by eosinophils, basophils, mast cells, and ILC2,[13] preventing its interaction with IL-5 and stimulating their apoptosis through antibody-dependent cell-mediated cytotoxicity (ADCC).[13,14] Benralizumab effectively reduced asthma exacerbations rate, oral corticosteroid (OCS) intake, and improved airflow limitation and asthma control in phase III trials.[15-17] Moreover, a secondary analysis of the SIROCCO and CALIMA trials identified CRSwNP as a predictor of treatment response,[18] and recently, the phase IIIb ANDHI trial[19] showed benralizumab effectiveness on CRSwNP symptoms.

Still, to date, except for small cohort studies,[20,21] limited real-world evidence exists regarding benralizumab efficacy on nasal polyps and how this comorbidity affects the response to treatment. This real-world multicenter observational study aimed to assess the effectiveness and impact of a 24-week add-on treatment with benralizumab on clinical, functional, laboratory parameters and nasal polyposis symptoms in a large cohort of subjects with SEA. We also performed a comparative evaluation of benralizumab efficacy according to the presence of nasal polyposis, an important aspect that has not been fully addressed previously.

METHODS

Study design

We conducted a multicenter, retrospective, observational study on patients with SEA treated with benralizumab between October 2019 and July 2020, who referred to 12 specialized Italian secondary care facilities, all of which are part of the "Southern Italy Network on Severe Asthma Therapy." A complete list of all the centers involved is available in this article's Online Repository at www.jaci-inpractice.org, section 1.

The study protocol was approved by the "Catania 1" Ethics Committee of the Policlinico University Hospital (Approval Number 33/2020/PO—April 6, 2020, Catania, Italy) and the local ethics committee of each study center. Written informed consent was obtained from all patients.

We evaluated the efficacy of benralizumab in patients with SEA after 4 and 24 weeks. In addition, we assessed the change in CRSwNP symptoms at week 24. Finally, we compared patients with SEA with and without CRSwNP at weeks 4 and 24 of treatment.

Patient population

Adult patients more than 18 years old, diagnosed with severe asthma according to the European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines,[1] with at least 300 eosinophils/μL in peripheral blood (SEA),[2] compliant to maintenance therapy and treated with subcutaneous benralizumab (30 mg, once every 4 weeks for the first 3 doses, and then once every 8 weeks) for at least 24 weeks were included. The indication for benralizumab prescription followed the Italian eligibility criteria (eosinophil count ≥300 cells/μL at baseline, a minimum of 2 exacerbations in the prior year despite GINA step 5 treatment[2] and/or maintenance OCS).

Data collection and assessment

An extensive registry was created for data collection with the collaboration and final approval of all the centers involved. Demographic characteristics (age, sex, body mass index) and clinically relevant parameters were collected before benralizumab initiation. Collected information included years of asthma, skin prick test positivity to perennial and seasonal common aeroallergens (dust mites, mold, pollen, pet dander), smoking history, medical comorbidities, asthma maintenance therapies, previous anti-IgE and/or anti−IL-5 treatment history, asthma exacerbations during the last year, Asthma Control Test (ACT) score,[22] pulmonary function test, daily OCS intake (prednisone mg/day), nasal polyposis assessment, 22-item Sino-Nasal Outcome Test (SNOT-22) score,[23] Lund-Mackay computed tomography (CT) score,[24] blood eosinophil and basophil count, IgE, and fractional exhaled nitric oxide (FeNO). The number of exacerbations since the last visit, ACT score, lung function test results, OCS dosage, and eosinophil and basophil

count in peripheral blood at weeks 4, 12, and 24 were also collected. We also evaluated the SNOT-22 score and Lund-Mackay score after 24 weeks.

Severe asthma exacerbations were defined as disease worsening requiring ≥3 days of treatment with systemic corticosteroids (or a doubling of prednisolone equivalent dose if already on OCS).[25] Exacerbations treated with cycles of corticosteroids <7 days from each other were considered as the same exacerbation. The severe asthma exacerbation rate during the 24 weeks was annualized: annualized exacerbation rate (AER): total number of exacerbations/24 weeks × 52.

Pulmonary function tests were performed according to the ERS/ATS guidelines.[26] Data on pre-bronchodilator forced expiratory volume in the first second (FEV_1% and L), forced vital capacity (FVC%), FEV_1/FVC%, and forced expiratory flow between 25% and 75% of FVC (FEF_{25-75}%) were collected.

The diagnosis of CRSwNP was formulated based on symptoms (nasal congestion, nasal discharge, facial pain/pressure, reduction/loss of smell for a minimum of 12 weeks) and objective confirmation of the presence of polyps through sinus CT scan or nasal endoscopy.[27] SNOT-22 (22-item questionnaire, each scored 0-5 [range 0-110], with higher values representing a worse quality of life) was used to assess CRSwNP symptom severity.[24] According to the final score, symptoms were considered mild (8-20), moderate (21-50), or severe (>50).[28] The Lund-Mackay CT score (range 0-24)[25] was independently calculated by an expert radiologist and an ENT specialist. Higher scores represent extensive involvement of facial sinuses.

Safety was assessed by reporting serious adverse events and monitoring laboratory values from the first benralizumab dose to week 24. Serious adverse events were defined as harmful events related to the use of benralizumab resulting in death, hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.[29] Patients were also accurately monitored for 2 hours after the administration because of the possible onset of severe injection-site reactions and anaphylaxis.

Statistical analysis

Categorical variables were presented as numbers (n) and percentages (%). Normally distributed continuous variables were expressed as mean and standard deviation or 95% confidence intervals. Continuous nonparametric variables were expressed as median and interquartile range. Agreement between Lund-Mackay score rates was estimated using the intraclass correlation coefficient (ICC). The Fisher's exact or McNemar tests were used for comparisons of categorical variables when appropriate. The normality of data distribution was checked using the Anderson-Darling and Kolmogorov-Smirnov tests. A *t*-test (paired or independent) was used for normally distributed variables. The Wilcoxon signed rank test (related) or the Mann-Whitney test (unrelated) was used for non-normally distributed variables. Dunnett's (parametric) or Friedman with Dunn's *post hoc* (nonparametric) tests were used for multiple comparisons of continuous variables in the entire population among baseline, 4 weeks, and 24 weeks of treatment. A mixed-effect model analysis, with Geisser-Greenhouse correction and Bonferroni *post hoc* for repeated measures, was used to compare treatment response differences of continuous variables between the SEA and SEA+CRSwNP groups at weeks 4 and 24. Statistical analysis was performed and figures were generated using Prism version 9.0.2 (GraphPad Software Inc., San Diego, California, USA). A P value of <.05 (2-sided) was considered statistically significant.

RESULTS

Baseline patient demographic and clinical characteristics

Among the 161 patients registered into the "Southern Italy Network on Severe Asthma Therapy" shared database, 137 patients received benralizumab for at least 24 weeks and were included in the analysis. A flow diagram of study participants is shown in Figure E1 (available in this article's Online Repository at www.jaci-inpractice.org, section 2).

Patient baseline characteristics and baseline comparisons between the SEA and SEA+CRSwNP groups are reported in Table I. None of the subjects discontinued the treatment because of side effects or suboptimal treatment response.

The mean age was 53.9 ± 13.5 years. The median age at onset was 38 (25-46) years. The majority of patients were female (91 of 137, 66.4%). All patients were prescribed high-dose inhaled corticosteroids—long-acting beta-agonist, with 59.1% (81 of 137) requiring maintenance OCS for asthma. Thirteen (9.5%) had previously received anti-IgE and/or anti—IL-5 therapy with mepolizumab. Seventy-nine of 137 (57.7%) had CRSwNP, with a median SNOT-22 of 46 (39.5-64.5). Forty of 79 (50.6%) patients underwent FESS, but 90% (36 of 40) resorted to at least 2 nonresolutive surgeries with nasal polyposis recurrence (median, 2 [1-2]). The Lund-Mackay score was calculated in 16 patients (16 of 79, 20.3%) who underwent sinus-CT scan before and after 24 weeks of benralizumab treatment, with a mean of 12.4 (8.8-16.1) at baseline. We noticed a higher, yet not statistically significant, proportion of patients with positive skin prick test in the SEA group (40 of 58 [69%] vs 42 of 79 [53.2%], $P = .0782$). No statistically significant differences were found in ACT score, OCS use, eosinophils and basophils in peripheral blood, IgE, and lung function, except for median pre-bronchodilator FVC% (80% [71.8-98.3] in SEA+CRSwNP vs 72% [61.8-93] in SEA, $P = .0375$). In 58 of 137 patients, FeNO was also measured at baseline. The FeNO value was 55 (38.1-78.0) ppb in SEA+CRSwNP (38 patients) in comparison with 37.9 (15-53.1) ppb in SEA (20 patients) ($P = .0099$).

Benralizumab effectiveness in severe eosinophilic asthma

The results of our analysis in the total cohort are reported in Table II and highlighted how benralizumab treatment significantly improved every examined outcome. AER decreased from 4 (3-6) to 0 (0-2) ($P < .0001$) (Figure 1, *A*). This was associated with a great improvement in ACT score, which shifted from 13 (11-16) at baseline to 22 (20-24) at 24 weeks ($P < .0001$). It is noteworthy that, already after the very first dose at 4 weeks, the ACT score reached a median of 20 (15.5-22.5) ($P < .0001$) (Figure 1, *B*). Parallel improvements in lung function were achieved as early as after 4 weeks in pre-bronchodilator FEV_1% ($P < .0001$) (Figure 1, *C*), FEV_1 (L) ($P < .0001$), FVC% ($P < .0001$), and FEV_1/FVC% ($P < .0001$) (Table II). FEF_{25-75}% shifted from 38% (24-55) to 41% (27-66.3) after 4 weeks ($P = .0022$), reaching 55% (38.8-70) after 24 weeks ($P < .0001$), as shown in Table II. Among the 59.1% of patients requiring maintenance OCS at baseline, there was a median reduction in the mg/day dosage at 24 weeks from 10 mg (5-25) to 0.0 mg (0.0-4.3) (Figure 1, *D*). Fifty-seven of 81 (70.4%) were able to discontinue their maintenance OCS ($P < .0001$) (Table II). Concerning the hematological effects, benralizumab suppressed eosinophils already at 4 weeks (0 cells/μL, $P < .0001$) and

TABLE I. Patients baseline demographic and clinical characteristics

Variable	All (n = 137)	SEA (n = 58)	SEA+CRSwNP (n = 79)	*P* value*
Age (y), mean (SD)	53.9 (13.5)	55.4 (14)	52.8 (13.2)	.2043
Female, n (%)	91 (66.4)	43 (74.1)	48 (60.8)	.1426
BMI, median (IQR)	26.2 (23.2-28.3)	27.0 (23.6-30.1)	25.8 (23.0-28.1)	.0687
Age at onset (y), median (IQR)	38 (25-46)	40 (25-47.8)	36 (25-45)	.1343
Patients with positive skin prick tests, n (%)	82 (59.9)	40 (69.0)	42 (53.2)	.0782
Patients with positive skin prick tests (perennial aeroallergens), n (%)	56 (40.9)	25 (43.1)	31 (39.2)	.7258
Smoking history, n (%)	33 (24.1)	18 (31)	15 (19)	.1111
Current smoker, n (%)	3 (2.9)	2 (3.4)	1 (1.3)	.5737
Patients with bronchiectasis, n (%)	33 (24.1)	15 (25.9)	18 (22.8)	.7892
Patients with osteoporosis, n (%)	29 (21.2)	13 (22.4)	16 (20.3)	.8412
High-dose ICS-LABA, n (%)	137 (100)	58 (100)	79 (100)	.9999
LAMA, n (%)	95 (69.3)	43 (74.1)	52 (65.8)	.3505
Previous anti-IgE/anti IL-5 mAbs, n (%)	13 (9.5)	6 (10.3)	7 (8.9)	.7763
Asthma exacerbations/year, median (IQR)	4 (2.5-6.0)	4 (2-6)	4 (3-6)	.4757
ACT, median (IQR)	13 (11-16)	13 (9.8-17)	14 (11-16)	.4789
FEV_1 (%), mean (SD)	64.7 (21.3)	64.4 (20.8)	64.8 (21.8)	.9150
FEV_1 (L), median (IQR)	1.66 (1.2-2.33)	1.58 (1.20-2.03)	1.66 (1.08-2.48)	.1461
FVC (%), median (IQR)	78 (68-95)	72 (61.8-93)	80 (71.8-98.3)	**.0375**
FEV_1/FVC (%), median (IQR)	66 (56-74.5)	66 (59-75)	65 (55-73)	.3572
FEF_{25-75} (%), median (IQR)	38.0 (24-55)	38 (24-59.5)	39.0 (23.5-54.3)	.5820
Patients on OCS, n (%)	81 (59.1)	34 (58.6)	47 (59.5)	.9999
OCS (mg/die), median (IQR)	10 (5-25)	11.25 (5-25)	10 (5-25)	.4497
Patients with CRSsNP, n (%)	17 (12.4)	17 (29.3)	n/a	n/a
Patients with CRSwNP, n (%)	79 (57.7)	n/a	79 (100)	n/a
Patients treated with at least 1 FESS, n (%)	n/a	n/a	40 (50.6)	n/a
Patients with nasal polyposis recurrence after FESS (n = 40), n (%)	n/a	n/a	36 (90)	n/a
Nasal polyposis recurrence after FESS, median (IQR)	n/a	n/a	2 (1-2)	n/a
SNOT-22 (n = 79), median (IQR)	n/a	n/a	46 (39.5-64.5)	n/a
Lund-Mackay score (n = 16), mean (SD)	n/a	n/a	12.4 (6.8)	n/a
Eosinophil counts in peripheral blood (cells/μL), median (IQR)	705 (472-1010)	700 (401.5-1165)	710 (500-1008)	.7675
Basophil counts in peripheral blood (cells/μL), median (IQR)	40 (20-90)	50 (20-90)	40 (30-97.5)	.6860
IgE (UI/mL), median (IQR)	158 (66-465)	168 (54-750)	149.5 (71.3-367)	.8555
FeNO (ppb), median (IQR)	46.5 (34.3-63.5)†	37.9 (15-53.1)‡	55 (38.1-78.0)§	**.0099**

ACT, Asthma Control Test; *BMI*, body mass index; *CRSsNP*, chronic rhinosinusitis without nasal polyps; *CRSwNP*, chronic rhinosinusitis with nasal polyps; FEF_{25-75}, forced expiratory flow between 25% and 75% of FVC; *FeNO*, fractional exhaled nitric oxide; *FESS*, functional endoscopic sinus surgery; FEV_1, forced expiratory volume in the 1st second; *FVC*, forced vital capacity; *ICS-LABA*, inhaled corticosteroids−long-acting beta-agonist; *IgE*, immunoglobulin-E; *LAMA*, long-acting muscarinic antagonist; *mAb*, monoclonal antibody; *OCS*, oral corticosteroids (prednisone); *SEA*, severe eosinophilic asthma; *SNOT-22*, 22-item Sino-Nasal Outcome Test.
For normally distributed data, values are mean (standard deviation [SD]). For non-normally distributed variables, values are median (interquartile range [IQR]).
Bold entries highlight statistically significant *P* values.
*SEA vs SEA+CRSwNP.
†Data from 58 patients.
‡Data from 38 patients.
§Data from 20 patients.

basophils at 24 weeks (0 cells/μL, $P < .0001$) in peripheral blood (Table II).

Efficacy according to the presence of chronic rhinosinusitis with nasal polyps

From baseline to weeks 4 and 24, we registered a significative overall positive trend both in SEA and SEA+CRSwNP, as summarized in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org, section 3), with the only exception of FEV_1/FVC% at week 4 in patients with SEA without nasal polyposis (from 66% [59-75] to 70% [55.5-76.5], $P = .0641$) (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

At week 24, more patients in the SEA+CRSwNP group achieved the ACT minimal clinically important difference (MCID) (increase ≥3 points from baseline)[30] (92.4% vs 79.3%, $P = .0387$) (Figure 2, *A*). Statistically significant differences in favor of the SEA+CRSwNP group were registered in pre-bronchodilator FEV_1% (+23.1% [17.3-28.9] vs +13% [8.4-17.6], $P = .0170$) (Figure 2, *B*) and pre-bronchodilator

TABLE II. Outcomes after 4 and 24 weeks of treatment in the total cohort (n = 137)

Variable	Baseline	4 wk	*P* value*	24 wk	*P* value†
Annual exacerbation rate, median (IQR)	4 (3-6)	n/a	n/a	0 (0-2)	**<.0001**
ACT, median (IQR)	13 (11-16)	20 (15.5-22.5)	**<.0001**	22 (20-24)	**<.0001**
FEV_1 (%), mean (95% CI)	64.7 (61.0-68.3)	74.3 (69.5-79.1)	**<.0001**	79.90 (75.40-84.40)	**<.0001**
FEV_1 (L), median (IQR)	1.66 (1.2-2.33)	1.94 (1.55-2.43)	**<.0001**	2.12 (1.68-2.62)	**<.0001**
FVC (%), median (IQR)	78 (68-95)	88 (70.8-99)	**<.0001**	90 (77-102)	**<.0001**
FEV_1/FVC (%), median (IQR)	66 (56-74.5)	70 (58.8-80)	**<.0001**	72.5 (64-80)	**<.0001**
FEF_{25-75} (%), median (IQR)	38 (24-55)	41 (27-66.3)	**.0022**	55 (38.8-70)	**<.0001**
Patients on OCS, n (%)	81 (59.1)	33 (24.1)	**<.0001**	24 (17.5)	**<.0001**
OCS (mg/die), median (IQR)	10 (5-25)	0 (0-5)	**<.0001**	0.0 (0.0-4.3)	**<.0001**
SNOT-22 (n = 79), median (IQR)	46 (39.5-64.5)	n/a	n/a	32 (19-46)	**<.0001**
SNOT-22 MCID (n = 79), n (%)	n/a	n/a	n/a	30 (38)	n/a
Lund-Mackay score (n = 16), mean (95% CI)	12.4 (8.8-16.1)	n/a	n/a	6.4 (3.5-9.4)	**.0200**
Eosinophil counts in peripheral blood (cells/μL), median (IQR)	705 (472-1010)	0.0 (0.0-0.0)	**<.0001**	0.0 (0.0-0.0)	**<.0001**
Basophil counts in peripheral blood (cells/μL), median (IQR)	40 (20-90)	5.5 (0-20)	**<.0001**	0.0 (0-10)	**<.0001**

ACT, Asthma Control Test; *FEF_{25-75}*, forced expiratory flow between 25% and 75% of FVC; *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in the 1st second; *FVC*, forced vital capacity; *MCID*, minimal clinically important difference; *OCS*, oral corticosteroids (prednisone); *SNOT-22*, 22-item Sino-Nasal Outcome Test.
Values are expressed as mean (95% confidence interval [CI]) for normally distributed data and as median (interquartile range [IQR]) for non-normally distributed variables. Bold entries highlight statistically significant *P* values.
*Baseline vs 4 weeks.
†Baseline vs 24 weeks.

FEV_1 (L) (Figure 2, *C*), the latter already at 4 weeks (+0.24L [0.02-0.66] vs +0.09L [−0.1 to 0.44], $P = .03$). Moreover, benralizumab elicited a greater effect on small airways obstruction in subjects with the copresence of nasal polyps, as shown by the pre-bronchodilator FEF_{25-75}% value shift from baseline to 24 weeks of treatment (+22% [9.5-35] vs +11% [−2 to 26.3], $P = .0362$) (Figure 2, *D*). At the end of the study period, we found a numerical difference in favor of patients with SEA+CRSwNP, who were able to suspend OCS (36 of 47 [76.6%] vs 21 of 34 [61.8%], $P = .2175$) and to remain exacerbation-free despite OCS discontinuation (33 of 47 [70.2%] vs 18 of 34 [52.9%], $P = .1617$). However, these findings were not statistically significant. The differences in response to treatment are reported in Table E2 (available in this article's Online Repository at www.jaci-inpractice.org, section 3).

Change in sino-nasal outcomes

In the 79 patients (57.7%) with comorbid CRSwNP, nasal-related symptoms improved, as shown by the SNOT-22 total score decrease from 46 (39.5-64.5) to 32 (19-46) ($P < .0001$) (Figure 3, *A*, and Table E1, available in this article's Online Repository at www.jaci-inpractice.org, section 3). In 16 patients who underwent sinus-CT scans before treatment initiation and after 24 weeks, a reduction of sinus opacification was noted. The ICC between raters was 0.96 (0.92-0.99) for assessing the Lund-Mackay score, which decreased from 12.4 (8.8-16.1) to 6.4 (3.5-9.4) ($P = .02$) (Figure 3, *B*).

According to SNOT-22 scores, 38 (48.1%) reported severe symptoms, 34 (43%) moderate symptoms, and only 7 (8.9%) mild symptoms at baseline. After 24 weeks, 15 (19%) subjects from the severe symptom cluster were reclassified into moderate, 2 (2.5%) into mild, and 4 (5%) went from moderate to mild (Figure 4).

Effect on upper and lower airway outcome measures

Among the 79 patients with SEA+CRSwNP, 73 (92.4%) reported ACT MCID and 30 (38%) showed SNOT-22 MCID (reduction ≥8.9 points)[31] (Tables E1 and E2, available in this article's Online Repository at www.jaci-inpractice.org, section 3). Twenty-nine patients (36.7%) obtained both ACT and SNOT-22 MCID, 1 patient (1.3%) only SNOT-22 MCID, and 5 (6.3%) did not show any clinically meaningful symptom improvements (Figure 5). Except for SNOT-22, which was higher in the ACT+SNOT-22 MCID group (42 [36.8-58] vs 58 [44-67], $P = .0037$), there were no statistically significant differences between patients with both upper and lower airway symptom improvement and those who improved only lower airway outcome measures (Table E3, available in this article's Online Repository at www.jaci-inpractice.org, section 4).

Safety

Add-on therapy with benralizumab was safe and well tolerated. No serious adverse events related to benralizumab occurred throughout the entire duration of the study and no patients suspended the treatment due to a severe inject-site reaction, anaphylaxis, or altered laboratory values.

DISCUSSION

The results of this real-world multicenter observational study demonstrated the rapid effectiveness of benralizumab in patients with SEA. We observed that benralizumab also improved nasal symptoms in case of CRSwNP and exerted a more beneficial response in terms of both asthma control and lung function improvement when these 2 diseases were associated.

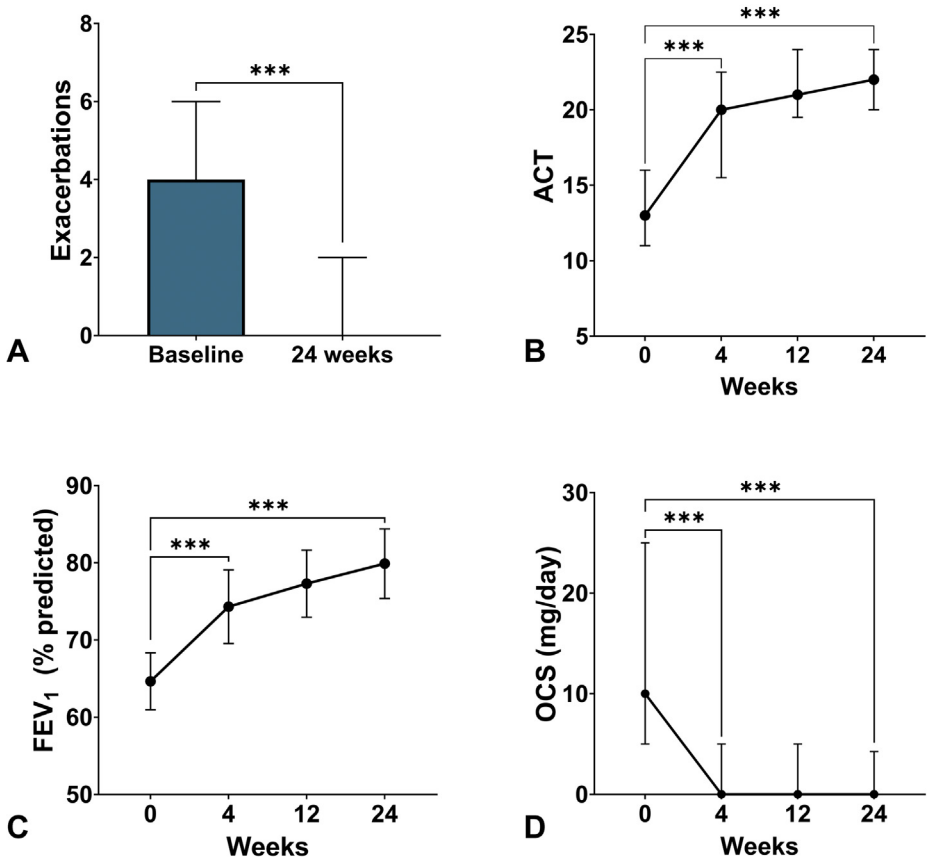


FIGURE 1. Effects of benralizumab on the entire population regarding (**A**) exacerbations (AER), (**B**) ACT score, (**C**) FEV_1%, and (**D**) OCS dose. FEV_1% values are expressed as mean (95% confidence interval). All other parameters are expressed as median values (interquartile range). ***$P < .001$. *ACT*, Asthma Control Test; *AER*, annualized exacerbation rate; *FEV_1*, forced expiratory volume in the 1st second; *OCS*, oral corticosteroids (prednisone).

The median age at onset of 38 years was consistent with late-onset SEA, and the high prevalence of CRSwNP (57.7%) was in keeping with the published literature.[5-8]

Considering the total population involved, we showed a remarkable reduction of asthma exacerbations. Indeed, 77.4% of patients were exacerbation free throughout the entire duration of the study. Simultaneously, the median OCS daily dose was reduced by 100%, and 51 of 81 (63%) were able to stop OCS long-term use, which is associated with significant adverse effects.[32,33] Such results were even more remarkable than those reported in the phase III trials SIROCCO[15] and CALIMA,[16] in terms of exacerbation reduction, and the phase III ZONDA trial[17] for OCS sparing.

These favorable outcomes might be related to parallel improvements in lung function because respiratory function impairment is a hallmark of severe asthma and is associated with disease severity.[34] Our patients benefited from substantial improvements in every respiratory function parameter, including FEF_{25-75}%, representative of distal airway obstruction, already after 4 weeks of treatment, due to the fast pharmacological activity of benralizumab.

In addition to the above-mentioned therapeutic benefits, patients' symptoms were also reduced, as shown by the significant ACT score increase, reinforcing the body of very positive clinical evidence of the phase III trials[15-17] using the Asthma Control Questionnaire 6 rather than ACT.[35] We found that the ACT score reached the critical threshold of 20, which is indicative of good overall asthma control by the time of the second dose at week 4.

These findings confirmed and expanded the already published evidence on the rapid effectiveness of benralizumab in patients with SEA in real-world settings.[36-40]

According to the latest GINA recommendations (2019),[2] the current procedures for diagnosing severe asthma should include both nasal endoscopy and/or CT of the nasal and paranasal sinuses, given the high prevalence of CRSwNP in late-onset SEA. Nasal polyposis *per se* severely affects patients' quality of life due to loss of smell and frequent exacerbations. The GALEN study found that polyp recurrence after FESS occurred in 59% of patients,[41] remarkably lower than what we observed in our cohort (90%). Indeed, surgical removal of inflamed sinus mucosal tissue does not address the cause of the underlying inflammation and the process leading to polyp formation. Furthermore, patients with both SEA and CRSwNP tend to achieve worse asthma control[9] and consume more OCS per year[8] with increased exposure to steroids' adverse effects.[42] Hence, there is a need for therapies that can dampen type 2 inflammation and treat both diseases. A pooled analysis of the SIROCCO and CALIMA trials[18] identified nasal polyposis as a predictor of response to anti−IL-5Rα. In this regard, our real-world study

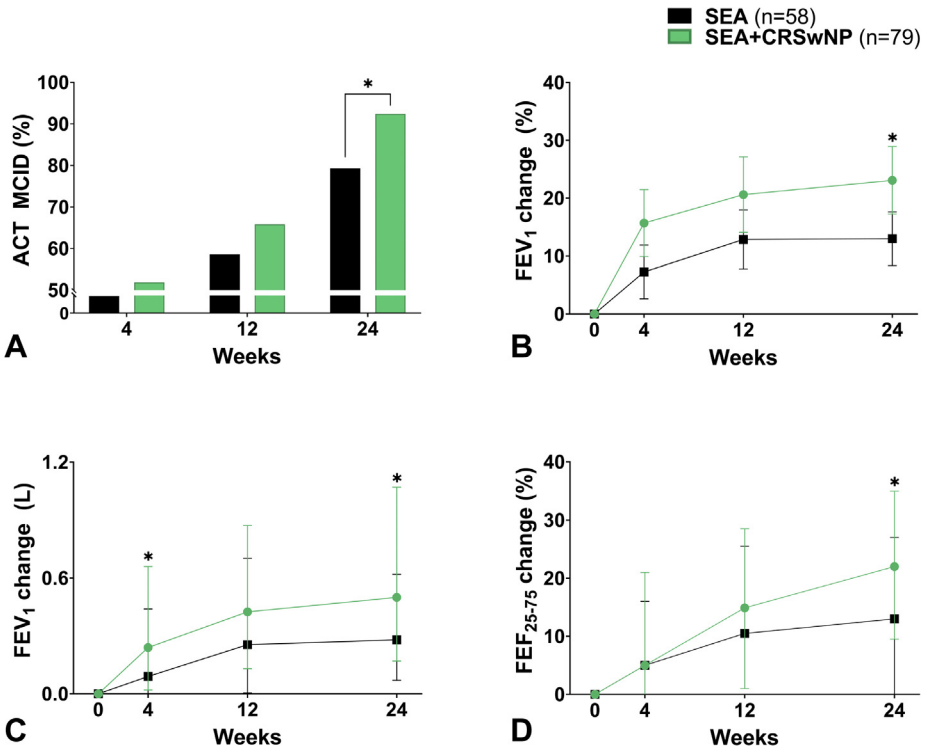


FIGURE 2. Improvements comparisons between SEA and SEA+CRSwNP on (**A**) ACT MCID, (**B**) FEV_1%, (**C**) FEV_1 Liters, (**D**) FEF_{25-75}%. FEV_1% values are expressed as mean (95% confidence interval). All other parameters are expressed as median values (interquartile range). *$P < .05$. *ACT*, Asthma Control Test; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *FEF_{25-75}*, forced expiratory flow between 25% and 75% of forced vital capacity; *FEV_1*, forced expiratory volume in the 1st second; *MCID*, minimal clinically important difference; *SEA*, severe eosinophilic asthma.

showed that 38% of patients with SEA+CRSwNP reported clinically meaningful improvements in nasal symptoms (SNOT-22 MCID), confirming the recent phase IIIb ANDHI[19] trial results as well as of some real-life experiences referring to small numbers of patients.[20,21] Surprisingly, 44.8% (17 of 38) of patients with severe symptoms were reallocated to moderate or mild disease after treatment. A small subgroup of 16 patients, who repeated sinus-CT scans by week 24, showed a partial resolution of their sinuses radiological opacification.

Overall, our results indicate that benralizumab exerted very positive therapeutic effects in both patients with SEA and patients with SEA+CRSwNP. Interestingly, when comparing patients with SEA with and without nasal polyps, we found a more pronounced response to treatment in the SEA+CRSwNP group in terms of ACT MCID, pre-bronchodilator FEV_1%, pre-bronchodilator FEV_1 L, and FEF_{25-75}%. These differences began to manifest numerically already after the very first administration.

To this extent, almost every patient with nasal polyps (92.4%) reported a minimally clinical substantial increase in ACT score (ACT MCID $\geq$3 points) compared with 79.3% of patients without polyposis. Furthermore, we showed a +10% pre-bronchodilator FEV_1% difference in favor of SEA+CRSwNP by week 24 of treatment, while a significant FEV_1 L delta of 150 mL was already present after 4 weeks. Although still debated, a minimum incremental advantage of lung function (FEV_1) of approximately 10%[25] is considered clinically meaningful; therefore, the clinically significant greater improvement in lung function of patients with SEA+CRSwNP could explain the high proportion of ACT improvement achieved in this subgroup of patients. Unlike FEV_1, FEF_{25-75} began to diverge by week 12, reaching a significant difference after 24, with +11% in favor of SEA+CRSwNP.

Although there is a strong link between upper and lower airway diseases, the mechanism that underlies this connection has not been fully unveiled yet. Both SEA and CRSwNP are sustained by a broad network of cytokines, including IL-4, IL-5, and IL-13.[11,12] IL-4 promotes the differentiation of CD4+ T cells into Th-2 lymphocytes. Together with ILC2, they secrete IL-5, inducing eosinophil proliferation, maturation, and mobilization.[43-45] Activated eosinophils deeply infiltrate distal airways of patients with SEA,[46] contributing to airway hyperresponsiveness and airflow limitation, triggering asthma exacerbations and promoting remodeling.[47] Moreover, eosinophils contribute to sinus mucosal injury by releasing their granule enzyme, leading to a positive loop of IL-13 and IL-4 hyperproduction and disabling the tissue plasminogen activator, enhancing fibrin deposition, retention of plasma proteins, and edema.[48] Because of its pleiotropic effects, benralizumab dampens type 2 inflammation pathways acting on different time points. First, the binding of IL-5Rα prevents IL-5 from interacting with its receptor. Subsequently, via ADCC, benralizumab induces apoptosis of eosinophils, ILC2, and basophils, and plays a crucial role in local IgE synthesis and tissue eosinophilia.[49] These therapeutic effects explain the rapid improvement of

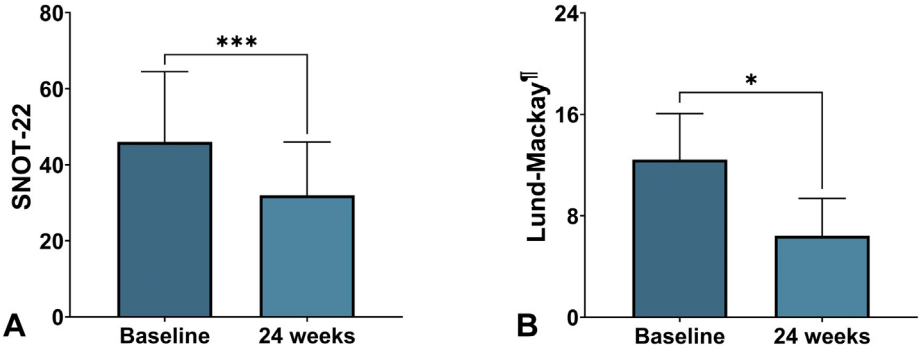


FIGURE 3. Changes on (**A**) SNOT-22 and (**B**) Lund-Mackay score. *$P < .05$, ***$P < .001$. ¶Calculated on 16 patients. *SNOT-22*, 22-Item Sino-Nasal Outcome Test.

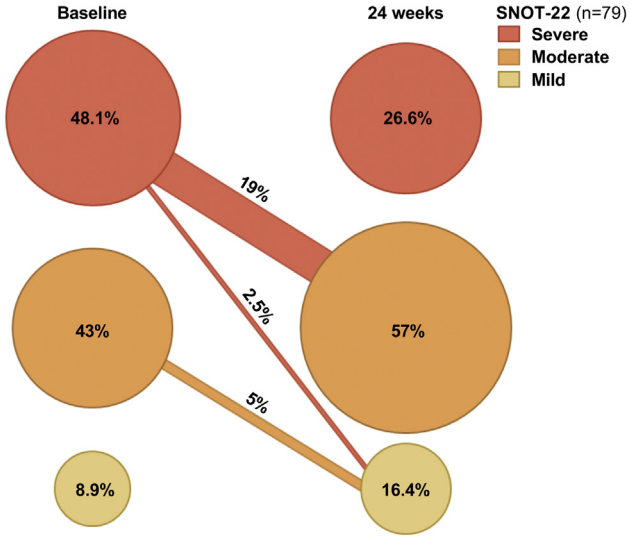


FIGURE 4. Changes on patients' nasal symptoms severity. *SNOT-22*, 22-Item Sino-Nasal Outcome Test.

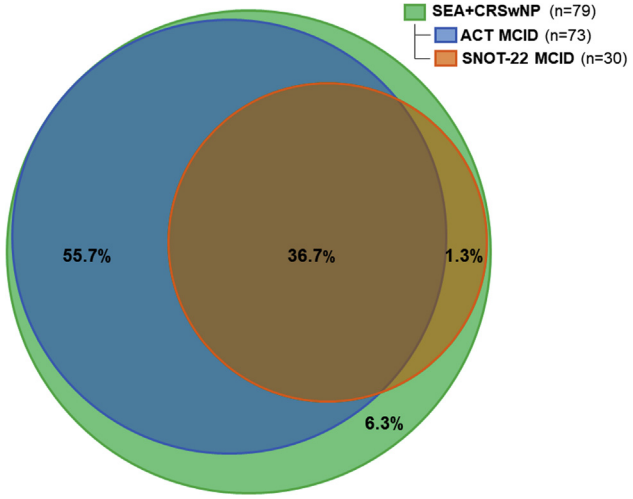


FIGURE 5. SEA+CRSwNP patients' distribution according to ACT MCID and SNOT-22 MCID. *ACT*, Asthma Control Test; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *MCID*, minimal clinically important difference; *SEA*, severe eosinophilic asthma; *SNOT-22*, 22-item Sino-Nasal Outcome Test.

lung function and the reduction in asthma exacerbation rate, preventing progressive lung deterioration[50] and limiting the IL-13 and IL-4 secretion, reducing excessive fibrin deposition and mucosal edema. Several studies have demonstrated that distal airways of patients with severe eosinophilic asthma and copresence of nasal polyps tend to have a greater degree of type 2 inflammation and eosinophilic infiltration compared with those without nasal polyps.[51] This important feature could represent a "treatable trait," explaining why SEA+CRSwNP might achieve a better response to benralizumab treatment.

The main strength of this study is that it is based on real-world data, which enabled us to include patients without restrictive eligibility criteria, tracking also subjects with significant smoking histories and medical comorbidities, often excluded from clinical trials,[52] and the relatively large size of the dataset. Moreover, data were collected by expert referral centers for the treatment of patients with SEA that are part of the "Southern Italy Network on Severe Asthma Therapy," whose purpose is to provide consistent patient care using a shared systematic clinical approach. Hence, the data collected are of high quality and harmonized, and findings coming from our study are robust and reliable. Furthermore, the results of the current real-world study are comparable to the *post hoc* analysis of the recent randomized controlled ANDHI trial.[53]

However, several limitations should be considered when interpreting these findings. First, because of the retrospective observational design, we cannot exclude the possibility of unmeasured confounding factors, which could reduce the strength of our results. Secondly, our follow-up period was restricted to 24 weeks; therefore, we are not able to assess whether short-term benefits remain over longer periods and to provide information on long-term safety. In addition, we did not evaluate the nasal polyp size change during the treatment, and only a small group of patients (16 of 79, 20.3%) underwent sinus-CT scans before and after 24 weeks of benralizumab treatment, limiting the generalizability of Lund-Mackay score improvements. One further limitation to be considered is the potential source of bias inherent to the lack of a control group.

To date, personalized treatment for patients diagnosed with SEA is one of the most significant advances in modern care for asthma. These findings confirm that benralizumab is a valuable

therapeutic choice for patients suffering from SEA, particularly if associated with nasal polyps, in which the biologic may determine synergistic beneficial effects for both diseases. These data reflect real-world practice patterns and the broad experience of both community and academic physicians involved in the treatment of severe asthmatic patients, providing further insights to clinicians involved in everyday clinical practice.

Acknowledgments

Collaborators: Danilo Di Bona: Department of Emergency and Organ Transplantation, School and Chair of Allergology and Clinical Immunology, University of Bari—Aldo Moro, Italy; Aikaterini Detoraki: Department of Translational Medical Sciences, University of Naples Federico II, Naples, Italy; Carmen Durante: PROMISE Department, University of Palermo, Palermo, Italy; Maria Pia Foschino Barbaro: Department of Emergency and Organ Transplantation, School and Chair of Allergology and Clinical Immunology, University of Bari—Aldo Moro, Italy; Pietro Impellizzeri: Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy; Angelantonio Maglio: Department of Medicine, Surgery and Dentistry, University of Salerno, Salerno, Italy; Stefania Principe: PROMISE Department, University of Palermo, Palermo, Italy; Carla Maria Irene Quarato: Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy; Massimo Triggiani: Department of Medicine, Surgery and Dentistry, University of Salerno, Salerno, Italy; Carolina Vitale: Department of Medicine, Surgery and Dentistry, University of Salerno, Salerno, Italy.

REFERENCES

1. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-73.
2. Global Initiative for Asthma. 2019 GINA report: Global Strategy for Asthma Management and Prevention. Available from: https://ginasthma.org/reports/2019-gina-report-global-strategy-for-asthma-management-and-prevention/. Accessed July 14, 2021.
3. Bardin PG, Rangaswamy J, Yo SW. Managing comorbid conditions in severe asthma. Med J Aust 2018;209(S2):S11-7.
4. Crimi C, Campisi R, Cacopardo G, Intravaia R, Nolasco S, Porto M, et al. Real-life effectiveness of mepolizumab in patients with severe refractory eosinophilic asthma and multiple comorbidities. World Allergy Organ J 2020;13:100462.
5. Heffler E, Blasi F, Latorre M, Menzella F, Paggiaro P, Pelaia G, et al. The severe Asthma Network in Italy: findings and perspectives. J Allergy Clin Immunol Pract 2019;7:1462-8.
6. John Staniorski C, Price CPE, Weibman AR, Welch KC, Conley DB, Shintani-Smith S, et al. Asthma onset pattern and patient outcomes in a chronic rhinosinusitis population: asthma onset and patient characteristics in CRS. Int Forum Allergy Rhinol 2018;8:495-503.
7. Denlinger LC, Phillips BR, Ramratnam S, Ross K, Bhakta NR, Cardet JC, et al. Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations. Am J Respir Crit Care Med 2017;195:302-13.
8. Canonica GW, Malvezzi L, Blasi F, Paggiaro P, Mantero M, Senna G, et al. Chronic rhinosinusitis with nasal polyps impact in severe asthma patients: evidences from the Severe Asthma Network Italy (SANI) registry. Respir Med 2020;166:105947.
9. Tay TR, Radhakrishna N, Hore-Lacy F, Smith C, Hoy R, Dabscheck E, et al. Comorbidities in difficult asthma are independent risk factors for frequent exacerbations, poor control and diminished quality of life: comorbidities in difficult asthma. Respirology 2016;21:1384-90.
10. Bhattacharyya N, Villeneuve S, Joish VN, Amand C, Mannent L, Amin N, et al. Cost burden and resource utilization in patients with chronic rhinosinusitis and nasal polyps. Laryngoscope 2019;129:1969-75.
11. Håkansson K, Bachert C, Konge L, Thomsen SF, Pedersen AE, Poulsen SS, et al. Airway inflammation in chronic rhinosinusitis with nasal polyps and asthma: The united airways concept further supported. PLoS One 2015;10:e0127228.
12. Chiarella E, Lombardo N, Lobello N, Aloisio A, Aragona T, Pelaia C, et al. Nasal polyposis: insights in epithelial-mesenchymal transition and differentiation of polyp mesenchymal stem cells. Int J Mol Sci 2020;21:6878.
13. Pelaia C, Vatrella A, Bruni A, Terracciano R, Pelaia G. Benralizumab in the treatment of severe asthma: design, development and potential place in therapy. Drug Des Devel Ther 2018;12:619-28.
14. Hillas G, Fouka E, Papaioannou AI. Antibodies targeting the interleukin-5 signaling pathway used as add-on therapy for patients with severe eosinophilic asthma: a review of the mechanism of action, efficacy, and safety of the subcutaneously administered agents, mepolizumab and benralizumab. Expert Rev Respir Med 2020;14:353-65.
15. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet 2016;388:2115-27.
16. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2016;388:2128-41.
17. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. N Engl J Med 2017;376:2448-58.
18. Bleecker ER, Wechsler ME, FitzGerald JM, Menzies-Gow A, Wu Y, Hirsch I, et al. Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma. Eur Respir J 2018;52:1800936.
19. Harrison TW, Chanez P, Menzella F, Canonica GW, Louis R, Cosio BG, et al. Onset of effect and impact on health-related quality of life, exacerbation rate, lung function, and nasal polyposis symptoms for patients with severe eosinophilic asthma treated with benralizumab (ANDHI): a randomised, controlled, phase 3b trial. Lancet Respir Med 2021;9:260-74.
20. Lombardo N, Pelaia C, Ciriolo M, Della Corte M, Piazzetta G, Lobello N, et al. Real-life effects of benralizumab on allergic chronic rhinosinusitis and nasal polyposis associated with severe asthma. Int J Immunopathol Pharmacol 2020;34. 2058738420950851.
21. Bagnasco D, Brussino L, Bonavia M, Calzolari E, Caminati M, Caruso C, et al. Efficacy of benralizumab in severe asthma in real life and focus on nasal polyposis. Respir Med 2020;171:106080.
22. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol 2004;113:59-65.
23. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. Clin Otolaryngol 2009;34:447-54.
24. Lund VJ. Mackay IS. Staging in rhinosinusitus. Rhinology 1993;31:183-4.
25. Reddel HK, Taylor DR, Bateman ED, Boulet L-P, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009;180:59-99.
26. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-38.
27. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. European position paper on rhinosinusitis and nasal polyps 2020. Rhinology 2020;58(Suppl S29):1-464.
28. Toma S, Hopkins C. Stratification of SNOT-22 scores into mild, moderate or severe and relationship with other subjective instruments. Rhinology 2016;54:129-33.
29. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Annex I—Definitions (Rev 4). Heads of Medicines Agencies; 2017. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4_en.pdf. Accessed July 10, 2021.
30. Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. J Allergy Clin Immunol 2009;124:719-723.e1.
31. Hopkins C, Rudmik L, Lund VJ. The predictive value of the preoperative Sinonasal Outcome Test-22 score in patients undergoing endoscopic sinus surgery for chronic rhinosinusitis: predictive value of the preoperative SNOT-22. Laryngoscope 2015;125:1779-84.
32. Manson SC, Brown RE, Cerulli A, Vidaurre CF. The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use. Respir Med 2009;103:975-94.

33. Walsh LJ, Wong CA, Oborne J, Cooper S, Lewis SA, Pringle M, et al. Adverse effects of oral corticosteroids in relation to dose in patients with lung disease. Thorax 2001;56:279-84.
34. Postma DS, Brightling C, Baldi S, Van den Berge M, Fabbri LM, Gagnatelli A, et al. Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): baseline data from a prospective cohort study. Lancet Respir Med 2019;7:402-16.
35. Crimi C, Campisi R, Noto A, Genco S, Cacopardo G, Nolasco S, et al. Comparability of asthma control test scores between self and physician-administered test. Respir Med 2020;170:106015.
36. Nolasco S, Campisi R, Intravaia R, Porto M, Pelaia C, Crimi N, et al. Case Report: Acute effect of benralizumab on asthma exacerbation without concomitant corticosteroid use. F1000Res 2020;9:637.
37. Renner A, Marth K, Patocka K, Idzko M, Pohl W. Benralizumab rapidly improves asthma control in Austrian real-life severe eosinophilic asthmatics. Allergy 2020;75:3272-5.
38. Pelaia C, Crimi C, Benfante A, Caiaffa MF, Calabrese C, Carpagnano GE, et al. Therapeutic effects of benralizumab assessed in patients with severe eosinophilic asthma: real-life evaluation correlated with allergic and non-allergic phenotype expression. J Asthma Allergy 2021;14:163-73.
39. Kavanagh JE, Hearn AP, Dhariwal J, d'Ancona G, Douiri A, Roxas C, et al. Real-world effectiveness of benralizumab in severe eosinophilic asthma. Chest 2021;159:496-506.
40. Padilla-Galo A, Levy-Abitbol R, Olveira C, Valencia Azcona B, Pérez Morales M, Rivas-Ruiz F, et al. Real-life experience with benralizumab during 6 months. BMC Pulm Med 2020;20:184.
41. Khan A, Vandeplas G, Huynh TMT, Joish VN, Mannent L, Tomassen P, et al. The Global Allergy and Asthma European Network (GALEN rhinosinusitis cohort: a large European cross-sectional study of chronic rhinosinusitis patients with and without nasal polyps. Rhinology 2019;57:32-42.
42. Canonica GW, Colombo GL, Bruno GM, Di Matteo S, Martinotti C, Blasi F, et al. Shadow cost of oral corticosteroids-related adverse events: a pharmacoeconomic evaluation applied to real-life data from the Severe Asthma Network in Italy (SANI) registry. World Allergy Organ J 2019;12:100007.
43. Upadhyaya B, Yin Y, Hill BJ, Douek DC, Prussin C. Hierarchical IL-5 expression defines a subpopulation of highly differentiated human Th2 cells. J Immunol 2011;187:3111-20.
44. Heffler E, Terranova G, Chessari C, Frazzetto V, Crimi C, Fichera S, et al. Point-of-care blood eosinophil count in a severe asthma clinic setting. Ann Allergy Asthma Immunol 2017;119:16-20.
45. Nussbaum JC, Van Dyken SJ, von Moltke J, Cheng LE, Mohapatra A, Molofsky AB, et al. Type 2 innate lymphoid cells control eosinophil homeostasis. Nature 2013;502:245-8.
46. Carroll N, Cooke C, James A. The distribution of eosinophils and lymphocytes in the large and small airways of asthmatics. Eur Respir J 1997;10:292-300.
47. Kariyawasam HH, Robinson DS. The role of eosinophils in airway tissue remodelling in asthma. Curr Opin Immunol 2007;19:681-6.
48. Takabayashi T, Kato A, Peters AT, Hulse KE, Suh LA, Carter R, et al. Excessive fibrin deposition in nasal polyps caused by fibrinolytic impairment through reduction of tissue plasminogen activator expression. Am J Respir Crit Care Med 2013;187:49-57.
49. Nouri-Aria KT, Irani AM, Jacobson MR, O'brien F, Varga EM, Till SJ, et al. Basophil recruitment and IL-4 production during human allergen-induced late asthma. J Allergy Clin Immunol 2001;108:205-11.
50. Bai TR, Vonk JM, Postma DS, Boezen HM. Severe exacerbations predict excess lung function decline in asthma. Eur Respir J 2007;30:452-6.
51. Bilodeau L, Boulay M-E, Prince P, Boisvert P, Boulet L-P. Comparative clinical and airway inflammatory features of asthmatics with or without polyps. Rhinology 2010;48:420-5.
52. Brown T, Jones T, Gove K. Randomised controlled trials in severe asthma: selection by phenotype or stereotype. Eur Respir J 2018;52:1801444.
53. Canonica GW, Harrison TW, Chanez P, Menzella F, Louis R, Cosio BG, et al. Benralizumab improves symptoms of patients with severe, eosinophilic asthma with a diagnosis of nasal polyposis. Allergy. Published online May 12, 2021. https://doi.org/10.1111/all.14902

ONLINE REPOSITORY

SECTION 1: "SOUTHERN ITALY NETWORK ON SEVERE ASTHMA THERAPY"

List of centers

1. Respiratory Medicine Unit, A.O.U. Policlinico "G. Rodolico—San Marco", Catania
2. Pulmonary Unit, A.O.U. "Mater Domini", Catanzaro
3. Respiratory Medicine Unit, A.O.U. Policlinico "Paolo Giaccone", Palermo
4. Allergology and Clinical Immunology, University Hospital of Foggia, Foggia
5. Department of Pneumology, A.O. "Dei Colli", Naples
6. Respiratory Medicine Unit, A.O.U. Policlinico di Bari "Giovanni XXIII", Bari
7. Respiratory Medicine Unit, A.O.U. "San Giovanni di Dio and Ruggi d'Aragona", Salerno
8. Allergology and Clinical Immunology, A.O.U. "San Giovanni di Dio and Ruggi d'Aragona", Salerno
9. Allergology, A.O.U. Policlinico di Bari "Giovanni XXIII", Bari
10. Institute of Respiratory Diseases, University Hospital of Foggia, Foggia
11. Allergology, A.O.U. "Federico II", Naples
12. Allergy and Pulmonary Medicine Unit, Center for Severe Asthma, ASP Palermo, Palermo

SECTION 2: STUDY PARTICIPANT

SECTION 3: EFFICACY IN SEVERE EOSINOPHILIC ASTHMA PATIENTS WITH AND WITHOUT NASAL POLYPS

SECTION 4: BASELINE DIFFERENCES OF ASTHMA SYMPTOMS RESPONDERS VERSUS ASTHMA AND NASAL SYMPTOMS RESPONDERS

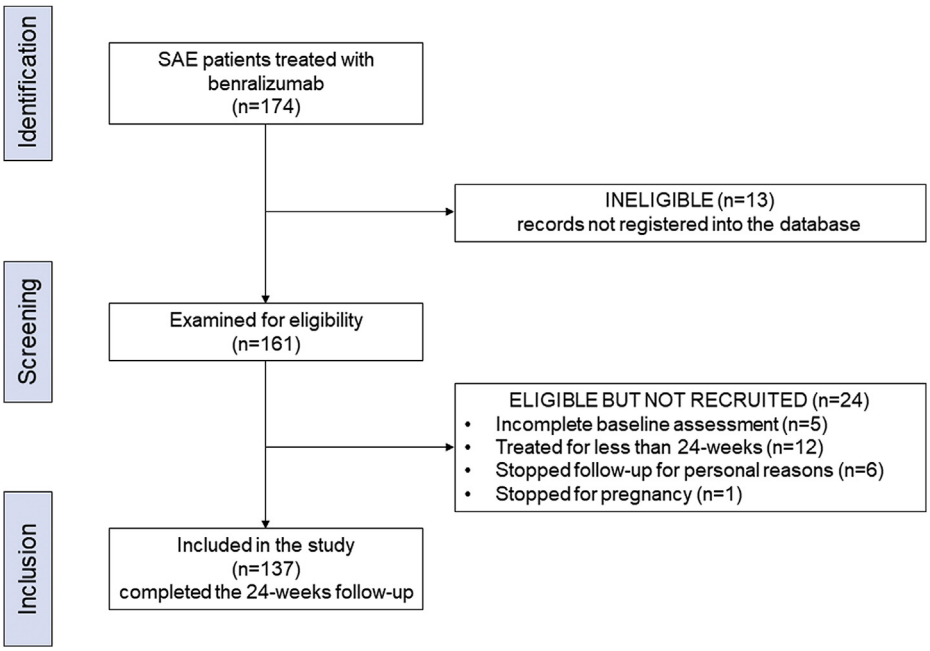


FIGURE E1. Participant flow diagram in accordance with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) recommendations. *SEA*, Severe eosinophilic asthma.

TABLE E1. Outcomes after 4 and 24 weeks of treatment in SEA and SEA+CRSwNP patients

	SEA (n = 58)					SEA + CRSwNP (n = 79)				
Variable	**Baseline**	**4 wk**	***P* value***	**24 wk**	***P* value†**	**Baseline**	**4 wk**	***P* value***	**24 wk**	***P* value†**
Annual exacerbation rate, median (IQR)	4 (2-6)	n/a	n/a	0 (0-2)	**<.0001**	4 (3-6)	n/a	n/a	0 (0-2)	**<.0001**
ACT, median (IQR)	13 (9.8-17)	20 (16-23)	**<.0001**	21 (19-24)	**<.0001**	14 (11-16)	20 (15.3-22)	**<.0001**	22 (20-25)	**<.0001**
FEV_1 (%), mean (95% CI)	64.4 (58.8-70.0)	67.6 (60.9-74.2)	**.0030**	73.69 (67.0-83.3)	**<.0001**	64.8 (59.9-69.8)	79.3 (72.7-85.8)	**<.0001**	85.4 (79.5-91.3)	**<.0001**
FEV_1 (L), median (IQR)	1.58 (1.20-2.03)	1.74 (1.31-2.14)	**.0091**	1.93 (1.45-2.42)	**<.0001**	1.66 (1.08-2.48)	2.12 (1.61-2.65)	**<.0001**	2.32 (1.96-3.0)	**<.0001**
FVC (%), median (IQR)	72 (61.8-93)	81 (65-92)	**.0021**	88.5 (73.5-97.8)	**<.0001**	80 (71.8-98.3)	93 (79-105)	**<.0001**	91.5 (82-108.8)	**<.0001**
FEV_1/FVC (%), median (IQR)	66 (59-75)	70 (55.5-76.5)	.0641	72 (65-78)	**<.0001**	65 (55-73)	71 (62.5-82)	**<.0001**	73 (64-82)	**<.0001**
FEF_{25-75} (%), median (IQR)	38 (24-59.5)	45 (20.3-66.8)	**.0323**	51 (32-66.0)	**.0001**	39 (23.5-54.3)	39.3 (29.8-64.8)	**.0287**	59 (42-82)	**<.0001**
Patients on OCS, n (%)	34 (58.6)	16 (27.6)	**<.0001**	13 (22.4)	**<.0001**	47 (59.5)	17 (21.5)	**<.0001**	11 (13.9)	**<.0001**
OCS (mg/die), median (IQR)	11.25 (5-25)	2.5 (0-5.3)	**<.0001**	0 (0.0-5.0)	**<.0001**	10 (5-25)	0 (0-5.6)	**<.0001**	0 (0.0-0.0)	**<.0001**
SNOT-22, median (IQR)	n/a	n/a	n/a	n/a	n/a	46 (39.5-64.5)	n/a	n/a	32 (19-46)	**<.0001**
SNOT-22 MCID, n (%)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	30 (38)	n/a
Lund-Mackay score (n = 16), mean (95% CI)	n/a	n/a	n/a	n/a	n/a	12.4 (8.8-16.1)	n/a	n/a	6.4 (3.5-9.4)	**.0200**
Eosinophil counts in peripheral blood (cells/μL), median (IQR)	700 (401.5-1165)	0.0 (0.0-0.0)	**<.0001**	0.0 (0.0-0.0)	**<.0001**	710 (500-1008)	0.0 (0.0-0.0)	**<.0001**	0.0 (0.0-0.0)	**<.0001**
Basophil counts in peripheral blood (cells/μL), median (IQR)	50 (20-90)	0.0 (0-10)	**<.0001**	0.0 (0-10)	**<.0001**	40 (30-97.5)	0.0 (0-2.5)	**<.0001**	0.0 (0-2.5)	**<.0001**

ACT, Asthma Control Test; *CRSwNP*, chronic rhinosinusitis with nasal polyps; FEF_{25-75}, forced expiratory flow between 25% and 75% of FVC; *FeNO*, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in the 1st second; *FVC*, forced vital capacity; *MCID*, minimal clinically important difference; *OCS*, oral corticosteroids (prednisone); *SEA*, severe eosinophilic asthma; *SNOT-22*, 22-item Sino-Nasal Outcome Test.

Values are expressed as mean (95% confidence interval [CI]) for normally distributed data and as median (interquartile range [IQR]) for non-normally distributed variables.

Bold entries highlight statistically significant *P* values.

*Baseline vs 4 weeks.

†Baseline vs 24 weeks.

TABLE E2. Changes from baseline after 4 and 24 weeks of treatment in SEA versus SEA+CRSwNP patients

	4 wk			24 wk		
Variable	**SEA (n = 58)**	**SEA+CRSwNP (n = 79)**	***P* value**	**SEA (n = 58)**	**SEA+CRSwNP (n = 79)**	***P* value**
Exacerbation free, n (%)	45 (77.6)	67 (84.8)	.3709	42 (72.4)	64 (81.0)	.3019
ACT, change from baseline, median (IQR)	5 (2 to 10.5)	5 (1.25 to 8.0)	.8841	8 (2 to 12)	7 (4.4 to 10.5)	.7354
ACT MCID, n (%)	28 (48.3)	41 (51.9)	.7309	46 (79.3)	73 (92.4)	**.0387**
FEV_1 (%), change from baseline, mean (95% CI)	7.3 (2.6 to 11.9)	15.7 (9.9 to 21.5)	.0584	13.0 (8.4 to 17.6)	23.1 (17.3 to 28.9)	**.0170**
FEV_1 (L), change from baseline, median (IQR)	0.09 (−0.1 to 0.44)	0.24 (0.02 to 0.66)	**.0300**	0.28 (0.07 to 0.62)	0.50 (0.17 to 1.07)	**.0200**
FVC (%), change from baseline, median (IQR)	5.5 (−1.3 to 13)	7.7 (0.0 to 18)	.4855	9.2 (2.5 to 18.8)	9.0 (1 to 26.1)	.6756
FEV_1/FVC (%), change from baseline, median (IQR)	3 (−3 to 7)	3 (0 to 14.5)	.1552	6 (0.8 to 11)	7 (0.3 to 18.8)	.4917
FEF_{25-75} (%), change from baseline, median (IQR)	5 (−4.5 to 15.5)	5 (−9 to 21)	.8209	11 (−2 to 26.3)	22 (9.5 to 35)	**.0362**
OCS withdrawal, n (%)	18 (52.9)	30 (63.8)	.3654	21 (61.8)	36 (76.6)	.2175
Patients on OCS, n (%)	16 (47.1)	17 (36.2)	.3654	13 (38.2)	11 (23.4)	.2175
OCS suspended + exacerbation free, n (%)	14 (41.2)	25 (53.2)	.3685	18 (52.9)	33 (70.2)	.1617
OCS, change from baseline (mg/die), median (IQR)	5.63 (−15.6 to −2.5)	5.0 (−12.5 to −2.5)	.8748	8.8 (−18.8 to −3.4)	8.8 (−19.7 to −5)	.8436

ACT, Asthma Control Test; *CRSwNP*, chronic rhinosinusitis with nasal polyps; FEF_{25-75}, forced expiratory flow between 25% and 75% of FVC; *FeNO*, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in the 1st second; *FVC*, forced vital capacity; *MCID*, minimal clinically important difference; *OCS*, oral corticosteroids (prednisone); *SEA*, severe eosinophilic asthma; *SNOT-22*, 22-item Sino-Nasal Outcome Test.
Values are expressed as mean (95% confidence interval [CI]) for normally distributed data and as median (interquartile range [IQR]) for non-normally distributed variables.
Bold entries highlight statistically significant *P* values.

TABLE E3. Baseline clinical and demographic characteristics of ACT MCID versus ACT and SNOT-22 MCID group

Variable	ACT MCID (n = 44)	ACT MCID + SNOT-22 MCID (n = 29)	*P* value
Age (y), mean (SD)	53.9 (12.8)	52.1 (13.9)	.9219
Female, n (%)	27 (61.4)	18 (62.1)	.9999
BMI, median (IQR)	25.8 (22.9-28.1)	25 (23.4-28)	.9233
Age at onset (y), median (IQR)	38 (23.8-46.8)	30 (25.5-40)	.4956
Patients with positive skin prick tests, n (%)	23 (52.3)	17 (58.6)	.6374
Patients with positive skin prick tests (perennial aeroallergens), n (%)	20 (45.5)	13 (44.8)	.9999
Smoking history, n (%)	7 (15.9)	6 (20.7)	.7560
Current smoker, n (%)	0 (0)	0 (0)	.9999
Patients with bronchiectasis, n (%)	8 (18.2)	8 (27.6)	.3938
Patients with osteoporosis, n (%)	11 (25)	4 (13.8)	.3756
High dose ICS-LABA, n (%)	44 (100)	29 (100)	.9999
LAMA, n (%)	26 (59.1)	22 (75.9)	.9999
Previous anti-IgE/anti−IL-5 mAbs, n (%)	8 (18.2)	5 (17.2)	.7763
Asthma exacerbations/year, median (IQR)	4 (3-5.8)	5 (3.5-8)	.0734
ACT, median (IQR)	15 (12-16)	13 (10-16)	.0731
FEV_1 (%), mean (SD)	64.4 (20)	66.3 (24.6)	.7208
FEV_1 (L), median (IQR)	1.66 (1.1-2.4)	1.74 (1.1-2.76)	.7603
FVC (%), median (IQR)	87 (72.5-97)	78 (62.7-100)	.2289
FEV_1/FVC (%), median (IQR)	62.5 (52.4-76.8)	69 (55-72.5)	.4552
FEF_{25-75} (%), median (IQR)	36.5 (24-50.5)	42 (21.8-56)	.4587
Patients on OCS, n (%)	23 (52.3)	20 (69)	.2244
OCS (mg/die), median (IQR)	10 (5-25)	10 (5-22)	.7447
Patients treated with at least 1 FESS, n (%)	25 (56.8)	14 (48.3)	.6320
Patients with nasal polyposis recurrence after FESS, n (%)	22 (88)	13 (93)	.8113
Nasal polyposis recurrence after FESS, median (IQR)	2 (1-2)	1.5 (1-2)	.5046
SNOT-22, median (IQR)	42 (36.8-58)	58 (44-67)	**.0037**
Lund-Mackay score (n = 14), mean (SD)	9.6 (6.5)*	13.1 (7.2)†	.4081
Eosinophil counts in peripheral blood (cells/μL), median (IQR)	663 (470-940)	745 (505-1079)	.5547
Basophil counts in peripheral blood (cells/μL), median (IQR)	49 (30-100)	40 (22.5-80)	.2439
IgE (UI/mL), median (IQR)	167 (74.5-346)	131 (65-440)	.9258
FeNO (ppb), median (IQR)	55 (42-68)‡	59 (30-110)§	.9588

ACT, Asthma Control Test; *BMI*, body mass index; FEF_{25-75}, forced expiratory flow between 25% and 75% of FVC; *FeNO*, fractional exhaled nitric oxide; *FESS*, functional endoscopic sinus surgery; FEV_1, forced expiratory volume in the 1st second; *FVC*, forced vital capacity; *ICS-LABA*, inhaled corticosteroids−long-acting beta-agonist; *IgE*, immunoglobulin-E; *LAMA*, long-acting muscarinic antagonist; *mAb*, monoclonal antibody; *MCID*, minimal clinically important difference; *OCS*, oral corticosteroids (prednisone); *SD*, standard deviation; *SNOT-22*, 22-item Sino-Nasal Outcome Test.

Values are expressed as mean (95% confidence interval) for normally distributed data and as median (interquartile range [IQR]) for non-normally distributed variables.
Bold entries highlight statistically significant *P* values.

*Data from 5 patients.

†Data from 9 patients.

‡Data from 23 patients.

§Data from 15 patients.