Original Article

Long-Term Clinical and Sustained REMIssion in Severe Eosinophilic Asthma Treated With Mepolizumab: The REMI-M Study

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What is already known about this topic? Mepolizumab, an anti-IL-5 monoclonal antibody, has been shown to induce clinical remission after 12 months of treatment. However, long-term evidence remains limited.

What does this article add to our knowledge? The REMIssion in Severe Eosinophilic Asthma Treated with Mepolizumab (REMI-M) study investigated the effectiveness of mepolizumab in achieving clinical and sustained remission over 24 months.

How does this study impact current management guidelines? Mepolizumab can elicit long-term clinical and sustained remission in a conspicuous proportion of patients with severe eosinophilic asthma, supporting its role as a possible disease-modifying agent. The management of comorbidities and timely identification of patients who may benefit from biological treatment are crucial for optimizing long-term outcomes.

BACKGROUND: Biological therapies, such as mepolizumab, have transformed the treatment of severe eosinophilic asthma. Although mepolizumab's short-term effectiveness is established, there is limited evidence on its ability to achieve long-term clinical remission.

OBJECTIVE: To evaluate the long-term effectiveness and safety of mepolizumab, explore its potential to induce clinical and sustained remission, and identify baseline factors associated with the likelihood of achieving remission over 24 months.

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Abbreviations used
ACT- Asthma Control Test
AERD- Aspirin-exacerbated respiratory disease
AIC- Akaike Information Criterion
AUC- Area under the curve
BMI- Body mass index
CI- Confidence interval
CRSwNP- Chronic rhinosinusitis with nasal polyps
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 1 second
FVC- Forced vital capacity
GERD- Gastroesophageal reflux disease
IQR- Interquartile range
OCS- Oral corticosteroids (prednisone equivalent dose)
OR- Odds ratio
REMI-M- Remission in Severe Eosinophilic Asthma Treated with Mepolizumab
SEA- Severe eosinophilic asthma

METHODS: The REMIssion in Severe Eosinophilic Asthma Treated with Mepolizumab (REMI-M) is a retrospective, real-world, multicenter study that analyzed 303 patients with severe eosinophilic asthma who received mepolizumab. Clinical, demographic, and safety data were collected at baseline, 3, 6, 12, and 24 months. The most commonly used definitions of clinical remission, which included no exacerbations, no oral corticosteroid (OCS) use, and good asthma control with or without assessment of lung function parameters, were assessed. Sustained remission was defined as reaching clinical remission at 12 months and maintaining it until the end of the 24-month period.
RESULTS: Clinical remission rates ranged from 28.6% to 43.2% after 12 months and from 26.8% to 52.9% after 24 months based on the different remission definitions. The proportion of patients achieving sustained remission varied between 14.6% and 29%. Factors associated with the likelihood of achieving clinical remission included the presence of aspirin-exacerbated respiratory disease, better lung function at baseline, male sex, absence of anxiety/depression, gastroesophageal reflux disease, bronchiectasis, and reduced OCS consumption. Adverse events were infrequent.
CONCLUSIONS: This study demonstrates the real-world effectiveness of mepolizumab in achieving clinical remission and sustained remission in severe eosinophilic asthma over 24 months. The identification of distinct factors associated with the likelihood of achieving clinical remission emphasizes the importance of comprehensive management of comorbidities and timely identification of patients who may benefit from biologics. **© 2024 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).** **(J Allergy Clin Immunol Pract 2024;■:■-■)**

Key words: *Severe asthma; Severe eosinophilic asthma; Remission; Biologics; Mepolizumab; Anti-IL-5; Eosinophils*

Biological therapies have represented a significant advancement in the precision treatment of severe asthma. By targeting specific pathological drivers, these therapies potentially exhibit disease-modifying properties and have transformed the treatment of severe asthma.[1-4] Mepolizumab is a humanized monoclonal antibody approved as add-on therapy for the treatment of severe eosinophilic asthma (SEA), and it neutralizes the circulating IL-5, which is involved in proliferation, differentiation, and survival of eosinophils.[5]

The clinical effectiveness of mepolizumab has been evaluated in several randomized clinical trials, demonstrating a significant decrease in annual SEA exacerbations,[6,7] a reduction in systemic oral corticosteroid (OCS) intake,[8] and improvements in symptom control and quality of life[9] with favorable long-term clinical effects and safety profile.[10,11] The benefits of mepolizumab on core asthma outcomes have been further confirmed in multiple real-world studies[12-15] that evaluated the overall effectiveness of mepolizumab in routine clinical practice, particularly in more complex patient populations, with multiple comorbidities that extend beyond those included in clinical trials.[16-21]

These positive outcomes have led to a more ambitious treatment goal: the potential achievement of clinical remission of the disease. This represents a paradigm shift from a reactive "*treat-to-failure*" approach to a proactive "*treat-to-target*" strategy. Expert consensuses agreed on the concept that clinical remission is a multidimensional therapeutic goal that involves criteria aimed at achieving high level of disease control, including the absence of exacerbations, symptoms, OCS withdrawal, and normalization/stabilization of lung function.[22-24] However, the role and definition of clinical remission in SEA is still evolving,[22,25-27] whereas it is well established in other clinical contexts, such as rheumatoid arthritis.[28] Recently, several studies have evaluated the effectiveness of anti-IL-5 therapies in achieving clinical remission after 1 year of treatment.[29] However, despite the growing body of evidence in this field, to date, studies assessing the impact of mepolizumab on achieving clinical remission at longer time points are lacking.

The REMIssion in Severe Eosinophilic Asthma Treated with Mepolizumab (REMI-M) study aimed to assess the long-term effectiveness of mepolizumab in achieving clinical remission and sustained remission after 1 and 2 years of treatment.

METHODS

Study design

This retrospective, longitudinal, multicenter study used anonymized medical records from patients referred to 11 specialized outpatients' facilities participating in the "Southern Italy Network on Severe Asthma Therapy." A complete list of all the participating centers is available in this article's Online Repository at www.jaci-inpractice.org.

Data collection spanned from November 2019 to November 2022. This study adhered to the Declaration of Helsinki and received approval from the Ethics Committee "Catania 1" at the Policlinico University Hospital (Protocol Number 33/2020/PO). The institutional review boards at all participating centers approved the study protocol before the initiation of the study. All patients signed a written informed consent.

Patient population

Data from adult patients (≥18 years) diagnosed with severe asthma according to the European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines,[30] who received add-on treatment with subcutaneous mepolizumab (100 mg, once every 4

weeks), were included. The indication for mepolizumab prescription followed the Italian eligibility criteria (baseline eosinophil count of ≥150 eosinophils/μL and a history of at least 300 eosinophils/μL in the previous 12 months, a minimum of 2 exacerbations in the previous year despite Global Initiative for Asthma step 5 maintenance therapy,[31] and/or OCS maintenance treatment).

Data collection

A shared database containing relevant variables for data acquisition was used across all participating centers. Demographic data and clinical variables were analyzed before the initiation of mepolizumab (baseline) and after 3, 6, 12, and 24 months of therapy. Clinical variables included number of exacerbations, pharmacologic therapies, Asthma Control Test (ACT)[32,33] scores, pulmonary function tests, blood eosinophil and basophil count, fraction of exhaled nitric oxide (FeNO), smoking habits, and comorbidities such as anxiety/depression, gastroesophageal reflux disease (GERD), bronchiectasis, atopic dermatitis, aspirin-exacerbated respiratory disease (AERD), osteoporosis, and chronic rhinosinusitis with nasal polyps (CRSwNP).

Severe asthma exacerbations were defined as disease worsening requiring ≥3 days of treatment with systemic corticosteroids (or a doubling of the dose if already on OCS).[34] Exacerbations treated with <7 days apart were considered as the same episode.

Pulmonary function tests were performed in accordance with the ERS/ATS guidelines.[35] Data on prebronchodilator forced expiratory volume in 1 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 retrieved. The FeNO test was performed according to ERS/ATS recommendations.[36]

Drug retention rate was defined as the percentage of patients remaining on mepolizumab over each time point. Safety assessment involved reporting adverse events and monitoring laboratory values from the initial mepolizumab dose up to month 24. Their severity was defined in accordance with the World Health Organization guideline.[37]

Definitions of clinical remission and sustained remission

Currently, no single unified definition for clinical remission of SEA exists. Therefore, we evaluated clinical remission using different criteria:

(1) Three-component definition: no annual exacerbations + no OCS + ACT ≥20[38]
(2) Four-component definition: no annual exacerbations + no OCS + ACT ≥20 + lung function criteria.[22-24]

As there are no widely accepted criteria to assess the normalization/stabilization of lung function, we performed sensitivity analysis with different profiles of 4-component definitions, including the 4 most frequently lung function parameters considered by expert opinions.[22-24] Thus, the different profiles of the *4-component definition* were classified as follows:

- Profile A: no annual exacerbations + no OCS + ACT ≥20 + FEV_1 ≥80%
- Profile B: no annual exacerbations + no OCS + ACT ≥20 + FEV_1 +100 mL from baseline
- Profile C: no annual exacerbations + no OCS + ACT ≥20 + FEV_1 decline ≤5% from baseline
- Profile D: no annual exacerbations + no OCS + ACT ≥20 + FEV_1 decline <100 mL from the best value of the first 12 months.[26]

Moreover, we explored the concept of *sustained remission* defined as the obtainment of clinical remission at month 12 with retention of this status up to month 24.

Statistical analysis

All available data on patients treated with mepolizumab from the "Southern Italy Network on Severe Asthma Therapy" were included. Data are presented as mean and standard deviation (SD) for normally distributed continuous variables and as median and interquartile range (IQR) for continuous nonparametric variables. Categorical variables are expressed as numbers (n) and percentages (%).

The normality of data distribution was checked using the Shapiro-Wilk and the Kolmogorov-Smirnov tests. The unpaired Student *t* test or the Mann-Whitney test was used for comparison of continuous variables at baseline. Fisher's exact test or McNemar's test was used for categorical variables, when appropriate. The Friedman test followed by Dunn's multiple comparison test was used to compare continuous outcomes from 3 to 24 months with baseline. We did not conduct imputation of missing values, and only patients with available data at all 4 time points were included in these analyses. Proportions of participants meeting the composite outcomes of clinical and sustained remission and individual remission criteria were reported descriptively.

The associations between pretreatment characteristics and remission were analyzed using multiple logistic regression, with clinical remission and sustained remission as the outcome variables (yes/no), according to all proposed definitions. Variable selection was informed by initial univariate analyses, literature reviews, expert consensus, and previous studies related to clinical remission. Analyses were adjusted for age, sex, body mass index (BMI), and study center. The Akaike Information Criterion (AIC) was used to compare the models, and the model with the lowest AIC was selected. Model discrimination was assessed using receiver operating characteristic curves, and the discriminatory performance was quantified using the area under the curve (AUC). Both crude and adjusted odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated. Statistical analysis was performed using SPSS Statistics 26 (IBM Corporation, Armonk, NY), and figures were generated using Prism version 10.1.0 (GraphPad Software Inc., Boston, Mass). A *post hoc* power analysis was performed for our primary outcome, the *3-component definition* of clinical remission, using G*Power software and a χ^2 test of goodness of fit. Employing our sample size of 138 patients treated with mepolizumab for 24 months and the effect size calculated from our data (Cohen's $W = 1.333$), this study demonstrated a power of 99% to detect the observed effect size at an α level of 0.05. A *P* value of <.05 (2-sided) was considered statistically significant.

RESULTS

Baseline patient demographic and clinical characteristics

Three hundred three adult patients diagnosed with SEA and treated with mepolizumab were included in the study (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). Baseline demographics and clinical characteristics are outlined in Table I. Overall, 63% were female, with a

TABLE I. Patient characteristics at baseline

Characteristic	N	Baseline
General characteristics		
Age (y), mean (SD)	303	56.9 (12.3)
Female, n (%)	303	191 (63)
BMI, mean (SD)	287	27.1 (5.5)
Obese (BMI $\geq$ 30), n (%)	287	72 (25.1)
Duration of disease (y), median (IQR)	293	20 (10-30)
Age at onset (y), median (IQR)	293	36 (25-48)
Patients with positive skin prick tests, n (%)	293	189 (64.5)
Patients with positive skin prick tests (perennial aeroallergens), n (%)	293	157 (53.6)
Smoking status, n (%)	303	106 (35)
Smoking history, n (%)	303	91 (30)
Current smoker, n (%)	303	15 (5)
Comorbidities		
Patients with anxiety/depression, n (%)	296	44 (14.9)
Patients with GERD, n (%)	296	104 (35)
Patients with bronchiectasis, n (%)	284	47 (16.5)
Patients with atopic dermatitis, n (%)	302	8 (2.6)
Patients with AERD, n (%)	261	31 (11.9)
Patients with osteoporosis, n (%)	269	29 (10.8)
Patients with CRSwNP, n (%)	262	130 (49.6)
Asthma outcomes		
Exacerbations/year, median (IQR)	285	4 (2-6)
Patients who required ER/ hospitalization, n (%)	285	83 (29.1)
ACT, median (IQR)	288	13 (10-17)
FEV_1 (%), median (IQR)	290	71 (57-85)
FEV_1 (L), median (IQR)	289	1.8 (1.31-2.41)
FVC (%), median (IQR)	281	88 (73.5-100)
FEV_1/FVC (%), median (IQR)	280	67 (58.5-76)
$FEF_{25-75\%}$, median (IQR)	228	37.5 (24-56.6)
Pharmacologic therapies		
High-dose ICS-LABA, n (%)	303	303 (100)
LAMA, n (%)	299	183 (61.2)
Patients on OCS, n (%)	294	204 (69.4)
OCS (mg/d), median (IQR)	294	10 (2.5-25)
Previous mAbs, n (%)	303	21 (6.9)
Biomarkers, median (IQR)		
Blood eosinophils (cells/μL)	282	490 (347-836)
Blood basophils (cells/μL)	122	50 (30-80)
IgE (UI/mL)	214	152 (57-365)
FeNO (ppb)	191	30 (14-55)

Data are presented as mean (SD), n (%), or median (IQR).
ACT, Asthma Control Test; *AERD*, aspirin-exacerbated respiratory disease; *BMI*, body mass index; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *ER*, emergency room; $FEF_{25-75\%}$, forced expiratory flow 25%-75%; *FeNO*, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *GERD*, gastroesophageal reflux disease; *ICS-LABA*, inhaled corticosteroids−long-acting β-agonists; *IQR*, interquartile range; *LAMA*, long-acting muscarinic agonists; *mAb*, monoclonal antibody; *OCS*, oral corticosteroids (prednisone equivalent dose); *SD*, standard deviation.

mean (SD) age of 56.9 (12.3) years and a mean (SD) BMI of 27.1 (5.5) kg/m^2. The median (IQR) duration of the disease was 20 (10-30) years. Over one-third were current/ex-smokers. Regarding comorbidities, 14.9% were affected by anxiety/depression, 35% by GERD, 16.5% by bronchiectasis, and 49.6% by CRSwNP. All patients were prescribed high-dose inhaled corticosteroids and long-acting β-agonists, and 61.2% were also on long-acting muscarinic antagonists; 69.4% of patients were on OCS, with a median maintenance dose of 10 mg/d (2.5-25 mg/d), and 6.9% received prior treatments with anti-IgE (omalizumab).

Effectiveness of mepolizumab therapy

The annual exacerbation rate significantly decreased from 4 (2-6) exacerbations/year at baseline to 1 (0-2) after 12 months and to 0 (0-1) after 24 months ($P < .0001$, Friedman with Dunn's *post hoc*) (Figure 1, *A*). Indeed, the percentage of patients requiring emergency room access or hospitalization decreased from 29.1% to 2% after 24 months (Figure 1, *B*). The ACT score significantly improved from 13 (10-17) to 21 (18-23) already after 3 months and reached the median value of 22 (20-24) at month 24 ($P < .0001$, Friedman with Dunn's *post hoc*) (Figure 1, *C*). Significant improvements in lung function were found, with the increase in FEV_1% (Figure 1, *D*), FEV_1 (L), FVC%, FEV_1/FVC, and $FEF_{25-75\%}$ (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). The proportion of patients on OCS decreased from 69.4% at baseline to 16.5% after 24 months ($P < .0001$, McNemar's test). The median daily OCS dose decreased from 10 mg/d (2.5-25) to 0.0 mg/d (0-0) at month 24 ($P < .0001$, Friedman with Dunn's *post hoc*) (Figure 1, *E*). The blood eosinophils (Figure 1, *F*) and basophils sharply dropped during treatment (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). No significant changes in FeNO were detected (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

Proportion of patients who met individual criteria for the definitions of clinical remission

Figure 2 illustrates the percentage of patients who met each criterion used for the different definitions of clinical remission. Notably, about half of the cohort had no annual exacerbations (Figure 2, *A*) at month 24. There was an increase in the number of patients who discontinued OCS, with 83.6% being OCS-free after 24 months (Figure 2, *B*). The ACT score rapidly improved, with 64.4% of patients reaching the threshold score of 20 within just 3 months and 78% at 24 months (Figure 2, *C*). The percentages of both the FEV_1 $\geq$80% (Figure 2, *D*) and the +100 mL increase in FEV_1 from baseline (Figure 2, *E*) progressively improved up to 6 months, followed by a gradual decrease. An FEV_1 decline of $\leq$5% from baseline was reported in over 80% of the entire cohort throughout the study period (Figure 2, *F*). However, an FEV_1 decline of <100 mL from the best value of the first 12 months was obtained only by 49.6% at month 24 (Figure 2, *G*).

Proportion of patients achieving long-term clinical and sustained remission

Two hundred eighteen patients completed 12 months of treatment, whereas 147 were treated for 24 months (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). The number of subjects with all the explanatory variables for each definition of remission is presented in Table E2 (available in this article's Online Repository at www.jaci-inpractice.org).

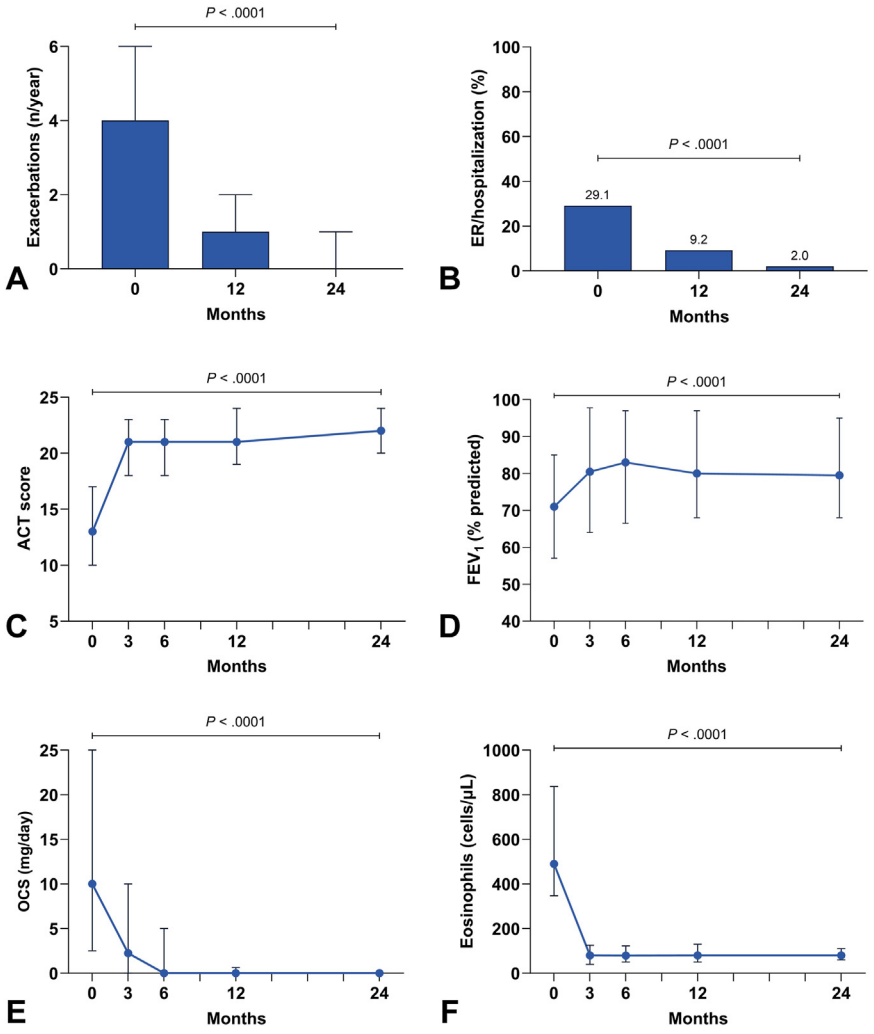

FIGURE 1. Effectiveness of mepolizumab on clinical outcomes. The proportion of patients requiring emergency room (ER) access or hospitalization during treatment is presented as percentage of the total and was analyzed using McNemar's test. All other variables are expressed as median and interquartile range and were assessed using Friedman with Dunn's *post hoc*. *ACT,* Asthma Control Test; *FEV_1,* forced expiratory volume in 1 second; *OCS*, oral corticosteroids (prednisone equivalent dose).

Three-component definition: no annual exacerbations + no OCS + ACT ≥20. Overall, 43.2% achieved all 3 main criteria after 12 months and 52.9% after 24 months (Figure 3); 29.7% remained in sustained remission during the observed period (Figure 3).

Four-component definition (profile A): no annual exacerbations + no OCS + ACT ≥20 + FEV_1 ≥80%. A total of 31.3% and 39.1% of patients fulfilled the criteria at 12 and 24 months, respectively, but only 21.9% remained in sustained remission throughout the second year (Figure 4, *A*).

Four-component definition (profile B): no annual exacerbations + no OCS + ACT ≥20 + FEV_1 +100 mL from baseline. A total of 28.6% and 34.1% of patients were in clinical remission at months 12 and 24, respectively, with 16.3% achieving sustained remission (Figure 4, *B*).

Four-component definition (profile C): no annual exacerbations + no OCS + ACT ≥20 + FEV_1 decline ≤5% from baseline. A total of 35.8% and 46.9% of patients were in clinical remission after 12 and 24 months, respectively, and 24.2% reached sustained remission (Figure 4, *C*).

Four-component definition (profile D): no annual exacerbations + no OCS + ACT ≥20 + FEV_1 decline <100 mL from the best value of the first 12 months. Only 26.8% of patients were in clinical remission and 14.6% in sustained remission at month 24, respectively (Figure 4, *D*).

Baseline predictors of long-term clinical and sustained remission

According to the proposed definitions, the associations between pretreatment characteristics and remission were analyzed using multiple logistic regression, with clinical remission and sustained remission after 24 months as the outcome variables.

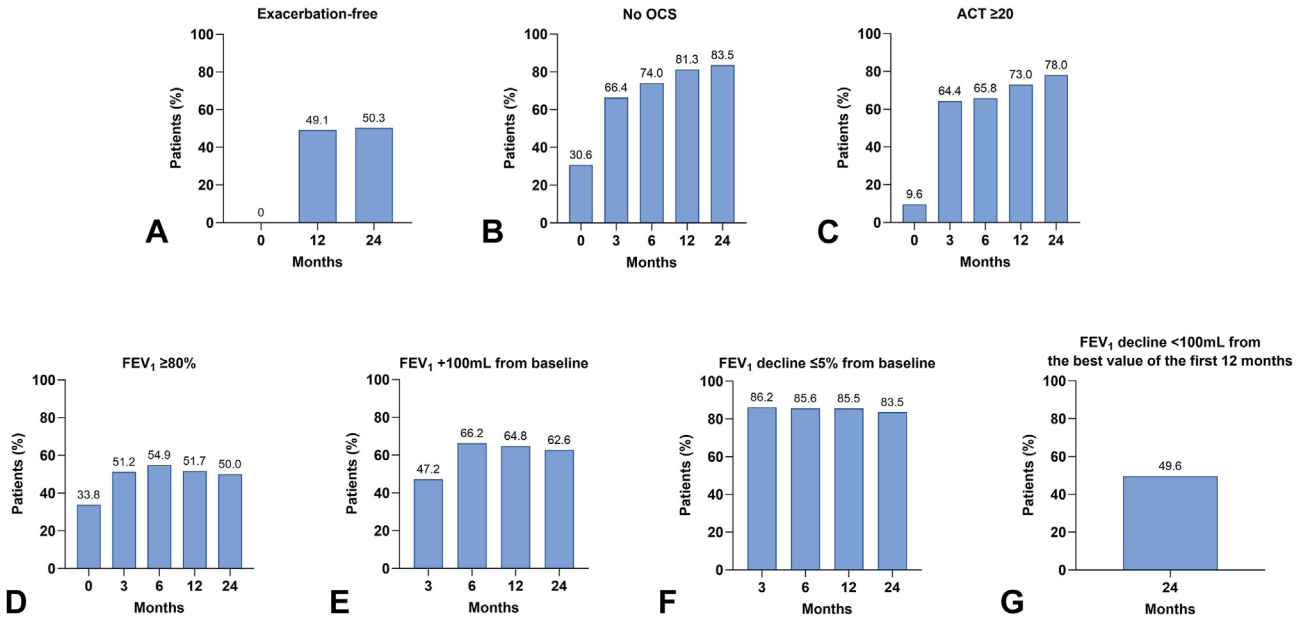

FIGURE 2. Percentages of patients who met each criterion used to define clinical remission. *ACT*, Asthma Control Test; *FEV_1*, forced expiratory volume in 1 second; *OCS*, oral corticosteroids.

For each model, variables were selected based on univariate screening (as detailed from Table E3 to Table E12 in this article's Online Repository at www.jaci-inpractice.org), literature reviews, expert consensus, and previous studies on this topic. Models were adjusted for potential confounders including age, sex, BMI, and study center. Final model AUCs are presented in Figure E2 (available in this article's Online Repository at www.jaci-inpractice.org). All models demonstrated fair to good discriminative ability, with AUC values ranging from 0.66 to 0.82, and the 95% CIs did not include 0.5. Crude and adjusted ORs of the predictors are presented in Table II.

Three-component definition: no annual exacerbations + no OCS + ACT ≥20. Females (adjusted OR = 0.240, 95% CI [0.075-0.681], $P = .0102$) and current/ex-smokers (adjusted OR = 0.278, 95% CI [0.092-0.756], $P = .0157$) showed reduced likelihood of clinical remission after 24 months (Figure 5), whereas pretreatment high OCS intake reduced the odds of sustained remission (adjusted OR = 0.941, 95% CI [0.895-0.984], $P = .0107$) (Figure 5).

Four-component definition (profile A): no annual exacerbations + no OCS + ACT ≥20 + FEV_1 ≥80%. The likelihood of achieving clinical remission was lower in patients with anxiety/depression (adjusted OR = 0.033, 95% CI [0.002-0.481], $P = .0144$) but 5-fold higher in patients with AERD ($P = .0095$) and better $FEF_{25-75\%}$ (adjusted OR = 1.049, 95% CI [1.011-1.094], $P = .0161$) (Figure 6, *A*). Those who achieved sustained remission had also better $FEF_{25-75\%}$ at baseline ($P = .0393$) (Figure 6, *A*).

Four-component definition (profile B): no annual exacerbations + no OCS + ACT ≥20 + FEV_1 +100 mL from baseline. The odds of achieving clinical remission were lower in females (adjusted OR = 0.199, 95% CI [0.062-0.568], $P = .0040$), in current/ex-smokers (adjusted OR = 0.119, 95% CI [0.029-0.392], $P = .0012$), and in patients with GERD (adjusted OR = 0.033, 95% CI [0.002-0.831], $P = .0241$) (Figure 6, *B*). Smoking status was also associated with lower odds of sustained remission (adjusted OR = 0.203, 95% CI [0.030-0.806], $P = .0459$) (Figure 6, *B*).

Four-component definition (profile C): no annual exacerbations + no OCS + ACT ≥20 + FEV_1 decline ≤5% from baseline. Females (adjusted OR = 0.283, 95% CI [0.103-0.722], $P = .0104$), current/ex-smokers (adjusted OR = 0.312, 95% CI [0.101-0.864], $P = .0315$), and patients with GERD ($P = .0416$) and bronchiectasis ($P = .0364$) demonstrated lower odds of achieving clinical remission (Figure 6, *C*). Higher FEV_1/FVC was associated with increased likelihood of achieving sustained remission (adjusted OR = 1.068, 95% CI [1.018-1.128], $P = .0112$) (Figure 6, *C*).

Four-component definition (profile D): no annual exacerbations + no OCS + ACT ≥20 + FEV_1 decline <100 mL from the best value of the first 12 months. GERD was associated with lower chances of clinical remission (adjusted OR = 0.255, 95% CI [0.070-0.731], $P = .0193$) (Figure 6, *D*). Regarding sustained remission, although the ORs for bronchiectasis did not cross the threshold of 1, indicating a directional effect of the predictors on outcomes, this variable was not statistically significant ($P = .0566$) (Figure 6, *D*). This could be attributed to the limited sample size of the cohort of patients achieving this definition of sustained remission.

Retention rate

At the 12-month follow-up, mepolizumab retention rate was 94%. Fourteen patients (6%) were switched to different biologics (Table E13, available in this article's Online Repository at www.jaci-inpractice.org). At the 24-month follow-up, 147 of 166

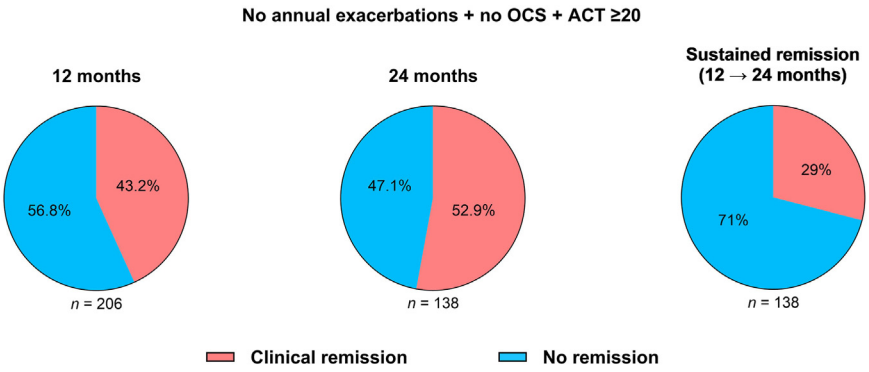

FIGURE 3. Percentages of patients achieving the 3-component definition of clinical remission and sustained remission after 12 and 24 months of treatment. *ACT*, Asthma Control Test; *OCS*, oral corticosteroids.

(88.6%) patients were still on treatment with mepolizumab (Table E13, available in this article's Online Repository at www.jaci-inpractice.org).

Safety

Table III shows the number and type of adverse events that occurred during the study period. Only 1 serious adverse event was reported. None of the patients discontinued mepolizumab because of adverse events.

DISCUSSION

In this large, multicenter, real-world cohort study, treatment with mepolizumab was associated with an overall clinical remission rate ranging from 28.6% to 43.2% after 12 months and from 26.8% to 52.9% after 24 months, depending on the definition applied. In addition, 1 in 5 patients was able to achieve sustained remission from months 12 to 24. To the best of our knowledge, this is the first study to report real-world data on clinical and sustained remission after 24 months of mepolizumab treatment in a large cohort of patients with SEA.

In our heterogeneous population affected by a wide range of comorbidities, the overall effectiveness of mepolizumab surpassed those reported in clinical trials,[6-9] while it was comparable or superior in some cases to the limited number of long-term (24 months or more) real-world studies conducted to date.[14,15,39-42] Remarkably, we observed a 75% reduction in the exacerbation rate after 12 months of treatment, with a 100% decrease at month 24. Interestingly, the reduction in exacerbation rates was more pronounced than the MENSA[7] (−53%) and MUSCA[9] (−58%) trials but similar to those reported in real-life studies such as REALITI-A (−79%)[40] and Matucci et al (−84%).[15] These findings are valuable from both physicians' and patients' perspectives, as the frequency and severity of exacerbations are associated with accelerated lung function decline[43] and worse quality of life.[6,15,44]

Another important finding of our study pertains to the use of OCS. Indeed, more than 80% of patients were OCS-free at 12 months and 24 months. These findings are consistent with data reported in REDES[29] (81% of patients were OCS-free at 1 year) and by Bagnasco et al[14] (79% of patients were OCS-free at 1 year and 89% at 2 years, respectively) but superior to REALITI-A[42] (57% of patients were OCS-free at 2 years).

In terms of clinical remission, to date, only a few studies have specifically investigated the effects of mepolizumab after 1 year of treatment.[29,45-47] Only 2 studies have evaluated the super-response to anti-IL-5/Rα biologics and the clinical and sustained remission with benralizumab after 2 years, respectively.[48,49] All studies that assessed clinical remission with anti-IL-5/Rα therapies (mepolizumab and benralizumab) and their characteristics and results are presented in Table E14 in this article's Online Repository at www.jaci-inpractice.org.

The definitions of remission may play a crucial role in the "*treat-to-target*" strategy in SEA; however, currently, there are no universal definitions or criteria to define clinical remission in SEA. In REMI-M, we explored a 3-component model for defining clinical remission that intentionally excluded lung function measurements in favor of an overall disease assessment, including resolution of symptoms, absence of systemic steroids use, and no interference with patients' activities of daily living, which we considered essential aspects from the patients' perspective. We also explored the most used composite criteria for defining clinical and sustained remission from a research/clinician point of view to ensure adequate reproducibility and allow for direct comparison with prior studies.[26] Specifically, according to the lung function parameter adopted, the percentage of patients achieving clinical remission at 12 months ranged from 28.6% to 35.8%, in concordance with the already available evidence.[29,38,45] However, the clinical remission rate after 1 year in our study was higher than the Danish (19%) and UK (18.3%) national registry cohorts and the International Severe Asthma Registry (20.3%) reports.[50-52] This difference may be attributed to the centers involved in the management of patients with SEA on biologics; thus, the uniform and systematic clinical approach adopted by the dedicated severe asthma facilities within the "Southern Italy Network on Severe Asthma Therapy" might have contributed positively to our findings, in contrast with national registries, which could be subject to variations in clinical practice. Furthermore, by focusing solely on mepolizumab, our study did not account for the potential impact of anti-IgE treatments on the overall clinical remission rates. Notably, anti-IgE therapy has demonstrated lower remission rates than anti-IL-5, likely due to the IgE's role as a downstream mediator of inflammation, resulting in less pronounced effects when targeted.[53]

Significantly, we found that clinical remission rates increased over the 24-month period. This increase may be attributed to a

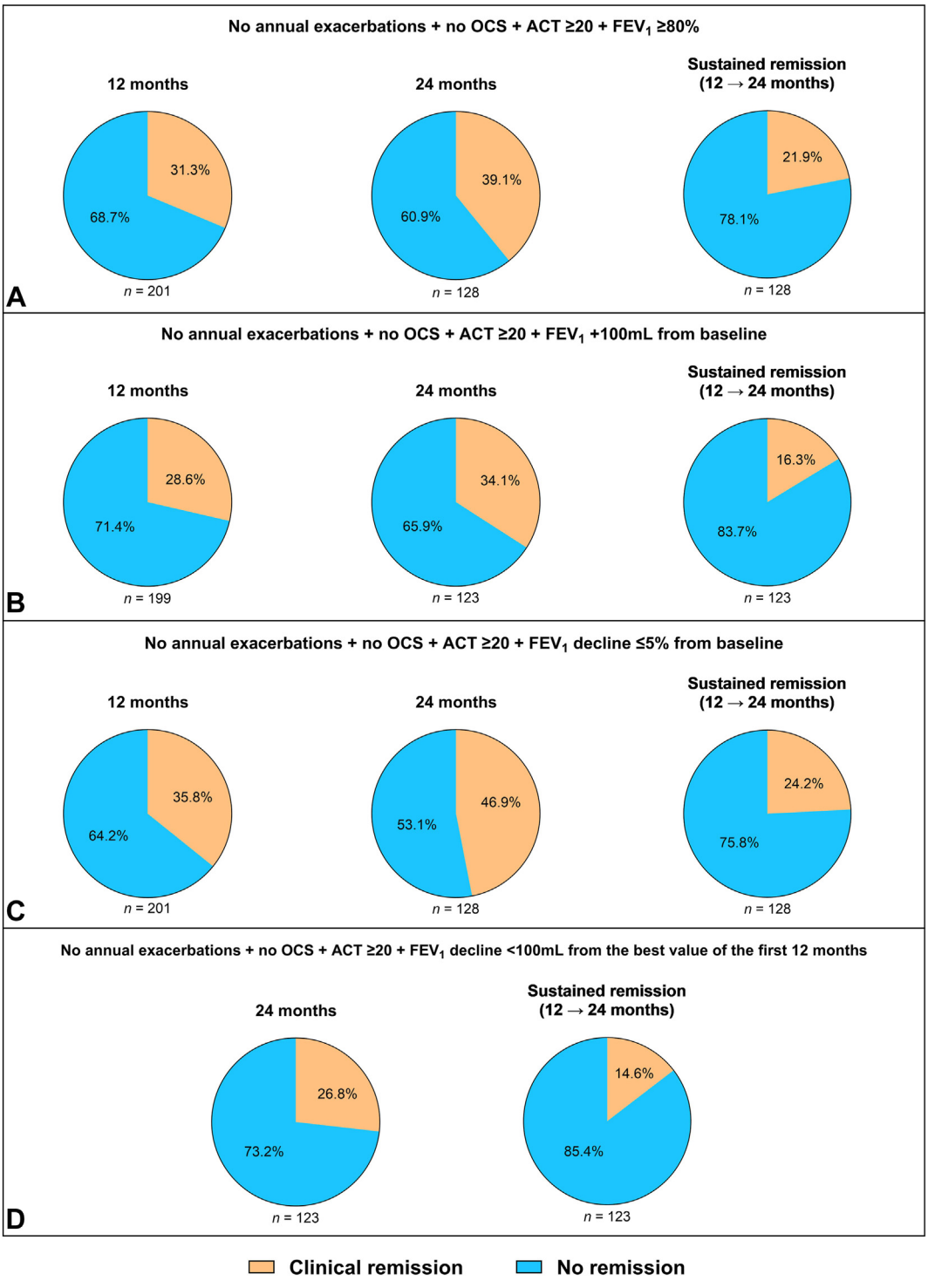

FIGURE 4. Percentages of patients achieving the 4-component definitions of clinical remission and sustained remission after 12 and 24 months of treatment. *ACT*, Asthma Control Test; *FEV$_1$*, forced expiratory volume in 1 second; *OCS*, oral corticosteroids.

concomitant progressive reduction in OCS use and the rise in the proportion of subjects with ACT $\geq$20.

Given that anti-IL-5 therapy is known to mitigate the decline in lung function,[54] we have introduced, for the first time, an assessment of lung function decline from the best value obtained within the first 12 months of treatment. The accelerated lung function decline among patients with SEA reflects uncontrolled inflammatory processes and airway remodeling. Consequently, assessing this decline over the long term could bridge the gap between the concept of clinical and biological remission.[26]

TABLE II. Crude and adjusted odds ratios for baseline predictors of long-term clinical and sustained remission

Remission (24 mo)				Sustained remission (12 → 24 mo)			
	Odds ratio (95% CI)				Odds ratio (95% CI)		
Variables	Crude	Adjusted	*P* value	Variables	Crude	Adjusted	*P* value
No annual exacerbations + no OCS + ACT ≥20							
Female	0.536 (0.261-1.086)	0.240 (0.075-0.681)	**.0102**	Age (y)	0.977 (0.946-1.010)	0.988 (0.950-1.026)	.5347
Current/ex-smoker	0.463 (0.218-0.987)	0.278 (0.092-0.756)	**.0157**	Anxiety/depression	0.145 (0.019-1.139)	0.229 (0.012-1.343)	.1760
Anxiety/depression	0.178 (0.048-0.656)	0.276 (0.068-1.118)	.1490	FEV_1L	1.012 (0.994-1.030)	0.985 (0.951-1.019)	.3922
GERD	0.388 (0.185-0.812)	0.599 (0.222-1.598)	.3043	FEV_1/FVC	1.024 (0.996-1.053)	1.006 (0.977-1.037)	.6970
FEV_1/FVC	1.041 (1.010-1.073)	1.030 (0.988-1.078)	.1709	$FEF_{25-75\%}$	1.019 (1.001-1.037)	1.020 (0.988-1.054)	.2273
$FEF_{25-75\%}$	1.019 (1.001-1.037)	0.999 (0.976-1.022)	.9275	OCS (mg/d)	0.948 (0.911-0.982)	0.941 (0.895-0.984)	**.0107**
LAMA	2.202 (1.091-4.447)	0.884 (0.320-2.440)	.8104				
OCS (mg/d)	0.956 (0.927-0.986)	0.974 (0.933-1.017)	.2363				
No annual exacerbations + no OCS + ACT ≥20 + FEV_1 ≥80%							
Current/ex-smoker	0.468 (0.207-1.059)	0.419 (0.150-1.172)	.1515	Anxiety/depression	0.257 (0.032-2.040)	0.351 (0.015-2.603)	.3882
Anxiety/depression	0.114 (0.014-0.892)	0.033 (0.002-0.481)	**.0144**	Bronchiectasis	0.388 (0.108-1.389)	0.570 (0.109-2.209)	.4508
AERD	2.730 (0.893-8.376)	5.398 (1.226-23.77)	**.0095**	FEV_1%	1.026 (1.007-1.048)	0.982 (0.906-1.061)	.6560
ACT	1.105 (1.008-1.211)	1.035 (0.902-1.188)	.6245	FVC%	1.016 (0.995-1.037)	1.000 (0.942-1.062)	.9869
FEV_1%	1.019 (1.002-1.037)	0.966 (0.903-1.027)	.2851	FEV_1/FVC	1.020 (0.990-1.051)	0.999 (0.963-1.041)	.9653
FVC%	1.013 (0.996-1.031)	1.015 (0.968-1.067)	.5356	$FEF_{25-75\%}$	1.036 (1.016-1.058)	1.044 (1.003-1.089)	**.0393**
$FEF_{25-75\%}$	1.026 (1.009-1.044)	1.049 (1.011-1.094)	**.0161**	LAMA	0.350 (0.150-0.818)	0.548 (0.171-1.733)	.3047
LAMA	0.460 (0.227-0.934)	1.665 (0.542-5.614)	.3879	OCS	0.667 (0.286-1.554)	0.668 (0.223-2.031)	.4697
OCS	0.514 (0.252-1.046)	0.523 (0.187-1.462)	.2130				
No annual exacerbations + no OCS + ACT ≥20 + FEV_1 +100 mL from baseline							
Female	0.510 (0.234-1.104)	0.199 (0.062-0.568)	**.0040**	Current/ex-smoker	0.206 (0.045-0.942)	0.203 (0.030-0.806)	**.0459**
Current/ex-smoker	0.255 (0.088-0.637)	0.119 (0.029-0.392)	**.0012**	Anxiety/depression	0.360 (0.044-2.923)	0.367 (0.018-2.374)	.3744
Anxiety/depression	0.288 (0.061-1.350)	0.299 (0.039-1.475)	.1755	GERD	0.358 (0.098-1.307)	0.358 (0.075-1.261)	.1408
GERD	0.340 (0.134-0.860)	0.290 (0.092-0.813)	**.0241**	FVC%	0.976 (0.951-1.001)	0.975 (0.949-1.000)	.0628
Bronchiectasis	0.321 (0.102-1.011)	0.518 (0.122-1.842)	.3318	FEV_1/FVC	1.016 (0.982-1.051)	1.000 (0.973-1.033)	.9734
FVC%	0.980 (0.961-1.039)	0.972 (0.948-1.045)	.1141				
No annual exacerbations + no OCS + ACT ≥20 + FEV_1 decline ≤5% from baseline							
Female	0.533 (0.261-1.085)	0.283 (0.103-0.722)	**.0104**	Anxiety/depression	0.205 (0.026-1.624)	0.300 (0.015-2.053)	.2999
Current/ex-smoker	0.474 (0.219-1.025)	0.312 (0.101-0.864)	**.0315**	Bronchiectasis	0.100 (0.013-0.771)	0.141 (0.007-0.877)	.0807
Anxiety/depression	0.276 (0.074-1.029)	0.250 (0.035-1.149)	.1045	FEV_1/FVC	1.027 (0.995-1.060)	1.068 (1.018-1.128)	**.0112**
GERD	0.402 (0.187-0.864)	0.367 (0.134-0.936)	**.0416**	$FEF_{25-75\%}$	1.019 (1.001-1.038)	1.007 (0.981-1.032)	.6036
Bronchiectasis	0.340 (0.126-0.915)	0.260 (0.065-0.852)	**.0364**	LAMA	0.538 (0.236-1.236)	0.839 (0.243-2.835)	.7779
FEV_1/FVC	1.016 (0.991-1.042)	1.010 (0.984-1.039)	.4649	OCS (mg/d)	0.949 (0.907-0.993)	0.997 (0.942-1.053)	.9327
LAMA	0.686 (0.340-1.387)	1.093 (0.434-2.786)	.8509				
OCS	0.917 (0.451-1.861)	1.469 (0.575-3.855)	.4254				
No annual exacerbations + no OCS + ACT ≥20 + FEV_1 decline <100 mL from the best value of the first 12 months							
Anxiety/depression	0.185 (0.023-1.475)	0.228 (0.012-1.285)	.1694	Anxiety/depression	0.260 (0.013-1.406)	0.224 (0.012-1.261)	.1649
GERD	0.238 (0.077-0.737)	0.255 (0.070-0.731)	**.0193**	GERD	1.088 (0.355-3.009)	1.429 (0.446-4.240)	.5283
CRSwNP	1.140 (0.511-2.545)	1.223 (0.525-2.836)	.6375	Bronchiectasis	0.144 (0.008-0.750)	0.133 (0.007-0.704)	.0566

Variables are presented as odds ratios (95% CI).

P values highlighted in bold are statistically significant.

ACT, Asthma Control Test; *AERD*, aspirin-exacerbated respiratory disease; *CI*, confidence interval; $FE_{F25-75\%}$, forced expiratory flow 25%-75%; FEV_1, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *GERD*, gastroesophageal reflux disease; *LAMA*, long-acting muscarinic agonists; *OCS*, oral corticosteroids (prednisone equivalent dose).

Indeed, the adoption of this stringent parameter revealed that less than half of the patients achieved it, substantially influencing both clinical and sustained remission rates.

Sustained remission rates were significantly lower, ranging from 14.6% to 29%; this was primarily attributed to exacerbations that occurred during the second year of treatment, along with a slight decline in lung function observed between months 6 and 24.

Our study reveals that patients who achieved long-term clinical and sustained remission exhibit distinctive baseline characteristics. Overall, nonremission was commonly associated with female sex, coexisting anxiety and/or depression, GERD, bronchiectasis, previous or active smoking, and OCS use. In contrast, remission was more likely in patients with AERD and a better baseline lung function. Notably, these determinants concur with findings from previous studies on clinical remission after 12 months,[38,45,50,51,55] thus confirming their influence also in the long term. These findings highlight the crucial role that effective management of comorbidities plays in the treatment of

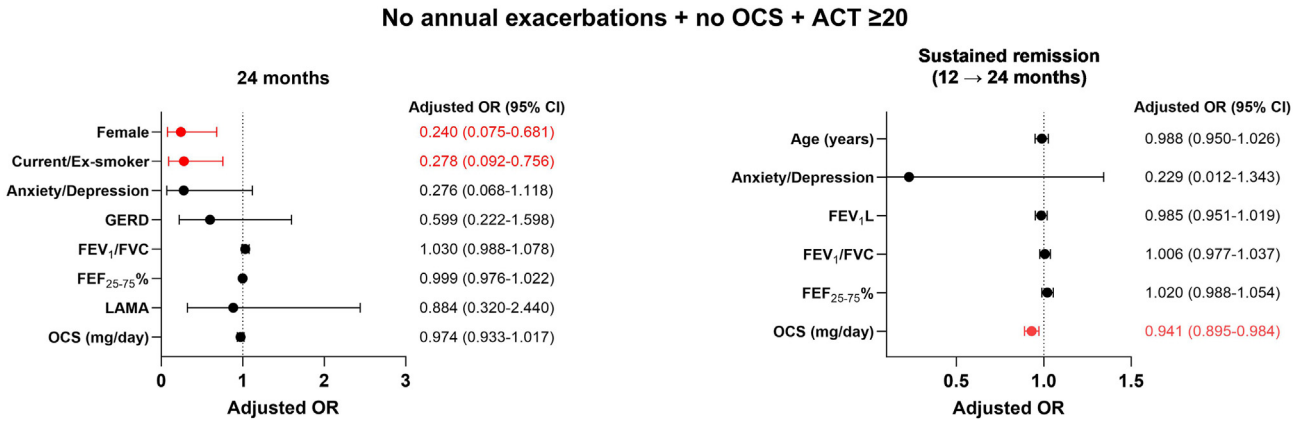

FIGURE 5. Forest plots illustrate the adjusted odds ratios (OR) for variables associated with long-term, 3-component definitions of clinical and sustained remission included in the regression analysis. Predictors significantly associated with the likelihood of remission are highlighted in green, whereas those negatively impacting remission are shown in red. *CI*, Confidence interval; *$FEF_{25-75\%}$*, forced expiratory flow 25%-75%; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *GERD*, gastroesophageal reflux disease; *LAMA*, long-acting muscarinic agonists; *OCS*, oral corticosteroids (prednisone equivalent dose).

SEA and suggest that the timely introduction of biologics may improve the likelihood of achieving clinical remission, emphasizing the importance of prompt patients' referral to SEA dedicated facilities. We believe that our data have important clinical implications in the management of patients with SEA and provide useful insights for future research.

Moreover, the selection of biomarkers can also limit the obtainment of clinical remission. Commonly, blood eosinophils, FeNO, and serum IgE are used to determine the choice among biologics, often overlooking other critical indicators such as airway eosinophils and their activation markers.[56,57] Indeed, blood eosinophils, FeNO, and IgE may only partially capture the inflammatory processes occurring within the airways. Consequently, residual type 2 inflammation, which may persist despite biologic therapy, has been shown to contribute to exacerbations and alterations in airway geometry.[58]

Our study has several strengths. First, it included a large and heterogeneous population of patients with SEA. Indeed, unlike clinical trials and as in every real-world evidence, the study was not constrained by stringent patient selection based on specific inclusion criteria, encompassing a broader patient population that reflects the complexities and diversity of everyday clinical practice. In addition, the 24-month follow-up period has allowed us to assess both the clinical remission rates over 2 years of treatment and the variables that promote or hinder the achievement of long-term clinical and sustained remission in patients treated with mepolizumab. However, the study also has limitations, including its retrospective design and its related potential variability in reporting. Our findings highlight the need for prospective studies to confirm these observations and clarify causal relationships. Nonetheless, the data collection protocol was rigorously followed across multiple sites within a network with recognized expertise and extensive experience in SEA management and biological treatment, ensuring consistency in patient criteria for SEA assessment and mepolizumab prescription. Finally, as is common with retrospective study designs, there is a possibility that adverse events were underreported.

In summary, our study provides valuable real-world evidence confirming the effectiveness of mepolizumab in achieving clinical and sustained remission in patients with SEA over 12 and 24 months and identifying factors associated with increased or reduced likelihood of achieving clinical remission at 24 months.

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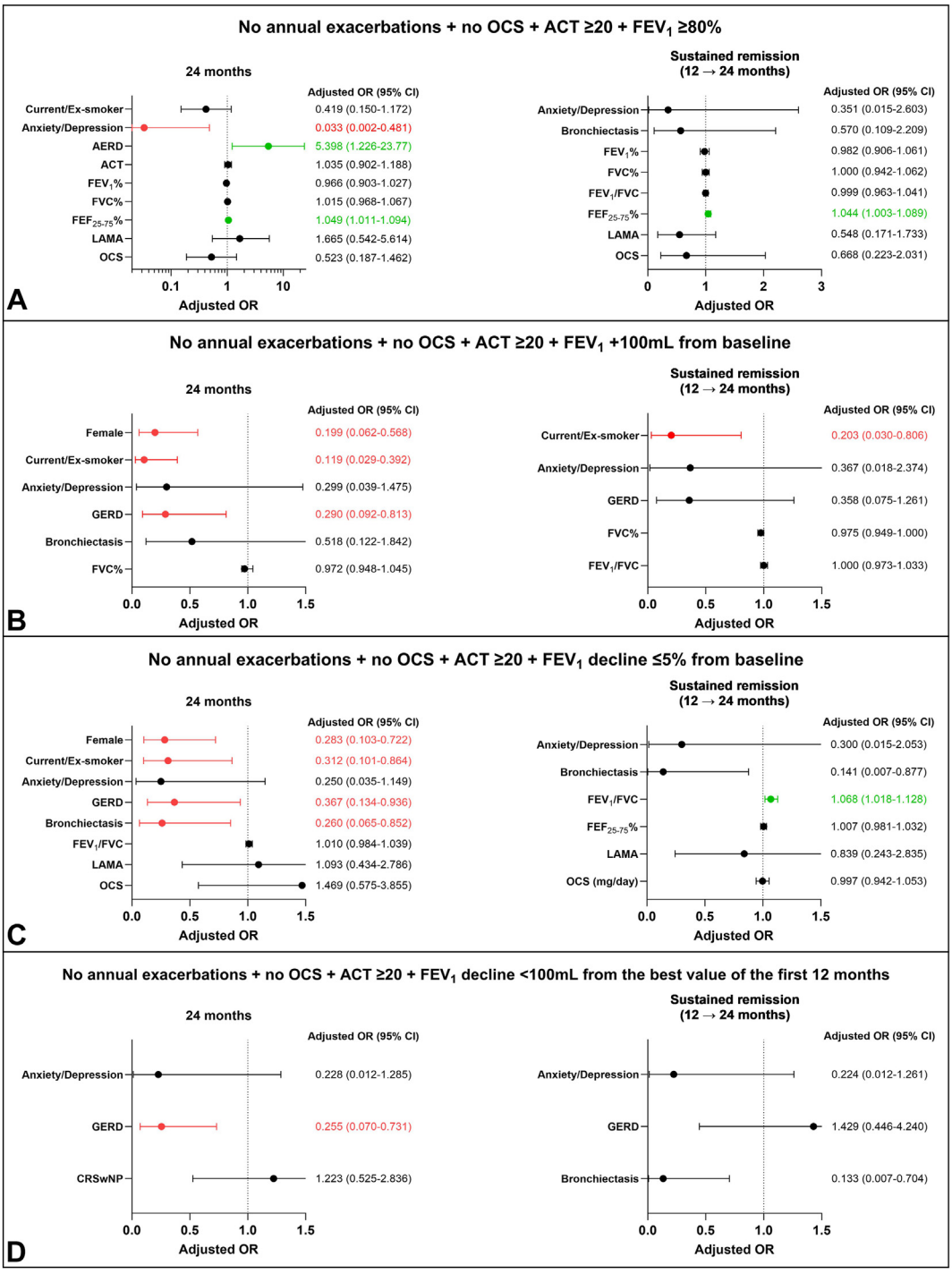

FIGURE 6. Forest plots of adjusted odds ratios (OR) for variables associated with long-term, 4-component definitions of clinical and sustained remission included in the regression analysis. Predictors that favor remission are highlighted in green, whereas those with a negative impact are shown in red. *ACT*, Asthma Control Test; *AERD*, aspirin-exacerbated respiratory disease; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *$FEF_{25-75\%}$*, forced expiratory flow 25%-75%; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *GERD*, gastroesophageal reflux disease; *LAMA*, long-acting muscarinic agonists; *OCS*, oral corticosteroids (prednisone equivalent dose).

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TABLE III. Adverse events

	12 mon (n = 218)	24 mo (n = 147)
Total adverse event, n (%)	7 (3.2)	1 (0.7)
Mild-moderate adverse event, n (%)	6 (2.8)	1 (0.7)
Fever, n (%)	3 (1.4)	0 (0)
Urticaria, n (%)	2 (0.9)	0 (0)
Otitis, n (%)	1 (0.5)	0 (0)
Atrial fibrillation, n (%)	0 (0)	1 (0.7)
Serious adverse event, n (%)	1 (0.5)	0 (0)
Bronchospasm, n (%)	1 (0.5)	0 (0)
Adverse event requiring treatment discontinuation, n (%)	0 (0)	0 (0)

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