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Asthma and Rhinitis

Real-life evaluation of mepolizumab efficacy in patients with severe eosinophilic asthma, according to atopic trait and allergic phenotype

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Abstract

Background: Anti-interleukin-5 (IL-5) monoclonal antibodies can be used as add-on biological therapies in allergic and non-allergic patients with severe eosinophilic asthma. However, within such a therapeutic context real-life investigations are lacking.

Objective: Therefore, the aim of the present observational study was to evaluate the effects of mepolizumab in allergic and non-allergic subjects with severe eosinophilic asthma.

Methods: Relevant clinical, functional, laboratory, and pharmacotherapeutic parameters were assessed in the above patient subgroups.

Results: After one year of add-on biological treatment with mepolizumab, our 88 patients experienced a remarkable improvement of their severe asthma, documented by a better symptom control, expressed by a significant improvement in asthma control test (ACT) score. Indeed, the mean value ($\pm$ standard deviation) of ACT score increased from 12.55 ($\pm$ 3.724) to 21.08 ($\pm$ 3.358). Moreover, significant improvements were also detected with regard to the median values (interquartile range) of forced expiratory volume in one second (FEV₁), blood eosinophil numbers, annual rate of disease exacerbations, and daily intake of oral corticosteroids (OCS). In particular, FEV₁ enhanced from 1640 mL (1110-2275) to 1920 mL (1525-2615), blood eosinophil count dropped from 711.0 cells/ μ L (500.0-1022) to 90.00 cells/ μ L (50.00-117.5), the annual rate of asthma exacerbations decreased from 3.000 (2.000-6.000) to 0.000 (0.000-1.000), and the daily prednisone intake fell from 6.250 mg (0.000-25.00) to 0.000 mg (0.000-0.000). After one year of mepolizumab treatment, the improvements in clinical, functional, and haematological parameters were quite similar in patient subgroups characterized by skin prick test (SPT) negativity or positivity, respectively. A significant correlation was observed between serum IgE levels and OCS intake decrease ($r = -0.2257$; $P < .05$).

Conclusion and Clinical Relevance: Hence, our real-life data suggest that mepolizumab can represent a valid add-on therapeutic option for patients with severe eosinophilic asthma, irrespective of IgE serum concentrations, and allergic sensitization.

KEYWORDS

allergen sensitization, atopy, exacerbations, IL-5, mepolizumab, severe eosinophilic asthma

1 | INTRODUCTION

Asthma affects more than 300 million people worldwide and is usually characterized by reversible airflow limitation and bronchial hyperresponsiveness, whose underlying pathobiologic substrates mainly consist of heterogeneous inflammatory patterns.¹⁻⁵ With regard to the different phenotypes/endotypes of asthma, airway eosinophilia can be detected in more than 50% of patients with either allergic or non-allergic disease, and high blood/sputum eosinophil counts are often associated with frequent asthma exacerbations and severe bronchial obstruction.⁶ Indeed, eosinophilic airway inflammation predominates in severe asthma and is sustained by type-2 (T2) immune/inflammatory responses driven by T helper 2 (Th2) lymphocytes and group 2 innate lymphoid cells (ILC2).⁷⁻⁹ These cells secrete a well known array of pro-inflammatory cytokines including interleukins (IL)-4, 5, 9, and 13, which are responsible for abnormal immunoglobulin E (IgE) production (atopy), eosinophilia, mast cell growth, and airway hyperresponsiveness, respectively.¹⁰ Therefore, allergic and eosinophilic phenotypes often coexist and overlap.¹¹ Most subjects with atopic eosinophilic asthma are responsive to both inhaled corticosteroids (ICS) and allergen-specific immunotherapies, which induce eosinophil apoptosis and inhibit the allergic inflammatory cascade, respectively.^{12,13} Nevertheless, patients with severe eosinophilic asthma are frequently refractory to ICS and even to oral corticosteroids (OCS) because of several potential reasons such as an excessive release of IL-5 and IL-13, an enhanced expression of the dysfunctional β isoform of glucocorticoid receptor, a decreased activity of histone deacetylases, and an increased activation of p38 mitogen-activated protein kinase.¹⁴⁻¹⁶

Hence, patients with T2-high severe asthma experience recurrent disease exacerbations and an unsatisfactory symptom control, thus being featured by relevant unmet needs¹⁷ resulting in non-programmed medical visits, frequent accesses to emergency room, and hospital wards, as well as in significant losses of work and school days. For such severe asthmatic patients, GINA (Global Initiative for Asthma) guidelines recommend an intense and optimized standard treatment, including high dosages of ICS/LABA (long-acting β_2 -adrenergic agonists) combinations, tiotropium and eventually a leukotriene inhibitor, integrated by one of currently approved biological drugs.¹⁸ The latter include the humanized anti-IgE monoclonal antibody omalizumab, the humanized anti-IL-5 monoclonal antibodies mepolizumab and reslizumab, the humanized monoclonal antibody benralizumab which targets the IL-5 receptor, and the fully human monoclonal antibody dupilumab that behaves as a dual IL-4/IL-13 receptor antagonist.¹⁹⁻²⁷ Because of the possible coexistence and overlapping of allergic and eosinophilic phenotypes

within the context of severe type 2 asthma, many patients can be eligible to more than one biologic drug,²⁸ thus making quite challenging the therapeutic choice of clinicians. In this regard, the efficacy of omalizumab in atopic eosinophilic asthma has been well documented over the last 15 years by both randomized controlled trials and real-life studies.^{19,20} In addition, recent post hoc analyses of some phase 3 trials,²⁹⁻³¹ as well as a few real-world investigations performed on very small numbers of severe asthmatics,^{22,32} suggest that mepolizumab, benralizumab, and dupilumab can be effective in severe eosinophilic asthma regardless of patient atopic status.

Therefore, the aim of the present multi-centre, observational, real-life study has been to evaluate, in patients with severe eosinophilic asthma, the therapeutic effects of mepolizumab after one year of add-on therapy. Moreover, the efficacy of mepolizumab was comparatively assessed with regard to the allergic or non-allergic trait of enrolled asthmatic patients.

2 | METHODS AND PATIENTS

2.1 | Study design and patient recruitment

This was a multi-centre, real-life study that included subjects with severe persistent eosinophilic asthma, treated with mepolizumab. These patients were evaluated at the following four centres: Allergy and Respiratory Medicine, University of Catania, Italy; Respiratory Unit of University "Magna Graecia" of Catanzaro, Italy; Personalized Medicine, Asthma and Allergy Clinic, Humanitas Research Hospital, Rozzano (Milan), Italy; and Allergology and Pulmonology Unit, Provincial Outpatient Center of Palermo, Italy.

Enrolled subjects were defined allergic on the basis of skin prick test (SPT) positivity, and atopic if an abnormal IgE production was documented.^{33,34} All patients met the European Respiratory Society (ERS)/American Thoracic Society (ATS) criteria that define severe uncontrolled asthma.³⁵ A shared database was used by all the recruiting centres to collect clinical, functional, and biological characteristics of asthmatic patients. Smoking habit and comorbidities (obesity, nasal polyposis, chronic rhinosinusitis, gastroesophageal reflux disease, bronchiectasis) were identified before starting mepolizumab treatment. Spirometry was performed according to ATS/ERS guidelines³⁶ at baseline and 12 months after the first injection of mepolizumab. Nasal endoscopy and/or computerized tomography (CT) of paranasal sinuses were made to confirm the clinical suspicion of nasal polyposis.

Mepolizumab was prescribed according to current eligibility indications, and it was administered subcutaneously at the dosage

of 100 mg every 4 weeks. This observational investigation met the standards of Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki. All recruited patients gave their written informed consent. Our retrospective observational study was also performed in accordance with what stated by the local Ethical Committee of Calabria Region (Catanzaro, Italy; document n. 22 - 16th January 2020).

2.2 | Patient characteristics

Subjects over the age of 18 years and with severe eosinophilic asthma were enrolled. All patients had eosinophil counts in peripheral blood of at least 150 cells/ μ L at baseline and at least 300 cells/ μ L within the past 12 months. They were treated with high dosages of ICS-LABA combinations. Furthermore, all recruited patients used an inhaled long-acting muscarinic antagonist (LAMA), and a large majority of them needed a permanent or near continuous intake of OCS. Despite such an intense therapy, the asthmatic subjects enrolled in this observational study experienced frequent daily and nocturnal symptoms, as well as recurrent asthma exacerbations.

In total, 88 patients were included (57 females and 31 males). The mean ($\pm$ standard deviation – SD) age of our study population was 54.51 ($\pm$ 10.80) years; the mean age of asthma onset was 33.48 ($\pm$ 12.90) years. The median (interquartile range-IQR) disease duration was 20.00 years (10.00-30.00). Median (IQR) baseline FEV₁ was 64.50% (49.00-77.75) of predicted value. Median (IQR) body mass index (BMI) was 26.85 (22.78-30.00). Median (IQR) blood

eosinophil count was 711.0 cells/ μ L (500.0-1022). SPT was positive in 60 patients. 23 subjects were smokers. 69 patients complained of chronic rhinosinusitis (CRS), 53 suffered from nasal polyposis, and 33 had gastroesophageal reflux disease (GERD). Moreover, bronchiectasis was detected in 27 participants.

Baseline patient characteristics, also stratified according to SPT positivity or negativity, are reported in Table 1. In particular, no significant difference was found in regard to the allergic or non-allergic phenotype, with the exception of the occurrence of CRS which resulted to be more frequent in allergic patients, whereas GERD was more common among non-allergic subjects.

2.3 | End-points and assessments

The primary outcome of this observational study was to evaluate the effectiveness of mepolizumab in a real-life environment. Asthma control test (ACT) score, FEV₁, blood eosinophil count, asthma exacerbation rate, daily OCS intake (mg), and exhaled fraction of nitric oxide (FeNO) were recorded at baseline and 12 months after the first mepolizumab injection.

The secondary outcome was to assess the effectiveness of mepolizumab across different eosinophilic phenotypes. SPT positivity was chosen to establish that patients carried a type 2 allergic-eosinophilic trait. After 12 months of add-on treatment with mepolizumab, we evaluated the eventual relationships existing between baseline IgE levels and the observed changes regarding ACT score, FEV₁, blood eosinophil count, asthma exacerbation number, daily OCS intake, and FeNO levels.

TABLE 1 Baseline patient characteristics

Baseline characteristics	Total population N = 88	Negative skin prick test N = 28	Positive skin prick test N = 60	P
Female gender, N (%)	57 (64.77)	15 (53.57)	42 (70.00)	.1553
Male gender, N (%)	31 (35.23)	13 (46.43)	18 (30.00)	.1553
Age, mean ($\pm$ SD), years	54.51 ($\pm$ 10.80)	55.44 ($\pm$ 9.917)	54.14 ($\pm$ 11.18)	.6133
Age of asthma onset, mean ($\pm$ SD), years	33.48 ($\pm$ 12.90)	34.07 ($\pm$ 14.15)	33.20 ($\pm$ 12.39)	.5594
Duration of asthma, median (IQR), years	20.00 (10.00-30.00)	22.00 (13.25-35.00)	20.00 (10.00-25.00)	.2195
FEV ₁ , median (IQR), % predicted	64.50 (49.00-77.75)	60.50 (46.25-85.00)	65.00 (50.00-76.75)	.8598
Blood eosinophils, median (IQR), cells/ μ L	711.0 (500.0-1022)	650.0 (500.0-1070)	791.0 (450.0-1070)	.0914
BMI, median (IQR), Kg/m ²	26.85 (22.78-30.00)	24.50 (21.55-30.38)	27.00 (23.00-30.00)	.5090
Obesity, N (%)	22 (25.00)	8 (28.57)	14 (23.33)	.6063
Smokers, N (%)	23 (26.14)	8 (28.57)	15 (25.00)	.7964
Chronic rhinosinusitis, N (%)	69 (78.41)	15 (53.57)	54 (90.00)	.0002
Nasal polyposis, N (%)	53 (60.23)	19 (67.86)	34 (56.67)	.3577
Gastroesophageal reflux disease, N (%)	33 (37.50)	17 (60.71)	16 (26.67)	.0041
Bronchiectasis, N (%)	27 (30.68)	9 (32.14)	18 (30.00)	>.9999

Bold entries emphasize the statistical significance of the detected differences.

During the first two hours after drug administration, patients were carefully monitored in order to detect the eventual onset of adverse events. A once-weekly telephone call was then made, with the aim of asking to patients if they had experienced headache, pharyngitis, anaphylaxis, or fever, thereby soliciting them to refer if any worsening of their health status had occurred.

2.4 | Statistical analysis

Statistical analysis was performed using Prism version 8.2.1 (GraphPad Software Inc). Normally distributed data were expressed as mean ($\pm$ SD), whereas median values with interquartile range (IQR) were preferred to express skewed data distributions. Parametric and non-parametric tests were selected according to data normality. Anderson-Darling test and Kolmogorov-Smirnov test were used to assess the normal distribution of data. Student t test or Mann-Whitney U test were utilized to compare variables, when, respectively, appropriate. Categorical variables were compared using the Fisher exact test. Linear regression analysis was developed to evaluate the association between baseline IgE levels and changes in clinical, functional, and haematological parameters. Spearman's rank correlation coefficient was calculated. Post hoc power analysis was performed when appropriate. *P* values <.05 were considered to be statistically significant.

3 | RESULTS

3.1 | Efficacy of mepolizumab in the entire population

After 12 months of treatment with mepolizumab, the ACT score significantly increased from a baseline value of 12.55 ($\pm$ 3.724) to 21.08 ($\pm$ 3.358) (*P* < .0001) (Figure 1A). This clinical result was associated with a significant improvement in lung function expressed as a FEV₁ increase, when compared to pre-mepolizumab treatment, from 1640 mL (1110-2275) to 1920 (1525-2615) (*P* < .0001) (Figure 1B). With regard to the haematological effects of mepolizumab, after one year of add-on treatment the median blood eosinophil count dropped from 711.0 cells/ μ L (500.0-1022) to 90.00 cells/ μ L (50.00-117.5) (*P* < .0001) (Figure 1C).

Moreover, when compared to the 12 months preceding the first injection of mepolizumab, the median number of asthma exacerbations drastically decreased from 3.000 (2.000-6.000) to 0.000 (0.000-1.000) after one year of anti-IL-5 therapy (*P* < .0001) (Figure 1D). Such an excellent therapeutic effect allowed a reduction in daily prednisone intake from 6.250 mg (0.000-25.00) to 0.000 mg (0.000-0.000) (*P* < .0001) (Figure 1E). Furthermore, the percentage of patients that received OCS every day fell from 76% before starting mepolizumab treatment to 12% after one year of therapy.

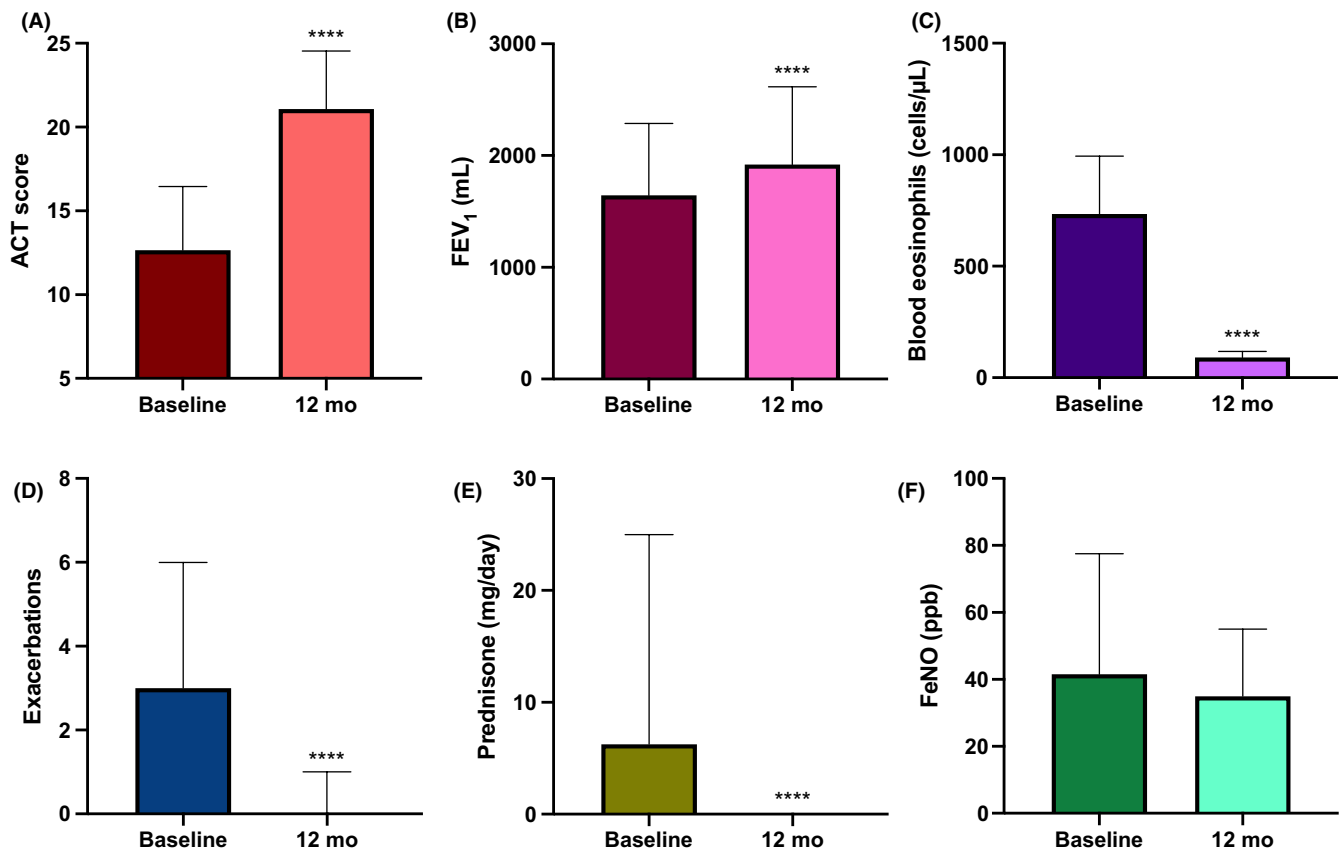


FIGURE 1 Effects of mepolizumab on the overall population of patients with severe type 2 asthma, with regard to ACT score (panel A), FEV₁ (panel B), blood eosinophil numbers (panel C), asthma exacerbation rate (panel D), prednisone intake (panel E), and FeNO levels (panel F). ACT score values are expressed as mean ($\pm$ SD). All other parameters are expressed as median values (IQR). **** *P* < .0001

In 68 out of 88 patients, FeNO was also measured at baseline and 12 months after the first mepolizumab administration. We observed a not significant trend towards a reduction in FeNO levels from 43.00 parts per billion (ppb) (24.00-78.00) to 35.00 ppb (23.00-55.00) ($P = .1252$) (Figure 1F).

3.2 | Efficacy of mepolizumab across different type-2 asthma phenotypes

The improvements in clinical, functional, and haematological parameters after one year of mepolizumab treatment were quite similar in patient subgroups characterized by SPT negativity or positivity, respectively. In particular, median ACT score changes were 6.500 points (5.000-8.250) and 9.000 points (6.000-13.00) in patients with negative and positive SPT, respectively ($P < .01$) (Figure 2A). Median FEV₁ increases were 225.0 mL (2.500-532.5) in patients with negative SPT, and 290.0 mL (-10.00-620.0) in subjects with positive SPT; this difference was not statistically significant ($P = .6063$) (Figure 2B). Furthermore, blood eosinophil count reductions were -550.0 cells/ μ L (-735.0 to -420.0) in patients with negative SPT, and -650.0 cells/ μ L (-950.0 to -400.0) in subjects with positive SPT, but also in this case the difference did not reach the threshold of statistical significance ($P = .5466$) (Figure 2C). The decreases in asthma

exacerbation numbers were -2.000 (-3.000 to -1.000) in patients with negative SPT, and -2.000 (-6.000 to -2.000) in subjects with positive SPT, respectively ($P < .05$) (Figure 2D). The daily dose of prednisone dropped off -12.50 mg (-25.00 to 0.000) in patients with negative SPT, and -5.00 mg (-12.50 to -0.000) in subjects with positive SPT, respectively ($P = .0840$) (Figure 2E). Twelve months after the first injection of mepolizumab, FeNO level changes were -6.500 ppb (-32.75 to 40.00) in patients with negative SPT, and -2.000 ppb (-36.00 to 11.00) in subjects with positive SPT, respectively ($P = .6871$) (Figure 2F).

Moreover, we detected the following correlations between serum IgE levels and mepolizumab-induced changes with regard to these parameters: ACT score increase ($r = 0.1015$; $P = .3583$) (Figure 3A), FEV₁ increment ($r = 0.02845$; $P = .8009$) (Figure 3B), blood eosinophil decrease ($r = 0.09584$; $P = .4102$) (Figure 3C), asthma exacerbation decrement ($r = 0.03625$; $P = .7419$) (Figure 3D), prednisone reduction ($r = -0.2257$; $P < .05$) (Figure 3E), and FeNO level decrease ($r = 0.3445$; $P < .01$) (Figure 3F).

3.3 | Safety and tolerability profile of mepolizumab

Treatment with mepolizumab was well tolerated, and no side effects or adverse events were reported.

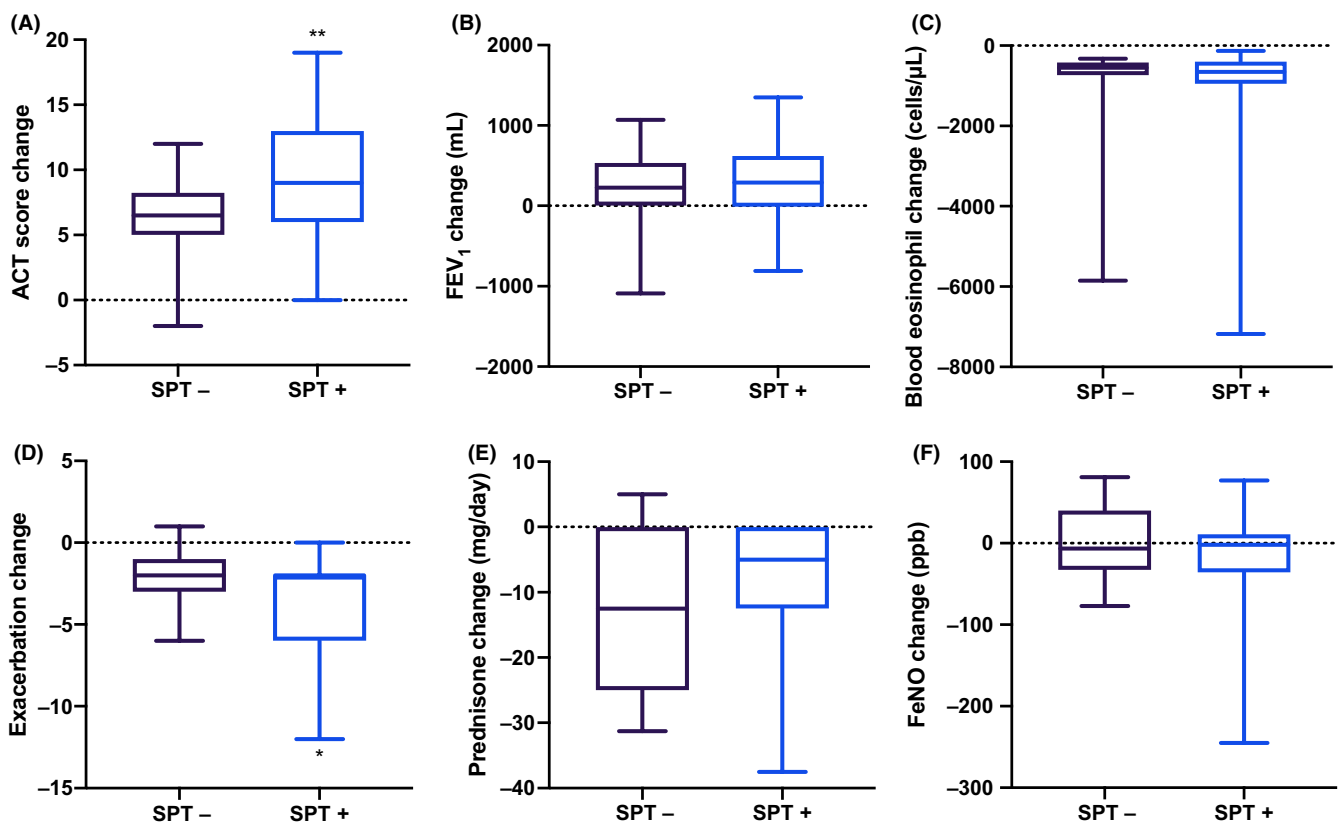


FIGURE 2 Effects of mepolizumab, stratified with respect to SPT negativity or positivity, in regard to ACT score (panel A), FEV₁ (panel B), blood eosinophil numbers (panel C), asthma exacerbation rate (panel D), prednisone intake (panel E), and FeNO levels (panel F). Boxes show median and IQR, and whiskers indicate maximum and minimum. * $P < .05$; ** $P < .01$

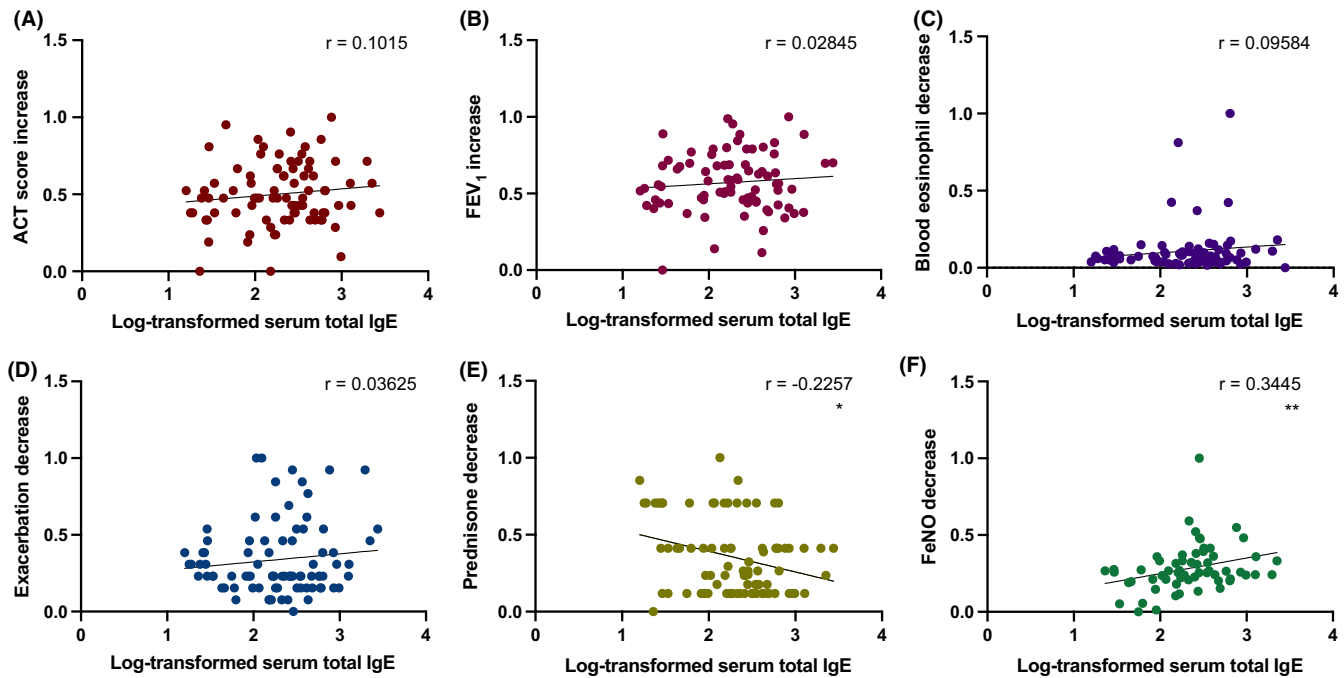


FIGURE 3 Correlations between IgE serum levels, expressed as logarithmic transformation, and mepolizumab-induced changes with regard to ACT score (panel A), FEV_1 (panel B), blood eosinophil numbers (panel C), asthma exacerbation rate (panel D), prednisone intake (panel E), and FeNO levels (panel F). * $P < .05$; ** $P < .01$

4 | DISCUSSION

The present multi-centre observational study, performed within a real-world context, confirms that mepolizumab is able to provide an extensive therapeutic coverage for both allergic and non-allergic patients with severe eosinophilic asthma, refractory to inhaled, and systemic corticosteroids. With respect to baseline conditions, after 12 months of treatment mepolizumab remarkably improved symptom control and lung function. These effects were associated with significant decreases in blood eosinophil count, annual rate of asthma exacerbations, and OCS intake. Moreover, mepolizumab induced a mild trend towards a reduction in FeNO levels, which however did not reach the threshold of statistical significance. Taken together, such results are consistent with those reported by other real-life studies.^{22,23,37-41} Furthermore, we found a significant correlation between baseline lower serum levels of IgE and the decrease in OCS intake elicited by mepolizumab. We also observed a significant correlation between baseline higher serum concentrations of IgE and the reduction in FeNO levels caused by mepolizumab. Moreover, this anti-IL-5 biological drug resulted to be safe and well tolerated.

The improvement of asthma symptom control was shown by the significant increase in ACT score, which after one year of treatment with mepolizumab overcame the crucial number 20, that expresses the value corresponding to an adequate and satisfactory clinical achievement. This result confirms in a real-life setting the findings of some phase 3 studies such as SIRIUS and MENSA,^{42,43} which utilized the asthma control questionnaire (ACQ)-5 to evaluate the effects of mepolizumab on respiratory symptoms. However, in daily clinical

activity ACT can be more practical and accessible than ACQ,⁴⁴ thus probably representing the best tool to assess the control of asthma symptoms in real life. Our present study also shows that mepolizumab produced a significantly greater enhancement of ACT score in allergic patients, when compared to non-allergic ones.

In addition to providing a better symptom control, mepolizumab also induced a significant improvement of lung function, documented by a FEV_1 increase which after 12 months of treatment almost reached 300 mL versus baseline. This result differs from several data obtained by randomized clinical trials. In particular, MENSA and MUSCA studies reported FEV_1 improvements of only 98 and 120 mL, respectively,^{43,45} whereas the previous DREAM trial did not demonstrate any difference between FEV_1 changes elicited by either mepolizumab or placebo.⁴⁶ We also observed a slightly higher, though not statistically significant FEV_1 increment in allergic versus non-allergic patients.

According to our current real-life study, the clinical and functional effects of mepolizumab were associated, after a 1-year therapy, with a sharp drop of blood eosinophil count, which fell from a pre-treatment median value of approximately 700 cells/ μ L to a normal median level of 90 cells/ μ L. This result, which is consistent with the findings of the phase 3 DREAM trial,⁴⁶ reflects the proven ability of mepolizumab to dampen the cellular responses underlying type 2 asthma. Indeed, blood eosinophils are regarded as quite trustworthy biomarkers of bronchial eosinophilic inflammation in severe asthma.⁴⁷ We also noticed a trend towards a mildly higher reduction of blood eosinophil numbers in allergic patients when compared to non-allergic subjects, but this difference did not reach the level of statistical significance.

The most important therapeutic action exerted by mepolizumab in our patients refers to the impressive reduction in the annual rate of asthma exacerbations, which abundantly overcame the 50% threshold set up by the British National Institute for Health and Care Excellence (NICE) as a clinically relevant parameter to establish the efficacy of anti-asthma treatments.⁴⁸ This remarkable effect of mepolizumab appears to be closely related to its anti-eosinophil therapeutic activity. In fact, blood eosinophil counts higher than 300/400 cells/ μ L resulted to be associated with a greater risk of asthma exacerbations.^{49,50} Therefore, one of the main aims of add-on biological treatments for severe asthma is to maintain blood eosinophil numbers at a lower level than 300 cells/ μ L,⁵¹ as confirmed by the present real-world study. Our findings also suggest that there is a close association between mepolizumab-dependent prevention of asthma exacerbations and the observed improvement in lung function. Indeed, it is well known that more severe is bronchial obstruction, higher is the frequency of asthma exacerbations, which in turn contribute to accelerate the progressive worsening of airflow limitation.⁵² Hence, mepolizumab can play a key therapeutic role in disengaging such a deleterious pathogenic vicious circle. Moreover, we detected a significantly greater decrement of the annual number of asthma exacerbations in allergic patients, with respect to non-allergic ones. In addition, the very effective reduction of asthma exacerbation rate granted by mepolizumab made also possible to significantly decrease OCS intake in our patients, many of whom were able to lastingly interrupt such a potentially dangerous systemic therapy.⁵³ These results further corroborate, in a real-life context, the findings of the phase 3 trials SIRIUS and COSMOS.^{42,54}

Finally, we observed mixed effects of mepolizumab on FeNO. Indeed, when globally considering the 68 (out of total 88) patients who underwent FeNO measurements, a not significant trend towards a decrease in FeNO levels was found in comparison with pre-treatment values.

Taken together, our real-life results clearly reaffirm the pivotal importance of IL-5 as a key cytokine target for add-on anti-eosinophil biological therapies potentially useful for both allergic and non-allergic patients with severe eosinophilic asthma. Indeed, we herein demonstrate that mepolizumab is very effective for treatment of patients with uncontrolled eosinophilic refractory asthma, irrespective of their allergic status. In this regard, our observations are consistent with those inferred from a recent post hoc meta-analysis of MENSA and MUSCA trials.²⁹ Similar conclusions have also been reported as result of a pooled analysis of the phase 3 studies SIROCCO and CALIMA, focusing on the therapeutic efficacy of the IL-5 receptor antagonist benralizumab.³⁰ It can thereby be argued that IL-5, in addition to being involved in eosinophil maturation, activation, chemotaxis, and survival,⁵⁵ is also associated with the pathobiologic mechanisms underlying allergic asthma. For instance, it is noteworthy that high IL-5 concentrations, as well as elevated numbers of both mature eosinophils and eosinophil progenitors, have been detected in the induced sputum obtained from subjects with atopic asthma.⁵⁶ Besides stimulating

eosinophil functions, IL-5 also acts as a relevant growth factor for basophils, being implicated in maturation, migration, and releasability of these cells.⁵⁷ Basophils significantly contribute to the pathogenesis of both sensitization and effector phases of allergic asthma through the release of IL-4, which plays a central role in Th2 cell differentiation and IgE synthesis.^{9,58} Furthermore, since IL-5 is produced in large amounts by Th2 lymphocytes and ILC2,^{55,59} this cytokine actively participates in the cellular interactions connecting the innate and adaptive immune responses that characterize the pathophysiology of atopic asthma. Therefore, it is reasonable to hypothesize that mepolizumab, by inhibiting the biological functions of IL-5, is able to effectively interfere with the pathogenic mechanisms underlying eosinophilic inflammation in both allergic asthma and non-allergic asthma.

Similar to all real-life studies, also our present investigation is limited by the lack of a randomization design. Another potential limitation of observational studies refers to regression towards the mean.⁶⁰ However, our results appear to be not so definitely conditioned by such a bias because enrolled patients were monitored, due to the severity of their asthma, with the same frequency before and after introduction of mepolizumab as add-on biological therapy. Indeed, clinical, functional, and laboratory features of our patients did not significantly change for a long time prior to treatment with mepolizumab. A further limitation of this study regards the post hoc power analysis,⁶¹ which could be inadequate for detection of all existing differences between patient subgroups. In particular, statistical power was higher than 90% when differences were analysed between allergic and non-allergic severe asthmatics, with regard to changes in ACT scores and yearly rates of asthma exacerbations. However, statistical power was lower than 80% when applied, in the above subject subgroups, to the other study findings.

In conclusion, the results of our real-life observational study clearly suggest that mepolizumab, by targeting IL-5 and neutralizing its bioactivities, is able to effectively modulate type 2 eosinophilic inflammation sustained by both allergic and non-allergic pathways. Because of these pharmacologic properties, mepolizumab improved symptom control and lung function, as well as decreased asthma exacerbation rate and OCS intake in subjects with either allergic or non-allergic phenotype. Therefore, mepolizumab can be reasonably considered as a valid therapeutic option for add-on biological treatment of either atopic or non-atopic patients with severe eosinophilic asthma.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

All authors contributed to design and carry out the study protocol, as well as to write the text and draw the figures.

DATA AVAILABILITY STATEMENT

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

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