International Archives of Allergy and Immunology

Clinical Allergy – Brief Report

Int Arch Allergy Immunol 2021;182:311–318
DOI: 10.1159/000511147

Received: June 16, 2020
Accepted: August 25, 2020
Published online: October 28, 2020

Mepolizumab Effectiveness and Allergic Status in Real Life

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Keywords
Mepolizumab · Severe asthma · Eosinophilic · Allergic · Outcomes · Real life

Abstract
Background: It is not clear whether mepolizumab is differently effective in allergic and nonallergic severe eosinophilic asthmatics (SEA) in real life. ***Objective:*** We tested mepolizumab effectiveness in allergic/nonallergic SEA in real life. A strict criterion to identify the 2 phenotypes was used. ***Method:*** We retrospectively considered 134 consecutive patients divided into allergic, with a positivity to at least 1 allergen to prick tests and/or IgE values ≥100 UI/mL (severe allergic eosinophilic asthma [SAEA]; *n*: 97–72.4%), and nonallergic, with no prick test results and normal IgE levels <100 UI/mL (severe nonallergic eosinophilic asthma [SNAEA]; *n*: 37–27.6%). They had taken mepolizumab for at least 6 months. ***Results:*** After 10.9 ± 3.7 months, improvements in FEV_1%, $FEF_{25–75}$%,

Edited by: H.-U. Simon, Bern.

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exacerbation numbers, blood eosinophil (BE) counts, fractional exhaled nitric oxide (FENO) (ppb), percentages of patients that stopped/reduced short-acting β2-agonists (SABAs) or oral corticosteroid (OC), observed after treatment, were similar in both groups. Only Asthma Control Test (ACT) increases were higher in SNAEA (8 [5–9]) than in SAEA (5 [2.5–8.5]; $p = 0.016$). However, no differences were found after treatment in percentages of subjects with ACT ≥20, as well as with FEV_1 >80%, $FEF_{25–75}$ >65%, exacerbations ≤2, BE <300 cells/μL, and FENO <25 ppb between SAEA and SNAEA. Besides, no significant relationships were found, comparing SNAEA with SAEA, for FEV_1% (β = −0.110; $p = 0.266$), $FEF_{25–75}$% (β = −0.228; $p = 0.06$), BE counts (β = −0.012; $p = 0.918$), FENO (β = 0.234; $p = 0.085$), ACT (β = 0.046; $p = 0.660$), and exacerbations (β = −0.070; $p = 0.437$). No different associations between lung function and SNAEA occurrence when compared to SAEA condition (FEV_1 >80%: OR = 1.04 [95% CI: 0.43–2.55], $p = 0.923$; $FEF_{25–75}$ >65%: OR = 0.41 [95% CI: 0.08–2.03], $p = 0.272$) were detected. Neither all other parameters, such as ACT >20 (OR = 0.73 [95% CI: 0.32–1.63], $p = 0.440$), presence of exacerbations (OR = 1.35 [95% CI: 0.55–3.27], $p = 0.512$), SABA discontinuation (OR = 1.16 [95% CI: 0.40–3.39], $p = 0.790$), and OC cessation/reduction (OR = 3.44 [95% CI: 0.40–29.27], $p = 0.258$), were differently associated with 1 or the other phenotype. ***Conclusion:*** Mepolizumab can be considered as a valid therapeutic choice for either allergic or nonallergic SEA in real life.

Introduction

Severe allergic eosinophilic asthma (SAEA) and severe nonallergic eosinophilic asthma (SNAEA) are phenotypes being currently treated with available targeted biologic therapies, namely, anti-IgE and anti-IL-5 antibodies. Both phenotypes can overlap [1], thus making it challenging to choose the most appropriate biologic asthma therapy. The 2 of them show eosinophilia but diverge for different pathways leading to eosinophilic inflammation. In fact, in SAEA, allergens cause Th2 cell activation and the release of cytokines interleukin IL-4, IL-5, IL-9, and IL-13, resulting in IgE production, eosinophilia, and mast cell activation [1]. Conversely, in SNAEA, ILC2 cells (type 2 innate lymphoid cells) are involved in the innate immune response independent of allergen sensitization, producing IL-5 and IL-13 [1] and thus eosinophilia. Therefore, both asthma phenotypes are characterized by a high number of eosinophils. Diagnosing eosinophilic asthma is fundamental because uncontrolled eosinophilic airway inflammation is related with reduced response to glucocorticoids and an increased risk of severe exacerbations. The diagnosis of eosinophilic asthma (which is time-consuming and requires specific technical expertise) is based on sputum eosinophil measurements [2]. Alternatively, biomarkers (such as blood eosinophils (BEs), fractional exhaled nitric oxide (FENO), serum IgE, and periostin) are being used as Th2 inflammation surrogates [2]. As already said, several immunotherapeutics that target and deplete eosinophils or limit their numbers are currently widely used and provide improved disease outcome in severe eosinophilic asthma. Mepolizumab is a monoclonal antibody which by blocking circulating IL-5 can reduce eosinophil counts improving asthma outcome [3]. Mepolizumab prescription is indicated either in patients with severe uncontrolled asthma showing BE count ≥300 cells/μL in the last 12 months or in patients who had a BE count greater than or equal to 150 cells/μL while being treated with oral corticosteroids (OCs) in the last year [4]. In fact, different mepolizumab trials have shown, through a meaningful BE lowering, to reduce exacerbations, to have a significant glucocorticoid-sparing effect, and to improve asthma control [5, 6]. However, both trials and real-life studies [5, 6] analyzed subjects with severe eosinophilic asthma regardless of allergic and nonallergic pathways leading to eosinophilic inflammation. Recently, post hoc meta-analysis and real-life studies have shown mepolizumab effectiveness in subjects affected by SAEA identified by using omalizumab eligibility or previous omalizumab treatment failure criteria [7, 8]. However, these studies compared eligible with ineligible omalizumab patients, although the latter may also include both individuals with seasonal allergies and high allergy-induced IgE levels. This mixture of patients could influence mepolizumab results. Only the above cited [7] meta-analysis highlighted mepolizumab benefits regardless of IgE levels or atopic status not only in subjects with omalizumab eligibility. However, as we do not know yet whether mepolizumab can show a similar response in subjects with aeroallergens sensitization/high IgE levels and in nonsensitized/low-IgE individuals in real life, we analyzed mepolizumab effectiveness in a group of severe asthmatics considering allergic sensitization status/IgE levels (but not omalizumab eligibility).

Materials and Methods

We retrospectively considered 134 poorly controlled severe eosinophilic asthmatics with an asthma guideline step 5 treatment who were prescribed mepolizumab. Twenty Italian severe asthma

Table 1. Characteristics of mepolizumab-treated severe asthmatics subdivided according to allergic status

	SAEA	SNAEA	*p* value
Patients, *n* (%)	97 (72.4)	37 (27.6)	**0.0001**
Age	58 [49–66]	61 [54–71]	0.127
Males, *n* (%)	44 (45.4)	17 (45.9)	0.951
Months of mepolizumab treatment	10 [6–12]	12 [8.5–14]	**0.043**
BMI	26.7 [24–30.2]	24.8 [22.5–27.4]	**0.012**
Smokers, *n* (%)	3 (3.1)	3 (8.1)	0.441
Ex-smokers, *n* (%)	31 (32)	12 (32.4)	
Age of asthma onset, yr	31.5 [20–45.7]	47 [32.2–53.7]	**0.003**
Total serum IgE UI/mL	218.5 [121–480.8]	44.2 [24–73.7]	**0.0001**
FEV_1% premepolizumab	69 [56–88]	70 [59.1–90]	0.599
FEV_1/FVC premepolizumab	65.4 [58–72.9]	66 [57.2–72]	0.988
BEs, cells/μL	696±804.5	753.6±496.2	**0.050**
FENO, ppb (evaluated only on 66 patients)	47 [34–77]	45 [18–54.5]	0.162
Exacerbations	3 [2.2–5]	3 [3–5]	0.156
ACT	14 [11.5–17.5]	12 [10–15]	**0.029**
House dust mite, *n* (%)	48 (49.5)	–	–
Pollens, *n* (%)	9 (9.3)	–	–
Molds, *n* (%)	18 (18.6)	–	–
Cat/dog dander, *n* (%)	36 (37.1)	–	–
Monosensitized (to 1 allergen), *n* (%)	40 (41.2)	–	–
Polysensitized (≥2 allergens), *n* (%)	48 (49.5)	–	–
Subjects with rhinitis, *n* (%)	62 (65.3)	16 (43.2)	**0.021**
Subjects with sinusitis, *n* (%)	48 (50.5)	15 (40.5)	0.302
Subjects with nasal polyposis, *n* (%)	50 (52.6)	19 (51.4)	0.894
Subjects with 0 comorbidity, *n* (%)	40 (43)	15 (40.6)	0.796
Subjects with ≥1 comorbidities, *n* (%)	53 (57)	22 (59.4)	
High dose of ICS, *n* (%)	36 (37.1)	14 (37.8)	0.364
Medium dose of ICS, *n* (%)	44 (45.4)	20 (54)	
Low dose of ICS, *n* (%)	17 (17.5)	3 (8.2)	
LABA, *n* (%)	93 (94.8)	35 (94.6)	0.748
Tiotropium, *n* (%)	54 (61.3)	17 (48.6)	0.367
Montelukast, *n* (%)	46 (47.9)	12 (32.4)	0.124
OC, *n* (%)	68 (70.1)	31 (83.8)	0.107
SABA use, *n* (%)	54 (58)	34 (91.9)	**0.0017**

Data are shown as median and interquartile range (IQR) or number of subjects (%). The data shown in the table were evaluated prior to treatment with mepolizumab. Significant differences between the groups have been put in bold SAEA, severe allergic eosinophilic asthma; SNAEA, severe nonallergic eosinophilic asthma; ACT, Asthma Control Test; SABA, short-acting β2-agonist; ICS, inhaled corticosteroids; OC, oral corticosteroids; FENO, fractional exhaled nitric oxide.

centers shared a common database reporting the clinical, functional, and biological characteristics of the enrolled patients. Mepolizumab was prescribed to subjects that had had a peripheral BE count above 300/μL in at least one occasion during the previous year and >150/μL before the first MEP injection. All the included patients received 100 mg MEP subcutaneously every 4 weeks. The study was undertaken in accordance with the Helsinki Declaration, and the use of data for this study was approved by the local Ethics Committee of Pisa University Hospital, within the context of an observational multicenter project on severe asthma in Italy (n.1245/2016). Informed consent was obtained from each patient. All underwent prick tests for common allergens (*Dermatophagoides pteronyssinus*/*farinae*, grass mix, *Parietaria*, *Olea europaea*, *Cupressus sempervirens*, *Betula pendula*, *Alternaria tenuis*, *Aspergillus fumigatus*, dog-cat dander, and in many cases for other allergens) and total serum IgE measurements before therapy. Patients were subdivided into SAEA and SNAEA groups. SAEA individuals were selected for a positivity to at least 1 allergen to prick tests and/or IgE values ≥100 UI/mL. SNAEA subjects were chosen because they showed no results to prick tests and normal IgE levels <100 UI/mL. Unlike SNAEA subjects, all SAEA individuals showed clinical evidence of allergen triggered symptoms. All patients took mepolizumab for at least 6 months (mean duration: 10.9 ± 3.7 months).

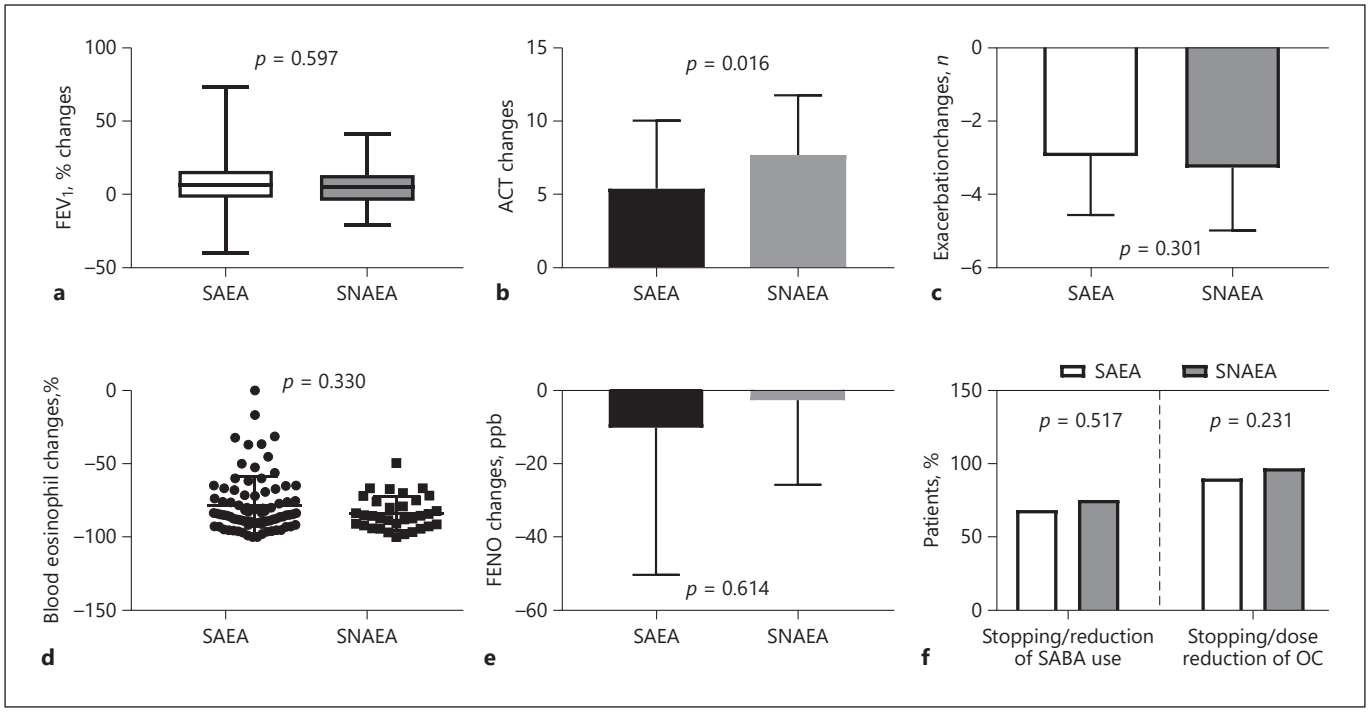

Fig. 1. Changes in FEV_1% (**a**), ACT (**b**), number of exacerbations (**c**), blood eosinophils (**d**), FENO (**e**), as well as the percentage of subjects that stopped/reduced SABA and OC use (**f**) obtained after about 11 months of mepolizumab treatment. BE, blood eosinophil; SAEA, severe allergic eosinophilic asthma; SNAEA, severe nonallergic eosinophilic asthma; ACT, Asthma Control Test; FENO, fractional exhaled nitric oxide; SABA, short-acting β2-agonist; OC, oral corticosteroids.

Baseline comorbidities, smoking habits, BMI, asthma onset age, and mepolizumab treatment period were considered for each patient. Lung function variables (FEV_1% and $FEF_{25–75}$%), Asthma Control Test (ACT), BE counts, FENO, and number of moderate/severe exacerbations were evaluated before mepolizumab prescription and at the end of patients' treatment periods. OC and short-acting β2-agonist (SABA) use as needed were also evaluated before and after treatment. BE count reduction < or >85% (value corresponding to the median rate we observed) obtained after mepolizumab treatment was considered for this study. BE percentage variations were calculated by subtracting postvalues from prevalues; the result was then divided by the prevalue × 100, a criterion used as an independent variable in logistic models. Linear and logistic regression models were also applied to assess whether there was a different association between various outcomes/biological markers and SAEA occurrence compared to SNAEA incidence. Each model was adjusted for all confounding factors: sex, age, smoking habits, BMI, age of asthma onset, mepolizumab treatment duration, various allergen sensitizations, IgE value, baseline BE counts, aspirin-exacerbated respiratory disease presence, comorbidities, nasal symptoms, daily doses of inhaled corticosteroids (ICS), LABA, LAMA, montelukast, SABA, and OC use.

Results

All the characteristics of the 2 groups are reported in Table 1. Ninety-seven (72.4%) patients were affected by SAEA, whereas 37 (27.6%; $p = 0.0001$) were affected by SNAEA. The 2 groups differed only for their treatment periods (10.4 ± 3.7 vs. 11.5 ± 3.5; $p = 0.043$), BMI (27 ± 4.5 vs. 25 ± 3.4; $p = 0.012$), asthma onset age (33.5 ± 16.6 vs. 43.5 ± 15.6; $p = 0.003$), baseline BE (696 ± 804.5 vs. 753.6 ± 496.2 cells/μL; $p = 0.05$), baseline ACT (14.8 ± 4.4 vs. 13 ± 4.1; $p = 0.029$), and obviously for baseline serum IgE (386 ± 462.1 vs. 50 ± 25.8 UI/L; $p = 0.0001$). No other differences between the 2 groups were found.

FEV_1%, exacerbations, BE%, and FENO improvements obtained after treatment were similar in both groups (Fig. 1). Also $FEF_{25–75}$% increases were comparable in SAEA (8.8 ± 25.8%) and in SNAEA (10.6 ± 18.9%) (data not shown). Only changes in ACT were higher in SNAEA (Fig. 1b). Percentages of patients that stopped/reduced SABA or OC were similar in both groups (Fig. 1e). When we also considered the percentages of patients with

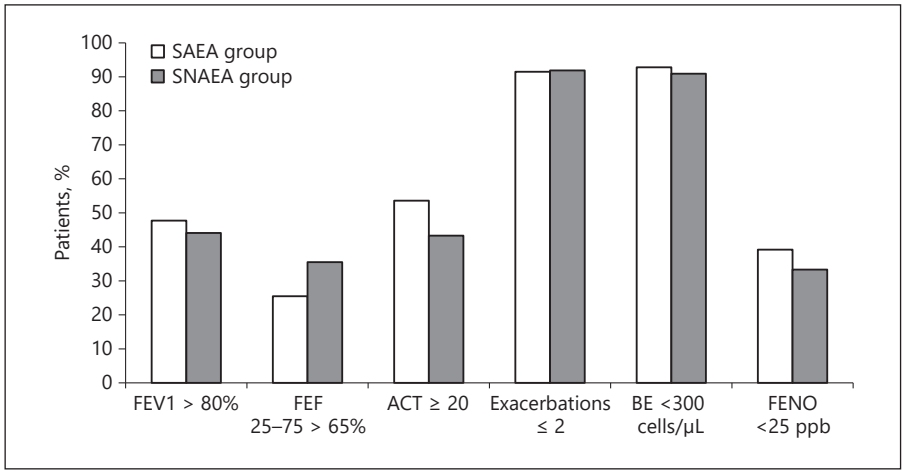

Fig. 2. Percentage of patients with FEV_1 >80%, $FEF_{25–75}$ >65%, ACT ≥20, exacerbations ≤2, BE <300 cells/μL, FENO <25 ppb obtained after mepolizumab treatment in the 2 groups. Comparisons between SAEA and SNAEA groups were made by using χ^2 test. FEV_1 >80%: $p = 0.725$; $FEF_{25–75}$ >65%: $p = 0.130$; ACT ≥20: $p = 0.295$; exacerbations ≤2: $p = 0.940$; BE count <300 cells/μL: $p = 0.735$; FENO <25 ppb: $p = 0.680$. BE, blood eosinophil; ACT, Asthma Control Test; FENO, fractional exhaled nitric oxide; SAEA, severe allergic eosinophilic asthma; SNAEA, severe nonallergic eosinophilic asthma.

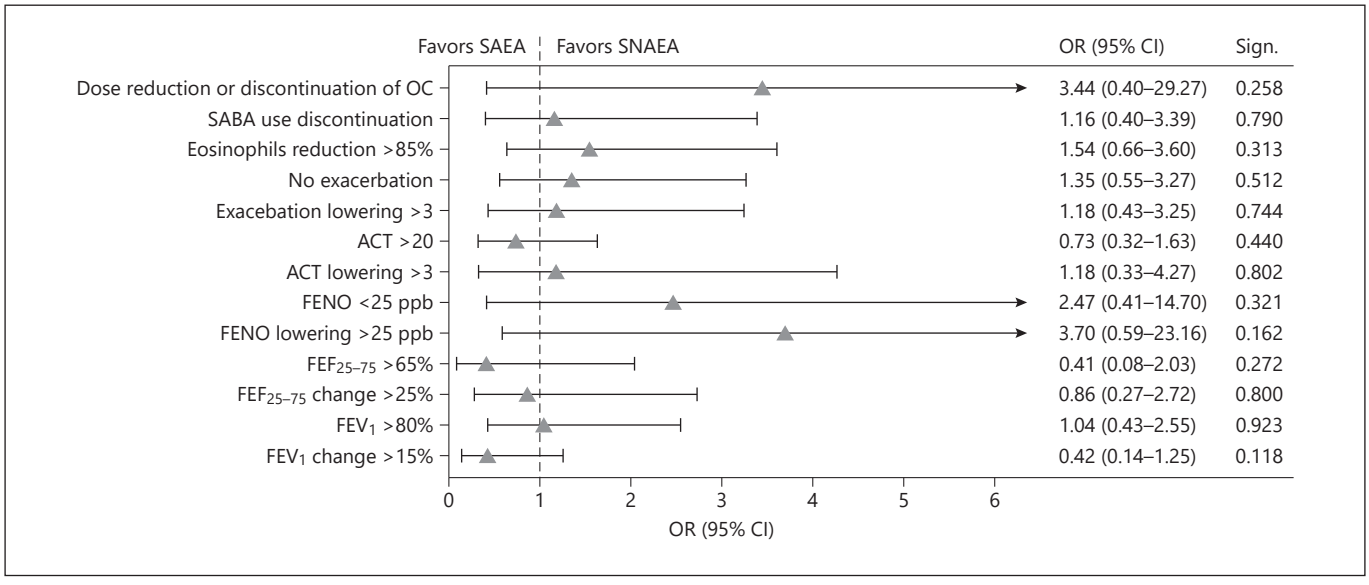

Fig. 3. Response to mepolizumab treatment of various outcomes comparing SAEA and SNAEA subjects. Logistic regression models were used for this analysis. For each outcome, a logistic regression model (adjusted for all possible confounding factors) was applied to compare SAEA with SNAEA. Models were adjusted for all confounding factors observed before mepolizumab treatment: age, sex, BMI, FEV_1%, each allergen sensitization, IgE value, baseline BEs, baseline FENO, rhinitis/sinusitis, nasal polyposis, other comorbidities, smoking, age of asthma onset, AERD presence, mepolizumab treatment duration, daily doses of ICS, OC, and various other combined treatments. BE, blood eosinophil; ACT, Asthma Control Test; FENO, fractional exhaled nitric oxide; SAEA, severe allergic eosinophilic asthma; SNAEA, severe nonallergic eosinophilic asthma; AERD, aspirin-exacerbated respiratory disease; ICS, inhaled corticosteroids; OC, oral corticosteroids.

a significant improvement after mepolizumab in the other outcomes, no differences were found between the 2 groups. In fact, in SAEA and SNAEA, the percentages of patients with FEV_1 >80% were 47.7 and 44.1%, respectively ($p = 0.725$), with $FEF_{25–75}$ >65% were 25.5 and 35.5% ($p = 0.130$), with ACT ≥20 were 53.6 and 43.2% ($p = 0.295$), with exacerbations ≤2 were 91.5 and 91.9% ($p = 0.940$), with BE count <300 cells/μL were 92.8 and 90.9% ($p = 0.735$), and with FENO <25 ppb were 39.2 and 33.3% ($p = 0.680$) (Fig. 2).

As the comparison between SAEA and SNAEA showed some baseline differences (see Table 1), we decided to compare the various outcomes in the 2 groups by applying correct linear and logistic regression models corrected for all the confounding variables. When a linear regression model was applied, no significant relationships

were found for FEV_1% (β = −0.110; $p = 0.266$), $FEF_{25–75}$% (β = −0.228; $p = 0.06$), BE counts (β = −0.012; $p = 0.918$), FENO (β = 0.234; $p = 0.085$), ACT (β = 0.046; $p = 0.660$), and exacerbations (β = −0.070; $p = 0.437$) when comparing SNAEA with SAEA. Adjusted logistic regression models as well highlighted no different risks for a better mepolizumab response in different outcomes comparing the 2 groups (Fig. 3).

Discussion

This study highlighted similar mepolizumab-induced improvements in the various outcomes considered in both SAEA and SNAEA, identified by using allergic sensitization to prick test and IgE level criteria and not only by means of omalizumab eligibility condition. By selecting asthmatics on the basis of prick-test/IgE level criteria, we identified 2 asthma phenotypes with different clinical and biological characteristics. SNAEA patients showed also a lower BMI, an elevated asthma onset age, worse symptoms (lower ACT), a larger use of SABA as needed, significantly lower IgE values, and higher BE counts than SAEA individuals. This underlines that an allergic state identifies a phenotype with different characteristics compared to a nonallergic condition. In fact, SNAEA subjects showed characteristics leading to a more significant asthma severity (late asthma onset and a higher BE number). This confirms that mepolizumab can be equally effective in both allergic and nonallergic eosinophilic asthma, although the 2 phenotypes showed different clinical and biological features. Mepolizumab treatment period was longer in the SNAEA group, and this could have influenced the results. For this reason, we used multivariate analysis to analyze data. In fact, we adjusted both linear and logistic regression models also for treatment time. However, no differences were found between the 2 groups confirming that a difference in treatment time did not influence results.

Only ACT changes were significantly higher in SNAEA patients. More SAEA subjects showed a higher BMI than the SNAEA group. Obesity may influence mepolizumab response in terms of symptoms in the SAEA group as it is well known that obese asthmatics have more symptoms. However, adjusting for all confounding/influencing factors, both SAEA and SNAEA showed no differences in mepolizumab effectiveness. In fact, we observed that eosinophils and FENO were similarly reduced by mepolizumab in the 2 groups. Such result confirms that eosinophilic airway inflammation reduction should be the goal to achieve in both SAEA and SNAEA, regardless of whether it is allergy induced. The eosinophilic asthma phenotype is characterized by high eosinophil levels in induced sputum and peripheral blood and is associated with more frequent symptoms/exacerbations and a greater air flow limitation [9, 10]. In fact, medications such as ICS, mepolizumab, or benralizumab, by acting on airway eosinophilic inflammation (reducing airway eosinophil numbers) [11–14], can improve lung function, symptoms, and reduce asthma exacerbations, even if mepolizumab does not influence the functional phenotype and airway eosinophil activation state, including surface markers and degranulation or the release of granule proteins in lung tissue [15, 16]. Failure to reduce eosinophils, even after maximal therapy, could be associated with unstable asthma and with a reduced clinical and functional response to treatment [17, 18]. In addition, failure to reduce eosinophils, even after omalizumab or OC/ICS treatments in allergic asthma, may be associated to poorer clinical and functional responses [18, 19]. Therefore, the reduction of eosinophilic airway inflammation is the target that must be sought for the treatment of eosinophilic asthma phenotype. Mepolizumab, significantly reducing eosinophils, may be the drug to be used in eosinophilic asthma regardless of allergic or nonallergic characteristics. Our real-life observational study clearly suggests that mepolizumab, by neutralizing IL-5 and its activities, is able to modulate type 2 eosinophilic inflammation sustained by both allergic and nonallergic pathways.

We know that IL-5, in addition to being involved in eosinophil maturation, activation, chemotaxis, and survival, is also associated with the pathophysiological mechanisms of allergic asthma [20]. In fact, high IL-5 concentrations, as well as elevated numbers of both mature eosinophils and eosinophil progenitors, have been detected in the induced sputum of subjects with atopic asthma [21]. Furthermore, IL-5 also acts, through eosinophil action, as a relevant growth factor for basophils, being implicated in maturation, migration, and activation of such cells [22]. Basophils significantly contribute to the pathogenesis of allergic asthma through the release of IL-4, which plays a central role in Th2 cell differentiation and IgE synthesis [20, 23]. Furthermore, since IL-5 is mostly produced by Th2 lymphocytes and ILC2 [20, 24], this cytokine significantly contributes in the cellular interactions connecting the innate and adaptive immune responses that characterize the atopic asthma inflammation. Therefore, it is possible that mepolizumab, by inhibiting the biological functions of IL-5, is able to effectively interfere with the pathogenic mechanisms lead-

ing to IL-5-induced allergic asthma inflammation, thus reducing allergic response.

Our study also highlighted that the prevalence of NP was similar in the 2 groups characterized both by higher BE counts but with a different allergic status. NP is probably associated with eosinophilic inflammation independently of allergic flogosis. NP typically associates with late-onset eosinophilic asthma characterized by frequent exacerbations with increased OC dependence [25]. Furthermore, all anti-eosinophilic treatments, including omalizumab, can significantly improve nasal polyposis, and this improvement appears to be associated with a significant eosinophil reduction [25–29]. In conclusion, this real-life analysis indicates that mepolizumab has clinical benefits in patients with severe eosinophilic asthma, regardless of allergic or nonallergic characteristics.

Statement of Ethics

The study was undertaken in accordance with the Helsinki Declaration and the use of data for this study was approved by the local Ethics Committee of Pisa University Hospital, within the context of an observational multicentre project on severe asthma in Italy (No. 1245/2016). Informed consent was obtained from each patient.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors did not receive any funding.

Author Contributions

B.S. conceived, designed, and wrote the study. M.S. was the biostatistician. All the listed authors contributed to the clinical work, data collection, and analysis. All authors also contributed to the drafting of the manuscript, read the final version, and approved its submission. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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