

Proportion of Severe Asthma Patients Eligible for Mepolizumab Therapy by Age and Age of Onset of Asthma



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What is already known about this topic? Mepolizumab is an anti-IL-5 antibody approved for the treatment of severe eosinophilic asthma. The prevalence of patients with severe asthma with an eosinophilic phenotype and eligible for mepolizumab remains unknown, especially in the pediatric population.

What does this article add to our knowledge? Among our cohort of patients with severe asthma, 33%/24% of children, 48%/26% of adults with childhood-onset asthma, and 60%/47% adults with adult-onset asthma would have qualified for mepolizumab on the basis of eosinophil counts of greater than or equal to 150 cells/ μ L or greater than or equal to 300 cells/ μ L, respectively.

How does this study impact the current management guidelines? Up to 60% of patients with severe asthma studied were eligible for mepolizumab. Children were less likely to qualify compared with adults with severe asthma. Adult-onset asthma appears to be a distinct phenotype characterized by greater eosinophilia and nasal polyposis and would likely comprise most patients eligible for mepolizumab therapy.

BACKGROUND: Mepolizumab is an anti-IL-5 antibody approved for the treatment of severe eosinophilic asthma. However, the prevalence of patients with severe asthma eligible for mepolizumab remains unknown, especially among children. **OBJECTIVE:** To determine, in a population of patients with severe asthma from a tertiary referral center, the proportion of patients with an eosinophilic phenotype who would be eligible for mepolizumab, when stratified for the age of onset of asthma,

and the prevalence of phenotypic features that favor mepolizumab therapy.

METHODS: An extensive database of 245 adults and children referred for severe asthma was used. The prevalence of severe asthma was estimated by using the European Respiratory Society/American Thoracic Society criteria. Patients with an eosinophilic uncontrolled phenotype qualified for mepolizumab. **RESULTS:** In our cohort, 216 (88%) had severe asthma. Based on blood eosinophils of either greater than or equal to 150 cells/ μ L or greater than or equal to 300 cells/ μ L, 61%/41% had an eosinophilic phenotype, while 49%/34% were eligible for mepolizumab therapy. A greater percentage of adults (60%/47% of adults with asthma onset in adulthood [AoA] and 48%/26% adults with childhood-onset asthma [<18 years, CoA]) were eligible compared with children (33%/24%), for eosinophil counts of ≥ 150 and ≥ 300 cells/ μ L, respectively; $P < .05$.

Compared with adults, children had a similar number of exacerbations while having better lung function ($P < .05$). Among adults, those with AoA were older, were more likely to have nasal polyps (28% vs 5%; $P < .05$), and had higher blood eosinophil counts (272 vs 150 cells/ μ L; $P < .05$) compared with those with CoA, with no difference in lung function noted between the 2 groups. Subjects showing greater than or equal to 500 eosinophils/ μ L, a strong indicator for mepolizumab therapy, had more nasal polyps, higher inhaled steroid dose, lower lung function, and AoA predominance than did those with less than 500 eosinophils/ μ L ($P < .05$).

CONCLUSIONS: A smaller percentage of children with severe asthma were eligible for mepolizumab compared with their adult peers. Severe AoA has distinct phenotypic features that favor treatment with mepolizumab, including greater eosinophilia and

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Abbreviations used

AoA- Asthma onset in adulthood

ATS- American Thoracic Society

CoA- Childhood-onset asthma

DREAM- Dose Ranging Efficacy and Safety with Mepolizumab in Severe Asthma

ERS- European Respiratory Society

FENO- Fraction of exhaled nitric oxide

ICS- Inhaled corticosteroid

OCS- Oral corticosteroid

SA- Severe asthma

SARP- Severe Asthma Research Program

nasal polyposis, in contrast to CoA, which appears to have fewer features of type 2 mucosal inflammation. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2689-96)

Key words: Adult; Adult-onset; Severe asthma; Children; Childhood-onset; Corticosteroid; Eosinophil; IL-5; Mepolizumab; Prevalence

INTRODUCTION

Approximately 5% to 10% of patients with asthma are estimated to suffer from severe disease, which significantly impairs quality of life due to continued symptoms, frequent exacerbations, and high risk of life-threatening attacks.¹⁻³ These patients are responsible for most of the asthma-related mortality, morbidity, and health care costs, and despite receiving high-intensity treatment, they continue to have uncontrolled disease in a subset of cases.¹⁻³ As such, severe asthma (SA) constitutes a major therapeutic unmet need.

There is increasing recognition that SA comprises several heterogeneous phenotypes with regard to clinical characteristics and physiological features, which require targeted treatment approaches.⁴⁻⁶ Although these phenotypes have not been fully characterized yet, they are broadly distinguished in type 2-high and type 2-low phenotypes based on the level of T_H2 and innate lymphoid cells and cytokines involved. Over the last decade, this evidence has led to the development of biological therapies blocking specific immunologic pathways of SA, most of which currently target type 2-high phenotypes.⁷ The first mAbs approved for both children and adults with type 2-high SA were omalizumab and mepolizumab. The former interrupts the basis of allergic reactivity by targeting IgE, and it is approved for subjects 6 years or older with severe allergic asthma.⁷ The latter neutralizes IL-5, a critical cytokine for eosinophil proliferation, survival, and activation, and it is approved in the United States for patients 12 years or older with severe eosinophilic asthma.⁷ Both biologics have been demonstrated to be effective in reducing asthma symptoms, exacerbation rates, and corticosteroid use in clinical trials.⁸⁻¹²

Age of onset of asthma seems a critical factor distinguishing SA phenotypes. Allergic asthma tends to begin during childhood and is associated with a personal and often a family history of atopy and markers of T_H2-mediated inflammation including elevated total and specific IgE levels and blood eosinophilia, making this overlapping phenotype eligible for treatment with

multiple biologic therapies.^{13,14} A recent study in preschool-aged children with asthma found elevated blood eosinophils and aeroallergen sensitivity as independent and additive predictors of response to daily inhaled corticosteroid (ICS) therapy.¹⁵ Children with allergic asthma often have a male predominance and normal lung function, and are at risk for viral-induced asthma exacerbations. Eosinophilic asthma tends to develop in adulthood, has a female predominance, and is associated with a low rate of atopy, reduced pulmonary function from the beginning, comorbidities, such as obesity and nasal polyposis, and high rates of exacerbations and medical resources use.¹⁶

The proportion of patients with SA eligible for treatment with mepolizumab is poorly understood, especially among the pediatric population. This study sought to determine, in a sample of adults and children with SA, the proportion of patients with an eosinophilic phenotype who would be eligible for mepolizumab, when stratified for the age of onset of asthma, and the prevalence of phenotypic features that favor mepolizumab therapy.

METHODS

Study design and patients

This was a retrospective review conducted within a cohort of adults and children referred for suspected SA at National Jewish Health, a national referral center for respiratory diseases, between 2010 and 2013. The study was reviewed and approved by the National Jewish Health Institutional Review Board. Informed consent was obtained from all participants or their legal guardians.

Asthma diagnosis was confirmed by a respiratory specialist, on the basis of characteristic symptom patterns and objective evidence of variable airflow limitation documented with spirometry (ie, increase $\geq 12\%$ and 200 mL in FEV₁ following inhalation of 400 μ g of albuterol) performed either at first visit or in the previous 12 months. All subjects were evaluated by a single physician (J.D.S.) who used the same questionnaire to obtain information on all subjects studied. For adults to have asthma onset in adulthood (AoA), they had to clearly recall having no respiratory symptoms as children or adolescents.

Subjects were considered eligible if they were 6 years or older and suffered from doctor-diagnosed asthma requiring treatment with either medium-to-high ICS dose (defined according to Global Initiative for Asthma guidelines¹⁷) plus at least 1 additional controller (either long-acting β_2 -agonist, a leukotriene receptor antagonist, theophylline, or tiotropium) for 12 months, or maintenance oral corticosteroids (OCSs) or anti-IgE mAb omalizumab. We chose this age group because most of the children can perform adequate spirometry to confirm asthma. Subjects with a history of mild to moderate asthma (Global Initiative for Asthma steps 1-3) or lung disease other than asthma were excluded from this analysis.

All the data presented were gathered at the time point of the first visit with the respiratory specialist who reviewed the patients' medical records for the previous 12 months, and included patients' demographic characteristics, medical history (including smoking habits and comorbidities), self-reported asthma medication history, asthma-related acute exacerbations and visits to health care or hospitalizations, clinical examination measurements, pulmonary function testing, and laboratory assessment including blood eosinophil count.

Lung function

Pulmonary function measurements were performed with a spirometer according to the American Thoracic Society (ATS)

guidelines.¹⁸ Participants underwent at least 3 acceptable maneuvers. The 3 highest forced vital capacity and FEV₁ values were recorded using a Jaeger MasterScreen Pneumo running JLab 5.20 software (Erich Jaeger, Inc, Wurzburg, Germany). The measures for forced vital capacity, FEV₁, and forced expiratory flow at 25% to 75% of forced vital capacity were expressed as percentage predicted, using the Third National Health and Nutrition Examination Survey (NHANES III) reference values.¹⁹

Severe eosinophilic uncontrolled asthma

SA was defined according to the latest European Respiratory Society/American Thoracic Society (ERS/ATS) criteria, which require treatment with high ICS dose (≥ 500 $\mu\text{g}/\text{d}$ fluticasone equivalent for age 6-12 years or ≥ 1000 $\mu\text{g}/\text{d}$ fluticasone equivalent for age >12 years) plus 1 additional controller medication (either long-acting β_2 -agonist, tiotropium, leukotriene receptor antagonist, theophylline, or omalizumab) for the previous year and/or continuous or near-continuous systemic corticosteroids to prevent it from becoming uncontrolled or which remains uncontrolled despite this level of treatment.¹

Eosinophilic asthma was defined as either a blood eosinophil count of greater than or equal to 150 cells/ μL or greater than or equal to 300 cells/ μL , at the time of study visit. These thresholds were based on mepolizumab inclusion criteria and are in the package insert.⁹⁻¹²

Participants qualified as having uncontrolled asthma when showing frequent significant or severe exacerbations (ie ≥ 2 OCS bursts for at least 3 days each, or ≥ 1 asthma-related hospitalization/intensive care unit admission/mechanical ventilation) during the previous year.¹

Outcome measures

The primary objective of this study was to assess what proportion of patients with SA (fulfilling ERS/ATS criteria) would have an eosinophilic phenotype and potentially qualify for mepolizumab treatment, after being stratified for the age of onset of asthma into 3 groups: children, adults with asthma that occurred before age 18 years (ie, childhood-onset asthma [CoA]), and adults with AoA. All the following criteria determined eligibility for mepolizumab: (1) age 12 years or more; (2) SA according to ERS/ATS criteria; (3) 2 or more asthma exacerbations in the previous year requiring at least a 3-day course of OCS; and (4) evidence of blood eosinophil level of either greater than or equal to 150 cells/ μL or greater than or equal to 300 cells/ μL at the study visit.⁹

The secondary objective was to assess the prevalence of phenotypic features of type-2 mucosal inflammation, which favor treatment with mepolizumab stratified by the age of onset of asthma. These features were peripheral blood eosinophil count greater than or equal to 300 cells/ μL or greater than or equal to 500 cells/ μL , 2 or more clinically significant exacerbations per previous year, and nasal polyps, as determined by phase II and phase III clinical trials on mepolizumab for asthma.^{9,10}

Statistical analysis

The characteristics of each group were summarized using descriptive statistics and compared across the groups using ANOVA for continuous measures and the Pearson chi-square test or the Fisher exact test for categorical measures. When overall ANOVA tests were significant, pairwise comparisons were made using Tukey's Honestly Significant Difference (HSD) method. Comparisons between subjects with greater than or equal to 500 eosinophils/ μL and less than 500/ μL were evaluated using independent sample *t* tests

(for parametric continuous variables), or Wilcoxon rank-sum tests (for variables that were not normally distributed), and using either the chi-square test or the Fisher exact test (for small expected numbers) for categorical variables. All statistical analyses were performed using JMP Pro, Version 13 (SAS Institute, Inc, Cary, NC, 1989-2007). A *P* value of less than .05 was considered statically significant.

RESULTS

Characteristics of the study population

Of 351 patients screened, 245 had SA as defined in the protocol of the retrospective chart review. Of these, 216 (88%) fulfilled the ERS/ATS criteria for SA and were included in the analysis (Figure 1). The characteristics of subjects with SA included versus those excluded in the final analysis are presented in Table E1 in this article's Online Repository at www.jaci-inpractice.org and are comparable, except for the ICS dose and the need for OCS.

The study cohort consisted of 59 children (mean age, 11 years) and 157 adults (mean age, 47 years). Most patients had severe uncontrolled asthma (94%), despite 155 (78%) requiring high ICS dose therapy plus at least a second controller, 132 (64%) were using OCS as maintenance therapy for more than half of the previous year, and 53 (25%) had already received treatment with omalizumab. Children were mostly males (59%) and showed a high prevalence of overweightness (ie, body mass index ≥ 85 th percentile, 21%) and obesity (27%). Adults were mostly female (64%), obese, and nonsmokers, and had AoA (59%) (Table I).

When compared with both adults with CoA and AoA, children were more likely to be treated with ICS at high dose ($P = .04$) and less likely to receive OCS as maintenance therapy ($P < .0001$). Children had also significantly greater lung function compared with both groups of adults (Table I), independent of the eosinophil count (data not shown), but they had no difference in terms of lifelong severe exacerbations (ie, hospitalization or intensive care unit admission or intubation) and peripheral blood eosinophils count (geometric mean, 151 vs 150 cells/ μL ; $P = \text{NS}$), when compared with adults with CoA (Table I). Adults with AoA, compared with adults with CoA, were older, and despite having a shorter duration of asthma, had similar lung function parameters, had fewer lifelong severe exacerbations ($P < .05$), while having significantly higher peripheral blood eosinophilia (geometric mean, 272 vs 150 cells/ μL ; $P = .01$) (Table I).

Primary outcome

When stratified by an eosinophil threshold of greater than or equal to 150 cells/ μL , 61% (95% CI, 54%-68%) of the study cohort showed an eosinophilic phenotype, with no significant difference by age of onset of asthma (Figure 2). The proportion qualifying for mepolizumab therapy based on an eosinophil threshold of greater than or equal to 150 cells/ μL was 49% (95% CI, 42%-56%), and it increased significantly, ranging from 33% in children to 60% in adults with AoA (Figure 2).

When a blood eosinophil cutoff was set at 300 cells/ μL , 41% (95% CI, 35%-48%) of patients showed an eosinophilic phenotype. Of these, 54% of adults with AoA had an eosinophil threshold of greater than or equal to 300 cells/ μL , compared with 26% of adult with CoA and 39% of children, with a significant difference noted between the 2 adult groups (Figure 2). When

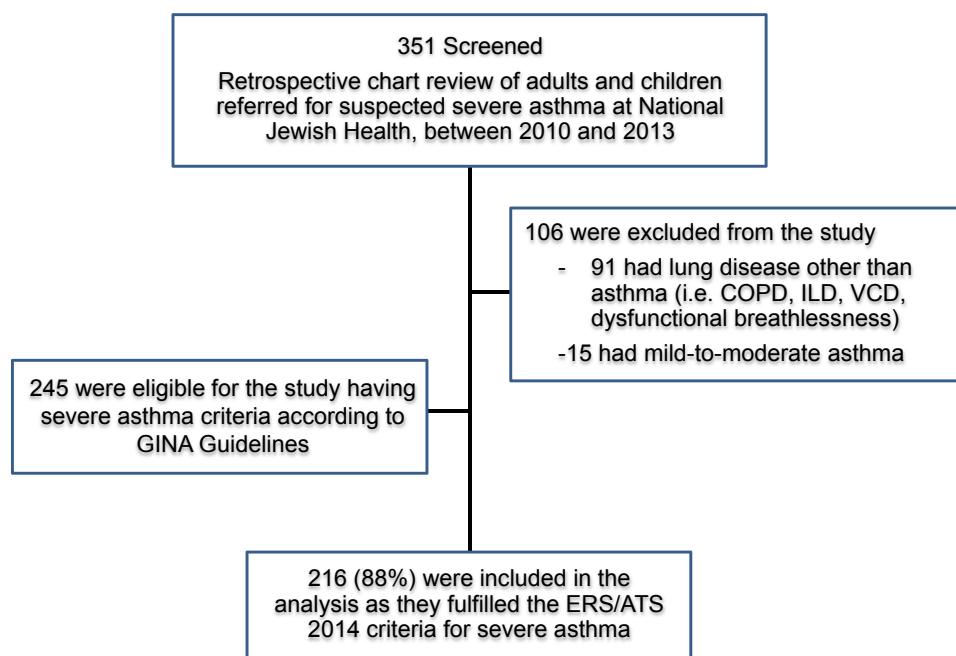


FIGURE 1. Flowchart of the study design. *COPD*, Chronic obstructive pulmonary disease; *GINA*, Global Initiative for Asthma; *ILD*, interstitial lung disease; *VCD*, vocal cord dysfunction.

stratified by an eosinophil threshold of greater than or equal to 300 cells/ μ L, the proportion qualifying for mepolizumab treatment was 34% (95% CI, 28%–41%). Of these, adults with AoA showed significantly higher treatment eligibility with mepolizumab than did both adults with CoA and children (47% vs 26% vs 24%, respectively; $P = .005$).

Among mepolizumab-eligible patients, 32% (if ≥ 150 cells/ μ L) or 35% (if ≥ 300 cells/ μ L) were being treated with or had been treated with omalizumab. Subjects requiring maintenance OCS therapy had lower blood eosinophil counts, lower proportion of subjects with eosinophil thresholds of greater than or equal to 150 cells/ μ L and greater than or equal to 300 cells/ μ L, and were less likely to be eligible for mepolizumab based on an eosinophil threshold of greater than or equal to 300 cells/ μ L (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

Secondary outcome

With regard to the prevalence of phenotypic features that favor mepolizumab therapy, although there was no difference in terms of acute exacerbations per previous year among the 3 groups, adults with AoA were significantly more likely to self-report nasal polyps, and showed a greater proportion of greater than or equal to 300 blood eosinophils/ μ L and 2 or more exacerbations requiring acute OCS than did both adults with CoA and children (Figure 3).

Subjects with blood eosinophil count of greater than or equal to 500 cells/ μ L had more nasal polyps (23% vs 10%; $P = .02$), were treated with higher ICS dose (mean fluticasone equivalent dose 1029 vs 902 μ g; $P = .03$), had lower lung function parameters (mean % predicted FEV₁ 56.6% vs 68.1%; $P = .007$), and showed an AoA predominance (Figure 3), compared with those with less than 500 cells/ μ L. Patients with greater than or

equal to 500 cells/ μ L tended to have similar exacerbation rate per previous year than did those with less than 500 cells/ μ L (mean number of OCS bursts, 7.7 vs 6.6; $P = \text{NS}$).

DISCUSSION

By using an extensive database of adults and children with ERS/ATS-defined SA evaluated at a tertiary university hospital, we characterized patients by the age of onset of asthma and determined the proportion of subjects with an eosinophilic phenotype who would be eligible for mepolizumab therapy. In addition, we evaluated the prevalence of phenotypic features that favor treatment with mepolizumab. In our cohort, based on blood eosinophil count of either greater than or equal to 150 cells/ μ L or greater than or equal to 300 cells/ μ L, 61%/41% had an eosinophilic phenotype, while 49%/34% were eligible for mepolizumab therapy. A greater proportion of adults with AoA had eosinophilic asthma, were mepolizumab eligible, and had indicators for mepolizumab therapy such as nasal polyps and eosinophil count of greater than or equal to 500 cells/ μ L, compared with both children and adults with CoA. We only included children 12 years or older in our analysis of mepolizumab eligibility because this is the current indicated age for mepolizumab therapy in the United States. When all children were included in the analysis, the percentage eligible based on eosinophil count and exacerbation frequency increased substantially to 56%. Thus, if mepolizumab were to become available in children 6 years or older in the United States as it is in Europe, more than 50% of children would have been eligible.

Those with SA with baseline eosinophil counts of greater than or equal to 150 cells/ μ L have some element of corticosteroid insensitivity, as type 2 cytokines and eosinophils are very responsive to the suppressive effects of corticosteroids in most

TABLE I. Characteristics of patients with SA by age and age of onset of asthma

Characteristic	All	Children	Adults with CoA	Adults with AoA	P value
No. of patients	216	59 (27)	64 (30)	93 (43)	NS
Sex: female, n (%)	124 (57)	24 (41)	42 (66)*	58 (62)*	.009
Age (y), mean $\pm$ SD	37 $\pm$ 20	11 $\pm$ 3.6	40 $\pm$ 12.5*	51 $\pm$ 12*†	< .001
Duration of asthma (y), mean $\pm$ SD	18.7 $\pm$ 15	9 $\pm$ 4	35 $\pm$ 13*	13 $\pm$ 11*†	< .001
BMI (kg/m ²), mean $\pm$ SD	29.4 $\pm$ 8.8	22 $\pm$ 6	32 $\pm$ 8*	32 $\pm$ 8*	< .001
BMI $\geq$ 30 kg/m ² or 95 ^o pc, n (%)	94 $\pm$ 44	16 $\pm$ 27	32 $\pm$ 52*	46 $\pm$ 49*	.01
Smokers, n (%)	10 (5)	0 (0)	6 (9)*	4 (4)*	.04
ICS, n (%)	198 (92)	57 (97)	56 (87)	85 (91)	NS
ICS dose (fluticasone equivalent) (μ g/d), mean $\pm$ SD	936 $\pm$ 353	851 $\pm$ 268	976 $\pm$ 389	967 $\pm$ 372	NS
LABA, n (%)	167 (77)	49 (83)	52 (81)	66 (71)	NS
High ICS dose, n (%)	160 (81)	52 (91)	43 (77)*	65 (76)*	.04
High ICS dose and $\geq$ 1 controller, n (%)	155 (78)	51 (89)	43 (77)*	61 (72)*	.04
Maintenance OCS, n (%)	134 (62)	18 (30)	50 (78)*	66 (70)*	< .001
Omalizumab, n (%)	53 (25)	13 (22)	13 (20)	27 (29)	NS
Omalizumab failed, n (%)	16 (30)	8 (61)	2 (15)*	6 (22)*	.027
FVC (% predicted), mean $\pm$ SD	80 $\pm$ 21	99.9 $\pm$ 17.2	72.9 $\pm$ 20.9*	74.7 $\pm$ 16.5*	< .001
FEV1 (% predicted), mean $\pm$ SD	65 $\pm$ 24	84.6 $\pm$ 20.6	57.6 $\pm$ 24.1*	60.8 $\pm$ 20*	< .001
FEV ₁ /FVC ratio, mean $\pm$ SD	66 $\pm$ 14	73.1 $\pm$ 11.3	62.5 $\pm$ 14.7*	64.1 $\pm$ 14.5*	.0007
FEF ₂₅₋₇₅ (% predicted), mean $\pm$ SD	44 $\pm$ 30	60.6 $\pm$ 31	34.1 $\pm$ 29.5*	42.9 $\pm$ 28*	.003
Blood eosinophil, (cell/ μ L), mean $\pm$ SD‡	193 $\pm$ 404	150 $\pm$ 215	150 $\pm$ 333	272 $\pm$ 500*†	.003
Blood eosinophil $\geq$ 150 cell/ μ L, n (%)	126 of 206 (61)	35 of 57 (61)	32 of 62 (52)	59 of 87 (68)	NS
Blood eosinophil $\geq$ 300 cell/ μ L, n (%)	85 of 206 (41)	22 of 57 (39)	16 of 62 (26)	47 of 87 (54)*†	.002
OCS bursts/past year, n $\pm$ SD	7 $\pm$ 5	8 $\pm$ 4.5	6.7 $\pm$ 4.3	6.5 $\pm$ 4.7	NS
Uncontrolled asthma, n (%)§	196 of 209 (94)	57 of 58 (98)	58 of 61 (95)	81 of 90 (90)	NS
Hospitalization lifelong, n (%)	152 of 210 (72)	49 of 57 (86)	51 of 62 (82)	52 of 91 (57)*†	< .001
Intensive care unit (lifelong), n (%)	71 of 212 (33)	29 of 58 (50)	27 of 62 (43)	15 of 92 (16)*†	< .001
Intubated (lifelong), n (%)	44 of 212 (21)	16 of 58 (28)	19 of 62 (31)	9 of 92 (10)*†	.002

BMI, Body mass index; FEF₂₅₋₇₅, forced expiratory flow at 25% to 75% of forced vital capacity; FVC, forced vital capacity; LABA, long-acting β_2 -agonist.

Shown are n (%) for categorical variables, and mean $\pm$ SD for continuous variables. Statistically significant ($P < .05$) differences between groups are depicted in bold font.

* $P < .05$ vs children.

† $P < .05$ vs adults with CoA.

‡Geometric mean on natural Log scale.

§If ≥ 2 OCS bursts/past year.

patients with asthma.²⁰ In contrast, patients with corticosteroid-resistant asthma have blunted responses to the suppressive effects of corticosteroids.²¹ That a smaller percentage of children were eosinophilic may be related to the observation that lymphocytes from children are more responsive to the suppressive effects of corticosteroids compared with those from adults with SA.²² Severe Asthma Research Program (SARP) III compared the clinical, physiologic, and inflammatory profiles of 111 children and 313 adults with SA to 77 children and 213 adults without SA.²³ Fewer children with SA required maintenance OCS while having better lung function and higher eosinophil counts compared with adults with SA. The children in our study had lower eosinophil counts than in SARP III. Because a greater proportion of children in our cohort required maintenance OCS therapy (30% vs 13.5%) and because circulating eosinophils are responsive to the suppressive effects of corticosteroids,²⁰ greater OCS exposure may explain this difference. That adults with CoA had lower eosinophil counts compared with adults with AoA may be explained by the observation that factors that help drive eosinophilic asthma (eg, degree of allergen sensitization) wane with age as noted in SARP III where advancing age was found to be associated with lower rates of aeroallergen sensitization among those with SA.²³

mAbs, in particular those targeting the T_H2-high phenotypes, are being increasingly considered as treatment options for patients with severe refractory asthma. However, most of these biologic therapies have been studied in adult populations, with little information regarding the response of these medications in children in addition to the proportion of children who would be eligible for biologic agents.²⁴ Furthermore, there is limited data characterizing the proportion of adults with SA who are eligible for mepolizumab, especially when stratified by the age of onset.

This is the first study to describe the prevalence of mepolizumab-eligible SA based on age and age of asthma onset. In the Belgian SA registry that enrolled only adults, 30% fulfilled the same eligibility criteria for mepolizumab used in our study.²⁵ Despite including adults with both early and late-onset asthma, these results were not stratified for the age of onset. Fewer subjects in the Belgian cohort required maintenance OCS, and they averaged fewer courses of OCS for acute exacerbations.²⁵ The Identification and Description of Severe Asthma Patients (IDEAL) study, which recruited subjects with SA,²⁶ found 20% to have met mepolizumab phase III clinical trial inclusion criteria and despite including both adolescents and adults, the results were not stratified by age. Although reporting a similar blood eosinophil count, the IDEAL cohort

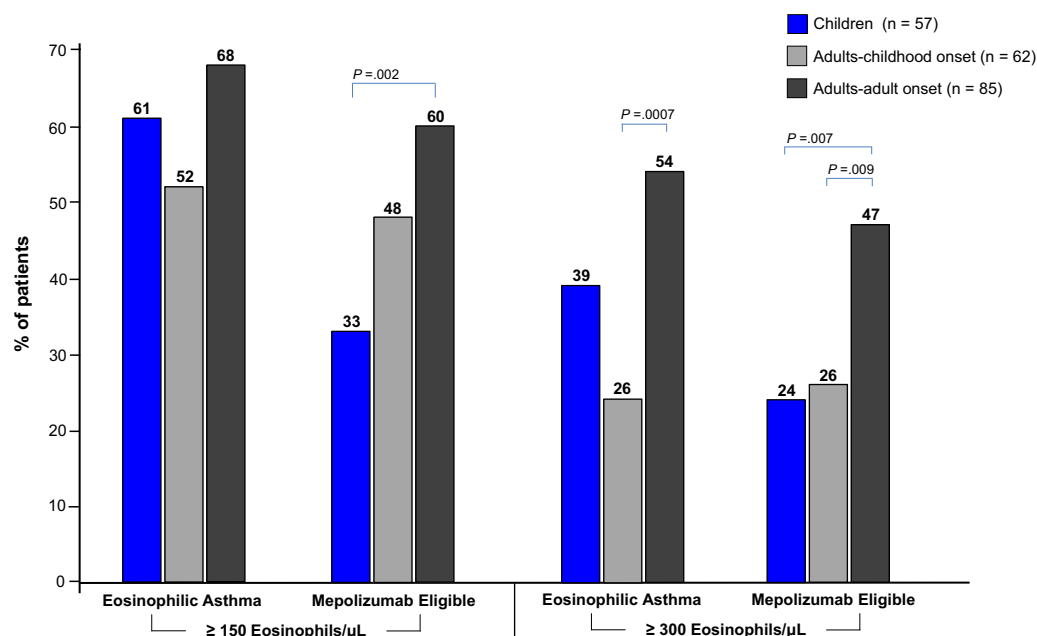


FIGURE 2. Prevalence of severe eosinophilic asthma and eligibility for mepolizumab by age and age of onset, using different blood eosinophil thresholds.

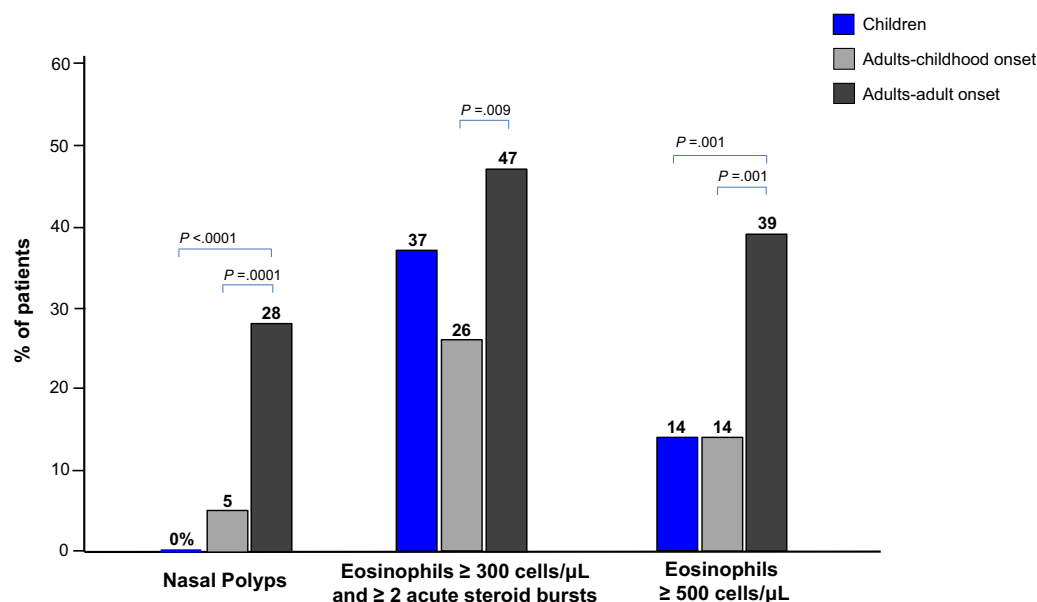


FIGURE 3. Prevalence of phenotypic features that favor treatment with mepolizumab by age and age of onset.

had a significantly lower proportion of severe uncontrolled patients compared with our population, which resulted in a lower prevalence of mepolizumab-eligible patients. The Finnish Seinajoki Adult Asthma Study (SAAR) cohort, which exclusively focused on AoA, reported a prevalence of ERS/ATS-defined SA of 5.9% (95% CI, 2.9%-9.4%), with 27% of these fulfilling the eligibility criteria for mepolizumab.² However, these results are difficult to compare with our findings due to different patient cohorts (general *vs* severe asthmatic patients).²

Given that patients with SA can be phenotypically similar yet have different underlying endotypes, recent research has focused on the identification of biomarkers to predict response to biologics.¹³ The Dose Ranging Efficacy and Safety with Mepolizumab in Severe Asthma (DREAM) study, a large phase IIb trial of mepolizumab for SA, enrolled 621 adult patients with asthma with frequent asthma exacerbations and evidence of eosinophilic inflammation (ie, sputum eosinophil count $\geq 3\%$, a fraction of exhaled nitric oxide [FENO] value of ≥ 50 ppb, peripheral blood eosinophil count of ≥ 300 cells/ μ L, or prompt

deterioration in symptoms when ICS and/or OCS was tapered (<25%). DREAM participants were largely adults with AoA, with a significant minority having nasal polyposis. Response to mepolizumab was predicted by only 2 variables, which were peripheral blood eosinophil count and exacerbations.⁹ A subsequent cluster analysis of the DREAM study found 2 subgroups of adult-onset asthmatic patients that showed the greatest response to mepolizumab: (1) patients with eosinophilia, low airway reversibility, sinusitis, and nasal polyposis, and (2) obese females with eosinophilia and higher airway reversibility.²⁷ In our population, adults with AoA showed higher eosinophil count and were more likely to have uncontrolled eosinophilic asthma and nasal polyps compared with the other 2 groups. A post hoc analysis of the DREAM and Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) (phase IIB and phase III) studies involving more than 1000 patients with SA found a relationship between baseline eosinophil count and exacerbations in the previous year, with 1.94 exacerbations in those with a baseline eosinophil count of greater than or equal to 150 cells/ μ L versus 2.49 exacerbations in subjects with greater than or equal to 500 cells/ μ L.²⁸ In addition, the exacerbation rate reduction with mepolizumab progressively increased from 52% in subjects with a baseline eosinophil count of greater than or equal to 150 cells/ μ L to 70% in those with baseline eosinophil counts of greater than or equal to 500 cells/ μ L, suggesting that subjects with eosinophil counts of greater than or equal to 500 cells/mL are likely to have the most robust response to this form of therapy. In our cohort, adults with AoA were significantly more likely to have greater than or equal to 500 eosinophils/ μ L compared with both children and adults with CoA (Figure 3). Therefore, AoA would seem the SA phenotype to derive the greatest benefit from mepolizumab therapy.

Whether eosinophilia is associated with diminished lung function has yielded conflicting results.^{14,23,29-31} We found no correlation between eosinophils in our cohort and FEV₁. A cluster analysis of children with SA enrolled in SARP also found no association between eosinophils and lung function impairment.¹⁴ This finding was reinforced in SARP III where children with SA, despite having lower baseline lung function, had similar circulating eosinophil counts as children with non-SA.²³ Thus, the association between eosinophilic inflammation and lung function decline is complex and yet to be fully elucidated.

This study has a number of limitations. First, given its retrospective nature, the availability of data for all patients, such as atopic status, FENO levels, and postbronchodilator response in FEV₁, was limited. However, none of these parameters are required by current eligibility criteria for mepolizumab approved by the Food and Drug Administration and the European Medicine Agency. Indeed, the DREAM trial showed that the efficacy of mepolizumab was independent of atopic status, IgE concentration at baseline, FEV₁ levels, and acute bronchodilator response.^{9,32} Although an increased FENO (≥ 50 ppb) was an entry criterion in the DREAM trial, treatment with mepolizumab did not reduce FENO levels, while dramatically decreasing both exacerbation frequency and eosinophil counts.^{9,33} This is not unexpected considering that FENO is a marker of T_H2 allergic inflammation primarily mediated by IL-13 and IL-4.³³ Supporting this contention comes data evaluating the IL-4R α antagonist dupilumab, which demonstrated significant reductions in FENO levels in patients with severe eosinophilic asthma while having no effect on blood eosinophil

counts.³⁴ Second, recall bias is a significant issue especially in retrospective studies when patients attempt to recall events in the distant past. To address this, all subjects were interviewed by the same physician (J.D.S.) who attempted to document age of onset by medical record review whenever possible. A third potential limitation comes from the cutoff point used to define CoA (<18 years) versus AoA (≥ 18 years) especially as other studies have used less than 12 years to describe “early-onset” and 12 years or more to describe “late-onset” asthma.^{6,35} Eighteen years was chosen because it is often used to distinguish adults from children and had been used in a previous publication from our group before the term “early- and late-onset” asthma was coined.³⁵ Fourth is the concern regarding the generalizability of our results compared with the wider population of patients with SA. Because this was a single-site study where many of the patients with most SA in the country are evaluated, our cohort likely constitutes the patients with most SA, many of which have some degree of steroid insensitivity.³⁶ Finally, we included in our analysis patients who were actively or formerly and unsuccessfully treated with omalizumab, which could have impacted the exacerbation rate and mepolizumab eligibility. However, the proportion of omalizumab-treated patients was similar across the 3 age groups. Also, when excluding the subgroup of patients who were actively treated with omalizumab at the time of the first visit, the prevalence of uncontrolled eosinophilic asthma and mepolizumab eligibility among the 3 groups was fully comparable with the ones in the total population (data not shown). This is in line with findings from Albers et al,²⁶ who reported that current treatment with omalizumab did not modify the proportion of mepolizumab-eligible patients with SA.

In summary, up to 60% of adults with SA would be eligible for mepolizumab therapy, with a smaller proportion of children with SA being eligible. This discrepancy comes largely from the fact that mepolizumab is currently approved in the United States only for use in children 12 years or older. If children 6 years and older were included (the age approved for mepolizumab use in Europe), the percentage of children eligible increases substantially. Among adults, those with AoA appear to comprise phenotypic features that favor treatment with mepolizumab, including greater eosinophilia and nasal polyposis compared with adults with CoA. Because children with SA often have concurrent allergen sensitization and eosinophilia or either alone, studies evaluating mepolizumab in children must be performed to determine the response profile of anti-IL-5 targeted therapies in this group of patients with SA.

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TABLE E1. Demographic characteristics of patients with SA included vs those excluded in the final analysis

Characteristic	SA ERS/ATS included in the analysis (n = 216)	SA non-ERS/ATS excluded (n = 29)
Sex: female, n (%)	57	59
Children: Adults, %	27:73	45:55
Age (y), mean $\pm$ SD	32 $\pm$ 21	37 $\pm$ 20
Asthma onset before 18 y, n (%)	123 (57)	18 (62)
Duration of asthma (y), mean $\pm$ SD	18.7 $\pm$ 15	14.6 $\pm$ 15
BMI (kg/m ²), mean $\pm$ SD	29.4 $\pm$ 8.8	28.3 $\pm$ 8.8
Smokers, n (%)	10 (5)	0 (0)
Nasal polyps (self-referred), n (%)	29 (13)	0 (0)
ICS, n (%)	198 (92)	28 (97)
ICS dose (fluticasone equivalent) (μ g/d), mean $\pm$ SD	936 $\pm$ 353	508 $\pm$ 224
ICS and LABA, n (%)	164 (76)	17 (59)
Maintenance OCS, n (%)	134 (62)	0 (0)
Omalizumab, n (%)	53 (25)	0 (0)
FVC (% predicted), mean $\pm$ SD	80 $\pm$ 21	82 $\pm$ 18
FEV ₁ (% predicted), mean $\pm$ SD	65 $\pm$ 24	69 $\pm$ 23
FEV ₁ /FVC ratio, mean $\pm$ SD	66 $\pm$ 14	67 $\pm$ 14
FEF ₂₅₋₇₅ (% predicted), mean $\pm$ SD	44 $\pm$ 30	44 $\pm$ 31
Blood eosinophil (cells/ μ L), mean $\pm$ SD*	193 $\pm$ 404	185 $\pm$ 233
Blood eosinophil $\geq$ 150 cells/ μ L, n (%)	126 of 206 (61)	17 of 27 (63)
Blood eosinophil $\geq$ 300 cells/ μ L, n (%)	85 of 206 (41)	10 of 27 (37)
OCS bursts/past year, n $\pm$ SD	7 $\pm$ 5	6 $\pm$ 5
Hospitalization, n (%)	152 (72)	19 (65)
ICU, n (%)	71 (33)	7 (24)
Intubation, n (%)	44 (21)	2 (7)
Uncontrolled asthma, n (%)†	196 of 209 (94)	24 of 29 (83)
Eosinophilic uncontrolled asthma, n (%)‡	114 of 204 (56)	13 of 27 (48)
Eosinophilic uncontrolled asthma, n (%)§	77 of 204 (38)	9 of 27 (33)

BMI, Body mass index; FEF₂₅₋₇₅, forced expiratory flow at 25% to 75% of forced vital capacity; FVC, forced vital capacity; ICU, intensive care unit; LABA, long-acting β_2 -agonist.

Shown are n (%) for categorical variables and mean $\pm$ SD for continuous variables. The bold font indicates a statistically significant difference ($P < .05$) between the 2 columns (SA ERS/ATS included in the analysis vs SA non-ERS/ATS excluded).

*Geometric mean on natural Log scale.

†If $\geq$ 2 OCS bursts/past year.

‡If $\geq$ 150 eosinophils/ μ L and $\geq$ 2 OCS bursts/past year.

§If $\geq$ 300 eosinophils/ μ L and $\geq$ 2 OCS bursts/past year.

TABLE E2. Characteristics of the study population (n = 216) by treatment with OCSs or omalizumab

Characteristic	Maintenance OCS		Omalizumab*	
	No	Yes	No	Yes
No. of patients, n (%)	82 (38)	134 (62)	162 (75)	53 (25)
Sex: female, n (%)	45 (55)	79 (59)	94 (58)	29 (58)
Child: Adult (%)	50 : 50	13 : 87	28 : 72	24: 75
Age (y), mean $\pm$ SD	28 $\pm$ 19	43 $\pm$ 17	37 $\pm$ 20	37 $\pm$ 17
Asthma onset before 18 y, n (%)	55 (67)	68 (51)	97 (60)	26 (49)
Duration of asthma (y), mean $\pm$ SD	14 $\pm$ 10	21 $\pm$ 17	19 $\pm$ 16	17 $\pm$ 11
BMI (kg/m ²), mean $\pm$ SD	25.5 $\pm$ 8	31.7 $\pm$ 8	28.8 $\pm$ 9	31 $\pm$ 9
Smokers, n (%)	2 (2)	8 (6)	7 (4)	3 (7)
Nasal polyps (self-referred), n (%)	7 (8)	22 (16)	19 (12)	10 (19)
ICS, n (%)	81 (99)	117 (87)	147 (90)	50 (94)
ICS dose (fluticasone equivalent) (μ g/d), mean $\pm$ SD	980 $\pm$ 326	904 $\pm$ 368	904 $\pm$ 319	1037 $\pm$ 424
ICS and LABA, n (%)	71 (87)	93 (69)	120 (74)	43 (81)
FVC (% predicted), mean $\pm$ SD	88 $\pm$ 20	74 $\pm$ 20	79 $\pm$ 21	81 $\pm$ 20
FEV ₁ (% predicted), mean $\pm$ SD	75 $\pm$ 24	59 $\pm$ 21	66 $\pm$ 24	62 $\pm$ 23
FEV ₁ /FVC ratio, mean $\pm$ SD	70 $\pm$ 13	63 $\pm$ 13	66 $\pm$ 13	63 $\pm$ 15
FEF ₂₅₋₇₅ (% predicted), mean $\pm$ SD	59 $\pm$ 33	35 $\pm$ 24	45 $\pm$ 29	42 $\pm$ 33
Blood eosinophils (cells/ μ L), mean $\pm$ SD†	235 $\pm$ 418	169 $\pm$ 393	183 $\pm$ 404	221 $\pm$ 406
Blood eosinophil $\geq$ 150 cells/ μ L, n (%)	57 of 81 (70)	69 of 125 (55)	91 of 154 (59)	34 of 51 (67)
Blood eosinophil $\geq$ 300 cells/ μ L, n (%)	42 of 81 (52)	43 of 125 (34)	59 of 154 (38)	25 of 51 (49)
OCS bursts/past year, n $\pm$ SD	8 $\pm$ 5	6 $\pm$ 4	7 $\pm$ 4	8 $\pm$ 5
Hospitalization, n (%)	58 (72)	94 (73)	113 (72)	39 (73)
ICU, n (%)	26 (32)	45 (35)	48 (30)	23 (43)
Intubation, n (%)	16 (19)	28 (21)	29 (18)	15 (28)
Uncontrolled asthma, n (%)‡	78 (95)	118 (93)	147 (93)	48 (96)
Eosinophilic uncontrolled asthma, n (%)§	55 of 81 (68)	59 of 123 (48)	81 of 152 (53)	32 of 51 (63)
Eosinophilic uncontrolled asthma, n (%)	41 of 81 (51)	36 of 123 (29)	52 of 152 (34)	24 of 51 (47)
Mepolizumab eligibility $\geq$ 150 eosinophils/ μ L, n (%)	46 of 81 (57)	54 of 123 (44)	67 of 152 (44)	32 of 51 (63)
Mepolizumab eligibility $\geq$ 300 eosinophils/ μ L, n (%)	35 of 81 (43)	35 of 123 (28)	45 of 152 (30)	24 of 51 (47)

BMI, Body mass index; FEF₂₅₋₇₅, forced expiratory flow at 25% to 75% of forced vital capacity; FVC, forced vital capacity; ICU, intensive care unit; LABA, long-acting β_2 -agonist.

Shown are n (%) for categorical variables and mean $\pm$ SD for continuous variables. Statistically significant *P* values (*P* < .05) are shown in bold.

*Both actively or formerly and unsuccessfully treated with omalizumab.

†Geometric mean on natural Log scale.

‡If $\geq$ 2 OCS bursts/past year.

§If $\geq$ 150 eosinophils/ μ L and $\geq$ 2 OCS bursts/past year.

||If $\geq$ 300 eosinophils/ μ L and $\geq$ 2 OCS bursts/past year.