

Disparate Eosinophilic Phenotypes with Age: Impact on Eligibility for Anti-IL-5 Therapies in Severe Asthma



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The advent of biological therapies targeting type 2 inflammation has great promise in the treatment of inadequately controlled asthma. However, biological therapies are expensive, and most involve repeated visits to provider offices for safe administration. An important barrier to the fulfillment of a “precision medicine” approach to asthma is gaps in knowledge as to how to optimally match dominant patterns of inflammation found in specific patients to the selection of a specific biological therapy. In this issue of the *Journal of Allergy and Clinical Immunology: In Practice*, Comberiati et al¹ report that most adults and approximately one-third of children with severe eosinophilic asthma meet criteria for treatment with mepolizumab, an anti-IL-5 biological. An important finding in the study was that adult patients with asthma onset during adulthood qualify more often for mepolizumab treatment compared with adults with childhood-onset asthma.

The population most providers consider for treatment with a biological therapy has “severe asthma,” inadequately controlled despite high-intensity treatment with inhaled and/or oral corticosteroids.^{2,3} A common pattern of inflammation in both adults and children with severe asthma is type 2^{HIGH}, characterized by peripheral blood eosinophilia, driven by genetic and environmental factors including allergen (IgE-mediated) sensitization and expansion of T_H2 lymphocytes. This has led to the development of biological therapies targeting type 2 inflammatory pathways including omalizumab (anti-IgE), mepolizumab and reslizumab (both anti-IL-5), benralizumab (anti-IL-5 α receptor), and dupilumab (IL-4 α receptor) to improve symptom control and reduce exacerbations. Patient selection is linked to blood biomarkers including total IgE or the absolute blood eosinophil count. Appropriately selected patients respond very well to these therapies as adjuncts to standard care.^{4–7} However, many questions remain, including consideration of patients with

neutrophil-dominated patterns of inflammation, and disparate patterns of inflammation with age, specifically eosinophilia with allergen sensitization, the dominant pattern in children, and eosinophilia in the absence of allergen sensitization, a common pattern in adult women. Comberiati et al found that up to 60% of adult patients with severe asthma fit criteria for an anti-IL-5 biological mepolizumab, more so than children, and adults with adult-onset asthma and nasal polyposis comprised most eligible patients.¹

We advise caution before assuming that the findings of Comberiati et al can be applied to general practice. First, this was a single-center study, conducted in a third-line, severe asthma center, with a treatment-refractory patient sample. It is highly likely that the poorly controlled asthma population included in the study represents a more severe phenotype than in a community-based clinic. Hence, the proportion of patients eligible for mepolizumab was likely greater than would be found in a typical community setting. Second, when considering biological treatments, remedial factors that inform asthma control should be addressed before assigning a diagnosis of “severe, treatment-refractory asthma.” Such factors include mistakes in inhaler technique, poor adherence, unmitigated allergen exposure, and inadequate management of comorbid conditions.^{8,9} In asthma centers integrating this approach, it is estimated that as many as 50% of patients who present with “problematic asthma” have improvements in symptom control after remedial factors are addressed. Third, Comberiati et al applied the same criteria for mepolizumab eligibility to children and adults. In so doing, they report 2 features of type 2 inflammation, nasal polyposis and absolute blood eosinophil counts greater than 500 cells/ μ L, as more prevalent in adults compared with children. However, disparate patterns of type 2 inflammation are reported with age. In keeping with the experience of practicing allergists and pulmonologists and as reported in 2 large European and US cohort studies, children with severe asthma have a significant type 2 inflammatory burden based on blood eosinophilia and a high level of allergen sensitization.^{10,11} Although it does occur, children with severe asthma are less likely than adults to have eosinophilia in the absence of allergen sensitization, and nasal polyposis is an unusual finding until late adolescence.^{11,12} Fourth is the vexing problem of recall bias in obtaining accurate historical information both in practice and in clinical research. Adults questioned about atopic history and onset of asthma may not recall with accuracy the precise age of onset of their symptoms,¹³ and in practice, estimates of age of onset of asthma symptoms in queries directed at adults are older than those obtained when questions are directed at parents with regard to age of symptom onset in their children.

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Another important consideration in the application of Comberiati et al to general practice is the reliability of a single absolute blood eosinophil count as the basis for mepolizumab eligibility. Blood eosinophil numbers fluctuate with time in severe asthma,¹¹ and typically decrease with corticosteroid therapy but increase with seasonal allergen exposure. Although blood eosinophil counts are the basis for consideration of anti-IL-5 therapies, they do not reliably predict granulocytic patterns in lung fluid and correlate poorly with lung fluid eosinophil counts.¹² We propose that repeated measures of blood eosinophils interpreted with regard to clinical symptoms, treatment, and allergen seasons are a more robust means to estimate anti-IL-5 eligibility. Although widely touted by the manufacturers of biologicals, the status of the absolute blood eosinophil count as a robust marker of treatment response for an anti-IL-5 drug in patients with severe asthma is still not clear. Questions to be answered relate to differences between blood and lung inflammatory environments, disparate inflammatory patterns with age, corticosteroid treatment, and allergen exposures on eosinophil production and survival, and the complex phenotypic heterogeneity of severe asthma. Finally, an important “elephant in the room” typically not considered in selecting targeted therapies is the interaction of lower respiratory tract infections and inflammatory patterns in asthma. Particularly in children, infection with human rhinovirus significantly augments type 2 inflammatory responses and eosinophilia.^{12,14}

Given the significant cost and systemic nature of biological therapies, improved patient and treatment selection practices based on age, phenotypic features, and biomarkers are urgently needed. First, major advances must be made in understanding specific asthma endotypes linked to molecular mechanisms and the natural course of disease. Head-to-head comparison trials of different biologicals in carefully characterized samples need to be done, and we would exhort regulatory agencies to require these in the future. Major advances must be made by implementing solid, internationally aligned difficult-to-control asthma programs, different for children and adults. These should lead to detailed assessment of remediable factors in these patients and prevent overtreatment with steroids and biologics.¹⁵ Finally, we have to consider that even though children with severe asthma place a great burden on health care systems the world over, biological therapies are developed for and marketed primarily to adults. This is a clear example of health care injustice, and can be fixed only with an integrated approach among providers,

regulatory agencies, pharmaceutical companies, and the payers of care to improve safe access to biological therapies in what really is a highly treatable disease.

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