

Spotlight

Precision medicine in pediatric severe asthma:
Targeted blockade of type 2 inflammationAllyson S. Larkin¹ and Sally E. Wenzel^{2,*}¹Division of Allergy and Immunology, Department of Pediatrics, University of Pittsburgh Medical Center, Pittsburgh, PA USA²Department of Environmental and Occupational Health, School of Public Health, University of Pittsburgh, Pittsburgh, PA USA*Correspondence: swenzel@pitt.edu<https://doi.org/10.1016/j.xcrm.2022.100570>

A study by Bacharier et al. demonstrated that children with uncontrolled moderate-to-severe asthma with elevated type 2 biomarkers who received dupilumab had fewer exacerbations and better lung function.¹ These results highlight precision medicine approaches in pediatric asthma.

Our understanding of asthma has dramatically improved over the last 20 years. Perhaps most striking is the recognition that asthma is a heterogeneous disease driven by complex biologic processes that presents with combinations of cough, wheeze, airway obstruction, and inflammation.² Age at presentation can span a lifetime and severe or poorly treated disease can still lead to death. While many children and adults have mild to moderate disease controlled by inhaled corticosteroids, a portion have severe disease that associates with poorer quality of life, increased healthcare utilization, and systemic corticosteroid dependence.³ Recent pharmaco-immunologic advances have greatly improved the lives of specific types of severe asthmatic adult and pediatric patients, highlighting the importance of understanding this heterogeneity.

Clinical guidelines have shifted from treating asthma using a “one size fits all” approach to emphasizing the importance of assessing asthma phenotypes.^{2,4} A remarkable advance has been the ability to differentiate type 2 from non-type 2 inflammatory disease.⁵ Targeting IL-4, IL-5, and IL-13, canonical type 2 cytokines, produced by Th2 cells and other innate immune cells, led to rapid growth of biologic therapies. By using biomarkers (blood eosinophils and fraction

exhaled nitric oxide [FeNO] in exhaled breath) physicians can generally predict response to type 2-directed therapies.³ Intriguingly, total and specific IgE levels to environmental allergens, considered hallmarks of allergic disease and type 2 biomarkers, have more limited utility in severe asthmatic adults than children. Whereas most severe pediatric asthma has a type 2 high phenotype, allergic sensitization is generally a negative predictor of severe asthma in adults.⁶ This suggests that immune differences may exist in adults and children and that efficacy of biologic therapy in one group may not translate to the other (Figure 1).

Realization that the umbrella term for asthma could be differentiated into at least two biomolecular phenotypes on the basis of readily obtainable biomarkers contributed to development of six biologic monoclonal antibodies.⁵ The treatments target IL-5/5R, IL-4R α , IgE, and TSLP. Five of these therapies are approved for use in adolescents³ 12 years old and up and three are available for children³ 6 years old and up. Anti-IgE therapy was the first biologic approved for children, with large studies of hundreds of children demonstrating efficacy and safety, showing reductions in exacerbations and inhaled corticosteroid use. Contrast this to anti-IL-5 and anti-TSLP therapies that have small numbers of adolescents enrolled and even smaller numbers of young children.⁷ Thus, data to support efficacy and safety of biologics in children are extremely limited, illustrating the crucial need for more studies and the impact of this recent publication.

Bacharier’s study¹ offers substantial novel insight into the use of dupilumab in pediatrics. Dupilumab is a monoclonal antibody that binds to the IL-4R α , a receptor shared by both IL-4 and IL-13, which blocks signaling by both. When dimerized with the common gamma chain, IL-4 (alone) promotes Th2 cell differentiation and downstream IgE production.^{8,9} When present on smooth muscle and

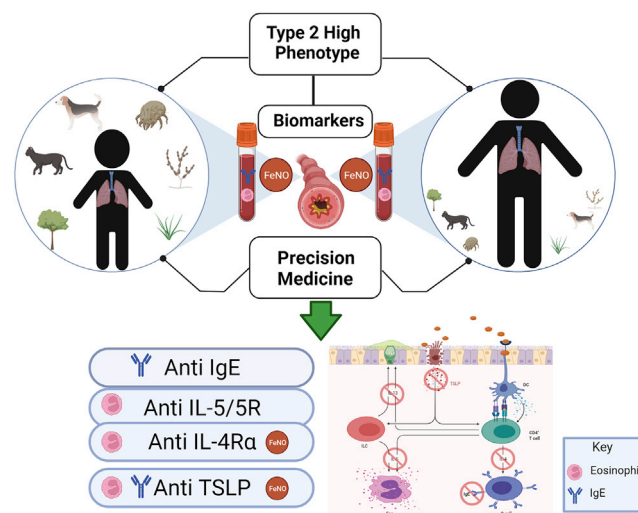


Figure 1. Biomarkers and biologic therapies for type 2 high asthma

Although both adults and children can have a type 2 high phenotype, allergic disease is more commonly associated with severe pediatric asthma. A blood sample measuring total and specific IgE as well eosinophils and measurement of FeNO can help predict response to various type 2 high targeted therapies. Created with [BioRender.com](https://www.biorender.com).



epithelial cells, IL-4R α dimerizes with the IL-13R α chain, binding both IL-4 and -13 to influence their function, in particular goblet cell differentiation. In adults with asthma, dupilumab is most effective in patients with elevated type 2 biomarkers (FeNO and blood eosinophils). It is also effective in other type 2-related diseases including chronic rhinosinusitis with nasal polyposis and atopic dermatitis.

The publication by Bacharier et al.¹ is a major contribution to the field of pediatric severe asthma. Importantly, it is a large study (408 children) and one of the few which targets young (6- to 11-year-old) patients. It uses a double blind and placebo-controlled design over a full year. The target population includes children with elevated type 2 biomarkers (blood eosinophils and FeNO). The primary endpoint is annualized rate of severe exacerbations, with the secondary endpoint change from baseline at week 12 in airway obstruction. Dupilumab is superior to placebo in all endpoints and importantly children had less exposure to systemic corticosteroids. There is a rapid onset of efficacy, with lung function improvements seen by week two. The safety profile is encouraging and similar to dupilumab in adults. However, there was one case of systemic eosinophilia. This side effect has been seen in about one-third of adults, typically as an asymptomatic lab finding but rarely, as in this case, associated with symptoms and prompting cessation of drug. As in adults, the mechanisms behind this eosinophilia remain an unanswered, intriguing, but troubling question. Overall, however, these findings support a precision medicine/biomarker-driven approach to treatment of children with severe asthma.

Despite these recent advances in severe asthma, there is a pressing need for more studies, particularly in children. This study was done primarily in White children (<7% were Black). Yet, in the

US, Puerto Rican and Black people are more likely to have asthma, with Black patients three times more likely to die from asthma than other groups. Diversity in clinical trials will help our understanding of treatment options.¹⁰ In addition, while head-to-head comparisons are unlikely, double-blind placebo-controlled efficacy studies of other biologics, particularly anti-IL-5 approaches in pediatric patients, are clearly needed, matched to biomarkers to identify the most responsive patients. Furthermore, we need a better understanding of duration of treatment, especially in children. Finally, given the profound impact on central immune pathways, it is important to learn whether nearly eliminating type 2 pathways in childhood can “reset” the immune system and lead to disease cures or conversely, whether inhibition of these biologic processes could potentially overshoot and cause immune deviation towards Th1/autoimmunity or cancer. The scientific community can use responses to these therapies to better understand human disease, particularly in children where the disease may persist for decades. The future of understanding and treating “severe asthmas” will benefit from a laser sharp focus on practicing precision medicine.

DECLARATION OF INTERESTS

S.E.W. is co-principal investigator on an investigator-initiated study of dupilumab with Regeneron. There are no other conflicts of interest.

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