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CME Review

Future of biologics in pediatric asthma

Optimizing response, early introduction, and equitable access to treatment

Ianthe R.M. Schepel, BMBCh, MPhil, MS*; Tina M. Banzon, MD†; Wanda Phipatanakul, MD, MS†

* Department of Pediatrics, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts
† Division of Allergy and Immunology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts

Key Messages

- There is an urgent need for more long-term efficacy and safety data for asthma biologics, particularly for children younger than 12 years of age.
- Patients are often eligible for multiple asthma biologics, but their comparative effectiveness and thus the optimal choice of treatment is largely unknown.
- Multi-omics research approaches have the potential to capture the complexity and heterogeneity of asthma pathogenesis on a molecular level, which could lead to more precise classification of asthma endotypes and phenotypes, along with the identification of new pediatric-specific biomarkers to more accurately predict and monitor response to biologics.
- The Preventing Asthma in High Risk Kids study is currently investigating whether early targeted inhibition of the type 2 inflammatory pathway with omalizumab may prevent the development of pediatric asthma.
- Inequities remain in access to biologic treatment and research participation for low-income and racial/ethnic minoritized groups, populations that have high need for biologic treatment.

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ABSTRACT

Objective: To evaluate the current evidence, its limitations, and future research directions for the use of biologics in pediatric asthma, with a particular focus on the potential use of biologics to prevent pediatric asthma and equity issues in access to biologic treatment and research participation.
Data Sources: PubMed articles about the use of biologics in pediatric asthma were searched up to May 2023.
Study Selections: Recent (2019-2023) original research articles and reviews were prioritized.
Results: Although there are now 5 U.S. Food and Drug Administration-approved biologics for use in pediatric asthma, there are important knowledge gaps that ongoing research seeks to address, which include (1) the long-term efficacy and safety of using biologics in children, (2) the comparative efficacy of different biologics, (3) multi-omics-based classification of asthma endotypes and phenotypes in children to find potential new therapeutic targets and enable identification and validation of new biomarkers that may predict and help monitor response to treatment, and (4) whether starting biologics in early childhood can modify the natural history of asthma and potentially prevent asthma development.
Summary: To promote equitable access to biologics and optimize asthma outcomes, future research should recruit patients across the full spectrum of socioeconomic and racial/ethnic backgrounds. Large-scale national and international collaborations between asthma researchers and clinicians are also necessary to fully understand the role of biologics in pediatric asthma.

Introduction

Asthma affects 1 in 12 children in the United States, approximately 5% of whom have severe asthma.[1,2] Within severe asthma, there is a distinction between severe therapy-resistant asthma and difficult-to-treat asthma, the latter of which is related to poor adherence to medications, incorrect inhaler technique, exposure to environmental

Address correspondence to: Wanda Phipatanakul, MD, MS, Boston Children's Hospital, Division of Immunology, 300 Longwood Avenue, Fegan 6, Boston, MA 02115. E-mail: Wanda.Phipatanakul@childrens.harvard.edu.

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Learning Objectives

At the conclusion of this activity, participants should be able to:

- Summarize the current evidence for the efficacy, safety, and choice of biologics in pediatric asthma.
- Specify the limitations of the current evidence and important areas of future research, including multi-omics-based classification of asthma endotypes and phenotypes, potential use of biologics to prevent asthma development, and ensuring equitable access to biologic treatment and research participation.

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Physicians involved in providing patient care in the field of allergy/asthma/immunology.

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- Kurt Shulenberger has no relevant financial relationships with ineligible companies to disclose.

Authors:

- Ianthe RM Schepel, BMBCh, MPhil, MS, has no relevant financial relationships with ineligible companies to disclose.
- Tina M. Banzon, MD, has no relevant financial relationships with ineligible companies to disclose.
- Wanda Phipatanakul, MD, MS, Consultant: Astra Zeneca, Genentech, GSK, Novartis, Regeneron, Sanofi,

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triggers, or comorbidities.[2] Severe asthma is associated with more frequent asthma exacerbations, impaired lung function, reduced health-related quality of life, and increased risk of death.[3] Severe asthma accounts for a substantial proportion of health care spending on asthma, mostly due to increased health care resource utilization.[3] In the United States, asthma prevalence, morbidity, and mortality are highest in low-income and racial/ethnic minoritized groups.[4]

Asthma is increasingly understood as a heterogeneous disease with different phenotypes (observable patient traits) and endotypes (underlying pathophysiological mechanisms). In most children, the pathogenesis of asthma is driven by a type 2 inflammatory response, involving the release of proinflammatory cytokines (including thymic stromal lymphopoietin, interleukin [IL]-4, IL5, and IL13), production of immunoglobulin E (IgE), and recruitment of innate immune cells (eosinophils, mast cells, and basophils) to the lung.[5] Traditional medications for asthma broadly aim to reduce airway inflammation (corticosteroids and leukotriene receptor antagonists) and reverse bronchoconstriction (β-agonists and muscarinic antagonists). Biologic medications now offer a targeted and personalized treatment approach to asthma.

There are currently 5 biologics that are approved by the U.S. Food and Drug Administration for use in pediatric asthma: omalizumab (anti-IgE), mepolizumab (anti-IL5), benralizumab (anti-IL5Rα), dupilumab (anti-IL4Rα), and tezepelumab (anti-thymic stromal lymphopoietin), each targeting a specific component of the type 2 inflammatory pathway (Fig 1). These medications are indicated for patients with moderate to severe persistent asthma that remains uncontrolled despite adherence to high-level treatment, correct inhaler technique, interventions to reduce environmental exposures, and optimized treatment of comorbidities. Omalizumab is indicated for allergic asthma, benralizumab and mepolizumab for eosinophilic asthma, and dupilumab for eosinophilic asthma and oral corticosteroid-dependent asthma, whereas tezepelumab can be prescribed for all phenotypes of asthma, including nonallergic noneosinophilic asthma. This CME Review article will evaluate the current evidence, its limitations, and future research directions for the use of biologics in pediatric asthma. Particular attention will be paid to the potential use of biologics to prevent pediatric asthma and equity issues in access to biologic treatment and research participation.

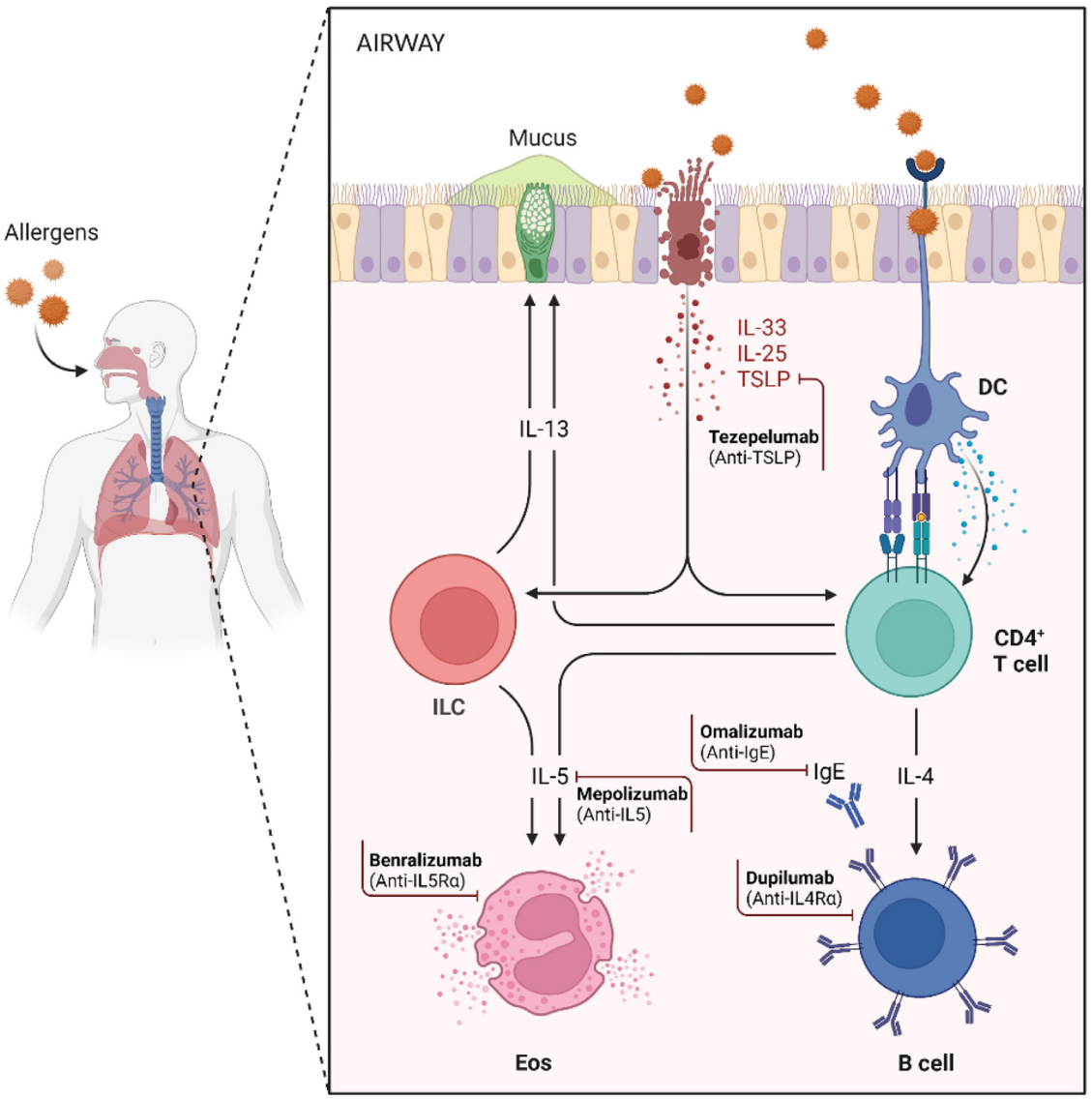

Figure 1. Mechanism of action of biologic agents for severe pediatric asthma. DC, dendritic cell; Eos, eosinophil; IgE, immunoglobulin E; IL, interleukin; IL4Rα, interleukin-4 receptor α; IL5Rα; interleukin-5 receptor α; ILC, innate lymphoid cell; TSLP, thymic stromal lymphopoietin. Created with BioRender.com.

Efficacy and Safety of Biologics for Pediatric Asthma

Randomized controlled trials (RCTs) of asthma biologics have generally determined their efficacy using a number of primary and secondary end points: severe asthma exacerbation rate, corticosteroid use, asthma control, lung function (prebronchodilator forced expiratory volume in 1 second), and health-related quality of life. These studies have shown that in selected patients with uncontrolled, moderate to severe persistent asthma, biologics reduce the annualized rate of asthma exacerbations by approximately 50% compared with placebo.[6-9] In patients with allergic asthma, omalizumab has a significant steroid-sparing effect, reducing use of both inhaled and oral corticosteroids compared with placebo.[6] In patients with eosinophilic asthma, benralizumab, dupilumab, and mepolizumab all reduce use of oral corticosteroids compared with placebo.[7] Asthma biologics also improve asthma control, lung function, and health-related quality of life, although these beneficial effects seem to be more modest.[6-9] Few RCTs of asthma biologics have focused on children; most studies have primarily enrolled adults, with small numbers of adolescents. Omalizumab is the only biologic with robust evidence for efficacy in children with severe asthma—large RCTs have found it to be equally effective in children compared with adults in reducing the annualized rate of asthma exacerbations, reducing use of inhaled corticosteroids and rescue medications, and improving health-related quality of life.[6] There is an urgent need for more long-term efficacy and safety data for asthma biologics, particularly for children younger than 12 years of age and for other biologics in addition to omalizumab.

Overall, asthma biologics have very favorable short-term safety profiles (Table 1).[10,11] The most common adverse effects for all biologics are injection site reactions; dupilumab may cause conjunctivitis and transient eosinophilia; headache has been associated with omalizumab, mepolizumab, and benralizumab; and tezepelumab is associated with pharyngitis and arthralgia.[10,11] Rare side effects include anaphylaxis and, for dupilumab, eosinophilic granulomatosis with polyangiitis.[10] Clinical trials have found lower rates of serious adverse events in biologic-treated groups than placebo groups because complications from uncontrolled asthma (eg, severe asthma exacerbations requiring hospital admission) were higher in placebo groups.[12] Gaining a better understanding of the long-term immunomodulatory effects of asthma biologics is essential, especially for the pediatric population whose immune system is still developing and maturing and in whom the use of biologics may affect the immune response to essential childhood vaccinations. In clinical practice, questions often arise around the safety of live-attenuated vaccines with biologics. The prescribing information for dupilumab recommends the avoidance of live-attenuated vaccines during treatment as a precaution. There is currently no clear evidence for increased risk of infection or other adverse events, largely because live-attenuated vaccines were excluded from major RCTs of dupilumab. Similarly, little is known about the incidence of antidrug antibody development to asthma biologics in children, which can lead to reduced biologic efficacy and adverse immune reactions. A recent systematic review and meta-analysis of 46 studies of asthma biologics (including 4 studies conducted in pediatric patients) found that the incidence of antidrug antibodies was less than 3%, highest with benralizumab and dupilumab (both approximately 8%) and lowest with omalizumab (undetectable).[13] Further long-term efficacy and safety data on asthma biologics in pediatric patients can be obtained from real-life observational studies. International consortia on severe pediatric asthma in Europe are now combining cohort studies with preclinical research studies to develop better clinical decision-making tools for the use of biologics in children, investigating the comparative efficacy and safety of asthma biologics, and seeking to identify and validate biomarkers that can guide treatment selection.[14]

Choosing Between Asthma Biologics

Current treatment algorithms for asthma biologics use certain biomarkers to guide the choice of biologic agent for patients (Fig 2).[15] Key biomarkers are blood eosinophil count, fractional exhaled nitric oxide (F_ENO), and IgE; cutoff levels of these biomarkers for pediatric patients have been extrapolated from adult studies.[2] Eosinophilic asthma is characterized by high blood eosinophil count (≥150 cells/μL) and F_ENO (≥20 ppb), whereas allergic asthma is characterized by elevated total serum IgE level and evidence of perennial aeroallergen sensitization (ie, elevated specific serum IgE level or positive skin prick test).[5] Higher baseline blood eosinophil counts have been found to be predictive of good asthma response to all biologics currently available for pediatric asthma, and higher baseline F_ENO is also predictive of a good asthma response to dupilumab, omalizumab, and tezepelumab.[10] Higher baseline total serum IgE levels notably do not predict the response to omalizumab.[16] It is important to recognize that in some patients with asthma, the levels of these biomarkers fluctuate considerably, whereas in others, they remain persistently elevated over time. Beyond biomarkers, selection of asthma biologics is guided by patients' age and comorbid atopic conditions targeted by biologics, such as chronic idiopathic urticaria (omalizumab), hypereosinophilic syndrome (mepolizumab), or atopic dermatitis and eosinophilic esophagitis (dupilumab).[10] Omalizumab is more effective in childhood-onset asthma (which is usually allergic in phenotype), whereas benralizumab and mepolizumab are more effective in adult-onset asthma and in patients with more frequent severe asthma exacerbations.[10] Patients are often eligible for multiple asthma biologics, but their comparative effectiveness and thus the optimal choice of treatment is unknown.

No RCTs to date have directly compared asthma biologics with each other for efficacy and safety. For adult patients, a number of recent studies have attempted to determine their comparative efficacy by performing indirect treatment comparisons using data from different RCTs or by conducting a retrospective cohort study emulating a target trial.[17-19] Although these studies are relevant in the absence of RCT data, such retrospective studies have inherent

Table 1
U.S. Food and Drug Administration-Approved Biologic Agents for Severe Pediatric Asthma[10,11]

Biologic agent	Mechanism of action	Age	Indication	Eligibility by biomarkers	Side effects
Omalizumab	Anti-IgE	≥6 y	Allergic asthma	6-11 y: IgE 30-1300 IU/mL ≥12 y: IgE 30-700 IU/mL	Common: injection site reactions, headache; rare: anaphylaxis
Mepolizumab	Anti-IL5	≥6 y	Eosinophilic asthma	Eosinophil count ≥ 150/μL	Common: injection site reactions, headache; rare: anaphylaxis
Benralizumab	Anti-IL5Rα	≥12 y	Eosinophilic asthma	Eosinophil count ≥ 300/μL	Common: injection site reactions, headache; rare: anaphylaxis
Dupilumab	Anti-IL4Rα	≥6 y	Eosinophilic or OCS-dependent asthma	Eosinophil count ≥ 150-300/μL (maximum 1500/μL)	Common: injection site reactions, conjunctivitis, transient eosinophilia; rare: eosinophilic granulomatosis with polyangiitis
Tezepelumab	Anti-TSLP	≥12 y	Any phenotype of asthma	Not applicable	Common: injection site reactions, pharyngitis, arthralgia; rare: anaphylaxis

Abbreviations: IgE, immunoglobulin E; IL, interleukin; IL4Rα, interleukin-4 receptor α; IL5Rα; interleukin-5 receptor α; OCS, oral corticosteroid; TSLP, thymic stromal lymphopoietin.

		F_ENO <20 ppb	F_ENO ≥20 ppb
Age 6-11 years	Eos <150/μL	Omalizumab*	Dupilumab Omalizumab*
	Eos ≥150/μL	Dupilumab** Omalizumab* Mepolizumab	Dupilumab** Omalizumab* Mepolizumab
Age ≥12 years	Eos <150/μL	Omalizumab* Tezepelumab	Dupilumab** Omalizumab* Tezepelumab
	Eos ≥150/μL	Benralizumab Dupilumab Mepolizumab Omalizumab* Tezepelumab	Benralizumab Dupilumab** Mepolizumab Omalizumab* Tezepelumab

Figure 2. Biomarkers to consider in choosing a biologic agent for severe pediatric asthma.[15] NB: Biologic agents listed in alphabetical order. *Only for allergic asthma; **Only if eosinophil count ≤ 1500/μL. Eos, eosinophil; F_ENO, fractional exhaled nitric oxide; ppb, parts per billion. Figure adapted from Saxena S, et al. Curr Opin Allergy Clin Immunol. 2023;23(2):111-118.

methodological limitations. At present, they would be challenging to conduct specifically for pediatric patients, given the very small numbers of children who have completed RCTs for asthma biologics. In the United Kingdom, a group of National Health Service foundation trusts is now running an industry-independent RCT to address this gap in the literature: the "Treating severe pediatric asthma; a randomized controlled trial of mepolizumab and omalizumab" (TREAT trial) is seeking to establish the comparative efficacy of mepolizumab and omalizumab and the features that predict a good asthma response to these biologics in children.[20]

Predicting and Monitoring Response to Biologics

Although certain biomarkers may predict response to asthma biologics and guide treatment selection, there are no validated biomarkers to monitor for response during and after treatment. Measures of response are currently clinical, such as asthma symptom control, exacerbation frequency and severity, oral corticosteroid use, and side effects of biologics.[10] The Global Initiative for Asthma recommends trialing asthma biologics for at least 4 months.[10] If clinically effective, the recommendation is to continue biologic treatment indefinitely, evaluating its efficacy and side effects every 3 to 6 months, and reducing concomitant oral and inhaled corticosteroid use as tolerated.[10] If biologic efficacy is unclear, the recommendation is to continue treatment for up to 6 to 12 months; if clearly ineffective, it is suggested to trial a different biologic agent if the patient is eligible for one.[10] The optimal duration of treatment with asthma biologics is unknown, and limited research in adults suggests that cessation of biologic therapies often leads to recurrence of asthma symptoms and increased risk of exacerbations.[21,22] Ideal biomarkers to predict and monitor response to biologic treatment would reflect patients' endotype, or the pathogenic inflammatory pathways that underlie asthma symptoms and risk of severe exacerbation. Asthma is currently categorized into 2 broad endotypes: type 2-high asthma, characterized by eosinophilic airway inflammation, and type 2-low asthma, more common in adults, characterized by neutrophilic, paucigranulocytic, or mixed granulocytic airway inflammation.[5] Most currently available biologics target type 2-high inflammatory pathways, where dampening these pathways may lead to compensatory promotion of disease activity by other inflammatory pathways, which could explain the variable treatment response to asthma biologics observed in patients.[23] Of note, tezepelumab has been shown to be effective and safe in both patients with type 2-high and patients with type 2-low asthma.[9]

Multi-omics research approaches have the potential to capture the complexity and heterogeneity of asthma pathogenesis on a molecular level, which could lead to more precise classification of asthma endotypes and phenotypes, along with the identification of new pediatric-specific biomarkers to more accurately predict and monitor response to biologics.[24] Compared with current biomarkers such as blood eosinophil count and F_ENO, markers of inflammatory pathway gene expression are likely to be more sensitive and specific biomarkers of biologic treatment response. A recent RCT in urban children with severe eosinophilic asthma sought to investigate the molecular mechanisms underlying variable treatment response to mepolizumab by comparing expression of nasal airway gene clusters (transcriptome modules) before and after 12 months of treatment with mepolizumab.[23] This study found that mepolizumab reduced the rate of asthma exacerbations in children significantly by 27%, less than what has been found in adult RCTs.[23] Of 52 nasal airway transcriptome modules analyzed, 12 were associated with altered risk of asthma exacerbation.[23] Expression of 8 of the 12 transcriptome modules was significantly changed by mepolizumab treatment compared with none in the placebo group.[23] Mepolizumab down-regulated expression of 3 eosinophilic transcriptome modules associated with increased risk of asthma exacerbation but also up-regulated expression of 5 epithelial transcriptome modules associated with increased risk of asthma exacerbation.[23] Mepolizumab treatment did not significantly alter expression of 2 other transcriptome modules associated with increased risk of asthma exacerbation or expression of 2 transcriptome modules associated with reduced risk of asthma exacerbation.[23] Importantly, these transcriptome modules proved to be more accurate biomarkers of exacerbation risk and treatment response than blood eosinophil count and F_ENO.[23] The study's airway transcriptome findings offer insight into molecular mechanisms beyond the type 2 inflammatory pathway that underlie asthma exacerbations in children, the effects of mepolizumab on different inflammatory pathways, and potential reasons for incomplete treatment response to this biologic. Continuing this line of research will help to not only discover improved biomarkers and develop more individualized treatment guidelines for asthma biologics but also identify novel targets for disease intervention. Because cessation of currently available biologics, at least in adults, seems to result in disease relapse, new asthma therapies may be necessary to inhibit other pathogenic pathways, such as involving structural airway cells, to be disease-modifying.[25]

Should We Be Starting Asthma Biologics Early?

While fundamental questions remain about the efficacy and safety of biologics in pediatric asthma, the approval of some asthma biologics for use in young children has led to great interest in whether early targeted inhibition of the type 2 inflammatory pathway could prevent the development of pediatric asthma altogether. The Preventing Asthma in High Risk Kids (PARK) study—a National Institutes of Health (NIH)-funded RCT of omalizumab in toddlers at high risk of developing asthma—is currently investigating this concept.[26] Two key risk factors for the development of persistent asthma are (1) aeroallergen sensitization via

allergen-specific IgE antibody production and (2) viral lower respiratory tract infections, especially with rhinovirus, likely worsened by IgE-mediated reduction in the innate antiviral immune response.[26] Omalizumab has previously been shown to reduce the rate of asthma exacerbations in school-aged children during the respiratory viral season and improve the innate immune response to rhinovirus.[27,28] By blocking circulating IgE and IgE-mediated responses, the hypothesis is that early treatment with omalizumab can prevent asthma development and, in children who do develop asthma, reduce asthma severity.[26] The PARK trial enrolls children aged 2 to 3 years who have had 2 to 4 episodes of wheezing in the past 12 months without an established diagnosis of asthma, are sensitized to at least one aeroallergen, and have a first-degree relative with allergy or asthma.[26] These inclusion criteria are in line with the modified Asthma Predictive Index used to predict the likelihood of developing asthma in preschool children with a history of wheezing. The PARK trial has a 2-year treatment phase (with omalizumab or placebo) followed by a 2-year observational phase (to monitor for diagnosis of asthma and asthma severity).[26] An important question in the PARK study is whether omalizumab may actually prevent asthma development, vs simply delay its onset. If omalizumab is indeed found to be disease-modifying in the first few years of life, further research is required to refine eligibility criteria for the treatment of young children. Treatment should target those children most at risk of developing asthma, while avoiding overmedicalization of children with transient wheeze.

Predicting which children may benefit most from starting biologics for asthma early requires careful phenotyping of wheeze trajectories in young children and characterizing the underlying etiology and pathophysiology of these phenotypes. Various birth cohort studies have described distinct phenotypes of early childhood wheeze, and wheeze trajectory modeling has become increasingly sophisticated with new machine learning methods. For example, a recent study embedded in the Canadian Healthy Infant Longitudinal Development (CHILD) Cohort Study performed both group-based trajectory modeling and longitudinal latent class analysis of more than 3000 children who had at least 2 episodes of wheezing from 3 months to 5 years of age and collected detailed information about participants' genetic, early-life health, and environmental risk factors.[29] The study identified 4 longitudinal trajectories of childhood wheezing and associated risk factors.[29] These trajectories were never/infrequent wheeze, transient wheeze, intermediate-onset wheeze, and persistent wheeze.[29] Transient, intermediate-onset, and persistent wheeze trajectories were associated with increased odds of physician-diagnosed asthma at age 5 years; odds were the highest for the intermediate-onset and persistent wheeze groups.[29] Certain risk factors were shared across different trajectories (eg, elevated body mass index and respiratory tract infections), whereas others were specific to trajectory groups (eg, atopy and genetic risk score for asthma were associated with intermediate-onset wheeze; maternal asthma was associated with persistent wheeze).[29] As outlined by the CHILD Cohort Study researchers, trajectory group-specific risk factors have varied between different birth cohort studies.[29] A major limitation of this line of research is that it assigns patients into wheeze categories retrospectively using complex machine learning methods, whereas ideally physicians would have sensitive and specific biomarkers that can be readily used in clinic to predict an individual child's risk of developing asthma. More research incorporating a multi-omics approach is required to better delineate phenotypes of early childhood wheeze, identify potentially modifiable risk factors, and determine the likelihood of developing persistent and severe asthma to inform prognosis and facilitate targeted asthma prevention strategies.[29] Compared with modifying early-life health or environmental risk factors, biologics are attractive as a potential targeted prevention strategy because they inhibit components of asthma pathogenesis likely shared across wheeze phenotypes. If omalizumab or other biologics are proved to prevent asthma development in a defined subset of young children, the cost-effectiveness of this medical intervention will require further evaluation. Any such economic evaluation in the United States should take health equity into consideration, given the disproportionate burden of asthma in underrepresented minority and low-income populations, who are largely publicly insured.

Equitable Access to Biologics

A major inequity in asthma treatment in the United States is the lower use of biologics for asthma in the publicly insured population compared with the privately insured population, despite the former having much higher asthma prevalence, morbidity, and mortality.[30] A study that analyzed data from a nationally representative, all-payer audit of ambulatory care in the United States in 2019 found that—controlling for age, sex, and race—publicly insured individuals were approximately 16% less likely to have a biologic treatment visit for asthma than privately insured individuals.[30] In the publicly insured population, racial and ethnic minority groups were overrepresented, yet White patients were significantly more likely to be prescribed a biologic for asthma than patients of other racial categories, in particular Black patients.[30] These findings may be explained by a wide range of social determinants of health, including system-level factors, such as differences in insurance coverage and reimbursement policies for biologics and unequal access to subspecialists; physician biases, leading to underestimation of disease severity and undertreatment of asthma in racial and ethnic minorities; and patient factors, such as health literacy and medication adherence.[30] There are also known to be racial/ethnic differences in the levels of blood biomarkers and presence of comorbidities that guide the prescription of biologics, which was not controlled for in this study.[30] There is no clinical trial evidence to support the differential prescribing of asthma biologics solely by race/ethnicity. Although racial/ethnic minorities have generally been underrepresented in clinical trials of asthma biologics, omalizumab has been shown to be effective in reducing asthma symptoms and exacerbations in inner-city children and young adults with persistent allergic asthma (>90% of whom were Black or Hispanic) and equally efficacious in Black and White adolescents and adults with moderate to severe persistent allergic asthma.[27,28,31] To reduce disparities in asthma prevalence and outcomes, it is critical to ensure equitable access to treatment with biologics, regardless of insurance status, income level, or race/ethnicity. Optimizing biologic treatment for minorities, in turn, requires more inclusive recruitment for research studies.

Disentangling the complex gene-environment interactions that underlie disparities in asthma prevalence and outcomes hinges on the recruitment of diverse study participants into translational and clinical research studies. In children, as in adults, asthma phenotypes have been found to differ across racial/ethnic groups, affecting their eligibility for biologics, as highlighted by a recent study analyzing data from 2 case-control studies of moderate to severe asthma in pediatric minority populations.[32] There is a need to better characterize clinical subgroups to guide physicians in choosing the most effective biologic for their patients, while recognizing the genetic heterogeneity within racial/ethnic groups and the role of social determinants of health in driving asthma phenotypes. Increasing and sustaining minority participation in asthma research requires a multimodal approach, including further developing federal mandates for appropriate representation of diverse populations in clinical research, strengthening community outreach in remote and underserved areas, and engaging minority study participants in data and safety monitoring boards.[33]

An ongoing National Institute of Allergy and Infectious Diseases-funded RCT called the Investigating Dupilumab's Effect in Asthma by Genotype (IDEA) study illustrates the importance of recruiting diverse study participants into asthma clinical trials to develop a

precision-based approach to biologic treatment.[34] The disproportionately high prevalence of severe asthma in racial/ethnic minoritized groups is explained in part by the interaction between genetic factors and environmental exposures such as indoor allergens and air pollution.[35] Specifically, a gene variant of IL4Rα (IL4RαR576) that is associated with severe asthma has been found to be more common in some Black and Hispanic populations.[35] This gene variant promotes T helper 2/T helper 17 (T_H2/T_H17)–driven mixed eosinophilic and neutrophilic airway inflammation by stimulating allergen-specific induced regulatory T cells in the lung to transform into T_H2- and T_H17-like cells.[36-38] Dupilumab (anti-IL4Rα) is thought to inhibit this reprogramming of induced regulatory T cells into T_H2 and T_H17 cells, which may result in sustained immune tolerance to allergens and ambient pollutant particles.[34,39] The IDEA study enrolls patients with asthma of ages 12 years and older and stratifies them by IL4Rα allele: (1) wild-type allele (Q576/Q576), (2) heterozygous allele (Q576/R576), or (3) homozygous mutant allele (R576/R576), which is associated with the highest degree of asthma severity.[34,36] The study has a 48-week treatment phase with dupilumab or placebo, both administered every 2 weeks. The primary outcome is severe asthma exacerbation rate, and secondary outcomes include asthma control and lung function (prebronchodilator forced expiratory volume in 1 second), which are each measured at 5 time points during the treatment phase.[34] The hypothesis is that dupilumab will be most effective in improving these primary and secondary outcomes in patients who are homozygous for the IL4Rα gene variant. If this is the case, basic science research has already identified biomarkers of T_H2/T_H17-driven airway inflammation (expression of Notch4 and its downstream Hippo and Wnt effectors) that correlate with asthma severity and may prove useful for monitoring disease activity and treatment response to dupilumab.[37,38]

Conclusion

Although there are now 5 U.S. Food and Drug Administration-approved biologics for use in severe, therapy-resistant pediatric asthma, there are important knowledge gaps that ongoing research seeks to address: (1) the long-term efficacy and safety of using biologics in children, (2) the comparative efficacy of different biologics, (3) multi-omics-based classification of asthma endotypes and phenotypes in children to find potential new therapeutic targets and enable identification and validation of biomarkers that may help predict and monitor response to treatment, and (4) whether starting biologics in early childhood can modify the natural history of asthma and perhaps even prevent asthma development at the forefront. To optimize biologic treatment and asthma outcomes for all, these research efforts must ensure recruitment of patients across the full spectrum of socioeconomic and racial/ethnic backgrounds. There is also a need for more industry-independent funding for this area of research, which to date has been largely funded by pharmaceutical companies that maintain close financial ties with asthma researchers, risking conflicts of interest. These lines of research are extremely complex, and their success depends on large-scale national and international collaborations between asthma researchers and clinicians to progress from hypothesis-generating studies to truly personalized asthma care.

Disclosures

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References

1. Centers for Disease Control and Prevention. Asthma in children. Accessed June 24, 2023. Available at: https://www.cdc.gov/vitalsigns/childhood-asthma/index.html.
2. Bush A, Fitzpatrick AM, Saglani S, Anderson 3rd WC, Szefler SJ. Difficult-to-treat asthma management in school-age children. *J Allergy Clin Immunol Pract*. 2022;10(2):359–375.
3. Chen S, Golam S, Myers J, Bly C, Smolen H, Xu X. Systematic literature review of the clinical, humanistic, and economic burden associated with asthma uncontrolled by GINA steps 4 or 5 treatment. *Curr Med Res Opin*. 2018;34(12):2075–2088.
4. Davis CM, Apter AJ, Casillas A, Foggs MB, Louisias M, Morris EC, et al. Health disparities in allergic and immunologic conditions in racial and ethnic underserved populations: a work group report of the AAAAI Committee on the Underserved. *J Allergy Clin Immunol*. 2021;147(5):1579–1593.
5. Brusselle GG, Koppelman GH. Biologic therapies for severe asthma. *N Engl J Med*. 2022;386(2):157–171.
6. Agache I, Rocha C, Beltran J, Song Y, Posso M, Solà I, et al. Efficacy and safety of treatment with biologicals (benralizumab, dupilumab and omalizumab) for severe allergic asthma: a systematic review for the EAACI Guidelines – recommendations on the use of biologicals in severe asthma. *Allergy*. 2020;75(5):1043–1057.
7. Agache I, Beltran J, Akdis C, Akdis M, Canelo-Aybar C, Canonica GW, et al. Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the EAACI Guidelines – recommendations on the use of biologicals in severe asthma. *Allergy*. 2020;75(5):1023–1042.
8. Agache I, Song Y, Rocha C, Beltran J, Posso M, Steiner C, et al. Efficacy and safety of treatment with dupilumab for severe asthma: a systematic review of the EAACI Guidelines – recommendations on the use of biologicals in severe asthma. *Allergy*. 2020;75(5):1058–1068.
9. Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. *N Engl J Med*. 2021;384(19):1800–1809.
10. Global Initiative for Asthma. 2022 GINA report, global strategy for asthma management and prevention. Accessed June 24, 2023. Available at: www.ginasthma.org.
11. Anderson 3rd WC, Banzon TM, Chawes B, Papadopoulos NG, Phipatanakul W, Szefler SJ. Factors to consider in prescribing asthma biologic therapies to children. *J Allergy Clin Immunol Pract*. 2023;11(3):693–701.
12. Fu Z, Xu Y, Cai C. Efficacy and safety of omalizumab in children with moderate-to-severe asthma: a meta-analysis. *J Asthma*. 2021;58(10):1350–1358.
13. Chen ML, Nopsopon T, Akenroye A. Incidence of anti-drug antibodies to monoclonal antibodies in asthma: a systematic review and meta-analysis. *J Allergy Clin Immunol Pract*. 2023;11(5):1475–1484.e20.
14. Vijverberg SJH, Brinkman P, Rutjes NWP, Maitland-van der Zee AH. Precision medicine in severe pediatric asthma: opportunities and challenges. *Curr Opin Pulm Med*. 2020;26(1):77–83.
15. Saxena S, Rosas-Salazar C, Fitzpatrick A, Bacharier LB. Biologics and severe asthma in children. *Curr Opin Allergy Clin Immunol*. 2023;23(2):111–118.
16. Brusselle G, Michils A, Louis R, Dupont L, Van de Maele B, Delobbe A, et al. "Real-life" effectiveness of omalizumab in patients with severe persistent allergic asthma: the PERSIST study. *Respir Med*. 2009;103(11):1633–1642.
17. Bateman ED, Khan AH, Xu Y, Guyot P, Chao J, Kamat S, et al. Pairwise indirect treatment comparison of dupilumab versus other biologics in patients with uncontrolled persistent asthma. *Respir Med*. 2022;191: 105991.
18. Akenroye A, Lassiter G, Jackson JW, Keet C, Segal J, Alexander GC, et al. Comparative efficacy of mepolizumab, benralizumab, and dupilumab in eosinophilic asthma: a Bayesian network meta-analysis. *J Allergy Clin Immunol*. 2022;150(5):1097–1105.e12.
19. Akenroye AT, Segal JB, Zhou G, Foer D, Li L, Alexander GC, et al. Comparative effectiveness of omalizumab, mepolizumab, and dupilumab in asthma: a target trial emulation. *J Allergy Clin Immunol*. 2023;151(5):1269–1276.
20. Saglani S, Bush A, Carroll W, Cunningham S, Fleming L, Gaillard E, et al. Biologics for paediatric severe asthma: trick or treat? *Lancet Respir Med*. 2019;7(4):294–296.
21. Ledford D, Busse W, Trzaskoma B, Omachi TA, Rosén K, Chipps BE, et al. A randomized multicenter study evaluating Xolair persistence of response after long-term therapy. *J Allergy Clin Immunol*. 2017;140(1):162–169.e2.
22. Moore WC, Kornmann O, Humbert M, Poirier C, Bel EH, Kaneko N, et al. Stopping versus continuing long-term mepolizumab treatment in severe eosinophilic asthma (COMET study). *Eur Respir J*. 2022;59(1): 2100396.
23. Jackson DJ, Bacharier LB, Gergen PJ, Gagalis L, Calatroni A, Wellford S, et al. Mepolizumab for urban children with exacerbation-prone eosinophilic asthma in the USA (MUPPITS-2): a randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet*. 2022;400(10351):502–511.
24. Ray A, Das J, Wenzel SE. Determining asthma endotypes and outcomes: complementing existing clinical practice with modern machine learning. *Cell Rep Med*. 2022;3(12): 100857.
25. Custovic A, Siddiqui S, Saglani S. Considering biomarkers in asthma disease severity. *J Allergy Clin Immunol*. 2022;149(2):480–487.
26. Phipatanakul W, Mauger DT, Guilbert TW, Bacharier LB, Durrani S, Jackson DJ, et al. Preventing asthma in high risk kids (PARK) with omalizumab: design, rationale, methods, lessons learned and adaptation. *Contemp Clin Trials*. 2021;100: 106228.

27. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med*. 2011;364(11):1005–1015.
28. Teach SJ, Gill MA, Togias A, Sorkness CA, Arbes Jr SJ, Calatroni A, et al. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol*. 2015;136(6):1476–1485.
29. Dai R, Miliku K, Gaddipati S, Choi J, Ambalavanan A, Tran MM, et al. Wheeze trajectories: determinants and outcomes in the CHILD cohort study. *J Allergy Clin Immunol*. 2022;149(6):2153–2165.
30. Akenroye AT, Heyward J, Keet C, Alexander GC. Lower use of biologics for the treatment of asthma in publicly insured individuals. *J Allergy Clin Immunol Pract*. 2021;9(11):3969–3976.
31. Szefler SJ, Jerschow E, Yoo B, Janampally P, Pazwash H, Holweg CTJ, et al. Response to omalizumab in Black and White patients with allergic asthma. *J Allergy Clin Immunol Pract*. 2021;9(11):4021–4028.
32. Wohlford EM, Huang PF, Elhawary JR, Millette LA, Contreras MG, Witonsky J, et al. Racial/ethnic differences in eligibility for asthma biologics among pediatric populations. *J Allergy Clin Immunol*. 2021;148(5):1324–1331.e12.
33. Hvisdas C, Louisias M, Laidlaw TM, Akenroye A. Addressing disparities in biologic drug development in the United States. *J Allergy Clin Immunol*. 2021;148(5):1154–1156.
34. ClinicalTrials.gov. Investigating Dupilumab's Effect in Asthma by Genotype (IDEA). Accessed June 27, 2023. Available at: https://www.clinicaltrials.gov/study/NCT03694158?term=phipatanakul&rank=1.
35. Lai PS, Massoud AH, Xia M, Petty CR, Cunningham A, Chatila TA, et al. Gene-environment interaction between an IL4R variant and school endotoxin exposure contributes to asthma symptoms in inner-city children. *J Allergy Clin Immunol*. 2018;141(2):794–796.
36. Massoud AH, Charbonnier LM, Lopez D, Pellegrini M, Phipatanakul W, Chatila TA. An asthma-associated IL4R variant exacerbates airway inflammation by promoting conversion of regulatory T cells to Th17-like cells. *Nat Med*. 2016;22(9):1013–1022.
37. Harb H, Stephen-Victor E, Crestani E, Benamar M, Massoud A, Cui Y, et al. A regulatory T cell Notch4-GDF15 axis licenses tissue inflammation in asthma. *Nat Immunol*. 2020;21(11):1359–1370.
38. Benamar M, Harb H, Chen Q, Wang M, Chan TMF, Fong J, et al. A common IL-4 receptor variant promotes asthma severity via a T_{reg} cell GRB2-IL-6-Notch4 circuit. *Allergy*. 2022;77(11):3377–3387.
39. Harb H, Chatila TA. Mechanisms of dupilumab. *Clin Exp Allergy*. 2020;50(1):5–14.