



Monoclonal Antibody Therapy in Childhood Asthma

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Abstract

Purpose of Review There has been an explosion of monoclonal antibodies in the treatment of severe uncontrolled adult asthma. Studies have now been published in severe pediatric asthma. There are numerous questions that need to be answered in determining whether these modalities are appropriate and safe in children.

Recent Findings This is a narrative review examining the latest pediatric literature on monoclonal antibodies, both approved and in the pipeline, for uncontrolled asthma. Presently, all of the biologics are positioned to treat patients with underlying type 2 high disease. Two monoclonal antibodies are approved for children 6 years of age and older, omalizumab and mepolizumab, with more likely approved in the near future.

Summary The effect of these agents in controlling severe pediatric asthma is promising. Data is limited to long-term efficacy and safety, and whether any agent has an effect on the natural history of asthma.

Keywords Pediatric asthma · Biologics · Monoclonal antibodies · Biomarkers · Eosinophils · Severe asthma

Introduction

Asthma is the most common chronic condition seen in the pediatric population with estimates that 7.5% of children and adolescents in the United States suffer from it [1]. During 2013, children with asthma aged 5–17 years missed 13.8 million days of school per year (2.6 days per child). The good news is that control has improved for children with mild to moderate persistent disease as the percentage of children with asthma who experienced an asthma attack decreased significantly, from 61.7% in 2001 to 53.7% in 2016 [2].

Unfortunately, the burden of uncontrolled childhood asthma continues to be a major public health issue in the United States and throughout the world. For the 5%

of the pediatric asthma population with severe disease, optimal control has been difficult to achieve. It is this group of patients that account for a disproportionately high amount of the direct and indirect costs seen in the disease [3]. Frequent asthma exacerbations affect the quality of life of those with uncontrolled disease in addition to their parents/caregivers and are associated with an accelerated loss of lung function [4]. In defining severe asthma, a panel consensus report developed by allergists and pulmonologists in 2017 stated it is “Asthma that, despite patient adherence, requires high-dose inhaled corticosteroid (ICS) plus long-acting beta-agonist (LABA) and/or additional controller medication or requires oral corticosteroids (OCS) to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy” [5]. There is a need in children that meet this definition for newer therapies which can lead to better long-term outcomes and improved quality of life with minimal risk of side effects with chronic use.

In this review, we will assess the use of monoclonal antibodies in the management of the child with uncontrolled asthma as related to their different asthma phenotypes and endotypes. Our examination will include the approved monoclonal products in children in addition to ones in the pipeline. For each biological agent, we will assess the current data on the mechanism of action, efficacy, and safety in the pediatric population.

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Phenotypes and Endotypes in Pediatric Asthma

The pathophysiologic model of asthma has evolved from a mostly singular entity to a multifaceted network of interrelated inflammatory pathways leading to more distinct clinical presentations. Asthma endotypes refer to distinct mechanistic pathways, broadly known as either type 2 (T2) high or T2-low, that lead to variable clinical presentations or phenotypes [6••]. Characterizing asthma endotypes and phenotypes has inherent prognostic and therapeutic implications. Pediatric asthma has historically been described as an atopic disease with a Th2 predominant cytokine profile that includes interleukin (IL) 4, IL-5, and IL-13 leading to eosinophilic airway inflammation. Th2 CD4⁺ T cells were initially identified as the source of these cytokines, but further evidence showed that these cytokines and others in the Th2 pathway are produced by non-Th2 cells including basophils, mast cells, eosinophils, and group 2 innate lymphoid cells (ILC2s). To recognize this more diverse immunologic origin, the inflammatory state associated with asthma was recategorized as type 2 inflammation [7]. The dual endotype classification of T2 versus non-T2 asthma has direct clinical implications as the eosinophilia seen in T2 asthma correlates with corticosteroid response, the onset of disease, and severity of symptoms [8].

Allergen sensitization and subsequent exposure are thought to drive the characteristic eosinophilic inflammation in over half of pediatric asthma patients [9]. It is estimated that up to 80% of pediatric asthma and more than 50% of adult asthma cases may have an allergic component [10]. When exposed to small molecules such as allergens, pollutants, or microbes, airway epithelia release “alarmins” such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) that start a cascade of multiple inflammatory pathways. TSLP primes dendritic cells to stimulate type 2 inflammation via activation of CD4⁺ Th2 cells and B cells while IL-25 and IL-33 principally activate ILC2s. The Th2 cytokines IL-4 and IL-5 produced by CD4⁺ Th2 cells lead to B cell differentiation into immunoglobulin E (IgE) secreting plasma cells and promote eosinophil differentiation and survival respectively [11]. IL-4 and IL-13 secretion leads to increased goblet cell expression and thus mucous secretion and airway hyper-responsiveness which are central to asthma pathophysiology [12].

The three biomarkers of type 2 inflammation most thoroughly characterized in the literature and therefore used to guide the selection of biologic agents for asthma treatment include serum IgE, peripheral blood eosinophils, and exhaled nitric oxide (FeNO) [13, 14]. A systematic review investigating the accuracy of serum IgE, blood eosinophils, and FeNO as single markers for airway eosinophilia in patients with asthma found that these markers had only moderate sensitivities and specificities [15]. Of these T2 biomarkers, clinical experience has been greatest with peripheral blood eosinophilia which most likely reflects both the ease of measurement and

near-universal involvement of eosinophils in T2-high inflammation [13, 16]. Allergic asthma, a Th2-driven process, is defined as asthma associated with symptomatic sensitization to aeroallergens as measured by serum specific IgE or skin prick test positivity and is commonly comorbid with allergic rhinitis and atopic dermatitis [17]. Allergic sensitization and blood eosinophilia in children with asthma can be used to predict response to inhaled corticosteroid therapy. A multicenter, randomized, double-blind clinical trial found that children with aeroallergen sensitization and blood eosinophilia experienced the best response to daily ICS therapy [18]. In a similar fashion, another study found that children with FeNO > 25 ppb, blood eosinophilia > 350 cells/mm³, and serum IgE > 200 kU/L exhibited a better response to ICS over montelukast. An association between allergic asthma and elevated total serum IgE has been shown. In the epidemiological study on the Genetics and Environment of Asthma (EGEA) study, total IgE was positively associated with a history of hospitalization for asthma and ICS treatment in the past 12 months. Data examining pediatric asthma severity and total serum IgE has been mixed. In one study, total serum IgE level was not associated with clinical severity score [19] while another found that children with severe asthma had significantly higher serum IgE compared with subjects with mild to moderate asthma [20].

IL-13 induces nitric oxide synthase function which in turn generates FeNO [21]. FeNO has been used as a corollary of eosinophilic airway inflammation in asthma and has the advantage of being both easily measured and noninvasive [22, 23]. Per the American Thoracic Society guidelines, a FENO of > 50 ppb in adults or 35 ppb in children is an indicator of eosinophilic inflammation and likely response to corticosteroids [22]. In a cohort of 495 individuals enrolled in the Severe Asthma Research Program showed that patients with high FeNO were more likely to have early-onset asthma, greater number of positive skin testing to aeroallergens, higher serum IgE, and both blood and sputum eosinophilia. A systematic review investigating the utility of a FENO-based strategy to guide asthma management found a reduction in asthma exacerbation in both children and adults, but this benefit was inconsistent and did not extend to other asthma outcomes such as asthma symptoms or rescue medication use [24]. However, caution must be taken when incorporating FeNO into asthma management decisions as FeNO can be elevated in allergic rhinitis, eosinophilic bronchitis, dietary inorganic nitrate consumption, and viral and allergen exposure [22].

Patients with Th2-high asthma had increased allergen skin prick test reactivity, higher serum IgE levels, and higher peripheral blood and bronchoalveolar lavage eosinophil counts relative to those with T2-low asthma [9]. T2-low (or non-T2) asthma is characterized by either a neutrophilic or paucigranulocytic infiltrate. A paucicellular asthma phenotype has been defined as low sputum eosinophil and

neutrophil counts (eosinophils < 3%, neutrophils < 60%) in both children and adults [25]. The cytokines produced in neutrophilic inflammation are a mix of Th1 and Th17 cytokines such as IL-8, IL-17A, and IL-22. Neutrophilic inflammation is thought to be triggered by either infections, tobacco smoke, or inhaled pollutants [26]. In children, neutrophilic airway inflammation is uncommon and tends to vary over time [27]. The trigger for the paucicellular phenotype is largely unknown. The paucicellular phenotype is poorly defined in pre-school children, but has been proposed to correspond with the early onset (average age of 18 months) of the “Mild Episodic Viral Wheeze” or EVW phenotype that was seen in children with symptoms in the setting of upper respiratory tract infections only, overall mild disease course, and higher likelihood of a normal chest X-ray [28, 29]. Overall, non-T2 asthma is more prevalent in obese and older patients which suggests a role for systemic or metabolic inflammation [30]. As of yet, there are no successful trials of targeted therapies in adult and pediatric asthmatic patients without evidence for type 2 inflammation [31].

The Need for New Therapies in Children with Severe Uncontrolled Asthma

Although most children respond well to safe and evidence-based stepwise pharmacological treatment, about < 5% of children show a severe therapy-resistant asthma phenotype who require increasing doses of ICS and an additional controller medication to either achieve or maintain control [32]. This diminished responsiveness to standard therapy demonstrates the need for alternative treatments that target the heterogeneous causes of severe asthma, specifically biologic therapy. Evaluating patients for adherence to and proper use of evidence-based, stepwise pharmacologic treatment prior to proceeding to biologic therapy is also essential [33]. We will review the different monoclonals approved and in the pipeline for severe uncontrolled pediatric asthma and summarize the relevant studies performed in this population with these agents in Table 1.

Biologic Therapy: Omalizumab

Omalizumab was the first biologic therapy approved for asthma and is currently the only anti-IgE therapy in use. Omalizumab is a recombinant, humanized IgG1 monoclonal antibody that binds to the constant region (C3) of free circulating IgE thereby preventing IgE binding to both high-affinity and low-affinity IgE receptors, FcεR1 and CD23, respectively, on mast cells and basophils. The reduction of free IgE leads to the downregulation of FcεR1 expression on inflammatory cells, including mast cells, basophils, and dendritic cells [61, 62]. The downregulation of FcεR1 expression on dendritic cells reduces antigen presentation to T cells and subsequent

attenuation of the Th2 immune response [63, 64]. Most importantly, the decreased mast cell activation and sensitivity ultimately reduces eosinophilic tissue infiltration [65, 66]. An additional mechanism by which omalizumab mediated IgE depletion may reduce exacerbation frequency is by restoring normal production of interferon-α following rhinovirus exposure as some asthmatic subjects have been shown to have increased rhinovirus susceptibility with increased expression of IgE on mononuclear and dendritic cells [45, 67–70]. There is also data to support that omalizumab therapy reduces circulating basophils which correlated with clinical outcomes which suggests a possible mechanistic relationship between IgE levels and circulating basophil populations [71].

Omalizumab is administered via subcutaneous injection every 2 or 4 weeks. A nomogram guides dosing and administration frequency derived from pre-treatment total serum IgE (eligible if measured between 30 and 1500 IU/mL) and patient’s weight [72]. Prior to approval of the first biologic therapy, asthma treatment efficacy was largely assessed via improvement in lung function as a primary outcome. Early clinical studies found that omalizumab reduced the frequency of exacerbations and decreased the clinical need for other controller medications (including ICS), but did not improve lung function when added onto standard controller therapies [73, 74]. This has led to an overall paradigm shift towards a focus on reducing risk of exacerbations and hospitalizations as a primary outcome in biologic therapy trials and marker of disease control [16••]. A number of studies have established the efficacy and safety of omalizumab for the treatment of children with moderate to severe persistent allergic asthma uncontrolled on high-dose inhaled corticosteroid (ICS) plus a long-acting beta-agonist (LABA) [16, 75–78]. The US Food and Drug Administration (FDA) first approved omalizumab’s use in adolescents and adults ≥ 12 years of age in 2003 with expanded approval down to as young as 6 years of age in July 2016 [79]. The expanded pediatric approval was largely based on the results of 3 multicenter, randomized, double-blind, placebo-controlled phase III studies in children age 6 to 11 years [36, 45, 47]. The scope and longevity of available data, extensive safety profile, and longer term real-world clinical experience of omalizumab’s use with allergic asthma makes it the current biologic therapy of choice in children.

Busse’s sentinel 2011 Inner-City Anti-IgE Therapy for Asthma (ICATA) Study in 419 inner-city children aged 6–20 years of age showed that omalizumab utilized as “add-on” therapy to guideline-directed care compared to placebo significantly reduced the number of days that patients experienced asthma symptoms (24.5% decrease) and proportion of participants who had ≥ 1 exacerbation over the study period (48.5 to 30.3%) that persisted despite reducing the use of ICS and LABA therapy [36]. Interestingly, the predominant beneficial effects of omalizumab therapy were greatest on seasonal asthma exacerbations in the spring and fall. Johnston had

Table 1 Reviews the current available evidence for use of biologic therapy in asthma in children and adolescents aged 6–17 years (omalizumab [34–50], mepolizumab [51, 52], benralizumab [53–55], and dupilumab [56–60])

Medication	name & duration	Key inclusion criteria	Study design	Main outcomes
Omalizumab	Berger (Study 010) [34]	6–12 y of age Moderate-to-severe AA (≥ 1 -year duration Total serum IgE level of 30–1300 IU/mL Well controlled for ≥ 3 mo with ICS (168–420 mg/day BDP equivalent) + 1 reliever as needed FEV1 (pred) $\geq 60\%$	OLE 24-week extension 28-week core study: OMA received during the double-blind core study (as described in Milgrom et al. [47]) 24-week extension phase: open-label OMA therapy con- tinued without interruption and minimum effective ICS dose was maintained Treatment dose frequency: 0.016 mg/kg/IgE (IU/mL) per 4 weeks	Mean percentage reduction of ICS maintained: core, 74.3%; extension, 72.5% Exacerbation rate weeks 28–52: 27.6% Proportion of patients free from exacerbation (core 1 extension): 55%
	Brodie (Observational therapeutic trial, UK) [35]	5–16 years of age Severe asthma maintained on oral prednisolone for ≥ 3 months before commencing trial	16 weeks Diagnosis of severe asthma confirmed in a tertiary pediatric respiratory clinic Therapeutic trial of omalizumab was performed as part of routine clinical management Other asthma therapies were not altered during the trial Treatment dose frequency: 75–375 mg according to dos- ing table every 2–4 weeks	Baseline to week 16 (subgroup analysis of children aged < 12 years): Median OCS dose reduced from 20 to 5 mg/day ($P < .0001$) Median mini-AQLQ score significantly increased from 2.3 to 5.2 ($P = .0078$) Median ACT score significantly increased from 11 to 18 ($P = .0021$) Median FEV1 significantly increased from 1.8 to 2.1 L ($P = .0058$)
	Busse (ICATA Study and Post hoc analyses at 56 weeks) [36, 37]	6–20 years of age Persistent AA (> 1 -year duration) Total serum IgE level 30–1300 IU/mL Uncontrolled asthma indicated by persistent symptoms or hospitalization/unscheduled urgent care in prior 6–12 months	RDBPCT 60 weeks 4-week run-in phase: asthma control optimized before randomization to OMA or Pbo 60-week treatment period: ongoing treatment adjustments were made to achieve good asthma control Treatment dose frequency: 0.016 mg/kg/IgE (IU/mL) per 4 weeks Post hoc analysis: Exacerbation rate reduction for OMA vs Pbo at 56 weeks Stratified by baseline % predicted pre-broncho-dilator FEV1 ($< 90\%$, $\geq 90\%$) and any hospitalization in the prior 6 months Exacerbations were defined as those requiring systemic gluco-corticoids, hospitalization, or both	Number of days with asthma symptoms (OMA vs Pbo): 24.5% reduction. Mean (SEM) number of days: 1.48 (0.10) vs 1.96 (0.10); $P < .001$ [36] Percentage of patients with ≥ 1 exacerbation: OMA, 30.3%; Pbo, 48.8%; $P < .001$ Reduction in controller medication: Mean (SEM) ICS (mg/d): OMA, 663 (23.3); Pbo, 771 (23.5); difference, 2109 (95% CI, 2172 to 245); $P < .001$ Mean (SEM) LABA (% prescribed): OMA, 55.4 (2.44); Pbo, 65.5 (2.47); difference, 210.1 (95% CI, 216.8 to 23.4); $P = .003$ Reduction in seasonal exacerbations after OMA treatment (post hoc analysis) Placebo: fall 9.0%, spring 8.1%, vs summer 4.6% OMA: fall 4.3%, spring 4.2%, vs summer 3.3% $P < .001$ for interaction vs placebo Post hoc analysis at 56-weeks [37**] Exacerbation rates reduced (95% CI, P value) for OMA vs Pbo: ppFEV1 $< 90\%$, 36% (0.59; $P = 0.05$) and $\geq 90\%$, 18% ($-29, 48$; $P = 0.39$) Hospitalization in prior 6 months: Yes, 46% (4, 70; $P = 0.04$), and No, 24% ($-10, 48$; $P = 0.15$)

Table 1 (continued)

Medication	name & duration	Key inclusion criteria	Study design	Main outcomes
	Busse (pooled analysis) [38]	Data from 67 phase I to IV clinical trials	Varied	No association was observed between OMA treatment and risk of malignancy in RDBPC trials Rate ratio below unity
	Deschildre (real-life observational study, France) [39, 40]	6–18 y of age Severe AA Partially/poorly controlled asthma (18%/82%); mean ICS dose 703 µg/day FP or equivalent	104 weeks Multicenter survey conducted in pediatric pulmonology and allergy tertiary care centers Treatment dose frequency: 75–375 mg according to dosing table every 2–4 weeks	Week 52 vs baseline (initiation) [39]: Control improvement: good control, 67% vs 0% Rate of exacerbation: 72% reduction (mean, 1.25 [95% CI, 0.55–1.95] vs 4.4 [95% CI, 3.7–5.2]; $P < .0001$) Proportion of patients requiring hospitalization: 6.7% vs 44% (in 1 year before initiation), $P < .001$ Mean improvement in FEV1 (pred): 4.9% (95% CI, 0.69–9.19); $P = .023$ Mean ICS dose (µg/d): 30% reduction; 481 (95% CI, 412–551) vs 703 (95% CI, 642–764), $P < .0001$ 46.7% of patients achieved $\geq 50\%$ reduction At week 104 vs week 52 [40]: Control improvement: good control, 80% vs 67%, respectively Rate of exacerbation: 83% reduction (mean, 0.22 [95% CI, 0.03–0.41]; $P = .0001$) No additional gain in FEV1(pred) Mean ICS dose unchanged
	Deschildre (real-life observational study, France) [41]	6–18 years of age Severe AA Minimum 24-month course of OMA	10 French pediatric pulmonology tertiary centers OMA discontinued at physician discretion Data assessed prospectively at baseline, at 24 months, and at the last scheduled follow-up visit	1/3 with good control and no severe exacerbation stopped OMA after a course of at least 24 months of treatment. Of these, 3/4 successfully achieved discontinuation with no clinical or lung function worsening compared to those still on OMA. OMA restarted for worsening asthma in 8/35 patients within 3–17 months after discontinuation Phenotypic markers that argue for treatment continuation: female gender; allergic comorbidities (atopic dermatitis, food allergy), and lung function (greater airflow limitation)
	Kulus (Study IA05 subgroup analysis) [44]	6 ≤ 12 years of age Severe AA Total serum IgE level 30–1300 IU/mL Inadequately controlled with high-dose ICS (≥ 500 mg/day FP or equivalent) + LABA ± additional controller	RDBPCT 52 weeks As described in Lanier, et al. [45] Treatment dose frequency: 75–375 mg according to dosing table every 2–4 weeks	Exacerbation rate reduction (OMA vs Pbo): Baseline to week 24: 34% (RR, 0.662 [95% CI, 0.441–0.995]; $P = .047$) Baseline to week 52: 50% (RR, 0.504 [95% CI, 0.350–0.725]; $P < .001$) Physicians' evaluation (GETE) excellent or good: OMA, 74.2%; Pbo, 55.3%; $P < .001$ for comparison across all 5 GETE categories
	Lanier (Study IA05) [45]	6 ≤ 12 years of age Moderate-to-severe AA Total serum IgE level 30–1300 IU/mL	RDBPCT 52 weeks, 8-week run-in phase: asthma control optimized. ICS/controller medication dose adjustment during first 4 weeks only. Patients who remained	Exacerbation rate reduction (OMA vs Pbo): Baseline to week 24: 31% (RR, 0.69 [95% CI, 0.53–0.90]; $P = .007$)

Table 1 (continued)

Medication	name & duration	Key inclusion criteria	Study design	Main outcomes
		Uncontrolled with ICS (≥ 200 $\mu\text{g}/\text{d}$ FP or equivalent + 1 reliever as needed) History of severe exacerbation within prior 2 years	symptomatic during the last 4 weeks were randomized to OMA or Pbo 24-week stable-steroid phase: constant ICS dose 28-wk steroid-adjustable phase: ICS dose reduced only if patients met strict predefined criteria Treatment dose frequency: 75–375 mg according to dosing table every 2–4 wk	Baseline to week 52: 43% (RR, 0.57 [95% CI, 0.45–0.73]; $P < .001$) Severe exacerbation rate reduction (OMA vs Pbo): Baseline to week 24: 44% (RR, 0.55 [95% CI, 0.32–0.95]; $P = .031$) Baseline to week 52: 50% (RR, 0.49 [95% CI, 0.30–0.80]; $P = .004$) GETE, excellent or good: Physicians' evaluation OMA, 79%; Pbo, 56%; $P < .001$ for comparison across all 5 GETE categories Patients' evaluation OMA, 80%; Pbo, 72%; $P < .001$ for comparison across all 5 GETE categories Mean (SD) change in pediatric AQLQ domain scores from baseline to week 28: Activity limitations OMA, 0.5 (1.4); Pbo, 0.1 (1.3); $P < .05$ Symptoms domain OMA, 0.3 (1.2); Pbo, 20.0 (1.3); $P < .05$ Emotional function OMA, 0.5 (1.1); Pbo, 0.3 (1.1); $P = \text{ns}$ Overall domains OMA, 0.4 (1.1); Pbo, 0.1 (1.1); $P < .05$ Proportion of patients achieving a clinically relevant improvement in AQLQ domain scores at week 28: Activity limitation OMA, 50.6%; Pbo, 39.5%; $P < .05$ Symptoms OMA, 41.1%; Pbo, 32.6%; $P = \text{ns}$ Emotional function OMA, 45.1%; Pbo, 41.9%; $P = \text{ns}$ Overall domains OMA, 46.9%; Pbo, 33.7%; $P < .05$ Median percentage reduction of ICS dose: OMA, 100%; Pbo, 66.7%; $P = 0.001$ Proportion of patients in whom ICS use was withdrawn completely: OMA, 55%; Pbo, 39%; $P = .004$ Exacerbation rate during steroid-reduction phase: OMA, 18.2%; Pbo, 38.5%; $P < .001$ Physicians' evaluation (GETE) excellent/good: OMA, 31.5/44.7%; Pbo, 16.3/32.7%; $P < .001$ for comparison across all 5 GETE categories
Lemanske (Study 010: AQLQ) [46]	6–12 years of age Moderate-to-severe AA (≥ 1 -year duration) Total serum IgE level of 30–1300 IU/mL Well controlled for ≥ 3 months with ICS (168–420 $\mu\text{g}/\text{day}$ BDP equivalent) + 1 reliever as needed FEV1 (pred) $\geq 60\%$	RDBPCT 28 wk. As described in Milgrom, et al. [47] The pediatric AQLQ was administered at baseline, week 16, and week 28 Treatment dose frequency: 0.016 mg/kg/IgE (IU/mL) per 4 weeks*		
Milgrom (Study 010) [47]	6–12 years of age Moderate-to-severe AA (≥ 1 -year duration) Total serum IgE level of 30–1300 IU/mL Well controlled for ≥ 3 months with ICS (168–420 $\mu\text{g}/\text{day}$ BDP equivalent) + 1 reliever as needed FEV1 (pred) $\geq 60\%$	RDBPCT 28 weeks 4- to 6-week run-in phase: all children switched to equivalent BDP dose, adjusted to maintain asthma control achieved with previous ICS, before randomization to OMA or Pbo 16-week stable-steroid phase: constant ICS dose 12-week steroid-reduction phase: 8-week steroid--reduction phase to minimum effective dose and then maintained for the final 4 weeks Treatment dose frequency: 0.016 mg/kg/IgE (IU/mL) per 4 weeks		
Milgrom (pooled safety analysis) [48]	6–12 years of age Moderate-to-severe AA	RDBPCT $\times 2$; Lanier et al. [45] and Milgrom et al. [47] Children on optimized asthma care (inhaled corticosteroids $\pm$ other controller medications) Randomized (2:1) to OMA (75–375 mg sc, q2 or q4 week) or Pbo		AEs more frequently reported in the Pbo (91.7%) than OMA (89.7%) group Most common AEs were nasopharyngitis, upper respiratory tract infection and headache Suspected treatment-related AEs included headache, erythema and urticaria. None of which were reported by 2% of patients receiving OMA

Table 1 (continued)

Medication	name & duration	Key inclusion criteria	Study design	Main outcomes
Mepolizumab	Silkoff (Study 010) [49]	6–12 years of age Moderate-to-severe AA (≥ 1 -year duration) Total serum IgE level of 30–1300 IU/mL Well controlled for ≥ 3 months with ICS (168–420 $\mu\text{g/day}$ BDP equivalent) + 1 reliever as needed FEV1(pred) $\geq 60\%$	Addendum (2 centers) 52 weeks 28-week core study: patients randomized to receive OMA or Pbo (study design as described in Milgrom et al. [47]) 24-wk extension phase: open-label OMA therapy continued without interruption. Those randomized to Pbo were switched to OMA. Minimum effective ICS dose was maintained Treatment dose frequency: 0.016 mg/kg/IgE (IU/mL) per 4 weeks	Serious AEs (SAEs) reported by 3.4% and 6.6% of patients receiving OMA and Pbo, respectively Most common SAEs: appendicitis, pneumonia, and bronchitis No deaths reported Mean (SD) percentage reduction of ICS dose at week 52 (vs baseline): OMA, 67.4 (65.7); Pbo, 94.2 (15.4) Mean (SEM) reduction in AUC for adjusted FENO: OMA: baseline, 41.9 (29.0) ppm; week 52, 18.0 (21.8) ppb; $P = .032$ Pbo (switched to OMA): week 28, 82.1 (55.6) ppm; week 52, 33.3 (21.6) ppb; $P = .076$
	Teach (PROSE Study) [50]	6–17 y of age Persistent AA (> 1 -year duration) Total serum IgE level 30–1300 IU/mL Uncontrolled with ICS (≥ 200 $\mu\text{g/d}$ FP or equivalent) and ≥ 1 exacerbations requiring OCS or hospitalization in prior 19 mo	RDBPCT 8- to 13-month intervention 4- to 9-month prefall run-in phase: Patients receiving 500 $\mu\text{g/bid}$ FP or equivalent (treatment step 5) randomized (3:1) to OMA or Pbo Patients receiving < 500 $\mu\text{g/bid}$ FP or equivalent (steps 2–4) were randomized (3:3:1) to OMA (1 inhaled placebo), ICS boost (1 injected Pbo), or guidelines-based care with injected and inhaled Pbo 90-day intervention period: Commenced 4–6 wk. before start of school. Treatment step levels remained fixed. Treatment dose frequency: 75–375 mg according to dosing table every 2–4 weeks Multinational, nonrandomised, open-label Mepolizumab SC 40 mg (bodyweight < 40 kg) or 100 mg (≥ 40 kg) every 4 weeks for 12 weeks	Significant reduction in fall exacerbation rate (steps 2–5): OMA, 11.3%; Pbo, 21.0% OR, 0.48 (95% CI, 0.25–0.92); $P = .03$ Reduction in fall exacerbation rate in patient subgroup with ≥ 1 exacerbation during the run-in phase OMA vs Pbo (steps 2–5): 6.4% vs 36.3% OMA vs Pbo (step 5): 18.9% vs 53.0% OMA vs ICS boost (steps 2–4): 2.0% vs 27.8% Reduction in fall exacerbation rate during the run-in phase in patients with ≥ 1 exacerbation vs no exacerbations
Mepolizumab	Gupta [51]	6–11 y of age Severe eosinophilic asthma Blood eosinophil count ≥ 150 cells/ μL at screening or ≥ 300 cells/ μL < 12 months of screening AND ≥ 2 exacerbations in the prior year	Open-label, uncontrolled, repeat-dose extension study 52 weeks Mepolizumab SC 40 mg (bodyweight < 40 kg) or 100 mg (≥ 40 kg) every 4 weeks	At week 12: blood eosinophils were reduced by 89% and 83% from baseline to 42 and 55 cells/ μL in the 40 mg and 100 mg groups, respectively No new safety signals were observed compared with previous adult/adolescent studies 30 children received mepolizumab; 27 (90%) and 7 (23%) experienced on-treatment AEs and serious AEs, respectively Compared with baseline values, mepolizumab treatment reduced blood eosinophil counts and asthma exacerbations and improved asthma control across all treatment groups No serious AEs were treatment-related No fatal AEs
	Gupta [52]	6–11 years of age Severe eosinophilic asthma Blood eosinophil count ≥ 150 cells/ μL at screening or ≥ 300 cells/ μL < 12 months of screening and ≥ 2 exacerbations in the prior year	Open-label, uncontrolled, repeat-dose extension study 52 weeks Mepolizumab SC 40 mg (bodyweight < 40 kg) or 100 mg (≥ 40 kg) every 4 weeks	At week 12: blood eosinophils were reduced by 89% and 83% from baseline to 42 and 55 cells/ μL in the 40 mg and 100 mg groups, respectively No new safety signals were observed compared with previous adult/adolescent studies 30 children received mepolizumab; 27 (90%) and 7 (23%) experienced on-treatment AEs and serious AEs, respectively Compared with baseline values, mepolizumab treatment reduced blood eosinophil counts and asthma exacerbations and improved asthma control across all treatment groups No serious AEs were treatment-related No fatal AEs

Table 1 (continued)

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Medication	name & duration	Key inclusion criteria	Study design	Main outcomes
	Corren [58, 59]	≥ 12 years of age ICS + 1–2 other controller medications Allergic asthma (total serum IgE ≥ 30 IU/mL and ≥ 1 perennial aeroallergen-specific IgE ≥ 0.35 kU/L at baseline)	screening period, 52-week randomized treatment period, and 12-week post-treatment follow-up period. Multinational, multicenter RDBPCT 52 weeks Randomized 2:2:1:1 to receive add-on therapy with subcutaneously administered dupilumab 200 or 300 mg every 2 weeks or matched placebo 4 ± 1-week screening period, 52-week randomized treatment period, and 12-week post-treatment follow-up period.	dupilumab as compared with 4 patients (0.6%) who received placebo Both dupilumab doses significantly improved 5-item Asthma Control Questionnaire (ACQ-5) and Asthma Quality of Life Questionnaire (AQLQ) scores through week 24 (all outcomes, overall population) [58] In the allergic asthma subgroup (<i>n</i> = 1083), dupilumab 200/300 mg every 2 weeks versus placebo reduced severe asthma exacerbation rates (− 36.9%/− 45.5%; both <i>P</i> < .01), improved FEV1 at week 12 (0.13 L/0.16 L; both <i>P</i> < .001 [59]) Improvements were evident by the first evaluation at week 2 with greater efficacy observed in patients with elevated type 2 inflammatory biomarkers (blood eosinophils and fractional exhaled nitric oxide) at baseline, and improved asthma control.
	Rabe (LIBERTY ASTHMA VENTURE) [60]	≥ 12 years of age Physician diagnosed asthma ≥ 1 year Regular systemic glucocorticoids in the previous 6 months (5 to 35 mg per day of prednisone or prednisolone or equivalent)	RDBPCT 24 weeks Add-on dupilumab (at a dose of 300 mg) or placebo every 2 weeks for 24 weeks After a glucocorticoid dose-adjustment period before randomization, glucocorticoid doses were adjusted in a downward trend from week 4 to week 20 and then maintained at a stable dose for 4 weeks	% in the glucocorticoid dose − 70.1% in the dupilumab group, as compared with − 41.9% in the placebo group (<i>P</i> < 0.001) 48% versus 25% completely discontinued oral glucocorticoid use Despite reductions in the glucocorticoid dose, in the overall population, dupilumab treatment resulted in a severe exacerbation rate that was 59% (95% confidence interval [CI], 37 to 74) lower than that in the placebo group Injection-site reactions were more common with dupilumab than with placebo (9% vs. 4%) Transient blood eosinophilia observed in more patients in the dupilumab group than in the placebo group (14% vs. 1%)

Abbreviations: FEV1 forced expiratory volume in 1 s; IgE immunoglobulin-E; IL interleukin; SC subcutaneously; IV intravenous; OCS oral corticosteroid; QoL quality of life; TSLP thymic stromal lymphopoietin; CPK creatine phosphokinase; FP fluticasone propionate; GETE Global Evaluation of Treatment Effectiveness; *ns* no statistically significant difference; OLE open-label extension; RDBPCT Randomized, Double-Blind, Placebo-Controlled Trial; OMA omalizumab; OR odds ratio; *Pbo* placebo; RR rate ratio

previously described the “September Epidemic of Asthma” which refers to the increase in asthma exacerbations when children return to school in the fall. This has been attributed to both increased allergen and respiratory virus exposure [80]. Busse’s study showed the most notable reduction in exacerbations during high-risk times of the year from children which was further supported by nasal swabs that confirmed a rhinovirus upper respiratory infection in a significant proportion of patients with seasonal exacerbations [36]. The Preventative Omalizumab or Step-up Therapy for Fall Exacerbations (PROSE) protocol was designed to detect if the addition of omalizumab prior to school resuming the fall session and for the following 4 months would protect children ages 6–17 years of age at high risk for asthma exacerbation due to higher prevalence of respiratory viruses during this time of the year [50]. A unique strength of this study was the 4–9 month pre-trial period where asthma control was achieved in each enrolled subject with guideline-directed care prior to randomization to omalizumab or placebo at 1 month prior to their re-entry into school. As predicted, the frequency of fall exacerbations was patients receiving omalizumab was significantly reduced [50].

Omalizumab was generally well tolerated with the most common adverse effect being transient injection site reactions [81]. A small study from Hendeles, et al. with 15 participants showed that omalizumab may represent an alternative therapy for patients with recalcitrant non-adherence to daily ICS therapy that fails to improve with conventional educational interventions [82]. Har et al. showed that children with moderate to severe persistent asthma and sensitization to multiple aeroallergens who received either omalizumab or combination therapy (omalizumab and subcutaneous immunotherapy or SCIT) had significantly lower rates of systemic reactions compared to SCIT alone which suggests that omalizumab may be used as a bridge to safely administer SCIT in patients with allergic asthma.

The safety data derived from multiple sources including clinical trials, observational studies, and post-marketing monitoring show an overall favorable safety and tolerability profile for omalizumab in children and adolescents [34, 38, 48, 83, 84]. Anaphylaxis has not been observed in pediatric studies unlike in adolescent and adult studies [39, 40]. The most frequently reported side effects were mild to moderate injection site reactions in up to 44% of patients in the initial studies that lasted 3–14 days, but resolved without specific intervention [34, 83]. Finally, there is no evidence to support an increased risk of malignancy in patients treated with omalizumab [38, 48]. Long-term monitoring of treated patients is still ongoing to further support this overall favorable safety profile. Despite the above evidence, the optimal selection of pediatric patients remains somewhat unanswered. Phenotypic features that predict a favorable clinical response include severe asthma with multiple allergic disease comorbidities, elevated serum

eosinophils, high total IgE, and elevated FeNO [37, 81]. Currently, there is limited evidence to support the use of omalizumab in children < 6 years of age, very high IgE levels > 1500 IU/mL, and non-allergic severe asthma phenotypes. Preliminary studies have been performed in non-allergic children [85] and children with excessively high IgE levels [86] with encouraging results, but more study would be needed.

Omalizumab is currently being evaluated as a potential disease-modifying and preventative therapy. The Preventing Asthma in High-Risk Kids (PARK; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02570984) Identifier: NCT02570984) study is a randomized, double-blind, placebo-controlled trial designed to examine if 2 years of omalizumab therapy can reduce the risk of progression to persistent asthma in high-risk 2–3-year-olds as reflected in the prevalence of active asthma in the final 12 months of a 2-year observation period of the study of drugs [87]. Asthma severity would be another primary outcome. Secondary outcome measures include the number of new allergic sensitization measured via skin prick test (SPT) and a decrease in the number of wheezing episodes. This study is actively recruiting and the estimated study completion date is November 27, 2025. Overall, the combination of clinical trial and real-world data supports the use of omalizumab for the treatment of both adults and children with severe asthma with evidence of Th2 inflammation and comorbid allergic sensitization [16••].

Biologic Therapy: Mepolizumab

Mepolizumab is a humanized, IgG1 monoclonal antibody (mAb) targeting interleukin-5 (IL-5) used to treat severe asthma with an eosinophilic phenotype. IL-5, whose expression has been associated with the exacerbation of later-onset or less-atopic asthma [88, 89], regulates various aspects of eosinophilic inflammation including their proliferation, maturation, and activation [90].

Mepolizumab is indicated for use in patients aged 6 years or older with severe eosinophilic asthma in several countries including the United States, European Union, and Japan. The safety and efficacy of mepolizumab in adolescents have been evaluated in multiple trials [91–94]. These studies established that mepolizumab was efficacious, reduced asthma exacerbations in a durable manner, and improved health-related quality of life (HRQoL) in patients with severe eosinophilic asthma. Long-term studies have also suggested a safety profile that was mostly similar to placebo [92]. In a network meta-analysis that compared the relative efficacy of several biologics used in the treatment of eosinophilic asthma, mepolizumab demonstrated the biggest improvement in terms of asthma control questionnaire (ACQ) scores and the second greatest magnitude of effect in asthma quality of life questionnaire (AQLQ) scores among all anti-IL-4, IL-5, and IL-13 mAbs studied. However, it also had the least improvement

in forced expiratory volume in 1 s (FEV1), compared to all other approved mAbs in the study [88].

Mepolizumab received approval by The US Food and Drug Administration (FDA) to treat severe asthma with an eosinophilic phenotype in the pediatric population aged 6–11 years based on evidence from a non-randomized, open-label, phase 2 trial and its long-term extension study that evaluated safety and pharmacodynamics [51, 52]. In the first part of the study, children aged 6–11 years ($N = 36$) received either 40 mg or 100 mg of mepolizumab subcutaneously once every 4 weeks during the treatment period of 12 weeks (a total of 3 doses) based on their body weight group. There was an additional 8-week follow-up period after which patients who completed all doses and assessments and opted to continue receiving mepolizumab entered the long-term extension where they received 13 more doses of the medication subcutaneously once every 4 weeks. At the end of the initial treatment period, mepolizumab reduced blood eosinophil counts by 83–89%. In the long-term safety study, adverse events (AEs) were reported in 90% of patients, of which 27% were deemed as mepolizumab-related and resolved without treatment interruption. The most common AEs were bronchitis, headache, and asthma exacerbation. Twenty-three percent of patients had a serious adverse event (SAE), but none of the SAEs were judged to be mepolizumab-related. It should be noted that the study had several limitations. Due to the open-label nature and the objectives of the study, no placebo or comparator groups were included, making direct efficacy or safety comparisons impossible. Recruiting challenges for trials in the age group also meant a small sample size, further limiting efficacy assessments. While there is ample amount of data for mepolizumab use in adolescents, the use of mepolizumab in the age group 6–11 years has only been studied up to a period of 80 months so far and may require additional investigation to validate the long-term safety and efficacy in this population [52]. However, at the time of writing, mepolizumab remains the only therapy approved to treat severe eosinophilic asthma in this younger pediatric population. Given the relatively similar safety profile compared to adolescents and the limited treatment options for eosinophilic asthma in younger children, mepolizumab may be considered a viable therapy choice.

Biologic Therapy: Benralizumab

Benralizumab is another humanized, IgG1 monoclonal antibody (mAB) targeting interleukin-5 (IL-5) used to treat severe eosinophilic asthma. It is the first and currently only anti-eosinophil monoclonal antibody that binds directly to the IL-5 receptor α on eosinophils [95]. In addition, it attracts natural killer cells to induce apoptosis of eosinophils without the release of inflammatory mediators [95]. As a result, it decreases the eosinophil count and reduces asthma exacerbations.

Benralizumab was initially approved for use in patients 18–75 years with severe eosinophilic asthma. It showed a reduction in asthma exacerbations and improved lung function as measured by the forced expiratory volume in 1 s (FEV1) [53–55]. Benralizumab later received approval by the US Food and Drug Administration (FDA) as add-on maintenance treatment for patients with severe eosinophilic asthma aged 12–75 years as supported by data in randomized, double-blind, parallel-group, placebo-controlled phase 3 studies [53, 55]. Presently, there is a study enrolling children aged 6 to 11 years with severe eosinophilic asthma to assess the pharmacokinetics, pharmacodynamics, and long-term safety of benralizumab administered subcutaneously (ClinicalTrials.gov, NCT04305405).

In the CALIMA and SIRROCO studies, patients were randomly assigned to receive benralizumab 30 mg every 4 weeks, benralizumab 30 mg every 8 weeks, or placebo. For the CALIMA study, they received treatment for 56 weeks and for the SIRROCO study for 48 weeks. The primary endpoint was the annual exacerbation rate ratio versus placebo and secondary endpoints of prebronchodilator FEV1 and total asthma symptom score [53, 55]. The results confirmed a reduction in annual asthma exacerbation rate with increased prebronchodilator FEV1 in patients. The most common adverse events were nasopharyngitis and upper respiratory tract infections with the rate of AEs to be similar in both groups. Overall, benralizumab appears to have clear benefits including a reduction in asthma exacerbations with an improvement in FEV1 and the added benefit of the least frequent dosing schedule among the biologics.

Biologic Therapy: Dupilumab

Dupilumab is a fully human IgG4 monoclonal antibody which targets the interleukin-4 receptor alpha (IL-4R α) subunit. Since the cytokines IL-4 and IL-13 signal through IL-4R α , dupilumab binding to the shared receptor complex inhibits signaling by both cytokines and thus inhibits their overlapping functions [96]. IL-4 and IL-13 are secreted primarily by Th2 cells and innate lymphoid type 2 cells (ILC2) and are central drivers of type 2 inflammation [97–99]. These cytokines are also produced by basophils, natural killer (NK) cells, mast cells, and eosinophils [98, 99]. IL-4 plays a critical and unique role in Th2 cell differentiation that then produce large quantities of IL-4, IL-5, and IL-13 [96, 98]. IL-4 and IL-13 recruit and activate inflammatory cells, including eosinophils, and induce class switching of B cells, thus mediating the production of allergen-specific IgE [98, 100, 101]. IL-13 has been implicated in airway remodeling through its effects on airway epithelium and smooth muscle [98, 101]. Since pediatric asthma is most commonly distinguished by a Th2 cytokine profile and IgE-mediated allergen sensitization, blocking the underlying cytokines simultaneously via their shared functional receptor represents a viable therapeutic strategy [102, 103].

Dupilumab is currently approved in the United States as an add-on maintenance therapy to treat patients aged 12 years and older with poorly controlled moderate-to-severe eosinophilic asthma. It is also approved in Europe as an add-on maintenance treatment in adolescents aged 12 years and older for severe asthma. Multiple global clinical trials that investigated the safety and efficacy of dupilumab in treating asthma in this population have demonstrated improved outcomes including lower oral glucocorticoid use, reduced rates of exacerbation of asthma, better lung function, and improved quality of life as well as a somewhat benign safety profile [56–60]. However, it should be noted that somewhat higher rates of eosinophilia were observed in patient groups receiving dupilumab compared to those in the placebo groups [57, 60]. In a network meta-analysis comparing the relative efficacy of biologics used to treat eosinophilic asthma, dupilumab demonstrated the greatest improvement in lung function and HRQoL as measured by FEV1 and AQLQ, respectively [88].

Dupilumab has also been approved in the US to treat other type 2 inflammatory disorders like atopic dermatitis (AD) in patients who are 12 years and older and in other regions such as Europe and Japan in adult patients [104]. Dupilumab is being investigated in a randomized, double-blind study for the treatment of uncontrolled persistent asthma in this younger pediatric population of 6–11 years (VOYAGE), and recruitment has been completed ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02948959), NCT02948959). As of February 2020, dupilumab is under priority review by the US FDA for approval as an add-on maintenance treatment for children aged 6–11 years with moderate-to-severe AD, based on phase 3 data that demonstrated that it improved clinical outcomes and HRQoL measures in this age group ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03345914), NCT03345914). Dupilumab is also being evaluated as an adjunct therapy to peanut oral immunotherapy in pediatric subjects with a peanut allergy ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03682770), NCT03682770).

Biologic Therapy: Reslizumab

Reslizumab, like mepolizumab, is a humanized mAB against IL-5 used to treat severe eosinophilic asthma. Its clinical efficacy was established in patients aged 12–75 years in multiple double-blind, randomized, placebo-controlled studies [105, 106]. Presently, there are no studies ongoing evaluating reslizumab in pediatric asthma, though there is data with this biologic in eosinophilic esophagitis down to the age of 5 [107].

The adult and adolescent studies in asthma demonstrated those who received intravenous reslizumab at 3 mg/kg every 4 weeks for 52 weeks had a significant reduction in asthma exacerbation frequency by up to 59% compared with placebo [106]. In addition, patients experienced a significant increase in FEV1 of 0.1–0.2 L relative to placebo over 16 weeks of therapy [106]. The benefit was noted at 4 weeks of reslizumab in all studies [105, 106] and maintained at 52 weeks [105]. Compared with placebo, reslizumab also showed significant

improvement in asthma symptoms as measured by the Asthma Symptom Utility Index (ASUI) and Asthma Control Questionnaire (ACQ), quality of life as measured by Asthma Quality of Life Questionnaire (AQLQ), and blood eosinophil count [105]. In an open-label extension study, reslizumab continued for up to 2 years was associated with durable lung function benefit [108].

One study investigated the safety profile of intravenous reslizumab by analyzing data from 5 placebo-controlled trials and 1 open-label extension and found AEs and serious AEs occurred in higher percentages of patients in the placebo group (81% and 9%) than the reslizumab group (67% and 6%) [109]. Overall, worsening asthma, nasopharyngitis, and upper respiratory infections were the most common AEs. Reslizumab is well tolerated, however, with a rare risk of anaphylaxis as documented in a few cases [109]. Reslizumab has shown long-term safety and sustained long-term efficacy in lung function.

Biologic Therapy: Tezepelumab

Recently, thymic stromal lymphopoietin (TSLP) has emerged as an important cytokine that modulates multiple inflammatory pathways including those in asthma [110, 111]. In fact, high concentrations of TSLP have been found in the lungs of asthmatics correlating with Th2 responses and disease severity [110, 111]. A genetic evaluation has also found specific TSLP polymorphisms being associated with a higher risk of developing asthma [112]. TSLP is involved in the inflammatory response by binding to a high-affinity receptor complex composed of the TSLP receptor and IL-7R α . In a pediatric study, TSLP was found to be significantly more elevated in patients with asthma and negatively correlated with asthma control test and T regulatory cells. Therefore, TSLP may be used as a biomarker for inflammation in pediatric asthma patients [113]. Tezepelumab is the first monoclonal antibody that binds to TSLP hindering the binding of it to the TSLP receptor complex. Studies are exploring this therapy as an add-on treatment option for those with moderate-to-severe poorly controlled asthma.

Tezepelumab was initially evaluated in a double-blind, placebo-controlled trial in 31 adult patients with mild allergic asthma. Patients received three monthly doses of tezepelumab (700 mg intravenous) or placebo. They found that those who received tezepelumab had a reduction in the allergen-induced bronchoconstriction during the early and late allergen challenges, decreased blood and sputum eosinophils, and a reduction in FeNO [114]. In a phase II randomized, double-blind, placebo-controlled trial, 584 adult patients were randomized to receive low (70 mg), medium (145 mg), or high doses (210 mg) of tezepelumab or placebo every 4 weeks. The primary endpoint showed a reduction in annual exacerbation rates of 61%, 71%, and 66% for low, medium, and high doses,

respectively. The overall prebronchodilator FEV1 was greater in the three tezepelumab groups than in placebo [115••].

At this time, tezepelumab has not been studied in the pediatric population; however, there is an anticipated study that will evaluate tezepelumab in adults and adolescents with severe uncontrolled asthma for those aged 12 to 80 years. Overall, tezepelumab appears to be a novel biologic therapy in patients with uncontrolled asthma. It may also be an option specifically for patients who are not responding to other biologic therapies.

Conclusion

Pediatric asthma is one of the most common chronic conditions of childhood. For most children, medications such as inhaled corticosteroids, leukotriene receptor antagonists, and long-acting beta-agonists, along with environmental control measures and allergen immunotherapy, can keep their asthma under control. Unfortunately, there is a small percent of pediatric asthma sufferers who fail these treatments and may need repeated courses of corticosteroids for exacerbations. These are the high-cost patients who are at a greater risk for emergency department visits and hospitalizations [116, 117].

Monoclonal antibody therapy may be an effective option in these difficult to control pediatric patients. In a review of the clinical studies published in the pediatric population, omalizumab has the most extensive database, showing improvement in asthma control and decreased exacerbations down to the age of 6. So far, its safety profile is encouraging with no serious adverse events in children. Mepolizumab, which has an indication for pediatric asthma with an eosinophilia phenotype down to 6 years, was extrapolated from efficacy in adults and adolescents with support from pharmacokinetic analyses and shows a safety profile similar to seen in adult and adolescent studies [51, 52]. Other monoclonal antibody treatments may be approved in the pediatric population in the near future. Very importantly, what is the efficacy and safety with the long-term use of these agents in young children? Are there safety differences over time than what is seen in the adult population? When is it safe to stop treatment once it is started in a child? We must be cognizant that we do not know if any of these targeted treatments will have an effect on the natural history of childhood asthma. Hopefully, over time, these questions will be answered.

Compliance with Ethical Standards

Conflict of Interest Michael S. Blaiss, MD, has received an honorarium for consulting and speaking for Sanofi/Genzyme and Regeneron. No other authors have any conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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