



Prospects for Monoclonal Antibody Therapy in Pediatric Asthma

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Abstract

Purpose of Review The profile of biologic therapies for asthma is growing rapidly. We discuss how to match the proper pediatric patient with the most effective therapy.

Recent Findings Currently available biologic therapies are most effective in patients with T2 high asthma. Newer drugs are currently being studied which target TSLP and interleukin 33. These newer drugs may provide options for asthmatics who do not respond to the current anti-IgE, anti-IL5, and anti-IL4/13 therapies.

Summary Asthma is a heterogeneous disease which can be driven by different inflammatory mediators in different patients. To select the most effective biologic therapy for a pediatric patient, the asthma phenotype must first be determined. The steep cost of biologics limits their use, which makes proper pairing of patient to therapy even more crucial. Presently, several therapies exist for T2 high asthma, but it is hoped in the future that development of drugs effective for T2 low asthmatics will be available as well.

Keywords Asthma · Children · Pediatrics · Biologic therapy · T2 high

Introduction

Asthma, a chronic inflammatory disorder characterized by reversible airflow obstruction, is the most common chronic lung disease of childhood [1, 2]. In 2016, more than 6.1 million pediatric patients were affected with asthma in the USA [3]. While most are well-controlled with low-to-medium dose inhaled corticosteroids (ICS), approximately 5% have severe disease, characterized by poor control despite treatment with high dose ICS or oral corticosteroids (OCS) [1, 4]. Many with severe asthma present between 6 and 11 years of age, but have onset of asthma symptoms in the first 3 years of life. In comparison, those with mild to moderate asthma present in the first 5 years of life [1].

Having severe asthma places children at risk for increased morbidity and mortality as a consequence of asthma exacerbations. Asthma lability can also negatively impact a child's quality of life, including academic performance and ability to participate in daily activities such as school-related functions

[4]. Asthma is also a very common cause of missed school days, with children missing a total of 13.8 million school days in 2013 due to asthma morbidity [5].

Asthma results in a profound economic burden, costing the USA approximately \$56 billion per year [6]. Though only 5% of asthmatics have severe disease, this group accounts for nearly 50% of all asthma-related spending [1, 4]. These expenditures include direct and indirect costs such as physician visits, hospitalizations, medications, and missed days from school and work [4].

In recent years, it has become well accepted that asthma is a heterogeneous illness with varying phenotypes [1, 2, 4]. The most common subgroup is characterized by a T helper 2 (T2) lymphocyte-mediated inflammation, which is present in about 50% of asthmatics. T2 lymphocyte-mediated asthma, or “T2 high” asthma, has biomarkers which include elevation of sputum and/or blood eosinophils, total serum IgE, and the fraction of exhaled nitric oxide (FeNO). Children with severe asthma typically are also more atopic (with increased allergic sensitization, demonstrated by specific IgE or skin prick testing to aeroallergens), have a higher prevalence of atopic dermatitis, and demonstrate an increase in bronchial hyperresponsiveness [1].

Biologic therapies, aimed at either IgE or eosinophils, are currently being utilized for T2 high inflammatory conditions, including asthma (Table 1). The 2016 GINA guidelines recommend that biologics be used as the ultimate add-on step for

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Table 1 Comparison of biologic therapies

Monoclonal antibody	Mechanism of action	Administration method and dosing schedule	Criteria for approval	Parameters of improvement	Currently approved ages	Currently approved indications
Omalizumab	Anti-IgE (binds circulating IgE)	For asthma: subcutaneous, every 2–4 weeks (dose and frequency guided by a nomogram derived from the total serum IgE level and BMI)	Positive skin or blood test result for ≥ 1 perennial aeroallergen; pretreatment total serum IgE levels within specified range*	Exacerbation rate, FEV1, ICS use, rescue medication use, asthma control***	≥ 6 years old for asthma	Asthma; chronic idiopathic urticaria
Mepolizumab	Anti-IL-5 (binds circulating IL-5)	Subcutaneous, 100 mg, every 4 weeks	Absolute eosinophil count ≥ 150 cells/ μ L at screening or ≥ 300 cells/ μ L within 12 months before initiation	Exacerbation rate, FEV1, health-related quality of life, maintenance OCS dose**	≥ 12 years old	Asthma; eosinophilic granulomatosis with polyangiitis
Reslizumab	Anti-IL-5 (binds circulating IL-5)	Intravenous, 3 mg/kg, every 4 weeks	Absolute eosinophil count ≥ 400 cells/ μ L	Exacerbation rate, FEV1, health-related quality of life, time to first exacerbation**	≥ 18 years old	Asthma
Benralizumab	Anti-IL-5 receptor α	Subcutaneous, 30 mg every 4 weeks for the first 3 doses followed by every 8 weeks thereafter	No specific eosinophil count	Exacerbation rate, FEV1, health-related quality of life, maintenance OCS dose**	≥ 12 years old	Asthma
Dupilumab	Anti-IL-4 receptor α	Not yet approved for asthma	Not yet approved for asthma	Exacerbation rates, FEV1, health-related quality of life, maintenance OCS dose**	Not yet approved for asthma	Atopic dermatitis

* ≥ 6 to 11 years old: total IgE level 30 to 1300 IU/mL; ≥ 12 years old: total IgE level 30 to 700 IU/mL)

**per phase 3 studies

severe persistent asthma in those with the appropriate phenotype [2]. These biologic agents are also presently approved for the treatment of patients with atopic dermatitis, chronic idiopathic urticaria, and eosinophilic granulomatosis with polyangiitis, and are being evaluated in related conditions such as eosinophilic esophagitis, hypereosinophilic syndrome, and sinusitis. With regard to asthma, these therapies have demonstrated improvement in asthma control by preventing chronic symptoms, decreasing use of short-acting β_2 -agonists, improving activity levels, preventing loss of lung function, preventing exacerbations, and minimizing requirement for emergency care and hospitalizations. They have also been shown to be steroid-sparing, which is especially beneficial in children, who are more susceptible to the adverse growth and bone maturation effects of ICS.

While some biologic agents are approved in children, others are currently indicated for adults only. Most however are now being studied in children, and will likely be available for children in the future. In this review, we focus on the current biologic treatments available for asthma, focusing specifically on their potential use in the pediatric population.

Pathophysiology of Asthma

The majority of our current knowledge regarding asthma pathophysiology surrounds the T2 high phenotype, which includes the following key mediators: IgE, IL-4, IL-5, and IL-13. It is these mediators that have become the targets for monoclonal antibody therapy in asthma, and thus our review will focus on this asthma subgroup.

The process of sensitization in an atopic asthmatic begins with exposure of the respiratory mucosal surfaces to an inhaled allergen. This results in production of IgE specific to that allergen. Allergen-specific IgE binds to mast cells where it awaits re-exposure. Upon re-exposure to the allergen, cross-linking of the IgE antibodies bound to mast cells and basophils occurs, resulting in degranulation and release of mediators, such as histamine, prostaglandins, and leukotrienes [2]. Dendritic cells, functioning as antigen presenting cells, then bind to T2 lymphocytes, resulting in the secretion of multiple cytokines including IL-4, IL-5, and IL-13 [2]. The release of IL-4 and IL-13 leads to proliferation of bronchial fibroblasts, myofibroblasts, and airway smooth muscle cells, which can result in airway remodeling [7]. IL-13 also has a role in goblet cell differentiation, mucus production, bronchial hyperresponsiveness, IgE synthesis, and the recruitment of eosinophils and basophils [7]. IL-4 stimulates further differentiation of T2 cells as well as promotes B cell class switching to IgE synthesis which helps to perpetuate the process [2].

In eosinophilic asthma, IL-5 and IL-33 are key drivers of the inflammatory process because they directly stimulate eosinophils, as well as basophils and mast cells [2]. IL-33 promotes naive T cell differentiation into T2 cells which results in

secretion of IL-5 [2]. IL-5 is then responsible for the growth, survival, and activation of eosinophils [2]. When activated, eosinophils release multiple inflammatory mediators including leukotrienes and thromboxane, as well as tissue-damaging proteins such as major basic protein and eosinophil cationic protein [2]. The release of these mediators leads to bronchoconstriction, bronchial hyperresponsiveness, and airway remodeling [2]. IL-33 also plays a crucial role in the chronic inflammatory process and the airway remodeling of asthma [2].

A very different asthma phenotype, known as T2 low, has also been recognized and is associated with a neutrophil predominance or pauci-cellular disease process [8, 9]. Not surprisingly, the T2 low phenotype is not responsive to therapy such as corticosteroids or present biologic therapies which are directed towards the eosinophil or other T2-associated mediators. Thus, before initiating therapy, it is important to determine T2 high versus T2 low phenotype in the patient as this will greatly impact response to treatment. Further research is necessary to better understand the pathophysiology of the T2 low response, as this is likely also a heterogeneous group which will require varied biologic agents to achieve optimal efficacy.

Anti-IgE Therapy

Omalizumab

Omalizumab was the first biologic agent approved by the FDA for use in asthma [2, 10]. It is a recombinant humanized monoclonal antibody directed against immunoglobulin E (IgE) [11•]. It decreases levels of circulating IgE by binding to the Fc portion of the free IgE, thus inhibiting the binding of IgE to high affinity IgE receptors [12•, 13]. This, in turn, results in downregulation of the expression of high-affinity IgE receptors on mast cells and basophils [12•, 13]. Through these mechanisms, the subsequent allergic inflammatory cascade is inhibited [12•, 13].

Current indications for omalizumab treatment include moderate-to-severe uncontrolled allergic asthma (for patients ≥ 6 years old) and chronic spontaneous urticaria (for patients ≥ 12 years old) that is inadequately controlled despite treatment with H1 antihistamines [14]. With regard to asthma, omalizumab is administered every 2–4 weeks in patients with allergic asthma who are sensitized to at least one perennial aeroallergen and a serum IgE level > 30 [1, 4].

Specifically in children aged 6–12 years with severe asthma, two randomized, placebo-controlled studies demonstrated reduction in ICS dose and number of exacerbations with the addition of omalizumab [4, 15, 16]. In a separate study by Busse and colleagues, the authors found that in inner-city children and young adults with allergic asthma, treatment with omalizumab as an add-on to guideline-based step-therapy

improved asthma control, nearly eliminated seasonal peaks in exacerbations, and reduced the need for additional medications to control asthma [17]. Moreover, Teach and colleagues found that in inner-city children (age 6–17 years old) with allergic asthma and ≥ 1 asthma exacerbations in the previous 19 months, adding omalizumab to ICS 4 to 6 weeks before the return of school reduced fall asthma exacerbations, especially in children with severe asthma and those with a recent exacerbation [18•].

Both randomized controlled trials (RCTs) and real world studies (RWS) strongly support the efficacy of omalizumab as an add-on treatment in children 6 to 11 years old with moderate-to-severe persistent allergic asthma [11•, 12•]. In both RCTs and RWS, treatment with omalizumab resulted in a decrease in the mean rate of annual exacerbations, reduction in inhaled corticosteroid use, and reduction in rescue medication use [11•, 12, 15, 17, 19–24]. RWS also demonstrated improvement in forced expiratory volume in the first second of expiration (FEV1) as well as significant improvement in the level of asthma control observed over 1 year [11•, 12, 20, 22–25].

There is also evidence that omalizumab treatment results in fewer hospitalizations, emergency department visits, and unscheduled medical visits [11•, 12, 15, 17, 20, 24, 26]. Moreover, a retrospective study evaluating pooled spirometry data of adolescents in eight clinical trials showed that omalizumab resulted in clinically meaningful improvement in lung function [27]. Building upon omalizumab's efficacy in children, there is a clinical trial, which is about to begin, evaluating whether asthma can be prevented with its early introduction in preschool children aged 2–3 years at high risk for asthma [28].

Regarding this agent's safety profile, a Cochrane review and systematic literature review has found that omalizumab is overall safe and well-tolerated for pediatric patients in the treatment of asthma. The most common adverse reactions in pediatric patients (6 to 12 years old) in the clinical trials were nasopharyngitis, headache, pyrexia, upper abdominal pain, streptococcal pharyngitis, otitis media, viral gastroenteritis, arthropod bites, and epistaxis [11•, 12•, 29]. However, a meta-analysis of three RCTs indicated that the frequency of adverse events and serious adverse events (anaphylaxis, urticaria, hypersensitivity reactions, or malignancies) were similar between omalizumab and placebo [11•, 12•]. Nevertheless, omalizumab still has a boxed warning about its potential for anaphylaxis, and patients are prescribed epinephrine autoinjectors.

Anti-IL-5 Therapy

As noted earlier, eosinophils are elevated in the lung and sputum of those with T2 high asthma. Because interleukin-5 (IL-5) is the cytokine that mediates eosinophil development, recruitment, and activation, it has been a focus in asthma

treatment for the eosinophilic phenotype [10, 30]. IL-5 binds to the IL-5 receptor (IL-5R) complex on the cell surface of eosinophils. Currently, there are three available monoclonal antibodies targeting IL-5 activity: mepolizumab, reslizumab, and benralizumab. All three of these biologic agents are approved as add-on maintenance treatment of patients with severe persistent asthma. All markedly reduce blood eosinophils, but benralizumab results in almost complete depletion [30, 31], possibly due to its unique mechanism of action which we will discuss below. It is however important to note that there have been no head-to-head studies between these agents, and thus it is uncertain whether this mechanistic difference between agents translates to greater clinical efficacy.

Mepolizumab

Mepolizumab is a humanized monoclonal antibody, which directly binds to IL-5 [10]. By binding circulating IL-5, mepolizumab prevents binding of IL-5 to IL-5R on eosinophils which effectively neutralize the cytokine. Mepolizumab is indicated for patients with severe asthma who are at least 12 years old, with an absolute eosinophil count ≥ 150 cells/ μ L at screening or ≥ 300 cells/ μ L within 12 months before initiation [30]. The dose for asthma is 100 mg administered subcutaneously every 4 weeks [32].

The Dose Ranging, Efficacy, and Safety with Mepolizumab in Severe Asthma (DREAM) study was a randomized, double-blind, placebo-controlled trial consisting of patients with a history of recurrent severe asthma exacerbations and eosinophilic inflammation [33]. In this study, mepolizumab was found to reduce blood and sputum eosinophils, rate of exacerbations per patient per year, and number of exacerbations requiring hospitalization or ED visit; additionally, it delayed the time to first exacerbation [33]. However, no significant difference was found in FEV1, asthma quality of life questionnaire (AQLQ) scores, or asthma control questionnaire (ACQ) scores [33]. Of note, demographics suggest that no pediatric patients were actually enrolled in this study even though eligibility included those 12 years and older [10, 33].

Meanwhile, in the Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) trial, a double-blind, double-dummy, and 32-week study consisting of patients 12 to 82 years old with recurrent asthma exacerbations and eosinophilic inflammation despite high dose ICS, mepolizumab was found to improve FEV1 and St. George's Respiratory Questionnaire (SGRQ; assesses quality of life) scores. Improvement in ACQ scores did not meet criteria for clinical importance [34]. Much like in the DREAM study, this trial showed improvement in rates of all exacerbations (reduced by approximately 50%), and exacerbations requiring a hospitalization or ED visit (reduced by 32–61%) [34].

Additionally, in the Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma (SIRIUS) study, a

randomized, double-blind trial of asthmatic patients at least 12 years old with serum eosinophilia and who required maintenance OCS for at least 6 months, mepolizumab was found to allow reduction in OCS dose compared with placebo [35]. Patients assigned to mepolizumab experienced a 50% median reduction in daily OCS use from baseline; in addition, these patients also had reduction in annualized rate of asthma exacerbations by 32%, and improved ACQ scores despite reducing their OCS dose [35]. There was not a significant improvement in FEV1 by the end of the 24-week trial, however.

An open-label extension of the MENSA and SIRIUS studies was performed for a further 52 weeks, known as the long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma (COSMOS) study [36•]. The COSMOS study (included patients ≥ 12 years of age) supported the durability of the findings of the MENSA and SIRIUS studies by demonstrating maintenance of a lower OCS dose and lower asthma exacerbation rate in patients who had received mepolizumab in their previous study, and improvements in these outcomes in patients who were given mepolizumab in this study after previously being assigned to placebo [36•].

Furthermore, the mepolizumab adjunctive therapy in subjects with severe eosinophilic asthma (MUSCA) trial (a randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase 3b trial that involved patients at least 12 years old) showed that mepolizumab was associated with significant improvements in health-related quality of life (based on SGRQ) [37•].

In the above studies, results stratified by age are not readily available. However, per the drug's package insert, a total of 28 adolescents aged 12 to 17 years old were enrolled in their phase 3 studies [32]. It was reported however that adolescents had a reduction in exacerbation rate that trended in favor of mepolizumab [32].

As for adverse events, headaches, nasopharyngitis, upper respiratory tract infections, back pain, asthma, bronchitis, sinusitis, and infusion-related non-allergic reactions were the most frequently reported [30, 33, 34, 37•]. Overall, it was well-tolerated, though it has been associated with rare hypersensitivity reactions and rare Herpes zoster infections [30].

Reslizumab

Reslizumab is also a humanized monoclonal antibody against IL-5, blocking binding of IL-5 to IL-5R [38•]. It is indicated for add-on maintenance therapy of severe asthmatics who are at least 18 years old and with eosinophil count ≥ 400 cells/ μ L [30]. It is given intravenously every 4 weeks [39]. It is dosed based on body weight, at the recommended dose of 3.0 mg/kg [39].

Two 52-week, duplicate, multicenter, double-blind, parallel-group, randomized, and placebo-controlled, and phase 3

trials showed that reslizumab improved outcomes in patients with inadequately controlled asthma on medium to high dose ICS who had blood eosinophil count ≥ 400 cells/ μL [40•]. Both trials enrolled patients aged 12–75 years. In these studies, reslizumab decreased annual rate of exacerbations by 50–59% compared with placebo [40•]. It decreased eosinophilia, reducing eosinophil counts in both blood and sputum [40•] and resulted in improvement in time to first exacerbation, FEV1, asthma control scores, and quality of life scores [40•]. The reduction in eosinophil count is notable as this indicates that it may be used as a surrogate marker for response to therapy.

It should be highlighted that the efficacy of reslizumab has been characterized specifically in patients with blood eosinophils ≥ 400 cells/ μL . This notion is further supported by a 16-week, randomized, double-blind, placebo-controlled, and phase 3 trial that found that reslizumab did not result in clinically meaningful effects on lung function and symptom control in patients with baseline eosinophils < 400 cells/ μL [38•]. Only patients ≥ 18 years old were enrolled in this particular study.

Per the drug's package insert, reslizumab was evaluated in a total of 39 patients aged 12 to < 18 years old with asthma in their two 52-week exacerbation studies and one 16-week lung function study [39]. Notably, in these studies, the asthma exacerbation rate was higher in the adolescents treated with reslizumab compared with placebo [39].

In these studies, reslizumab was overall well tolerated. Most commonly reported adverse events include worsening asthma, upper respiratory tract infection, nasopharyngitis, sinusitis, bronchitis, influenza, and headache [38•, 40•]. It does carry a boxed FDA warning for anaphylaxis, as two patients in the studies had anaphylactic reactions [30].

Benralizumab

Benralizumab is also a humanized monoclonal antibody affecting the IL-5 pathway of inflammation. Unlike mepolizumab and reslizumab, benralizumab targets the IL-5 receptor α subunit on eosinophils, as well as basophils [31]. It is unique that it induces direct, rapid, and near complete depletion of eosinophils by natural killer cell-mediated antibody-dependent cytotoxicity [30, 31]; that is, it results in apoptosis of eosinophils [41•]. It is indicated for add-on maintenance treatment of severe asthmatics who are at least 12 years old and with an eosinophilic phenotype, though there is no official cut-off for absolute number of eosinophils required for use. It is dosed at 30 mg administered subcutaneously every 4 weeks for the first three doses followed by every 8 weeks thereafter. It has been shown to reduce eosinophils in the airway, sputum, bone marrow, and blood [41•].

The SIROCCO study, a 48-week, randomized, multicenter, placebo-controlled, and phase 3 trial, included patients age 12

to 75 years old with physician-diagnosed asthma for at least 1 year and at least two exacerbations while on high-dose ICS plus long-acting beta-agonist (LABA) in the previous year [41•]. This study enrolled 1204 patients, including 53 patients between 12 and 17 years old. In this trial, benralizumab reduced annual asthma exacerbation rates and improved lung function when dosed every 4 or 8 weeks [41•]. The CALIMA trial, a 56-week, randomized, multicenter, double-blind, placebo-controlled, and phase 3 trial involving patients 12 to 75 years old, supported the SIROCCO findings, as it also showed significantly lowered exacerbation rates and improved FEV1 in the benralizumab group [42•]. The study population was similar to SIROCCO in that patients had severe asthma un-controlled with medium to high dose ICS plus LABA and at least two exacerbations in the previous year. This study enrolled 1306 patients, including 55 patients between 12 and 17 years old. The improvement in FEV1 was evident as early as 4 weeks after initiating treatment and was sustained throughout the study [42•], which may make FEV1 an important clinical parameter when assessing patient response to benralizumab. Of note, results stratified by age were not described in either study.

Additionally, the ZONDA trial, a 28-week, randomized, double-blind, parallel-group, and placebo-controlled trial involving only patients 18 years or older, investigated the oral corticosteroid-sparing effect of benralizumab in severe asthma [43•]. The study found that benralizumab allowed decreased use of maintenance OCS, with the median final oral steroid dose decreased by 75% with benralizumab versus by 25% with placebo [43•]. It is well known that the placebo arm of asthma studies is often associated with improvement in disease control measure. This is likely secondary to improve patient adherence with maintenance ICS and clinical follow-up while enrolled in a study. Nonetheless, a 50% differential in the reduction of oral steroid dose between benralizumab and placebo is a clinically important difference.

Furthermore, a randomized, double-blind, and placebo-controlled trial consisting of patients ≥ 18 years old found that one dose of benralizumab given after an acute asthma exacerbation reduced exacerbation rate by 49% and hospitalization rate by 60% over the following 12 weeks [44].

As for adverse effects, the most commonly reported have been worsening asthma, upper respiratory tract infection, and nasopharyngitis [41•, 42•].

Comparison of Anti-IL5 Therapies

A 2017 Cochrane review evaluated the effects of anti-IL-5 therapies on exacerbations, health-related quality of life (HRQoL) measures, and lung function [45•]. The review found that all three reduced exacerbation rates by approximately 50% in those with severe eosinophilic asthma [45•]. Meanwhile, only benralizumab showed a significant

reduction in exacerbation rate for non-eosinophilic asthma [45•]. As for HRQoL, all three resulted in improvements in HRQoL scores in severe eosinophilic asthma, but these did not exceed the minimum clinically important difference for ACQ and AQLQ [45•]. Lastly, all produced a small but statistically significant improvement in mean pre-bronchodilator FEV₁ (between 0.08 and 0.11 L), which may not meet clinically detectable levels [45•]. Overall, the findings did support the use of anti-IL-5 treatments in people with severe eosinophilic asthma.

Unfortunately, there are no head-to-head comparison studies to help determine which is most efficacious. It is highly unlikely that such studies will take place due to the staggering number of patients that would be needed to power such studies. Furthermore, their potential effects on the rest of the pediatric population can only be extrapolated from the above studies. As such, further research is needed to determine the effects of mepolizumab, reslizumab, and benralizumab in those specifically under 12 years of age.

Anti-IL-4/IL-13 Therapy

Dupilumab

Dupilumab is a humanized monoclonal antibody against IL4 receptor α , which is a receptor for both IL-4 and IL-13 [46•]. As such, dupilumab inhibits the signaling of these two cytokines, which are key drivers in T2 high diseases [46•]. It is currently approved for adults with moderate-to-severe atopic dermatitis [46•]. However, it is presently under FDA review as an add-on maintenance treatment in adults and adolescents, 12 years of age and older, with moderate-to-severe asthma.

The Liberty Asthma QUEST trial was a 52-week, randomized, double-blind, placebo-controlled, parallel-group, and phase 3 trial that included un-controlled asthmatics age 12 years and older. The study enrolled 1902 patients (107 were adolescents) [46•]. Castro and colleagues found that, when added to standard therapies, dupilumab reduced severe asthma exacerbations and improved lung function, specifically demonstrating that 200 mg of dupilumab (administered every 2 weeks) resulted in a 47.7% reduction of exacerbations in the overall group, with 65.8% reduction in those with baseline eosinophil counts of ≥ 300 cells/ μ L [46•]. As for lung function, at 12 weeks, the FEV₁ had increased by 0.32 L [46•]. Similar results for both exacerbations and lung function were observed with the higher dose of dupilumab (300 mg) [46•]. Notably, with increasing baseline levels of blood eosinophils and FeNO, greater treatment effects were observed, as is the trend with most biologics for T2 asthma [46•]. Unfortunately, results stratified by age were not described in this study.

Meanwhile, the VENTURE trial assessed the OCS-sparing effect of dupilumab. This 24-week, randomized, double-blind,

placebo-controlled, and phase 3 trial enrolled patients ≥ 12 years old with severe OCS-dependent asthma regardless of eosinophil levels [47•]. Much like with the QUEST study, benefits were more pronounced in patients with a higher baseline blood eosinophil count and FeNO level [47•]. With dupilumab, there was 70.1% reduction in OCS dose compared to 41.9% with placebo [47•]. At 24 weeks, despite the reduction in OCS dose, patients on dupilumab still had 59% fewer exacerbations in the overall population and 71% fewer exacerbations in those with eosinophil counts ≥ 300 cells/ μ L [47•]. Also at 24 weeks, compared to placebo, dupilumab improved lung function; FEV₁ improved by 0.22 L (15%) in the overall population and by 0.32 L (25%) in those with eosinophil counts ≥ 300 cells/ μ L [47•]. Results stratified by age were also not described in this study.

The most common adverse events reported include injection-site reactions, upper respiratory tract infections, and headache [46•, 47•]. Of note, at the start of intervention, transient-elevated eosinophil counts occurred in 4.1–14% of patients on dupilumab [46•, 47•]. However, most of these did not have clinical consequences nor were they associated with adverse events [46•, 47•]. It is hypothesized that dupilumab inhibits IL-4- and IL-13-mediated productions of eotaxin and vascular-cell adhesion molecule [46•, 47•]. Consequently, eosinophil migration into tissues is blocked, but not eosinophil production or egress from bone marrow, which may result in the transient increase in blood eosinophil count [46•, 47•].

Anti-IL-13 Therapy

As mentioned earlier, IL-13 plays a role in airway remodeling as this cytokine leads to proliferation of bronchial fibroblasts, myofibroblasts, and airway smooth muscle cells. Three monoclonal antibodies targeting IL-13 have been studied for the treatment asthma: anrukinzumab, lebrikizumab, and tralokinumab. However, all three were ultimately found to be unsuccessful, suggesting that IL-13 alone does not have a key role in uncontrolled asthma.

Anrukinzumab

Anrukinzumab blocks IL-13, preventing the activation of IL-13R α 1 and IL-13R α 2 [7, 48]. It has been tested in asthma and ulcerative colitis in phase 2 studies [7]. However, it did not show any efficacy in a 12-week study of patients (≥ 18 years old) with uncontrolled persistent asthma, prompting discontinuation of its development for the treatment of asthma [49].

Tralokinumab

Tralokinumab also blocks IL-13 from binding to both IL-13R α 1 and IL-13R α 2 [50]. It has been tested in severe uncontrolled asthma, ulcerative colitis, and idiopathic

pulmonary fibrosis [7]. Two randomized, double-blind, parallel-group, placebo-controlled, and phase 3 studies (STRATOS 1 and STRATOS 2) assessed the efficacy and safety of tralokinumab in patients 12–75 years old with severe and uncontrolled asthma [51]. Findings were inconsistent as the drug reduced annualized asthma exacerbation rate only in those with baseline FENO $\geq$ 37 ppb in STRATOS 1, but not in STRATOS 2 [51]. As such, its use for asthma treatment has been found to be unpromising and the program for asthma was discontinued.

Lebrikizumab

Lebrikizumab binds to soluble IL-13, blocking the signaling pathway through the IL-13R α 1/IL-4R α heterodimer [7]. Lebrikizumab has also been tested in patients 18–75 years old with uncontrolled asthma in two phase 3 studies called LAVOLTA I and LAVOLTA II [52]. However, only one of the studies (LAVOLTA I) showed a statistically significant reduction in asthma exacerbations [52]. In light of the above, studies in asthma were discontinued.

Anti-TSLP and Anti IL-33 Therapy

Further investigations are in progress to assess the efficacy of biologic therapies against two novel targets: thymic stromal lymphopoietin (TSLP) and IL-33. TSLP is a cytokine secreted by epithelial cells in the lungs, skin, gut, and thymus. It potentiates the T2 immune response through multiple mechanisms, acting further upstream than the current cytokine targets of biologic therapies [53]. Because TSLP is an upstream cytokine, it seems to have broader downstream effects than the currently available biologics, which was demonstrated in a study of tezepelumab.

Tezepelumab is an investigational human IgG2 monoclonal antibody that binds to TSLP, preventing its binding to the TSLP receptor. This subcutaneous formulation is being studied at intervals either every 2 or 4 weeks. In 2017, a phase 2, randomized, double-blind, and placebo-controlled trial resulted in 61, 71, and 66% reduction in asthma exacerbations compared to placebo for each of the three different doses of tezepelumab studied [54]. The study population consisted of asthmatics age 18–75. Interestingly, the results were similar among T2 high and T2 low asthmatics, likely owing to the upstream origin of TSLP. Based on the impressive results of this phase 2 study, tezepelumab is now the subject of two phase 3 studies. The NAVIGATOR study is assessing the effect of tezepelumab on the annual rate of asthma exacerbation in patients age 12–80 while the SOURCE study is evaluating percent reduction from baseline OCS dose without losing asthma control while on tezepelumab in patients age 18–80 [55, 56].

Another mechanism of inflammation found to be an important step in the development and exacerbation of asthma in mouse models is the interaction between IL-33 and its ST2 receptor [57]. Expression of the ST2 receptor on eosinophils has been demonstrated to be upregulated in allergic asthmatics after inhaled allergen challenge [58]. These findings have led to the development of an anti-IL-33 receptor monoclonal antibody which is currently in its phase 2, a study to evaluate efficacy, safety, tolerability, pharmacokinetic, and pharmacodynamic profiles of the intravenous infusion in “moderately severe” asthmatics age 18 and older [59]. We are awaiting the outcomes of each of these newer therapies which may prove to be useful in a broader range of asthma phenotypes, including the T2 low population who presently have minimal therapeutic options.

Cost

A discussion of biologic therapies would be incomplete without mention of cost. The manufacturing of these drugs requires multiple steps, including cell culturing, rigorous purification of the product, and tedious quality assurance measures to name a few. As a result, the cost of biologic medications is prohibitive. For example, omalizumab in the USA is approximately \$1100–\$1700 per vial, and patients require one to three vials every 2 to 4 weeks depending on their weight, IgE level, and indication for use [14, 60, 61]. Per year, that amounts to \$15,400–\$132,600 for omalizumab therapy depending on the patient’s dose, schedule, and cost at which they obtained the medicine.

Several cost-effectiveness analyses have been performed for omalizumab in the treatment of severe persistent asthma. Each has used different models and assumptions regarding number of expected asthma exacerbations and hospitalizations per year as well as cost of therapy and adverse events which precludes the formation of a consensus statement on the topic. Two European studies, in particular, have labeled omalizumab for severe persistent asthma a cost-effective therapy. It is important to note, however, that they each assumed non-responders had therapy discontinued after 16 weeks and one of the analyses assumed an asthma exacerbation rate of two exacerbations per week which both seem to be aggressive assumptions [62–64].

Omalizumab is not an anomaly regarding cost. Mepolizumab carries a cash price of about \$5000 per vial, and the standard treatment for asthma requires one vial every 4 weeks (~\$65,000/year) [65]. The Institute for Clinical and Economic Review (ICER) conducted a cost-effectiveness analysis to determine the cost per quality-adjusted life-year (QALY) gained of mepolizumab. This analysis was meant to help determine if the benefit to the patient regarding survival and quality of life improvement balances the cost of the drug. A generally acceptable cost per QALY gained is about \$50,000–\$150,000.

ICER determined through their analysis that mepolizumab currently amounts to \$385,546 per QALY gained, and that an 89% discount on its current price would be required to achieve a threshold of \$50,000 per QALY gained [66].

Data on the cost-effectiveness of reslizumab and benralizumab for asthma is currently lacking. It is clear with the data available for omalizumab and mepolizumab, however, that physicians must be prudent in selecting patients with the optimal phenotype for biologic therapy, taking into account indices such as eosinophil count, FeNO, and number of exacerbations per year. Seasonal use of biologic therapy may prove to be a cost-effective strategy as well. Most importantly, we need to better identify those most likely to respond to a specific biologic therapy and likewise, parameters that quickly stratify responders from non-responders once they are started on biologic therapy need to be identified [67]. Through this optimization, the cost-effectiveness analysis of these agents should be much improved, as unfortunately the current practice of assessing a patient's frequency of asthma exacerbations after about a year of biologic therapy is not an economically sustainable strategy [67].

Conclusion

Severe asthma in the pediatric population is responsible for a significant reduction in quality of life as well as increased risk of morbidity and mortality. In the past, there was a very limited armamentarium for maintenance therapy for severe asthmatics, mostly consisting of varying forms of corticosteroids. As more becomes known about the pathophysiology and heterogeneity of asthma, more targeted therapies have become and rapidly continue to become available. Though most studies did not stratify results by age, the FDA has approved omalizumab, mepolizumab, and benralizumab for older children while further studies are ongoing in younger children. While the current biologics for asthma have been shown to in some cases improve FEV1, reduce need for OCS, and reduce number of exacerbations per year, it must be remembered that each drug is most effective for a very specific phenotype of asthma. The practice of precision medicine is paramount when deciding to start a patient on a biologic therapy for asthma both to achieve the desired effect of the drug and because the exorbitant cost limits its use to only the patients who will receive the most clinical benefit. Moving forward, we hope to see development of drugs which are effective in the T2 low asthmatic population as well because there remains a sizable group of severe asthmatics who are poor responders to the currently available biologics. In the meantime, we will continue to utilize biologic therapies as a steroid-sparing agent in the T2 high subset of pediatric patients with severe asthma.

Compliance with Ethical Standards

Conflict of Interest The authors declare no 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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