CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

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Biologics for Asthma and Allergic Skin Diseases in Children

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An estimated 7 million children in the United States have asthma, which causes a significant health care burden and affects quality of life. The minority of these children have asthma that does not respond to Global Initiative for Asthma steps 4 and 5 care, and biological medications are recommended at this level in the 2019 Global Initiative for Asthma recommendations. In addition, biologics have been introduced into the care of children with allergic skin diseases. Omalizumab and mepolizumab are approved for children as young as 6 years, and benralizumab and dupilumab are approved for people aged ≥12 years. Reslizumab is approved only for people aged ≥18 years. These monoclonal antibodies may be added for appropriate patients when asthma or allergic skin diseases are not well controlled. Pediatricians and pediatric subspecialists should work together and be aware of the benefits and risks of these medications for their patients, as well as the practical implications of providing these options for their patients. This clinical report serves as an evaluation of the current literature on these types of medications in the treatment of children with asthma and allergic skin disease.

ASTHMA

Asthma may not be controlled in 38% of affected children, and biological medications may be prescribed if appropriate, other pharmacologic treatment, treatment of comorbidities, and verification of medication adherence does not lead to an acceptable level of control.[1] The minority of these children have asthma that does not respond to Global Initiative for Asthma (GINA) steps 4 and 5 care, and biological medications are recommended at this level in the 2019 GINA recommendations.[2] It is important to first confirm the diagnosis of asthma and to verify adherence to and appropriate technique for using an inhaler before embarking on biological therapy. Limited numbers of clinical trials include children, resulting in minimal current information on biological use in the pediatric population. The exception is the oldest biological therapy, omalizumab,

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which has a more significant amount of data on use in children. Increasing numbers and types of biological therapies have become available to this population, however, and the niche for each product will be better defined as its role in asthma care evolves. Pediatricians and pediatric subspecialists should be aware of the current range of biological medications available to children with severe asthma. In addition, general pediatricians should monitor patients for evidence of poor response to traditional therapies and consider referring to pediatric subspecialists for evaluation of eligibility for these types of medications. Finally, those who administer this type of care for children with asthma should be aware of the potential for anaphylaxis for many biologics, especially omalizumab and reslizumab, and be prepared to treat and evaluate anaphylaxis and other potential treatment-related adverse effects. The American Academy of Pediatrics policy statement "Preparation for Emergencies in the Offices of Pediatricians and Pediatric Primary Care Providers" is a helpful reference in the preparation for such emergencies.[3] The purpose of this clinical report is to review the available literature for these types of medications in children.

ASTHMA MEDICATIONS

Anti–Immunoglobulin E Therapy

Omalizumab was approved by the US Food and Drug Administration (FDA) in 2003. It is a subcutaneously administered humanized anti–immunoglobulin E (IgE) antibody that is licensed for the treatment of patients aged >6 years with moderate to severe asthma who have a positive skin test result to a perennial allergen and whose IgE is between 30 and 1300 IU for people aged 6 to 12 years and between 30 and 700 IU for those aged ≥12 years.[1,4,5]

In 2001, Milgrom et al evaluated children aged 6 to 12 years with moderate to severe asthma in a double-blind, randomized, placebo-controlled trial.[6] The participants had asthma that was well controlled for 3 months by using inhaled corticosteroids (ICSs) (168–420 μg beclomethasone equivalent) and had a forced expiratory volume in the first second of expiration (FEV_1) of greater than 60% predicted. The primary outcome was ICS reduction. After 28 weeks of omalizumab therapy, the ICS dose was reduced, as tolerated, and the percentage of patients in whom ICS reduction occurred was 100% with omalizumab versus 66.7% of the placebo group patients. Fewer participants had asthma exacerbations during the steroid reduction phase in the omalizumab group versus placebo (18.2% versus 38.5%). The proportion of the participants who had ICS completely withdrawn in the omalizumab group was 55% and in the placebo group was 39%. Withdrawal of ICS did not compromise asthma control. Physician-rated global evaluation of treatment effectiveness was excellent or good in the omalizumab group at 44% and 32.7% in the placebo group.

Lanier et al conducted a 52-week trial in participants aged 6 to 12 years with moderate to severe, persistent asthma that was uncontrolled on greater than 200 μg of fluticasone or equivalent and who had a history of severe exacerbation within the previous 2 years of therapy.[7] Participants were randomly assigned 2:1 to receive omalizumab or placebo, and there was a 24-week, fixed inhaled-steroid phase followed by a 28-week, adjustable ICS steroid phase. From the baseline period to week 24 (fixed phase), there was a 31% reduction in exacerbations (defined as worsening of symptoms requiring doubling of baseline ICS dose and/or systemic steroids) in the omalizumab group versus placebo and a 43% reduction in exacerbations over the entire study time frame (52 weeks) with omalizumab versus placebo. The global evaluation of treatment effectiveness was also rated excellent or good by 79% in the omalizumab group and 56% in the placebo group.

Third and fourth studies were conducted by the Inner-City Asthma Consortium.[8,9] In these studies, researchers enrolled, predominantly, children from low-income families and people of color. The first of these included participants 6 to 20 years of age with persistent allergic asthma for greater than 1 year, at least 1 positive skin-prick test result for perennial allergens, weight between 20 and 150 kg, and serum IgE concentration 30 to 1300 IU/mL, per the omalizumab-insert dosing table.[8] Participants were randomly assigned to receive omalizumab or placebo, in addition to standard care during a 60-week treatment period. The mean age was approximately 11 years. The percentage of children with one or more exacerbation during the study period was 48.8% with placebo and 30.3% in the omalizumab group. In addition, seasonal analysis of exacerbations revealed that omalizumab reduced the spring and fall spikes in asthma exacerbations. The mean ICS dose in the omalizumab group was 663 μg per day versus 771 μg per day in the placebo group. This study underscored the efficacy of omalizumab in children from low-income families and people of color.

In a companion study, researchers enrolled participants aged 6 to 17 years who met package-insert criteria for omalizumab and who had uncontrolled asthma, defined as an ICS dose of greater than 200 μg

of fluticasone a day and more than 1 exacerbation in the last year.[9] Those receiving 500 μg twice a day of fluticasone or equivalent (treatment step 5 from the National Asthma Education and Prevention Program Expert Panel Report) were randomly assigned 3:1 to receive omalizumab or placebo, and participants receiving less than 500 μg per day of fluticasone or equivalent were randomly assigned 3:3:1 to receive omalizumab plus inhaled placebo, ICS boost plus injected placebo, or guideline-based care with injected placebo and inhaled placebo. The 90-day treatment period commenced 4 to 6 weeks before the start of the school year. There was a reduction in fall exacerbations with omalizumab, with 11.3% of participants in the omalizumab group having exacerbations, compared with 21% in the placebo group. The effect was even higher in those with more than 1 exacerbation during the run-in phase; the fall exacerbation rate was 6.4% for omalizumab and 36.3% for those in all placebo groups.

In a French, real-world study, researchers enrolled participants aged 6 to 18 years with severe allergic asthma who were partially or poorly controlled by GINA guidelines with a mean ICS dose of 703 μg fluticasone equivalent per day[10] and evaluated outcomes at baseline and after initiation of omalizumab add-on treatment. In week 52 versus baseline, control improved to good control (by GINA guidelines) in 67% of participants. Exacerbations were reduced by 72% and hospitalizations were reduced by 89% in the first year of therapy. FEV_1 increased by 4.9%, and there was a 30% reduction in mean ICS dose.

Omalizumab is indicated for allergic asthma and currently approved for people as young as 6 years. Injection dosing is based on IgE concentration and body weight, with injections administered either every 2 or every 4 weeks.[5] The cost is substantial. According to the 2018 Institute for Clinical and Economic Review report on biological therapies for asthma, the per-unit manufacturer net price of omalizumab is $802.64, with per-patient costs varying significantly depending on the dosage needed as well as provider and payer, with an average net adult cost per year of $28 895.[11] In addition, anaphylaxis is a risk with this medication; the patient should be under medical observation for anaphylaxis after every injection,[5] and epinephrine autoinjectors should be prescribed for use at home in the case of delayed anaphylaxis.[12] Safety outcomes were primarily studied in patients older than 12 years but have shown an incidence of postmarketing anaphylactic reactions of 0.2% in treated patients,[13,14] leading to a black box warning on anaphylaxis.[15] Initial pooled data from phase I through III clinical trials revealed a numeric imbalance in the number of malignancies in patients treated with omalizumab versus placebo; however, in further pooled analysis of 67 phase I through IV clinical trials, including 4254 patients who received omalizumab treatment, researchers found no significant association between malignancy and omalizumab treatment in the overall group, although specific conclusions in the pediatric subgroup were not possible because of small sample size.[16] The FDA recognizes the following most common adverse events for omalizumab for asthma: "[adults and adolescents >12 years] arthralgia, pain (general), leg pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, and earache; [pediatric patients 6 to <12 years of age] nasopharyngitis, headache, pyrexia, upper abdominal pain, pharyngitis streptococcal, otitis media, viral gastroenteritis, arthropod bites, and epistaxis." In addition, the FDA cautions not to use omalizumab for acute asthma symptoms, not to abruptly discontinue corticosteroids, and to monitor for signs of serum sickness, eosinophilia, vasculitic rashes, worsening pulmonary symptoms, cardiac complications, or neuropathy.[5]

Omalizumab has been shown to generate improved asthma control, reduce incidence and frequency of exacerbations, reduce health care use for severe exacerbations, have corticosteroid-sparing effects, and ultimately result in improved quality of life for qualifying patients with moderate and severe persistent asthma.

Anti–Interleukin 5 Therapy

Interleukin 5 (IL-5) is a cytokine involved in eosinophil activation, which makes it a key target for therapeutic intervention in eosinophil-driven diseases, including asthma. There have been multiple anti–IL-5 antibodies under development in recent years. The therapeutics described have been studied in populations of people with asthma as young as 6 years, although importantly, data on children have not been reported separately.

Mepolizumab

Mepolizumab is a fully humanized anti–IL-5 antibody, currently approved in the United States for the add-on maintenance treatment of severe asthma.[17] Mepolizumab binds to IL-5, blocking its interaction with the IL-5 receptor on the surface of eosinophils, obstructing its actions at that level.[18] The best response is observed in patients with eosinophil concentrations >300 cells/μL.

The first key study to evaluate the efficacy of mepolizumab was the DREAM study (Dose Ranging

Efficacy And Safety With Mepolizumab in Severe Asthma), a multicenter, randomized, placebo-controlled trial.[19] In this trial, researchers enrolled 621 participants with a history of recurrent severe asthma exacerbations and signs of eosinophilic inflammation. Although children aged 12 to 17 years were eligible for enrollment, demographics suggest that no pediatric participants were enrolled.[20] The investigators found the rate of clinically significant exacerbations was significantly reduced in the mepolizumab groups (2.40 per participant per year in the placebo group, 1.24 per participant per year in the low-dose mepolizumab group [75 mg, intravenous (IV)], 1.46 in the medium-dose group [250 mg, IV], and 1.15 in the high-dose group [750 mg, IV]). All mepolizumab-treated groups also had reduced circulating blood eosinophils and sputum eosinophils. One post hoc analysis of the DREAM trial data also showed that treatment response was unaffected by season or atopy.[21]

After the DREAM trial, there were 2 additional studies in which researchers evaluated the efficacy of mepolizumab in adults and adolescents. The Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) study, in which researchers enrolled 576 participants aged 12 to 82 years (only 25 patients in age range 12–17 years[22]), revealed a 47% reduction in exacerbation rates in those receiving IV mepolizumab and a 53% reduction in those receiving subcutaneous injections.[23] In addition, there was a reduction in exacerbations necessitating an emergency department visit or hospitalization (32% in the IV mepolizumab group and 61% in the subcutaneous mepolizumab group). There was an increase in FEV_1 in both mepolizumab-treated groups, as well as improvements in markers of asthma control.

In the Steroid Reduction with Mepolizumab Study (SIRIUS) study, researchers sought to evaluate the steroid-sparing effect of mepolizumab in people with severe eosinophilic asthma (enrolling 135 participants, 16–74 years of age) and found a 50% reduction in steroids from baseline in the treatment group, with no reduction in the placebo group.[24] Along with the reduction in steroid dosing, there was a reduction in exacerbations in the mepolizumab group by 32%, and a reduction in asthma symptoms. Importantly, the SIRIUS study did not report the number of pediatric participants; however, the mean age of both the placebo and mepolizumab groups was 50 years. Both the SIRIUS and MENSA studies revealed no significant safety concerns with mepolizumab.

Secondary data analyses were conducted on the MENSA and SIRIUS trials. In one such analysis, researchers evaluated mepolizumab in subjects who had previously received omalizumab therapy. In MENSA, mepolizumab reduced exacerbations by 57% and 47% in those who had and who had not previously received omalizumab, respectively.[25] The SIRIUS trial showed reduced oral corticosteroid (OCS) rates regardless of previous omalizumab use.[25] In addition, both studies showed that asthma control and quality of life were improved regardless of omalizumab use. A secondary analysis of the DREAM and MENSA studies revealed a "close relationship between baseline blood eosinophil levels and clinical efficacy of mepolizumab," with efficacy highest in those with eosinophil concentrations of at least 150 cells/μL, with one pooled analysis showing treatment-associated exacerbation rate reductions increasing from a 26% rate reduction in those with $<$150 eosinophils/μL to a 70% rate reduction in those with $>$500 eosinophils/μL.[26] The efficacy and safety of mepolizumab in children aged 6 to 11 years have been extrapolated from the adult and adolescent trials, as well as a clinical trial (NCT no. 02377427) that showed that a dose of 40 mg, subcutaneously, every 4 weeks showed similar drug-exposure levels in children aged 6 to 11 years as the 100-mg dose used in adults and adolescents.[22]

Safety evaluations of mepolizumab have raised no significant safety concerns,[19,23,24] although long-term evaluations are ongoing. The FDA recognizes "headache, injection site reaction, back pain, and fatigue" as the most common adverse reactions, and it warns to monitor for hypersensitivity reactions, herpes zoster (consider varicella immunizations before treatment), not to use mepolizumab for the treatment of acute bronchospasm, to use caution when reducing steroids during treatment, and to treat any existing helminthic infections before therapy and monitor for further infections.[22] Mepolizumab is approved for the add-on maintenance of children and adults 6 years and older with severe asthma and an eosinophilic phenotype, but it should be noted that the most robust data are in adults.[22] The FDA-recommended dose is 100 mg, administrated subcutaneously, every 4 weeks for patients 12 years and older, and 40 mg every 4 weeks for patients aged 6 through 11 years.[22] Self-injection may be an option for patients 12 years and older.[22]

Reslizumab

Reslizumab is another anti–IL-5 agent for use in severe asthma that binds to circulating IL-5 and

downregulates the IL-5 signaling pathway.[27] In one phase III trial in 315 participants aged 12 to 75 years (15 participants aged 12–17 years), it was found to improve lung function, asthma control scores measured by the Asthma Control Questionnaire, and quality of life scores measured by the Asthma Quality of Life Questionnaire.[27] Pooled data from 2 phase III trials of reslizumab showed a reduction in asthma exacerbations compared with placebo (rate ratios 0.5 and 0.41)[28]; however, in the small group of adolescents aged 12 to 18 years studied ($N = 25$), the exacerbation rate was higher with reslizumab than with placebo.[29] Therefore, reslizumab is not currently approved for use in children younger than 18 years, and further study would be required before considering this as a treatment option in this age group. Reslizumab is dosed as an IV infusion, 3 mg/kg every 4 weeks.[29] The FDA recognizes oropharyngeal pain as the most common adverse effect,[29] although there is an anaphylaxis risk of approximately 0.3%, prompting a black box warning from the FDA and the recommendation for in-office infusions and close monitoring.[15] In addition, the FDA warns that malignancies have been seen in clinical studies, that corticosteroids should not be abruptly discontinued and should not be used for acute bronchospasm, and that patients with helminthic infections should be treated and monitored for further infection during therapy.[29]

Benralizumab

Benralizumab is the third of the anti–IL-5 monoclonal antibodies and induces a nearly complete reduction in eosinophil concentration by binding to the α chain of the IL-5 receptor on eosinophils and possibly inducing destruction by natural killer cells.[30] The first large clinical trial in which researchers evaluated benralizumab was the CALIMA study.[30] Enrolled participants were 12 to 75 years of age (total $n = 728$, with 55 participants aged 12–18 years) with severe asthma. It was found that in patients with eosinophil concentrations >300 cells/μL, benralizumab significantly reduced asthma exacerbation rate ratios relative to placebo (by 36% and 28% in the every 4-week and every 8-week dosing groups, respectively) and was well tolerated.

Similarly, in the SIROCCO study, researchers evaluated 1204 participants 12 to 75 years of age with severe asthma (53 participants aged 12–18 years) and found that in patients with eosinophil concentrations >300 cells/μL, benralizumab reduced the annual asthma exacerbation rate over 48 weeks when given every 4 or 8 weeks (by 45% and 51%, respectively) and increased prebronchodilator FEV_1 (106 mL and 159 mL, respectively).[31] The most common adverse events were worsening of asthma and nasopharyngitis and were similar between treatment groups.

Benralizumab is approved in the United States for the add-on maintenance treatment of participants with severe asthma aged 12 years and older with an eosinophilic phenotype, although long-term and pediatric-specific safety data are still needed. The FDA recognizes headache and pharyngitis as the most common adverse reactions,[32] although hypersensitivity reactions such as anaphylaxis, angioedema, and urticaria occurred in about 3% of patients.[15] The FDA warns that it should not be used for an acute exacerbation, and that providers should not abruptly stop corticosteroids and should treat preexisting helminthic infections and monitor for such infections during therapy.[32] Benralizumab is dosed as a subcutaneous injection, 30 mg every 4 weeks for the first 3 doses, followed by once every 8 weeks thereafter, but it should be noted that the most robust data are in adults.[32]

Anti–Interleukin 4 Therapies

Dupilumab

Dupilumab is an interleukin 4 (IL-4) receptor α antagonist that was recently approved in treatment of people 12 years and older who have moderate to severe asthma as add-on therapy to maintenance therapy, specifically in patients who have eosinophilic phenotype or who are OCS dependent.[33] In one key study, 210 patients with severe oral glucocorticoid-dependent asthma older than 12 years were randomly assigned to receive dupilumab or placebo.[34] Adolescent data were not reported separately; however, the average age of all participants was 51.3 years. The dupilumab group experienced a 70.1% reduction in glucocorticoid dose (compared with a 41.9% reduction in the placebo group). Despite these reductions in oral steroids, the dupilumab group had a significantly lower severe exacerbation rate (59% lower than placebo). In another recently published study, researchers enrolled 1902 people 12 years or older with uncontrolled asthma and showed an annualized exacerbation rate that was 47.7% lower with dupilumab than with placebo, and this was accompanied by a 320-mL increase in FEV_1.[35] Of note, adolescent data were not reported separately; however, the average age of study participants was 47.9 years. In participants with eosinophil concentrations >300 cells/μL, the annualized exacerbation rate was reduced even further: 65.8% lower than placebo. Injection site reactions and hypereosinophilia were more common in the dupilumab study

groups,[34,35] although long-term and pediatric-specific safety data are still needed. The FDA recognizes injection site reactions, oropharyngeal pain, and eosinophilia as the most common adverse reactions in asthma treatment,[33] although hypersensitivity reactions have been described in 0.1% to 1%, usually generalized urticaria.[15] In addition, the FDA warnings for dupilumab include not to abruptly stop corticosteroids and to treat preexisting helminthic infections and monitor for infections during treatment, to monitor for eosinophilic conditions (especially vasculitic rash, worsening pulmonary symptoms, and neuropathy), and not to use it for acute bronchospasm.[33] For asthma, the dose is 400 mg, subcutaneously, as a loading dose and then 200 mg, every 2 weeks. For OCS-dependent patients or patients with coexisting atopic dermatitis, 600 mg is the loading dose and then 300 mg every 2 weeks, and dupilumab may be self-injected.[33]

SUMMARY: BIOLOGICS IN PEDIATRIC ASTHMA

There are multiple biologics available to treat moderate to severe persistent asthma in children and adults (Table 1). Omalizumab is approved for patients 6 years and older with sensitization to at least 1 perennial allergen and serum IgE concentration between 30 and 1300 IU for patients aged 6 to 12 years and between 30 and 700 IU for those 12 years and older. Health care providers now have 18 years of experience with omalizumab. With regard to anti–IL-5 drugs, there are data for mepolizumab and benralizumab in people aged 12 to 17 years, and both drugs work indirectly on eosinophils through blocking the receptor-ligand union. These drugs are particularly helpful in participants with an eosinophilic phenotype (peripheral blood absolute eosinophil count >150 cells/μL) and are particularly helpful when the absolute eosinophil count is >300 cells/μL. These drugs are under study for the treatment of eosinophilic esophagitis, nasal polyps, and sinus disease. Dupilumab may be effective by decreasing exacerbations and improving pulmonary function tests. Dupilumab has also been approved for the treatment of chronic rhinosinusitis with nasal polyposis in adults.[33] The final answer for which biological is indicated for each individual participant type will evolve as researchers develop more information in the pediatric age range. In addition, identification of useful biomarkers and surrogate end points for use in children to predict treatment response is needed.

URTICARIA

Chronic spontaneous urticaria (chronic idiopathic urticaria) and chronic inducible urticaria (physical urticaria, such as dermatographism, or cold and/or heat-induced urticaria) are diagnosed when itchy urticarial wheals are present for more than 6 weeks.[36,37] Although more common in adults than children, chronic urticaria can be important in this age group, with a prevalence estimated at between 0.1% and 0.3% of children.[38] Chronic inducible urticaria has a specific trigger that can be identified, as opposed to chronic spontaneous urticaria, in which symptoms occur at irregular intervals. There can be multiple triggers of both syndromes. These diagnoses may lead to recalcitrant symptoms that significantly affect quality of life. Standard treatment includes second-generation, nonsedating antihistamines at up to 2 times the standard dose. Omalizumab has been shown to be effective in this disease, with response rates in all comers ranging from 52% to 90%.[39] One systematic review of 43 studies found a strong body of evidence for the efficacy of omalizumab in adults and children with treatment-refractory, chronic inducible urticaria, although they did note that there were nonresponders.[37] The adverse effect profile was similar to that observed in asthma studies. More data are needed in the treatment of children, but omalizumab appears to be a promising treatment strategy for chronic spontaneous urticaria. Omalizumab is FDA approved for chronic idiopathic urticaria in people 12 years or older who are symptomatic despite H1 antihistamine treatment.[5] When used for urticaria, omalizumab is dosed at 150 to 300 mg, subcutaneously, every 4 weeks; dosing is not based on serum IgE concentration or body weight.[25] The FDA recognizes "nausea, nasopharyngitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection, arthralgia, headache, and cough" as the most common adverse events in the treatment of urticaria with omalizumab.[5] The other biologics previously discussed for treatment of asthma may show some promise for the treatment of chronic urticaria; however, they are still in the early stages of evaluation for efficacy[39] and have not yet been approved for use for this indication in children.

ATOPIC DERMATITIS

Atopic dermatitis is a common comorbidity in children that affects approximately 10% of the US population,[40] with onset usually before 5 years of age and with significant deleterious effects on quality of life.[41] The anti–IL-4 receptor antagonist, dupilumab, has shown promise in the treatment of atopic dermatitis in children 6 years or older. Landmark adult studies have included the SOLO1 (671 patients, 25–51 years of age) and SOLO2 (708 patients, 25–46 years of age) trials, conducted in adults 18

TABLE 1 Summary of the Biologics Currently Approved for the Treatment of Moderate to Severe Persistent Asthma With Type 2 High Phenotype

Therapy	Mechanism of Action	Indication	Dosing and Route	Adverse Effects
Omalizumab	Anti–IgE; prevents IgE from binding to its receptor on mast cells and basophils	People aged ≥6 years with moderate to severe persistent asthma, positive allergy testing, incomplete control with an ICS, and IgE 30-1300 IU/mL (United States, age 6–11 y), 30–700 IU/mL (United States, age ≥12 years), or 30–1500 IU/mL (European Union)	0.016 mg/kg per IU of IgE (in a 4-wk period) administered every 2–4 weeks subcutaneously (150–375 mg in United States; 150–600 mg in European Union)[a]	Black box warning: ∼0.1%–0.2% risk of anaphylaxis in clinical trials
Mepolizumab	Anti–IL-5; binds to IL-5 ligand; and prevents IL-5 from binding to its receptor	People aged ≥12 years with severe eosinophilic asthma unresponsive to other GINA steps 4–5 therapies. Suggested AEC ≥150–300 cells/μl	100 mg subcutaneously every 4 weeks	Rarely causes hypersensitivity reactions; can cause activation of zoster
Reslizumab	Anti–IL-5; binds to IL-5 ligand; and prevents IL-5 from binding to its receptor	People aged ≥18 years with severe eosinophilic asthma unresponsive to other GINA steps 4–5 therapies. Suggested AEC ≥400 cells/μl	Weight-based dosing of 3 mg /kg IV every 4 weeks	Black box warning: ∼0.3% risk of anaphylaxis in clinical trials
Benralizumab	Anti–IL-5; binds to IL-5 receptor α; and causes apoptosis of eosinophils and basophils	People aged ≥12 years with severe eosinophilic asthma unresponsive to other GINA steps 4–5 therapies. Suggested AEC ≥300 cells/μl	30 mg subcutaneously every 4 weeks for 3 doses; followed by every 8 weeks subsequently	Rarely causes hypersensitivity reactions
Dupilumab	Anti–IL-4R; binds to IL-4 receptor α; and blocks signaling of IL-4 and IL-13	People aged ≥12 years with severe eosinophilic asthma unresponsive to other GINA steps 4–5 therapies. Suggested AEC ≥150 cells/μl and/or FeNO level ≥25 ppb	200 or 300 mg subcutaneously every 2 weeks	Rarely causes hypersensitivity reactions; higher incidence of injection site reactions (up to 18%) and hypereosinophilia (4% to 14%)

Reprinted with permission from the American Thoracic Society. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.[44] AEC, absolute blood eosinophil count; FeNO, fractional exhaled nitric oxide; IL-13, interleukin 13.

[a]Upper limits exist for the dosing of omalizumab in patients with high IgE levels and increased weight.

years or older, which showed that over the 16-week study period, dupilumab improved scores on the Investigator's Global Assessment and Eczema Area and Severity Index and improved markers including pruritis and quality of life measures.[42] A phase IIa study with phase III open-label extension in adolescents revealed efficacy with regards to Eczema Area and Severity Index improvement over the study period.[43] Adverse effects in this study included nasopharyngitis and worsening of atopic dermatitis.[43]

Overall, the safety and efficacy is similar in adolescent and adult patients,[33] although long-term safety data collection is ongoing. The FDA recognizes "injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye" as the most common adverse reactions, and it cautions that patients should alert providers of worsening eye symptoms concerning for conjunctivitis and keratitis.[33] Dupilumab for atopic dermatitis is dosed by body weight in adolescents, with patients weighing <60 kg receiving a 400-mg initial dose and 200-mg doses every other week, and patients weighing ≥60 kg receiving a 600-mg initial dose and 300-mg doses every other week; self-injection may be considered for some patients.[33] Other emerging biological therapies in atopic dermatitis include interleukin 12 and interleukin 23 inhibitors ustekinumab, interleukin 13 inhibitors lebrikizumab and tralokinumab, interleukin 22 inhibitor fezakinumab, and oral Janus kinas inhibitor baricicitinib, as well as

TABLE 2 Key Recommendations

Key Recommendations for General Pediatricians	Key Recommendations for Pediatric Subspecialists
Evaluate adherence to medications in patients with poorly controlled atopic diseases, such as asthma, urticaria, and atopic dermatitis.	Evaluate adherence to medications in patients with poorly controlled atopic diseases, such as asthma, urticaria, and atopic dermatitis.
Refer to a pediatric subspecialist (allergist, dermatologist, or pulmonologist) for determination of whether a patient is an appropriate candidate for biological therapy, as well as for determination of which therapy best fits the patient's phenotype.	Partner with general pediatricians to identify appropriate patients for biological therapy.
Be familiar with adverse effects of biological therapy, particularly the risk of anaphylaxis with omalizumab, benralizumab, dupilumab, and reslizumab (if ever approved in the pediatric population).	Monitor for adverse effects that are particular to the particular therapy.
The home administration is approved for dupilumab, mepolizumab, and omalizumab. Further opportunities for home administration are likely in the future.	Monitor for clinical improvement in symptoms with therapy.
	Continue to work to identify new biomarkers and means to identify candidates for therapy, as well as monitor response to therapy

phosphodiesterase type 4 inhibitors, interleukin 17 inhibitors, thymic stromal lymphopoietin inhibitors, and neurokinin-1 inhibitors.[41]

CONCLUSIONS

Asthma and atopic skin conditions can be difficult to treat and lead to significant morbidity and child and family stress. Pediatricians are faced with a widening array of targeted therapies; however, the question of what therapy to choose for which patient remains an area of continued study. In many studies in biological therapies for asthma and other allergic diseases, researchers have focused on the adult population; however, drugs are becoming more and more readily available for pediatrics. In ongoing studies, researchers should focus on appropriate biomarkers (including IgE and circulating eosinophils, as well as further biomarkers yet to be determined), as well as other patient-focused factors to allow the choice of the right biological for the right patient and at the right time. In addition, further study is needed regarding the use of novel methods of administration and monitoring in resource-limited settings, such as rural areas where access to specialty care may be limited, because these medications are currently prescribed in subspecialty offices. Home administration may be possible for some biological medications (dupilumab and mepolizumab); however, assessment of the appropriate patients for such therapy, as well as monitoring adherence in these patients, will be of key importance. One of the key questions that pediatricians and pediatric subspecialists are faced with remains when to start biological therapy for continued poor asthma control versus continued focus on appropriate medication adherence. In this situation, referral to a pediatric asthma specialist may be warranted to determine when to start biological therapy and which therapy to initiate. In addition, all pediatricians should be aware of the real possibility of anaphylaxis to certain biological medications, especially omalizumab and reslizumab, although others may also have hypersensitivity reactions,[15] and be prepared to respond appropriately and immediately. Continued research is required to evaluate long-term tolerability and safety of these medications in pediatric populations, although no evidence exists for aberrations in immune function. Pediatric subspecialists, including allergists, dermatologists, and pulmonologists, are necessary and key partners in the determination of not only the appropriate children for this type of therapy but also the most appropriate therapy for each individual child. With collaboration, true personalization of medical care for these complex patients can be achieved (Table 2).

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ABBREVIATIONS

FDA: US Food and Drug Administration
FEV_1: forced expiratory volume in the first second of expiration
GINA: Global Initiative for Asthma
ICS: inhaled corticosteroid
IgE: immunoglobulin E
IL-4: interleukin 4
IL-5: interleukin 5
IV: intravenous
MENSA: Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma
OCS: oral corticosteroid
SIRIUS: Steroid Reduction with Mepolizumab Study

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