



The Role of Biologics and Precision-Based Medicine in Treating Atopic Diseases in Children

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Abstract

Purpose of Review Children with atopic diseases such as asthma and atopic dermatitis often have poorly controlled disease, which can occur as a result of noncompliance from the concern of side effects from prolonged use of medications. This fear is not unfounded as often increasing doses of inhaled, topical, or oral steroids are required for control and carry a cumulative risk burden for growth and development in this population. The availability of biologics in this patient population has been pivotal in expanding options to reduce disease burden and unfavorable side effects.

Recent Findings In addition to biologics expanding treatment options for children, their use has added insight into mechanisms of disease. In doing so, there is a better understanding of current biomarkers in tailoring treatment approaches. As novel biomarkers are studied, we are gaining more insight into targeted treatment options.

Summary This review discusses biologics currently available for children for the treatment of atopic diseases, with a focus on certain phenotypic and endotypic biomarkers that may help guide therapy.

Introduction

A central pathophysiologic mechanism of atopic disorders is the cross-linking of antigen to immunoglobulin E (IgE) located on the surface of effector cells, such as mast cells and eosinophils, causing the release of pro-inflammatory mediators including histamine, leukotrienes, and cytokines [1, 2]. This phenomenon, called a type 1 hypersensitivity reaction, elicits symptoms familiar to atopic disease such as the wheal and flare eruptions of the skin (urticaria), intermittent wheeze (asthma), or anaphylaxis (hypotension, multiple organ involvement). The antigen and surrounding milieu are important factors in influencing the direction of the immune response. Intercellular pathogens, such as *Mycobacterium tuberculosis*, stimulate TH1 cells that secrete cytokines such as IL-2 and IFN- γ , which suppress IgE synthesis through direct effects on B cells [3]. Extracellular pathogens such as Helminths or allergens stimulate TH2 cells that secrete a functionally distinct group of cytokines, IL-4, IL-5, IL-9, and IL-13, which are important mediators of IgE synthesis [4]. A complex interaction between the microbiome and a TH2-skewed inflammatory environment can redirect regulatory T cells towards a pro-inflammatory phenotype [5].

Until recently, therapy for atopic diseases such as severe asthma, atopic dermatitis, and urticaria has focused on controlling symptoms based on clinical characteristics, the phenotype. Despite consistent therapy for similar clinical characteristics, variation of response is seen. Based on the National Asthma Education and Prevention (NAEPP) guidelines, patients with poorly controlled severe asthma on a single controller agent are advised to be treated with a combination of high dose inhaled corticosteroids (ICS) and long acting β agonist (LABA), yet one-third continue to have inadequately controlled asthma [6, 7]. The relationship of individual variations in genetic, pharmacologic, physiologic, and immunological mechanisms to clinical differences in treatment response and/or disease course is a subtype of phenotypes called endotype [8]. The direction of therapy based on a patient's phenotype (characteristics) and endotype (underlying pathogenic mechanisms) has been termed precision or personalized medicine [9].

This review will focus on biologics currently available for pediatric atopic diseases and highlight associated phenotypes and endotypes (Table 1).

Asthma in Children

Children and adults with atopic asthma tend to have higher serum IgE levels which correlate with heightened bronchoconstrictor response and symptoms with exposure to different stimuli [10–12]. TH2 cells influence IgE production by producing IL-4 and IL-13 and influence eosinophilic function through the actions of IL-5 [13]. Pronounced eosinophil infiltration is seen in many atopic diseases including allergic rhinitis, atopic dermatitis, and asthma [14]. Compared with adults, children are more likely to be atopic, have rhinitis, and have lower airway resistance [15]. Four biologics that target these TH2-driven immune responses are FDA-approved for the treatment of children with allergic asthma—omalizumab, mepolizumab, benralizumab, and dupilimab (Table 2).

Omalizumab

Omalizumab is a recombinant humanized monoclonal antibody [16] that recognizes IgE at the same site as the high-affinity receptor for IgE (Fc ϵ R1) on mast cells, basophils and other effector cells [17]. By complexing to circulating free IgE, omalizumab prevents the binding of free IgE to receptors on cell membranes of these effector cells thereby impeding cell activation or release of pro-inflammatory mediators [18, 19]. Omalizumab does not bind to IgE bound to cell membrane (IgE receptors) so it does not activate mast cells or

Table 1. Biologics currently available for pediatric atopic diseases

Biologic name	Mechanism of action	Indication	FDA criteria for use in children
Omalizumab	Inhibits the binding of free IgE to the high-affinity IgE receptor (FcεR1) on the surface of mast cells, basophils, and other effector cells	- Moderate to severe uncontrolled allergic asthma in children 6 years of age and older - Chronic spontaneous urticaria (CSU) in children 12 years of age and older	- Moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms inadequately controlled with inhaled steroids - Chronic idiopathic urticaria in patients 12 years of age and older who remain symptomatic despite H1 antihistamine therapy
Mepolizumab	Prevents binding of free IL-5 to IL-5 receptor on effector cells by binding to free IL-5	Add on maintenance treatment for severe eosinophilic asthma in children 12 years of age and older	Severe persistent asthma in patients 12 years of age and older with an eosinophilic phenotype.
Benralizumab	- Inhibits interaction between IL-5 and IL-5 receptor by binding to IL-5 receptor (IL-5Ra) - Induces eosinophilic apoptosis by binding to FcγRIIIa receptor on natural killer cells	Add on maintenance treatment for severe eosinophilic asthma in children 12 years of age and older	Severe persistent asthma in patients 12 years of age and older with an eosinophilic phenotype.
Dupilumab	Blocks intracellular signaling of IL-4 and IL-13 by binding to IL-4 receptor alpha subunit (IL-4Ra4)	- Moderate to severe atopic dermatitis not well-controlled with topical therapies in children 12 years of age and older - Add on maintenance treatment for uncontrolled moderate to severe asthma in children 12 years of age and older	- Moderate to severe atopic dermatitis in patients 12 years of age and older whose disease is not controlled with topical therapies or topical therapies not advisable - Moderate to severe uncontrolled asthma in children 12 years of age and older

other effector cells [20]. The addition of omalizumab to standard asthma therapy in adults and children ages 6 or above with poorly controlled moderate to severe asthma with a positive skin or blood test to a perennial aeroallergen has been shown to be effective and well-tolerated [21–25]. Although a risk for anaphylaxis in use for allergic asthma is 0.1–0.2%, there were no reported deaths or malignancies in the trials [22].

A pooled analysis of two multicenter, double-blind, randomized, placebo-controlled phase 3 studies with omalizumab determined the baseline characteristics that predict beneficial response for omalizumab as add-on therapy—patients receiving high doses of inhaled beclomethasone dipropionate, poor lung function, and frequent emergency asthma exacerbations [26, 27]. In addition to these phenotypic biomarkers, baseline serum IgE, blood eosinophils, and periostin may be important endotype biomarkers

Table 2. Asthma studies overview

Biologic agent	Name of study	Type of study	Number of participants	Inclusion criteria	Primary outcome measures	Results	Conclusion
Mepolizumab	Flood-Page, et al. Am J Respir Crit Care Med 2001; 176:1062–1071.	Multicenter, randomized, double-blind, placebo-controlled study	362	18–55 years of age FEV1 50–80% Must demonstrate reversibility of FEV1 ≥12% with beta-agonist Must be on treatment with inhaled corticosteroid	Change from baseline PEF recorded at weeks 12 and 20, recorded as the mean PEF over the 7 days preceding the treatment period (baseline value) and preceding weeks 12 and 20	"There were no statistically significant changes in any of the clinical end points measured."	"Mepolizumab treatment does not appear to add significant clinical benefit in patients with asthma with persistent symptoms despite inhaled corticosteroid therapy."
Mepolizumab	Nair P, et al. N Engl J Med. 2009;360(10): 985–993.	Randomized, double-blind, parallel-group trial	20	Prednisone-dependent Persistent sputum eosinophilia (3% of cells in induced sputum) despite therapy with oral and inhaled corticosteroid	Proportion of patients with exacerbations in each study group Mean reduction in prednisone dose as a percentage of the maximum possible reduction	"Patients who received mepolizumab were able to reduce their prednisone dose by a mean (+/-SD) of 83.8+/-33.4% of their maximum possible dose, as compared with 47.7±40.5% in the placebo group (P=0.04)."	"Mepolizumab reduced the number of blood and sputum eosinophils and allowed prednisone sparing in patients who had asthma with sputum eosinophilia despite prednisone treatment."
Mepolizumab	Haldar P, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med 2009;360: 973–984.	Randomized, double-blind, placebo-controlled, parallel-group study	61	>18 years of age Must meet at least one of the following criteria: – variability in the maximum diurnal PEF >20% over the course of 14 days – an increase in FEV1 >15% after albuterol –20% reduction in FEV1 in response to a provocative concentration of inhaled methacholine (PC20) <8 mg/mL	Refractory asthma according to ATS criteria Sputum eosinophil >3% on at least one occasion in the previous 2 years despite high-dose corticosteroid treatment At least 2 exacerbations requiring rescue prednisolone treatment in the previous 12 months	"Mepolizumab was associated with significantly fewer severe exacerbations than placebo over the course of 50 weeks."	"Mepolizumab therapy reduces exacerbations and improves AQLQ scores in patients with refractory eosinophilic asthma."

Table 2. (Continued)

Biologic agent	Name of study	Type of study	Number of participants	Inclusion criteria	Primary outcome measures	Results	Conclusion
Mepolizumab	Pavord ID, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicenter, double-blind, placebo-controlled trial. Lancet 2012 Aug; 380(9842): 651–9.	DREAM (Dose Ranging Efficacy and Safety with Mepolizumab in Severe Asthma): Multicenter, double-blind, placebo-controlled trial	621	12–74 years of age Clinical diagnosis of asthma supported by one or more other characteristics: – variability in diurnal PEF >20% for at least 3 days during the 2-week run-in period – improvement in FEV1 >12% and 200 mL after inhaled salbutamol – a variability in FEV1 >20% between two consecutive clinic visits in 12 months – provocative concentration of inhaled methacholine needed to reduce FEV1 by 20% (PC20) of 8 mg/mL or less documented in the previous 12 months – 2 or more exacerbations requiring systemic corticosteroid treatment in the previous year – Evidence of eosinophilic inflammation (sputum eosinophil $\geq$ 3%, FENO $\geq$ 50 ppb, peripheral blood eosinophil count $\geq 0.3 \times 10^9$ per L)	Rate of clinically significant exacerbations (validated episodes of acute asthma requiring treatment with oral corticosteroids, admission, or a visit to an emergency department)	“The rate of clinically significant exacerbations was 2.40 per patient per year in the placebo group, 1.24 in the 75 mg mepolizumab group (48% reduction, 95% CI 31–61%; $p < 0.0001$), 1.46 in the 250 mg mepolizumab group (39% reduction, 19–54%; $p = 0.0005$), and 1.15 in the 750 mg mepolizumab group (52% reduction, 36–64%; $p < 0.0001$).”	“Mepolizumab is an effective and well tolerated treatment that reduces the risk of asthma exacerbations in patients with severe eosinophilic asthma.”
Mepolizumab	Ortega HG, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014 Sep;371(13): 1198–207.	Randomized, double-blind, double-dummy study	576	12–82 years of age Clinical diagnosis of asthma (adults, FEV1 <80%; adolescents, FEV1 <90% or FEV1/FVC <0.8) One or more of the following (FEV1 reversibility >12%, positive results on methacholine or mannitol challenge, and FEV1 $\geq$ 20% between two clinic visits in the past 12 months)	Rate of exacerbations (systemic glucocorticoid for at least 3 days or the patient visited an emergency department or was hospitalized)	“The rate of exacerbations was reduced by 47% (95% confidence interval [CI], 28 to 60) among patients receiving intravenous mepolizumab and by 53% (95% CI, 36 to 65) among	“Mepolizumab administered either intravenously or subcutaneously significantly reduced asthma exacerbations and was associated with improvements in markers of asthma control.”

Table 2. (Continued)

Biologic agent	Name of study	Type of study	Number of participants	Inclusion criteria	Primary outcome measures	Results	Conclusion
Mepolizumab	Khatri S, et al. Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. J Allergy Clin Immunol. 2019 May;143 (5):1742-1751.	COLUMBA (Open-label long-term extension safety study of mepolizumab in asthmatic subjects): open-label extension study in patients with severe eosinophilic asthma previously enrolled in DREAM (Dose Ranging Efficacy and Safety with Mepolizumab in severe asthma)	347	At least two asthma exacerbations in the previous year that were treated with systemic glucocorticoids while receiving treatment with at least 880 µg of fluticasone propionate or equivalent and at least 3 months of treatment with an additional controller Eosinophil count ≥150 cells per microliter in the peripheral blood at screening or ≥300 cells per microliter in the previous year		those receiving subcutaneous mepolizumab, as compared with those receiving placebo (P<0.001 for both comparisons). Exacerbations necessitating an emergency department visit or hospitalization were reduced by 32% in the group receiving intravenous mepolizumab and by 61% in the group receiving subcutaneous mepolizumab.”	
				Subjects had to be randomized and received at least 2 doses of treatment (mepolizumab or placebo) in the DREAM study Have been receiving an asthma controller medication for 12 or more weeks	Safety endpoint: frequency of all adverse events, serious adverse events, and adverse events of special interest Efficacy endpoint: frequency of exacerbations Immunogenicity endpoint: any antibody isotype directed against mepolizumab	“Overall, 347 patients were enrolled for an average of 3.5 years (maximum, 4.5 years; total exposure, 1201 patient-years). On-treatment AEs were reported in 94% of patients (exposure-adjusted rate, 3688 events/1000 patient-years). The most frequently reported on-treatment AEs were respiratory tract infection, headache, and bronchitis, and asthma worsening. Seventy-nine (23%) patients experienced 1 or more on-	“These data support the long-term safety and efficacy of mepolizumab in patients with SEA (severe eosinophilic asthma).”

Table 2. (Continued)

Biologic agent	Name of study	Type of study	Number of participants	Inclusion criteria	Primary outcome measures	Results	Conclusion
Dupilumab	Castro M, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med. 2018 Jun 28;378(26):2486-2496.	Randomized, double-blind, placebo-controlled, parallel-group trial	1902	≥12 years of age physician-diagnosed persistent asthma for 12 months or more, according to the Global Initiative for Asthma 2014 guidelines current treatment with a medium-to-high-dose inhaled glucocorticoid plus up to two additional controllers FEV1 before bronchodilator use of ≥80% of the predicted normal value (or ≥90% of the predicted normal value in those 12 to 17 years of age) FEV1 reversibility of ≥12% and 200 mL A score on ACQ-5 of 1.5 or higher Worsening of asthma in the previous year that led to hospitalization, emergency medical care, or treatment with systemic glucocorticoids for 3 days or more	Annualized rate of severe asthma exacerbations absolute change from baseline to week 12 in the FEV1 before bronchodilator use	treatment serious AEs; there were 6 deaths, none of which were assessed as related to mepolizumab. For patients with 156 weeks or greater enrollment, the exacerbation rate was 0.74 events/y (weeks 0–156), a 56% reduction from the off-treatment period between DREAM and COLUMBA.” “The annualized rate of severe asthma exacerbations was 0.46 (95% confidence interval [CI], 0.39 to 0.53) among patients assigned to 200 mg of dupilumab every 2 weeks and 0.87 (95% CI, 0.72 to 1.05) among those assigned to a matched placebo, for a 47.7% lower rate with dupilumab than with placebo ($P<0.001$); similar results were seen with the dupilumab dose of 300 mg every 2 weeks.”	“In this trial, patients who received dupilumab had significantly lower rates of severe asthma exacerbation than those who received placebo, as well as better lung function and asthma control. Greater benefits were seen in patients with higher baseline levels of eosinophils.”
Dupilumab	Rabe KF, et al. Efficacy and safety of	Randomized, double-blind,	210	≥12 years of age physician-diagnosed asthma for 1 year or more according	Percentage reduction in the	“The percentage change in the glucocorticoid dose was –70.1% in	“In patients with glucocorticoid-dependent

Table 2. (Continued)

Biologic agent	Name of study	Type of study	Number of participants	Inclusion criteria	Primary outcome measures	Results	Conclusion
	dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med. 2018 Jun 28;378(26):2475–2485	placebo-controlled, phase 3 trial		to the Global Initiative for Asthma 2014 guidelines receiving treatment with regular systemic glucocorticoids in the previous 6 months (5 to 35 mg per day of prednisone or prednisolone or equivalent)	glucocorticoid dose at week 24	the dupilumab group, as compared with – 41.9% in the placebo group ($P<0.001$); 80% versus 50% of the patients had a dose reduction of at least 50%, 69% versus 33% had a dose reduction to less than 5 mg per day, and 48% versus 25% completely discontinued oral glucocorticoid use.”	severe asthma, dupilumab treatment reduced oral glucocorticoid use while decreasing the rate of severe exacerbations and increasing the FEV1.”

in predicting response to omalizumab. The optimal total serum IgE is between 30 and 700 (1300 for children ages 6–11 in the USA, 1500 in Europe) international units/mL allowing for omalizumab to reduce enough free IgE for therapeutic benefit [28]. Busse et al. randomized 328 patients between the ages of 12 to 75 with uncontrolled atopic asthma despite inhaled glucocorticoids and normal lung function (FEV1 greater than or equal to 80%) to examine the effectiveness of omalizumab on atopic asthma [29]. The primary endpoint of the study was a reduction of the average rate of asthma exacerbations during the 6-month study period. Although there was a 27% reduction in exacerbation rates between the omalizumab and placebo groups (0.21 vs 0.26 per patient during the treatment period; RR 0.73; 95% CI 0.44–1.24), the primary endpoint was not met as it was not statistically significant. However, an important finding was that the exacerbation rate was reduced by 45% (0.4 to 0.22 exacerbations/patient during the treatment period; 95% CI 0.25–1.22) in the high eosinophilic group with no change in the low eosinophilic group [29]. Data from analysis of two phase 3 clinical trials examining allergic asthma patients on omalizumab found a higher reduction in the mean exacerbation rate of patients on omalizumab with higher baseline blood eosinophil counts [30••]. In addition to higher FeNO (fractional exhaled nitric oxide) and eosinophil counts predicting reductions in asthma exacerbations, in a study of 850 patients (aged 12–75 years old) with uncontrolled severe persistent asthma on omalizumab, higher serum periostin levels were also associated with a greater reduction in asthma exacerbations [31••].

Mepolizumab

Mepolizumab is a humanized monoclonal antibody that binds with high affinity to free IL-5 preventing it from binding to IL-5 receptor (IL-5R). IL-5 is a cytokine that recruits eosinophils from the bone marrow and promotes activation and persistence in the blood [32]. In initial studies with mepolizumab, although sputum and blood eosinophil counts were decreased, no statistically significant changes were noted in morning asthma symptom scores, FEV1, inhaled B2 agonist use, or asthma-related quality of life scores [33].

However, in select patients with severe asthma and persistent sputum eosinophilia despite high doses of inhaled corticosteroids, mepolizumab was found to be effective in reducing blood and sputum eosinophil counts, reducing asthma exacerbations and improving asthma-related quality of life in patients 12 years or older [34–37]. As seen in multiple studies, severe asthma patients with higher blood eosinophil counts were more likely to have a clinical benefit from mepolizumab [35–37].

An open-label long-term extension study assessing the long-term safety of mepolizumab in patients with severe eosinophilic asthma who were previously enrolled in the DREAM study was recently published and showed that favorable safety and efficacy results [38]. For patients enrolled for 156 weeks or greater, the exacerbation rate was 0.74 events/year which was a 56% reduction from the off-treatment period between the DREAM study and the extension study (COLUMBA); for all patients, the mean Asthma Control Questionnaire 5 score was reduced by 0.47 points, and blood eosinophil counts were reduced by 78% [38].

Benralizumab

Benralizumab is a monoclonal antibody that binds to the IL-5 receptor alpha thereby targeting multiple effector cells driven by IL-5 (eosinophils, basophils) and causing programmed cell death [39, 40]. To assess the percentage change in oral glucocorticoid doses from baseline to week 28, Nair et al. randomly divided 220 adult patients with severe uncontrolled asthma (requiring daily oral glucocorticoid therapy for at least 6 continuous months directly before enrollment) and blood eosinophil counts of at least 150 cells per cubic millimeter, into 3 groups—dosing every 4 weeks, dosing every 8 weeks, and placebo. Both treatment groups (every 4 weeks and every 8 weeks dosing) significantly reduced the median final oral glucocorticoid dose by 75% as compared with a reduction of 25% in the placebo group ($P < 0.001$ for both comparisons). Further, the annual exacerbation rate was 55% lower for the every 4-week treatment group compared with placebo and 70% lower for the every 8-week treatment group compared with placebo [41]. In the pooled analysis of the SIROCCO and CALIMA phase 3 studies in 2295 patients ages 12–75, patients with severe asthma were randomly assigned to 3 treatment groups: 30 mg benralizumab subcutaneously every 4 weeks, 30 mg benralizumab subcutaneously every 8 weeks, and placebo every 4 weeks with the primary endpoint being annual exacerbation rate ratio versus placebo with different baseline eosinophil counts [42••]. In both the every 4-week and every 8-week benralizumab treatment groups versus placebo, the greatest reduction in annual exacerbation rates was seen in patients with both high blood eosinophil counts and history of more frequent exacerbations [42••].

Dupilumab

Dupilumab is a fully human monoclonal antibody that binds to the alpha subunit of the IL-4 receptor. Since both IL-4 and IL-13 bind to this receptor, it inhibits activity of both cytokines [43]. In a pivotal multicenter study of 1902 patients 12 years or older with poorly controlled asthma, the annualized rates of severe exacerbation were reduced by 50% in the dupilumab groups (randomized to either 200 mg or 300 mg every 2 weeks after loading doses) compared with that of the placebo, and the FEV1 significantly increased in the 200 mg treatment group compared with that of placebo [44]. The treatment effect seemed greater in patients with a baseline blood eosinophil count of 300/uL [44]. In a smaller study of 210 patients with oral glucocorticoid-treated asthma, the percentage reduction in the glucocorticoid dose was 70% in the patients receiving dupilumab 300 mg every 2 weeks for 24 weeks versus 41.9% in the placebo group ($P < 0.001$) with associated decrease in rates of severe exacerbations and increase in FEV1 in the treatment group [45].

Atopic Dermatitis

Atopic dermatitis is a chronic, pruritic inflammatory skin disease that has various phenotypes with different features such as the age of disease onset,

atopy, comorbidities, and most likely different pathophysiologic mechanisms [46]. In a recent PRACTALL document between the EAACI and AAAAI, three proposed phenotypes for atopic dermatitis are described as non-lesional skin, acute disease flares, and chronic relapsing atopic dermatitis, and 2 proposed endotypes are described: type 2 immune response and non-type 2 immune response (TH22 and TH1 driven). In all three phenotypes, a type 2 endotype is present with a peak during acute disease flares. However, in the non-lesional skin phenotype for atopic dermatitis, TH 22 and TH 1-driven inflammation is prominent and in the phenotype chronic relapsing atopic dermatitis, epithelial dysfunction is a key mechanism with TH1 and TH22-driven inflammation [8].

No biologics are currently FDA-approved for atopic dermatitis in children, but there are multiple ongoing and completed clinical trials with use of dupilumab in children (NCT02612454, NCT03389893, NCT03346434, NCT03054428) [47].

Chronic Spontaneous Urticaria

Chronic spontaneous urticaria (CSU) is defined as itchy hives that last for at least 6 weeks, with or without angioedema and have no apparent external triggers [48]. Although the pathogenesis is unclear, it is associated with histamine release from cutaneous mast cells and blood basophils [49•]. Evidence of autoreactivity is noted in positive autologous serum skin tests in 1/3 patients and the presence of IgG autoantibodies against FcεR1 or IgE in 1/3 patients [49•].

Omalizumab

Although the pharmacologic mechanism of omalizumab in CSU has not been determined, it has been approved for the treatment of CSU in ages 12 or greater based on three pivotal phase 3 trials—ASTERIA 1, ASTERIA 2, and GLACIAL, all of which showed consistent efficacy in reducing clinical symptoms associated with CSU resistant to antihistamines (itch severity) with favorable safety results [50–52]. An important caveat is that in each study, children ages 12–17 only accounted for a small proportion of the subjects (6% in ASTERIA 1, 3% in ASTERIA 2, unclear number of adolescents in GLACIAL) [50–52].

Conclusion

Biologics have transformed the management of atopic diseases in adults and children. In addition, they have added insight into mechanisms of action which fosters a better understanding of how different endotypes are associated with the heterogeneity of atopic diseases as we have seen that phenotype directed therapy alone does not account for the variability in the natural history and prognosis. The difficulty in endotype-differentiated therapy will be the redundancy of the immune system and overlap of atopic phenotypes. As we move

more towards precision-based medicine, it will be crucial for clinical studies to include the study of atopic endotypes and to have these biomarkers validated clinically to better predict response to therapy.

Compliance with Ethical Standards

Conflict of Interest

Rita Kachru, Kellie Lim, and Lorraine Anderson 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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