REVIEW

Novel therapeutic targets for allergic airway disease in children

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Abstract

The aim of precision medicine is setting up targeted therapies for selected patients that would ideally have high effectiveness and few side effects. This is made possible by targeted therapy drugs that selectively act on a specific pathway. Precision medicine is spreading to many medical specialties, and there is increasing interest in the context of allergic airway diseases, such as allergic rhinitis, chronic rhinosinusitis, and asthma. This review is an update of new targets in the treatment of childhood allergic upper airway diseases and asthma, including the most recent biologic drugs that have already been licensed or are in the pipeline to be tested with children.

Keywords: allergic airway disease, allergic rhinitis, asthma, biologics, children, chronic rhinosinusitis, immunotherapy.

Introduction

In the last decade, a large amount of research has provided consistent advances in molecular biology and 'omics' science (genomics, metabolomics, proteomics, and transcriptomics), which has led to the detailed characterization of the etiology, pathophysiological mechanisms, and subtypes of many diseases. Based on these developments, the concept of precision medicine was established. The aim of precision medicine is setting up targeted therapies, which would ideally have high effectiveness and few side effects, for selected patients. This is made possible because targeted therapy drugs selectively act on a specific pathway, corresponding to a particular endotype of the disease.[1] Originally applied in oncology, precision medicine is spreading to other specialties, and there is increasing interest in the context of allergic airway disease (AAD). AADs include allergic rhinitis (AR), chronic rhinosinusitis (CRS), and asthma and show high prevalence in children.[2]

The management of severe forms of AAD is a priority and a challenge for clinicians. Asthma represents the prototype of AAD, and its management should be focused on controlling symptoms, improving quality of life, and preventing asthma attacks. To achieve this, a multidisciplinary approach is needed, along with the assessment of asthma control at regular intervals and better ways to detect airway remodeling. The evolution of disease management may also be on the control of remodeling in addition to symptom control, by means of newer therapies that may affect remodeling, preventing a decline in lung function. Based on periodic evaluations, therapy is stepped-down or stepped-up until the symptoms are under control. Nevertheless, a subgroup of patients remains uncontrolled, which include patients with difficult-to-treat asthma and severe asthma. The former is related to comorbidities, poor adherence to treatment, or exposure to environmental factors, while the latter includes therapy-resistant asthma.[3,4] Patients with severe asthma are at high risk of developing acute severe exacerbations, also known as 'status asthmaticus,' a life-threatening condition unresponsive to repeated courses of β-agonist therapy.[5]

When the diagnosis of asthma is confirmed and comorbidities have been assessed, the European Respiratory Society and American Thoracic Society (ERS/ATS) guidelines define severe asthma as asthma that requires treatment with a high dose of inhaled corticosteroids (ICS) plus a second controller, asthma requiring systemic corticosteroids to prevent it from becoming 'uncontrolled,' or asthma that remains 'uncontrolled' despite this therapy.[6] The aim of this review is to provide an update on novel therapeutic targets for AAD in children.

Methods

This review was conducted using two databases: PubMed and ScienceDirect. On these websites, we searched for articles in English using the following key words: allergic airway disease, allergy in children, asthma in children, phenotypes and endotypes of asthma, biomarkers in AAD, allergen immunotherapy (AIT), and novel biologics. As a rule of thumb, we preliminarily selected articles that we judged relevant on the basis of title. Then, we decided to use the abstracts of articles to assess whether they fit the topic. We found 1364 abstracts suitable for the topic. Among these, 208 were selected for detailed review. We also reviewed the references of the selected articles and read those with titles that might be of interest for the topic.

United airway disease as a model of diagnosis and care in severe AAD

In the context of AAD, research has shown a close link between upper and lower airway diseases. Their interplay is supported by epidemiologic, anatomical, histological, pathophysiologic, and therapeutic data. A high prevalence of AR (30–80%) has been reported among patients affected by asthma. The histological features of the upper and lower airways are similar and include a pseudostratified epithelium. They generally show an inflammatory pattern that is predominantly

mediated by immunoglobulin-E (IgE).[7] Hence, the term 'allergic rhinobronchitis' was first proposed.[8]

Over the last two decades, a shared pathophysiological mechanism has been hypothesized for AAD, where the bone marrow plays a key role in the systemic inflammatory response after an inflammatory response following the triggering of a specific site of the airways. The released mediators, especially interleukin (IL)-5, might reach the bone marrow and stimulate the mobilization of CD34+ cells and their differentiation into eosinophils, as well as blood eosinophil activation and increased IL-5 production, which lead to systemic inflammation and infiltration in different areas of the airways.[9–10] Hallstrand and colleagues reported that nonallergic individuals who underwent bone marrow transplantation from donors with allergic disease had a high rate of developing AR and asthma during a long-term follow-up.[11] Therefore, it may be appropriate to define AR, CRS, and asthma as different expressions of the same disease. Hence, the term United Airway Disease has been defined (Figure 1).[12]

Many surveys, longitudinal studies, and retrospective studies have confirmed the association between AR and asthma.[13–17] In 8 years of follow-up, 33% of individuals with AR developed bronchial hyperreactivity to methacholine bronchial challenge and impaired forced expiratory flow at 25–75% of the pulmonary volume (FEF25–75), compared to the control group, which showed no spirometric alteration.[18] Reduced FEF25–75 in subjects with AR and in all subjects with normal forced expiratory value in 1 second (FEV1) may be an early marker

Figure 1.   United airway disease model.
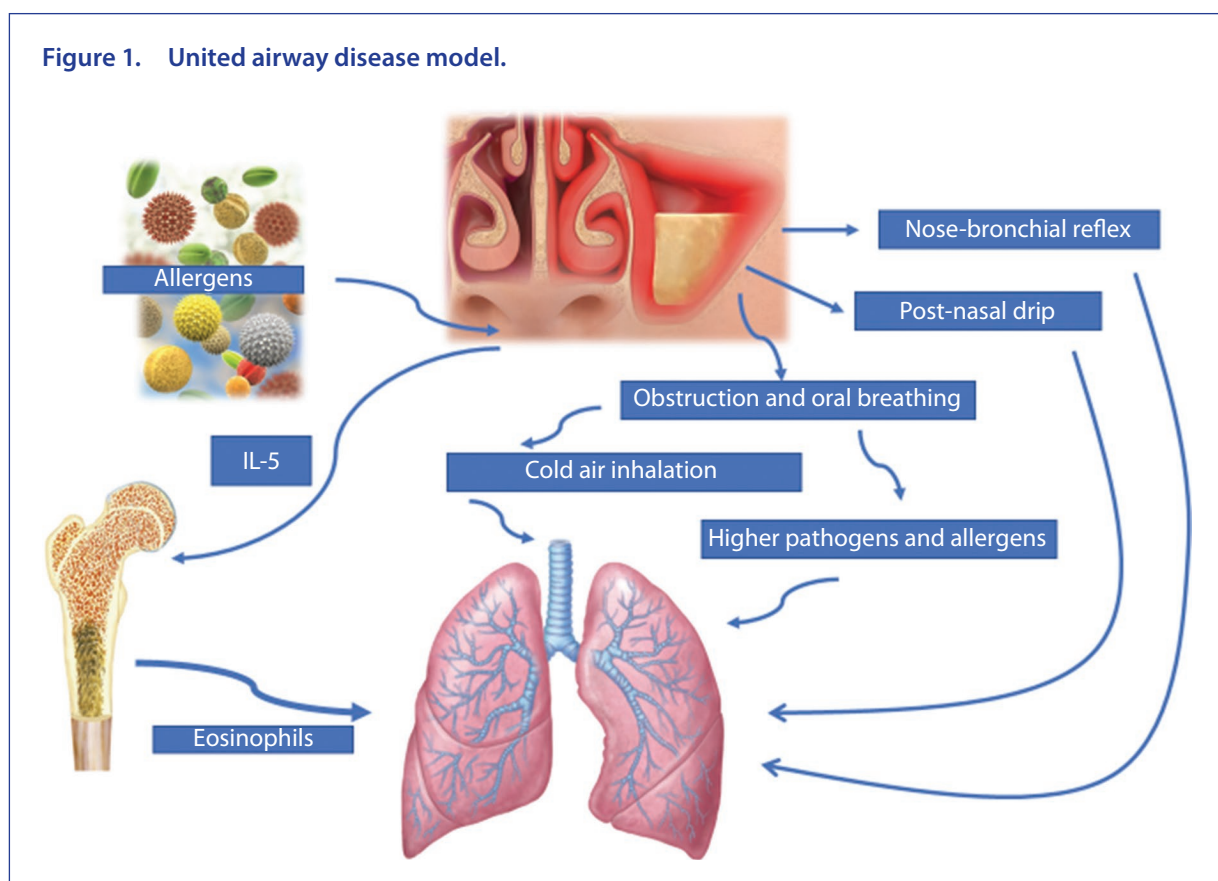
of small airway impairment. FEF25–75 reduction is positively correlated with the severity of allergic predictors.[19]

In a review by Sedaghat, AR also emerged as the most prevalent comorbidity associated with pediatric CRS (26.9%).[20] A hypothesis is that allergic inflammation might cause chronic obstruction of osteomeatal complex. Although their relationship remains controversial, children with CRS should be screened for allergies.[21] Indeed, AR is characterized by IgE-mediated inflammation after exposure to allergen in atopic individuals, causing rhinorrhea, nasal obstruction, nasal itching, and sneezing that are reversible spontaneously or with treatment. These symptoms occur during two or more consecutive days.[22] Different from AR, a clinical consensus statement defined pediatric CRS as at least 90 continuous days of two or more symptoms of purulent rhinorrhea, nasal obstruction, facial pressure/pain, or cough and either endoscopic signs of mucosal edema, purulent drainage, or nasal polyposis and/or CT scan changes showing mucosal changes within the osteomeatal complex and/or sinuses.[23]

The link between CRS and asthma has been widely investigated. Around 40% of children with asthma show radiological or endoscopic signs of rhinosinusitis.[24,25] It is still debated whether CRS is causative of asthma or if it is a part of United Airway Disease. Local mechanisms, that have been suggested, include nose-bronchial reflex, postnasal drip with inflammatory mediators spreading to the lower airways, and impaired sinus function. Sinonasal inflammation leads to obstruction and oral breathing and allows cold air, higher amounts of pathogens, and allergens to reach the lower airways, as well as the propagation of inflammation by both contiguity and the bloodstream. These effects might be responsible for epithelial barrier impairment and triggering bronchial constriction.[26] This interaction is complicated by the fact that the clinical expression of upper airway disease varies with age. A higher number of asthma symptoms are seen in children aged 6–10 years old who have been diagnosed with rhinosinusitis by endoscopy compared to other age groups of children. This is probably due to the progressive development of the paranasal sinuses during childhood.[27]

Phenotypes and endotypes

At the beginning of the 20th century, Wilhelm Johannsen introduced the term 'phenotype' as 'the observable structural and functional characteristics of an organism determined by its genotype and modulated by its environment.' AADs are heterogeneous and have been classified into different phenotypes based on the different clinical expressions of the disease. Advances in molecular biology have allowed for the investigation of AAD pathophysiology through the identification of endotypes. An endotype consists of the underlying molecular mechanisms that are involved in the phenotypic expression of the disease. The accurate identification and characterization of endotypes is essential to set up targeted therapies.[28,29]

Phenotypes and endotypes of AR
AR can be classified according to the causal allergen into two main phenotypes: seasonal (SAR) or perennial (PAR). Its pathophysiology is mainly mediated by IgE with eosinophilic infiltration. The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines revision from 2001 introduced a classification as intermittent or persistent AR based on the duration of symptoms (less or more than 4 weeks or 4 days per week). These terms are not synonymous with SAR and PAR. In fact, patients with SAR may have persistent symptoms, and patients with PAR may have intermittent symptoms.[30] The revision of the ARIA guidelines in 2016 kept the classifications of SAR and PAR. Severity classification ranges from mild to severe forms according to the symptoms.[31] Local AR (LAR) is a new phenotype proposed for AR, and LAR is characterized by a lack of systemic atopy evidence, positive response in the nasal allergen provocation test, and local IgE production in the nasal mucosa].[32]

A 10-year study follow-up confirmed that LAR is an independent phenotype, and conversion to systemic atopy was not significant compared to controls (9.7 *versus* 7.8%; *p*=0.623).[33] Interestingly, LAR worsens and increases the risk of suffering from asthma.[33] Polyallergic patients with AR experienced significantly more severe nasal symptoms than monoallergic ones and showed higher infiltration of eosinophilic and inflammatory mast cells in nasal cytology. Thus, the inflammatory pattern in nasal cytology may be a useful instrument to better characterize the phenotypes and endotypes of allergic and nonallergic rhinitis and realize personalized treatments.[34]

Phenotypes and endotypes of CRS
CRS is probably the least investigated AAD and has a low volume of published research, although it has high prevalence.[35] The two main phenotypes described are CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP).[36] Nasal polyposis is rare in childhood and might be a 'red flag' for systemic diseases, such as cystic fibrosis or primary ciliary dyskinesia. An Italian monocentric study reported 56 pediatric patients with nasal polyposis over a 17-year period, with 32% showing positive skin prick tests.[37]

A case control study on 173 patients, a tissue cluster analysis of inflammatory biomarkers, identified ten cluster endotypes. Four of them had predominant noneosinophilic inflammation; six had eosinophilic inflammation, of which three were characterized by high IL-5, eosinophilic cationic protein, and serum IgE expression; and three had intermediate levels of IL-5. It was found that IL-5 levels correlated with CRSwNP and increased prevalence of asthma.[38]

Phenotypes and endotypes of asthma
Asthma is the most heterogeneous among AADs, and its complexity can be summarized by the definition of 'asthma syndrome.' Asthma classification is based on the presence of atopy, comorbidities, triggering factors (exercise, drugs, and smoke), response to treatment, and inflammatory patterns. Hence,

the different phenotypes are early-onset allergic, late-onset eosinophilic, exercise-induced, obesity-related, and neutrophilic asthma.[39] The main endotypes of asthma include eosinophilic asthma (Th2-high) and neutrophilic or pauci-granulocytic asthma (Th2-low) according to the inflammatory pattern, induced sputum, bronchoalveolar lavage, or blood cell count.[40]

The Th2-high endotype is the most common in children, and it is often associated with early-onset severe asthma, atopy, and responsiveness to steroids. Th2-high cytokine pattern includes the so-called 'alarmins': IL-33, IL-25, and thymic stromal lymphopoietin. 'Alarmins' have been suggested to start eosinophilic inflammation and increase IL-5, IL-4, and IL-13 expression. These cytokines lead to the recruitment of eosinophils, mast cells, and basophils, as well as Ig-E synthesis. The cytokines involved in Th2-low asthma are IL-8, IL-17A, and IL-22, and this type of asthma is characterized by a neutrophilic or paucigranulocytic infiltrate. T2-low asthma is usually associated with severe and corticosteroid-resistant asthma.[41]

Definition and identification of validated biomarkers in AAD

Biomarkers are needed in precision medicine to achieve the goals of personalized treatment. A biomarker may be considered as 'a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention, including therapeutic interventions.' An ideal biomarker should be noninvasive, objective, reproducible, cost effective, and predictive of treatment response. They can serve as diagnostic, monitoring, predictive, treatment-response, or prognostic biomarkers.[42] Biomarkers provide an accurate characterization of endotypes that allows the treatment of selected subsets of patients with drugs acting selectively on a specific pathway. Indeed, biological drugs are labeled only for patients who fulfill strict criteria (e.g., eosinophils blood count for anti-IL5) – that is, the right drug for the right patient.

Role of IgE in AR, CRS, and asthma

IgE plays a key role in AAD. Its secretion is modulated by B cells after the switch from IgG to IgE induced by Th2 cytokines. It is a marker of atopy and allergen sensitization and acts as an early-phase effector of the Th2 hypersensitivity immune response. IgE represents a therapeutic target for anti-IgE drugs.[43] High serum levels of total IgE represent a diagnostic biomarker for AAD. Total IgE is associated with bronchial hyperreactivity as well.[44] Serum-specific IgE is a predictive biomarker of AR,[39,45] and total and serum IgE correlate with asthma severity.[46] Its role as a predictive biomarker of treatment response is questioned, but it is a reliable monitoring biomarker of the response to anti-IgE therapies.[47] Regarding AIT, serum-specific IgE is not predictive or a monitoring biomarker, although it represents a valid biomarker to select patients for treatment with AIT. The serum IgE/total IgE ratio may be a potential predictive biomarker in AIT.[42,48]

Role of eosinophils in AR, CRS, and asthma

Eosinophils are involved in high-Th2 inflammation, and induced sputum eosinophil count ≥3% is the gold standard as a diagnostic biomarker for eosinophilic airway inflammation. Nevertheless, their routine measurement is limited by the invasiveness of the process and the difficulties to obtain sputum, especially in children.[49] Sputum eosinophils correlate with disease severity. Blood eosinophils may represent an alternative, reliable, noninvasive biomarker that shows good correlation with the percentage of sputum eosinophils in asthma.[50]

Blood eosinophil count correlates with severe asthma and increased exacerbation rates if the count is ≥300 cells/μL.[46] Furthermore, blood eosinophil counts ≥300 cells/μL in patients with asthma are a predictive and monitoring biomarker of the response to biological therapies, especially anti-IL-5 drugs. The decrease in blood eosinophils can also serve as a monitoring biomarker during treatment with anti-IL-5.[51] The retrospective Next Steps Toward personalised care: EvaLuating responders to XoLAIR treatment in patients with SAA (STELLAIR) study questioned the role of blood eosinophils as a predictive biomarker of the response to omalizumab and found similar response rates and reductions in exacerbation rates, regardless of blood eosinophil counts.[52] In CRS, nasal and blood eosinophils are markers of CRSwNP, more severe disease, and the prediction of the response to corticosteroids, especially in patients from Western countries compared with Asians. It has been hypothesized because of a combination of both genetic and environmental factors.[53,54]

Role of fractional exhaled nitric oxide (FeNO) and other emerging biomarkers in AR, CRS, and asthma

Inducible nitric oxide synthase produces nitric oxide (NO) as a bronchodilator in airways. FeNO is a biomarker of eosinophilic inflammation. High FeNO in patients with AR is associated with bronchial hyperreactivity and future risk of the development of asthma.[55] Furthermore, elevated FeNO levels are predictive of good treatment response to corticosteroids.[56] Nevertheless, the role of FeNO in the management of asthma still remains controversial.[57] Emerging biomarkers include serum periostin,[58,59] dipeptidyl peptidase-4 (DDP-4),[60] eotaxin 1 and its receptor CCR3,[61] exhaled breath condensate (EBC),[62] volatile organic compounds (VOCs),[62] YKL-40,[63] and high mobility group box 1 (HMGB1).[64–66] However, new emerging biomarkers need more investigations for standardization and validation.

Therapeutic targets in UAD during childhood

AIT in AR in children

The management of AR based on allergen avoidance and symptomatic drugs (antihistamines, intranasal corticosteroids,

and leukotriene-receptor antagonists) is often suboptimal and characterized by inadequate symptom control and side effects, especially for PAR. AIT represents the best option in the treatment of AR. It is the only disease-modifying therapy and is indicated in moderate-to-severe intermittent or persistent AR.[67,68] It consists of low, increasing doses of allergen administration by a subcutaneous (SCIT) or sublingual (SLIT) route, and the effects usually last at least 3 years. This treatment modulates the immune system, particularly T regulator cells (T-regs), which induces tolerance to a specific allergen. T-regs seem to be defective in subjects with AR.[69]

Indeed, T-regs produce anti-inflammatory cytokines IL-10 and TGF-β. AIT has been found to increase IL-10 synthesis, which reduces Th2 cytokines (IL-13, IL-4, and IL-5), reduces eosinophil activation, and promotes IgG4 production.[70] A recent review summarized previous Cochrane reviews, systematic reviews, meta-analyses, and randomized clinical trials on AIT.[71] The study evidenced the efficacy and safety of both SCIT and SLIT in reducing AR symptoms and medication use and inducing long-term remission. The heterogeneity and small sample size of previous studies represented a limit in establishing the superiority of SCIT or SLIT.[71]

Long-term effectiveness was reported for symptoms and quality of life after 3 years of treatment and 2 years after discontinuation of house dust mite (HDM) SCIT in both children and adults with AR, but the effect was greater in children.[72] However, SLIT is easier and better tolerated than SCIT in children. After the first dose, the following doses can be administered at home. Poddighe and colleagues analyzed studies on SLIT in children.[73] SLIT for grass pollen rhinitis was shown to be effective, particularly if started preseasonally. However, evidence of the efficacy of SLIT in HDM-AR is less strong than in grass pollen rhinitis because of the small number and scale of randomized controlled trials available.[73]

The safety and effectiveness of SLIT *versus* a placebo have been confirmed in a Cochrane systematic review.[74] The side effects are usually limited to the upper airways or gastrointestinal tract. No patients with anaphylaxis were reported in the included studies, although isolated patients with anaphylaxis, who were almost all individuals with previous severe reactions to SCIT, were described. Thus, it might represent a valid and low risk alternative to SCIT.[74]

Local nasal immunotherapy is another alternative and safe route of administration, by means of spray or dry powder, although its effectiveness is lower compared with SCIT and SLIT in patients with allergic rhinitis and comorbid asthma. Local nasal immunotherapy seems to have a local effect only on nasal symptoms.[75]

To reduce the risk of systemic adverse reactions associated with SCIT, physically or chemically modified allergens, called allergoids, have also been tested, showing both efficacy and reduced IgE-binding capacity.[76] Nevertheless, there are few comparative studies between allergens and allergoids as immunotherapy.[77]

Anti IgE in AR and CRS

IgE is crucial in the pathophysiology of AAD, which makes it a potential therapeutic target. Omalizumab is a humanized IgG1 monoclonal antibody that binds to free IgE, thus preventing interaction with its receptors (Fc epsilon RI) and downregulating its expression by dendritic cells and mast cells.[78] Its use in AR treatment is still off-label, and its application in upper airway disease and asthma has been tested in several randomized clinical trials.[79] A multicenter randomized double-blind placebo-controlled trial examined 536 adults with moderate-to-severe SAR, and symptom severity significantly improved in the subgroup treated with 300 mg of omalizumab every 3 or 4 weeks compared to placebo.[80] A meta-analysis of 11 studies on 2870 patients with moderate-to-severe AR reported a statistically significant reduction in symptom score. However, the accuracy was limited by the different prevalence of comorbidities among studies.[81]

A combination of omalizumab and AIT contributed to improved symptom scores in 221 children with SAR and adolescents compared to AIT plus placebo.[82] Improvements were also seen in sinonasal symptoms and nasal polyps in a patient with refractory CRSwNP and comorbid asthma, which suggested that omalizumab may also have a role as a target therapy in CRS (particularly CRSwNP), where IgE is involved.[83] A systematic review analyzed two randomized clinical trials on the use of anti-IgE in comparison to a placebo for CRS treatment. One study included 23 adults with CRS and comorbid asthma. The authors concluded that there is little evidence for the efficacy of anti-IgE as a treatment for CRS, especially for quality of life. Indeed, only one of the two studies showed a significant reduction in symptoms, endoscopic scores, and radiological scores.[84–86] Further randomized clinical trials with larger samples and on populations of children are needed.

Anti-IL-5 in CRS

IL-5 is a cytokine involved in Th2 eosinophilic/high inflammation. It recruits, activates, and promotes the survival of eosinophils. CRSwNP has been associated with eosinophilic inflammation, but mainly in Caucasian subjects. Anti-IL5 drugs are currently approved only for asthma and include mepolizumab, and reslizumab, that targets circulating IL-5, and benralizumab, that binds to IL-5 receptors. Evidence has been reported for the effectiveness and safety of anti-IL5 drugs on refractory nasal polyposis but is limited to three trials. In a randomized double-blind controlled trial, reslizumab (3 mg/kg, intravenous) was effective in reducing the size of nasal polyps.[87] Two months of treatment with intravenous mepolizumab (750 mg) improved endoscopic and imaging scores in patients with refractory nasal polyposis.[88] A randomized double-blind controlled trial examined 105 adults with severe recurrent nasal polyposis, and monthly intravenous mepolizumab (750 mg) significantly reduced the need for surgery at 25 weeks, endoscopic nasal scores, and symptom scores compared to placebo.[89]

Therapeutic targets in childhood asthma

AIT in controlled asthma in children

The Global Initiative for Asthma (GINA) guidelines introduced AIT as an add-on therapy for HDM-sensitized adults affected by AA and comorbid AR. Its use is restricted to patients with partially controlled mild-to-moderate AA and FEV1≥70% predicted because of the high risk of systemic adverse reactions in those with uncontrolled asthma.[90] The effectiveness and safety of AIT have been assessed in both adults and children with AA, but few studies have been performed with children.[91–93]

A systematic review reported a reduction in asthma medication use for SCIT and improved quality of life in patients aged ≤18 years old. However, evidence was stronger for SCIT than SLIT.[94] Regarding SLIT, a meta-analysis found a reduction in symptom scores and medication use in pediatric AA, although the studies analyzed were heterogeneous.[95] Furthermore, SLIT demonstrated long-term effectiveness at 5 years after discontinuation in 60 children with asthma and AR due to HDM.[96]

A recent review used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for AIT.[97] However, the reviewed studies suffered from heterogeneity, high risk of bias, and lack of standardization for outcomes. The authors stated that there is currently little evidence to recommend AIT in childhood AA until further well-designed randomized clinical trials provide higher strength of evidence about its beneficial effects.[97] Interesting data have been obtained from the combination of SCIT and omalizumab, which might increase the efficacy of AIT and allow for restrictions on AIT to be overcome in patients with uncontrolled asthma.[98] In a retrospective study on 90 children, combined therapy with AA reduced the occurrence of systemic reactions in comparison to SCIT alone.[99]

Several studies have hypothesized that there is a disease-modifying effect of AIT that reduces the risk of developing new sensitizations and asthma in children, but they were limited to small groups.[93] Two large studies were performed: the prevention of allergy (PAT) study and the grass tablet asthma prevention (GAP) study. The PAT study enrolled 205 children with allergies to grass or birch pollen allergy, who were randomized to receive SCIT for 3 years. The treatment group had significantly lower risk of developing asthma and fewer asthma symptoms compared to the controls at the end of 3 years of treatment and at the 5- and 10-year follow-up.[100–102] As treatment to prevent the development of new sensitizations, AIT is controversial, and evidence is limited to short-term periods. The reduction in the risk of onset of the first allergic disease was not significant. Further studies are needed to evaluate long-term effects.

Anti-IgE in severe AA during childhood

The pathophysiology of AA is strictly related to IgE, which is involved in the early and late phases of the inflammatory response. There is evidence that blocking free IgE interferes with the inflammatory cascade, which was the rationale to develop and test the humanized anti-IgE monoclonal antibody omalizumab.[103] In 2001, two phase III trials were conducted with 1071 adolescents and adults with moderate-to-severe asthma, which demonstrated that omalizumab significantly reduced asthma exacerbations, symptoms, ICS, and the use of rescue medications compared with the placebo group. Improvement in pulmonary function test was also observed.[104,105] Milgrom and colleagues performed a randomized double-blind placebo-controlled trial on 334 children with asthma controlled by ICS, which showed that omalizumab led to a significant decrease in asthma exacerbations (18.2 *versus* 38.5%) and ICS used, but there was no significant improvement in spirometric parameters. No serious adverse reactions were reported.[106,107]

Thus, omalizumab was first approved by the Food and Drug Administration (FDA) in 2003 for asthma treatment at the age of 12 and up, and its use was extended to children in 2009 by the European Medicines Agency (EMA) and in 2016 by the FDA. It is indicated as an add-on therapy for patients aged 6 years or older with moderate-to-severe persistent AA who have symptoms that are not controlled with common medications, positive skin test reactions, or IgE specific to a perennial aeroallergen and total IgE of 30–1500 IU/mL. The additional criteria of the EMA are frequent daytime symptoms or nighttime awakenings along with multiple documented severe asthma exacerbations, despite daily high-dose ICS, plus a long-acting inhaled β2-agonist. Reduced lung function (FEV1<80% predicted) is an additional condition for patients aged ≥12 years. The frequency of subcutaneous administration (monthly or twice a month) and dosage are guided by total IgE levels and weight.[108–110]

Recently, a multicenter Italian study tested omalizumab in 47 children and adolescents suffering from severe AA. After 12 months of treatment, the rates of exacerbation were reduced by 91% ($p<0.001$). Furthermore, there were significant reductions in hospitalization rates and the use of oral and ICS compared with the previous year. FEV_1 improvement was not significant, however, which was probably due to the young age of the patients, who already had FEV1>80% at baseline.[111]

There have been concerns about omalizumab in relation to both immediate and long-term adverse events, particularly the risk of anaphylaxis and malignancy, respectively. Postmarket data have provided consistent evidence of its safety profile. Anaphylaxis was reported in 0.2% of treated patients, which is similar to the incidence of anaphylaxis in the general population. In controlled studies, the incidence of anaphylaxis was 0.14 *versus* 0.07% for the controls.[112] The safety profile has been confirmed in children with asthma as well, where no differences in adverse events were observed in comparison

with a placebo.[113] Data on the safety and effectiveness of omalizumab have led to an increasing number of trials to assess its efficacy in different pediatric IgE-mediated diseases, such as AR, nasal polyposis, severe refractory atopic dermatitis, allergic bronchopulmonary aspergillosis, food allergy, and anaphylaxis. Omalizumab is licensed as an add-on therapy for the treatment of chronic spontaneous urticaria in adolescents aged >12 years who have an inadequate response to H1-antihistamine treatment.[114–116]

The duration of treatment with omalizumab still remains a debated issue. It is a long-term treatment because it requires about 12 weeks to show any clinical improvement. Therefore, its effectiveness should be evaluated at 16 weeks of treatment, defined as primary endpoint by clinical trials and summary of product characteristics to continue the treatment.[108,109] A further assessment might be considered at 52 weeks of treatment.[117] A multicenter study in France assessed the effects of the immediate discontinuation of omalizumab in 35 children who had previously received a 24-month course of omalizumab and no severe exacerbation during the previous year. Asthma control worsened in only 8 out of 35 patients after 3–17 months. The 8 patients with poor control were also more atopic. This suggests omalizumab might have a potential role as a disease-modifying drug and preventing airway remodeling, probably when treatment is started in childhood. Nevertheless, further prospective studies on large samples are required.[118]

Anti-IL-5 in severe eosinophilic asthma during childhood

IL-5 regulates eosinophilic inflammation and is thus a therapeutic target in eosinophilic asthma.[119] Mepolizumab is an anti-IL-5 drug that is indicated as an add-on maintenance treatment for patients with severe refractory eosinophilic asthma aged 12 years and older (100 mg SC). The Dose Ranging Efficacy And Safety With Mepolizumab in Severe Asthma (DREAM) study, a double-blind placebo-controlled trial, evaluated the efficacy and safety of three doses (75, 250, and 750 mg) of intravenous mepolizumab every 4 weeks compared with placebo over a 52-week treatment period in subjects with severe uncontrolled refractory asthma. This study confirmed the effectiveness of mepolizumab in reducing exacerbation rates in patients with severe refractory eosinophilic asthma (621 adolescents and adults). Serum eosinophil counts fell.[120–122] The response to treatment is positively correlated with a blood eosinophil count of at least 150 cells/μL.[123] Similar results were obtained with 36 children, which led the EMA to license it for children aged 6–11 years old (40 mg).[124] Another study examined a small group of seven adolescents with severe eosinophilic asthma who were not eligible for omalizumab or nonresponders to it. Twelve months of treatment with mepolizumab reduced the severity and rates of asthma exacerbations and blood eosinophils. However, mepolizumab did not improve symptom scores or lung function test results.[125]

Benralizumab is a monoclonal antibody directed against the α-chain of the IL-5 receptor (CD125). An analysis of the Efficacy and Safety Study of Benralizumab Added to High-dose Inhaled Corticosteroid Plus LABA in Patients With Uncontrolled Asthma (SIROCCO) and Efficacy and Safety of benralizumab in Asthmatic Adults and Adolescents Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting β2 Agonist (CALIMA) phase III studies showed a statistically significant reduction in asthma exacerbations (46%) and improved FEV1 in adults with severe eosinophilic asthma (blood eosinophil counts >300 cells/μL) when treated with benralizumab every 8 weeks for a year, regardless of IgE levels.[126] Currently, there are no ongoing trials testing benralizumab in children. Reslizumab is a humanized monoclonal antibody to IL-5 that leads to a decrease in the production and maturation of eosinophils. This drug is indicated in severe uncontrolled eosinophilic asthma in patients aged >18 years old. Treatment with reslizumab at 3 mg/kg intravenously every 4 weeks significantly improved FEV_1 and symptom scores. Treatment for 1 year markedly improved FEV_1 and reduced asthma exacerbations and symptom scores *versus* a placebo in patients with severe eosinophilic asthma and comorbid self-reported CRSwNP.[127]

In 2017, a Cochrane review analyzed 13 randomized double-blind placebo-controlled clinical trials regarding the effects of anti-IL5 on 6000 individuals aged more than 12 years old, who mainly had severe eosinophilic asthma. Anti-IL-5 drugs reduced blood eosinophil counts and significantly reduced asthma exacerbation rates. Lung function improvement was significant but small. No serious adverse events were reported. Interestingly, benralizumab reduced exacerbation in noneosinophilc asthma as well.[128]

Future opportunities in therapy for AAD in children

Research on biologic drugs for the treatment of AAD is rapidly expanding, and experimentation with new molecules in the coming years will be able to further enrich the therapeutic alternatives available to reference specialists.[129] Regarding the future of anti-IgE therapy, it is appropriate to point out that a new monoclonal antibody, ligelizumab (anti-IgE-mAb), is currently being tested. This drug has shown an affinity for human IgE that is approximately 50 times higher in comparison to omalizumab, as well as a nine-fold increase in the suppression power of circulating free IgE levels.[130] From a clinical point of view, ligelizumab showed greater efficacy than omalizumab in the asthmatic response to inhalant allergens.[131]

In addition to anti-IgE monoclonal antibodies, a new category of drugs is currently being tested, which have a molecular target that is located further upstream than the direct blockade of circulating IgE. This category of monoclonal antibodies

is defined as anti-CemXmAb and provides an alternative mechanism of intervention for the IgE-mediated allergic inflammatory pathway. They bind to IgE expressed on the membrane of B IgE-switched lymphoblasts, which causes their lysis and thus prevents the allergen-mediated generation of IgE-producing plasma cells.[132]

Moreover, these biologic drugs do not bind to free IgE, and consequently, their action is independent of serum IgE levels. However, it should be noted that quilizumab, which belongs to this category of drugs, has not had any appreciable clinical benefit in adults with AA that is not controlled by standard therapy.[133] In addition, one of the most interesting areas in development involves the therapeutic vaccines that are able to trigger the immune system to produce therapeutic anti-IgE antibodies. This approach could potentially provide a further step forward in the treatment of allergic diseases.[134]

Regarding the new horizons of therapy with anti-IL-4 and IL-13 biologics, the only drug that has achieved satisfactory clinical evidence to date in efficacy and safety is dupilumab, which is an anti-IL-4 receptor monoclonal antibody that blocks both IL-4 and IL-13 signaling. These effects were confirmed by the results of two clinical trials (VENTURE and QUEST).[135,136] These multicenter studies examined 210 and 1902 patients, respectively, over 12 years old with steroid-dependent or uncontrolled asthma, and the results showed that dupilumab is effective in improving symptom control and respiratory function. Subsequently, in 2018, dupilumab received FDA approval as add-on treatment for moderate-to-severe asthma in patients aged 12 years or older with an eosinophilic

phenotype or with oral corticosteroid-dependent asthma.[137] In February 2019, the EMA approved it for severe asthma from the age of 12, adding raised blood eosinophils and/or raised FeNO as criteria.[138] An ongoing trial (NCT03560466) is evaluating dupilumab in children with asthma.[139] In the treatment of asthma, a potential and cheaper alternative therapteutic option to biologics may be represented by drugs, acting on airway inflammation, such as mast cells stabilizers (e.g., pemirolast) and tetomilast, a phosphodiesterase 4 inhibitor.[140–142] Nevertheless, few trials, limited to adults with asthma or chronic obstructive pulmonary disease, respectively, have been performed. There is an ongoing trial to evaluate tetomilast in chronic obstructive pulmonary disease associated with emphysema. Further studies are needed.[140–142]

Conclusions

In the field of allergic diseases and the era of the 'omics' sciences, we are increasingly turning to precision-tailored patient-specific medicine. The range of choices is wide and spans from the use of standard therapy to the use of new biologic drugs. Among these, omalizumab and, recently, mepolizumab are available for the pediatric populations (Table 1). New molecules such as reslizumab, benralizumab, ligelizumab, and dupilumab are currently being studied. To optimize treatment with biologic drugs in pediatric allergies, it is necessary to identify and validate biomarkers that are able to identify patients with particular severity characteristics, as well as to define the optimal duration of the treatment and directly compare between the various biologic treatments available.

Table 1. Summary of novel biologics in AAD.

	Mechanism of action	Indications	Administration
Omalizumab	Anti-IgE	• Severe persistent asthma (>6 years) • Chronic idiopathic urticaria (>12 years)	Subcutaneously q2 or q4 weeks (dosage depending on weight and IgE levels)
Ligelizumab	Anti-IgE	• Chronic urticaria (phase III >12 years) • Allergic asthma (phase II >18 years)	Subcutaneously q2 weeks (240 mg)
Mepolizumab	Anti-IL5	• Severe refractory eosinophilic asthma (>6 years) • Churg–Strauss syndrome (registered)	Subcutaneously every 4 weeks (100 mg ≥12 years; 40 mg 6–11 years)
Benralizumab	Anti-IL5 receptor	• Severe refractory eosinophilic asthma (>18 years)	Subcutaneously (30 mg q4 weeks for the first three doses, q8 weeks thereafter)
Reslizumab	Anti-IL5	• Severe refractory eosinophilic asthma (>18 years)	Intravenous infusion q4 weeks (dosage depending on weight)
Dupilumab	Anti-IL4 and IL-13	• Moderate-to-severe atopic dermatitis (>18 years) • Severe refractory eosinophilic asthma	Subcutaneously q week (first dose 600 mg then 300 mg)

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