Allergen Immunotherapy in Pediatric Respiratory Allergy

Ali Doroudchi, MD¹

Kamran Imam, MD²

Maria Ines Garcia Lloret, MD^{1,*}

Address

¹Department of Pediatrics, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA

Email: migarcia@mednet.ucla.edu

²Department of Internal Medicine, Adventist Health White Memorial Medical Center, Los Angeles, CA, USA

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Abstract

Purpose of Review Atopic diseases such as asthma and allergic rhinitis are highly prevalent in children. Common triggers include tree and grass pollens, house dust mites, molds, and animal dander. These diseases are most often treated symptomatically; however, many patients show partial or poor response and require long-term medication use. Allergen immunotherapy (AIT) stands as the only treatment modality that can alter the underlying disease process and potentially offer a cure. In this review article, we discuss the merits of AIT with particular emphasis on its efficacy and safety in pediatric patients. We also discuss the challenges for AIT implementation and present an overview of current research that aims at improving its applicability for the treatment of allergic diseases.

Recent Findings Subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) are both safe and efficacious treatment options in children with allergic rhinitis and allergic asthma. Additionally, AIT has efficacy in preventing the development of asthma in children. Although there are clear advantages with AIT, there are challenges to overcome to optimize treatment. Solutions include improved diagnostics with pre-treatment biomarkers and molecular multiplex assays, biomarkers for prediction of response (e.g., basophil activation markers), improved allergen immunogenicity with the use of recombinant AIT, adjuvants, and allergoids, and lastly improved safety with the concurrent use of omalizumab.

Summary AIT has shown safety and efficacy in major clinical trials for the treatment of allergic rhinitis and allergic asthma in children. AIT provides a curative treatment

option for atopic disorders and should be considered in children with allergic rhinitis and allergic asthma. There are many continued advances being made in the field of allergy to further improve the safety and efficacy profile and shorten the duration of AIT treatment.

Introduction

Allergic diseases such as atopic asthma and allergic rhinitis are among the most common chronic childhood illnesses, and their prevalence has grown worldwide over the last fifty years [1]. These diagnoses have a significant impact on children's quality of life and place considerable financial burden on families and healthcare systems.

Treatment for these disorders is classically addressed symptomatically, with the most common methods being allergen avoidance, oral or nasal antihistamines and/or intranasal steroids for allergic rhinitis, and bronchodilators and/or inhaled steroids for asthma. Surveys in the U.S. and the U.K. querying the efficacy of first-line treatment for allergic rhinitis have shown that up to 29% of children and 60% of adults have reported poor or partial response to standard treatments [2, 3]. As these medications are not curative, treatments are by necessity long term. This poses an additional problem in pediatrics due to factors such as poor adherence by young patients as well as parental concerns regarding the possible side effects of long-term medication use for a young, growing child.

In use since the early 20th century, allergen immunotherapy (AIT) stands as the only treatment known to have a modulating effect on the immunological cascade that drives atopic disease. It consists of exposing patients to increasing amounts of an allergen extract, with the goal of achieving tolerance, thereby reducing symptoms upon natural exposure to a sensitizing allergen. AIT is accepted as an effective therapy for allergic rhinitis (with or without conjunctivitis), well-controlled allergic asthma, hymenoptera hypersensitivity, and food allergy. It is currently recommended for patients 5 years and older and can also be considered for younger

children [4]. Traditionally, AIT had been delivered subcutaneously (SCIT), however, sublingual immunotherapy (SLIT) has emerged as a safer and comparably efficacious modality, with the WHO accepting SLIT as a viable alternative in 1998 [5].

In conventional SCIT, administration schedules consist of a build-up phase in which injections are administered once to twice weekly for 3-6 months, followed by a maintenance phase in which injections are administered at 4-8 week intervals for a total treatment duration of 3-5 years. Injections should be administered in the clinic with a 30-minute observation period for any adverse reactions. On the contrary, SLIT can be taken in a patient's home and involves anywhere from three-times weekly to daily sublingual administrations (tablet or liquid extracts) for a similar duration of 3-5 years. There are currently 4 FDA-approved SLIT tablet products (Timothy grass [Grastek], 5-grass [Oralair], ragweed [Ragwitek], and HDM [Odactra]), of which only Grastek is approved in children. Meanwhile, droplets are currently only used off-label in the United States. Intralymphatic and epicutaneous immunotherapy are the most novel modalities showing comparable efficacy to SCIT in grass pollen trials [6]. The former requires fewer injections relative to SCIT, while the latter requires no injections at all, as it is administered through an epidermal patch.

In spite of its long-standing usage, efficacy, and favorable safety profile, there remain gaps in knowledge and concerns regarding the practice of AIT, particularly within the field of pediatrics. Although these challenges exist, there are significant advances being made, ranging from improved diagnostic techniques, biomarkers for predicting efficacy, optimization of allergen extracts, and allergen modification together with a continued expansion in our

understanding behind the mechanisms of AIT. In this article, we will discuss the efficacy favoring the use of AIT in pediatrics, while also discussing the challenges facing this treatment modality.

Mechanisms of Allergy and AIT

The allergic response is initiated by allergen binding to its cognate IgE present on mast cells and basophils. Crosslinking of the high-affinity IgE receptor (FcεR1) by these antigen/IgE complexes triggers mast cell and basophil degranulation with the release of inflammatory mediators [7•]. The production of IgE against innocuous antigens (e.g., foods and pollens) is attributed to dysregulated type 2 responses, consisting of Th2 cells, ILC2s, and cytotoxic T cells (TC2) characterized by a signature cytokine profile that includes IL-4, IL-5, and IL-13 [8], in addition to recently uncovered cytokines, IL-25, IL-31, and IL-33 [9]. Besides facilitating IgE production through B-cell class switching, these interleukins also promote mast cell and basophil activation, eosinophilia, and directly affect endothelium permeability, mucus production, and smooth muscle contractility [10].

AIT has been shown to decrease mast cell and basophil degranulation within a single administration, and this suppression is sustained throughout the course of therapy [8]. This mechanism is not clearly understood, but appears to be similar to that occurring during rapid desensitization to drug hypersensitivities [9]. An important recognized downstream effect of AIT (after months to years) is the reduction in the population of mast cells, basophils, as well as eosinophils, and ILC2 cells in target organs [11–14].

AIT has also been shown to alter the Th2 profile toward a tolerant state via increased regulatory immune cells—Treg and Breg cells. Importantly, the induction of tolerant peripheral T cells appears to be driven by IL-10 and TGF-β [9]. TGF-β induces the conversion of naïve T cells into CD4+CD25+ T cells through the expression of FOXP3 [15]. Additionally, another regulatory cell subset—BR1 (regulatory B cells)—has been shown to increase in response to AIT [16].

When AIT is initiated, there is an initial transient increase in serum allergen-specific IgE, followed by a gradual decline over the treatment course. However, decreases in IgE alone do not always correlate with clinical improvement [8]. AIT also results in the increase of other immunoglobulins, particularly IgG4, as well as IgG1 and IgA2. This occurs in the setting of increased IFN-γ, IL-10, and TGF-β [7•]. IgG4 is thought to confer a protective effect by directly competing with allergen-specific IgE for the binding to the same epitopes on allergens [17]. The mechanisms of AIT discussed in this section are illustrated in Fig. 1.

Efficacy and Preventative Role of AIT in Pediatrics

The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines as well as the European Academy of Allergy and Clinical Immunology (EAACI) guidelines

Fig. 1. Illustrative summary of the major mechanisms of modulation in allergen immunotherapy. In summary, AIT results in suppression of Th2 cells, with a downstream reduction of IgE, eosinophils, basophils, and mast cells. There is an increase in Treg cells—with downstream increase in IL-10 and TGF-β expression, resulting in increased protective IgG4. Mechanisms not depicted include an increase in tolerogenic dendritic cells (DCs), B regulatory cells, and suppression of inflammatory DCs.

have determined that AIT is an effective modality for children with moderate to severe AR [18, 19••, 20••, 21].

The conclusions on efficacy are based on a large number of international trials demonstrating AIT's effectiveness in pediatric AR patients. The majority of studies are based on symptomatology. Symptoms are traditionally measured by a scoring system involving both ocular and nasal symptoms known as Total Nasal Scoring System (TNSS). It involves four conventional symptoms—sneezing, congestion, itching, and rhinorrhea—graded from 0 to 3 with 0 = no symptoms, 1 = easily tolerated, 2 = bothersome, but tolerable, and 3 = interferes with daily activities. The scoring symptoms were added up and stratified from 0 = best to 12 = worst, and symptoms were reassessed after the treatment period (Table 1).

In a major meta-analysis of 160 studies prepared during the development of EAACI's clinical recommendations on AIT for allergic rhinoconjunctivitis, standardized mean differences (SMD) were significant for symptom improvement (-0.53), medication usage (-0.37), and combined symptom and medication scores (-0.49). Importantly, the authors stratified data for adults versus children and demonstrated benefit in both groups for AIT (SCIT and SLIT) [19••]. Per this data, the EAACI stated that for children with moderate to severe AR, pre-seasonal, co-seasonal, and/or continuous AIT is recommended for clinical

Table 1. Approaches in use and in development for the improvement of AIT

Challenges	Solutions
Diagnostic accuracy	Biomarkers (e.g., sIgE/tIgE) Singleplex and multiplex assays
Response prediction	Biomarkers for efficacy: (1) sIgE >10 kU/l (HDM) (2) Basophils activation (CD63, CD203c, diamine oxidase (DAO), basophil histamine release) (3) IgG subclass quantification (sIgE/IgG4) (4) Serum inhibitory activity (IgE-FAB) (5) Quantification of Tregs and tolerogenic dendritic cells (6) Micro-RNA expression profiles
Immunogenicity	Adjuvants Recombinant AIT Allergoids
Safety of AIT	SLIT Concurrent omalizumab Recombinant AIT Adjuvants Allergoids
Duration of AIT	Cluster build-up phases Recombinant AIT Adjuvants Allergoids Alternate routes of delivery (e.g., intralymphatic)

benefit in both seasonal and perennial AR, despite the gaps in evidence in pediatric data relative to adults [20••].

Overall, the current data is insufficient to determine whether SCIT or SLIT is more efficacious. A meta-analysis of 37 studies showed that SLIT and SCIT had similar significant reductions in symptoms and medication usage in patients with grass pollen allergies, relative to placebo [22]. Similarly, randomized control trials (RCTs) of birch tree pollen have shown similar efficacy between the two forms of AIT relative to placebo [23]. The exception may rest with house dust mite (HDM), in which there have been conflicting results; some RCTs demonstrate an advantage towards SCIT, while others have shown similar efficacy between both SCIT and SLIT [19••, 24–27].

For allergic asthma, both SCIT and SLIT have demonstrated efficacy in symptom control and medication reduction in adults and children [28, 29]. A meta-analysis that included 441 pediatric patients (3–18 years old) with allergic asthma treated with SLIT showed significant reductions in symptoms and medication usage compared to placebo [30]. Furthermore, a prospective study of 60 pediatric asthma patients treated with HDM SLIT showed a reduction in asthma symptoms and medication usage 4–5 years after cessation of AIT [31]. In a retrospective study of 48 pediatric patients treated with HDM or both HDM/grass pollen SCIT, follow-up between 7 and 11 years after cessation of AIT showed a 3-fold reduction in asthma symptoms [32]. Comparisons between

SLIT and SCIT are summarized in Table 2.

In addition to its efficacy in the treatment of allergic disease, AIT has been shown to play a role in the prevention of asthma development in children. In 2006, the prevention of allergy (PAT) study investigated SCIT therapy in 205 children with allergic rhinoconjunctivitis (without asthma) to grass and/or birch pollen. This landmark study showed that patients had a reduced risk of developing asthma at 3-, 5-, and 10-year observations points following treatment [33]. A risk reduction for asthma development was found in two other randomized SLIT trials in 2004 and 2008 [34, 35]. The most robust SLIT trial to date, the Grazax Asthma Prevention (GAP) trial, was a randomized, double-blind, placebo-controlled study of 812 children published in 2018 [36••]. The use of grass SLIT for 3 years demonstrated a reduced risk of asthma symptoms and asthma medication usage at the end of 3 years of treatment and after a 2-year follow-up. Notably, the number needed to treat (NNT) increased with age, suggesting that earlier treatment may have the highest potential for benefit in patients. Indeed, there is increasing evidence for the efficacy of AIT in patients under 5 years old [37]. In further support of earlier treatment, children have a higher risk of respiratory disease despite a lower number of sensitizations compared to adults and are more frequently mono-sensitized at younger ages [38•].

Challenges Facing AIT and the Advances Being Made to Overcome Them

Despite the established merits of allergen immunotherapy, there still remain challenges to further improve its efficacy, safety, and duration of treatment. The lengthy duration associated with AIT has a negative impact on adherence, with studies demonstrating attrition rates of 45% and 41% for SCIT and SLIT, respectively [39]. Market data from European manufacturers has additionally shown similar attrition rates (~50%) within 2 to 3 years of initiating treatment [40, 41].

Table 2. Comparison profiles of SCIT versus SLIT

	Subcutaneous	Sublingual
Efficacy	✓✓✓	✓✓
Efficacy in seasonal rhinitis**	✓✓	✓✓✓
Efficacy in perennial rhinitis**	✓	✓✓
Prevention of asthma	✓✓	✓✓
Adherence monitoring	✓✓✓	✓
Ease of use	✓	✓✓✓
Safety/side effect profile	✓✓	✓✓✓

*Level of evidence regarding efficacy is comparable across subcutaneous and sublingual. **2017 ECAAI Guidelines on Allergen Immunotherapy Recommendations [12]: SCIT in seasonal pediatric allergic rhinitis—Grade B; SCIT in perennial pediatric allergic rhinitis—Grade B-C; SLIT in seasonal pediatric allergic rhinitis—Grade A; SLIT in perennial pediatric allergic rhinitis—Grade A-C

Improved patient selection and diagnosis, identification of biomarkers to predict response, optimization and standardization of extract content, and creating novel methods of design and delivery of AIT are all means by which AIT can gain more efficacy and safety, while shortening necessary treatment durations. Altogether, this can improve patient outcomes, making AIT an even more attractive therapy for individuals with respiratory allergies.

Biomarkers for Diagnosis and Patient Selection

Effective treatment of allergy begins with the identification of a specific allergen (or allergens) responsible for driving the disease. Such identification allows for allergen-specific interventions. There is a vast heterogeneity of sensitization profiles among allergic patients, which creates the challenge of identifying which allergen(s) are clinically relevant for any given patient. Tripodi et al. demonstrated this heterogeneity in patient sensitization profiles to *Pleum pretense*. Using serum IgE assays, the authors tested for reactivity against 9 different *P. pretense* molecules (rPh1 p1, rPh1 p2, etc.). They found that only 7 of 176 patients (4%) had a sensitization profile that actually matched the composition of a standardized immunotherapy extract, while the remaining 169 patients were classified into mismatch categories [42]. Additionally, up to 80% of patients are polysensitized [43], by that meaning that they produce high IgE against multiple allergens. Determining which allergens to include in the extracts is challenging but critical for AIT efficacy.

The established methods for identifying a patient's sensitization profile consist of a detailed allergic history, skin prick testing (SPT), and specific-IgE (sIgE) via a serum sample. While these are helpful in the identification of a suspected allergen, further improvement is needed in determining whether sensitization results in clinical symptomatology, particularly in patients with polysensitization, as well as for patients with non-specific and clinically-irrelevant cross-reactivity. Approaches under investigation include measuring sIgE/tIgE (specific IgE/total IgE (i.e., serum IgE)) prior to treatment [44•], as well as improved assays for the detection of allergen sensitization profiles. Molecular multiplex assays can provide both detailed sensitization profiles, while distinguishing genuine sensitizations from the abovementioned cross-reactions [45, 46]. Interestingly, an Italian study showed that when provided with molecular serological results of their patient, allergists were more likely to change their management in favor of AIT for 42-48% of patients [47]. This highlights the importance of an accurate allergic diagnosis prior to initiating AIT.

Biomarkers for Predicting Response

In the era of precision medicine, it is indispensable to look for reliable biomarkers that predict the efficacy of AIT in a particular patient. A study of 31 HDM-allergic children found that a sIgE cut-off level of >10 kU/l significantly correlated with AIT efficacy using a symptom and drug use scale ($r = 0.615$; $p < 0.001$) [48]. Other candidate response biomarkers under investigation for predicting efficacy includes basophil activation markers (CD63, CD203c, diamine oxidase (DAO), and basophil histamine release), IgG subclass quantification with sIgE/IgG4 ratio, serum inhibitory activity for IgE (IgE-FAB), quantification of Tregs, and tolerogenic dendritic cells, as well as micro-RNA expression profiles [44•, 49–51].

Extract Content, Potency, and Standardization

The lack of standardization of extracts used in trials and in clinical practice remains a confounding element in objectively assessing AIT's efficacy. There is a wide variety of allergen extracts on the market, ranging from unmodified extracts (including purified, adsorbed, recombinant, and synthetic peptides) as well as modified extracts [38•]. Additionally, there is variability in the units of measurement used between manufacturers, as well as the content and potency of allergens between different products [52, 53]. Lastly, there is inconsistency in the quality of extracts, as several studies analyzing the composition of natural extracts have demonstrated the presence of non-allergenic components as well as contaminants [54].

Optimal extract preparation is aimed at preserving the natural variability of any given allergen, while maximizing the amounts of major allergen—the allergen to which the majority of patients are sensitized to. After the process of extraction, comes the challenge of standardization among different manufacturers. As mentioned previously, there are both standardized and non-standardized extracts available on the market. Needless to say, standardized extracts are the preferred product for consistency, reliability, and patient safety, as they provide documented composition and potency [55]. In the U.S., only short ragweed pollen, cat hair/pelt, house dust mite, and grass pollen extracts are available in standardized form.

An added degree of variability in extract-based allergen products is the different units of measure for product content as well as product potency. Most allergen extracts on the market are not standardized and have no standard of potency. These often only have units of measure that reflect protein content, such as the protein nitrogen unit (PNU) or weight by volume ratio (w/v) [55]. Generally, these do not provide clinicians with useful information as to the potency or immunogenicity of the product. A much more valuable unit is the bioequivalent allergy unit (BAU), endorsed by the FDA in the United States and most often used in standardized extracts [55]. BAU provides a standardized measure of potency, based on intradermal skin tests elicited by dilution series of a reference extract [8].

Improving Allergen Content and Immunogenicity

An approach to resolving the problem presented with extract-based AIT is the use of recombinant allergens. Recombinant allergens could potentially improve the quality of introduced allergen, thereby maximizing the efficacy of treatment, while ensuring a standardized product for patients. Recombinant strategies include recombinant wildtype allergens, synthetic peptides, nucleic acids, hypoallergenic allergens, and peptides capable of inducing protective IgG responses. Although recombinant allergens are considered a safer and more specific form of AIT relative to allergen extract-based AIT, the progress of this modality has been slow since its inception over 30 years ago [56].

Another modality under continued investigation is allergoids—chemically modified allergens. The modifications result in decreased IgE binding activity while still inducing T cell tolerance, effectively allowing for higher doses of allergen administration while lowering safety concerns,

notably anaphylaxis [57]. Several different classes of allergoids have proven efficacy in trials for ragweed, grass, tree pollen, and house dust mite allergy [58–62].

Other platforms in development also aim to improve allergen immunogenicity. The adjuvant aluminum salt (alum) is the best example of an established and already licensed approach, currently used with SCIT in Europe. Alum, a depot, has the function of activating both innate and adaptive immune responses [63]. A more novel depot agent includes microcrystalline tyrosine (MCT), shown to have similar Th1 promoting properties [7•]. More novel adjuvant approaches include toll-like receptor (TLR) ligands, particularly monophosphoryl lipid A (MPL), a TLR-4 ligand. MPL leads to the activation of innate and adaptive pathways [64]. Grass pollen trials thus far have shown efficacy with as few as four pre-seasonal injections [65]. Other adjuvants with promising phase 2 efficacy include lipophilic liposomes [66] and virus-like particles [67], both of which increase antigen presentation efficiency directly into the lymphatic system, while minimizing the risk of mast cell degranulation in tissues [7•]. Other coupling methods include CpG oligonucleotide-conjugated allergens [68] and carbohydrate-based particles [69].

Strategies discussed above provide improved the introduction of tolerogenic components of an allergen to a patient, and thereby minimize adverse effects, while improving immunogenicity, and, thus, maximizing efficacy and safety. A summary of these approaches discussed are listed under Table 1.

Improving Safety

Safety during the administration of immunotherapy is a particular concern of providers, especially when dealing with pediatric patients. Although the safety data has been favorable for AIT, systemic reactions do occur and pose a source of hesitation for some families. Although AIT is considered efficacious in the treatment of allergic asthma, severe or uncontrolled asthma is an absolute contraindication due to the increased risk of systemic reaction [70].

In a SCIT study including 2441 children, 1.2% experienced systemic reactions, including anaphylaxis [71]. Notably, there have been reported fatalities caused by SCIT; by 1986, there were 26 deaths associated with SCIT [7•]. In recent decades, SLIT has become a well-validated alternative to SCIT, with fewer systemic adverse events. In a systematic review of SLIT (5131 patients, 1814 children), 0.056% experienced systemic reactions [72]. SLIT does carry the risk of local reactions (i.e., oral pruritus and tissue edema); however, these have been found to be self-resolving within the first few administrations of an extract [73].

Comparisons of treatment safety between standard, cluster, and rush build-up phases (i.e., more rapid allergen introduction schedules) have shown rush AIT to be the least safe method, with a 30-fold increase in per-shot incidences of systemic reactions in rush compared to standard build-up schedules [74]. Cluster build-up schedules, however, may represent a “middle ground” between standard and rush schedules. A meta-analysis of 6 studies showed no difference in local or systemic adverse reactions between cluster and standard build up [75].

The use of biologics, specifically anti-IgE (omalizumab), has been shown to have added a safety profile by decreasing the risk of anaphylaxis when administered with AIT [17].

Conclusion

In summary, AIT is a safe and effective treatment for children with allergic rhinitis and allergic asthma, particularly given its preventative role in future asthma development. SLIT can be a particularly advantageous modality for children as it has similar efficacy and a superior safety profile relative to SCIT, while avoiding the need for frequent injections for children. However, the drawbacks for SLIT include a lack of commercially-available tablets for children and the fact that droplets are non-FDA approved and are currently used off-label.

Although limitations exist, AIT stands as the only treatment modality that can alter the underlying disease process and provide a definitive cure for allergic disease. In addition to its established safety and efficacy, many exciting and promising advances are being contributed to the field to further solidify AIT's safety and efficacy profile, while improving patient adherence with shorter treatment regimens.

Author Contribution

AD and MGL were responsible for the original design and focus of the article. AD and KI performed the literature search and wrote sections of the article. MGL edited the final version and performed the final review.

Declarations

Conflict of Interest

Ali Doroudchi, Kamran Imam, and Maria Ines Garcia Lloret declare that they have no conflicts of interest.

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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