



Specific immunotherapy for allergic rhinitis in children

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Purpose of review

Allergic rhinitis is a highly prevalent inflammatory disease affecting 20–40% of the children worldwide. Allergen-specific immunotherapy (SIT) is an effective treatment for allergic rhinitis. This article reviews the recent advances in SIT for children.

Recent findings

In current clinical practice, immunotherapy is delivered as either subcutaneous immunotherapy or sublingual immunotherapy (SLIT). Most meta-analyses and reviews concluded a trend that subcutaneous immunotherapy was better than SLIT in reducing symptoms of allergic rhinitis and rescue medication use, however, SLIT has a better safety profile than subcutaneous immunotherapy. Additionally, the absence of pain on administration of therapy is a character of SLIT, which is well suited for children. T regulatory cells, especially Tr1 cells that secrete interleukin-10 and induce production of immunoglobulin G4, play a role during SIT.

Summary

Although there is substantial evidence for effectiveness of both subcutaneous immunotherapy and SLIT, safer and more effective SIT approaches are needed. New approaches to improve SIT include omalizumab pretreatment, use of recombinant allergens, and alternate routes of administration.

Keywords

allergic rhinitis, children allergen, immune tolerance, specific immunotherapy, T regulatory cells

INTRODUCTION

Allergic rhinitis is a highly prevalent inflammatory disease affecting 20–40% of the children worldwide [1,2]. Although pharmacological therapy and allergen avoidance are effective means of managing allergic rhinitis, allergen-specific immunotherapy (SIT) has been shown to be effective in the treatment of not only the symptoms, but also the underlying causes of the disease. Moreover, SIT has a preventive role against new sensitizations and development of asthma in allergic rhinitis patients [3–5]. Hence, SIT is recommended as an integrated part of an allergy management strategy in the treatment of allergic diseases, especially in children [6]. SIT has been used since the early 1900s in the management of allergic rhinitis with varying degrees of success, and over the course of one century, immunotherapy has been delivered by various routes, including oral, nasal, bronchial, subcutaneous, and sublingual. Oral and bronchial administrations have been abandoned because well controlled trials have failed to demonstrate clinical efficacy and safety. Local nasal immunotherapy, although effective and well

tolerated, is limited because it requires a specific technique to administer the therapy and is additionally only effective against rhinitis [7]. Thus, only subcutaneous immunotherapy (SCIT) and more recently sublingual immunotherapy (SLIT) are currently widely used in clinical practice. Although an indirect meta-analysis-based comparison between SCIT and SLIT has recently demonstrated that SCIT was more effective than SLIT for the treatment of grass-pollen-induced allergic rhinitis in children [8], SLIT appears to have great appeal to the pediatrician because of its ease of delivery and the potential to

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Curr Opin Otolaryngol Head Neck Surg 2014, 22:000–000

DOI:10.1097/MOO.0000000000000101

KEY POINTS

- Both SCIT and SLIT appear to be efficacious in preventing the development of asthma and new allergen sensitivities.
- Most meta-analyses and reviews have concluded that SCIT was better than SLIT in reducing symptoms of allergic rhinitis and rescue medication use, however, SLIT had a greater advantage over SCIT with regard to its safety and less serious adverse effects.
- Upregulation of allergen-specific Tr1 cells may play an important role in SIT and be a useful marker of successful SIT in allergic rhinitis children. The role of nTreg cells in SIT, however, is still not clear.
- Novel approaches to improve SIT include the use of adjuvants and recombinant allergens, together with alternate routes of administration.

avoid frequent injections and serious side-effects including the risk of severe systemic reactions, which are associated with the subcutaneous route. Thus, the use and efficacy of SLIT in the pediatric population is currently a subject of great debate. This review focuses on the efficacy and safety of SCIT and SLIT in children with allergic rhinitis and the mechanisms underlying SIT. The review further discusses the current approaches in clinical practice and research perspective of SIT.

ALLERGEN

A substantial body of evidence indicates that allergic rhinitis in children is most commonly caused by grass and/or tree pollens, such as mugwort, *parietaria*, ragweed, betulaceae, cypress, and olive [9,10]. In some developed countries, house dust mite (HDM) is an important allergen for children [9]. Similarly, cow's milk, peanuts, and eggs are very common sources of food allergen in children [11–13], whereas less common, but reaction-provoking allergens, such as allergens from spices, have also been reported recently [14]. There is evidence that exposure to the wide diversity of food in the first 2 years of life is associated with allergy in infants or children [12,15,16], and in some children leads to polysensitization to many kinds of allergens [9].

Johnstone and Crump [17] reported the use of SCIT in children, and during the past decades, the efficacy of SCIT for treatment of mites and venom allergy in children was well established [9,18,19]. However, some researchers found that this administration route was concomitant with a high risk of adverse events [20] and led to SLIT as a better

treatment for children. Thus far, SLIT has been shown to be appropriate for the treatment of allergic rhinitis caused by mites, grass, birch and *parietaria*, with a grass-pollen extract being commercially available [20]. To date, no significant differences have been observed in the type or rate of side-effects related to allergen type, including HDM, tree pollen, or grass pollen [9]. Furthermore, no significant differences have been reported in the rate or type of side-effects for SLIT in children compared with adults [9,21]. The adverse effects in children may nevertheless be underestimated because of their language skills and evolving development. However, although several studies have demonstrated severe systemic reactions to be associated with the use of polytherapy [9,22,23], there are no published reports of SLIT-related fatal reactions to date. In one study, Blazowski [24] reported that anaphylaxis to HDM SLIT occurred in a 16-year-old girl who self-administered 10 times the standard dose of allergen after a 3 week period of noncompliance.

EFFICACY OF SUBCUTANEOUS IMMUNOTHERAPY IN CHILDREN

SCIT, but not SLIT, is currently approved in the United States for the treatment of pediatric asthma and rhinitis; however, despite the lack of regulatory approval, SLIT is used off-label in clinical practice [25]. Thus, there is a growing interest in evaluating the comparative effectiveness of SCIT versus SLIT, and to identify whether one form of immunotherapy is better than the other [26].

The first well controlled clinical trial showing the clinical efficacy of immunotherapy in children with mould-induced asthma was performed in 1986 [27]. Thirty children with a clinical history suggesting mould-induced asthma and/or rhinoconjunctivitis were included in the trial and immunotherapy was given by injection for 10 months in a randomized double-blind manner with either Pharmedon/*Cladosporium herbarum* preparation or histamine placebo. The authors showed that medication scores were significantly lower in the treated group after treatment for 10 months, with bronchial and conjunctival sensitivity significantly reduced from baseline levels in the SIT group but not in the placebo group. One case-controlled study compared the effects of allergoid SCIT with control in children aged 6–18 years with grass-pollen-induced allergic rhinitis, and demonstrated significantly improved symptom scores and medication use after 1 year of maintenance therapy compared with control therapy [28]. Furthermore, allergoid immunotherapy significantly decreased the seasonal increase in immunoglobulin E (IgE) and prevented the seasonal increase

in bronchial reactivity and nasal lavage eosinophil cationic protein levels. However, a more recent systematic review of randomized controlled trials of children with allergic asthma or rhinoconjunctivitis treated with SCIT concluded that the strength of evidence that SCIT improves asthma and rhinitis symptoms was moderate, whereas the strength of evidence that SCIT improves conjunctivitis symptoms and asthma medication scores was low [25].

Nevertheless, a multicenter study involving 205 children aged 6–14 years (mean age, 10.7 years) with grass and/or birch pollen allergy, but without any other clinically important allergy, has provided evidence that SIT for 3 years can prevent the development of asthma in children with seasonal allergic rhinoconjunctivitis [29]. The authors demonstrated that 20% of the children had mild asthma symptoms during the pollen season(s), before the start of SIT and that the actively treated group of children had significantly fewer asthma symptoms after 3 years of treatment, compared with an open control treated group, as evaluated by clinical diagnosis. Additionally, bronchial hyperresponsiveness to methacholine provocation was significantly reduced in the active group. A 10-year follow-up in 147 of these individuals (aged 16–25 years) demonstrated that the longitudinal effect after adjustment for bronchial hyperresponsiveness and asthma status at baseline and all observations at 3, 5 and 10 years follow-up was statistically significant in favor of SIT-treated children, as evaluated by clinical symptoms [30]. The authors concluded that SIT has long-term clinical effects and the potential of preventing development of asthma in children with allergic rhinoconjunctivitis up to 7 years after treatment termination.

SAFETY OF SUBCUTANEOUS IMMUNOTHERAPY IN CHILDREN

The risk of serious adverse reactions, including anaphylaxis, to allergen immunotherapy has been recognized since the earliest use of immunotherapy. Adverse reactions to SCIT range from mild local reactions to severe systemic reactions. Because patients are being exposed to allergens to which they are known to react, local injection site reactions are common and adverse reactions are to be expected. Thus, it is imperative that the clinician administering the immunotherapy takes precautions to minimize the risk of systemic reactions by appropriate patient selection and dose adjustment and that SCIT takes place with full resuscitation facilities immediately available. The European Academy of Allergy and Clinical Immunology recommends at least 30 min of observation after each

injection [31]. The risk of death from anaphylaxis during immunotherapy is estimated at one in 2.5 million injections. In a prospective study of 1038 patients (23 047 injections), although systemic reactions occurred in one-third of patients, 78% of these were mild (grade 2) [32]. Eight patients had grade 4 reactions, which responded to adrenaline. Indeed, a Cochrane review [19] of immunotherapy in seasonal allergic rhinitis has indicated that adrenaline was administered in 0.13% (19 of 14 085 injections) of those on active treatment and in 0.01% (one of 8278 injections) of the placebo group for treatment of adverse events, suggesting that the risk of severe adverse events following SCIT is relatively low.

EFFICACY OF SUBLINGUAL IMMUNOTHERAPY IN CHILDREN

The first double-blind, placebo-controlled trial of SLIT for allergic rhinitis was conducted in Europe by Scadding and Brostoff [33], 75 years after the efficacy of SCIT was first reported by Noon (*Lancet* 1911; 177: 1572–1573). More than 70 double-blind, placebo-controlled clinical trials have subsequently demonstrated the superiority of SLIT over placebo in allergic rhinitis patients with or without asthma, with the first meta-analysis of 10 controlled trials investigating the efficacy of SLIT in children with allergic rhinitis demonstrating a significant reduction in both symptoms [standardized mean difference (SMD) = -0.56 ; $P = 0.02$] and medication use (SMD = -0.76 ; $P = 0.03$) in the SLIT group compared with placebo group [34]. Subgroup analysis indicated that SLIT longer than 18 months and with pollen extracts was more effective than treatment for less than 18 months and with dust mite extracts. Indeed, the most comprehensive meta-analysis of SLIT in allergic rhinitis conducted to date has further confirmed the findings for significant reductions in symptoms (SMD = -0.49 , $P < 0.00001$) and medication requirements (SMD = -0.32 , $P < 0.00001$) in participants receiving SLIT compared with placebo [35]. Furthermore, several large clinical trials have confirmed that grass-pollen SLIT is equally efficacious in pediatric and adult populations with allergic rhinitis [36,37].

Several studies have shown that the efficacy of grass-pollen tablets in improving symptoms, rhinitis quality of life, and medication scores was dose-dependent [38,39] and accompanied by changes in immunologic markers, including grass-pollen-specific immunoglobulin G4 (IgG4), grass-pollen-specific IgE, interleukin-10, and transforming growth factor beta (TGF- β) [40–42]. Sustained clinical improvements were demonstrated in the

second and third year and even maintained after discontinuation of treatment [43,44]. Two randomized, open treatment studies have indicated that SLIT may also prevent allergic disease progression, including onset of asthma in children with allergic rhinitis [45] and sensitization to new allergens [46]. Moreover, the preventive benefits of immunotherapy may be greater if initiated early in the course of the allergic disease in young children less than 5 years of age [47[■]], when indicated on the basis of the severity of the disease, risk/benefit ratios, and the ability of the physician to correlate the clinical presentation with appropriate and obtainable allergy testing.

Head-to-head comparison on the efficacy of SCIT and SLIT has been performed in some studies [26,41,48]. Although superiority of one mode of administration over the other could not be demonstrated consistently, most meta-analyses and reviews have indicated that SCIT was better than SLIT in reducing symptoms of allergic rhinitis and rescue medication use [26,48]. A randomized, open treatment study involving 48 children has compared the effect of treatment with SCIT, SLIT, or pharmacotherapy alone for 1 year and demonstrated that although SCIT and SLIT were not different in terms of clinical efficacy, both were superior to pharmacotherapy [41].

SAFETY OF SUBLINGUAL IMMUNOTHERAPY IN CHILDREN

One multicenter study involving over 600 allergic rhinitis patients from 51 centres in eight countries has demonstrated that local side-effects represent the majority of all reported adverse reactions in SLIT, with oropharyngeal pruritus and/or swelling being relatively common [49]. Most of the local symptoms were reported to be mild to moderate in severity and generally resolved without continued treatment. Conversely, the incidence of systemic reactions (such as asthma and urticaria) was low, and no severe systemic reactions were reported. In contrast to SCIT, although accelerated induction schedules with SLIT do not appear to be associated with a greater risk of systemic reaction, more adverse effects occur during the induction phase than during the maintenance phase. Furthermore, there does appear to be a relationship between allergen dose and adverse reaction rates, and no clear predictors for SLIT adverse effects have been identified. Previous severe adverse effects to SLIT or SCIT and a history of asthma seem to be risk factors [50].

One advantage of SLIT over SCIT is improved safety with less serious adverse effects. SLIT's

favorable safety profile may be associated with better adherence to treatment. Also, a regimen that does not require needles or frequent trips to a medical clinic may make SLIT more available and attractive to young children, allowing for treatment initiation at an early age. However, one study demonstrated that the most common reason for withdrawal in children less than 4 years old was '... the subjective discomfort in keeping under the tongue drops/tablets, or children's refusal, without apparent side-effects', indicating that tolerability plays an important role in adherence to SLIT. Thus, the World Allergy Organisation position paper on SLIT recommends that SLIT for allergic rhinitis should start after age 4 [47[■]].

REGULATORY T CELLS IN MECHANISMS OF ALLERGEN-SPECIFIC IMMUNOTHERAPY IN CHILDREN

Recent studies demonstrate that regulatory T (Treg) cells play a crucial role in modulation of the T cell response in allergic disease [51,52]. Generally, there are two types of T regulatory cells: natural and inducible. Naturally occurring CD4+CD25+ Foxp3+ T regulatory cells (nTreg) possess high levels of CD25 and express FOXP3, a key transcription factor required for their development, maintenance, and function [53,54]. The most important subset of inducible Treg cells is T regulatory type I (Tr1) cells, which was originally identified by its unique pattern of cytokine production (high levels of interleukin-10 and TGF- β , but no interleukin-4) that is distinct from that of classical T helper (Th)1 and Th2 cells. Tr1 cells inhibit the proliferation and cytokine production of CD4+ T cells mainly by interleukin-10 [55] and also regulate both Th1 and Th2 responses [56,57]. Moreover, the balance between allergen-specific Tr1 and Th2 cells is important in a physiological immune response to allergens [52].

Previous studies have demonstrated that CD4+CD25+ Treg and Tr1 cells are truly distinct subsets [58] and the frequency of these cell types may be low in peripheral blood from allergic patients [52,59]. Although some studies have reported that SIT induced interleukin-10+ CD4+CD25+ T cells in allergic individuals [60,61], other studies were unable to show any significant change in circulating CD4+CD25+Foxp3+ Treg cells following SIT in children after 1 year [62,63,64[■]]. In contrast, Aslam *et al.* [65] demonstrated that wasp-venom immunotherapy for 3–5 weeks induced Foxp3+ allergen-specific T cells. Similarly, in another study, Radulovic *et al.* [66] found that the numbers of Foxp3+CD25+CD3+ cells were increased in the nasal mucosa of grass-pollen

allergic patients following grass-pollen immunotherapy for 2 years. Collectively, the inconsistent findings from these studies indicate that the role of nTreg cells in SIT is still not clear. Additionally, these findings raise the possibility that SIT may preferentially induce CD4+CD25+Foxp3+ Treg cells in the local tissue, but not in the peripheral blood. Nevertheless, there are limitations to accurately evaluating the expression of Foxp3 in the suppressive activity of Treg cells and there is evidence that nonregulatory human CD4+ and CD8+ T cells can be induced to transiently express Foxp3, but without suppressive activity [67].

In healthy individuals, Tr1 cells represent the dominant subset for common environmental allergens, whereas a high frequency of allergen-specific interleukin-4-secreting T cells (Th2-like) is found in allergic individuals [52]. Thus, a change in the dominant subset might lead to a reduced 'allergic status'. One recent study has demonstrated that 1 year of cluster SIT with Der p did not increase the frequency of CD4+CD25+Foxp3+ Treg cells or enhance the suppressive capacity of CD4+CD25^{high} T cells, but did increase the frequency of Tr1 cells and the production of interleukin-10 in peripheral blood monocytes of children with allergic rhinitis [64²²]. Additionally, the increase in Tr1 cells was correlated with a decline in clinical symptom scores during 1 year of SIT [64²²]. These data suggest that SIT might preferentially result in an allergen-specific Treg cell response characterized by an increased number of Tr1 cells, but not CD4+CD25+Foxp3+ Treg cells; which is in line with previous finding of a deficiency of allergen-specific Tr1 cells in allergic rhinitis patients [68]. Thus, the level of Tr1 cells in peripheral blood might be considered a marker of successful SIT.

ALLERGEN-SPECIFIC IMMUNOGLOBULIN E AND IMMUNOGLOBULIN G4 IN MECHANISMS OF ALLERGEN-SPECIFIC IMMUNOTHERAPY IN CHILDREN

Although SIT rapidly induces peripheral T-cell tolerance, there is no evidence that it induces B-cell tolerance. Serum-specific IgE levels often transiently increase after SIT and then gradually decrease after years of treatment [69–71]. Changes in IgE levels cannot account for diminished responsiveness to specific allergen after SIT because the decrease in serum IgE levels is late, relatively small, and poorly correlated with clinical improvement after SIT. Nonetheless, increases in specific IgG4 levels accompany clinical improvement with SIT [72,73]. IgG4 is considered a blocking antibody, which suggests that IgG4 inhibits allergen-induced and IgE-mediated

release of inflammatory mediators from basophils and mast cells, IgE-facilitated allergen presentation to T cells, and allergen induced boost of memory IgE production during allergen exposure [72,73].

OUTLOOK

In spite of the advances with SIT, safer and more effective SIT strategies are needed. Novel approaches to improve SIT include use of adjuvants, recombinant allergens and alternate routes of administration.

Anti-IgE antibody

The monoclonal anti-IgE antibody omalizumab has been shown to lower serum free IgE levels and reduce IgE-mediated symptoms [74]. Children with allergic rhinitis are commonly sensitized to multiple allergens [75] and might have an enhanced IgE immune response, as shown by higher serum levels of total and specific IgE [76]. However, SIT with multiple allergens appears to be less effective than single-allergen SIT [77] because the mixture contains too many allergens for doses of the single allergens to be optimal. Thus, anti-IgE treatment appears to be particularly useful for polysensitized patients. Indeed, a randomized, double-blinded trial investigating a total of 221 polysensitized children and adolescents with seasonal allergic rhinitis for efficacy of a combination therapy comprising SIT plus omalizumab or SIT alone has demonstrated that the combination therapy reduced the symptom load significantly by 48% over two pollen seasons compared with SIT alone [78]. Another well controlled study has suggested that omalizumab may play a role in pretreatment of rush immunotherapy [79]. The study demonstrated that patients receiving omalizumab plus immunotherapy had fewer adverse events than those receiving immunotherapy alone after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. The authors concluded that combined therapy with omalizumab and rush immunotherapy may be an effective strategy to permit more rapid and higher doses of allergen immunotherapy to be given more safely and with greater efficacy to children with allergic rhinitis [79].

Recombinant DNA vaccines

Cloning of allergen proteins with use of recombinant DNA technology enabled the production of vaccines that have well defined molecular, immunologic, and biological characteristics [80]. Moreover, genetic engineering enables modifications of

molecular structure that can reduce allergenic activity, increase immunogenicity, or both [81].

Toll-like receptor (TLR) agonists can skew the cytokine response from Th2 to Th1, hence, reducing symptoms of allergic disease. Ligands for TLR4 and TLR9 with and without allergen have been studied most. Pollen extracts that are chemically modified (allergoids) and combined with a monophosphoryl lipid A (an adjuvant that binds to TLR4) have been used in Europe and Canada as a preseasonal, ultra-short SCIT course consisting of four weekly subcutaneous injections [81]. Nonetheless, conjugating immune-stimulatory sequences of DNA to specific allergens offers a new approach to SIT that reduces acute allergic responses. Short segments of DNA with CpG motifs, which are TLR9 agonists, have been used in many different modalities as immunotherapy. Covalently linking B-type CpG to major ragweed-pollen allergens (Amb a 1) initially looked promising [82].

Epicutaneous allergy immunotherapy

Several studies have investigated SIT for allergy, administered via the oral, nasal, bronchial, epicutaneous, intraepithelial, or intra-lymph node routes [83–85]. Intranasal and intrabronchial immunotherapy are not commonly used because of administration-associated local symptoms and safety considerations. Although intra-lymphatic SIT has shown benefit with several allergens, including cat and grass pollen [86,87], this is not adapted for children. In contrast, epicutaneous allergy immunotherapy (EPIT), which involves application of the allergen onto the skin, represents a potentially useful administration route for children for several reasons. In particular, the epidermis contains high numbers of potent antigen-presenting Langerhans cells, which enhance efficacy and thus shorten treatment duration. Moreover, as the epidermis is non-vascularized, inadvertent systemic distribution of the allergen and consequent systemic allergic side-effects are minimized. Importantly, epicutaneous administration can be done at home and is painless. Although the first case study of successful EPIT was reported by Vallery-Radot and Hangenau in 1921 [88], to our knowledge, only one prospective, double-blind randomized, placebo-controlled study has assessed the efficacy of grass-EPIT, in children with seasonal rhinoconjunctivitis [89]. The authors demonstrated that symptoms and use of antihistamines were significantly reduced in the group of children treated with grass-EPIT, administered as a mixed grass-pollen allergen-containing skin patch placed on the patient's back for 24h/week for 12 weeks during the pollen season, compared with

the group treated with placebo. Furthermore, no children showed systemic or local reactions, indicating that EPIT was a well tolerated and valid alternative to traditional SIT in children.

CONCLUSION

There is substantial evidence for effectiveness of both SCIT and SLIT. Most meta-analyses and reviews concluded a trend that SCIT was better than SLIT in reducing symptoms of allergic rhinitis and rescue medication use, however, SLIT has a better safety profile than SCIT. Additionally, the absence of pain on administration of therapy is a character of SLIT, which is well suited for children. T regulatory cells especially Tr1 cells that secrete interleukin-10 and induce production of IgG4, play a role during SIT. In the future, safer and more effective SIT approaches are needed.

Acknowledgements

This work was supported by grants from the Program for Changjiang Scholars and Innovative Research Team (IRT13082), the National Science Fund for Distinguished Young Scholars (81025007), Beijing Natural Science Foundation (7131006), Ministry of Health Foundation (201202005), the Capital Health Research and Development of Special (2011–1017–06), the Special Fund of Sanitation Elite Reconstruction of Beijing (2009–2–007) and Beijing Health Bureau Program for high level talents (2011–3–043).

Conflicts of interest

The authors declare no conflicts of interest.

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