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REVIEW

# Safety, Efficacy, and Preventive Role of Subcutaneous and Sublingual Allergen Immunotherapy for the Treatment of Pediatric Asthma

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**Abstract:** Allergen-specific immunotherapy is currently the only treatment with the potential to modify and prevent progression of allergic asthma in children. In clinical practice, it is available in two forms: subcutaneous immunotherapy and sublingual immunotherapy. Trials and meta-analyses showed both the safety and the short- and long-term benefits of allergen-specific immunotherapy in asthmatic children. However, its use and role in asthma remains controversial, since studies are largely heterogeneous. This is mainly due to the lack of consensus on the optimal primary outcome to be considered for clinical trials evaluating the efficacy of allergen-specific immunotherapy in asthma. Therefore, well-conducted researchis needed using standardized and validated tools to evaluate key outcomes in asthmatic children.

**Keywords:** asthma, allergen-specific immunotherapy, children, allergy, grass, house dust mite

## Introduction

Asthma is a serious global health problem affecting over 300 million people worldwide.[1] The prevalence is increasing in many countries, especially among children, and represents one of the leading causes for hospitalizations.[2]

GINA recommendation defines asthma as a heterogeneous disease usually characterized by chronic airway inflammation that is characterized by wheeze, dyspnea, chest tightness, and/or cough with obstruction of low airways.[1] At present, the term asthma is considered an umbrella diagnosis for several diseases with distinct mechanistic pathways (endotypes) and variable clinical presentations (phenotypes).[3] The precise definition of these endo-phenotypes is crucial for the therapeutic asthma management and for the prognosis.

In about 75% of all children with asthma, atopy is present.[1] Allergic asthma is probably the most common asthma phenotype[4] (high Th2) characterized by high IgE eosinophil inflammation and bronchial hyperreactivity. The presence of past and/or family history of allergic disease such as eczema, allergic rhinitis (AR) is common, and it often begins in childhood.[1] Currently asthma drugs can effectively control symptoms and the ongoing inflammatory process, but they do not affect the underlying immune response.

When inhaled corticosteroids were suspended, the relative risk for asthma exacerbations was shown to be 2.35 (1.88–2.92) in comparison with those who

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did not suspend, and 55% of the subjects did not succeedin halting treatment with inhaled corticosteroids/long-acting beta agonists.[5] Asthmatic symptoms can be induced by several allergens[1,6–9] including pollens, house dust mites (HDM), molds, furred animals, venom, drugs, and foods.

Allergen-specific immunotherapy (AIT) with one or multiple inhalant allergens currently represents the only causal treatment that can modify the natural history of allergic respiratory diseases.[8,9] It is also used in other allergic diseases such as hymenoptera venom hypersensitivity,[9] and AIT trials are ongoing for atopic dermatitis[10] and food allergy.[11]

AIT for aeroallergens consists of the administration of standardized allergen extracts to patients with respiratory IgE-mediated diseases (AR, allergic asthma) to the same allergen to achieve immune tolerance and prevent the onset of symptoms. AIT is mainly used in two forms: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). Despite the first treatment with SCIT which has been reported at the beginning of the past century,[12] the first randomized study on SLIT was performed in 1986.[13,14] SCIT is based on regular subcutaneous administration of allergen extract, that is available in either aqueous, physically adsorbed (depot), or chemically modified (allergoids) allergens. SLIT consists in putting under the tongue the extract contained in an aqueous solution as drops or in tablets and then swallowing. There is no international regulation on AIT. SLIT tablets for grass pollen, ragweed, Japanese cedar, and HDM[15] have been registered for children, adolescents, and adults. The other AIT products are available as "Patient Name Products".[16] Asthma guidelines do not provide clear recommendations about AIT use in asthmatic children, and their role in this disease remains controversial. This is mainly due to the scarce clinical trials evaluating relevant asthma outcomes as primary variables, because the AIT effect may only be evident following a long treatment period[17] and for other factors such as the risk of adverse reactions, the heterogeneity of allergen compounds, and commercial products.[18,19] There is a need for biomarkers of efficacy, safety, compliance, and immune monitoring in AIT trials.[20]

Recently, the Global Initiative for Asthma (GINA) recommendation states that AIT may be an option for adults with AR who are sensitized to HDM, with suboptimal controlled asthma despite low high dose inhaled corticosteroid, providing forced expiratory volume in the 1st second ($FEV_1$) is >70% predicted. However, potential benefits must be weighed against the risk of adverse effects, and the inconvenience and the cost to the patient and health system.[1]

The aim of our review is to assess the use of AIT in childhood asthma, focusing on the most relevant aspects of efficacy and safety.

## Immune Modulation of AIT

AIT effect (Figure 1) seems to be linked to modification of the function of monocytes, B-cells, and T-cells, as well as basophils, eosinophils, and mast cells count.[21–23] It has been shown that mediators of anaphylaxis (histamine and leukotrienes) are released during AIT without inducing a systemic anaphylactic response.[24] This is in agreement with findings of lower mediator release from mast cells and basophils[24,25] as a result of induction not only of IgG4 but also IgG2 and IgG3 that suppress FceRI-mediated responsiveness, following the start of AIT.[26]

Studies on cellular immunity has been mainly conducted in adults and there are some data that similar mechanisms occur in children.[9] Th2 cells have been considered as the main source of type 2 cytokines; the imbalance of Th1/Th2 is the key to the appearance of asthma. Furthermore, the immune responses of Th17 and T-regulatory cells (Treg) also play an important role. Th17 cell response increases, and Treg expression decreases in asthma. The severity and symptom control of asthma are closely related to the imbalance of Th17/Treg. It is believed that regulating Th1/Th2 and Th17/Treg immune balance may be the key to asthma treatment.[27]

Dendritic cells play an important role in SLIT since there is a massive exposure to the culprit allergen. The action of AIT on dendritic cells[9] leads to an increase in natural regulatory T-cells (nTregs) and induced regulatory T-cells (iTregs) production by the release of IL-12, IL-27, and IL-10. Specific Tregs and B-regulatory cells can modify the immune response from allergic Th2 to Th1 response. Moreover, Tregs downregulate mucosal mast cells, basophils, and eosinophils count and function.[28] Regarding the humoral immunity, AIT through Treg cells enhances specific IgG4 and diminished specific IgE to allergens. Furthermore, Tregs increase IgA that may block Ig receptors together with the specific IgG4.[29]

## Safety

AIT is contraindicated in patients with medical conditions that increase the risk of treatment-related severe systemic reactions, such as those with significant cardiovascular

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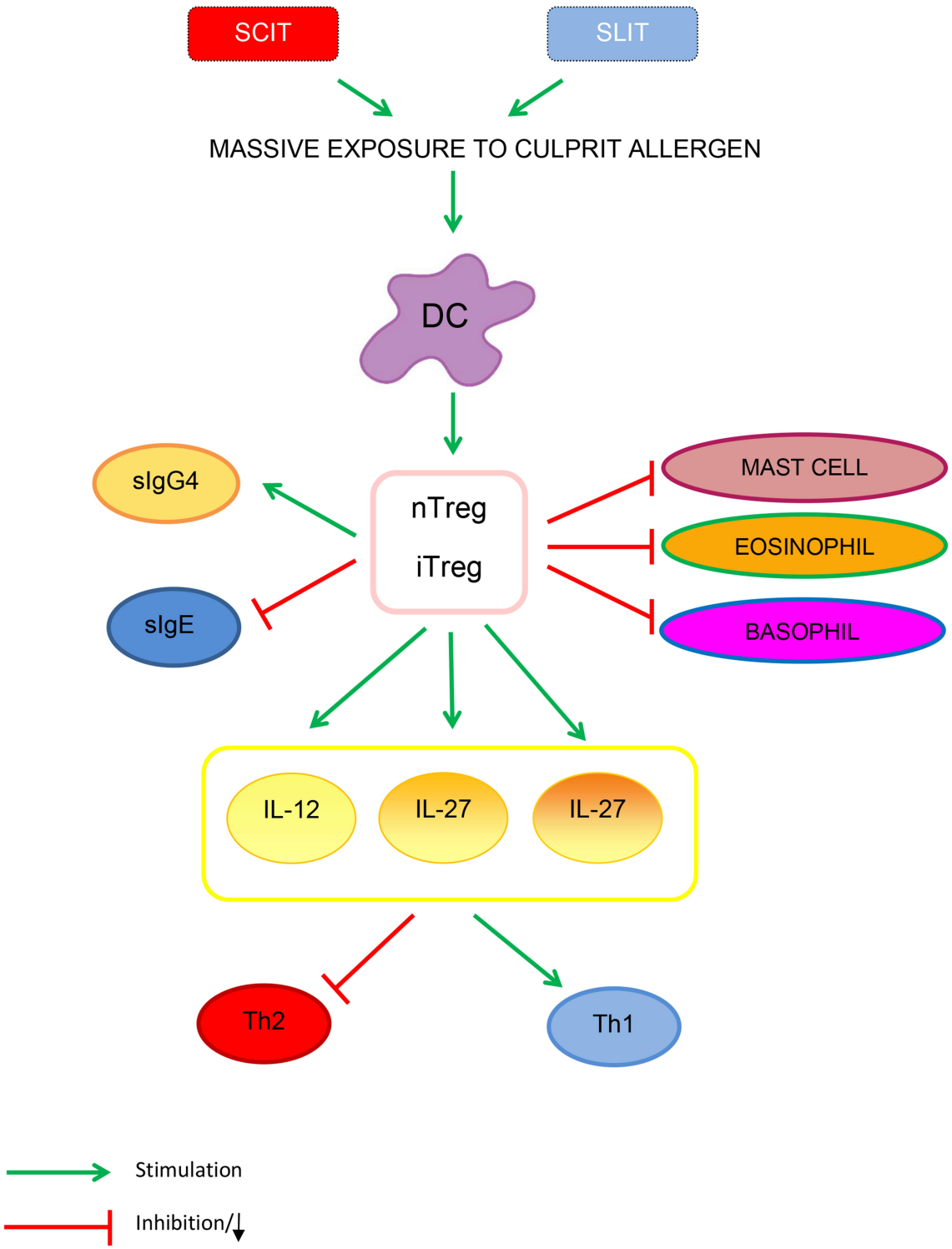


**Figure 1** Immune modulation of AIT. The action of AIT on dendritic cells leads to an increased nTregs and iTregs production by the release of IL-12, IL-10, and IL-27. Specific Tregs and B-regulatory cells can modify the immune response from allergic Th2 to Th1 response. Moreover, Tregs downregulate count and function of mucosal mast cells, basophils and eosinophils. AIT through Treg cells enhances specific IgG4 and diminished specific IgE to allergens.
**Abbreviations:** SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; DC, dendritic cells; nTreg, natural regulatory T-cells; iTreg, induced regulatory T-cells.

diseases (eg, unstable angina, recent myocardial infarction, arrhythmia, and uncontrolled hypertension). Severe or uncontrolled asthma or $FEV_1$<80% are the major independent risk factors for both nonfatal and fatal adverse reactions and, thus, a major contraindication for both SLIT and SCIT.[30–32] Neoplasms, chronic diseases, and

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autoimmune disorders should also be considered.[33] AIT should be administered with caution to patients receiving β-blockers or angiotensin-converting enzyme inhibitors.[30] Chronic and acute nasal or conjunctival inflammatory responses and nasal polyps are not a contraindication for AIT.[34]

## SCIT Safety

Injections must be performed by trained personnel staff in clinical settings with equipment to manage any possible systemic adverse reactions or anaphylaxis. The patients' general status should be assessed before each injection to reduce the risk of anaphylaxis.[30] Injection should be postponed in children with febrile illness or bronchospasm. All patients undergoing SCIT should be observed for at least 30 minutes after injection to ensure proper management of systemic adverse reactions.[30] Adverse events are more frequent when rush build-up schedules are used.[35] Uncontrolled asthma and human errors were the most common causes of SCIT-induced adverse events.[36] Adverse reactions to SCIT range from local site reactions, to systemic reactions, such as urticaria-angioedema, anaphylaxis. They have been classified in a grading system.[37] Local reactions are frequent, in 26–86% of SCIT injections, but are often well-tolerated.[38] A systematic review[39] found that anaphylaxis in asthmatic children receiving SCIT occurred in two of 232 patients, even though systemic reactions are rare when AIT is performed according to safety recommendations. One death was reproted.[39] Unspecified systemic reactions were also reported in 23% of children treated with SCIT in non-RCTs. Other reactions, including hives, wheezing, rhinorrhea, asthma, and congestion were also reported in non-RCTs.[39] Recently, Lee et al[40] found that 24% of patients experienced adverse reactions to SCIT and only one case of anaphylaxis developed. A multicenter study demonstrated that systemic reactions were slightly more frequent in patients with rhinitis with asthma than in those with isolated rhinitis.[41] Overall, there is insufficient evidence to draw conclusions on the rate of anaphylaxis or fatalities due to SCIT in asthmatic children.

## SLIT Safety

The SLIT-related systemic reaction rate is significantly lower compared with SCIT-related. No fatality has been reported until now, and only a few cases of suspected anaphylaxis have been described, none directly related to pre-existing asthma or to worsening of asthma.[32] Two of three reports of anaphylaxis to SLIT were in patients who received multiple allergen therapy.[42,43] This suggests that SLIT with multiple allergens poses higher risk for systemic adverse effects.[44] A comprehensive review[45] of 104 SLIT studies showed 1.4 serious adverse events per 100,000 SLIT administered doses.

Randomized controlled trials showed that local reactions (pruritus or dysesthesia at the oral cavity, swelling of the oral mucosa, throat irritation) to SLIT are common (up to 80% of patients). These reactions mirror those elicited in the pollen-food syndrome.[46] They usually appear at the beginning of SLIT, are mostly mild, and generally recede after 1–3 weeks of treatment.[47] Gastrointestinal symptoms such as vomiting, abdominal pain, and diarrhea may occur. SLIT for pollens has been associated with the onset of eosinophilic esophagitis.[48] A meta-analysis by Dhami et al[49] in children and adults showed a risk for adverse events, more frequent with SCIT than with SLIT. Because SLIT is administered at home, instructions should be given regarding management of adverse reactions and when the administration of SLIT should be avoided (eg fever, asthma exacerbation, stomatitis, or eosinophilic esophagitis).

## SCIT Efficacy

The results of the SCIT studies carried out in children with asthma are summarized in Table 1. Several meta-analyses reported the effectiveness of SCIT in improving asthma control.

A meta-analysis of double-blind randomized controlled trials on SCIT in asthmatics by Dhami et al[49] selected 98 studies. They found that SCIT reduced short-term symptom and medication scores both in adults and children. Moreover, the analysis of individual allergens highlighted a benefit for AIT with HDM, grass pollen, and cat/dog dander, no benefit for mold and a possible effectiveness (not confirmed) for tree pollen. Finally, the metanalysis did not find conclusive data on long-term efficacy, that is the clinical improvement for at least 1 year after cessation of the therapy, and on cost–benefit impact. Another meta-analysis[50] reported a significant reduction in the asthma symptom scores and medication scores in the mite-sensitized children and adults receiving SCIT compared with the control group. There were no significant differences between two groups in lung function and specific antibody levels of blood serum. In a systematic review that included a randomized controlled trial on SCIT efficacy in

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**Table 1** SCIT Studies Carried Out in Patients with Asthma

| Author | Age (Years) | Participants (No) | Study Type | Allergen Extract | Main Efficacy Results |
|---|---|---|---|---|---|
| Dhami et al[49] | Children and adults | 98 studies (SLIT and SCIT) on adults and children with confirmed diagnosis of allergic asthma | Meta-analyses of randomized clinical trials | Different (eg, pollens, HDM, animal dander, cockroach, and molds) | Reductions in short-term symptom and medication scores in allergic asthma without conclusive data on longer-term effectiveness and cost-effectiveness |
| Lu et al[50] | Children and adults | 796 patients with asthma alone or in combination with other symptoms (AR, conjunctivitis, dermatitis) | Systematic review and metaanalysis | HDM | Significant reduction in the asthma symptom scores and medication scores in the patient receiving SCIT compared with the control group. No significant differences between two groups in lung function and specific antibody levels of blood serum |
| Rice et al[39] | Children ≤18 | 40 studies (17 SCIT trials, 11 SLIT trials, 8 non-RCTs for SCIT safety, and 4 non-RCTs for SLIT safety) | Systematic review | Different (eg, grass, HDM, molds) | SCIT diminished long-term medication use and enhanced quality-of-life and FEV1 values |
| Di Bona et al[51] | Children and adults | 9 studies and a total of 168 children and 99 adults | Systematic review | Molds | Low strength evidence of efficacy of AIT for the treatment of respiratory allergies, although advocating the necessity of higher-quality research with an adequate sample size |
| Cools et al[52] | Children and adults | Asthmatic patients allergic to either HDM (34) or to both HDM and grass pollen (14) were re-evaluated in early adulthood after mean cessation of AIT for 9.3±2.76 years. The results were compared to those of a control group of asthmatic patients (42) with comparable asthma features, who were treated with appropriate antiasthmatic drugs during childhood, but who never received AIT | Retrospective study | HDM or to HDM and grass pollen | The 2 groups were then re-evaluated about 9 years after the discontinuation, the risk of frequent asthmatic symptoms was 3-times higher in the control group than in the AIT-treated group. The frequent use of antiasthmatic therapy was also more pronounced in the control group, although the difference was not statistically significant. Lung-function parameters were comparable in both groups. |
| Stelmach et al[53] | Children: Control group: 12.2 (SD=2.9), AIT3 group: 11.7 (SD=3.8), AIT5 group; 13.9 (SD=3.7) | 30 children with allergic asthma treated for 3 years with HDM AIT, 30 treated with a 5 years course of HDM AIT and other 30 who refused HDM AIT | Prospective study | HDM | Rate of asthma remission was significant higher in both treated groups compared with controls after 3 years discontinuation therapy, without clinical benefit continuing therapy for other 2 years |
| Pifferi et al[54] | 6–14 (mean: 10.61 ±2.75 SD) | 15 children receiving AIT and 14 controls (four drop-outs) with allergic asthma | Randomized clinical trial | HDM | Improves in asthmatic symptoms with marked reduction in drug intake and a significantly reduction in non-specific bronchial hyper-responsiveness |
| Zielen et al[55] | 6–17 | 65 patients after reaching asthma control with inhaled steroids during a 5-month baseline period, were randomized for SCIT plus fluticasone propionate (FP) or FP therapy alone for 2 year | Randomized clinical trial | HDM | Decrease in fluticasone propionate doses. A significant enhancement of the morning PEF and increased levels of IgG1 and IgG4 were also recorded |

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**Table 1** (Continued).

| Author | Age (Years) | Participants (No) | Study Type | Allergen Extract | Main Efficacy Results |
|---|---|---|---|---|---|
| Tsai et al[56] | Children: Immunotherapy group (mean age 8.6±2.99 SD) Control group (mean age 8.35±2.43 SD) | 40 children with moderate-to-severe allergic asthma were randomly assigned to two groups: half of them received HDM SCIT, while the other half were not given immunotherapy | Randomized clinical trial | HDM | Decrease in mean medication scores after 6 months |
| Chen et al[57] | 5−14 (mean age 7.0 ±1.9 SD) | 58 asthmatic children (35 received HDM AIT for 1 year, and the other 23 children treated with inhaled corticosteroids) | Clinical trial | HDM | No of emergency visiting for asthma attack in SCIT group was significantly less than that in inhaled corticosteroids group and that the pulmonary functions and PEF percentage were significantly improved in the SCIT group |
| Ibero et al[58] | 8–16 | 30 asthmatic children (15 were treated with the modified allergen extract and 15 received only pharmacologic treatment) | Randomized controlled trial | HDM | Significant improvement in skin reactivity, symptom and medication scores |
| Yukselen et al[59] | SCIT 10.9±3.2 SLIT 9.2±3.4 Placebo 10.1 ±2.7 | 30 children with rhinitis and asthma | Randomized, placebo-controlled, double-blind, double-dummy study | HDM | SCIT significantly diminished symptom and medication scores for rhinitis and asthma |
| Alzakar et al[60] | Primary school children | 197 children with allergic asthma | Single-blind, drug-controlled clinical trial | Various extracts (trees, mite, grass) | At the follow-up after 1 year indicated that the children treated with SCIT show a marked reduction in combined symptom and medication when compared with children treated with conventional therapy |
| Wahn et al[61] | age ≥5 | 9001 AIT patients and 45,005 matched non-AIT control | Retrospective cohort analysis of a German longitudinal prescription database | Birch pollen | Birch pollen AIT after to 6 years post-treatment cessation significantly reduced AR and asthma medication intake, and significantly decreased risk of new-onset asthma medication use on-treatment |
| Moller et al[62] | 6–14 (mean age=10.7) | 205 children with AR | Randomized, placebo controlled | Grass and/or birch pollen | After 3 years, the SCIT-treated patients developed significantly less asthma than the control group |

asthmatic children, Rice et al[39] found evidence that SCIT diminished long-term medication use and enhanced quality-of-life and FEV1 values. Di Bona et al[51] evaluated the efficacy of AIT on asthma in patients allergic to molds in a systematic review. They found low quality evidence for Alternaria and very low-quality evidence for Cladosporium. However, higher quality studies with larger sample of patients are needed to confirm the results.

In order to explore the long-term impact of SCIT on childhood asthma, a retrospective study was published by Cools et al,[52] in which asthmatics patients allergic to either HDM or to both HDM and grass pollen were treated with SCIT during childhood. The two groups were then re-evaluated about 9 years after the discontinuation, the risk of frequent asthmatic symptoms was 3-times higher in the control group than in the AIT-treated group. The use of anti-asthmatic therapy was also more frequent in the control group than in the intervention group, although the difference was not statistically significant. Lung function was comparable in both groups. The authors concluded

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that AIT has long-term effects on asthmatic symptoms in young adults. Along the same line, Stelmach et al[53] in 2012 performed a 3-year study of 90 asthmatic children who were sensitized only to HDM. Thirty patients completed 3 years of HDM SCIT, 30 completed 5 years of HDM SCIT, and 30 refused the treatment. The results showed efficacy in asthma remission in both treated groups compared to controls, and there was no further benefit in prolonging treatment after 3 years. Other studies compared HDM SCIT and inhaled corticosteroids therapy in allergic asthma to evaluate the steroid sparing effect of AIT. In a randomized clinical trial by Pifferi et al[54] on HDM allergic asthmatic children, SCIT significantly improved asthmatic symptoms with marked reduction in drug intake and a significantly reduction in non-specific bronchial hyper-responsiveness. Another randomized study performed by Zielen et al[55] on asthmatic children treated with HDM SCIT showed similar results with decrease in fluticasone propionate doses. Moreover, a significant enhancement of peak expiratory flow (PEF) and increased levels of IgG1 and IgG4 were reported.

Tsai et al,[56] in a randomized clinical trial, enrolled 40 children with moderate-to-severe allergic asthma, reporting that specific immunotherapy was effective in reducing mean medication scores. Chen et al[57] compared the efficacy of SCIT with a standardized *Dermatophagoides pteronyssinus* extract with inhaled corticosteroids for 1 year in asthmatic children. It was reported that the number of emergency visits for asthma attack in the SCIT group was significantly lower than in the inhaled corticosteroids group and that the pulmonary function, including PEF, significantly improved in the SCIT group.

In another study[58] on asthmatic children treated with SCIT to HDM, the results showed significant improvement in skin reactivity, symptom, and medication scores.

Yukselen et al,[59] in a 1-year, randomized, placebo-controlled, double-blind, double-dummy study on 30 children, showed that SCIT significantly diminished symptom and medication scores for rhinitis and asthma.

In a single-blind, drug-controlled clinical trial performed by Alzakar et al[60] on asthmatic children treated with SCIT with multiple allergens (trees, mite, grass) had a marked reduction in combined symptom-medication score when compared with long-term inhaled therapy.

Finally, Wahn et al,[61] in a retrospective cohort analysis of a German longitudinal prescription database, show that birch pollen AIT after to 6 years post-treatment cessation significantly reduced AR and asthma medication intake, and significantly decreased risk of new-onset asthma medication use on-treatment.

AIT, including SCIT, plays a preventive role in the development of asthma in children with allergic rhinitis. The Preventive Allergy Treatment (PAT) study[62] enrolled 205 children aged 5–13 years (mean age=10.7 years) with oculorhinitis to grass and/or birch pollen randomized either to receive specific immunotherapy or to an open control group. Children were evaluated for the development of asthma after 3 years of SCIT. Actively treated patients developed significantly less asthma than the control group. At re-evaluation after 5-years[63] and 10-years[64] from the beginning of SCIT, long-term asthma prevention was found.

## SLIT Efficacy

SLIT is effective in children with allergic rhinoconjunctivitis.[8,49,65] Unfortunately, in most studies the parameters related to asthma were assessed only as a secondary outcome.

The results of the SLIT studies carried out in children with asthma are summarized in Table 2.

The effectiveness of SLIT for childhood asthma has been shown in several meta-analyses over time. A meta-analysis by Penagos et al[66] included nine studies with 441 children (3–18 years of age), 232 and 209 of whom received SLIT and placebo, respectively. There was a significant reduction in asthma symptom scores and rescue medication. Olaguibel et al,[67] in another meta-analysis on the efficacy of SLIT in 256 asthmatic children (129 treatment and 127 placebo recipients), showed the decrease in symptom and medication use. Liao et al[68] evaluated the efficacy and safety of HDM SLIT in asthmatic children (230 patients treated with SLIT, and 224 with placebo/pharmacotherapy for 4 months to 3 years). They found a significant reduction in asthma symptoms score and an increase in sIgG4 levels greater than controls. In a GA$^2$LEN meta-analysis[69] nine trials involving 476 asthmatic children (243 mite SLIT vs 233 placebo) were included. The results showed a relevant reduction in symptom and medication scores, but a significant inter-study heterogeneity was found. A systematic review by Rice et al[39] reported that SLIT improved drug consumption and increased FEV1. Larenas-Linneman et al[47] systematically reviewed 29 clinical trials published from January 2009 through 2012 regarding SLIT in children.

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**Table 2** SLIT Studies Carried Out in Patients with Asthma

| Author | Age (Years) | Participants (N°) | Study Type | Allergen Extract | Main Efficacy Results |
|---|---|---|---|---|---|
| Penagos et al[66] | 3–18 | 9 studies with 441 children (232 and 209 of whom received SLIT and placebo, respectively) | Meta-analyses | Perennial, seasonal | Significant reduction in asthma symptom scores and rescue medication |
| Olaguibel et al[67] | ≤14 years-old | 256 children with rhinitis or asthma (129 treatment and 127 placebo recipients) | Meta-analyses | Perennial, seasonal | Decrease in symptom and medication requirement in asthma |
| Liao et al[68] | Children (<18 years of age) | 454 children (230 patients have used SLIT treatment, and 224 were treated with placebo/pharmacotherapy for 4 months to 3 years) | Meta-analyses | HDM | Significantly reduction in asthma symptoms score and increased sIgG4 levels greater than control in children (<18 years of age) with asthma |
| Compalati et al[69] | Children and adults | 476 patients with asthma (243 SLIT vs 233 placebo) | GA2LEN meta-analysis | HDM | A relevant reduction in symptom scores but a significant inter-study heterogeneity was found |
| Larenas-Linneman et al[47] | Younger than 18 years | 454 asthmatic children | Meta-analyses of randomized clinical trials | Perennial, seasonal | Evidence is lacking for the precoseasonal tablet and drop grass pollen SLIT efficacy in seasonal asthma. For HDM SLIT in asthma, there is high-quality evidence for medication reduction while maintaining symptom control. Nonspecific bronchial provocation testing does not improve with grass pollen and HDM SLIT |
| Stelmach et al[70] | 6–18 | 60 with rhinitis (20 patients had concomitant asthma) | Randomized, double-blind placebo-controlled study | Grass pollen | Decrease asthma symptoms and medication score |
| Majak et al[71] | 6–17 | 35 asthmatic children | Double-blind, placebo-controlled study | Grass pollen | High-dose ultrarush SLIT reduced the severity of allergic symptoms in the first 2 grass pollen seasons, but continuously improved bronchial hyperreactivity in children with asthma |
| Calamita et al[72] | Children and adults | 1,706 patients with asthma | Meta-analyses of randomized clinical trials | Perennial, seasonal | Immunotherapy is beneficial for asthma treatment, although the importance of the effect is not very large |
| Dhami et al[49] | Children and adults | 98 studies (SLIT and SCIT) on adult and children with confirmed diagnosis of allergic asthma | Meta-analyses of randomized clinical trials | Different (eg, pollens, HDM, animal dander, cockroach, and molds) | There were no significant effects on asthma control, exacerbations, lung function, and non-specific airway hyperreactivity |
| Normansell et al[73] | Children and adults | 5,077 patient (18 studies included only adults, 25 included only children, and nine recruited both or did not specify). Most of the participant having mild or intermittent asthma | Cochrane database systematic review | Different (eg, pollens, HDM, animal dander, cockroach, and molds) | Data on exacerbations and quality-of-life and different unvalidated symptom and drug scores are lacking |
| Di Rienzo et al[74] | Mean age 8.5 | 60 children with allergic asthma/AR (35 underwent a 4–5-year course of SLIT with standardized extract and 25 received only drug therapy) | Prospective study | HDM | In the SLIT group there was a significant difference vs baseline for the presence of asthma and the use of drugs asthma medications. The mean PEF result was significantly higher in the active group than in the control group after 10 years |

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**Table 2** (Continued).

| Author | Age (Years) | Participants (N°) | Study Type | Allergen Extract | Main Efficacy Results |
|---|---|---|---|---|---|
| Marogna et al[75] | Mean age of 22.2 ±5.2 | 59 patients and 12 controls | Prospective open controlled study | HDM | In the patients receiving SLIT for 3 years, the clinical benefit persisted for 7 years. In those receiving immunotherapy for 4 or 5 years, the clinical benefit persisted for 8 years |
| Tahamiler et al[76] | Mean age 27.91 ±9.73, range 12–51 years | 137 patients | Randomized controlled Trial | HDM | There is a greater improvement in the 3 years of sublingual immunotherapy compared to the 2 years of sublingual immunotherapy |
| Ozdemir et al[77] | 4–16 | Children with asthma SLIT + pharmacotherapy (n=62) or pharmacotherapy alone (n=28) | Controlled clinical trial | HDM | Decrease the duration and dose of inhaled corticosteroid |
| Eifan et al[78] | 5–10 | 48 patients SLIT (n=16), SCIT (n=16), or pharmacotherapy alone (n=16) | Open randomized controlled trial | HDM | Both SLIT and SCIT demonstrated clinical improvement compared with pharmacotherapy in asthma/rhinitis children sensitized to HDM |
| Novembre et al[79] | 5–14 (mean age=7.7 years) | 113 children | Open randomized study | Grass pollen | Three years of coseasonal SLIT improves seasonal allergic rhinitis symptoms and reduces the development of seasonal asthma in children with hay fever |
| Valovirta et al[80] | 5–12 | 812 children with seasonal allergic rhinitis | Double-blind, placebo-controlled study | Seasonal | Improve clinical effect on rhinoconjunctivitis and a decreased risk of experiencing asthma symptoms and using asthma drugs |
| Devillier et al[81] | Over 5 | 1,099 children with AR having received at least two prescriptions of grass pollen SLIT tablets per course of treatment over at least 2 consecutive years and 27,475 control patients with moderate-to-severe disease | Retrospective real-world analysis | Grass pollen | During the follow-up,1.8% vs 5.3% of patients started asthma treatment in the SLIT and control groups, respectively. In addition, the relative risk of drugs dispensing for new asthma was less in the SLIT group. SLIT group was also associated with a slower progression of asthma therapy delivery during follow-up period, relating to the control group |
| Zielen et al[82] | Over 5 | 2,851 SLIT and 71,275 control patients | Retrospective analysis of a German longitudinal prescription database | Grass pollen | Treatment of AR patients with grass pollen SLIT tablets was associated with slower AR progression, less frequent asthma onset, and slower asthma progression |

Evidence for precoseasonal tablet and drop grass pollen SLIT efficacy in asthma was lacking. There was evidence that mite SLIT reduced consumption of anti-asthmatic medication. Non-specific bronchial provocation testing did not improve with grass pollen and HDM SLIT.

Other randomized studies[70,71] concluded that immunotherapy with the grass tablet reduced asthma symptoms in a pediatric population, irrespective of SLIT given continuously along the year or (pre)-co-seasonally. In meta-analyses involving both adults and children are found more conflicting results. Twenty-five randomized-controlled clinical trials on SLIT in 1,706 adults and children with asthma were included in the meta-analysis by Calamita et al.[72] It was found that immunotherapy was of benefit for asthma treatment, although the importance of the effect was not very large. In contrast, in the meta-analysis by Dhami et al,[49]

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which included 98 studies in children and adults with asthma, SLIT did not produce significant effects on asthma control, exacerbations, lung function, and non-specific airway hyperreactivity. Normansell et al,[73] in a Cochrane database systematic review on SLIT in asthma, assessed 52 studies with 5,077 patients (18 studies included only adults, 25 included only children, and nine recruited both or did not specify). The authors found inconclusive results due to the lack of data on exacerbations and quality-of-life, and the use of different unvalidated symptom and drug scores.

In a prospective study[74] in children with HDM allergic asthma/AR, the long-term effects of SLIT were evaluated. The patients were divided into two groups: one underwent a 4- to 5-year course of SLIT with standardized extract, and the other received only medication therapy. In the SLIT group there was a significant difference vs baseline for the presence of asthma and the use of drugs asthma medications. The mean PEF result was significantly higher in the active group than in the control group after 10 years. The long-lasting effects of SLIT have also been shown by several studies.[75–77]

In a single-center, prospective, randomized, controlled, open labeled,[78] three parallel group trial, 48 patients mono-sensitized to HDM were randomized to receive either SLIT (n=16), SCIT (n=16), or pharmacotherapy alone (n=16). Both SLIT and SCIT demonstrated clinical improvement compared with pharmacotherapy in asthma/rhinitis children sensitized to HDM.

Onset of asthma in children with seasonal rhinoconjunctivitis was prevented by grass SLIT drops.[79] Furthermore, a large double-blind, placebo-controlled trial with grass tablets found that they improved rhinoconjunctivitis and reduced the risk of developing asthma.[80] Moreover, these benefits were maintained after cessation of SLIT.

A potential preventive role of immunotherapy on development of asthma was also suggested by Devillier et al[81] in a retrospective database study. They evaluated 1,099 children with AR who received at least two prescriptions of grass pollen SLIT tablets per course of treatment over at least 2 consecutive years, and 27,475 control patients with moderate-to-severe disease, defined as at least two prescriptions dispensed of nasal corticosteroids during two subsequent pollen seasons. During the follow-up, 1.8% vs 5.3% of patients started asthma treatment in the SLIT and control groups, respectively. In addition, the relative risk of drugs dispensing for new asthma was less in the SLIT group. There was also a slower progression of asthma therapy delivery during the follow-up period in the SLIT group than in the control group.

In another retrospective analysis of a German longitudinal prescription database,[82] treatment of AR patients with grass pollen SLIT tablets was associated with slower AR progression, less frequent asthma onset, and slower asthma progression.

**Table 3** Key Messages

| |
|---|
| 1. Allergen immunotherapy is the only treatment that can modify the immune response upon exposure to aeroallergens. |
| 2. Short- and long-term AIT benefits in the asthma treatment are documented. |
| 3. No consensus exists on the optimal endpoints of asthma. |
| 4. Increasing safety and efficiency is the main goal of research for novel immunotherapy development and improvement of treatment in asthma. |

## Conclusion

Currently, allergen immunotherapy is the only treatment that can modify the immune response upon exposure to aeroallergens (Table 3). There is evidence that AIT not only improves rhinoconjunctival symptoms, but also has short- and long-term beneficial effects in asthma treatment. The disease modification properties consist of a reduction in symptom severity, less drug consumption, and a long-term therapeutic effect. However, there are controversial recommendations on AIT in asthma guidelines. An explanation may be that, due to the heterogeneity of allergen extract, it is challenging to combine results of studies that use different AIT products in metanalyses. It would be advisable to evaluate every allergen extract separately in order to assess the safety and efficacy profile of each one. Moreover, no consensus exists on the optimal endpoints of AIT in asthmatics. Large trials using standardized and validated tools to evaluate key outcomes in asthma are warranted.

## Abbreviations

AR, allergic rhinitis; AIT, allergen-specific immunotherapy; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; GINA, Global Initiative for Asthma; HDM, house dust mite; $FEV_1$, forced expiratory volume in the 1st second; Treg, T-regulatory cells; nTreg, natural

regulatory T-cells; iTreg, induced regulatory T-cells; PEF, peak expiratory flow.

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