

Role of immunotherapy in the treatment of allergic asthma

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Abstract

Allergen-specific immunotherapy (SIT) induces clinical and immunological tolerance as defined by persistence of clinical benefit and associated long-term immunological parameters after cessation of treatment. Although the efficacy of SIT has been shown in terms of reducing symptoms, medication consumption and ameliorating quality of life in both allergic rhinitis and asthma, there has long been some controversies about effectiveness of SIT in the treatment of allergic asthma. The type of allergen, the dose and protocol of immunotherapy, patient selection criteria, the severity and control of asthma, all are significant contributors to the power of efficacy in allergic asthma. The initiation of SIT in allergic asthma should be considered in case of coexisting of other allergic diseases such as allergic rhinitis, unacceptable adverse effects of medications, patient's preference to avoid long-term pharmacotherapy. Steroid sparing effect of SIT in allergic asthma is also an important benefit particularly in patients who have to use these drugs in high doses for a long-time. Symptomatic asthma is a risk factor for systemic reactions and asthma should be controlled at the time of administration of SIT. Both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) have been found to

be effective in patients with allergic asthma. Although the safety profile of SLIT seems to be better than SCIT, the results of some studies and meta-analyses suggest that the efficacy of SCIT may appear better and earlier than SLIT in children with allergic asthma.

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Key words: Asthma; Efficacy; Safety; Subcutaneous immunotherapy; Sublingual immunotherapy

Core tip: Allergen specific immunotherapy is the only therapeutic approach that can change the immunologic response to allergens and thus can alter the natural evolution of allergic diseases. Both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) have been demonstrated to be beneficial in reducing of symptoms and drug intake, improving quality of life and preventing patients from possible side effects of high doses of steroids. This review examines the clinical effectiveness and safety of both SCIT and SLIT in patients with asthma by discussing recent studies.

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INTRODUCTION

Asthma is one of the most prevalent chronic conditions affecting roughly 300 million people in the world. It is supposed that asthma will affect an additional 100 million people by 2025^[1].

According to data of health statistics in United States, current asthma prevalence is 9.3% and 8%, in children and adults, respectively^[2]. This increment in the prevalence of asthma has been accompanied by an increment in other allergic disorders like rhinitis and eczema.

Asthma is characterized by chronic inflammation,

which result in recurrent attacks of cough, wheezing, sometimes chest tightness and variable airflow obstruction. As time progresses, this airflow obstruction may become irreversible due to airway remodelling. Since many years, asthma has been supposed as mainly a Th2 cell-mediated disorder^[3,4]. Nevertheless, in recent years, it is also discovered that many other cell types such as Treg, Th1 and Th17 are also involved in pathological process of asthma^[3,4].

Drugs, such as inhaled corticosteroids, long-acting beta agonists and montelukast can effectively control asthma symptoms and attacks. However, it is known that, pharmacotherapy can not affect the underlying immune response; when these medications are stopped the symptoms may recur.

Specific allergen immunotherapy (SIT) is a unique therapy which capable to change the natural evolution of allergic diseases^[5]. With this treatment mode, allergens are given to patients in repeated and increasing doses to provide immune tolerance^[6].

The effectiveness of both subcutaneous (SCIT) and sublingual (SLIT) immunotherapy is documented for both perennial and seasonal allergic respiratory disease by systematic reviews and meta-analyses^[6-11]. For almost 100 years now, subcutaneous route has been used to treat allergic diseases; however, there are many studies to confirm the administration of SLIT because of discomfort of repeated injections and higher risk of adverse reactions.

In most published studies, effectiveness of SIT has been assessed primarily in patients with allergic rhinitis, and the results concerning asthma mostly were given as secondary outcome. Thus, there are a few studies which were organised to evaluate the efficacy of SIT specifically in asthma alone.

In this paper we will review primarily the clinical efficacy and safety of both SCIT and SLIT in patients with allergic asthma in the light of the literature.

CLINICAL EFFICACY OF SCIT IN ASTHMA

The first of the studies which evaluate the efficacy of SCIT in asthmatic patients published by Abramson in 1995^[12].

In the meta-analysis carried out by Ross *et al*^[13], 24 prospective, randomized, studies involving 962 asthmatic patients were evaluated. They reported significant amelioration in symptoms and drug intake related with asthma as well as in pulmonary function in the SCIT group in comparison to the placebo. It was deduced that immunotherapy was beneficial in 17 (71%) studies, inefficacious in 4 (17%) studies, and equivocal in 3 (12%) studies. Similar to the previous meta-analyses, the authors concluded that SIT is effective in patients suffering from allergic asthma.

In a study of Basomba *et al*^[14], 55 mild and moderate asthmatic patients (aged 14-50 years) allergic to house dust mites (HDM) were treated with *D pteronyssinus* ex-

tract encapsulated in liposomes, in a double-blind placebo-controlled manner. At the end of one year, 45.8% of the patients treated with SCIT decreased symptom and medication scores by at the minimum 60%. There were also notable improvements in results of skin test and allergen-specific bronchial challenge.

In another study, fifteen children aged 6-14 years with asthma due to HDM were treated with SCIT for three years; the results were remarkable reduction in the number of asthma exacerbations and marked decrease in drug intake^[15]. Additionally, significant improvement in lung functions and non-specific bronchial hyperreactivity (BHR) were observed.

García-Robaina *et al*^[16] administered SIT with HDM in 64 adult asthmatic patients and they observed notable amelioration in the active group over placebo in terms of symptom (53.8 %) and medication scores (58%) in addition to improvement in allergen-specific BHR.

Roberts *et al*^[17] studied the efficacy of grass pollen SIT in 35 asthmatic patients (aged 3-16 years) over 2 pollen season in a double-blind manner. They found that SIT provided significant decreases in asthma symptom and medication scores, marked improvements in cutaneous ($P = 0.002$), conjunctival ($P = 0.02$), and bronchial ($P = 0.01$) reactivity to allergen.

In the study of Zielen *et al*^[18], 65 mite allergic children aged 6-17 years were treated with subcutaneous allergoid immunotherapy plus fluticasone propionate (FP) or FP therapy alone for 2 years. Before starting SIT, asthma control was achieved using inhaled corticosteroids for 5 mo follow-up. Children treated with SCIT plus FP were able to markedly decrease the FP dose, in comparison to the control group given only FP. After 2 years of treatment, the mean daily FP dose decreased from 330.3 µg to 151.5 µg in the immunotherapy group while there was no significant reduction in the control group.

In a recent Cochrane review of SCIT, 88 studies on 3459 subjects with asthma were evaluated; there were 42 trials for dust mites, 27 for pollen, 10 for animal dander, two for molds, two for latex, and six for multiple allergens^[19]. It was reported that SCIT improved asthma symptoms, reduced medication use, and diminished BHR. The conclusion of this review was summarized as: "it would require treating three subjects to prevent an exacerbation for one individual, four subjects to improve medication use in one, and four subjects to avoid nonspecific or allergen-specific BHR in one patient, respectively". Additionally, mite and pollen immunotherapy were found more effective on symptom scores.

There are several studies of SCIT (particularly with mites^[20,21] or mixed-allergen up to seven aeroallergens^[22]) which demonstrated the improvement in asthma symptom and medication scores to a lesser degree than the other published studies. Nevertheless, significant steroid-sparing effect of immunotherapy was shown in moderate persistent asthmatics included in those studies. Thus, it should be kept in mind that the maintenance of asthma control is very important before and during the study in order to obtain optimal benefit of the immunotherapy.

CLINICAL EFFICACY OF SLIT IN ASTHMA

World Allergy Organization Position Paper on Sublingual Immunotherapy declared that SLIT is effective in the treatment of allergic rhinitis in adults and in allergic rhinitis and asthma in children^[23]. However, it is also stated the presence of some important points about current status of SLIT effectiveness. It is known that there are significant heterogeneity between studies included in SLIT meta-analyses, and this may bring significant limitation on the conclusion of them.

The first meta-analysis on SLIT in asthma was conducted by Olaguibel *et al.*^[24] and comprised of seven studies in 256 children aged up to 14 years. This study showed marked improvements in symptom scores (SMD: -1.42) and medication requirement scores (SMD: -1.01) related with asthma.

In 2006, a meta-analysis about SLIT in asthma included 25 trials and involved 1706 adults and children^[25]. This meta-analysis reported a significant efficacy of SLIT for symptoms and medication use in seven studies, and improvement in pulmonary function in four studies. But, when asthma symptoms and drug intake were analysed as ongoing parameters, the reductions were not significant.

Penagos *et al.*^[26] evaluated the efficacy of SLIT by conducting a meta-analysis which included nine studies on 441 asthmatic children. Six of these studies were with mites and three of them with pollen. The authors found significant decrease in symptom and medication scores with SLIT in comparison to placebo.

In 2009, Compalati *et al.*^[10] published a meta-analysis which evaluate nine studies in 452 patients treated with SLIT in HDM-allergic asthma. They reported marked improvement in symptom and medication scores related with asthma. As in SCIT, the steroid sparing effect of SLIT was also demonstrated in some recent published studies^[27,28].

In the study of Marogna *et al.*^[28], 84 asthmatics were randomized to four treatment arms for three years: first group received budesonide 800 µg/d; second group received budesonide 1600 µg/d; third group treated with budesonide 400 µg/d plus montelukast 10 µg/d; and fourth group was given budesonide 400 µg/d plus allergoid of betulaceae pre-coseasonally. Low-dose inhaled corticosteroids plus SLIT provided a marked advantage over the other options on symptoms plus medications decrease, FEV1 increase, rescue medications usage, and was comparable to low-dose inhaled corticosteroids plus montelukast on MEF25 and BHR.

Similarly, in a study involving 602 mite allergic asthmatic patients, it was shown that daily treatment with SLIT tablet reduced inhaled budesonide more than 80 µg/d in comparison to placebo after 1 year^[27].

HEAD-TO HEAD STUDIES

There are 4 randomized controlled trials with 171 participants which compare SCIT with SLIT directly in asthmatic patients. All these studies enrolled mite allergic

patients with rhinitis and/or asthma. Efficacy of SIT was investigated by evaluating the clinical outcomes for both rhinitis and asthma.

In the first of these studies, Mungan *et al.*^[29], randomized 36 adults with HDM-allergic rhinitis and asthma to receive SCIT, SLIT or placebo. They found that one-year of SCIT improved symptom scores of both rhinitis and asthma while SLIT had benefit only on symptoms of rhinitis. However, medication scores of both rhinitis and asthma decreased significantly in both actively treated groups. After 1 year of immunotherapy, it was also shown marked rises in specific IgG4 concentrations in comparison to the baseline both in SLIT and SCIT groups.

Eifan *et al.*^[30] evaluated the effectiveness of SCIT and SLIT in children with asthma/rhinitis sensitized to mites. Forty eight children were randomized to treat either SCIT, SLIT or pharmacotherapy. This study demonstrated that both SLIT and SCIT have a significant positive effect on symptoms and medication usage related with both rhinitis and asthma in comparison to the pharmacotherapy group. Additionally, after 1 year of treatment, Der p 1-driven IL-10 significantly increased in SLIT in comparison to pharmacotherapy, whereas Bet v 1-driven TGF-β increased significantly in SLIT only.

In the study of Keles *et al.*^[31], 48 patients (aged 5-10 years) with mild persistent asthma and rhinitis mono-sensitized to mites were randomized to three treatment arms: they received either SLIT ($n = 16$), SCIT ($n = 16$) or pharmacotherapy alone ($n = 16$). After 12-mo of treatment, total asthma symptom scores ($P = 0.02$) and visual analog scores ($P = 0.02$) decreased markedly in SLIT when compared with the pharmacotherapy group. Similarly, SCIT also reduced both total asthma symptom-scores ($P = 0.04$) and visual analog scores ($P = 0.001$) when compared with the pharmacotherapy group. The percentage of improvement was 100% and 93% in SLIT and SCIT group respectively, in comparison to the pharmacotherapy group. A marked increment was seen in the levels of regulatory and Th1 cytokines both in the SCIT and SLIT groups. Antigen-specific IgG4 levels increased in the SCIT and SCIT plus SLIT groups but not in the SLIT group.

In a recent randomized, placebo-controlled and double-dummy study we investigated the effectiveness of SCIT and SLIT in HDM-allergic children with asthma and/or rhinitis^[32]. We showed that one-year SCIT had significant effect on symptom and medication scores related with both rhinitis and asthma. An important observation in this study was the better effect of only SCIT over placebo on reduction of rhinitis and asthma symptoms at the end of one-year-treatment. Bronchial challenge doses and sputum eosinophil increments after bronchial challenge decreased only with SCIT. There was no change in terms of IFN-γ levels in both immunotherapy groups. Serum sIgG4 levels increased significantly only in the SCIT group. This study then carried on one subsequent year in an open scheme and the placebo group was randomized to treat SCIT or SLIT. Thus, all patients

received active treatment with SCIT or SLIT during one subsequent year^[33]. We observed that the effect of SLIT on asthma symptoms and drug intake was less eminent than SCIT in the first year; however this effect was more pronounced in the second year of SLIT. With this study, we concluded that both clinical and immunologic improvement starts earlier with SCIT in comparison to the SLIT in mite-allergic children with rhinitis and asthma.

The summary of these 4 head-to-head studies was shown in Table 1. Recently, a systematic review of studies with head-to-head comparison of SCIT and SLIT in the treatment of allergic rhinoconjunctivitis and asthma was published^[34]. Four trials conducted in patients with rhinitis and/or asthma^[29-32]. This review demonstrated that low-grade evidence confirms more efficacy of SCIT than SLIT regarding reduction of asthma symptoms and combined measure of rhinitis symptoms and drug intake; moderate-grade evidence confirms more efficacy of SCIT than SLIT for nasal and/or eye symptom reduction. It was deduced that low-grade evidence confirms that SCIT is more beneficial than SLIT for reduction in asthma symptoms and moderate-grade evidence for reduction of allergic rhinoconjunctivitis. Further studies are required to support this results for clinical decision making.

SAFETY OF SCIT AND SLIT

It is known that SCIT has a risk for both local and systemic adverse reactions but, in most of the cases, symptoms are reversible if they are diagnosed early and treated rapidly. All allergen preparations (standardized extracts^[35], allergoids^[36] or recombinant allergens^[37]) can cause these side effects.

The incidence of systemic reactions of SCIT varies between 0.06% and 1.01% in those receiving injections^[38].

A recent multicenter study suggested that systemic reactions were slightly more frequent in rhinitis with asthma than rhinitis patients alone^[39]. Some reports have been suggested that asthma may be a risk factor for severe systemic reactions due to SCIT, notably in patients with uncontrolled asthma. Conversely, another retrospective study reported no significant association between systemic reactions and the presence of asthma^[40]. As noted by official documents, the patients's general condition and pulmonary functions should be assessed before injection in order to reduce the risk of anaphylaxis^[41].

The safety of SLIT seems better than subcutaneous therapy regarding severe systemic reactions. Local side effects (oral itching or mild swelling) may be encountered in three-fourths of patients especially in the early phase of SLIT.

In the study of Dahl *et al*^[42] the safety of SLIT investigated specifically in grass pollen allergic patients with asthma. They evaluated side effects which may be related with asthma, *e.g.*, cough, wheezing, and they found no difference in the number of such effects between active and placebo group. Additionally, no asthma exacerbation

related with SLIT was reported in this study.

There are also some recommendations about administering of SLIT in patients with systemic reactions after subcutaneous immunotherapy^[43]. Nonetheless, some patients suffering from these adverse reactions with subcutaneous route may entertain the same risk for sublingual route of immunotherapy^[44]. Thus, our recommendation is that immunotherapy should be customized to each patient on the basis of the degree of sensitization, concomitant allergies, exposures and patient's preference.

PREVENTIVE CAPACITY OF SIT

SIT builds up clinical and immunological tolerance as shown by persistence of improvement both in clinical and immunologic parameters after the cessation of treatment. Additional long-term benefits of SIT include prevention of new sensitizations and progression from rhinitis to asthma.

There are some studies which demonstrated the preventive effect of SIT in pediatric population. At the 10-year follow-up (7 years after cessation of immunotherapy) the children in the immunotherapy group had significantly less asthma in comparison to the control group: 16/64 (25%) with asthma in the immunotherapy group compared with 24/53 (45%) of the untreated control group^[45]. The authors concluded that immunotherapy for 3 years with grass and/or birch allergen extracts provides long-term preventive effect on the development of asthma in children with only seasonal rhinoconjunctivitis.

A similar preventive effect was also shown with SLIT in a 3-year open study of 113 children (aged 5-14 years) having grass pollen rhinitis^[46]. This study demonstrated that asthma development was 3.8 times more frequent in the control subjects.

There is another study which show no significant difference in symptom and medication scores in the subsequent three pollen seasons after 3-4 years of grass-pollen SCIT^[47].

Marogna *et al*^[48] have noted that clinical benefit persists for 8 years after SLIT treatment is given for a 4- to 5-year duration; new sensitizations were also reduced in SLIT group.

It has been documented that SCIT with a single allergen has a preventive effect against sensitization to different inhalant allergens^[49-52]. There are some studies which reported significantly lower rate of the development of new allergen sensitizations in monosensitized patients who received SCIT in comparison to the controls^[49-52]. In these studies, the percentage of the development of new sensitizations were 23%, 24%, 24.7% and 54% in patients treated with SCIT while 68%, 67%, 53.3% and 100% in untreated monosensitized patients.

Recent studies have shown such effects with SLIT^[48,53-55]. In a 3-year open study, 5.9 % of 511 patients with allergic rhinitis and asthma treated with SLIT showed new allergen sensitizations, while this rate was 38% in the control patients^[55].

Table 1 Head-to-head studies which included patients with asthma treated by subcutaneous and sublingual immunotherapy¹

Ref.	Year	Study Design	Age	No of patients	Asthma symptom score				Medication score				Findings
					Before SIT		After SIT		Before SIT		After SIT		
					SCIT	SLIT	SCIT	SLIT	LSCIT	SLIT	SCIT	SLIT	
Mungan <i>et al</i> ^[29]	1999	Single-blind, placebo controlled	Adults	SCIT (n = 10) SLIT (n = 15) Placebo (n = 11)	1.2	0.63	0.59	0.41	6.8	4.93	3.9	1.97	Reduction in symptom scores with only SCIT Reduction in medication scores with both SCIT and SLIT
Eifan <i>et al</i> ^[30]	2010	Open label, randomized, controlled	5-10	SCIT (n = 16) SLIT (n = 16) Pharmacotherapy (n = 16)	0.9 ± 0.7	1.4 ± 1.5	0.4 ± 0.6	0.2 ± 0.4	2.4 ± 1.4	2.8 ± 1.2	1.7 ± 1.4	1.2 ± 0.9	Reduction in symptom and medication scores and visual analog scores with both SCIT and SLIT
Keles <i>et al</i> ^[31]	2011	Open label, randomized, controlled	5-12	SCIT (n = 11) SLIT (n = 13) SCIT plus SLIT (n = 14) Pharmacotherapy (n = 12)	0.25	0.12	0	0	0.52	0.69	0.06	0.23	Reduction in symptom scores and visual analog scores with both SCIT and SLIT
Yukselen <i>et al</i> ^[32]	2012	Randomized, double-blind, double-dummy, placebo-controlled	6-14	SCIT (n = 10) SLIT (n = 11) Placebo (n = 10)	2.4	3.7	1	2.7	2.3	2.3	1	1.7	Only SCIT was found superior to placebo on reduction of symptom and medication scores

¹All studies used HDM immunotherapy. SCIT : Subcutaneous immunotherapy; SLIT: Sublingual immunotherapy; SIT: Specific immunotherapy.

CONCLUSION

SIT is the only therapeutic approach which capable to modify the natural evolution of allergic respiratory diseases. However, there are some shortcomings in trials conducted in patients with allergic asthma. In most of these studies, efficacy of SIT was not evaluated specifically in allergic asthma alone. Additionally, many of these trials had significant limitations such as low number of patients, difference in treatment protocols and doses, inadequate evaluation of pulmonary functions or absence of a placebo group. Moreover, there is a great heterogeneity between studies included in meta-analyses; the most important point in this respect is the assessment of results of SIT with different allergens in the same meta-analysis.

Despite these shortcomings, the clinical efficacy of SIT has been established in allergic asthma in objective and subjective parameters such as titrated skin tests, allergen-specific bronchial hyperreactivity, and symptom and medications scores.

Steroid sparing effect of SIT gives an important advantage for patients who have to use these drugs in high doses in order to control their asthma symptoms for many years.

SIT should be considered in asthmatic patients who experience side effects of medications, to reduce or avoid long-term pharmacotherapy and the economic burden of medications and in the presence of allergic rhinitis and/or other comorbid allergic conditions^[41].

Official documents recommend that SIT should not be started in patients with unstable asthma; in these cases, SIT can be initiated after well asthma control with appropriate pharmacotherapy.

Although both SCIT and SLIT have been reported to be effective on allergic asthma, the results of some studies or meta-analyses suggested that the efficacy of SCIT may be better and start earlier than SLIT.

Further studies are needed to discover patients who will benefit more from immunotherapy, novel vaccines and new routes of administration to increase efficacy and safety.

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