

Sublingual Immunotherapy: Other Indications

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KEYWORDS

- Sublingual immunotherapy • Atopic dermatitis • Food allergy
- Latex allergy • Hymenoptera venom

Subcutaneous immunotherapy (SCIT) has been the only available and accepted route of administration for several decades. It still represents the standard immunotherapy route for the treatment of respiratory allergy and hymenoptera venom hypersensitivity. SCIT is effective and safe when properly prescribed and administered, although there is a potential risk of severe side effects, such as life-threatening anaphylaxis. The SCIT risk/benefit ratio has prompted the search for safer administration routes such as nasal, bronchial, oral, and sublingual.¹ Among those noninjection routes, sublingual immunotherapy (SLIT) is the most recent, but it was immediately recognized as a promising approach. In less than 20 years, an impressive amount of clinical data has conferred credibility to SLIT, such that it was introduced in the literature as a viable alternative to the standard SCIT.^{2,3} To date, SLIT is commercialized and routinely used in almost all European countries and in many other parts of the world. However, in the United States, no SLIT product has been approved by the Food and Drug Administration for clinical use to date, although several large studies are ongoing.

THE RATIONALE FOR EXPANDING THE INDICATIONS

During the last 20 years, more than 60 randomized clinical trials of SLIT in respiratory allergy have been published.⁴ Despite considerable design heterogeneity, the clinical results in these studies were generally favorable, confirming the efficacy of SLIT. This efficacy is further supported by several meta-analyses performed in rhinitis only,^{5–7} asthma only,⁸ and asthma and rhinitis in children.^{9,10} The other relevant aspect of SLIT is the favorable safety profile, which seems to be superior to that of SCIT.^{4,11} Mild local side effects (oral itching/swelling, altered taste perception, itching of the

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tongue, nausea) account for most of the adverse events associated with SLIT. In most cases, these side effects are usually self-limiting and require no medical intervention. In the published literature, there have been no reported fatalities associated with SLIT in more than 20 years, although 6 cases of SLIT-associated anaphylactic reactions have been described.⁴ The tolerability of SLIT is good even in children less than the 5 years of age.^{12–14} SLIT also exerts a systemic immunologic effect that seems to be similar to that of SCIT; a reduction in symptoms or reactivity on organ-provocation challenge has been shown in multiple organ systems, such as the nose, eye, and bronchi.^{15,16} Recent studies suggest that the mechanisms of action of SLIT are similar to those of SCIT, involving the Th1/Th2 balance and the activation of T regulatory cells.^{17–22}

Safety, systemic effects, and immunologic mechanisms represent the main rationale for exploring the use of SLIT in allergic disease other than respiratory allergy. The clinical effect of specific immunotherapy in allergic diseases is expected to correlate with the immunoglobulin E (IgE)–mediated component of the disease (as in food allergy or hymenoptera venom allergy; **Fig. 1**).

SLIT IN FOOD ALLERGY

IgE-mediated food allergy reactions (eg, nut anaphylaxis), for which dietary avoidance is the standard treatment, represents an target for specific allergen immunotherapy. In the past, attempts to vaccinate peanut-allergic patients subcutaneously have been made. In a preliminary study investigating the efficacy of SCIT with an aqueous extract of peanut, there was a reduction of symptoms during oral challenge, which ranged from 60% to 100%.²³ In a subsequent study of 12 peanut-allergic subjects, the clinical benefits of peanut SCIT were found to be incomplete, and the treatment induced an unacceptably high rate of systemic reactions.²⁴ For this reasons, the SCIT approach was virtually abandoned.

Enrique and colleagues²⁵ performed a randomized, double-blind, placebo-controlled trial with SLIT in 23 hazelnut-allergic subjects, evaluating the oral threshold dose before and after treatment, which was administered in a 4-day rush buildup. A significant increase of the oral threshold dose was seen only in the active group, paralleled by an increase in hazelnut-specific immunoglobulin G4 (IgG4). The rate of systemic reactions was 0.2% of administered doses. A similar study was conducted in 49 peach-allergic subjects, with a purified extract standardized for Pru p 3 content.²⁶ In this study, a significant increase in the oral challenge threshold dose was seen, along with a reduction of the skin test response to the Pru p 3 extract. There were 16 systemic reactions in more than 1500 adverse events, all mild and spontaneously resolving. Other studies have been performed with a peanut extract. In these

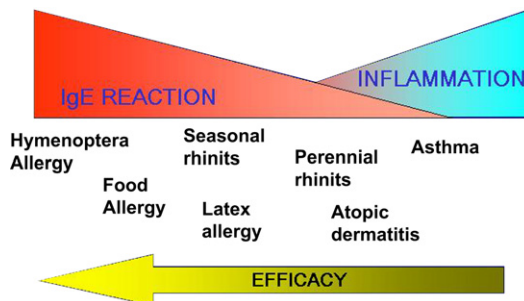


Fig. 1. Where immunotherapy works in allergic diseases.

studies, the treatment was administered orally and not sublingually. The results were similar to those reported with peach or hazelnut SLIT, with a significant reduction of the threshold provocative dose and an increase of specific IgG4.²⁷ Follow-up of the patients during the home maintenance dose phase confirmed the clinical efficacy and safety profile of this treatment.²⁸ Blumchen and colleagues²⁹ treated 23 children with severe peanut allergy by a rush protocol and found that, after 7 to 8 months of maintenance, more than 50% of patients had reached clinical protection. At the end of the study, the oral provocation dose at the food challenge had increased tenfold compared with baseline. Mild to moderate side effects were observed in 2.6% of doses and the treatment was discontinued in 4/22 patients because of adverse events. In this study there was also a significant increase in peanut-specific serum IgG4 and a decrease interleukin (IL)-5 and IL-4 production.

SLIT IN HYMENOPTERA VENOM ALLERGY

Specific immunotherapy with hymenoptera venom (venom immunotherapy [VIT]) is the cornerstone of the management of hymenoptera venom allergy, and results in an almost complete protection against severe allergic reactions from stings in the most patients. Although no fatal events have been described with VIT, its potential risks require administration in a medical facility with appropriate staff and resuscitation/emergency equipment. A safer route of immunotherapy, which allows for home administration, may increase the convenience, and possibly the adherence, to this highly effective, protective treatment. Because of its excellent safety profile, SLIT was considered a potential candidate for VIT. To date, there has been a single randomized controlled trial with honeybee venom (maintenance dose 525 µg/month) conducted in 30 subjects with a history of large local reactions only. The diameter of the local reaction was assessed before and after 6 months of SLIT by means of a sting challenge.³⁰ In the active group, the median of the peak large local reaction maximum diameter significantly decreased, from 20.5 to 8.5 cm ($P = .014$), whereas no change was seen in the placebo group. The diameter was reduced by more than 50% in 57% of patients. A similar clinical effect (reduction of local reactions) has also been shown for SCIT.³¹ Although appealing, this was only a proof-of-concept study, and SLIT cannot yet be recommended for the treatment of hymenoptera venom allergy.^{32,33}

SLIT IN LATEX ALLERGY

Although its incidence has been decreasing with time, latex allergy remains an important clinical problem, probably because it is often an occupational disease. In these cases, total latex avoidance may only be achieved by changing the occupation. However, specific immunotherapy is expected to reduce or prevent symptoms when individuals are exposed to the offending allergen. Several attempts to vaccinate against latex have been made with SCIT. Three randomized trials investigating the efficacy and safety of latex SCIT have been conducted.^{34–36} The first, which included 20 patients, showed a significant reduction in symptom scores and medication usage along with an increase in the latex conjunctival provocative dose. Nonetheless, all patients displayed local reactions after injections and 50% also experienced systemic reactions. In the second trial, which included 24 patients, there was no change in symptom scores, and systemic reaction (including severe reactions) occurred in 67% of patients. In the third trial, no clinical effect could be shown, but the rate of systemic reactions was reported to be as high as 50% of patients. Based on these results, the subcutaneous approach for latex allergy was abandoned.

There have been at least 5 clinical trials with SLIT for latex allergy.^{37–41} The trials had different experimental designs and durations (**Table 1**), but all were in agreement in showing significant clinical efficacy in the measured parameters. Four of the trials used a 5-day rush buildup regimen. Unlike the latex SCIT studies, all of these latex SLIT trials showed good safety profiles. In 2 trials no side effect was reported,^{37,40} 1 trial reported only local side effects in 11% of patients,³⁹ and the remaining trial reported that 10% of the reactions (local) were reported as requiring a medical intervention.³⁸

A new ultrarush protocol has recently been described.⁴¹ It lasted only 3 days and therefore can be administered under medical supervision in a convenient way for patients. In this ultrarush trial of 21 patients, which only evaluated safety, there was 1 local reaction (8%) in the active group and 3 (33%) nonspecific reactions in the placebo group.

The case reports of SLIT anaphylaxis were reported with a latex extract during the rush buildup phase.⁴² This suggests that, if used, SLIT for latex should be administered under direct medical supervision during the induction phase.

In the pediatric SLIT latex trial, children who received active treatment⁴⁰ subsequently received latex SLIT for a further 2 years.⁴³ In those children, the glove test became completely negative at the third year of treatment, suggesting that a sufficiently prolonged SLIT can virtually abrogate the specific reactivity.

SLIT FOR ATOPIC DERMATITIS

Atopic dermatitis (AD) may be easy to diagnose from a clinical point of view, but it still represents a mystery from the pathogenic and immunologic points of view.⁴⁴ The prevalence of atopy in AD is largely variable and the reported prevalence may differ between population-based and physician-based studies.⁴⁵ Nevertheless, it is generally agreed that there may be a link between some forms of AD and allergic sensitization (eg, dust mite or foods). Based on these clinical consideration, it was hypothesized that specific immunotherapy could beneficially affect the disease by acting on the allergic component. The first trial of SCIT in AD was published about 20 years ago⁴⁶ and, despite the equivocal results, stimulated new research in this field. Several trials of SCIT in AD have been conducted, most have used with house dust mite extracts (for review see Refs.^{47,48}), and many of them reported a measurable and significant improvement of cutaneous symptoms after immunotherapy.^{49,50}

Table 1 SLIT for latex allergy: controlled studies				
Author	Patients	Build	Duration	Results
Patriarca et al, ³⁷ 1999	12+12	4d rush	6 mo	All active tolerated the glove. No side effects
Cistero et al, ³⁸ 2001	26	4d rush	3 mo	Improvement in glove test, 21% side effects, 10% needing treatment
Nettis et al, ³⁹ 2006	18+17	4d rush	1 y	Improvement in glove test, symptoms, and medication, 11 % local reactions
Bernardini et al, ⁴⁰ 2006	12+8 children	4d rush	1 y	Improvement in glove test and symptoms. No side effects

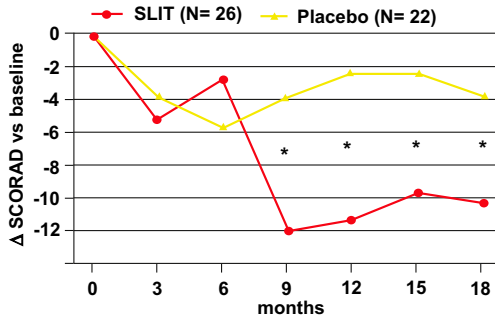


Fig. 2. Reduction in SCORAD versus baseline in children with AD treated for 18 months with mite SLIT. (From Pajno GB, Caminiti L, Vita D, et al. Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: a randomized, double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2007;120:167; with permission.)

Some trials in AD were also performed with SLIT.^{51–53} Mastrandrea and colleagues⁵² evaluated the efficacy of SLIT in an open, prospective, uncontrolled study of 53 patients with AD only or AD plus respiratory allergy, and found that, after 2 years, about 70% of subjects had a complete disappearance of cutaneous lesions. Another open, noncontrolled, nonrandomized pilot trial investigated the efficacy of dust mite SLIT in 86 patients with AD.⁵¹ After 1 year of treatment, there was a mean reduction in Scoring Atopic Dermatitis (SCORAD) score of about 50%, and that only 6% of patients had no change. These results are of interest, but the open, uncontrolled design strongly limits their validity. However, there has been a single randomized, double-blind, placebo-controlled trial that investigated the efficacy of SLIT in AD.⁵³ Fifty-six children with AD, monosensitized to mite and without asthma or food allergy, were randomized to receive dust mite SLIT or placebo for 18 months. Starting from the ninth month of treatment, a clear-cut decrease in the SCORAD was observed in the active group, and this improvement was maintained until the end of the study (Fig. 2). Nonetheless, a subanalysis showed that the clinical improvement was limited to the mild and moderate patients, whereas, in the more severe subjects, the improvement was only marginal.

SUMMARY

SLIT represents a significant advance because of its efficacy, safety, and convenience, and it seems particularly suitable in pediatric patients, for whom an optimal safety profile is required.⁵⁴ The clinical efficacy and safety in respiratory allergy, along with the systemic immunologic effect, suggest that SLIT can be used in other allergic conditions.⁵⁵ There are favorable results for food allergy in controlled trials. Nonetheless, many aspects of food allergy need to be clarified, such as the optimal induction regimen, the maintenance dose, and the duration. The investigators who researched peanut desensitization caution that the treatment is still not ready for clinical use.⁵⁶ For latex allergy, the results of several controlled trials are encouraging. Latex allergy is not considered an indication to SLIT in the World Allergy Organization position paper on sublingual immunotherapy.⁴ Nonetheless, commercial, standardized extracts are available and may be considered, providing they are administered in the appropriate medical setting to selected patients with occupational allergy who cannot avoid latex.⁵⁷ For AD, previous experience with SCIT and the results of a few trials suggest the possible application of SLIT. Demonstrated efficacy with SLIT in AD suggests

limiting it to children with mild to moderate forms and ascertained sensitization to dust mite, but this recommendation is not considered to be sufficiently evidence based. In hymenoptera allergy, the only trial available is a proof-of-concept study in the treatment of large local reactions that needs to be confirmed in well-controlled studies.

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