
Update on sublingual immunotherapy

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Objective: To obtain a current understanding of the mechanisms, clinical indications, efficacy, and safety of sublingual immunotherapy (SLIT) for the treatment of children and adults with allergic rhinitis, asthma, and allergic conjunctivitis.

Methods: A MEDLINE and *Index Medicus* search for peer-reviewed articles on SLIT was performed.

Results: Since the approval of SLIT by the World Health Organization in 1988, the efficacy and safety of SLIT have been confirmed in several new double-blind, placebo-controlled studies for monosensitized patients who are allergic to house dust mites, grass pollens, ragweed, and birch pollen. Documented immunologic responses to SLIT have included a decrease in serum eosinophilic cationic protein and interleukin 13 (IL-13) levels, an elevation in IL-12 levels, a reduction in late-phase responses, and increases in IgG4/IgE ratios. A Cochrane review of 22 studies confirmed the efficacy and safety of SLIT for patients with allergic rhinitis. A long-term asthma study showed sustained efficacy 5 years after discontinuing the vaccine. The safety of SLIT has been confirmed in postmarketing studies, and severe systemic adverse effects have never been reported. In view of its safety profile, SLIT is taken by the patient at home (away from specialized centers), and no specialized resuscitation facilities are required.

Conclusion: SLIT is a safe and effective therapeutic option for patients with allergic rhinitis and asthma. Because of its efficacy, safety, and ease of administration, it has been accepted in Europe, Southern Africa, Australasia, Southeast Asia, and the Middle East as a promising therapeutic option that can significantly alter the natural history of allergic disease without the risks of injection immunotherapy.

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INTRODUCTION

Since sublingual immunotherapy (SLIT) was approved by the World Health Organization and the European Association of Allergy and Clinical Immunology in 1998,^{1,2} worldwide interest in the use of this treatment for allergic patients has surged because of its effectiveness, safety, and applicability beyond specialized centers. The oral route for administration of allergen immunotherapy has been explored since the 1900s. With the oral route, the allergen is swallowed immediately. Although some studies³ confirmed statistically significant improvement of symptoms with oral therapy, gastrointestinal adverse effects, although not life threatening, resulted in the abandonment of this form of therapy.

SLIT, by contrast, involves the daily administration of incremental amounts of a purified allergen, which is held under the tongue for 2 minutes and then swallowed. A maintenance dose is achieved in approximately 4 weeks. The allergen may be administered as drops, oral spray, or a more convenient rapidly dissolving tablet. The maintenance dose is continued on alternate days for 3 to 4 years. Efficacy and safety have been well substantiated in recent reviews.^{4,5} This review aims to obtain a current understanding of the mechanisms, clinical indications, efficacy, and safety of SLIT for the treatment of children and adults with allergic rhinitis, asthma, and allergic conjunctivitis. A MEDLINE and *Index*

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MECHANISMS OF TOLERANCE INDUCED BY SLIT

Although the efficacy of SLIT is proven, much needs to be learned about the immunologic mechanisms that cause tolerance or unresponsiveness to allergens during SLIT. Clinical observations and recent studies suggest that the long-lasting tolerance achieved in 3 to 4 years appears to be occurring in several phases, which may be invoking different immunologic mechanisms, either simultaneously or sequentially, and may possibly be related to dosing. The cumulative doses of allergen, given in micrograms in SLIT, are up to 375 times greater than the total doses given during subcutaneous immunotherapy (SIT).

An early phase of oral tolerance is observed within weeks of initiating SLIT. Patients who initially react to the sublingual drops with oral itching report that the itching goes away within a few weeks, and increasing oral doses are tolerated, without local clinical effects, before any relief of nasal or asthma symptoms or reduction in concomitant medicines for allergy relief is observed.

The next phase is an intermediate phase of short-lived tolerance. This phase was typically observed in patients who received preseasonal SLIT for pollen-induced allergic rhinitis. Within 3 months of initiating SLIT, a reduction in clinical symptoms is observed. A similar fairly rapid acquisition of significant protection and tolerance to latex allergens has been reported⁶ within 3 months of SLIT. There is no evidence that the clinical tolerance induced within such a short period is long lasting if the vaccine is not continued. A later phase of

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long-lasting tolerance is achieved after 2 to 4 years of SLIT, typically in patients with persistent (perennial) nasal allergies, but also for patients with asthma.⁷

There are no published sequential long-term studies that provide information on what is occurring immunologically during these phases of tolerance induction by SLIT. Cross-sectional studies, however, provide strong evidence of the induction of significant changes in immunoglobulins, cytokines, mediators, cell populations, and surface markers during SLIT.

In the early phase, a decrease in serum eosinophilic cationic protein and interleukin 13 (IL-13) levels has been reported by Ippoliti et al.⁸ By 6 months, in children treated with SLIT for asthma, elevated phytohemagglutinin-stimulated IL-12 and *Dermatophagoides pteronyssinus*-stimulated interferon- γ is released by the peripheral mononuclear cells compared with controls.⁹

Studies at 12 months have shown a reduction in nasal specific IgE and tryptase levels and an attenuation of the expected increase in eosinophilic cationic protein levels following nasal challenge.¹⁰ After 18 months, significant reductions ($P < .003$) in late-phase skin prick test responses and increases in IgG4/IgE ratios ($P = .05$) were reported by Lima et al.¹¹ Although these studies by Lima et al show that the changes of the measured immune responses were similar to but weaker than those achieved during SIT, it is possible that use of the mucosal route by SLIT may invoke additional more powerful mechanisms of immunosuppression involving T-regulatory cells, transforming growth factor β , and IL-10. These have not yet been studied.

Traditionally it is believed that SIT induces a shift from T_H2 - to T_H1 -type response in T cells, particularly in the target organ. It is possible that SLIT also induces a different type of mucosal tolerating immune response, which regulates and counteracts but does not necessarily switch off existing allergic (or T_H2) responses.¹²

The pharmacokinetics of SLIT have been investigated by Bagnusco et al¹³ using iodine 123-radiolabeled purified *Parietaria* allergen (Par j 1) and sequential scintiscans, plasma radio activity, and plasma chromatographs. The investigators found that allergen was retained up to 40 hours in the oral mucosa and that native allergen could not be detected in the blood stream after swallowing. Oral dendritic cells and retained allergen and Fc ϵ receptor bearing cells in the oral mucosa of allergic patients may be important in the induction of tolerance during SLIT.

CLINICAL INDICATIONS AND EFFICACY

SLIT has been shown to be effective and safe for adults and children with allergic rhinoconjunctivitis sensitive to grass pollen, birch pollen, *Parietaria*, ragweed, and mite. The results of 23 randomized SLIT trials were recently summarized by Passalacqua et al,¹⁴ and a Cochrane meta-analysis of 22 of the studies that involved 970 patients has confirmed that SLIT is effective in reducing both the symptoms of allergic rhinitis and allergy medication.¹⁵ SLIT is also effective for

the treatment of mild to moderate asthma in patients who are monosensitive,^{7,9} particularly in children. In a study by Pajno et al¹⁶ of 24 patients with mild to moderate asthma who were monosensitized to house dust mite vaccine or placebo for 2 years, a significant reduction in asthma symptoms ($P = .0001$) and asthma medication ($P = .0001$) in the actively treated group occurred, although only in the second year of treatment. By contrast, significant improvements in asthma symptoms and reductions in inhaled corticosteroid use and β_2 -mimetic use were seen as early as 6 months in patients with house dust mite SLIT in the study by Arikan et al.⁹

When assessing efficacy of a new therapy such as SLIT, it is important to compare the magnitude of the clinical improvement with SIT. Although some studies have suggested that the magnitude of clinical improvement may be less than SIT, a recent randomized, placebo-controlled, double-dummy study that compared subcutaneous with sublingual birch pollen immunotherapy during a 3-year period found that SLIT diminished the median disease severity to half and SLIT to one third of placebo treatment. No statistically significant difference between SIT and SLIT was observed. SLIT may be favored because of its safety profile, because although only local adverse effects were noted in the SLIT group, SIT resulted in a few serious systemic adverse effects.¹⁷ This small study involved 58 patients, and larger comparative studies would be important.

In another smaller comparative study by Mungan et al¹⁸ of 36 patients (12 receiving SLIT, 12 receiving SIT, and 12 receiving placebo), patients benefited significantly from SIT and SLIT for medication and symptoms. In this study the decrease in skin prick test wheal size was observed in the subcutaneously treated group in whom asthma scores also improved, but not in the sublingual group. It is clear that larger and longer comparative studies should be conducted. In addition to SLIT resulting in clinically meaningful efficacy in patients with rhinitis and asthma, efficacy has also been recently demonstrated in 60 adults with severe house dust mite-sensitive perennial allergic conjunctivitis. This was demonstrated by a significant increase in the antigen concentration required to obtain a positive conjunctival challenge test result with house dust mite allergen after 18 months of SLIT.¹⁹

Recently, some exploratory studies have investigated the efficacy of SLIT for latex and fruit (oral) allergy. A small study of 24 patients by Patriarca et al⁶ provides evidence that within 3 months the 12 patients who underwent desensitization via the sublingual route showed significant improvement in symptom scores and could tolerate latex exposure, wear latex surgical gloves, and undergo gloved medical procedures without any symptoms. In another study by Mempel et al,²⁰ successful sublingual desensitization was demonstrated in a patient with severe anaphylaxis to kiwi fruit.

SAFETY

The excellent safety record of SLIT during the past 10 years has resulted in this form of immunotherapy becoming ac-

cepted and used in specialized centers and a preferred therapy beyond specialized centers worldwide. SLIT is currently a therapeutic option in Europe, South America, Southeast Asia (eg, Malaysia), Southern Africa, and Australasia. Although thousands of patients have received SLIT, a serious systemic adverse effect has never been reported. Adverse effects that have been reported in patients receiving SLIT, from numerous published studies, fall into the following 8 groups: lip, mouth, and tongue irritation; eye itching and ocular symptoms; gastrointestinal symptoms; rhinitis; asthma; urticaria; angioedema; and other (nonspecific).

The safety of swallow SLIT was investigated by Andre et al.²¹ Eight double-blind, placebo-controlled studies performed in France, Italy, and Greece that involved 690 patients who were receiving the Stallergene SLIT vaccines were reviewed. In these studies, only mild adverse events were found, and they occurred in both placebo and actively treated groups in both children and adults. Unusual events mainly involved the buccal cavity (61 in the SLIT group and 13 in the placebo group) and the gastrointestinal tract (47 in the SLIT group and 15 in the placebo group). Interestingly, wheezing, however, was more frequent in placebo-treated patients. In most cases the reported adverse effect only occurred once. Analysis of the patients who dropped out of the studies revealed that the main causes were buccal phenomena and abdominal pain.

In another postmarketing survey by Di Rienzo et al,²² 268 children aged 2 to 15 years who received the ALK-Abello vaccines were studied. SLIT had been administered between 3 months and 7 years (mean, 36 months) and involved 96,000 doses of the extracts. Overall adverse effects occurred in 3%, and these were mild (oral itching) and occurred early in the treatment. Systemic reactions occurred in 1 in 12,000 doses.

Seven systemic adverse effects occurred. These effects included abdominal pain, conjunctival itching, and rhinitis. None of these required specific treatment. One case of urticaria that required antihistamine treatment was reported. Rhinitis as an adverse effect always occurred within 30 minutes of vaccine administration, and all the others occurred after 30 minutes. The outcome of SLIT was judged to be excellent or good by 80% of the patients. In the review of 22 SLIT studies by Wilson et al,¹⁵ no serious adverse effects were found.

Although SLIT has been found to be extremely safe, to our knowledge no studies of SLIT in severe asthmatic patients have been performed. We therefore recommend that asthma be optimally controlled pharmacologically before commencing SLIT. SLIT is thus given as a combination therapy with the usual asthma medications to modify the natural history of the disease, reducing asthma medications and affecting a cure.

PATIENT SELECTION: MONITORING AND FOLLOW-UP

It is essential that before commencing SLIT proper and intelligent allergy tests (radioallergosorbent tests and/or skin prick tests) are conducted to confirm specific sensitivity.

SLIT is indicated for patients with monosensitive rhinitis and/or mild to moderate asthma due to dust mites, grass pollens, weed pollens, or tree pollens. Patients who have other immune diseases (immunodeficiency or autoimmunity), severe asthma, or other serious medical conditions should not receive SLIT. Pregnancy is not a contraindication to continuing immunotherapy once it has been initiated.

Patients should ideally maintain telephone contact with their medical practitioners, particularly in the first month of SLIT, since the treatment is given at home. Baseline symptoms and allergy and asthma medications should be carefully recorded in the patient's clinical notes and reviewed at 1 month and then 3-month intervals. A diary card is useful to document adverse effects and reduction in medication requirements.

It is also informative to record quality-of-life issues at the 3- to 6-month follow-up visits to encourage adherence to medication. Long-term follow-up studies⁷ have shown that in 60 house dust mite-sensitive asthmatic children significant improvements in asthma symptoms ($P < .001$) and the use of asthma medications ($P < .01$) is sustained even 5 years after discontinuation of the SLIT vaccine. Furthermore, in a recent real-life setting study of 500 patients with rhinitis and/or mild intermittent asthma²³ randomized to receive SLIT or pharmacologic treatment, adherence was found to be more than 80% in 72% of the patients, more than 60% in 18%, and less than 60% in 10%. Interestingly, the rate of occurrence of new sensitizations was 5.8% in the active group and 38% in the control group ($P = .001$).

SLIT is an effective and safe therapeutic option for the treatment of allergic patients. It does not require specialized facilities. It is able to modify the natural history of the disease,⁷ unlike pharmacotherapy, and should be recommended as a therapeutic option in monosensitized allergic patients whenever indicated. However, SLIT should be evaluated by larger and longer multicenter studies, in the future, in view of its potential to benefit allergic patients worldwide.

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