Will this soon be an option for some of your patients?

Sublingual immunotherapy, part 1: Review of clinical efficacy

ABSTRACT: Subcutaneous allergen immunotherapy is clearly beneficial in the treatment of select patients with allergic rhinitis or asthma. However, this therapy is underused, partly because it requires administration in a medical facility. Sublingual immunotherapy (SLIT) may be a promising alternative; it appears to be associated with fewer adverse effects, which suggests that it might be administered at home. Currently, there is no FDA-approved formulation for SLIT in the United States. However, allergists are showing increased interest in this therapy, and an approved formulation may be available in the near future. A number of studies have shown the clinical efficacy of SLIT, but many questions remain unanswered, including the effective dose, optimal treatment schedules, and overall duration of treatment. (*J Respir Dis.* 2007;28(4):162-168)

KEY WORDS: Immunotherapy, Allergy, Allergic rhinitis

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Specific allergen immunotherapy is currently the only treatment intervention that can potentially modify allergic disease. Multiple controlled studies have demonstrated its efficacy in the treatment of allergic asthma, allergic rhinitis, and Hymenoptera venom hypersensitivity. Subcutaneous immunotherapy (SCIT) is the predominant form of allergen immunotherapy in the United States. Despite its clear benefits, only a minority of allergic patients receive this treatment.

SCIT does carry a risk of systemic allergic reactions. Most of these reactions are mild, but because severe reactions can occur, it is recommended that SCIT be administered in a medical facility with at least a 30-minute wait period in the facility after the injection. The inconvenience caused by the travel time and the recommended wait period is probably why this treatment is underused and is one of the most frequent reasons for discontinuing treatment.

Sublingual immunotherapy (SLIT) is a form of allergen immunotherapy that involves administration of the allergen under the tongue. It appears to be associated with fewer serious adverse effects than SCIT, which would allow for home administration.

SLIT is currently under investigation in the United States, and an FDA-approved formulation may be available in the near future. At present, there is no *Current Procedural Terminology* code for SLIT. Without an FDA-approved formulation, most insurers would consider it "off-label" and would not provide reimbursement for SLIT.

In this article, I will review the evidence concerning the effectiveness of SLIT. In a subsequent article, to be published in *The Journal of Respiratory Diseases*, I will review the data on safety and discuss practical considerations concerning the use of this form of therapy.

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Background
Allergen immunotherapy is one of the oldest immunomodulatory treatments, with the earliest investigations and clinical “trials” dating back more than 100 years. The earliest successful allergen immunotherapy was reported in the early 1900s by 2 English physicians, Noon and Freeman. In 1911, Noon reported on his work with subcutaneous immunization using a distilled aqueous extract of Timothy grass pollen in patients with hay fever.

Shortly after successful treatment of grass pollen allergy with a conventional weekly immunotherapy build-up schedule, Noon and Freeman began using accelerated schedules. Freeman concluded that the advantages of the accelerated method were the saving of time, convenience, and patient compliance. However, he also reported what probably was the first systemic reaction to allergen immunotherapy (urticaria and a fluttering heart in a 7-year-old girl).

Investigations of alternative (noninjective) routes of immunotherapy, such as nasal, bronchial, and sublingual routes, began not long after Freeman’s and Noon’s first successful reports of SCIT. These investigations were driven by an interest in finding safer routes of allergen immunotherapy.

The first double-blind placebo-controlled study of SLIT was reported in 1986. Patients with allergic rhinitis (associated with dust mites) were treated with low-dose SLIT or placebo for a relatively short duration. A significant improvement was seen in morning peak nasal inspiratory flow rate in the SLIT group.

In the ensuing 20 years, the number of published SLIT studies steadily increased. MEDLINE, EMBASE, and BIOSIS had 21 SLIT citations in English in 1999 and 58 in 2004. From 1999 to 2006, there were 273. In the past 20 years, SLIT has been used with increasing frequency in Europe. In Italy and France, for example, 80% of the new allergen immunotherapy prescriptions were for SLIT.

Currently, there is no FDA-approved formulation for SLIT in the United States. However, allergists are showing increased interest in SLIT; several studies are under way, and an approved formulation may be available in the near future. Recognizing the interest in this novel form of treatment, the American College of Allergy, Asthma, and Immunology and the American Academy of Allergy, Asthma, and Immunology formed a task force to provide a comprehensive updated report on SLIT for the North American allergy community.

Indications for allergen immunotherapy
Allergen immunotherapy (SCIT or SLIT) is indicated for the treatment of allergic rhinitis, rhinoconjunctivitis, asthma, and insect sting hypersensitivity in persons whose allergy skin tests or laboratory tests yield positive results for clinically relevant allergens. The decision to begin allergen immunotherapy depends on the degree to which the patient’s symptoms can be controlled by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications (Table).

There is some evidence that allergen immunotherapy may prevent the development of new allergies and the progression from allergic rhinitis to asthma, which would lend some weight to earlier consideration of allergen immunotherapy in the treatment algorithm for patients with allergies.

Patients with poorly controlled asthma or other medical conditions that would reduce their ability to survive an immunotherapy reaction or the resultant treatment (epinephrine) are not candidates for allergen immunotherapy.

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Table – Clinical indications for allergen immunotherapy

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<thead>
<tr>
<th>Indications for patients with allergic rhinitis and/or allergic conjunctivitis</th>
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<tr>
<td>Allergy symptoms after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE (positive allergy skin test and/or allergy blood test), and 1 of the following:</td>
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<tr>
<td>• Poor response to pharmacotherapy and/or allergen avoidance.</td>
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<td>• Unacceptable adverse effects of medications.</td>
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<td>• Wish to reduce or avoid long-term pharmacotherapy and the cost of medication.</td>
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<tr>
<td>• Coexisting allergic rhinitis and asthma.</td>
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<td>• Possible prevention of asthma in patients with allergic rhinitis.</td>
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Additional considerations for sublingual immunotherapy
Increased safety may allow:
• Use in young children. Current practice parameters recommend careful consideration in prescribing subcutaneous immunotherapy for children younger than 5 years for the following reasons: difficulty in cooperating with an immunotherapy program and in communicating symptoms of an adverse reaction to immunotherapy.
• Use in patients who had to discontinue subcutaneous immunotherapy because of an adverse reaction. No studies have been done in this population.
• Administration at home. This may be useful in patients who have difficulty in complying with the office-based immunotherapy protocol.

Adapted from J Allergy Clin Immunol. In press. [19]
immunotherapy. Immunotherapy practice parameters generally caution against prescribing SCIT for inhaled allergens in children younger than 5 years because they may have difficulty in cooperating with an immunotherapy program, particularly in communicating symptoms of an adverse reaction, which in rare cases can be severe and life-threatening, especially if there is a delay in treatment. Another reason for caution in prescribing SCIT for young children is injections can be traumatic to very young children.

However, the above-mentioned evidence that allergen immunotherapy in children may prevent the progression to asthma or the development of new allergen sensitivities is a compelling argument for earlier use of allergen immunotherapy in children. In addition, SLIT, because of its greater safety, may be a viable option for the younger child, since early intervention with allergen immunotherapy may prevent the progression of allergic disease.

Methods of allergen delivery
SLIT can be delivered by 2 methods. With the sublingual-spit method, the vaccine is kept under the tongue for a short period and then spit out. With the sublingual-swallow method, the vaccine is kept under the tongue for 1 to 2 minutes and then swallowed. Most studies have used the sublingual-swallow method.

In a study of the pharmacokinetics of SLIT, the major allergen of *Parietaria judaica* (Par j 1) was radiolabeled with iodine 123 and administered to healthy persons who were instructed to keep it under their tongue for 30 minutes and then swallow and rinse. Plasma radioactivity and dynamic scintigraphy were measured over time. The plasma radioactivity began to increase only after swallowing. The labeled allergen rapidly degraded and was absorbed in the GI tract after swallowing.

Plasma radioactivity peaked at about 1.5 to 3 hours and was mostly represented by free radioidine and small radiolabeled peptides. Local persistence of a small amount (about 2%) of radioactivity was demonstrated up to 20 hours after the dose was administered.

In another study, radiolabeled Par j 1 was administered to healthy persons who were instructed either to keep it under their tongue for 3 minutes and then spit it into a container or to keep it under their tongue for 20 minutes and then swallow. The plasma radioactivity began to increase only after swallowing and did not differ between the 2 methods, except that about 30% of the dose was recovered with the sublingual-spit method.

The authors concluded that contact with the oral mucosa was crucial and that the sublingual-swallow method was the more appropriate way to administer the allergen because the sublingual-spit method led to a loss of allergens. These studies suggest that there is virtually no systemic absorption of the allergen through the oral mucosa with SLIT.

Allergen dosing
The effectiveness of SCIT appears to depend on the allergen dose, which ranges from 5 to 20 μg of major allergens. One method of comparing dosing expresses the content in mass units of 1 or more major allergens in the extract. Although the use of extracts with potency expressed in units ensures consistency in the product, it is difficult to determine the absolute potency of such preparations.

Since subcutaneous maintenance doses are commonly given once a month and sublingual maintenance doses are given more often, SCIT and SLIT dosing can be compared per single dose and per cumulative monthly dose (CMD). The SLIT CMDs have ranged from 0.017 to more than 500 times the recommended subcutaneous maintenance dose.

Several SLIT studies designed to compare the response to different allergen doses demonstrated a dose-response effect. However, comparisons between the effective doses failed to demonstrate a consistent pattern; a CMD of 450 μg of major grass pollen allergen was effective in one study, whereas 2054 μg of major ragweed allergen was not effective in another study.

The optimal maintenance dosing frequency of SLIT has not been established. The frequency of maintenance doses in the SLIT studies published to date are as follows: once a week, twice a week, every other day, 3 times a week, 5 times a week, daily, and twice a day. Very few studies have compared different dosing frequencies. One 4-year open study of various allergens compared a daily regimen (CMD of 6 μg of the major dust mite allergen Der p 1) with a 3-times-a-week regimen (CMD of 13 μg Der p 1) and found that the daily lower-dose regimen was more effective in terms of medication use.

Duration of treatment
The optimal duration for allergen immunotherapy has not been established. At present, there are no specific tests or clinical markers that distinguish between patients who will relapse and those who will have long-term clinical remission after they discontinue allergen immunotherapy.

Few studies have investigated the duration of SCIT efficacy after discontinuation. A few studies demonstrated sustained efficacy after discontinuation of a 3-year treatment course of SCIT for grass pollen-- or
tree pollen–induced allergic rhinitis. However, one study of patients with allergic asthma reported a 55% relapse rate within 3 years of discontinuation of SCIT.

Immunotherapy practice parameters suggest that a decision about continuing SCIT should generally be made after the initial period of up to 5 years of treatment.

In the reviewed studies, the duration of SLIT treatment varied from 2 months to 5 years. Treatment was given pre-seasonally, co-seasonally, pre- and co-seasonally, or perennially. Twenty-nine studies reported a cumulative or continuous treatment period of more than 12 months. A few studies demonstrated sustained clinical efficacy after 18 months of tree pollen SLIT and 4 to 5 years of dust mite SLIT of up to 5 years after discontinuation of treatment.

**Clinical effectiveness**

The efficacy parameters that are used to assess response to allergen immunotherapy are usually reduction in symptoms and reduction in medication use. The degree of reduction in symptoms and medications in relation to the pretreatment period or in comparison with a matched randomized control or placebo group should also be considered in assessing the efficacy of allergen immunotherapy.

Most of the studies focused on adults with allergic rhinitis. Several studies included allergic rhinitis patients, with and without asthma; in a few studies, asthma was the primary disease studied. A few studies were limited to children.

One meta-analysis of SLIT for allergic rhinitis determined that there was no significant reduction in symptoms and medication scores in studies involving only children; however, the total number of participants in each of the pediatric-only studies was too small to make a reliable conclusion. Three studies investigated the safety of SLIT in children younger than 5 years.

Sixty-four of the 104 articles reviewed by the SLIT Joint Task Force provided some information about clinical efficacy. However, most studies did not provide information about the degree of reduction in symptoms and/or medication scores. Other measures of efficacy that were provided include visual analog scale, quality-of-life assessment, and patients' and investigators' overall clinical efficacy assessment.

Most of the SLIT studies reviewed demonstrated some evidence of clinical efficacy in the form of either improved symptom scores, medication scores, or both. However, a significant minority of studies failed to demonstrate efficacy in the first year, which is the period during which SCIT is expected to demonstrate clinical efficacy before treatment failure and discontinuation are considered. When symptom and medication scores for the principal disease being treated were used as the primary outcome measure of clinical efficacy, the SLIT Joint Task Force found that:

- In 14 (36%) of 39 SLIT studies that provided both medication and symptom scores, there was a significant improvement in both parameters in the SLIT group compared with the placebo or randomized control group during the first treatment year. The doses used in these studies ranged from 0.3 µg of major cat allergen (Fel d 1) CMD, the lowest dose in the reviewed studies, to 4468 µg of major ragweed allergen (Amb a 1) CMD, one of the highest doses in the studies reviewed.
- In 15 (38%) of 39 SLIT studies that measured medication and symptom scores, there were no statistically significant improvements in either parameter in the SLIT group compared with the placebo or randomized control group. The doses used in these studies ranged from 1 µg of major P. judaica allergen (Par j 1) CMD to 9420 µg of major ragweed allergen (Amb l 1) CMD.

**Clinical efficacy beyond the first year**

Generally, clinical efficacy with SCIT is seen shortly after reaching the maintenance dose. Current practice guidelines for SCIT suggest that discontinuation of immunotherapy should be considered and other treatment options pursued if there is no clinical improvement after 1 year. Interestingly, 8 of the 47 SLIT studies reviewed that did not show improvement in symptoms or medication scores in the first year of treatment demonstrated improvement in the subsequent years of treatment in medication scores, symptom scores, or both.

**Other efficacy parameters**

Some studies that demonstrated no significant improvement in symptoms or medication scores reported improvement in other clinical assessment parameters, such as investigator global clinical efficacy evaluation or patient assessment of severity compared with previous years.

**Sublingual compared with subcutaneous immunotherapy**

Four studies included some comparison of SLIT and SCIT. In a study of 36 adults with house dust mite–induced asthma randomly assigned to either SCIT, SLIT, or placebo SLIT for 1 year, there was a significant improvement in rhinitis and asthma symptom scores compared with baseline in the SCIT group, but only the rhinitis symptom scores were significantly improved in the SLIT group.
trolled study comparing SLIT with SCIT, medication and symptom scores significantly improved in both treatment groups compared with placebo and baseline. There was a greater magnitude of improvement in symptom and medication scores in the SCIT group than in the SLIT group, but the differences were not significant, perhaps because of the small number of persons in the study. Only 48 of the 71 randomized patients completed the 2 years of treatment. In the SLIT group, the 2-year cumulative median dose was 11.2 μg, and in the SCIT group, it was 5 μg, corresponding to an approximate 200-fold difference between the SLIT and SCIT dose.

In an open 2-year study comparing low-dose Alternaria SLIT with SCIT, there was greater improvement in rhinitis scores in the SLIT group than in the SCIT group. Finally, a double-blind study comparing SCIT with a low-dose SLIT regimen in patients who had allergic rhinitis (either with or without asthma) found a significant improvement in symptom and medication scores in both groups. However, only the SCIT group demonstrated a significant improvement in the objective parameters (total IgG, specific IgG4, and skin test reactivity).

Sublingual immunotherapy efficacy summary

The studies of SLIT include doses that vary by 30,000-fold, frequency of dosing varying from daily to weekly, and duration of treatment varying from 2 months to 5 years. There have been very few comparative studies of SLIT and SCIT, different sublingual allergen doses, or different administration regimens. One of the 4 studies that compared SLIT with SCIT suggested that SCIT may be more effective in treating asthma symptoms.

The only comparative study between SLIT and SCIT that included a placebo arm for both treatments suggested that the magnitude of improvement is greater with SCIT than with SLIT at an allergen dose that is 200-fold lower than the SLIT dose. Considered collectively, the studies reviewed in the American Academy of Allergy, Asthma, and Immunology/American College of Allergy, Asthma, and Immunology Task Force on Sublingual Immunotherapy report failed to demonstrate a consistent relationship between allergen dose, treatment duration, and clinical efficacy.

REFERENCES

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