

# Sublingual Immunotherapy and Allergic Rhinitis

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This paper reviews the safety and efficacy of sublingual immunotherapy (SLIT) in the treatment of allergic rhinitis. The literature from 1986 through 2007 shows approximately a 6000-fold range in doses found to be effective with SLIT. However, recent studies in large patient populations have demonstrated a clear dose response with an effective dose range that appears to be equivalent to one to two times the monthly subcutaneous immunotherapy dose administered daily or weekly (ie, 15 to 30 µg of major allergen). Further study is needed to establish the optimal dose and dosing schedule for each formulation. Local reactions (eg, oral itchiness) are common, and serious adverse reactions, although rare, have been reported. Cost-effective analysis cannot be made until the effective dose is established. SLIT appears to be a promising treatment for allergic rhinitis, but it is currently considered investigational in the United States until a formulation approved by the US Food and Drug Administration is available.

## Introduction

Specific allergen immunotherapy (SIT) is currently the only treatment intervention for allergic rhinitis that may provide a prolonged clinical remission after discontinuation [1,2]. In addition, SIT may prevent the progression of allergic rhinitis to asthma and the development of new allergen sensitivities [3-6]. Compared with pharmacotherapy, SIT appears to be more cost-effective in the long term [7,8]. The cost-effectiveness of SIT is likely due to the combination of reduced need for medications and medical services—a benefit that may be sustained after SIT is discontinued [8,9]. In contrast, the benefits of pharmacotherapy may be lost shortly after medication is discontinued

[10,11]. Subcutaneous immunotherapy (SCIT) is the only method with a US Food and Drug Administration (FDA)-approved formulation in the United States. Despite the proven clinical benefits and the potential preventive effect of SIT, only a small percentage (approximately 5%) of individuals with allergic rhinitis in the United States subscribe to this treatment. The reason for this low utilization is probably related to the recommended measures intended to optimize the safety of SCIT administration. Potential adverse effects of SCIT range from large local reactions (common) to life-threatening anaphylaxis and death (rare). Because of the potential risks associated with SCIT, the Allergen Immunotherapy Practice Parameter (AIPP) recommends that SCIT only be administered in a location with appropriate staff and equipment to recognize and treat anaphylaxis—a physician's office or other medical facility [12]. The AIPP also recommends a 30-minute wait after administration of the injection in the office or medical clinic. In most nonaccelerated build-up schedules, the injections are administered at a frequency of 1 to 2 times a week for 3 to 6 months until the maintenance dose is achieved; thereafter, the dosing interval is lengthened. The time required for the frequent visits during the build up phase is likely a significant deterrent for many individuals with allergic rhinitis, who may have little free time outside of family and work commitments.

Sublingual immunotherapy (SLIT) is an alternative method for delivering SIT. A purported advantage of SLIT over SCIT is greater safety, which would allow for home administration and possibly treatment of high-risk patients. In the past 20 years, SLIT has been prescribed with increasing frequency in Europe, but this method is not often prescribed in the United States. The absence of an FDA-approved SLIT formulation and an American Medical Association Current Procedural Terminology (CPT) code for SLIT are probably the major reasons for the limited use of SLIT in the United States. The purpose of this paper is to review the efficacy and safety of SLIT in the treatment of allergic rhinitis and to discuss the current US status of SLIT. The review includes the papers discussed in the American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI) Sublingual Immunotherapy Joint Task Force (SLIT Joint Task Force) report [13••]

and papers published subsequent to this report (November 2005 through October 2007) identified through the following PubMed search terms: sublingual immunotherapy, allergic rhinitis, and allergen immunotherapy.

### Efficacy

The SLIT Joint Task Force report reviewed 64 studies of various designs that provided information on SLIT efficacy in allergic rhinitis, asthma, or both diseases and concluded that a consistent relationship between dose and efficacy has not been established [13••]. Studies published subsequent to this review continue to show a wide range of allergen doses that have been found to be effective and ineffective. For example, a randomized, double-blind, placebo-controlled (DBPC) study of 50 cat-allergic patients with allergic rhinoconjunctivitis with or without asthma treated with a low dose of cat 50% glycerol saline sublingual solution (0.05 µg Fel d 1 daily) or placebo demonstrated a marked reduction (62%) in symptoms and a reduced peak expiratory flow rate response during a 90-minute natural cat challenge ( $P < 0.001$ ) in the active group after 12 months of treatment compared with the pretreatment challenge, whereas no change was seen in the placebo group [14]. The active group also showed an improvement in titrated prick skin test reactivity ( $P < 0.05$ ). No significant changes were seen in the placebo group in any of the measured parameters. The cumulative allergen over the 12-month treatment period was 17 µg of Fel d 1. In contrast, another study using a daily dose that was 2.3 times this study's cumulative yearly dose found no significant difference in change in nasal blockage index or symptoms during a 90-minute cat dander challenge between the treated and placebo groups [15]. In this DBPC study of 41 cat-allergic patients treated with a 50% glycerol saline extract (about 40 µg of Fel d 1 daily) for 105 days, similar improvement occurred in symptoms and nasal blockage index, but the median change in either variable was not different between the treated and placebo groups. Also, no significant change was seen in either group in cat-specific immunoglobulin (Ig) E or IgG. There was an approximately 800-fold difference in the sublingual doses employed in these two studies, which utilized the same allergen and similar efficacy parameters but found different outcomes.

Contrary to the individual studies in the sublingual immunotherapy literature, there appears to be a clear dose response in studies specifically designed to evaluate this effect in allergic rhinitis (Table 1). Several studies that included large patient populations (up to 855 patients) have demonstrated a clear dose-response relationship for SLIT tablets [16•,17•]. The effective dose in these large patient population studies appears to be in the range of 15 to 25 µg of major allergen administered daily as a sublingual tablet. These studies have used either a very brief [16•] or no build up [17•] phase.

When considering how soon before the onset of the season to begin immunotherapy, one study found a statistically significant dose response improvement in both symptom and medication scores in the high dose group only when the analysis was limited to the patient population who had received at least 8 weeks of preseason treatment [17•], which apparently led to a revised design in subsequent studies in which treatment began 12 to 16 weeks before the season [18–20]. Results of these studies have demonstrated significant improvement in medication and symptom score compared with placebo in the first treatment season: 30% to 37% reduction in rhinitis total symptom score (RTSS) and 38% to 46% reduction in rhinoconjunctivitis medication score/use [16•,18].

With continuous daily treatment, a greater magnitude of improvement was seen in both parameters in the second treatment year: a mean reduction of 36% in RTSS ( $P < 0.0001$ ; median reduction 44%) and a mean reduction of 46% in rhinoconjunctivitis medication score ( $P < 0.0001$ ; median reduction 73%) in the grass tablet group compared with the placebo group [21].

In these grass tablet studies, the magnitude of clinical improvement is similar to that of effective SCIT for grass-pollen-induced allergic rhinitis. For example, in a DBPC SCIT study of 410 grass pollen seasonal allergic rhinitis (SAR) patients randomized to one of two doses of a depot preparation of grass pollen (2 and 20 µg of P111 p 5) or placebo, mean symptom and medication scores were reduced 29% and 32%, respectively, in the higher-dose group compared with placebo [22]. Compared with placebo, the lower-dose group only had a significant reduction in symptom scores (22%,  $P < 0.01$ ) and a 16% reduction in medication scores that was not statistically significant ( $P = 0.16$ ). Although the vast majority of SLIT studies have utilized a solution formulation, the evidence for a dose response and clinical efficacy is not as strong as the SLIT tablet formulation studies. One DBPC study investigated the effect of two SLIT doses of a glycerinated mixture of *Betula verrucosa*, *Corylus avellana*, and *Alnus glutinosa* (30 µg vs 3.6 µg of Bet v 1/Aln g 1/Cor a 1 administered weekly as five doses) on clinical efficacy in 88 children with tree pollen-induced allergic rhinoconjunctivitis with or without seasonal asthma, and demonstrated a dose response similar to that seen in the grass-pollen dose-response SCIT study [23•]. Significant improvement in symptom and medication scores compared with placebo was seen only in the higher dose group (30 µg of Bet v 1/Aln g 1/Cor a 1 per week). Similar to the previously discussed grass-pollen SCIT study, the lower-dose group only demonstrated significant efficacy in symptom scores. In a subset of 30 patients (10 placebo, 10 in high-dose SLIT, and 10 in low-dose SLIT), allergen-induced in vitro expression of cytokine messenger (m) RNA in peripheral blood mononuclear cells was investigated after 1 and 2 years of treatment [24•]. Compared with the highest-dose group, interleukin (IL)-5 levels were higher in the placebo

Table 1. Summary of sublingual immunotherapy dose-response studies

Study	Formulation	Intervention	Significance/difference	Safety	
André [49]	DBPC study of dose-response by tolerance for use; 99 adults; 6.5 mo	Ragweed (Stallergenes, solution then tablet) — 100 IR–300 IR tablet 3/wk; 100 IR = 160 µg of Amb a 1; CMD range, 2015–6048 µg of Amb a 1	100-IR group compared with placebo	300-IR group compared with placebo: rhinitis scores ( $P = 0.05$ ); conjunctivitis scores ( $P = 0.04$ ); corticosteroid use ( $P = 0.05$ )	AE more frequent in SLIT: 70% vs 13% in placebo — 4 in SLIT group discontinued treatment because of AE (1 oral burning; 1 oral pruritus; vomiting, 1 h; 1 pruritus; ip edema, GI, 1 asthma, GI); 7 placebo withdrew due to CI AE
Bordignon [50]	open study of 5 low-dose regimens given 1, 2, or 3 times/d in first year; all groups 3/d in year 2; 64 patients (aged 4–50 y); 36 mo	Crass or birch (ALK-Abello, solution) — highest dose = 0.075 µg/d of group 5 allergen (2.25 µg CMD); lowest = 0.025 µg/d (0.75 µg CMD)*	1/d group: 5 IR, antihistamine use compared with baseline or control in year 1	Less antihistamine in 3/d and 2/d compared with baseline ( $P < 0.001$ ) and in all groups compared with control in year 2 ( $P < 0.001$ )	No AE reported; no dropouts
Dür [16]	DBPC dose-response study of grass tablet administered pre- (16 wk before) and concomitantly; 628 adults randomized to 3 treatment groups or placebo; about 5 mo	Crass tablet (Stallergenes, Orinair) — 100 IR, 300 IR, 500 IR; 300 IR = 25 µg of group 5 allergen	No difference in symptom scores between 100-IR and placebo	Compared with placebo: 300 IR and 500 IR had significant improvement in RTSS ( $P = 0.0031$ and $0.0006$ , respectively), which corresponded to 300 IR — 37% reduction in RTSS, 46% rescue medication use; 500 IR — 35% reduction in RTSS, 47% reduced rescue medication use	All treatment groups "were well tolerated"
Durrant [17]	DBPC dose-response study of 855 adults randomized to 3 treatment groups or placebo; mean 18 wk	Crass tablet (ALK-Abello, GRAZAX) — 0.5, 5, and 15 µg of Phil p 5	No difference in symptom or medication score in 0.5- or 5-µg groups compared with placebo	15-µg Phil p 5 group compared with placebo: entire group, medications reduced by 28% ( $P = 0.047$ ); symptoms reduced by 16% ( $P = 0.071$ ); group treated for at least 8 wk before season, medications reduced by 29% ( $P = 0.012$ ), symptoms reduced by 21% ( $P = 0.002$ )	"No safety concerns observed"; 1 patient in 5 µg group hospitalized for "swirl edema" subsequently completed study without AE

\*Crass or birch (ALK-Abello, solution) — highest dose = 0.075 µg/d of group 5 allergen (2.25 µg CMD); lowest = 0.025 µg/d (0.75 µg CMD).  
 †No difference in symptom scores between 100-IR and placebo.  
 ‡Compared with placebo: 300 IR and 500 IR had significant improvement in RTSS ( $P = 0.0031$  and  $0.0006$ , respectively), which corresponded to 300 IR — 37% reduction in RTSS, 46% rescue medication use; 500 IR — 35% reduction in RTSS, 47% reduced rescue medication use.  
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 ¶All treatment groups "were well tolerated".  
 ††"No safety concerns observed"; 1 patient in 5 µg group hospitalized for "swirl edema" subsequently completed study without AE.

Table 1. Summary of sublingual immunotherapy dose-response studies (continued)

Study design, number of patients, duration	Allergen(s) company, formulation, dose, CMO	Intervention	Significant difference	Safety
Marcucci [49]—randomized study of 2 doses with no comparative placebo or untreated control group; 71 children (aged 5–14 yr; 6 mo)	Grass (S)allergenes, Stalora 300—“375 vs 85 times” cumulative dose of SCIT; approx. 28 µg vs 50 µg of grass group; 5 allergen/vwk or 117 µg vs 211 µg CMO*	Sublingual immunotherapy	Symptom-medication scores better in higher-dose (375x) than lower-dose group ( $P = 0.024$ )	All occurred with comparable frequency in both groups: 25.8% in higher-dose group, 27.5% in lower-dose group; almost all AE oral (3 GI)
Valovska [23]—DRPC to investigate dose-response effect on tree-pollen; SAR; randomized to 2 treatment groups or placebo; 88 children (aged 5–15 yr; 18 mo)	Trees (Birch, alder, hazel) (ALK-Abello glycerinated mixture)—high = weekly dose of 200,000 SQ-U (30 µg Bet v 1/Alh g 1/Cor a 1); low = weekly dose of 24,000 SQ-U (3.6 µg Bet v 1/Alh g 1/Cor a 1); or placebo	Sublingual immunotherapy	Spring pollen season: high-dose group showed significant reduction of symptom ( $P = 0.01$ ); and medication scores ( $P = 0.04$ ) compared with placebo; lower-dose group showed significant reduction of symptom scores ( $P = 0.03$ )	*All children tolerated the treatment well. High-dose group—2 patients had allergic reactions: 1 had abdominal pain, 1 had 3 episodes of flushing. Local reactions in 50% of high, 36% of low, and 25% of placebo groups

group. At the end of 2 years, mRNA expression of IL-10 was increased in both dose groups compared with placebo, and the change in the expression of allergen-induced transforming growth factor (TGF)  $\beta$  correlated directly with IL-10 and inversely with IL-5.

Interestingly, a telephonic survey 5 years after the study began found that most subjects reporting asthma symptoms were in the placebo or low-dose groups (6/10 in each group), whereas only 2/10 patients in the high-dose group reported asthma symptoms ( $P = 0.38$ ). Parameters at the end of treatment that correlated with subsequent development of asthma were higher levels of IL-5, less decrease in late phase skin test reactivity ( $P = 0.003$ ), and less improvement in symptom and medication scores ( $P = 0.002$  for both). A significant decrease of IL-4/interferon (IFN)  $\gamma$  ratio was associated with a lower incidence of subsequent asthma ( $P = 0.036$ ).

In summary, although there is a 6000-fold range of reported effective doses with SLIT (0.05–300  $\mu$ g of major allergen) in the published literature, recent dose-response studies using solution or tablet formulations suggest that the effect dose may be in the range of 15 to 30  $\mu$ g of major allergen administered daily or weekly. One study found greater efficacy in patients treated at least 8 weeks before the season, but no studies published to date have been designed to compare the efficacy of different preseasonal starting time points (eg, 8 vs 12 vs 16 weeks before season) nor have any studies compared different regimens in the second treatment year (eg, perennial vs preseasonal and coseasonal). Such studies would be important to determine the most cost-effective effective SLIT dose regimen.

### Monosensitized versus Polysensitized Patients

The majority of allergic patients in the United States are sensitive to more than one allergen. In one skin test survey of a large population of asymptomatic people (National Health and Nutrition Examination Survey III), the median number of positive skin tests was three [25]. The number of positive skin tests is greater in the allergic population. Unfortunately, only a limited number of studies with SCIT or SLIT have investigated the efficacy or safety of allergen immunotherapy with multiple allergens.

With the exception of one study [26], no SLIT studies have utilized more than one non-cross-reacting allergen. This open-label, controlled study investigated the efficacy of combined birch and grass SLIT compared with single-allergen SLIT or medications only in patients allergic to both allergens. Efficacy was seen during both the birch and grass season in the group who received both allergens, but clinical scores and nasal eosinophil counts also improved in the patients treated with a single allergen compared with baseline and the untreated control group in both seasons (ie, the target and unrelated season). In addition to questions of efficacy and safety, the cost of treating with multiple allergens may be prohibitive if the

dose requirement is significantly greater than SCIT, as it was in the SLIT grass tablet study of 855 patients, which determined the effective SLIT dose for timothy grass was equivalent to 22.5 times the cumulative monthly dose given by SCIT [17•].

### Comparison of SLIT with SCIT

Few studies have directly compared SLIT with SCIT. One double-blind, double dummy, placebo-controlled study of SLIT versus SCIT in birch allergic rhinitis patients found a greater magnitude of improvement in the SCIT group compared with the SLIT group. SLIT diminished the median symptom scores to one half and SCIT to one third of those recorded with placebo treatment. The difference between the active treatment groups (SLIT vs SCIT) was not statistically significant, possibly due to the small number of patients at the completion of the study (type II statistical error) [27].

A comparison of two Cochrane meta-analyses of SLIT [28] and SCIT [29••] for allergic rhinitis also found that the magnitude of improvement with SCIT may be greater than SLIT: symptom reduction with SCIT—standardized mean difference (SMD) of -0.73 (95% CI, -0.97 to -0.50,  $P < 0.00001$ ) compared with SLIT—SMD of -0.42 (95% CI, -0.69 to -0.15,  $P = 0.002$ ); medication reduction with SCIT—SMD of -0.57 (95% CI, -0.82 to -0.33,  $P < 0.00001$ ) compared with SLIT—SMD of -0.43 (95% CI, -0.63 to -0.23,  $P = 0.00003$ ).

### SLIT Efficacy: Preventive and Prolonged Effect

Several studies have suggested that SCIT may prevent the progression from allergic rhinitis to asthma in adults [4,30] and children [2,6]. A similar preventive effect was seen in one prospective, parallel group, controlled study of 60 children divided into two matched groups: 35 received SLIT for 4 to 5 years and 25 were treated with pharmacotherapy alone [31]. An evaluation 4 to 5 years after discontinuing SLIT found a significant difference compared with baseline in the presence of asthma ( $P \leq 0.001$ ) and asthma medication use ( $P < 0.01$ ) in the SLIT group, whereas no significant change in these parameters occurred in the pharmacotherapy-alone group. Another randomized controlled study of 123 children with grass-pollen SAR treated for 3 years with coseasonal SLIT or standard symptomatic therapy found a significantly lower incidence of asthma in the SLIT group after 3 years (odds ratio [OR] 3.8, 95% CI, 1.5–10.0) [32]. The magnitude of the asthma preventive effect is similar to that found in a 3 year prospective, randomized, open, controlled SCIT study of 147 children with grass and/or birch pollen SAR [6]. At the 10-year follow-up evaluation—which was 7 years after discontinuing a 3-year course of SCIT—significantly fewer SCIT-treated subjects had developed asthma

as determined by clinical symptoms compared with the open control group (OR 2.5, 95% CI, 1.1–5.9).

Few studies have been designed specifically to determine the optimal duration of effective inhaled allergen SCIT or the duration of efficacy after treatment termination. Relapse rates after discontinuation have ranged from 0 to 55% of patients [1,33]. One review of duration of SCIT efficacy after discontinuation suggested that length of treatment and allergen type (ie, perennial vs seasonal) may be variables that affect the duration of clinical remission after SCIT cessation [34].

Similarly, few studies have investigated the duration of clinical efficacy of SLIT after discontinuation. One retrospective study evaluated 65 dust mite-allergic patients who had been treated 13 years earlier with either standard pharmacotherapy alone (12 patients) or SLIT (53 patients). The SLIT group was further divided according to duration: 1-year SLIT (15 patients), 2-year SLIT (10 patients), 3-year SLIT (14 patients), and 4-year SLIT (14 patients) [35]. A positive effect on symptom-medication scores (SMS) was seen in the SLIT groups versus the standard pharmacotherapy-alone group 2 to 3 years after the treatment ended. After 7 to 8 years, SMS were significantly better in the 4-year SLIT group than in the other groups, and the authors concluded that 4-year SLIT had a greater positive effect on clinical parameters than shorter courses.

### Efficacy Summary

The collective literature describes a 6000-fold range of doses demonstrated to be effective in SLIT; conversely, a similarly wide range of doses were found to be ineffective. Several large studies using a tablet formulation have demonstrated a clear dose response in terms of clinical efficacy and some objective parameters, with the effective dose being 1 to 1.5 times the usual monthly SCIT dose. The dose-response studies with SLIT solutions have not clearly demonstrated an effective dose range. Some studies have suggested that a preseasonal period of at least 8 weeks is required to see clinical improvement in the first season, but the optimal timing of subsequent pre-season regimens has not been studied, nor has continuous treatment been compared with pre-season and co-seasonal treatment. Optimal duration of effective SLIT has not been established, although one study found that 4 years of SLIT provided greater clinical efficacy than shorter durations, which is an effect similar to that found in one controlled, prospective SCIT study that investigated duration of efficacy [33].

In conclusion, each formulation will need to establish its effective dose. More studies are needed to determine optimal dosing schedule for all formulations.

### Safety

SLIT appears to be associated with a lower incidence of adverse reactions than SCIT. However, a difficulty

in evaluating SLIT safety is that the majority of adverse reactions occur outside the medical setting, even during clinical trials. The accuracy of reporting the adverse reactions would depend on patient recall because very few reactions are likely to occur in or near a supervised medical setting. Local adverse reactions that are oral-pharyngeal symptoms (eg, pruritus, lip swelling) are relatively common during the SLIT build up phase.

In the 66 studies reviewed by the SLIT Joint Task Force that provided some information about SLIT-related adverse events, no fatalities occurred in approximately 1,181,654 doses administered to 4378 patients [13••].

The estimated systemic reaction rate was 0.056% of administered doses. Systemic reactions included asthma, urticaria, and gastrointestinal symptoms. In the SLIT Joint Task Force report, 14 probable SLIT-related serious adverse reactions were noted. Seven of these were asthma; three were characterized as severe and due to exceeding maximum tolerated dose [36] and one required hospitalization [37].

In comparison, the systemic reactions rate with nonaccelerated SCIT build-up schedules ranges from 0.05% to 3.2% of injections and 0.84% to 46.7% of patients (mean, 12.92% of patients) [38]. The highest rate occurred in a study of patients who were highly sensitive to ragweed. When this study was excluded, the rate of systemic reactions was 0.6% per injection (or less) and 0.84% to 28.6% of patients [39]. In a survey of fatal and near-fatal immunotherapy and allergy skin test reactions sent to physician members of the AAAAI, the incidence of unconfirmed near-fatal reactions was 23 per year (5.4 events/million injections) during 1990 to 2001 [40]. The estimated fatality rate was 1 per 2.5 million injections (an average of 3.4 deaths per year) [41], which is similar to two previous surveys of AAAAI physician members dating back to 1945 [42,43].

There has been one case of anaphylaxis to SLIT during latex rush induction and two cases of anaphylaxis to mixtures of inhaled allergens [44,45]. One episode occurred in a 13-year-old girl who had tolerated a course of SLIT 1.5 years earlier [45]. The reaction occurred shortly after administration of the pollen drops 1 month after she had reached the maintenance dose during the peak of the spring season. The other case was a patient with allergic rhinitis and asthma who was prescribed a sublingual immunotherapy extract composed of multiple non-cross-reacting allergens (*Alternaria*, dog, cat, ragweed mix, weed mix, and grass mix) [46]. She developed generalized pruritus followed by angioedema, shortness of breath, and dizziness within a few minutes of self-administering six drops of the 1:100 w/v dilution on the third day of treatment. This episode was preceded by a milder systemic reaction (generalized pruritus) the previous day.

There have been no studies of SLIT in high-risk patients, such as those with severe asthma or patients who have had multiple severe systemic reactions with SCIT.

### Safety Summary

SLIT appears to be associated with a lower incidence of systemic reactions, although local oropharyngeal symptoms are common during the build up phase. Systemic reactions have been reported. A few cases of probably serious SLIT-related adverse events have been reported, and two reported cases of SLIT anaphylaxis in individuals treated with multiple inhalant allergens, but no fatalities have been reported with SLIT. The safety of SLIT has not been studied in high-risk populations.

### SLIT Practical Considerations:

#### Cost, Compliance, and Patient Instructions

Presently, no FDA-approved formulations for SLIT are available, and use of US-licensed extracts for SLIT would be considered off-label. There is also no CPT code that could be used to bill for SLIT, primarily because there is no FDA-approved formulation. It is not possible to perform a cost-effective analysis of SLIT without knowing the effective dose, duration, or dosing schedule. One prospective pharmaco-economic analysis using pooled data on resource use and health outcomes collected from a large, international (eight countries), randomized, DBPC trial of patients randomized to receive grass-pollen tablets ( $N = 316$ ) or placebo ( $N = 318$ ) found significantly greater clinical efficacy in the grass-tablet group in all outcome parameters, including quality adjusted life years (QALY) [47]. Assuming the effectiveness of the 3-year SLIT treatment would be maintained 6 years after discontinuation, and assigning a dollar amount for QALY, the authors concluded that SLIT would be cost effective if the cost were 6 Euros per tablet or less. The cost of the grass tablet in Germany at the time of this study's publication was 2.95 Euros per tablet (1 Euro = 1.4626 US dollars). Even considering the value of improved quality of life (measured as QALY), cost-effectiveness of this treatment would be diminished if multiple allergens were required and if each allergen cost 2.95 Euros or more per day.

Because SLIT treatment is administered at home with no direct medical supervision, patient compliance is another consideration. The patient would need specific instructions regarding management of adverse reactions, unplanned treatment interruptions, situations in which the dose should be withheld, and dosing adjustments for any or all of these variables. However, most of these situations have not been studied in the SLIT clinical trials, and therefore providing evidence based patient instructions would be difficult.

### Conclusions

In the past 20 years, SLIT has been used with increasing frequency in Europe and is viewed with great interest in the North American allergy community. A wide range of effective SLIT doses continue to appear in the published

literature, but several large patient population studies have suggested the effective dose may be in the range of one to two times the monthly SCIT dose administered daily or weekly. Adverse reactions with SLIT are less common than with SCIT but serious reactions have been reported, and SLIT safety in high-risk patients has not been studied. Cost-effectiveness of SLIT cannot be determined without knowing the effective dose and dosing schedule. Currently, no FDA-approved SLIT formulation exists, but clinical studies aimed at producing an FDA-approved formulation are in progress. As a home-based treatment, special consideration should be given to patient compliance and the development of specific instructions for managing treatment variables that may be encountered with SLIT. If the FDA approves a formulation and cost is not prohibitive, SLIT may make specific immunotherapy, a disease-modifying treatment, available to a much larger population than those now receiving SCIT.

### Disclosures

The author has been a member of the medical advisory boards or has been a consultant for Greer, Schering-Plough, Allergy Therapeutics, Planet Technology, and Genentech/Novartis. The author has also been a member of the speakers' bureaus for AstraZeneca and Genentech/Novartis. Grant support from AAAAI.

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