Sublingual immunotherapy: A comprehensive review

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Sublingual immunotherapy (SLIT) has been used with increasing frequency in Europe and is viewed with increasing interest by allergists in the United States. To address this interest, a Joint Task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology's Immunotherapy and Allergy Diagnostic Committees reviewed the available literature on SLIT and prepared this report. The task force concluded that despite clear evidence that SLIT is an effective treatment, many questions remained unanswered, including effective dose, treatment schedules, and overall duration of treatment. Until these have been determined, an assessment of the cost/benefit ratio of the treatment cannot be made. SLIT does appear to be associated with few serious side effects, but it has not been administered in high-risk asthmatic patients, nor in the studies reviewed has it been administered as a mixture of non–cross-reacting allergens. Furthermore, there is currently no allergy extract approved for this use in the United States, nor is there a Current Procedural Terminology code for billing purposes. All of these factors should be given careful consideration by anyone contemplating initiating SLIT treatment for their allergic patients. (J Allergy Clin Immunol 2006;117:1021-35.)

Abbreviations used	
AAAAI:	American Academy of Allergy, Asthma and Immunology
AE:	Adverse event
CMD:	Cumulative monthly dose
CPT:	Current Procedural Terminology
DBPC:	Double blind, placebo controlled
ECP:	Eosinophil cationic protein
FDA:	US Food and Drug Administration
HDM:	House dust mite
ICAM:	Intercellular adhesion molecule
NFR:	Near-fatal immunotherapy reaction
RC:	Randomized controlled
SCIT:	Subcutaneous immunotherapy
SLIT:	Sublingual immunotherapy
SPT:	Skin prick test
SR:	Systemic reaction

Sublingual immunotherapy (SLIT) has been used with increasing frequency in Europe and is being viewed with increased interest by US allergists. In Medline, Embase, and Biosis there were 21 SLIT citations in English in 1999 and 58 in 2004. From 1999 through 2005, there were 258. At the 2005 World Allergy Organization congress, there were 25 abstracts on SLIT. In light of this increasing interest, the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology's (AAAAI) Immunotherapy and Allergy Diagnostics Committees formed a joint task

force with the purpose of providing a comprehensive, updated report on SLIT for the North American allergy community. A reference list was compiled from articles known to task force members, references from review articles,[1-14] and PubMed (referenced through October 2005). One hundred four articles in English, French, and German were reviewed.[1-104]

The task force was divided into working groups that reviewed dosing, efficacy, immunologic response, and safety. Each working group reviewed all of the articles and extracted those relevant to their section. In addition, the committee selected 16 articles that met predetermined criteria (randomized, double-blind, placebo-controlled [DBPC] studies using defined allergens and dose with well-defined inclusion criteria and well-defined outcome measurements and including at least 45 evaluable subjects) and summarized them in an evidence table (see Table E1 in the Online Repository at www.jacionline.org).

SUBLINGUAL SWALLOW OR SPIT?

SLIT can be delivered by means of 2 methods. With sublingual spit, the vaccine is kept under the tongue for a short period and then spat out. This method was used in some of the earlier studies, but the majority of the studies used the sublingual swallow method. In this method the vaccine is kept under the tongue for 1 to 2 minutes and then swallowed. All articles with either of these methods were reviewed, but articles that used the oral route without a sublingual phase were excluded.

In a study that investigated the pharmacokinetics of the 2 techniques, the authors concluded that contact with the oral mucosa was a crucial step, and the sublingual swallow method was the more appropriate and advantageous way to administer the allergen because the sublingual spit method led to a partial loss of allergen.[15]

ALLERGEN DOSING

The efficacy of subcutaneous immunotherapy (SCIT), the standard to which SLIT is compared, is dependent on the dose and quality of the allergen[105-108] and the duration of administration.[109,110] One method that might offer a common denominator for comparing dosing is the content in mass units of 1 or more major allergens in the extract. Fifty-seven of the 104 SLIT studies reviewed provided doses in micrograms of major allergen. The rest reported doses only in in-house units, histamine equivalent prick units, or other biologic units. 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. One of the task force members was able to translate most of the allergy extract units into micrograms of major allergen through communication with many of the extract manufacturers. This facilitated dosage comparisons between the different studies, making it possible to assess the relationship between SLIT dose and treatment efficacy.

Because subcutaneous maintenance doses are commonly given once per month and sublingual maintenance doses are given more often, comparisons between dosing by means of SCIT and SLIT can be made both per single dose and per cumulative monthly dose (CMD). Individual sublingual allergen doses varied between 0.0006[16] and 21[17] times the SCIT dose customarily used by the investigators, and CMDs varied between 0.017 and more than 500 times the customary subcutaneous maintenance dose. The SLIT monthly dose in micrograms of major allergen varied from 0.3 μg of Fel d 1[16] to 9000 μg of Amb a 1.[17] The cumulative monthly dosing of the 16 selected articles (see Table E1 in the Online Repository at www.jacionline.org) varied between 0.6 and more than 500 times the customary SCIT dose, with a mean and median of 87 and 49 times the SCIT dose, respectively. No SLIT studies used mixtures of non–cross-reacting allergens.

Only 2 SLIT studies were specifically designed to compare the response to different doses.[18,19] One study of patients with grass-induced rhinitis compared 2 maintenance dose regimens (24 drops of 300 IR vs 40 drops of 100 IR per week), which administered 85 and 375 times the cumulative dose that would be used with a standard SCIT regimen over the same period. They found greater improvement in symptom-medication scores in the higher-dose group ($P = .024$).[18] The study was randomized in terms of the administered SLIT dose, but it did not include a placebo or untreated control group. The other dose-response study was a randomized, placebo-controlled, multicenter, multicountry study of 855 patients with grass-induced allergic rhinitis who were treated with either placebo or one of 3 treatment doses (2500, 25,000, and 75,000 SQ-T units of *Phleum pratense)* daily for a mean duration of 18 weeks.[19] There was a significant improvement in medication and symptom scores only in the highest-dose treatment group, 75,000 SQ-T (equivalent to 15 μg of Phl p 5 or a CMD 22.5 times that recommended by the same company for SCIT, Table I).[19]

Dosing frequency

The optimal maintenance dosing frequency of SLIT has not been established. Dosing regimens varied from daily[16,17,19-30] to once weekly.[31] One 4-year open study of various allergens compared 1 drop daily (6 μg of Der p 1 CMD) with 5 drops 3 times a week (13 μg of Der p 1 CMD) and found that the daily lower-dose regimen resulted in a greater decrease in skin prick test end-point reactivity ($P < .001$), a higher rate of no drug use ($P = .013$), and at least a 50% reduction in drug consumption compared with pretreatment use ($P = .001$).[20]

The duration of treatment varied from 2 months[22] to 5 years.[32] Treatment was given preseasonally, coseasonally, preseasonally and coseasonally, or perennially. Twenty-nine studies reported a cumulative or continuous treatment period of more than 12 months.[20,21,24,27,28,32-55] Only 2 studies evaluated patients randomly assigned to different maintenance dosing schedules.[20,56]

Dosing summary

The studies reporting 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 are very few comparative studies.

CLINICAL EFFICACY

Sixty-four studies provided some information on the clinical efficacy of SLIT.[16-41,44-49,51,55-85] However, most studies did not provide information about the degree of reduction in symptoms, medication scores, or both. Other measures of efficacy that were provided include visual analog scale, quality-of-life assessment, and patient and investigator's overall (or global) clinical efficacy assessment. The study designs varied and included observational, with and without a parallel control, postmarketing surveillance, randomized controlled (RC), and randomized DBPC trials.

Forty-seven studies were chosen for efficacy analysis because they were either DBPC studies (n = 39)* or RC studies (n = 5).[31,35,36,76,79] Three additional studies were included in the analysis: a double-blind, double-dummy study comparing SLIT versus SCIT in patients with grass pollen allergy with rhinitis, asthma, or both without a placebo control group[82]; a placebo-controlled study comparing SLIT with SCIT and placebo SLIT in patients with house dust mite (HDM) allergy with rhinitis, asthma, or both[70]; and a randomized study comparing the efficacy of 2 maintenance doses without a comparative placebo group.[18] A summary of these studies can be found in 2 tables in the Online Repository at www.jacionline. org. Table E2 summarizes the placebo and RC studies, and Table E3 summarizes the 17 studies that provide efficacy information but did not include a placebo or randomized control group.

Studies can be categorized by duration, allergen type (seasonal vs perennial), and allergen dose (expressed as major allergen if this information was available). Outcomes such as provocation challenges, immunologic changes, and titrated skin tests are not considered in this efficacy analysis and are discussed elsewhere in this article.

Consideration of symptom and medication scores for the principal disease being treated as the primary outcome measurement of clinical efficacy and only considering the 43 DBPC or RC studies that provided information on either parameter and a comparative untreated control group (31 seasonal and 12 perennial allergens) in the first year of SLIT treatment reveals the following:

- In 14 (35%) of 39 studies that provided both medication and symptom scores, there was a significant improvement in both parameters compared with that seen in the placebo or randomized control groups during the first treatment year. Three were with perennial

TABLE I. Medication scores and symptom scores for 855 patients with seasonal allergic rhinitis treated with one of 3 sublingual doses of *Phleum pratense* or placebo tablets for a mean duration of 18 weeks[19]

Treatment group	Medication scores	Symptom scores
2500 SQ-T (~0.5 μg of Phl p 5)	$P = .38$	$P = .96$
25,000 SQ-T (~5 μg of Phl p 5)	$P = .96$	$P = .46$
75,000 SQ-T (~15 μg of Phl p 5)	Reduced by 28%, $P = .047$	Reduced by 16%, $P = .071$
If only patients treated with 75,000 SQ-T for at least 8 wk were considered	Reduced by 29%, $P = .012$	Reduced by 21%, $P = .002$

P values are versus placebo.

allergens,[39,61,70] and the remainder were with seasonal allergens.† However, in 2 dose-response studies, one based on tolerance[59] and the other based on design,[19] a significant improvement was only demonstrated in the highest dose group (CMDs of 4468 μg of Amb a 1 and 450 μg of Phl p 5). The lowest dose in the ragweed study that contained 1489 μg of Amb 1 CMD was ineffective, as were doses in the grass study containing 15 and 150 μg of Phl p 5 CMD.

- In 15 (38%) of 39 studies that measured medication and symptom scores, there were no statistically significant improvements compared with that seen in the placebo or randomized control groups in either parameter; 3 used perennial allergens,[42,49,66] and the remainder used seasonal allergens.‡ However, a multicenter study of patients with ragweed-induced allergic rhinitis treated with a high-dose SLIT regimen (3480-9420 μg of Amb 1 per month) for a short duration (approximately 4 months) demonstrated efficacy in 2 of the nasal symptoms assessed (sneezing and pruritus, $P = .04$) if data from the treatment center that reported low pollen counts that season were not included.[17]

- Five studies showed statistically significant improvements in medication scores, but not symptom scores, compared with those in the control group, one with a perennial allergen[34] and the remainder with seasonal allergens.[23,38,63,73] Twenty (46%) of the 43 studies that provided symptom scores demonstrated no significant improvement in symptom scores.

- Five studies showed significant improvements in symptom scores, but not medication scores, compared with the control group, one with a perennial allergen[28] and the remainder with seasonal allergens.[29,35,76,84] A total of 20 (51%) of 39 studies that provided medication scores demonstrated no significant improvement in symptom scores.

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*References 16, 17, 19, 21-26, 28-30, 33, 34, 37-39, 42, 45-49, 59-63, 65-69, 71-74, 78, 84.

†References 19, 26, 31, 36, 45, 59. 60, 62, 65, 71, 78.

‡References 17, 21, 22, 24, 30, 33, 37, 46, 68, 72, 74, 79.

- Four studies that did not provide information about medication scores demonstrated a significant improvement in symptom scores.[16,47,48,69]

Eight of the 47 studies that did not show improvement in symptoms or medication scores in the first year of treatment demonstrated improvement in subsequent years of treatment in medication scores, symptom scores, or both.

Six studies that failed to demonstrate a statistically significant improvement in either symptom or medication scores in the first treatment year demonstrated a significant improvement in symptom scores, medication scores, or both in the second year, 5 with seasonal allergens[37,46,72,74,79] and 1 with a perennial allergen.[42] In an HDM study that showed improvement in medication scores in the first year, there was a significant improvement in asthma symptoms in the second year,[34] and a 3-year study of patients with grass allergy demonstrated efficacy in combined symptom-medication scores in the group with the most severe baseline symptoms after 3 years of treatment.[21] Details of these studies can be found in Table E4 in the Online Repository at www.jacionline.org.

Some studies did not demonstrate efficacy in the primary disease studied but did show a significant improvement in other respiratory symptoms. Three studies designed to investigate the efficacy of SLIT in patients with rhinitis failed to demonstrate an improvement in rhinitis symptoms but did report a significant improvement in asthma or "dyspnea" symptoms compared with that seen in the placebo group.[22,23,30] Two studies designed to investigate the effect of SLIT on asthma demonstrated efficacy in upper respiratory tract symptoms.[33,42] One study of patients with dust mite–induced allergic rhinitis and asthmatic patients demonstrated efficacy in rhinitis scores in the first year and asthma scores in the subsequent year.[42] Another study that examined the effect of SLIT in patients with *Parietaria* species–induced asthma receiving fluticasone found no improvement in chest symptoms but a significant improvement in eye symptoms compared with that seen in the open control group ($P = .025$).[33] In one study of children with dust mite–induced asthma and/or rhinitis treated with a low-dose regimen (48 μg per month of Der p 1), the actively treated asthmatic patients in the SLIT group had improved pulmonary symptoms after 12 months but no improvement in bronchial reactivity, whereas the placebo group had a greater improvement in sensitivity to nasal provocation.[66] The authors concluded that there was "no consistent clinical or immunological benefit *(with SLIT)* compared to placebo."

Some of the studies that demonstrated no significant improvement in symptom or medication scores reported improvement in other clinical assessment parameters, such as investigator global-clinical efficacy evaluation[17] or patient assessment of severity compared with previous years.[24]

SLIT compared with SCIT

Four studies included some comparison of SLIT and SCIT.[45,51,70,82] In a study of 36 adults with HDM-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 in the SCIT group ($P < .05$ and $P < .01$, respectively), but there was only a significant improvement in rhinitis symptom scores in the SLIT group ($P < .01$).[70] Both groups demonstrated a significant improvement in medication scores compared with baseline values at both 6 and 12 months ($P < .01$ at 12 months for both groups). The placebo group demonstrated no significant change in symptom or medication scores compared with baseline values.

In a DBPC study comparing SLIT (high-dose regimen, 738 μg of Bet v 1 CMD) with SCIT (3.28 μg of Bet v 1 CMD), there was a significant improvement in medication and symptom scores in both treatment groups compared with those in the placebo group and baseline values.[45] There was a greater degree of improvement in the SCIT group compared with the SLIT group in symptom and medication scores, but the differences were not significant, perhaps because of the small number of subjects in the study. The rhinitis score decreased by 0.75 points in the SCIT group compared with 0.36 points in the SLIT group, and the medication scores increased by 0.29 in the SLIT and 1.35 in placebo groups but did not change in the SCIT group.

In an open 2-year study comparing low-dose *Alternaria* species SLIT with SCIT, there was greater improvement in rhinitis scores in the SLIT group compared with that seen in the SCIT group ($P = .013$).[51] Finally, a double-blind, double-dummy study compared SCIT with a low-dose SLIT regimen (6.4 μg of major grass group 5 allergen CMD, 2.4 times higher than the SCIT dose) in patients with grass allergy. The study did not include a placebo or untreated control group. There was a significant improvement in symptom and medication scores in both groups, but only the SCIT group demonstrated a significant improvement in the objective parameters (total IgG, specific IgG4, and skin reactivity).[82]

Determinants of efficacy of SLIT

The few studies that evaluated dose response (2 by design[18,19] and 1 by tolerance[59]) did demonstrate greater efficacy in the highest-dose group, which did not appear to be offset by a reduction in safety, as is often the case with SCIT. However, in considering all of the studies reviewed, there did not appear to be a consistent relationship between dose and efficacy. Allergen dose classification was based on the CMD in relationship to the authors' recommended dose for SCIT: low (<1-5 times SCIT), intermediate (6-50 times SCIT), and high (>50 times SCIT). Combining treatments of all durations in the seasonal allergen studies that provided symptom and medication scores, 5 (31%) of 16 of the low-dose studies, 3 (42%) of 7 of the intermediate-dose studies, and 4 (57%) of 7 of the high-dose studies did not demonstrate a significant improvement in both symptom and medications scores (see Table E2 in the Online Repository at www.jacionline.org). In the perennial allergen group one study in the high-dose group and one study in the intermediate-dose group failed to demonstrate significant efficacy in either parameter.[49,66]

Considering only symptom scores at all time points and subgroups in the seasonal allergen studies, 12 (75%) of 16 of the low-dose studies, 7 (100%) of 7 of the intermediate-dose studies, and 6 (75%) of 8 of the high-dose studies reported significant improvement compared with that seen in the untreated control groups in either the primary disease studied or a related allergic disease symptom or symptoms. In 10 (83%) of 12 of the perennial allergen studies that provided symptom scores, there was significant improvement in at least one of the symptom scores related to the disease studied at some time point. There was also no clear pattern of improvement with the duration of immunotherapy in the perennial or seasonal allergen groups, although a few studies (previously discussed) that failed to demonstrate clinical efficacy in the first year reported efficacy in the second or third year of treatment.

Efficacy summary

Although the majority of SLIT studies reviewed demonstrated some evidence of clinical efficacy in the form of either improved symptom scores, medication scores, or both, approximately 35% of the randomized DBPC studies did not demonstrate efficacy in either parameter. Recent studies have suggested a relationship between dose and efficacy with SLIT, but a consistent relationship between allergen dose, treatment duration, and clinical efficacy has not been established. Further research is clearly needed to determine the optimal dosing and treatment duration for SLIT.

IMMUNOLOGIC RESPONSE

The immunologic responses examined in studies of SLIT include local effects at the site of administration, systemic antibody and cellular responses, end-organ inflammation, and sensitivity to both specific and non-specific challenges. These changes are summarized in Table E5 in the Online Repository at www.jacionline.org. Additionally, sublingual therapy has been evaluated for its effect on progression of the atopic state, the development of new skin test reactivity, and the progression from allergic rhinitis to asthma. The immunologic responses were assessed in relation to the size of the maintenance dose in relation to the author's customary injected immunotherapy and the duration of administration (Table II).[17]

Local immune responses

Although many investigators believe local immunologic changes are important for the mechanism of action of SLIT, very few studies have addressed this. Local persistence of a small (approximately 2%) amount of radioactivity was demonstrated in healthy volunteers up to 20 hours after being given a sublingual dose of iodine 123–labeled Par j 1. This might be explained by local uptake of the allergen by dendritic cells.[86] In one study sublingual mucosal biopsy specimens were obtained in 24 patients (14 receiving active treatment and 10 receiving placebo)

TABLE II. The immunologic response to SLIT: variables of treatment category by dosing expressed as CMD in comparison with recommended monthly dose for SCIT[106]

Very low dose: <2× SCIT
Low dose: 2-5× SCIT
Intermediate dose: 6-50× SCIT
High dose: more than 50× SCIT
Category by duration of treatment
    Patients treated ≤6 mo
    Patients treated ≤12 mo
    Patients treated ≥18 mo
    Patients treated ≥24 mo

after treatment for 18 months. There were no differences in $CD3^+$, $CD1a^+$, or $CD68^+$ cell counts in the epithelium or the lamina propria. There were very few IL-12p40 $mRNA^+$ cells, and no significant difference was seen between groups.[24] Sublingual salivary eosinophil cationic protein (ECP) levels measured before and after 7 months of SLIT showed a significant reduction ($P = .01$).[87]

Systemic immune responses

Inflammatory mediators. Many investigators have focused on systemic immunologic changes, and a great variety of markers have been studied in allergic patients treated with SLIT for periods of 6 months to almost 3 years. The most consistent systemic change is a reduction of serum ECP levels. A decrease in the concentration of this marker of eosinophil degranulation has been reported in all but one study in which it was measured in adult and pediatric patients after 6, 12, and 24 months of treatment[16,29,48,69] and also after 2 preseasonal 6-month courses of SLIT.[77] The SLIT doses varied widely, from 0.017 to 100 times the CMD microgram dose of major allergen usually recommended for SCIT. A reduction in serum ECP levels is consistent with the reduction of peripheral blood eosinophil counts, which has also been reported.[57,81] Moreover, serum myeloperoxidase levels were reduced after 2 years of SLIT in one study.[48]

Serum intercellular adhesion molecule (ICAM) 1, IL-2 receptor, E-selectin, and IL-12 levels remained unchanged in one study,[88] but cytokine IL-13 levels and levels of the T_H2-related hormone prolactin were reduced.[69] Only one recent report investigated the effect of SLIT on serum IL-10 production.[89] PBMCs from patients with HDM allergy treated for at least 3 years with SLIT showed significantly increased IL-10 production after *Candida* species and PHA stimulation compared with those from patients with untreated rhinitis ($P < .001$ for both).

Antibody response. The most frequently assessed immunologic responses are allergen-specific IgE and IgG4. In the very-low-dose SLIT studies, those that included 87% of the patients showed no significant change in allergen-specific IgE levels, whereas in the studies with the 3 higher dose ranges, progressively fewer patients were in studies that showed no change (increase or decrease) in allergen-specific IgE levels (low dose, 52%; intermediate dose, 32%; and high dose, 17%). There was,

however, no dose-related trend in these 3 dosing ranges in the percentage of patients who were in studies showing a decrease in specific IgE levels.

Serum allergen-specific IgG4 levels, on the other hand, demonstrated a clear dose response to increasing maintenance doses of allergen (see Table E6 in the Online Repository at www.jacionline.org). There was no relationship between the duration of SLIT and the likelihood of having an IgG4 response. In the 6 studies that reported serial serum allergen-specific IgG4 measurements, most reported a significant increase in the first year,[21,24,39,40,46,72] often with no further increase despite continued treatment.[21,46,72] In general, serum allergen-specific IgG4 levels increased 2- to 30-fold by 12 months and then reached a plateau.

Allergen-specific IgG1 levels were also reported to be increased after 12 months of SLIT,[21,40] and this increase was sustained at 24 and 36 months of SLIT.[21] In 17 patients studied after 6 months of SLIT, there was a normalization of the reduced serum IgA level to a level similar to that found in nonatopic control subjects.[57] These findings have recently been confirmed in a large study using grass tablets, in which the increase in IgA level was clearly dose and time dependent.[19]

Lymphocyte responses. $CD40^+$ B cell counts and $CD3^+$, $CD4^+$, and $CD8^+$ cell counts in unstimulated peripheral blood remained unchanged in one study.[69] However, in another 12-month study in which HDM extract containing approximately 16 µg of Der p 1 per month was administered, peripheral blood $CD8^+$ T cells were significantly increased ($P = .005$), and the $CD4^+/CD8^+$ ratio significantly decreased ($P = .005$).[39]

After 1 year of SLIT with grass extract, there was a decrease in the lymphoproliferative response of PBMCs to grass allergen but not tetanus toxoid stimulation ($P < .001$).[90] In the same study allergen-specific T-cell clones from the peripheral blood did not reveal any changes in the T_H1/T_H2 cytokine ratio during the course of SLIT. In a 6-month study using HDM extract at 20 times the monthly SCIT dose, stimulated PBMCs showed an increase of IL-12 and INF-γ production, which was greater when SLIT was preceded by a single administration of BCG.[81] In a 32-month study using low-dose SLIT (0.5 µg of group 5 grass allergen 3 times weekly),[38] stimulation of PBMCs with grass revealed no change in the secretion of INF-γ, IL-4, IL-10, or IL-13.

The peripheral blood T cells of healthy control subjects more frequently expressed β V8b than those of untreated allergic patients.[52] After 2 or more years of SLIT with low-dose HDM (approximately 10 µg per month of Der p 1), β V8b frequency normalized in the treated allergic patients, and β v5a, v8a, and v12a were all more frequent than in untreated symptomatic allergic subjects.

Urinary leukotrienes. Levels of urinary leukotriene E_4 and leukotriene B_4 were measured before and after 12 months of SLIT. There was a statistically significant reduction in urinary leukotriene levels in patients with rhinitis but not in asthmatic patients after treatment with SLIT.[78]

CHANGES IN END-ORGAN INFLAMMATION
Nasal

No changes have been detected in spontaneously occurring nasal eosinophils after SLIT[41,81]; however, there was a reduction in the increase in eosinophil counts after an allergen challenge in comparison with that seen in placebo-treated patients.[26] In a study using allergoid grass pollen, there was a significant increase in nasal ECP levels in the SLIT and placebo groups in the pollen season, with no statistically significant difference between groups. However, the placebo group had an increase ($P < .01$) in nasal EG2/EG1 values during the pollen season, reflecting a percentage of activated eosinophils that was not observed in the SLIT group.[84] EG1 and EG2 are monoclonal antibodies; EG2 is an anti-ECP monoclonal antibody that recognizes activated eosinophils and a minority of resting eosinophils while EG1 is an anti-ECP monoclonal antibody that recognizes resting and activated eosinophils. After SLIT, there was no change in spontaneously occurring nasal fluid ECP levels,[38,87] but the seasonal increase of nasal tryptase levels observed in the placebo group was not present in the SLIT group.[91] In a small study of 7 patients, a significant reduction in ICAM-1 expression on nasal epithelial cells was seen after 24 months of SLIT.[41]

Conjunctival

Conjunctival ICAM-1 levels and eosinophil and neutrophil counts were all significantly reduced after 12 months of SLIT, with a further reduction after 24 months.[48]

Sputum

There is one report of inflammatory markers in human sputum after 12 months of SLIT, showing no change in ECP and a reduction of sputum tryptase levels.[91]

Provocation tests

The effect of SLIT on the specific response to challenge with allergen and the nonspecific response to histamine or methacholine has been examined in the eyes, nose, and lower airway. There was a significant reduction in sensitivity to allergen bronchial challenge in all trials that investigated this response.[39,75,81] In studies that included 80% of all patients who underwent nonspecific bronchial challenge, there was a statistically significant increase in mean threshold that occurred in all studies with more than 12 months of SLIT administration.[31,35,39,41,57,92] In one study with serial measures of methacholine sensitivity, there was a progressive increase in threshold from 6 months to 18 to 24 months of SLIT.[35]

In studies that included 71% of all patients who underwent specific nasal challenge, there was a statistically significant increase in mean threshold. In studies that included 50% of all patients that underwent specific conjunctival challenge, there was a statistically significant increase in mean threshold. However, there was no clear dose response, which might be due to the small number of studies in which these challenges have been performed.

Immediate skin tests

The response to quantitative skin prick tests (SPTs) was documented in a number of studies. There appeared to be a relationship between SPT suppression and increasing dose. There also appeared to be a relationship between duration of treatment and SPT suppression (see Table E7 in the Online Repository at www.jacionline.org). This was very clear in 3 studies with serial measurements showing no SPT changes at 12 months and suppression at 18 to 24 months of SLIT.[28,39,46]

In 2 studies the late cutaneous response to allergen was assessed, and in both there was a significant reduction.[24,33]

Progression of atopy

The development of new skin test sensitivities was assessed in 3 studies. In 2 studies, one of 3 years' duration[79] and the other of between 4 and 5 years' duration,[32] there was no difference between treated and untreated subjects, whereas in a large study of 29 months' duration, new positive SPT responses developed in 5.9% of the treated subjects and 38% of the control subejcts.[36] The progression from rhinitis to asthma was specifically examined in one of these articles.[79] One hundred thirteen children aged 5 to 14 years with hay fever limited to grass pollen and no other important allergies were randomized to 3 years of SLIT or to observation only in an open study. At entry, none of the children reported more than 3 episodes of seasonal asthma per year. Treatment was administered preseasonally and coseasonally for 3 years, with a monthly cumulative dose of 10 μg of grass group 5 allergen (half of the recommended SCIT dose). In the active treatment group the cumulative development of asthma was 6 patients in the first season, 7 patients by the second season, and 8 patients by the third season. The corresponding numbers in the control group were 6, 16 ($P = .058$), and 18 ($P = .0412$) patients.

Summary of immunologic changes with SLIT

Many studies of SLIT have demonstrated decreased circulating eosinophils, decreased serum ECP levels, and increased allergen-specific IgG4 and IgA levels. Peripheral blood lymphocytes have been shown to have a reduced proliferative response to allergen and enhanced secretion of IL-10, IL-12, and IFN-γ. Both immediate- and late-phase cutaneous responses to allergen are reduced. Both specific and nonspecific bronchial responsiveness is reduced. SLIT has been shown to reduce the development of new skin test reactivity and progression of rhinitis to asthma in some studies.

MECHANISM OF SLIT

It has long been known that oral administration of an allergen favors the development of tolerance. Current understanding is that regulatory T cells secreting TGF-β are involved in this type of tolerance. Administration of high-dose allergen immunotherapy by means of subcutaneous injection also induces the development of regulatory T cells, with evidence that the secretion of both IL-10 and TGF-β is important in the mechanism of tolerance.[93] Because many patients receiving SLIT show immunologic changes similar to those observed in patients receiving SCIT, such as suppression of the immediate- and late-phase skin test responses, increased levels of allergen-specific IgG4, and in some studies suppression of allergen-induced lymphocyte proliferation, it is not unreasonable to suggest that stimulation of regulatory T cells underlies the response to immunotherapy by both routes. Whether there are significant differences between SCIT and SLIT in the site of T-cell stimulation and the subsets of regulatory T cells stimulated remains to be determined.

SAFETY OF SLIT

All studies, including retrospective DBPC and observational studies with and without an open control group, that provided any information on safety or tolerance were considered.§ Some studies were designed specifically to evaluate the efficacy and safety of SLIT. Others were included if they provided information about treatment tolerance, adverse events (AEs), or dropouts.

The amount of information on adverse treatment-related events varied greatly, ranging from general summary statements, such as ''no relevant side effect,'' to a detailed breakdown of AEs. Some studies reported adverse reactions but failed to specify which ones were believed to be treatment related. None of these studies reported any SLIT-related systemic reactions (SRs) accompanied by hypotension or any fatalities.

Incidence and number of adverse reactions

One of the purported advantages of SLIT over SCIT is greater safety. There were 66 SLIT studies that provided some information about SLIT-related AEs (see Table E8 in the Online Repository at www.jacionline.org). Six studies with allergoid SLIT will be discussed separately, as well as an additional study investigating SLIT for latex allergy[94] and 2 studies looking exclusively at side effects during an ultrarush induction phase, one with sublingual allergoid[95] and the other with various commercial allergen extracts.[96] Three studies designed to evaluate safety in very young children will also be discussed separately.[53,97,98]

Most of the studies did not report the actual number of doses, and therefore the estimated number of doses was calculated from the immunotherapy schedule, treatment duration, and the number of enrolled patients and dropouts. The percentage of patients with AEs varied widely between the studies (from 0% to 100%) because some studies[24] included even mild local itching as a side effect, whereas others did not include information about local reactions.

In the approximately 1,181,654 doses administered to 4378 patients in the 66 studies reviewed (not including the latex study, ultrarush build-up, or allergoid studies), there were no serious life-threatening reactions reported. The same holds true for the 6 studies of allergoid SLIT, totaling approximately 70,000 doses in 380 patients.[31,48,50,53,84,99] However, in 41 studies that gave information on total number of AEs, there were 1047 adverse reactions in a total of 386,149 doses (2.7 reactions per 1000 doses). In 49 studies that gave information on total numbers of patients with adverse reactions, 529 (12%) of 4378 patients reported an AE. In the studies that specified the type of reaction, 169 of 314,959 (0.056% of doses administered) were classified as SRs. Severe SLIT treatment-related AEs were uncommon. There were 14 probable SLIT-related serious AEs during the 5377 SLIT treatment years, which is 1 serious AE per 384 treatment years. Most SLIT-related AEs were asthma or gastrointestinal symptoms. (See Table E9, available at www.jacionline.org, for description of serious AEs.)

Active versus placebo-treated patients

Considering only the 38 placebo-controlled studies with unmodified allergen SLIT and information on AEs, approximately 282,894 SLIT doses administered to 1688 patients resulted in 353 (21%) patients reporting 823 AEs (2.9 per 1000 doses) and 226,261 placebo doses administered in 1302 patients, resulting in 152 (11.7%) patients reporting 207 (0.9 per 1000 doses) adverse reactions (see Table E8 in the Online Repository at www.jacionline.org). Adverse reactions accounted for withdrawal in 3% of all enrolled patients receiving SLIT versus 1.4% of all enrolled patients receiving placebo, but the total percentage of withdrawals for any reason was similar (9% of all enrolled patients receiving SLIT and 12% of all patients receiving placebo).

Considering only those studies that mentioned the exact number of adverse reactions (22 DBPC studies), there were 112 (0.81 per 1000 doses) SRs in the SLIT group and 50 (0.4 per 1000 doses) SRs in the placebo group, excluding reactions classified as "other." In the 22 DBPC studies reporting the exact number of adverse reactions, rhinitis, conjunctivitis, or both were mentioned more frequently in the SLIT group than in the placebo group (38 AEs vs 15 AEs, respectively). There were also more local (oral mucosal) and gastrointestinal tract reactions in the SLIT group compared with those in the placebo group. However, asthma, urticaria and "other respiratory reactions" were less frequently reported in the active group.

Adverse reactions: Classification of severity

Ten studies classified the severity of the adverse reactions according to varying criteria. In these 10 studies approximately 250,000 doses were given to 1102 patients: 37 AEs were classified as "moderate," and 24 were classified as "severe" (including some cases of "severe rhinitis"). However, not all of the studies provided a description of the type of reaction in each severity group, and some provided seemingly conflicting information. For that reason, we made the following classification of

AEs using the good clinical practice (GCP) definition of serious AEs, and adding a moderate category as follows:

- serious AE: potentially life-threatening, including hospitalization and asthmatic attacks;
- moderate AE: requiring some action, such as study withdrawal, medication, or dose modification; and
- mild AE: all the rest, local or systemic.

Fifty-eight studies with allergen SLIT contained enough information to classify serious AEs. In 3984 patients treated for a total of 5377 SLIT treatment years with a total of 1,019,826 doses, there where 16 serious AEs, of which 14 were probably SLIT related (see Table E9 available in the Online Repository at www.jacionline.org).[**] Asthma exacerbations accounted for 7 of the 14 probable SLIT-related serious AEs,[38,39,66,77,100] one of which required hospitalization.[38] One study reported 3 serious asthma reactions that were attributed to the allergen dose.[39] There was 1 asthma exacerbation per 498 patients receiving SLIT.

Fifty studies with unmodified allergen SLIT contained enough information to classify moderate AEs. In 2939 patients treated for a total of 4586 SLIT treatment years with a total of 810,693 doses, there were 244 moderate AEs that required dose adjustment or medication or resulted in study withdrawal. The majority of the moderate reactions were due to gastrointestinal complaints, rhinoconjunctivitis, urticaria, or some combination of these symptoms. Cough accounted for 2 reactions classified as moderate.[44] One urticarial reaction in a 4-year-old child might have been the result of a 2-month gap in treatment.[55]

Three studies classified the reactions according to the recommendations of the European Academy of Allergology and Clinical Immunology.[22,45,72] Grade 1 reactions are nonspecific, grade 2 reactions are mild SRs, grade 3 reactions are non–life-threatening SRs (including urticaria), and a grade 4 reaction is anaphylactic shock. In a DBPC study of SLIT and SCIT in patients with birch-induced allergic rhinitis, there were 15 grade 2 reactions in the SLIT group.[45] However, patients in the SCIT group had 14 grade 2 reactions, 5 grade 3 reactions, and 1 grade 4 reaction, and patients in the placebo group had 11 grade 2 reactions and 1 grade 3 reaction. In a DBPC study of patients with *Olea europea*–induced allergic rhinitis, there were 2 probable grade 1 or 2 SLIT treatment-related reactions (rhinitis, ocular itching, and "spongy sensation in the mouth").[22] The corresponding placebo group also had 2 grade 1 or 2 reactions (urticaria and "pharyngeal sensation of oppression"). In a DBPC preseasonal and coseasonal study of patients with grass-induced allergic rhinitis, there were 2 grade 2 reactions in the SLIT group (both transient breathlessness and throat tightening) and 1 grade 3 reaction in the placebo group (urticaria).[72]

Local reactions

In general, oral symptoms (oral mucosal pruritis and burning and lip swelling) were considered local reactions

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[**]References 19, 24, 30, 38, 39, 66, 77, 97, 100, 101.

in SLIT, analogous to the injection site swelling associated with SCIT. In the 66 studies considered, there were 823 "local reactions" (0.68 per 1000 doses). This is likely an underestimation because several studies reported safety information as a general statement or a patient-rated tolerability scale of poor to very good, which was obtained retrospectively by questionnaire.[44] Some studies stated that local oral reactions were not considered in the safety analysis. Thus in these cases it was not possible to estimate or calculate the actual number of local reactions. The reaction types are summarized in Table E8 in the Online Repository at www.jacionline.org.

RELATIONSHIP BETWEEN ADVERSE REACTIONS, ALLERGEN DOSE, AND IMMUNOTHERAPY SCHEDULE

Adverse reaction frequency and allergen dose

In the 66 SLIT studies that provided safety information reviewed in this article, there did not appear to be a consistent relationship between the adverse reaction rate or severity and the administered dose. In an 18-month study of 58 asthmatic children with dust mite allergy treated with a maintenance dose of 1.2 μg of Der p 1 3 times a week (15.4 μg of Der p 1 CMD), there were 32 SRs in approximately 6933 administered doses (0.46% per dose); 17 of these were classified as dose related ("exceeded maximum tolerated dose").[39] However, in a 24-month study of adults and children with HDM-induced rhinitis using a higher dose regimen (equivalent to 7.3 μg of Der p 1 3 times a week and 91 μg of Der p 1 CMD), only 2 (5%) of 36 patients receiving SLIT reported an AE (0.02% per dose; both oral mucosal and "no severe adverse effects were reported or detected").[49] A similar comparison of high- and low-dose regimens in patients with grass-induced allergic rhinitis yielded comparable results. In the low-dose regimen study of 75 children treated for 32 months with 0.5 μg of group 5 major grass allergen 3 times a week (6 μg of group 5 major grass allergen CMD), adverse reactions were reported in 49% of the SLIT group compared with 27% of the placebo group.[38] In the high-dose regimen study 132 children were treated with 9.1 μg of Phl p 5 daily (273 μg of Phl p 5 CMD) for 3 years, and only 18 adverse reactions were reported in the SLIT group, 17 of which were local (oral mucosal). This results in an SR rate of 0.015% per dose for a dosing regimen that is nearly 50 times greater than the dose used in the previous study.[21]

Adverse reaction frequency and induction schedule

The adverse reaction rate in SLIT studies did not seem to correlate with the type of immunotherapy induction (ultrarush or rush) or maintenance schedules (daily or weekly).[28,49,50] Generally, accelerated induction schedules, such as rush immunotherapy, are associated with increased SR rates in SCIT, but this does not appear to be the case with SLIT.[111-113]

In a recent pilot study 679 patients with allergic rhinitis, asthma, or both underwent 20- to 25-minute ultrarush SLIT induction, receiving increasing doses of allergen every 5 minutes and reaching cumulative allergen doses after half an hour that were several times the SCIT dose (range, 4.7-525 μg of major allergens).[96] They reported that all patients tolerated the treatment well, with 122 (17.96%) patients reporting mild local symptoms, primarily pruritis of the oral cavity. Two patients experienced urticaria 2 hours later, and 1 patient had urticaria and rhinitis 3 hours later.

In a study of 855 patients that compared 3 doses of grass allergen tablets administered with no induction phase, with the highest dose being equivalent to 15 μg of Phl p 5 daily (analogous to the recommended maintenance dose of 20 μg for SCIT), it was reported that the tablet was well tolerated and showed "no safety concerns," although there was one patient with "mild uvula swelling" who was hospitalized for observation but not treated in the middle-dose treatment group (25,000 SQ-T or 5 μg of Phl p 5).[19] The patient continued in the study from the day after and had no further problems. These studies would suggest that there is no need for a build-up phase with SLIT.

SLIT adverse reactions: Induction versus maintenance phase

Although the adverse reaction rate does not appear to depend on the type of induction schedule, many studies report that the majority of adverse reactions occurred during the induction phase, without giving any exact numbers.

SAFETY OF SLIT IN YOUNG CHILDREN

There were 3 studies, 2 observational and 1 postmarketing survey, which were specifically designed to assess the safety of SLIT in young children.[53,97,98] In the first study 33 children with intermittent (12 patients) or mild persistent (17 patients) asthma or persistent rhinitis (33 patients), aged 1 year and 11 months to 3 years and 10 months (mean, 3 years and 2 months), were treated with a monomeric allergoid (Lofarma, various allergens, 4 drops of 3000 AU/mL daily).[53] The mean follow-up was 22.3 months, and approximately 22,200 doses were administered. Two children experienced 1 episode of abdominal pain (5% of patients; 0.071 per 1000 doses); one was mild, and the other was characterized as moderate, requiring a temporary dose adjustment. The parents' assessment in 21 children was highly improved, moderately improved in 9 children, slightly improved in 9 children, and unchanged in 2 children.

In the second study 65 children aged 38 to 80 months (mean ± SD, 60 ± 10 months) were treated with SLIT to various pollens or dust mite for a mean of 246 ± 161 days.[97] The target maintenance dose was 300 IR 3 times a week (300 times higher than the standard dose recommended with SCIT). The investigators compared 2 subgroups:

38 to 60 months (33 patients, 52 ± 6 months) and 61 to 80 months (32 patients, 70 ± 10.6 months). There were 6 AEs (4 urticarial, 1 gastrointestinal, and 1 orolabial itch) in 5 (15%) patients in the younger group and 7 AEs (2 urticarial, 3 gastrointestinal, and 2 orolabial itch) in 6 (18%) patients in the older group. Six AEs occurred during the build-up phase and 7 in the maintenance phase. The severity of the AEs ranged from mild to moderate, and none resulted in discontinuation of treatment.

The third study was a postmarketing survey of 126 children aged 3 to 5 years (mean age, 4.2 years) with allergic rhinitis, asthma, or both treated for 2 years with SLIT to various allergens.[98] Side effects were recorded by the parents on diary cards. The total number of doses was 39,000. Nine side effects were reported in 7 children (5.6% of patients and 0.2 per 1000 doses). All side effects occurred during the induction phase. There were 2 local (oral itching) side effects that required no treatment and 7 SRs (one was an episode of mild abdominal pain that did not require treatment). The remaining 6 cases were moderate (abdominal pain with diarrhea) and controlled by means of dose reduction achieved by changing the SLIT method from sublingual swallow to sublingual spit.

SLIT FOR LATEX ALLERGY

One study investigating the tolerability of SLIT for the treatment of latex allergy in 26 patients reported 257 adverse reactions in 1044 doses (24.6% of doses), 223 (21.4%) of which were classified as local reactions and 38 (3.6%) as SRs.[94] The rate of adverse reactions during the induction phase (90/366, 24.59% per dose) was almost the same as that during the maintenance phase (167/678, 24.63% per dose). No treatment was required in 44.7% of SRs, antihistamines alone were required in 26.3%, β-agonists alone were required in 5.3%, and antihistamine, corticosteroids, or both were required in 18.4% of SRs. One patient was treated twice with adrenaline as a "precautionary" measure because of immediate dyspnea in one case and abdominal pain, cough, headache, rhinitis, dyspnea, and chest tightness in the other. Only 2.3% of local reactions were treated with antihistamines. All patients reached the planned maximum dose corresponding to 500 μg of latex proteins. Significant improvement was demonstrated in the glove-use test ($P = .003$ after 5 days and $P = .0004$ after 10 weeks of treatment), doctor's assessments ($P = .003$ after 5 days and $P = .004$ after 10 weeks), and the rubbing test ($P = .036$ after 10 weeks of treatment), but no change was detected in SPTs.

SAFETY OF SCIT VERSUS SLIT

Four studies provide some safety comparison of SLIT and SCIT. In a 12-month, double-blind, double-dummy study of 20 patients with grass allergy, minor side effects were reported in the SCIT group, but there were no systemic side effects in either group.[82] In a 23-month study comparing SCIT (11 patients) with SLIT (12 patients) treatment with *Alternaria tenius* for 2 years, "no local or systemic side-effects" were reported in the SLIT group, but SRs (character not described) were reported in the SCIT group.[51]

In a study of 36 patients with HDM-induced allergic rhinitis and asthma treated with one of 3 treatments, SLIT (n = 15), SCIT (n = 10), or placebo SLIT (n = 11), there was one episode of bronchospasm in the SCIT group and one patient with nausea in the SCIT group, which disappeared with dose reduction.[70] In a DBPC study comparing 18 SLIT-, 21 SCIT-, and 19 placebo-treated patients previously discussed, there were European Academy of Allergology and Clinical Immunology–defined grade 2 reactions in all 3 groups (SLIT, 15 patients; SCIT, 14 patients; placebo, 11 patients), but only the SCIT (5 patients) and placebo (1 patient) groups had grade 3 reactions, and only 1 patient receiving SCIT had a grade 4 reaction.[45]

SLIT in oral allergy syndrome

In an open study of 30 patients with oral allergy syndrome treated with SLIT for respiratory allergies (28 with pollen allergy and 2 with dust mite allergy), there were no oral side effects reported during the 3 years of treatment.[102]

Summary of SLIT safety in the context of SCIT

Comparing the safety of SLIT with that of SCIT is complicated by the fact that they are administered in 2 completely different venues. SCIT is generally administered in a medical setting, with trained personnel available to assess, treat, and document adverse reactions. On the other hand, SLIT is generally administered in the home setting, and the reporting of adverse reactions is dependent on the patient's or a family members' recollection through questionnaires or accurate, consistent diary logs. Thus there is considerable potential for inaccurate accounting of SLIT AEs on the basis of the patient's or family member's recall bias and compliance with diary documentation.

The incidence of SRs in SCIT studies varies greatly depending on several factors, including allergen dose and schedule, use of premedication, and patient selection.[111-114] The 2003 Joint Task Force Practice Parameter on Allergen Immunotherapy states that "severe SRs are rare after appropriately administered allergen immunotherapy."[106]

In a recent AAAAI survey of physician members on near-fatal immunotherapy reactions (NFRs), defined as respiratory compromise, hypotension requiring emergency epinephrine, or both, there were 273 incidents over the 11-year period between 1990 and 2001.[115] The unconfirmed near-fatal reaction rate was 23 per year or 5.4 events per million injections (0.0054 per 1000 injections).

A retrospective analysis from Europe reported on the incidence and characteristics of NFRs to SCIT over a 20-year period (1981-2000). During this period, when 435,854 injections were administered to 4000 patients, there were 115 SRs (5.2% of patients and 0.06% of injections) in the first 10 years and 26 SRs (1.08% of

patients and 0.01% of injections) in the second 10 years ($P < .0001$), with fewer episodes of asthma and urticaria in the second 10 years and no fatalities.[116]

In another prospective multicenter study, there were 158 SRs (0.9 % per injection) and no fatalities in 17,526 doses administered to 423 patients.[117] The authors noted that 40% of the SRs would have been avoided if SCIT was discontinued after 3 SRs because 18 (3.7%) patients had 33% of the SRs.

Comparison of serious treatment-related AEs between the 2 treatment modalities is made difficult by the variability in characterizing and describing these reactions, but assuming some similarity between the NFRs identified in the AAAAI immunotherapy survey and the combined SLIT studies' ''serious reactions,'' the per-dose incidence is very low for both groups. In the SLIT DBPC studies reactions associated with 0.0011% of the doses were classified as severe, and in the AAAAI SCIT survey 0.00054% of the doses resulted in an NFR reaction.

In an AAAAI survey there were 41 fatalities from immunotherapy injections identified over a 12-year period.[118] The estimated fatality rate was one per 2.5 million injections (average of 3.4 deaths per year), which is similar to results in 2 previous surveys of AAAAI physician members.[119,120] To the authors' knowledge, there has been no formal survey similar to the AAAAI's membership survey on fatal reactions and NFRs with SLIT, and thus the absence of any severe life-threatening reactions of fatalities with SLIT is only presumed.

Fifteen of the 17 SCIT fatalities occurred in patients with asthma, which was considered the susceptibility factor contributing to fatal outcomes in 9 patients.[118] In 5 of the 10 patients who had baseline pulmonary function tests before starting SCIT, the FEV_1 was less than 70% of predicted value. The primary disease in most of the SLIT studies was allergic rhinitis, and most of the studies designed to study asthma excluded patients with FEV_1 values of less than 70% of the predicted value. The safety of SLIT in this population and other high-risk populations, such as patients with a high degree of hypersensitivity or patients experiencing exacerbations of their allergy symptoms, requires further study. Surveillance of the safety of SLIT should continue to assess and confirm its professed safety in the out-of-office setting. Table III contains a synopsis of the SLIT Joint Task Force's SLIT safety analysis and recommendations.

Summary of safety with SLIT

SLIT is associated with adverse reactions. By far the most common are local symptoms in the oral cavity; however, abdominal complaints, urticaria, and asthma have been reported, although all are uncommon. Thus far, anaphylactic reactions accompanied by hypotension and fatal reactions have not been reported. It should be recognized, however, that there has been little reported use of SLIT in patients with severe asthma, and multiple allergen SLIT has not been reported.

TABLE III. Summary of adverse reactions to SLIT

No reports of SLIT-related SRs accompanied by hypotension or any fatalities
Oral-mucosal symptoms
  Common: affecting up to 75% of patients
  Self-limiting and not requiring treatment
  Dose modifications sometimes required
  More common during up-dosing phase
Severe reactions have been reported
  Predominantly asthma or gastrointestinal
  Leading to discontinuation in some patients or dosage modification
Fourteen probable SLIT-related serious AEs (as defined by GCP)
  Asthma exacerbations accounted for 7 severe AEs, one of which required hospitalization
  Three severe asthma reactions were attributed to allergen dose
One moderate SR occurred after a 2-month gap in treatment (urticaria)
There appeared to be no consistent relationship of adverse reactions and SLIT dose or induction or maintenance schedule
Majority of studies have been done in rhinitis-rhinoconjunctivitis with or without mild-to-moderate asthma
No studies in severe asthma
Few studies in high-risk patients; therefore cannot extrapolate the current safety data to this subgroup of patients

SLIT PRACTICAL CONSIDERATIONS
Economics

Of the 55 million patients with allergy in the United States, approximately 2 to 3 million receive allergy immunotherapy injections. SLIT might present an opportunity for broadening the use of immunotherapy by extending it to those patients who are not candidates for SCIT because they dislike injections, find the frequent visits to the physician's office inconvenient, or are concerned with its safety. Thus the disease-modifying benefits of immunotherapy could be extended to a greater portion of the allergic population.

It is difficult to predict the likely cost of SLIT without having a clear concept of what dose is required to achieve optimal efficacy. One study demonstrated efficacy only in the highest-dose group, who were treated with a CMD that was 410 times the usual monthly SCIT dose,[59] and another demonstrated efficacy only in the group treated with 22.5 times the usual monthly SCIT dose.[19] If this dose requirement for SLIT efficacy is confirmed, then the treatment might be cost prohibitive. There might also be some logistic problems in trying to produce enough extract to provide these doses. Only one reported study has used US Food and Drug Administration (FDA)–approved allergen extracts for high-dose SLIT. In that study patients with cat allergy were treated with a total dose of 45,000 BAU (containing 3240 μg Fel d 1) over 105 days. The active treatment was at most marginally more effective than placebo. In this example the cost per patient using the FDA-standardized cat extract would be nearly $500 (list price is $116 per 10 mL of 10,000 BAU/mL cat hair extract) for 105 days of treatment.[25]

SLIT coding status

The definition of immunotherapy from the American Medical Association's Current Procedural Terminology (CPT) 2005 manual is as follows[121]: "Immunotherapy (desensitization, hyposensitization) is defined as the parenteral administration of allergenic extracts as antigens at periodic intervals, usually on an increasing dosage scale to a dosage which is continued as maintenance therapy. Indications for immunotherapy are determined by appropriate diagnostic procedures coordinated with clinical judgment and knowledge of the natural history of allergic diseases."

The CPT code used to bill for preparation of antigens for allergen immunotherapy (95165) is defined as follows: "Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy single or multiple antigens (specify number of doses)" and included in the group of codes (95115-95199) that are described as "professional services necessary for allergen immunotherapy."[121]

Considering the CPT definition of immunotherapy as the "parenteral administration of allergenic extracts," it can be inferred that the 95165 CPT code is intended for preparation of allergen extracts that will be administered by means of the parenteral route. At present, there are no FDA-licensed products for SLIT in the United States. At the present time, physicians practicing in the United States who decide to provide this form of treatment off label might be incurring increased medical liability because of its off-label use and its status as outside of the current US allergy community's standard of care.

ADHERENCE

Another factor to consider before SLIT treatment is prescribed is how adherence will be monitored and the patient's likely adherence with this home-based treatment. Few of the studies reviewed provided information about treatment adherence. Only one multicenter observational study was specifically designed to provide a quantitative measure of SLIT adherence.[99] Eighty-six patients with allergic rhinitis, asthma, or both prescribed SLIT for a single relevant allergen (41 HDM and 45 pollens) were treated with a monomeric allergoid prepared as a soluble tablet for a mean of 18 ± 2 weeks (pollen) or 1 year (HDM). Adherence was assessed through unscheduled telephone interviews after 1 year of treatment for HDM-treated patients or at the beginning of the pollen season for the pollen-treated group. During the interview, patients were asked to count the remaining tablets. The count of the taken-expected tablets was 5080 (96.8%) of 5248 in the HDM group and 3952 (97.6%) of 4050 in the pollen group. Omitted doses were reported in 11 patients, with most postponing 1 or 2 doses because of concurrent illness or forgetfulness. One patient skipped multiple doses because of work schedule. In a randomized, 4-year open study of 511 patients with allergic rhinitis, asthma, or both caused by various allergens, adherence was assessed

by measuring with a pipette the remaining volume of extract in the returned vials and comparing it with the expected amount consumed during a given treatment period.[36] At the end of the observational year, 311 patients were randomized to the SLIT group, and 192 patients were randomized to the medication-only group. Adherence to SLIT over the 3-year period was excellent (>80%) in 195 (72%) of 271 patients, good (from 60% to 80%) in 49 (18%) of 271 patients, and poor or insufficient (<60%) in 27 (10%) of 271 patients.

Because this treatment is administered at home with no direct medical supervision, prescribing physicians would need to provide specific instructions on how to manage adverse reactions, unplanned treatment interruptions, situations in which the dose should be withheld, and dosing adjustments for any or all of these variables. In addition to assessing a patient's likely adherence to SLIT, physicians should consider the patient's ability to follow these instructions before prescribing this treatment

SLIT SUMMARY

- Many questions remain unanswered regarding SLIT, including effective dose and schedule, timing (ie, preseasonal and both preseasonal and coseasonal), mechanism, and safety in high-risk groups.
- Until the optimal effective dose and dosing schedule is established, a cost/benefit analysis of SLIT cannot be made.
- Currently there is no CPT code for SLIT.
- One barrier to endorsement of SLIT is the absence of an FDA-approved product for SLIT.
- Physicians prescribing SLIT should provide specific instructions for managing the different variables that might be anticipated with this home-based therapy, such as gaps in treatment and clinical situations for which the treatment should be withheld.
- Mechanisms to monitor patient adherence and adverse treatment events should be carefully considered before this treatment is prescribed.

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