

Sublingual Immunotherapy in Pediatric Allergic Rhinitis and Asthma: Efficacy, Safety, and Practical Considerations

Linda Cox, MD

Corresponding author

Linda Cox, MD

Nova Southeastern University College of Osteopathic Medicine, 5333 North Dixie Highway, Suite 210, Fort Lauderdale, FL 33334, USA.

E-mail: lindaswolfcox@msn.com

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Specific allergen immunotherapy (SIT) is the only disease-modifying treatment for allergic rhinitis and asthma. Subcutaneous immunotherapy (SCIT) is the only method with a US Food and Drug Administration (FDA)-approved formulation, but safety concerns limit administration to medical facilities. Sublingual immunotherapy (SLIT), under investigation in the United States, appears to have a more favorable safety profile, which may expand its use to populations generally not treated with SIT (eg, young children). This paper reviews SLIT studies that were specifically limited to the pediatric population. Most demonstrated evidence of clinical efficacy, but approximately 29% failed to demonstrate efficacy in symptom and medication scores in the first treatment year. Efficacy was seen in a broad range of allergen doses, but optimal dose range has not been established. SLIT appeared to be well tolerated in children as young as 2 years, but serious adverse reactions, including anaphylaxis, were reported. SLIT is a promising immunotherapy that may expand the population receiving SIT because of the convenience of home administration due to its favorable safety profile. However, questions remain unanswered, including optimal therapeutic dose.

Introduction

Specific allergen immunotherapy (SIT) is the only treatment for allergic rhinitis and asthma that may potentially modify the disease. In contrast to pharmacotherapy, the benefits of SIT may persist years after treatment is discontinued [1–4]. Studies suggest that early intervention with SIT may prevent asthma in children with allergic rhinitis [5–7] and the development of new allergen sensitizations [8,9].

The potential disease-modifying effects of SIT are particularly compelling in children, considering their likely long duration of allergic symptoms [10], which in turn may require years of medications. In addition to the benefit of sustained remission of allergic symptoms, SIT may offer a significant cost-benefit due to reductions in medication and other costs [4,11,12].

Subcutaneous immunotherapy (SCIT) is the only SIT method with a US Food and Drug Administration (FDA)-approved formulation. Despite its proven efficacy, only a minority of allergic patients receive this treatment. Inconvenience is probably the primary reason for its underutilization: treatment is time consuming because SCIT is recommended to be administered in a medical facility, with a waiting period of 30 minutes after injection because of the risk of a systemic reaction, which can, in rare cases, be life-threatening or fatal [13,14]. The conventional (non-accelerated) SCIT induction phase requires weekly visits for several months before the target maintenance dose is reached, and compliance with this regimen may be difficult for an overscheduled individual or family.

Sublingual immunotherapy (SLIT) appears to be associated with a lower incidence of systemic reactions than SCIT [15,16], and safe enough to allow for home administration. The use of SLIT has increased significantly over the past 20 years in Europe, where in some areas it is the predominant form of newly prescribed specific allergen immunotherapy. In response to the growing interest in SLIT in the North American allergy community, an American Academy of Allergy, Asthma, and Immunology/American College of Allergy, Asthma, and Immunology Joint Task Force (SLIT Joint Task Force) was formed to perform a comprehensive review of the literature on this topic, which was referenced through October 2005 [17••].

This paper reviews the efficacy and safety of SLIT in the pediatric population. In addition to studies limited to the pediatric population that were included in the SLIT Joint Task Force review, studies published after October 2005 up to May 2007 were identified through PubMed using the keywords *sublingual immunotherapy*, *asthma*, and *allergic rhinitis*. Studies were selected if the patient

population was limited to pediatrics (≤ 18 years old). The study designs reviewed included randomized controlled; double-blind placebo-controlled [6,7,18•]; open-observational; and postmarketing surveillance.

Efficacy

Clinical parameters

Twenty-four studies provided information on clinical efficacy of SLIT in pediatric patients with allergic rhinitis and/or asthma [19–25,26•,27•,28–32,33•,34–42]. Nineteen studies representing 1208 patients (663 SLIT, 511 placebo, and 34 controls) were chosen for efficacy analysis because they were double-blind, placebo-controlled (18 studies) [19–25,27•,28–31,34–38] or randomized controlled (two studies) [32,33•]. The duration of SLIT in these studies ranged from 3 months [19] to 3 years [28]. In the 17 double-blind placebo-controlled or randomized controlled studies that provided both medication and symptom scores and a comparative untreated control, six of 17 (35%) demonstrated efficacy in both parameters [19,23,24,27•,36,37] and five of 17 (29%) did not demonstrate efficacy in either parameter [22,28,31,33•,38] in the first year of treatment compared to the untreated control patients. Both groups included high- and low-dose SLIT regimens, and seasonal and perennial allergens.

In addition to the five studies that did not show efficacy in symptom and medication scores, an additional four studies showed no efficacy in symptom scores (two studies) or medication scores (two studies) in the first treatment year. Thus, seven of 18 (38%) studies that included symptom scores and seven of 17 (41%) studies that included medication scores did not demonstrate improvement in these parameters in the first treatment year.

In subsequent treatment years, five of the 17 studies that failed to show efficacy in symptom and medication scores in the first year demonstrated improvement in symptoms, medication scores, or both [22,28,31,33•,34]. Two studies demonstrated improvement in symptoms: asthma symptoms in children treated with low-dose dust mite SLIT [34] and rhinitis symptoms in children treated with high-dose *Parietaria judaica* pollen SLIT [31]. One study demonstrated improved symptom and medication scores in the second year, but only the medication score improvement was sustained in the third year [33•]. Using a subgroup analysis, one study demonstrated improvement in the combined index of medication and symptom scores in the most severe group after 3 years of treatment with an intermediate dose of grass SLIT [28]. One study that utilized a low dose of grass SLIT demonstrated improvement in symptoms in the first year and reduced medication requirements in the second year [22].

These findings suggest that SLIT efficacy may require a longer duration of treatment. However, no clear relationship can be seen between allergen type and dose to distinguish the studies that did not show efficacy in the first

year from those that did. In contrast, clinical improvement with SCIT—the standard to which SLIT is compared—may be demonstrated very shortly after the patient reaches the maintenance dose [4,43–46]; furthermore, the Allergen Immunotherapy Practice Parameter recommends considering discontinuing SCIT if clinical improvement is not apparent after 1 year of maintenance therapy [14].

Relationship among dose, duration, and efficacy

The efficacy of SCIT depends on dose. SCIT dose-response studies have been performed for dog [47], cat [48,49], ragweed [50], dust mite [51], and grass [52,53], and the therapeutic dose range appears to be fairly consistent: between 5 and 20 μg of the major allergen. The doses used in the SLIT efficacy studies reviewed above ranged from 0.12 μg of Par j 1 (1.56 μg cumulative monthly dose [CMD]) [20] to 210 μg of Par j 1 (2730 μg CMD) [31], with the former (lowest dose, short duration) demonstrating efficacy and the latter (highest dose) not demonstrating efficacy until the second year. Two studies were designed to compare different doses. One study compared two doses of grass SLIT (defined as 85 times and 375 times the usual SCIT dose) and found greater improvement in symptom and medication scores in the higher group compared with baseline; this study had no comparative untreated control [32]. The other study compared two doses of tree pollen (3.6 μg vs 30 μg of Bet v 1/Aln g 1/Cor a 1 per week) in children with tree pollen-induced rhinitis, and found greater clinical improvement in the high-dose group compared with the low-dose and placebo groups [27•]. In this study, the low-dose group demonstrated efficacy in symptom scores but not in medication scores in the first year, whereas the high-dose group showed efficacy in both parameters. In a subgroup of patients, the effect of SLIT on allergen-induced *in vitro* mRNA expression of interleukin (IL)-4, IL-5, IL-10, transforming growth factor (TGF)- β , and interferon- γ in peripheral blood mononuclear cells (PBMC) was investigated [26•]. There was a dose-dependent response in allergen-specific cytokine production with significantly lower mRNA expression of IL-5 in the high-dose group compared with placebo at the end of the first year. In a 5-year telephonic survey (conducted ~ 3 years after discontinuing SLIT), the majority of subjects (eight of 10) in the high-dose group did not report asthma symptoms, whereas the majority of subjects in the low-dose and placebo groups (six of 10 in each group) did report symptoms of asthma ($P = 0.038$).

A clear response has been demonstrated in a large multicenter study of adults with grass pollen-induced rhinitis treated with one of three doses of grass tablets (0.5 μg , 5 μg , or 15 μg of Phl p 5) [54••]. Duration also appeared to be a factor in determining efficacy because greater improvement occurred in symptom and medication scores in the individuals who had at least 8 weeks of therapy before the grass pollen season. One open study compared the efficacy of 6 months with 12 months of treatment

with SLIT in 31 children with dust mite rhinitis with or without asthma, and found significant improvement in inhaled corticosteroid use in both groups, but only found improvement in rhinitis and asthma symptoms compared with baseline in the 12-month treatment group [41].

Allergen type and efficacy

Clinical efficacy was seen in patients with both seasonal and perennial allergic rhinitis and asthma. The only perennial allergen studied was dust mite. Of the double-blind placebo-controlled or randomized controlled studies (seven) of dust mite SLIT, clinical efficacy was demonstrated in the first treatment year in symptom scores only (three studies) [25,29,30], medication scores only (one study) [34], and both medication and symptom scores (three studies) [24,36,37]. Grass was the allergen most often used in the seasonal allergen studies (seven). The other allergens studied were olive and birch tree pollen (one study each) or *Parietaria* pollen (two studies). No improvement in medication or symptom score was seen in five of 11 seasonal allergic rhinitis studies (four grass studies, one *Parietaria* study) in the first treatment year.

Allergic disease and efficacy

Allergic rhinitis with or without asthma was the disease most often investigated in the double-blind placebo-controlled or randomized controlled studies. Significant improvement in medication and symptom scores compared with the untreated control was seen in only three of 11 (27%) seasonal allergen studies during the first treatment year, whereas five of 11 (45%) studies did not demonstrate efficacy in either parameter during this period. Four studies were designed to study asthma in children allergic to dust mites [24,25,30,34]. In a multicenter study of 97 children with mild-to-moderate asthma who were monosensitized to dust mite and treated with high-dose SLIT (783 µg CMD of mixed mites), a statistically significant improvement was seen in daily, nighttime, and daytime asthma scores in the SLIT group compared with the placebo group after 24 weeks of treatment [24]. There was also improvement in pulmonary function tests (forced expiratory volume in 1 second [FEV₁], forced vital capacity [FVC], and peak expiratory flow rate [PEFR]) and medication scores compared with baseline. However, a smaller study (20 patients total) with a similar design demonstrated significant improvement only in nighttime asthma symptoms compared with the placebo group [25]. In another study of 21 children treated with a low-dose dust mite (10.4 µg CMD of Der p 1) SLIT regimen, improved asthma scores were not seen until the second year [34]. However, the same dose proved to be effective in reducing asthma symptoms in another 6-month study of 86 children with mild asthma [30]. This study also investigated the immune response associated with SLIT and found a significant decrease in eosinophil cationic protein (ECP),

IL-13, and prolactin (PRL) in the SLIT group compared with placebo after 6 months of treatment.

Efficacy: Other Considerations

Prescribing physician

According to the Allergen Immunotherapy Practice Parameter: “the selection of the components of an allergen immunotherapy extract, that is most likely to be effective, should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive tests for specific IgE antibodies” [14]. A physician trained in allergy and immunology is more likely than a primary care physician to have the expertise to select appropriate allergens and patients for SIT. One double-blind placebo-controlled study investigated the efficacy of SLIT (intermediate dose 176 µg CMD of Lol p 5) for 2 years in 168 children (6–18 years) with grass pollen-induced rhinoconjunctivitis in a primary care setting [38]. At the end of the 2-year treatment period, no differences were found between the SLIT and placebo groups for rescue medication-free days, disease-specific quality of life, overall evaluation of the treatment effect or the primary outcome parameter, and mean daily total symptom score.

SLIT lack of efficacy: could it be due to stress?

One study investigated the effect of psychologic stress on SLIT efficacy in 40 children with mild asthma due to dust mites [39]. After 6 months of SLIT, two groups of patients (24 stressed and 16 nonstressed) were established based on the results of the stress integrated measure test. All clinical parameters improved in both groups, but significantly greater improvements in symptom scores, PEFR, and ECP were seen in the nonstressed patients. The authors concluded that psychologic stress can affect response to SLIT, and suggested that a stress evaluation may become a useful prognostic factor in immunotherapy.

SLIT effect on atopy progression

Several studies have suggested that SCIT prevents the development of new allergen sensitizations [8,9,55] or progression from allergic rhinitis to asthma [5–7,56,57]. The preventive effect of SIT may be an important consideration in the pediatric population, who may be just beginning their “allergic march.” In a 10-year observational study, 60 children (mean age 8.5 years) with allergic rhinitis and/or asthma due to dust mites were divided into two matched groups (35 received SLIT and 25 received only drug therapy for 4 to 5 years). Researchers found a significant difference in the SLIT group compared to baseline for asthma 4 to 5 years after discontinuing treatment, with no difference seen in the control group [42]. There was also an improvement in mean PEFR in the SLIT group, but no difference between the groups in terms of new allergen sensitizations. A similar preventive effect was seen in a 3-year open study

of 113 children, ages 5 to 14 years, with grass pollen rhinitis randomized to receive co-seasonal SLIT (low dose; 11 µg CMD of major grass allergen group 5) for 3 years or to standard symptomatic therapy [33•]. Development of asthma after 3 years occurred 3.8 times more frequently in the control subjects (Fig. 1).

SLIT clinical efficacy in the pediatric population:

summary

Most of the pediatric SLIT studies demonstrated clinical efficacy in the form of either improved symptom scores or medication scores, or both. However, approximately 29% of the double-blind placebo-controlled or randomized-controlled studies did not demonstrate efficacy in either parameter in the first treatment year, which is the recommended time point for evaluating SCIT efficacy.

Efficacy (or lack thereof) was seen in a broad range of allergen doses. Some studies have suggested a relationship between dose and efficacy, but different studies using the same or similar dosing regimens have not produced consistent results. There also appeared to be a relationship between duration and efficacy in the studies that examined this parameter, but this relationship was not consistent in the literature: efficacy was seen in studies as short as 3 months' duration, whereas no efficacy was seen in studies as long as 3 years. These findings are consistent with the SLIT Joint Task Force comprehensive review, which concluded that "a consistent relationship between allergen dose, treatment duration, and clinical efficacy has not been established and further research is clearly needed to determine the optimal dosing and treatment duration for sublingual immunotherapy" [17••].

Safety of SLIT

Safety in the pediatric population

According to the SLIT Joint Task Force review, no serious life-threatening reactions were reported in the estimated 1,181,654 doses administered to 4378 patients in 66 studies that provided information on SLIT-related adverse events (AE) [17••]. In studies that provided specific information about AEs, incidence of systemic reactions was 0.056% of injections. This is approximately 10-fold less than the systemic reaction rate reported with SCIT [58]. However, the range of reported systemic reactions with SCIT can vary greatly depending on allergen dose and induction schedule.

In contrast, neither dose nor induction schedule seem to influence the adverse reaction rate with SLIT. Similar AE rates are seen in studies that utilized a multiweek induction schedule [31], "ultra-rush" (< 1 hour) induction [59], and no induction [54••].

In a study of 100 children who underwent a 40-minute ultra-rush induction, with increasing doses given every 10 minutes, adverse reactions were reported in 19% of patients [59]. All patients completed the protocol and all reactions were characterized as mild (primarily oral symptoms). One

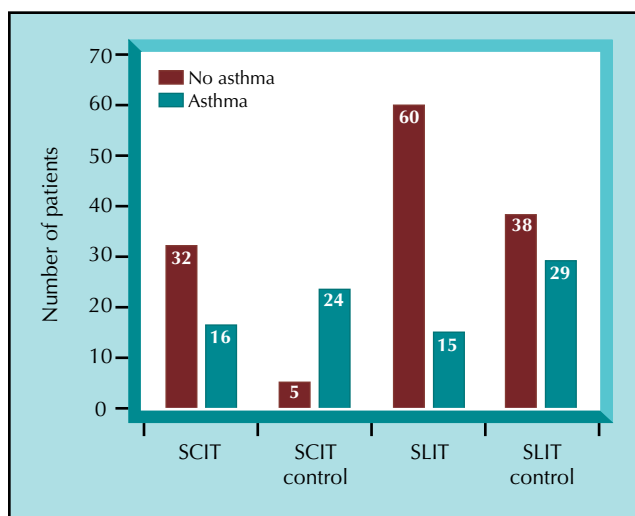


Figure 1. Preventive effect of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) in children: SCIT 5-year OR = 2.68 (1.3–5.7); SLIT 3-year OR = 3.80 (1.5–10.0). In a prospective study, 205 children with clinical history of grass- or birch-induced rhinoconjunctivitis were randomized to receive SCIT for 3 years or to an open control group; there was a statistically significant reduction in risk for developing asthma at 5-year follow-up (2 years after discontinuing immunotherapy). SCIT group: 15 of 75 with asthma compared with 38 of 67 in untreated control group (OR = 2.68 [1.3–5.7]) in favor of immunotherapy to prevent asthma. This effect was sustained in 10-year follow-up, with 16 of 48 in SCIT group with asthma compared with 24 of 29 with asthma in control group (OR = 2.48 [1.1–5.4]). (Data from Moller et al. [6], Niggemann et al. [7], and Jacobsen et al. [18•].) An open study of 113 children, ages 5 to 14 years, with grass pollen rhinitis, randomized to receive co-seasonal SLIT for 3 years or to standard symptomatic therapy, found that development of asthma after 3 years was 3.8 times more frequent in control subjects (95% confidence limits, 1.5–10.0). (Data from Novembre et al. [33•].)

patient developed rhinorrhea and cough, and another patient had diarrhea and abdominal pain. In a postmarketing surveillance study of 268 children (ages 2–15 years) who had received approximately 96,000 doses of SLIT during treatment periods ranging from 3 months to 7 years (mean 34 months), adverse reactions were reported in 3% of patients (0.083 per 1000 doses). Seven patients developed systemic side-effects (abdominal pain, conjunctival itching, and rhinitis) that were mild and required no treatment; one patient with urticaria required antihistamines [15].

All the double-blind placebo-controlled or randomized controlled studies reviewed in this article utilized a gradual induction over several dilutions (Table 1). There was no consistent pattern with allergen dose and incidence or severity of adverse effects. One dose-response study comparing 30 µg with 3 µg of major tree pollen per week found a greater number of adverse reactions in the higher dose group [27•]. A similar dose-related increase in adverse reaction was seen in a dosing safety study of grass tablets in adults with allergic rhinitis [60]. One low-dose dust mite study (15.4 µg CMD of Der p 1) reported 17 severe adverse reactions, three of which were asthma, attributed to exceeding maximum tolerated dose [37],

Table 1. Safety summary of double-blind, placebo-controlled, or randomized controlled pediatric SLIT studies

Study	Disease; patient; allergen	Buildup schedule and dose	Adverse event: SLIT	Adverse event: control or placebo
Low dose, 1–5 times monthly SCIT				
Caffarelli et al. [19]	Rhinitis ± asthma; 24 S/20 P	Tablets every other day: seven dose increases. Maintenance dose 1000 AU every other day (low)	No systemic or local AE	One withdrew due to abdominal pain
Hirsch et al. [29]	Rhinitis ± asthma; 13 S/14 P	3-week buildup; 1–7 drops over three concentrations. Maintenance dose = 3.7 µg Der p 1 3/wk (47 µg CMD)	One withdrew due to generalized weakness, with one episode of severe bronchial obstruction; relationship to SLIT not clear: “questionably induced by the therapy”; 5 pts oral AE	1 pt oral AE
Ippoliti et al. [30]	Asthma; 47 S/39 P	Buildup: 1–5 drops through five concentrations. Maintenance dose = 5 drops of 10 BU/mL 3/wk (2.4 µg Der p 1/wk)	“Tolerance was excellent: there were no side-effects and no patient interrupted therapy”	
Novembre et al. [33•]	Rhinitis; 48 S/49 P; grass	Buildup: 1–5 drops through five concentrations. Maintenance dose = 0.5 µg major grass 5/wk	One throat itching, one GI, one rash; AE rate: 0.44/1000 during buildup and 0.083/1000 during maintenance	One rash
Pajno et al. [72]	Rhinitis ± asthma; 14 S/13 P/7 C; <i>Parietaria</i>	Five concentrations, increase by 1 drop daily up to 5 drops in each concentration. Maintenance dose = 0.12 µg Par j 1, 3/wk	All reached maintenance, no AE reported	No AE reported
Pajno et al. [34]	Asthma; 12 pts in each group; dust mite	Same as above. Maintenance dose = 2.4 µg Der p 1, 3/wk	Two pts: one swelling of mouth, lips, face; one mouth itchiness in buildup	
Rolinck-Werninghaus et al. [21]	Rhinitis; 38 S/37 P; grass	4-wk buildup; five concentrations: increase by 1 drop every second day in lowest concentration, then increase by 1 drop in subsequent concentrations until 5 drops of maintenance dose = 0.5 µg major grass; 3/wk	AE reported in 24 (49%) pts; local AE 30.6%; nasal AE 14.3%; one withdrew due to AE—asthma exacerbation requiring hospitalization, classified as serious AE	AE reported in 13 (27.1%) pts; local 18.8%; nasal 6.3%; three withdrew due to AE
Tari et al. [37]	Rhinitis ± asthma; 30 S/28 P; dust mite	15-d buildup; 1–15 drops over four concentrations. Maintenance dose = 1.2 µg Der p 1, 3/wk	32 AEs reported; 17 classified as severe (three asthma, eight nasal, six eye) attributed to maximum tolerated dose with a greater number occurring in first 6 wk	No AE reports
Vourdas et al. [35]	Rhinitis ± asthma; 34 S/32 P; olive	Buildup over four concentrations: 2–10 drops in first two and 2–20 drops in final two concentrations. Maintenance dose = 40 µg Ole e, 1 daily	Eight pts had AE: eight oral pruritus, one lip swelling, one conjunctivitis during buildup	Two pts had AE (one oral pruritus, one lip swelling)
Wuthrich et al. [22]	Rhinitis ± asthma; 10 S/12 P; grass	Schedule and maintenance dose same as above	“Tolerance turned out to be excellent”	
Intermediate dose, 6–50 times SCIT				
Bahceciler et al. [36]	Rhinitis +/- asthma; 8 S/7 P; dust mite	28-d buildup over four concentrations: 1–10 drops in first three concentrations, 1–20 drops in maintenance. Maintenance dose = 8 µg Der p 1 2/wk	None of the patients reported local or systemic side effects	

AE—adverse event; C—control; CMD—cumulative monthly dose; GI—gastrointestinal; P—placebo; pt(s)—patient(s); S—SLIT; SAE—serious adverse event; SCIT—subcutaneous immunotherapy; SLIT—sublingual immunotherapy.

Table 1. Safety summary of double-blind, placebo-controlled, or randomized controlled pediatric SLIT studies (Continued)

Study	Disease; patient; allergen	Buildup schedule and dose	Adverse event: SLIT	Adverse event: control or placebo
Bufe et al. [28]	Rhinitis +/- asthma; 68 S/64 P; grass	3-wk buildup from 100 AU to 2500 AU/d over 3 weeks. Maintenance dose: 9.1 µg Phl p 5 daily	17 pts with mild oral allergy and one with facial urticaria, but study did not specify to which group AEs belonged	
Roder et al. [38]	Rhinitis; 91 S/77 P; grass	20-d buildup, increase by 1 drop/d until 20 drops. Maintenance dose = 21 µg Lol p 5 given 2/wk	Local side effects 39%	Local side effects 17%
Valovirta et al. [27•]	Rhinitis ± asthma; 32 low/27 high/29 P; tree	5-wk buildup over five concentrations. Maintenance dose: 5/wk-cumulative weekly dose of either 30 or 3.6 µg Bet v 1/Aln g 1/Cor a 1a	High dose: greater number of AEs—two “allergic reactions,” one abdominal pain, one flushing. Low dose: one rhinitis, one withdrew due to abdominal pain. Placebo: one rhinitis.	
High dose, > 50 times monthly SCIT				
La Rosa et al. [31]	Rhinitis; 20 S/21 P; <i>Parietaria</i>	Four concentrations: increase in first two concentrations by 1 drop up to 10, then by 2 drops up to 20 in third and maintenance concentrations. Maintenance dose = 20 drops of 300 IR 3/wk (100 IR = 70 µg Par j 1)	12 pts had 26 AE: 19 GI, five oral, one pruritus; four withdrew due to AEs	Seven pts had 10 AEs: one pt hospitalized for severe asthma attack, one withdrew due to AE
Lue et al. [24]	Asthma; 10 in each group; dust mite	3-wk buildup through three concentrations: 1–10 drops first, 1–20 drops in second then 8–20 drops in maintenance. Maintenance dose: 30 drops of 300 IR (783 µg CMD mixed mites)	All patients completed the study. No drug-related SAE reported during trial period.	
Marcucci et al. [32]	Rhinitis; 45 in each group	11- and 28-d buildup to either 24 drops of 300 IR or 40 drops of 100 IR/wk	Eight AE reported in high dose: one GI, seven oral; 11 AE lower dose: two GI	
Niu et al. [25]	Asthma; 56 S/54 P	Same as Lue [24]	Five pts had drug-related AE; one SAE, not described	Three pts had drug-related AE; four SAE, not described

AE—adverse event; C—control; CMD—cumulative monthly dose; GI—gastrointestinal; P—placebo; pt(s)—patient(s); S—SLIT; SAE—serious adverse event; SCIT—subcutaneous immunotherapy; SLIT—sublingual immunotherapy.

whereas another study using doses approximately 52 times greater than the previous study's CMD, or 26 times the single dose, reported "no serious drug-related adverse events" [24]. In general, safety comparisons were difficult due to the great variability in adverse reaction details provided in these studies.

Subsequent to the SLIT Joint Task Force review, two cases of anaphylaxis related to SLIT with mixed inhalants were reported [61,62]. One case involved a 13-year-old girl with allergic rhinitis and asthma sensitized to dust mite and mixed pollens, who developed swelling of the lower lip, high fever, chest pain, nausea, and abdominal pain 3 minutes after taking her pollen drops during the height of pollen season [62]. She was treated for anaphylaxis in the hospital and admitted for observation. This episode occurred 1 month after she had reached maintenance.

Safety in young children

Immunotherapy is not generally prescribed to young children, primarily because of safety concerns. The Allergen Immunotherapy Practice Parameter states that "children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore, the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years" [14]. Considering the relatively rare incidence of severe adverse reactions with SLIT, this modality may be a feasible option for young children. Three studies—two observational and one postmarketing survey—were specifically designed to assess the safety of SLIT in young children (Table 2) [60–62]. A total of 231 children younger than age 5 years were treated with various pollen and mite allergens (33 patients received allergoid). Adverse reactions were reported in 5% to 15% of patients in a total of 68,975 doses (0.268, 0.0766, and 1.767 AE per 1000 doses). Most reactions appeared to be mild or moderate and resolved without treatment. Dose reduction by changing from a sublingual-swallow to a sublingual-spit method controlled gastrointestinal reactions in one study [65]. Another study reported a serious gastrointestinal reaction (vomiting; grade 4 on a scale of 5) [64•].

Only one study provided information about clinical efficacy via the parent's evaluation of improvement: 21 highly improved, nine mildly improved, four slightly improved, and two unchanged [63].

Safety: summary

In general, SLIT appears to be associated with fewer serious adverse effects and may be tolerated in children as young as 2 years. However, local reactions (oral-mucosal symptoms) are relatively common (up to 75% of patients) and severe reactions have been reported, predominantly asthma or gastrointestinal symptoms. There appeared to

be no consistent relationship between adverse reactions and SLIT dose or induction and maintenance schedules.

Most studies have been done in patients with allergic rhinitis with or without mild-to-moderate asthma, generally excluding patients with FEV₁ less than 70% of predicted. No studies have been done in patients with severe asthma, and few studies in high-risk patients; therefore, greater safety in these subpopulations cannot be assumed. To date, no fatalities from SLIT have been reported, but two cases of anaphylaxis to inhalant allergens have been reported.

Practical Considerations

Economics

It is difficult to perform a cost-benefit analysis of SLIT without a clear concept of what dose is required to achieve therapeutic efficacy. At present, no American Medical Association Current Procedural Terminology (CPT) exists for the preparation of SLIT. Furthermore, because there is no FDA-approved formulation for sublingual immunotherapy in the United States, most third-party payers do not cover the costs; therefore, prescribing currently available allergen extracts for SLIT would be considered "off-label" use.

An Italian study used allergy clinic medical records to retrospectively identify patients with 1 year of data before receiving SLIT and those with 3 years of data while receiving SLIT; investigators analyzed direct and indirect costs, and several outcome measures (eg, exacerbations, office visits, missed days of work/school) for the year before, and during, SLIT treatment [66]. Annual medical costs per patient (based on prescriptions and outpatient visits but not hospitalizations) during the year before SLIT were €506 (US \$685 in 2005 dollars) compared to €224 (US \$303 in 2005 dollars) during the 3 years of SLIT. In an analysis of a subgroup of 41 asthma patients treated with SLIT compared with 35 untreated asthma controls, outcome measures were reduced substantially: mean number of exacerbations declined from 46.1 to 7.2 per patient per year; missed work and/or school days declined from 37.5 to 7.2 per patient per year; and medical visits declined from 9.6 to 2.5 per patient per year. The direct cost per patient over the entire 4 years was similar in both groups: €1182 (US \$1600 in 2005 dollars) for SLIT patients and €1100 (US \$1489 in 2005 dollars) for the untreated controls.

In a larger retrospective study of costs, clinical outcomes, and cost-effectiveness ratios in an Italian population, 1000 patients treated with SLIT were compared with 1000 patients who received usual pharmacotherapy over a 6-year period. Investigators found a significant difference in direct and indirect costs per patient: SLIT group costs were €626 direct (US \$789, exchange rate 1.26) and €1487 indirect (US \$1874, exchange rate 1.26)—less than pharmacotherapy alone [67•].

Table 2. Safety of SLIT in children under 5 years of age

Study design	Patient number; disease; age (mean); allergen	Doses given; duration; maintenance dose	Adverse reactions	Comments
DiRenzo et al. [65]; postmarketing surveillance	126 pts; asthma and/or allergic rhinitis; 3–5 y (4.2 y); various allergens	39,000 doses; 2 y; two buildup schedules: 15 (twice daily) and 30 d through four concentrations; 0.02–2.1 µg major allergen per dose 3/wk	Seven (5.6%) children reported nine AE: two local; seven GI—abdominal pain: one mild, six moderate (pain, diarrhea); 0.2 AE per 1000 doses	GI AE controlled by dose reduction, achieved by changing SLIT method from sublingual-swallow to sublingual-spit. All AEs in buildup phase.
Agostinis et al. [63]; observational	33 pts; asthma and/or allergic rhinitis; 1 yr 11 mo–3 yr 10 mo; various allergens-allergoid	22,500 doses; 22.3 mo; 3-wk buildup; 4 drops 3000 AU/d	Two (5%) patients; abdominal pain: one mild, one moderate; 0.07 AE per 1000 doses	Parent's evaluation of improvement: 21 high; nine mild; four slight; two unchanged
Fiocchi et al. [64•]; observational	65 pts; asthma and/or allergic rhinitis; 38–80 mo (60 ± 10 mo); various allergens	7475 doses; 246 ± 161 d; 11-d buildup through four concentrations; 11–210 µg of major allergen 3/wk	Two subgroups. First group: 33 pts; 38–60 mo: five (15%) pts had six AEs: four urticaria, one GI, one oral. Second group: 32 pts; 60–80 mo: six (18%) pts had seven AEs: three GI, two urticaria, two oral; 1.7 AE per 1000 doses	One GI reaction in older group was graded 4/5 (vomiting); six AEs in buildup, seven in maintenance

AE—adverse events; GI—gastrointestinal; pts—patients; SLIT—sublingual immunotherapy.

Adherence

One important factor is that SLIT is administered at home with no direct medical supervision. Prescribing physicians should consider how adherence will be monitored, and whether the child has the ability to comply with the SLIT regimen. In addition, physicians would need to provide specific instructions—including dosing adjustments—to parents on how to manage adverse reactions and unplanned treatment interruptions, and situations in which the dose should be withheld.

No studies have specifically examined adherence to the SLIT regimen in the pediatric population; however, three studies in a mixed-age population have assessed compliance with either unscheduled telephone requests to count remaining tablets [68,69] or measurement of remaining extract on clinic visits [70•]. High compliance, defined as taking medications more than 80% or 90% of the time, was reported in 72% [69], 76% [70•], and 97% [68] of patients. One study prospectively investigated the compliance with three immunotherapy methods—SLIT, SCIT, and nasal immunotherapy—in 2774 children (ages 6 to 15 years) by measuring the number of patients who withdrew before completing 3 years of treatment [71]. The highest noncompliance rate was seen in the nasal immunotherapy group (73.2% of patients), followed by SLIT (21.5%) and SCIT (10.9%). Expense was the most frequently cited reason for discontinuation in the SLIT and SCIT groups (36.4% and 39.6%, respectively). The second most common reason was amount of time required for SCIT (24.2%) and inefficacy for SLIT (24.9%).

Conclusions

Many questions remain unanswered regarding SLIT in populations of any age, including effective dose, schedule, duration, and mechanism. Further research is clearly needed to determine the optimal dose for each formulation because SLIT (unlike SCIT) does not appear to have a consistent therapeutic dosing range. SLIT appears to be well tolerated in young children, but efficacy in this group has not been well established. Although serious side effects associated with SLIT appear to be rare, they have been reported, and safety has not been studied in high-risk groups. Currently SLIT is under investigation in the United States, but there is no FDA-approved formulation or CPT code for SLIT. Physicians prescribing SLIT should provide specific instructions for managing the variables that might be anticipated with this home-based therapy, and carefully consider the patient's ability to comply with the regimen before prescribing this treatment. Mechanisms to monitor patient adherence and adverse treatment events should also be included in the SLIT treatment plan.

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