

Clinical Utility of Sublingual Immunotherapy in Pediatric Patients With Allergic Rhinitis and/or Asthma

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Although sublingual immunotherapy (SLIT) is a common adjuvant treatment for allergic rhinitis and allergic asthma in Europe, it is used minimally in the United States because of lack of approval by the US Food and Drug Administration (FDA) of allergen extracts for sublingual treatment and inconsistent study findings on extract potency, dosing levels, and dosing schedules. Data are particularly lacking on use of SLIT in pediatric patients, who may represent a potential patient population for this type of immunotherapy delivery because of its favorable safety and acceptability to children compared to subcutaneous immunotherapy (SCIT). Differences in the mechanism of action of SLIT compared to SCIT may also confer some treatment and safety advantages. Clinical trials on SLIT in pediatric patients have provided inconsistent results, but this inconsistency may be due in part to less than optimum dosing and durations of treatment. The appeal of SLIT as a treatment in children is further enhanced by its potential for possibly preventing progression to asthma if initiated at a young age. This article reviews the clinical evidence on studies in pediatric populations regarding efficacy and safety, and its implications in the treatment of allergic rhinitis and allergic asthma in children.

Introduction

ALTHOUGH SUBLINGUAL IMMUNOTHERAPY (SLIT) has been designated a legitimate therapeutic consideration for patients with allergic rhinitis and allergic asthma in many parts of the world,¹ it remains unapproved in the United States. A key factor that has curtailed the use of SLIT is the paucity of clinical studies comparing SLIT to long-established subcutaneous immunotherapy (SCIT). As the extract concentrations in SLIT studies have varied widely, overall trial results have been inconclusive. Much confusion remains as to how much extract makes an effective dose, and contributing to this uncertainty are the different units of measurement (eg, bioequivalent allergen units [BAU], biological units [BU], index of reactivity [IR], etc) (Table 1) used to quantify concentrations.²⁻⁴

The current gap in understanding in the clinical community and the lack of guidelines for usage has made SLIT less likely to be employed in the treatment of children with allergic rhinitis or allergic asthma. Pediatric patients, however, may represent a potential patient population for SLIT, because SLIT is less invasive and less painful than SCIT,

especially in children with significant local reactions to injections.⁵ SLIT is also associated with fewer side effects (SEs) than SCIT.⁶ However, SLIT also presents potential disadvantages as a treatment for children. It provides clinicians with less control over therapy, because it is administered at home, and requires greater education of parents or caregivers to assure proper administration and monitoring of efficacy and safety.

Still to be determined is the degree of insurance coverage that may be available for SLIT when extracts begin receiving FDA approval, and how the use of SLIT would affect the overall cost of care. One recent European study⁷ found that, while the annual per patient cost of treatment is higher with SLIT compared to standard care in patients with allergic rhinitis (euro 288 versus euro 116, respectively) or allergic rhinitis and asthma (euro 362 versus euro 230, respectively) due to grass pollen allergy, the use of SLIT resulted in considerable savings in the cost of symptomatic drugs (↓22% in the allergic rhinitis group, ↓34% in the allergic rhinitis and asthma group). Another study⁸ of health care resource utilization data for 2,200 patients with allergic rhinitis or asthma

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TABLE 1. UNITS OF ALLERGEN PRODUCTS/EXTRACTS BASED ON BIOLOGICALLY STANDARDIZED REFERENCES

<i>Unit</i>	<i>Meaning</i>
Biological unit (BU)	10,000 BU/mL is equivalent to 10 HEP
Bioequivalent allergen unit (BAU)	BAU is based on the ID50EAL method (dilution required to elicit a 50 mm erythema skin test response). Example: Extract with a D50 of 14.0 contains 100,000 VAU/mL
Histamine equivalent in prick testing (HEP)	10 HEP is equivalent to the allergen concentration, which elicits the same wheal size in skin prick testing as the histamine dihydrochloride control (10 mg/mL)
Index of reactivity (IR)	IR is based on the amount of extract that elicits a predetermined geometric mean wheal diameter

Adapted from: American Academy of Allergy, Asthma, & Immunology,² Hrabina et al.,³ and Becker et al.⁴

reported long-term savings with SLIT plus pharmacotherapy compared with pharmacotherapy alone. Over a treatment period of 6 years, the direct costs (appointments, tests, pharmacotherapy, immunotherapy, hospitalizations) in the SLIT plus pharmacotherapy group were euro 2,400 per patient versus euro 3,026 with pharmacotherapy alone. The cost picture with SLIT demands further investigation, which is beyond the scope of this article.

Efficacy of SLIT

The Joint Task Force on Practice Parameters of the American Academy of Allergy, Asthma, & Immunology (AAAAI); American College of Allergy, Asthma, & Immunology (ACAAI); and the Joint Council of Allergy, Asthma, and Immunology confirm that SLIT has demonstrated efficacy in placebo-controlled studies.⁹ At the same time, these authorities also noted that results have been inconsistent with SLIT.⁹ One review⁶ reported that SLIT was effective for rhinitis, conjunctivitis, or asthma in 30 out of 36 trials comparing active SLIT treatment with placebo or controls with placebo ($n = 1,817$). In contrast to this report, another meta-analysis¹⁰ reported that first-year symptoms and medication scores were reduced significantly with SLIT in only about 35% of 39 double-blind, placebo-controlled (DBPC) SLIT clinical trials. This review noted, however, that the lack of efficacy in some of these trials may be due to ineffective doses, less-than-optimum treatment schedules, and limited durations of treatment.

Efficacy of SLIT in pediatric patients

Use of SLIT is more accepted in Europe; up to 85% of children in Italy who are prescribed specific immunotherapy, for example, receive SLIT rather than SCIT.¹¹ However, most DBPC trials with SLIT have been conducted in adults, and it is not acceptable to extrapolate from SLIT studies performed in adults exclusively (particularly due to the tendency for remission of allergic diseases in children).¹¹ Efficacy with SLIT has been shown in some studies, with a wide range of allergen doses and durations of treatment, and reviews evaluating the efficacy of SLIT in pediatric patients have reported mixed results. In a meta-analysis of 22 trials⁵ ($n = 979$) with SLIT in allergic rhinitis, Wilson and colleagues found no significant reductions in symptoms (Table 2) or medication scores (Table 3) with SLIT versus placebo in the five trials involving only children. The authors conceded, however, that this conclusion may be unreliable due to the small number of participants in the studies ($n = 122$). Another review¹² identified 19 DBPC or randomized, controlled studies that reported data on clinical efficacy of SLIT in pediatric patients with allergic rhinitis and/or asthma. Of the 17 studies that provided both medication and symptom scores and a comparative untreated control, 35% demonstrated efficacy in both parameters, while 29% did not demonstrate efficacy in either parameter during treatment year 1 compared to the control group. These groups encompassed both high- and low-dose SLIT treatments, as well as seasonal and perennial allergens. It should be noted that in

TABLE 2. SUBGROUP ANALYSES—SYMPTOM SCORES

<i>Subgroup</i>	<i>N (active)</i>	<i>N (placebo)</i>	<i>SMD</i>	<i>95% CI</i>	<i>P value</i>
Seasonal allergens	346	344	-0.3	-0.53 to 0.07	0.011
Perennial allergens	138	131	-0.58	-1.28 to -0.12	0.1
Studies involving children only	111	107	-0.31	-1.32 to -0.7	0.5
Adult/adult and child studies	373	368	-0.4	-0.61 to -0.18	<0.01
Duration <6 months	183	175	-0.36	-0.67 to -0.06	0.02
Duration 6–12 months	193	195	-0.21	-0.54 to -0.11	0.2
Duration >12 months	108	105	-0.95	-1.97 to -0.06	0.07

Source: Wilson et al.⁵ Reprinted with permission by Blackwell Publishing.

TABLE 3. SUBGROUP ANALYSES—MEDICATION SCORES

Subgroup	N (active)	N (placebo)	SMD	95% CI	P value
Seasonal allergens	346	344	-0.36	-0.54 to -0.18	<0.01
Perennial allergens	138	131	-0.85	-1.93 to 0.23	0.12
Studies involving children only	111	107	-0.02	-0.34 to 0.37	0.9
Adult/adult and child studies	373	368	-0.5	-0.7 to -0.29	<0.01
Duration <6 months	183	175	-0.6	-1.09 to -0.18	<0.01
Duration 6–12 months	193	195	-0.35	-0.6 to -0.11	<0.01
Duration >12 months	108	105	-0.27	-0.62 to 0.08	0.13

Source: Wilson et al.⁵ Reprinted with permission by Blackwell Publishing.

the five studies not demonstrating significant symptom and medication reductions during the first year of treatment, significant improvements were achieved in either or both of these parameters in subsequent treatment years. Although this trend may imply that some SLIT studies have had too short a duration, this explanation may be too simplistic; efficacy with SLIT has been reported in some studies after 3 months of treatment, while other studies have demonstrated no efficacy after 3 years of treatment.¹² Another meta-analysis¹³ by Olaguibel and colleagues identifying seven randomized DPBC studies in allergic rhinitis or asthma (*n* = 256; age ≤14 years) found that only reductions in asthma symptoms (*P* = 0.01) and drug dosage (*P* = 0.06) were considered statistically significant versus placebo, while changes in rhinitis and conjunctivitis symptoms did not achieve significance. It seems apparent that the success or failure of SLIT depends on a number of factors including dosing schedule, duration, and extract potency.

Efficacy of SLIT in allergic rhinitis in pediatric patients

Results have been mixed in studies of SLIT in children with allergic rhinitis. In a prospective, randomized, DBPC trial¹⁴ of patients with grass pollen seasonal allergies (*n* = 97; age range: 3–14 years), subjects were administered 0.5 µg of a five-grass extract three times a week during maintenance treatment. Median duration of treatment was 32

months with a median cumulated dose of 188 µg allergens. Significant reductions in the SLIT group versus placebo were demonstrated for both multiple-symptom–medication score (↓22.7%, *P* = 0.05) and medication score alone (↓32.9%, *P* < 0.01), but not for symptom score alone (↓14.9%, *P* = 0.22) (Table 4).

The impact of treatment duration was shown in a study of children (*n* = 161, including 68 with asthma symptoms) with severe grass pollen allergy who were treated with high-dose SLIT.¹⁵ In this randomized DBPC trial, patients were built up over 3 weeks from 100 AU daily to a maintenance dose of 2,500 AU daily of grass allergen extract. All patients completing 1 year of treatment (*n* = 132) were treated for another 2 years in an open-controlled setting. At 1 year, no significant differences were noted between treatment and placebo in combined symptom and medication score. Subgroup analysis utilizing a repeated measures model, however, revealed that patients with severe symptoms who were treated with SLIT had a significant improvement of clinical symptoms after 3 years.

A randomized DPBC trial¹⁶ in children with allergic rhinitis (*n* = 168, intention-to-treat population; age range: 6–17 years) found no significant difference in total symptom score between groups treated for 2 years with either grass pollen extract or placebo. There were also no significant differences reported in rescue medication-free days, disease-specific quality of life, and overall evaluation of treatment

TABLE 4. ADJUSTED SYMPTOM AND MEDICATION SCORES FOR 6 WEEKS WITH PEAK POLLEN COUNTS IN THE FIRST AND THIRD GRASS POLLEN SEASON

Mean score (SD)	SLIT (N = 39)			Placebo (N = 38)			SLIT versus Placebo (P value ^a)
	G1	G3	Change G3 versus G1	G1	G3	Change G3 versus G1	
Eyes	10.22 (11.78)	6.83 (13.63)	-3.39 (12.36)	5.27 (6.29)	5.15 (9.81)	-0.12 (7.80)	0.1437
Nose	19.39 (18.25)	13.71 (23.12)	-5.68 (22.13)	15.57 (19.03)	12.66 (21.65)	-2.91 (17.39)	0.2120
Bronchi	4.01 (6.75)	2.54 (5.00)	-1.46 (4.18)	3.92 (7.13)	2.50 (5.06)	-1.41 (5.31)	0.9959
Medication	6.00 (5.80)	2.54 (3.58)	-3.46 (4.75)	3.18 (3.99)	2.85 (3.87)	-0.34 (5.06)	0.0025

^aU-test.

Abbreviations: G1, first grass pollen season; G3, third grass pollen season.

Standard deviation given in parentheses.

Source: Rolinck-Werninghaus et al.¹⁴ Reprinted with permission by Blackwell Publishing.

effect. Maintenance dose in this study was 20 drops (9,500 BU; 21 µg equivalent Lol p5, twice weekly).

Efficacy of SLIT in pediatric patients with asthma

Data on treatment of pediatric asthma with SLIT remain scarce, and clinical trials tend to have low numbers of subjects. A recent meta-analysis¹⁷ identified nine randomized DBPC trials in asthmatic patients ranging in age from 3 to 18 years ($n = 441$). Overall, this review found statistically significant reductions in both symptom scores ($P = 0.02$) and the use of rescue medications ($P < 0.01$) in the SLIT groups compared with placebo. Significant symptom reduction was reported in five of the trials, whereas reduction in rescue medication was significant in all nine trials. Significance versus placebo was found to be most likely in studies utilizing treatment with HDM extracts.

In a study¹⁸ in 31 asthmatics with house dust mite allergies (mean age = 8.3 years), SLIT significantly reduced rhinitis symptoms (sneezing, rhinorrhea), asthma symptoms (cough, dyspnea, wheezing), and asthma attacks at 6 months (Fig. 1).¹⁸ Dosing for this study included a 1-month build-up phase of once-daily SLIT treatment, with gradual titration upward from 1 drop of the weakest strength (0.1 IR/mL) up to 20 drops of the strongest (100 IR/mL). This sequence was followed by a maintenance phase of 20 drops of the 100 IR extract once daily for 28 days, followed by 20 drops given twice weekly for the remainder of the trial (4 or 10 months).

A longer-term randomized controlled trial¹⁹ (2 years) in mild/moderate asthma patients with grass pollen season allergies ($n = 30$; age range: 8–14 years) reported that SLIT decreased seasonal increase in bronchial hyperreactivity (BHR) and prevented seasonal drop in FEV₁ (although the latter was not statistically significant). At 18 months, the SLIT group demonstrated PC₂₀ and FEV₁ scores similar to “out-of-season” values, whereas the placebo group continued to show seasonal changes in BHR and lung function. Extracts in this study were standardized in BU, and five strengths were used (0.0016, 0.08, 0.4, 2.0, and 10.0 BU/mL). Patients started on the lowest dose once daily and built up

to a maintenance dose of five drops of the 10.0 BU concentration three times weekly. During the first year, patients also used fluticasone dipropionate 50 mcg bid for their seasonal asthma, which was discontinued during year 2.

Efficacy of SLIT compared to SCIT

There are few studies in any age group comparing SLIT to SCIT, and none to date conducted solely in pediatric populations. In adult studies comparing SLIT and SCIT, clinical efficacy has been comparable, with a reduction in disease severity of ~50% and no significant difference between the two treatments.²⁰ One randomized, DPBC, double-dummy study²¹ ($n = 71$) in adults with birch pollen allergy found that median disease severity (based on a measure of change between pretreatment values and posttreatment values) in the SLIT group was one-half of the placebo group, whereas in the SCIT group it was one-third of the placebo group. Although these results were significantly better than placebo but not significantly different from each other, the lack of difference between the SLIT and SCIT groups does not denote equivalence; investigation of larger groups would be necessary to detect minor differences.

Safety of SLIT

Safety of SLIT in pediatric patients

The safety profile of SLIT has been well established in clinical studies, and it does not appear to differ between adults and children.²² Moreover, rates of adverse events (AEs) have been similar whether low- or high-allergen doses were used.²³ In clinical trials, good tolerability has been documented in children as young as 3 years of age.²⁴ An observational study²⁵ ($n = 65$; age range: 38–80 months) of high-dose SLIT (maintenance dose, 300 IR three times weekly) reported AEs in 11 children, none of which was severe enough to discontinue immunotherapy (Table 5). There were six reactions in patients 60 months of age or younger and seven reactions in patients 60 months of age and older, with no differences

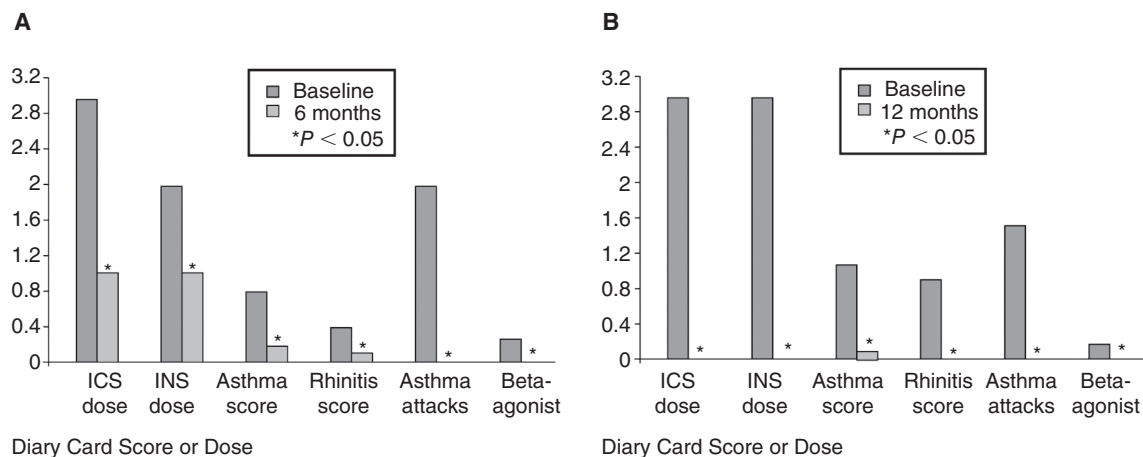


FIG. 1. Symptom and medication outcomes after (A) 6 months of SLIT in 17 children with HDM allergies and (B) 12 months of SLIT in 14 children with HDM allergies. Adapted from: Bahceciler et al.,¹⁸ with permission.

TABLE 5. ADVERSE REACTIONS AND SEVERITY IN 11 CHILDREN

Patient no.	Allergen used for SLIT	Treatment phase	Age (months)	Symptom	Severity	Time to adverse event (min)
<i>Children < 60 mo.</i>						
1	Grass	Build-up	46	Urticaria	2	<30
2	Grass	Build-up	57	Urticaria	1	<30
3	Cypress	Maintenance	58	Gastrointestinal (colic)	2	30–60
4	Mites	Build-up	59	Urticaria	2	30–60
		Maintenance		Urticaria	3	>60
5	Mites	Maintenance	59	Orolabial itch	2	<30
<i>Children > 60 mo.</i>						
6	Mites	Maintenance	64	Gastrointestinal (colic)	3	30–60
7	Mites	Maintenance	69	Gastrointestinal (vomit)	4	30–60
8	Mites	Build-up	74	Urticaria	2	<30
9	Mites	Build-up	74	Urticaria	2	30–60
10	Mites	Build-up	75	Orolabial itch	1	<30
		Maintenance		Orolabial itch	1	<30
11	Mites	Maintenance	78	Gastrointestinal (colic, diarrhea)	3	<30

Abbreviation: SLIT, sublingual-swallow immunotherapy.
 Source: Fiocchi et al.²⁵ Reprinted with permission by Blackwell Publishing.

between the age groups. Allergens used in the treatment included dust mite, grass pollen, olive pollen, *Parietaria* pollen, and cypress pollen, with an average cumulative dose of 36,900 IR. These findings support the safety of SLIT in patients 5 years of age and younger, which has been considered an age limitation for allergen immunotherapy. In another study²⁶ of patients with intermittent asthma, mild persistent asthma, or persistent rhinitis (*n* = 36; age range: 23–46 months; mean = 38 months) who were treated with a monomeric allergoid (various allergens, four drops of maximum concentration [3,000 AU/mL] daily), two children experienced one episode of abdominal pain (one mild/transient [<30 min], one moderate requiring temporary dose adjustment) over a mean follow-up of 22.2 months and ~25,200 doses (5% of patients; 0.071% per 1,000 doses).

Postmarketing surveys have documented a rate of AEs associated with SLIT at $<10\%$ (ie, <1 AE per 1,000 doses), which is superior to the safety profile of SCIT.²² One survey²⁴ followed up patients aged 2–15 years (*n* = 268; age range: 2–15 years) who were treated with SLIT extracts for respiratory allergy over a period ranging from 3 months to 7 years (mean: 34 months). Most of the patients were treated with dust mite extracts (53.7%), followed by grasses (25.4%), multiple sensitization extracts (14.6%), *Parietaria* (5.6%), and *Alternaria* (0.75%). Eight SEs were reported across 96,000 doses of extract (3% of patients; 0.083/1,000 doses), and local SEs were found to be of no clinical relevance (Table 6). The seven systemic AEs, which included abdominal pain, conjunctival itching, and rhinitis, were mild and required no treatment. There were no life-threatening events. Another survey²⁷ focusing on the safety of SLIT in patients aged 3–5 years (*n* = 126; mean age: 4.2 years) also found SLIT to be well tolerated. During a period of 2 years or more, there were reports of nine SEs in seven children (5.6% of patients; 0.2/1,000 doses). All of the SEs occurred during the up-dosing phase and were mild or moderate. Seven of the SEs were

systemic and involved the gastrointestinal tract. In the four cases involving diarrhea with or without abdominal pain, the problems were eliminated after patients took the suggested advice of spitting the allergen out after keeping it in the mouth. (Although the specific time of retaining allergen in the mouth was not identified in this published study, the typical standard for the sublingual-spit technique is 2 min.)²⁸ Rates of SEs were similar between the different extracts used: 5.1% with dust mite extracts, 7% with grass extract, and 6.5% with *Parietaria* extract. The finding that an accelerated build-up phase (15 days versus the standard 30 days) used in 18 patients did not increase the rate of AEs suggests that a slow build-up phase may not be necessary in children. Other pediatric studies have also shown AE rates associated with SLIT to be similar to either a multi-week induction schedule^{12,29} or ultra rush (<1 h) induction.³⁰ Anaphylaxis, however, must remain a concern. There have been reports

TABLE 6. CHARACTERISTICS OF REPORTED SIDE EFFECTS

Side effect reported	Episodes	Percentage of patients	Grade	Onset
Conjunctival itching	1	0.37	Mild	>30 min
Abdominal pain (*)	1	0.37	Mild	>30 min
Rhinitis	5	1.9	Mild	<30 min
Urticaria	1	0.37	Moderate	>30 min
Total	8	3		

* Wrong (high) dose administered.
 Source: Di Rienzo et al.²⁴ Reprinted with permission by Blackwell Publishing.

in recent years of anaphylaxis with SLIT: in one patient on a rush SLIT regimen for latex allergy,³¹ in one patient treated with a mixture of six standardized and unstandardized pollen extracts,³² and in one patient (11-year-old girl) treated with high-dose, multi-pollen, and house dust mite SLIT.³³

Safety of SLIT compared to SCIT

In one of the few studies²¹ comparing SLIT to SCIT ($n = 71$ adults), the SLIT group experienced fifteen grade 2 systemic SEs (mild) while the SCIT group experienced six that were grade 2, five that were grade 3 (non-life-threatening), and one that was grade 4 (anaphylactic shock).^{10,21} It also appears that SLIT may be safer than SCIT in asthmatics who are at-risk of serious reactions; in a survey³⁴ sent to members of the AAAAI ($n = 2,404$), the 646 responders reported that 15 out of the 17 fatal reactions associated with allergen injections occurring from 1990 to 2001 were in asthmatic patients. A total of 59% of fatal reactions reported in the survey occurred with maintenance allergen doses. In one meta-analysis¹⁰ assessing safety data from 66 SLIT studies that provided information about treatment-associated AEs, no serious life-threatening reactions were reported across 1,181,654 SLIT doses administered to 4,378 patients.

Fewer severe reactions also allow maintenance dosing to be achieved sooner with SLIT compared to SCIT. Safety concerns with SCIT may necessitate 8–12 months of dose adjustment before achieving the projected maintenance dose.³⁵ The relative safety of SLIT and SCIT requires more investigation via well-controlled comparative trials.

Mechanism of Action of SLIT

The primary action of SLIT is thought to involve the capture of allergen within the oral mucosa by Langerhan's-like dendritic cells, which helps trigger a T-cell response.³⁶ Evidence remains lacking, however, on whether SLIT induces a true T-cell response.³⁷ Oral delivery of extract may offer clinical advantages due to the resulting contact with the gut-associated lymphoid tissue (GALT) that may serve as a portal to the immune system.^{6,38,39} High-dose SLIT (200,000 SQ-U weekly) has been found to activate regulatory cytokine IL-10, while inhibiting the expression of IL-5 associated with allergen-induced TGF- β .⁴⁰ SLIT has also been shown to reduce ICAM-1 expression.^{41,42} (Expression of ICAM-1 promotes the adhesion of both polymorphonuclear leukocytes and eosinophils to epithelial cells in the airway, which plays a key role in chronic inflammatory reactions.⁴³)

The superior safety profile of SLIT compared to SCIT may be due in part to the oral mucosa having a limited number of mast cells.³⁶ Other differences in the mechanism of action between SLIT and SCIT have also been reported. In their investigation⁴⁴ of SLIT treatment with two concentrations of a three-grass extract (100 IR, 300 IR), Marcucci and colleagues reported a blunting of seasonal increase of specific IgE in serum at the higher dosage level, but without a concomitant rise of specific nasal IgG4. This effect differs from what has been observed with SCIT, which is associated with a rise of IgG4 along with a seasonal blunting of IgE.⁴⁴ SLIT has also been found to have an impact on specific IgA levels. In house dust mite-allergic asthma patients treated with SLIT ($n = 31$)¹⁸ for either 6 months or 12 months, IgA levels that were decreased at baseline compared to normal

controls were similar to controls in both treatment groups by the end of the treatment period.

Although concerns have been raised about SLIT causing an onset of local oral symptoms, this may be a nonissue. One study⁴⁵ in children with allergic rhinitis and asthma ($n = 30$ children; age range: 7–12 years) found that levels of nasal tryptase and ECP increased significantly after nasal challenge ($P < 0.001$), but detected no change in sublingual tryptase after SLIT administration.

Potential for Disease Modification in Pediatric Allergy Patients

As SLIT appears to have acceptable safety for patients 5 years of age and younger,^{25,27} it seems worth further investigation to determine whether treatment early in life can deter the allergic march. Atopic disorders are more common in young patients today, and allergic conditions responsive to immunotherapy may be present at a very early age. In a study⁴⁶ of 147 patients who first presented with symptoms of recurrent wheezing, eczema, or both (mean age, 2.0 years), 41% were found to have IgE-mediated allergy. Moreover, monosensitized children frequently become polysensitized over time. In a retrospective study⁴⁷ of 165 asthmatic patients, transition from monosensitization to polysensitization occurred in 47.9% of patients aged 18 months to under 5 years and 37.3% of children aged 5–8 years. The older patients tend to be sensitized to more classes of allergens than the younger group. Polysensitization was more likely in patients originally monosensitized to house dust mites (45.4%) than in those originally allergic to pollens (32.1%). Another assessment⁴⁸ of patients first showing allergic or asthmatic symptoms ($n = 340$) reported that 59% of 3 year olds were sensitized at their first visit, with the percentage increasing to 88% by the third visit. In those patients presenting only with allergic symptoms, polysensitization was found to be more common than monosensitization by age 11. In a study⁴⁹ of infants younger than 1 year of age ($n = 98$) with wheezing symptoms, the presence of polysensitization was investigated at initial visit and after 2 and 5 years. At the onset of wheezing, ~20% were sensitized, whereas more than 60% were sensitized by age 6. Although polysensitization was not present in any infants at baseline, it was the norm among sensitized children at 6 years (Fig. 2). Moreover, the number of sensitizations increased with age. These findings underscore the importance of differential diagnosis with proper tests in children that can discriminate between IgE- and non-IgE-mediated symptoms (allergy skin tests or RAST). This diagnosis should be performed at an early age in patients suspected to have allergy (ie, infants with wheezing).

Role of SLIT in Asthma Prevention

Progression from sensitization to asthma is not uncommon; approximately two-thirds of asthmatic patients are sensitized to at least one inhalant allergen.^{49,50} On the basis of the data from a range of studies,¹⁴ 11%–73% of children who develop seasonal allergic rhinoconjunctivitis by 7 years of age will also have bronchial hyper-responsiveness, and 20% of these children will develop asthma later in life.

It is rational to assume that attempts to deter the allergic march, which can lead to asthma, can be more successful

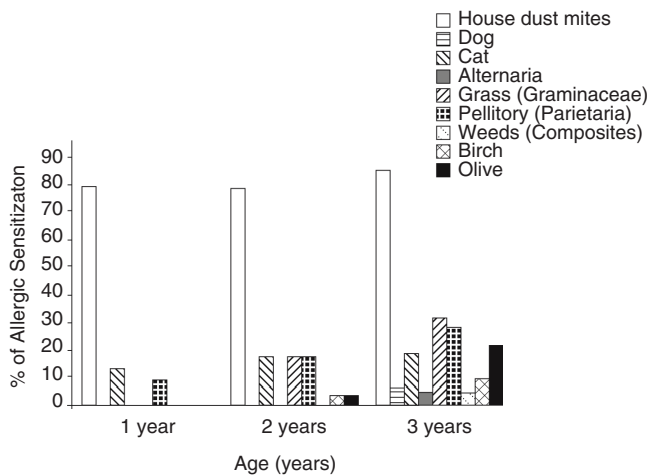


FIG. 2. Percentage of sensitization to a single allergen. Data were calculated as percent between the number of single sensitizations and the number of allergic children. Source: Fasce et al.⁴⁹ Reprinted with permission.

at a younger age when allergen-specific sensitivities are less well established and children are more likely to be mono-sensitized.⁴⁹ The effects of SLIT against the development of future asthma⁵¹ or worsening of current asthma⁵² have been demonstrated in a number of clinical studies. One study⁵² evaluated children with allergic asthma and rhinitis due to house dust mites who received either a 4- to 5-year course of SLIT with standardized extract or drug therapy only ($n = 60$; mean age, 8.5 years). Asthma symptoms and the use of asthma medications were significantly reduced in the SLIT group ($P \leq 0.001$, $P \leq 0.01$, respectively). Mean peak expiratory flow in the SLIT group was significantly higher at 4–5 years after discontinuation of therapy, and there was no evidence of new sensitizations. The potential of short-term coseasonal SLIT was investigated in an open randomized study⁵¹ in children with hay fever ($n = 113$; age range: 5–14 years). By the second and third years of therapy, symptoms and use of medication tended to be lower than the control group receiving standard symptomatic therapy only. Development of asthma after 3 years of treatment was 3.8 times more frequent in the control group. These findings support the value of SLIT as a treatment in patients with a known risk of developing asthma (eg, those with older siblings who have asthma), but more study is warranted.

Role of SLIT in Food Allergy

Food allergy affects as many as 8% of children,⁵³ and food anaphylaxis is the most common single cause of anaphylaxis treated in US emergency departments.⁵⁴ Strict allergen avoidance and ready availability of self-injectable epinephrine are the current standards of treatment. However, evidence suggesting that patients with life-threatening anaphylaxis will accidentally ingest the allergen again⁵⁵ makes these treatment options less than ideal. One survey, for example, found that 52% of adolescents and young adults with serious food allergies had experienced more than three episodes of food anaphylaxis in their lifetime.⁵⁵ SCIT has proved unsafe in this type of treatment,⁵⁶ making oral treatment an attractive

option for consideration. Buchanan and colleagues conducted a small, open, uncontrolled study ($n = 7$; age range: 14–84 months) of egg oral immunotherapy in children with egg allergy who had no history of egg-induced anaphylaxis. Patients ingested a maintenance egg protein dose of 300 mg daily in baby food or other acceptable vehicle food after a modified rush phase (increasing doses every 30 min) and standard build-up phase (increasing by 25 mg every 2 weeks until reaching 150 mg, then increasing each week up to a maintenance dose of 300 mg). During DBPC food challenges at study conclusion, all patients tolerated significantly more egg protein than at study onset. Although two of the subjects experienced oral tolerance, it cannot be determined from this initial cohort whether oral immunotherapy will induce this tolerance.

Another small study by Nash and colleagues investigated three phases of treatment of children with peanut allergy ($n = 20$; ages 1–16 years): (1) a modified rush initial day of multiple doses; (2) a build-up phase of daily doses, with dose increases every 2 weeks; and (3) a daily maintenance phase for 4 months followed by an open food challenge (OFC) using peanut flour.^{57,58} Thirteen subjects completed the study and were able to tolerate the full OFC (7.8 g of peanut flour [3,900 mg peanut protein], or ~13 times their usual oral SLIT dose).^{57,58} Eight subjects experienced no symptoms, five experienced mild symptoms, and four were treated with diphenhydramine.⁵⁶ During the modified rush phase, most of the children had mild allergic symptoms, but two experienced significant, systemic allergic symptoms.⁵⁷

Interestingly, development of food allergy has been shown to occur even without actual ingestion of the allergy-inducing substance.⁵⁷ A recent study found that sensitization to peanut via the skin may be associated with the development of peanut allergy, while oral sensitization may induce tolerance.⁵⁷ More study is required to determine the potential role of SLIT as a treatment option for food allergy in children.

Dosing Issues in Pediatric Patients

Although optimal doses and dosing schedules have been more or less established for SCIT in allergy treatment, this optimization is lacking with SLIT. Contributing to this challenge is the fact that especially high doses of allergen can be administered without significant SEs.¹³ This has resulted in a wide dosing range with acceptable tolerability, which has thereby made it difficult to pin down doses offering the best balance of efficacy and safety. As reported in a number of meta-analyses of SLIT,^{5,10} optimum doses for SLIT remain to be determined. Efficacy has been demonstrated at dosages ranging from 3-fold to 375-fold the corresponding dosage of SCIT.⁵⁹ SLIT studies have utilized doses that vary by 30,000-fold,¹⁰ but many of these studies have not shown a consistent relationship between allergen dose or treatment duration and outcome.¹⁰ Moreover, SLIT studies involving only pediatric patients often have small numbers of patients, which makes assessment challenging.⁵

Duration of treatment is also an important factor. In a meta-analysis of SLIT studies,¹³ the SLIT study with the shortest maintenance period (6 months) was the only one out of the seven analyzed that demonstrated no improvement in either asthma or rhinitis symptoms. This study, however, also had a low patient population ($n = 15$)—a common roadblock in

the assessment of data in pediatric studies. Another review of SLIT studies¹² found that ~29% of the studies (5 out of 17) in pediatric patients failed to show efficacy in the first treatment year, but demonstrated improvement in symptom and medication scores in subsequent years.

Efficacy with SLIT has been shown to be dose-dependent in pediatric patients. Valovirta and colleagues reported findings⁶⁰ on a randomized DBPC trial involving treatment with tree pollen extract 5 days a week at two accumulated weekly dosages (group 1: 3.6 µg; group 2: 30 µg) compared to placebo. Patients aged 5–15 years ($n = 88$) had a history of tree pollen-induced allergic rhinoconjunctivitis with or without seasonal asthma for 2 years or more. In birch pollen season, group 2 showed significant reductions in symptom ($P = 0.01$) and medication scores ($P = 0.04$) compared with placebo, whereas the lower dose showed a significant reduction of symptom scores only ($P = 0.03$). All patients tolerated SLIT well. In another randomized, controlled study⁴³ of treatment with grass pollen extracts ($n = 71$; age range: 5–15 years) at two dosage levels (40 drops of 100 IR or 24 drops of 300 IR weekly), symptom and medication scores were significantly lower at the higher dosage (Fig. 3). Importantly, there were comparable rates of AEs with the higher dosage (27.5%) compared to the lower dosage (25.8%). Good tolerability at higher dosages, even in children, supports the safety of increasing dosage in patients where efficacy is suboptimal.

Best Pediatric Candidates for SLIT

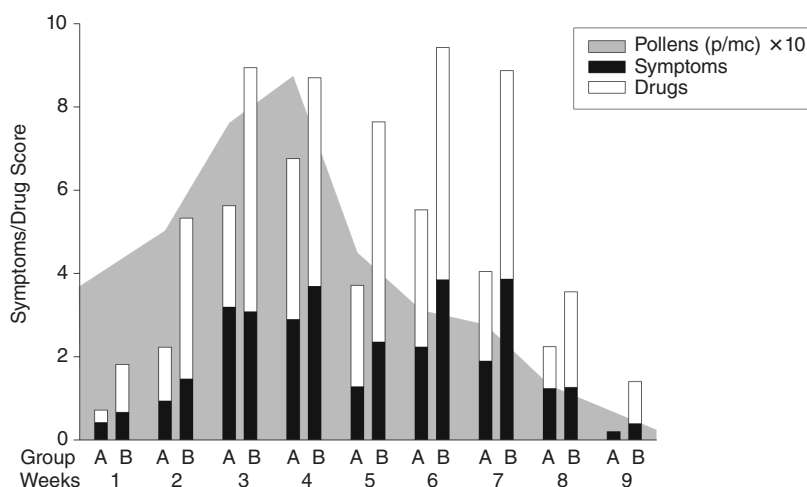
Owing to its greater tolerability and painless administration, SLIT potentially may be a more desirable first-line option than SCIT in some pediatric patients and may result in greater compliance. Its potential for preventing progression to more severe allergic conditions makes it a worthwhile consideration for patients at greatest risk of developing asthma based on family history. Although ideal dosing levels are yet to be determined, the consistent safety of SLIT

at higher dosage levels may reduce concerns about titrating up if efficacy is less than desirable. As compliance is a prevalent concern in the treatment of pediatric patients, it is important to note that patient adherence to SLIT appears to be favorable. A survey⁶¹ of patients ($n = 443$) including adolescents reported that 75% of the patients took >90% of their prescribed doses of SLIT, and that compliance was >75% in ~88% of the patients. Cost of treatment was cited as a primary concern by only 2 out of the 443 patients. In patients who were more compliant, the compliance was comparable whether treatment was fully, partially, or not reimbursed (81%, 70%, and 82%, respectively).

Summary and Conclusions

Although the record on SLIT remains inconclusive, its safety profile and potential for possibly halting the atopic march warrant further research and testing of this immunotherapy approach. Consideration of higher dosing levels may be justified due to study data demonstrating that efficacy is dose responsive and safety is not dose responsive. This combination implies safety at higher doses, potentially justifying more potent regimens and longer terms of therapy that may yield more favorable outcomes. Although SLIT has been effective in pediatric asthma in some studies, more evidence is necessary before it can be determined whether it can be effective in children with severe asthma. Food allergy, which is more common in young children and can present a serious risk of anaphylaxis, may also prove to be treatable with SLIT, but more studies are needed before such a determination can be made.

Demonstration of safety in very young patients (2 years of age) invites further study for initiating treatment at an age when it may be more likely to have an impact on reducing disease progression (ie, before monosensitization progresses to more difficult to treat polysensitization). Imperative to early treatment is testing to determine the nature of allergy,



	Group A	Group B	$P =$
Symptoms score	1.64 ± 1.19	2.36 ± 1.55	0.057
Drug score	1.92 ± 1.36	3.98 ± 1.92	0.013
Total score	1.81 ± 1.67	3.28 ± 1.87	0.024

FIG. 3. Pollen counts, symptoms, and drug scores in the two groups of patients during the grass pollen season. Source: Marcucci et al.⁴⁴ Reprinted with permission by Blackwell Publishing.

as well as screening to determine the risk of future asthma (eg, based on sibling history, allergen exposure).

More comparative studies between SLIT and SCIT are needed to better determine the relative efficacy of these treatment modalities. Dose response studies are also imperative to establish optimum dose concentrations, dose build-up, maintenance, and timing. Further study on how contact with the oral mucosa may differentiate the mechanism of action of SLIT from SCIT should also be conducted. The development for standardized extracts will be an important step in FDA approval of these agents and will allow more uniformed assessment of results and comparison of study findings.

Acknowledgments

The authors would like to thank MarCom Group International, Inc., for its editorial assistance with the manuscript. Editorial support was funded by Greer Laboratories, Inc.

Author Disclosure Statement

No competing financial interests exist for either M.S.B. or T.A.M.

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Received for publication September 17, 2008; accepted after revision February 24, 2009.