

Sublingual immunotherapy for aeroallergens: Status in the United States

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ABSTRACT

Sublingual immunotherapy (SLIT) has been used in the treatment of allergic disease for nearly 30 years and is prescribed at least as frequently as subcutaneous immunotherapy (SCIT). Several large U.S. clinical trials using single allergen tablets (grass and ragweed) or extract solution (ragweed) have met their primary clinical efficacy outcome. In December, 2013 the Federal Drug Administration (FDA) Allergenic Products Advisory Committee favorably reviewed two grass tablet product formulations; the FDA usually follows the recommendations of their advisory committees. Industry-sponsored and investigator-initiated aeroallergen SLIT clinical trials conducted in the United States are the focus of this article. To provide a basis for evaluation of this treatment, SLIT mechanisms, pharmacokinetics, efficacy as reported in systematic reviews, and safety are also discussed. Practical considerations of SLIT in the clinical setting are reviewed. These include patient instructions and adherence, which appear to be as poor as SCIT. Estimated treatment costs based on U.S.-licensed allergen extract manufacturers' list prices and doses reported to be effective in studies using U.S.-licensed allergen extracts or the allergen immunotherapy practice parameters are presented. Unmet needs, which include unknown effective dose for many allergen extracts, optimal schedule (daily versus other) and timing of treatment initiation (perennial versus pre-seasonal, ≥ 8 weeks before or just at the start of season), and whether epinephrine autoinjectors should be routinely prescribed for SLIT patients are discussed.

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In 1986, the first double-blind, placebo-controlled (DBPC) study confirming the efficacy of sublingual immunotherapy (SLIT) in dust-mite (DM)-allergic patients was published,¹ 75 years after the first reports of successful treatment of grass pollen-induced hay fever with subcutaneous immunotherapy (SCIT).² Subsequently, the use of SLIT has grown rapidly. Worldwide, it is prescribed at least as frequently as SCIT as estimated by allergen extract manufacturing sales data and expert opinion.^{3–5} In some countries, such as France and Italy, SLIT is the most prescribed route and represents up to 80% of new allergy immunotherapy (AIT) prescriptions.⁵

In the United States, SCIT is the only route with a Federal Drug Administration (FDA)-approved formulation. Although, survey studies suggest only a small percentage of U.S. allergists prescribe SLIT, the number of prescribers appears to have doubled in a 4-year period, from 5.9% of respondents in 2007⁶ to 11.4% in 2011 ($p < 0.007$).⁷ Lack of an FDA-approved SLIT formulation was cited as the most common reason for not prescribing SLIT in both surveys. Other reasons cited

for not prescribing SLIT include “effective dose not known,” “no established practice parameters,” and “inadequate training or experience.”⁷ Since the initial 2007 survey, several U.S. SLIT clinical trials have met their primary outcome; and formal approval of a SLIT formulation is soon anticipated.

The purpose of this article is to evaluate the current status and future role of aeroallergen SLIT in the United States. Industry-sponsored and investigator-initiated U.S. clinical trials are reviewed, as well as practical considerations related to prescribing SLIT, *e.g.*, adherence, patient instructions, and treatment costs. Although the focus of this article is SLIT in the United States, to provide a basis for evaluating this treatment, this article includes a discussion of SLIT mechanisms and pharmacokinetics, efficacy as reported in meta-analyses and systematic reviews, and SLIT safety.

SLIT MECHANISMS AND PHARMACOKINETICS

The mechanism(s) responsible for SLIT efficacy is thought to be similar to SCIT when the allergen is systemically absorbed. However, the initial sublingual processing of the allergen is different. Whether administered as a tablet or a solution, the allergen is kept under the tongue for 1–2 minutes, and then swallowed. While underneath the tongue, the allergen binds immediately to the epithelium, likely a consequence of electrostatic interactions with a negatively charged glycocalyx at the surface of the epithelial cells.⁸ Subsequently, the allergen crosses the mucosa within 15–30 minutes, where it is

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Table 1 Summary of symptoms scores in SLIT systematic reviews

Disease	Author	Studies (n)	Population Age	Symptom Scores		Effect Size SMD (95% CI)	Heterogeneity I2
				Participants			
				Active (n)	Placebo (n)		
SCIT							
Rhinitis	Calderon 2007	15	Adults	597	466	-0.73 (-0.97, -0.50)	63%
Asthma	Abramson 2010	34	Adults and children	1284		-0.59 (-0.83, -0.35)	90%
SLIT							
Rhinitis	Wilson 2003	21	Adults and children	484	475	-0.42 (-0.69, -0.15)	74%
Rhinitis	Penagos 2006	10	Children	245	239	-0.56 (-1.01, -0.10)	81%
Rhinitis	Radulovic 2011	49	Adults and children	2333	2256	-0.49 (-0.64, -0.34)	81%
Asthma	Calamita 2006	9	Adults and children	150	153	-0.38 (-0.79, 0.03)	64%
Asthma	Penagos 2008	9	Children	232	209	-1.14 (-2.10, -0.18)	94%
Conjunctivitis	Calderon 2011	36	Adults and children	1725	1674	-0.41 (-0.53, -0.28)	59%
House DMs	Compalati 2009	8	Adults and children	194	188	-0.95 (-1.77, -0.14)	92%
Grass allergens	Di Bona 2010	19	Adults and children	1518	1453	-0.32 (-0.44, -0.21)	56%

Source: Modified with permission from Ref. 4.

Effect size: SMD, poor < -0.20; medium, -0.50; high > -0.80.

Heterogeneity: low, I2 < 25%; moderate, I2 = 50%; high, I2 > 75%.

SMD = standardized mean difference; DMs = dust mites; SLIT = sublingual immunotherapy; SCIT = subcutaneous immunotherapy.

captured and processed by antigen-presenting cells. The antigen-presenting cells migrate within 24–48 hours to draining cervical lymph nodes and tonsils where they present allergen-derived peptides to native CD4⁺ cells.⁸ Within a few days, enlisted TH1 and regulatory T cells migrate into the bloodstream and mucosa, where systemic effects similar to SCIT occur.

Studies examining the SLIT pharmacokinetics have used radiolabeled *Parietaria* (Par j 1) and dust mite (DM; Der p 2).^{9,10} The radiolabeled allergen was placed under the tongue of healthy (*Parietaria*) or allergic (DM) volunteers, who were instructed not to swallow for 30 or 6 minutes, respectively. Although the extract was underneath the tongue, there was no detectable plasma radioactivity, which "...confirmed the absence of direct systemic absorption of allergens."⁸ After swallowing, the plasma radioactivity peaked at 1–3 hours and was associated with free radioiodine and small radiolabeled peptides from degraded allergens. However, small amounts of radioactivity associated with the oral mucosa were found up to 20 hours after administration. No difference was found in the pharmacokinetics of the two SLIT delivery methods; SLIT-swallow (under the tongue and then swallowed), or the SLIT-spit (under the tongue 2 minutes, and then spit out), except with the SLIT-spit method ~30% of the allergen dose was recovered in the spat solution.¹¹ One study recommended switching to the SLIT-spit method as a means to reduce or minimize local reactions in individuals that were experiencing significant adverse local reactions with the SLIT-swallow method.¹² To this author's knowledge, there have been no published pharmacokinetics studies of SLIT tablets.

The optimal duration to keep the allergen under the tongue has not been studied in humans, but 20 seconds was the optimal duration in mouse studies based on the rise in bronchial and nasal lavage-specific IgA.¹³

SLIT EFFICACY: META-ANALYSIS AND SYSTEMATIC REVIEWS

Multiple meta-analysis and systematic reviews have been conducted examining the efficacy of SLIT for allergic rhinitis, asthma, and conjunctivitis, as well for specific allergens such as grass or DM (see Table 1). Efficacy is reported in these analyses as the standardized mean difference, which is the difference of the means of both treatment arms divided by the pooled standard deviation, with a large effect being -0.8 or greater, medium effect is -0.5, and a small effect of -0.2 or less. There is a considerable range in the symptom score standardized mean differences in both the rhinitis and the asthma SLIT clinical trials with many in the mid-efficacy range of -0.5 (Table 1). In comparison, the two Cochrane systematic SCIT reviews for asthma¹⁴ and allergic rhinitis¹⁵ found a moderate to a high effect at -0.59 and -0.73, respectively. In the individual studies, the magnitude of improvement over placebo for SCIT and SLIT appears similar for symptoms scores (29–37%) and medication use (32–46%).^{16–18}

There are few well-designed, placebo-controlled trials that have directly compared SLIT with SCIT. One DBPC double-dummy design (DD) comparing the efficacy of SLIT with SCIT in birch pollen allergic rhinitis found a greater magnitude in improvement with SCIT than SLIT compared with placebo.¹⁹ SLIT reduced the

Table 2 SLIT Efficacy per Allergen

Effective dose reported in clinical trials (daily unless specified otherwise)				
Allergen	Formulation	Major Allergen	Source	Comment
Grass	Tablet	15 μg of Phl p 5	Timothy only	
	Tablet	25 μg of Ph p 5	5 grass pollen	
	Extract solution	40 μg of Phl p 5	6 grass pollen	
Ragweed	Tablet	12 μg of Amb a 1	Short ragweed	
	Extract solution	50 μg of Amb a 1	Short ragweed	
DM	Tablet	28/120 μg of Der p 1/Der f 1*	Mixed dust mite	16/68 μg of Der p 1/Der f 1 dose also effective vs placebo but lesser magnitude (20% vs 17.9%)
Cat	Extract solution	~ 70 μg of Der f 1	<i>D. farinae</i>	
	Extract solution	0.05 μg of Fel d 1	Cat extract	Note, 40 μg found not effective in another trial
<i>Alternaria</i>	Extract solution	1.5 μg Alt a 1/mL every other day	<i>Alternaria</i> ⁶⁰	
Cockroach	Extract solution	No effective dose established		
Trees	Extract solutions	Birch, olive, cypress studied—only birch with a dose–response study that showed greater efficacy of 30 μg compared with 3.6 μg of major allergen of Bet v 1/Aln g 1/Cor a 1 cumulative weekly dose administered over 5 days ⁶¹		
Dog	Not studied			

*Bergmann K, unpublished.

DM = dust mite; SLIT = sublingual immunotherapy.

median disease severity to one-half and SCIT to one-third of the placebo group but these differences were not significant. The authors speculated that this may have been caused by the small number of subjects completing the study.

Great clinical efficacy with SCIT compared with SLIT was reported in two subsequent randomized controlled trials.^{20,21} One was a randomized, controlled, four parallel group study that compared the efficacy of SCIT alone, SCIT followed by SLIT maintenance, SLIT alone, and pharmacotherapy in DM allergic rhinitis asthma patients.²¹ Greater clinical efficacy was found in the SCIT and SCIT followed by SLIT groups compared with SLIT alone. The other study was a DBPC-DD study of dust-allergic patients that showed a significant improvement in asthma and rhinitis symptoms with both methods.²⁰ However, the difference compared with placebo was only significant in the SCIT group.

A much greater magnitude of symptom improvement has been reported with both routes in studies that examined patients with a presumed higher degree of symptomatology: SCIT, 61%,²² and SLIT, 40%.²³ In comparison, the mean treatment effect for antihistamines and nasal steroids is between 8 and 18% greater than placebo (data from U.S. prescribing information and provided by Stephen Durham, M.D., presentation's to FDA Allergenic Products Advisory Committee on May 12, 2011).²⁴

SLIT: LESSONS LEARNED FROM NON-U.S. STUDIES: DOSE, ONSET OF EFFICACY, AND DURATION

Unlike SCIT, where the effective dose appears to be 5–20 μg of the major allergen, there does not appear to be a consistent relationship with allergen dose and efficacy. The effective dose for SLIT may vary significantly with the allergen and the form of the allergen, *e.g.*, tablet versus extract solution (see Table 2 for summary of SLIT effective doses). However, the effective dosing range for grass tablets has been shown in several clinical trials that included hundreds of patients, to be consistently between 15 and 25 μg of Phl p 5 administered daily. This dose is nearly 30 times the usual SCIT maintenance dose administered monthly. Although the SLIT effective dose range in the published literature is fairly large—between 5 and 375 times the equivalent SCIT course²⁵—recent studies using extract solution and tablets suggest the effective dose may be equivalent to the SCIT monthly dose administered daily and possibly greater for the extract solution version of the allergen.^{26,27}

In the first clinical trial to show a clear SLIT dose–response, significant efficacy in terms of reduced symptoms was only seen in the highest-dose grass tablet group (15 μg of Phl p 5) who had received at least 8 weeks of preseasonal treatment.²⁸ Subsequently,

in a study comparing the efficacy of 2-month versus 4-month pre-seasonal treatment found similar efficacy in the first season with both schedules.²⁹ One study indicated a significant improvement in the first season symptoms scores and progressive improvement in combined symptoms–medications scores in a 3-year study, during which treatment was started at the beginning of each grass pollen season and terminated at the end of each season.³⁰ Finally, a significant difference was seen between the placebo and grass tablet SLIT groups within 1 month of treatment in an environmental chamber challenge.³¹

There have been no randomized controlled trials that have compared different dosing frequency schedules, *e.g.*, daily versus 3 times a week. However, most recent SLIT trials have used daily dosing schedules citing better patient adherence as the rationale.

Additional studies are needed to determine the optimal dosing frequency and schedule for clinical efficacy as well as the most cost-effective approach.

The clinical improvement associated with SLIT has been shown to persist for up to 2 years after treatment discontinuation in DBPC trials^{29,32,33} and considerably longer in open studies.^{34,35}

SLIT U.S. CLINICAL TRIAL: INDUSTRY SPONSORED AND INVESTIGATOR INITIATED

Since the publication of the first DBPC SLIT study in 1986, >71 randomized controlled SLIT trials have been published. Most of these studies have been conducted in patients with grass pollen or DM allergic rhinitis. Most studies allowed patients with asthma and polysensitization, providing the former did not require a daily controller medication and the latter did not cause symptoms during the grass pollen season. The first U.S. SLIT trial was published in 1993 and failed to show a significant improvement compared with placebo after 105 daily administrations of high-dose cat extract.³⁶

There were no subsequent U.S. SLIT studies until 2005, when an allergen extract manufacturer (Greer Laboratories, Lenoir, NC) began the multiphase process required for obtaining FDA approval for SLIT use of an existing U.S.-licensed glycerinated allergenic extract (*i.e.*, a product information label change).³⁷ The initial open-label study investigated the safety and tolerability of U.S.-licensed DM, timothy grass pollen, cat hair, and short ragweed extract administered in a single seven incremental dose escalation session followed by 8 weeks of daily administration of the maximal tolerated dose (MTD). The MTD ranged from 50 to 2090 bioequivalent allergy units/allergy units (BAU/AU) for cat hair and DM extract, 31–91 Amb a 1 μg for short ragweed pollen extract, and 50–21,090 BAU for timothy grass pollen extract. Subsequently, a DBPC study compared the safety and efficacy of two short

ragweed pollen extract doses (4.8, 48 μg of Amb a 1) with placebo using the same 1-day, 7-dose escalation protocol.³⁸ There was a 15% reduction in total rhinoconjunctivitis symptom scores in both SLIT groups but improvement was not statistically significant compared with placebo. However, in an analysis of covariance correcting for pre-seasonal symptoms, the higher-dose group did show a significant improvement in both symptom and medication scores compared with placebo. In a subsequent study of 429 ragweed allergic rhinitis using the same extract and a three-step escalation protocol (placebo, 18 mcg and 50 mcg), SLIT was associated with a 43% reduction of the change from baseline of the combined symptom and medication relative to placebo ($p = 0.0005$).²⁷ Ninety-four percent of the patients achieved the MTD of 50 μg of Amb a 1 units, 3% of subjects remained on 18 μg of Amb a 1, and 3% stepped down from 50 to 18 μg of Amb a 1. There were no reported cases of anaphylaxis and no reaction-prompted epinephrine administration.

A similar safety–efficacy profile has been shown with a short ragweed lyophilized tablet (Merck & Co., Kenilworth, NJ). Dose–response, DBPC studies conducted in North America and Europe investigating the safety and efficacy of 3 doses of a ragweed tablet showed significant reductions in combined symptom–medication scores, immunologic parameters, and other secondary outcomes with 6 and 12 μg of Amb a 1 doses.^{39,40} The 12- μg Amb a 1 dose showed the most favorable efficacy–safety profile. Most of the adverse reactions were local reactions but one patient in the 6-Amb a 1 group “... received epinephrine at an emergency facility for sensation of localized pharyngeal edema.”³⁹ In an earlier phase I study designed to investigate the safety of 6 doses of this ragweed tablet ranging from 3 to 100 μg of Amb 1, recruitment to 50 Amb a 1U was discontinued and the 100 Amb a 1U dose was not initiated after three subjects experienced SRs at doses ≥ 24 μg of Amb a 1.⁴¹ The 50 Amb a 1 group was “terminated due to the adverse event profile.” Of note, 50 μg of Amb a 1 administered as an extract solution was both effective and well tolerated in the study discussed earlier.²⁷ These studies suggest that efficacy and safety may vary with the specific allergen extract formulation.

The efficacy of two different grass pollen tablet products containing ~ 15 μg of Phl p 5 (Merck & Co.) and ~ 25 μg of Phl p 5 (Stallergenes, Antony, France) has been established in three U.S. multicentered trials in both the pediatric⁴² and the adult population.^{43,44} Reductions in combined symptom–medication scores compared with placebo ranged from 20⁴⁴ to 28%.⁴³ A small number of patients in the placebo (2) and SLIT (3) groups used the epinephrine autoinjector.^{42,44} In three instances, it was used for symptoms not caused by active treatment. One patient in the placebo group

used it 12 hours after the 137th dose because of wheezing related to exposure to a grassy field⁴² and another placebo patient used it in response to what was, subsequently, deemed to be an anxiety attack. In the SLIT group, self-administered epinephrine was used in three patients for symptoms diagnosed later as viral pharyngitis,⁴² flushing and chest tightness,⁴⁴ and lip angioedema and cough.⁴² Notably, the FDA stipulates that epinephrine autoinjectors be prescribed to subjects participating in U.S. SLIT clinical trials. However, epinephrine autoinjectors are not routinely prescribed or recommended in countries where SLIT is registered and commercially available. In the U.S. grass tablet clinical trials conducted, to date, that collectively include over 1000 patients, only three SLIT patients used their epinephrine autoinjectors. In general, safety and efficacy was similar to the multiple European studies, where both products are currently registered: GRAZAX (ALK-Abelló Hørsholm, Denmark) since 2006 and ORALAIR (Stallergenes) since 2008.

In addition to these industry-funded studies, there have been investigator-initiated studies that explored several unmet needs, one of which is the efficacy of multiallergen SLIT. This is an important consideration because most of the allergic population is polysensitized and most U.S. physicians prescribe multiallergen SCIT.^{45,46} To evaluate this question, a DBPC single-site study compared the efficacy of timothy pollen glycerinated extract alone with the same dose of timothy extract mixed with nine additional allergens.⁴⁷ There was significant improvement in multiple outcomes in the timothy alone group but only in the titrated skin test results in the multiallergen group. This study suggests that the "... clinical efficacy of SLIT may be reduced by the addition of multiple allergens potentially limiting its use in polysensitized individuals."⁴⁷ In contrast, dual-allergen SLIT with DM and grass pollen glycerinated extract administered separately was found to be effective in terms of reduction in symptoms scores, medication use, and several immunologic markers.⁴⁸ Additional studies are clearly to address several questions regarding multiallergen SLIT efficacy, including

Is it effective?

Is it only effective, if the allergens are administered separately?

If effective as a mixture, how many allergens can be mixed together?

Other studies using U.S.-licensed glycerinated extracts for SLIT have shown efficacy of 4200 AU of *Dermatophagoides farinae* (~70 µg of Der f 1) administered daily for 12–18 months in terms of bronchial allergen challenge and *D. farinae*-specific IgG4.⁴⁹ No consistent change in biomarkers with cockroach SLIT

at 5.2 µg of Bla g 2 administered daily for 6 months was found.⁵⁰

To date, there have been no U.S. clinical trials using tree, dog, or any mold/fungi extract.

Collectively, the effective dose and safety of single grass and ragweed allergen tablets and ragweed glycerinated extract has been established in several large U.S. clinical trials. Two small investigator-initiated studies have established efficacy of a U.S.-licensed DM extract (see Table 3 for summary of U.S. clinical trials).

However, several questions remain regarding the use of SLIT in the United States:

- What is the effective dose of almost all of the U.S.-licensed extracts allergens (*e.g.*, trees, *Alternaria*, dog, *etc.*)?
- What is the efficacy of multiple allergen extract solutions, the practice commonly used in the United States for SCIT?
- What are the risk/benefits of routine prescribing of epinephrine autoinjectors for all SLIT patients?

SLIT SAFETY

In general, SLIT appears to be better tolerated than SCIT. There have been no reports of SLIT-related fatalities, to date, in an estimated ≥1 billion doses. Most SLIT adverse events are local reactions (*e.g.*, oromucosal pruritus) that occur at the beginning of treatment and resolve within a few days or weeks without any medical intervention, such as dose reductions or medications (*e.g.*, antihistamines).

There is a relationship with dose and adverse events in dose–response studies but a consistent relationship between the allergen dose and SLIT systemic reactions (SR) in the collective literature has not been established.

Additionally, there does not seem to be a relationship with adverse events and dosing schedules, with studies using rush, ultrarush, and no undosing schedules reporting comparable safety data as studies that use multiple-week build-up schedules. There have been at least 11 cases of SLIT anaphylaxis in the reported literature.⁵¹ No risk factors for SLIT SRs have been established to date. However, there have been a few cases of SLIT-associated anaphylaxis in individuals, who had previous SCIT SRs. In some cases, the anaphylaxis occurred with the first SLIT dose.⁵² Currently, in Europe, it is recommended practice that the first SLIT dose be administered in a medical-supervised setting (Giovanni Passalacqua, Allergy and Respiratory Diseases, University of Genoa, Genoa, Italy, June 23, 2013, personal communication). This was a requirement in the U.S. SLIT clinical trials.

As SLIT is administered in a medically unsupervised setting, the patient and/or family should be provided with specific instructions regarding the management of

Table 3 Summary of U.S. industry and investigator-initiated placebo-controlled clinical trials conducted since 2006

Allergen	Industry or Investigator*	Patient Population	Regimen	Dose/Formulation	Primary Outcome#	Safety
Grass	Merck & Co. ^{42,44}	Adults (439) and pediatric (345; 2 trials) ARC ± asthma	4 mo pre- and coseasonal,	15 µg of Phl p 5 tablet	Adults: 20% CS Pediatrics: 25% CS	Epinephrine (2): Placebo anxiety attack SLIT: flush/rash, chest tightness, and uvula/pharyngeal edema Epinephrine (3): SLIT, 1 placebo SLIT: cough, lip angioedema 1st dose. SLIT: ER visit—dx with viral pharyngitis; placebo: 12 hr after 137 dose No epinephrine/anaphylaxis
	Stallergenes ⁴³	473 Adults ARC ± asthma	4 mo pre- and coseasonal	25 µg of 5-grass pollen tablet	28% CS	No systemic reactions
	Nelson ⁴⁷	54 Adults ARC ± asthma	10 mo: September–July	Timothy alone at 19 µg of Phl p5 or same dose with 9 allergens glycerinated extract solution	Tomothy alone: significant improvement in multiple outcome vs one in multiallergen CS 12 µg: 26% 6 µg: 21%	
Ragweed	Merck & Co ³⁹	565 Adults: ARC	4 mo before for total of 52 wk,	6 and 12 µg of Amb a 1 tablet		Epinephrine (2) 6 µg of SLIT- ER 12 µg of SLIT—not TRAE used for food-allergic reaction No asthma-related AE
	Greer ³⁸	115 Adults: ARC	8–10 wk pre- and coseasonal	4.8 and 48 µg of Amb a 1 glycerinated extract solution	15% Symptoms in both groups (<i>p</i> > 0.10) 43% CS compared with baseline	“No pt experienced anaphylaxis or required administration of epinephrine” Two withdrawals for abdominal sx; other TRAE high dose: Aphthous ulcer ×4 hr (1); asthma (1), low dose: IBS pt moderate diarrhea for 30 days No significant difference in TRAE from placebo
DM	Bush ⁴⁹	31 Adults ARC ± asthma	12–18 mo, end points assessed q. 6 mo	µg of glycerinated extract solution Maximum tolerated dose up to 42 1 and 70 µg of Der f 1 glycerinated extract solution	No difference in symptom-medication scores, significant improvement in allergen specific BHR and specific IgG	
Dust plus grass	Swamy/Nadeau ⁴⁸	30 Adults and pediatrics	4 mo before grass season for 12 mo	15 µg of Phl p 1 20 µg of Der p 1 and 2 glycerinated extract solution	Decreased symptom, medication, titrated SPT and nasal challenge and favorable immunologic parameters	

*Company listed for industry sponsored and investigator if investigator-initiated trial.

#Percentage improvement over placebo.

ARC = allergic rhinoconjunctivitis; CS = combined symptom-medication score; S = systemic reaction; BHR = bronchial hyperreactivity; SPT = skin-prick test; TRAE = treatment related adverse event; IBS = irritable bowel syndrome; AE = adverse event; DM = dust mite; ER = emergency room; SLIT = sublingual immunotherapy.

Table 4 SLIT estimated costs based on U.S.-licensed extract manufacturers' list price

Allergen	Monthly Costs*	Average Cost/mL Average of Two U.S. Allergen Extract Manufacturers' 2013 List Price
Cat	\$82.74 (2000 BAU) ⁵⁹	50 mL vial/\$13.79/mL
DM	\$121.68 (2800 AU) ⁴⁸	50 mL vial/\$14.48/mL
Standardized grass	\$7.33 (~2800 BAU daily) ⁴⁷	50 mL vial/\$8.56 per mL
Ragweed	\$66.00 (~50 µg) ²⁷	30 mL vial 1:20 w/v#/\$6.60 per mL
Cat, DM, and grass	\$211.75/mo or 2541.00/yr	

*Cost-based average of two U.S.-licensed extract manufacturers' 2013 catalogue: using highest bulk extract available 30 or 50 mL, estimated dose from clinical trials or Allergen Immunotherapy: A Practice Parameters Third Update,⁵⁹ and assumes daily dosing, which is listed in parentheses.

#1/20 w/v = ~150 µg of Amb a 1 per mL.

DF = Dermatophagoides farinae; AU = allergy units; BAU = bioequivalent allergy units; DM = dust mite; SLIT = sublingual immunotherapy.

adverse reactions, unplanned interruptions in treatment, when and what to report to the prescribing physician, and situations when SLIT should be withheld (e.g., oropharyngeal infection, oral abrasion, acute gastroenteritis, asthma exacerbation, etc.).⁵³ In selecting patients for SLIT, careful consideration should also be given to the ability of the patient and/or their family to adhere to these instructions and the treatment.

SLIT IN THE UNITED STATES: PRACTICAL CONSIDERATIONS

Treatment initiation and adherence with SCIT is very low with an estimated 5% of the allergic population subscribing to it⁵ and only 16% adhering to the recommended 3-year treatment course.⁵⁴ Inconvenience related to the time/travel/costs of receiving SCIT in a supervised medical facility is one of the most commonly cited reasons for both. Because SLITs favorable safety profile allows home administration, thus theoretically improving the "convenience of AIT," it is expected that this will increase the number of patients subscribing to this disease-modifying treatment. Similarly, improved adherence would be expected because SLIT does not require much treatment-related patient time. However, several studies have indicated that SLIT adherence is equally as poor as SLITs.

Sales figures from the two large extract manufacturers representing 60% of the Italian AIT market in Italy were compared over 3 years to assess the number of SLIT refills sold as a first prescription in 2006.⁵⁵ Only 43.7% of the patients refilled their SLIT prescription after 1 year of treatment. Adherence rate progressively worsened over time with only 13.2% refilling their SLIT prescription in the 3rd year. Adherence rate did not vary with allergen type: DM versus pollen. Insurance status—fully covered, partially reimbursed, or not reimbursed—had some effect in the 2nd and 3rd year with a significantly

better adherence in the fully versus no coverage groups but both coverage groups had a dismal, <30%, adherence rate.

Another 2-year study that evaluated adherence in young children between 3 and 6 years old reported an overall 46% discontinuation rate.⁵⁶ In the 3- to 4-year old group, 52% discontinued SLIT—all within 3 months of treatment. The most common reasons for discontinuation were "... subjective discomfort or refusal without any apparent side effects." One randomized controlled study evaluating the effect of office visit frequency on SLIT adherence found significantly better adherence in the four-visit-a-year group compared with the one-visit-a-year group (2-year adherence: 81.5% versus 29.6%, respectively; $p < 0.0005$).⁵⁷ These studies suggest that adherence with SLIT can be equally problematic as with SCIT. Nonadherence would likely be more apparent with SCIT because the patient receives treatment in a medical facility. SLIT nonadherence will likely result in a poor clinical outcome and this will give the appearance that the SLIT treatment is ineffective. Strategies aimed at monitoring and, if need be, improving SLIT adherence are needed for this to be a successful treatment option in the United States where quality performance, comparative effectiveness, and cost efficacy have become increasingly more important.⁵⁸

Cost may be another consideration and limiting factor in the use of SLIT if the common U.S. practice of prescribing multiallergen AIT is used. The limited data on potential effective dose of U.S.-licensed allergen extract suggests the dose may be equal to the monthly SCIT dose administered daily. This may be fairly costly if multiple allergens are used (see Table 4 for estimated costs for SLIT based on U.S.-licensed allergen extract list price).

SUMMARY AND UNMET NEEDS

In summary, the proof of concept of SLIT efficacy and safety has been clearly established both in meta-analyses and many large U.S. and European clinical trials. Questions remain regarding effective dose for many allergens including almost all of the U.S.-licensed extracts. Optimal dosing regimen in terms of dosing frequency and treatment initiation/schedule for seasonal allergens warrants further study. Daily dosing is currently the most common approach in recent studies. Preseasonal treatment may be as effective as perennial for seasonal allergens. How soon before the season does treatment need to be started to ensure efficacy is another unanswered question. There are conflicting data in the literature on how early treatment must be started to ensure first season efficacy. It is fairly clear that each formulation may vary in terms of safety and efficacy even within an allergen class. Thus, each formulation will need to establish its safe and effective dosing regimen.

The safety of SLIT appears to be very well established in clinical trials and postsurveillance studies but there have been rare cases of SLIT-associated anaphylaxis. Prescribing physicians need to provide appropriate patient instructions, which includes treatment of adverse reactions, when to withhold treatment, and management of uninterrupted treatment gaps. Prescribers will also need to consider whether to prescribe epinephrine autoinjectors, which was an FDA requirement for U.S. SLIT clinical trials but not standard practice in Europe and other parts of world where SLIT is registered and commercially available. Finally, SLIT adherence has been shown to be as problematic as SCIT. Strategies need to be developed to address this.

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