

Sublingual Immunotherapy in Patients with Allergic Rhinoconjunctivitis

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Abstract Sublingual immunotherapy (SLIT) is a well-established treatment option for allergic rhinitis in several European countries, but it is considered investigational in the United States. Studies conducted in Europe provided a large body of evidence supporting the safety and efficacy of SLIT, but those studies used allergen products that are different from those that are likely to be approved in the United States, and many of them were not controlled, randomized, double-blinded trials. This review summarizes research conducted on the efficacy, safety, and mechanisms of SLIT published during the past year, with a focus on ragweed and grass antigens. Results of recent US studies document the safety and efficacy of SLIT and have started to yield insight into the mechanisms of SLIT.

Keywords Sublingual immunotherapy · Allergic rhinitis · Safety · Efficacy

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Introduction

Sublingual immunotherapy (SLIT) is a well-established treatment option for allergic rhinitis in several European countries, but it is considered investigational in the United States. Specific allergen immunotherapy has been almost exclusively delivered subcutaneously in the United States, but SLIT has recently undergone extensive evaluation for efficacy and safety. This review summarizes research conducted on the efficacy, safety, and mechanisms of antigen delivery via the sublingual route and published during the past year identified using PubMed, with a preferred focus on ragweed and grass antigens.

Efficacy and Safety

Studies conducted in Europe provided a large body of evidence supporting the safety and efficacy of SLIT, but those studies used allergen products that are different from those that are likely to be approved in the United States. Esch et al. [1] determined the safety and tolerability of four US-licensed, standardized SLIT allergenic extracts, including ragweed. Adults with or without asthma and with allergic rhinitis caused by Timothy grass pollen, short ragweed pollen, house dust mite, or cat hair completed a single-session dose escalation followed by an 8-week, open-label daily course of SLIT. Daily adverse effects and adherence were documented using an electronic diary. Ninety-one individuals (18–50 years of age) initiated treatment, 77 of whom completed the phase 1 testing. Maximum tolerable doses ranged from 50 to 2,090 bioequivalent allergy units (BAU) for cat hair and dust mite extract, 31 to 91 Amb a 1 U for short ragweed pollen extract, and 50 to 21,090 BAU for Timothy grass pollen

extract. During the 8 weeks of treatment, 98.9% of participants reported at least one mild adverse event, 70.4% at least one moderate adverse event, and 13.6% at least one severe adverse event. Most adverse events (94.6%) were rated as mild, but 5.2% were rated as moderate, and 0.1% were rated as severe. Nasal and oral/mucosal adverse events were most commonly reported. No life-threatening events were observed in more than 4,500 administered doses, supporting an acceptable safety profile. The authors concluded that sublingual/oral dosing of standardized allergenic extracts at maximum tolerable doses was generally well-tolerated and that US-licensed SLIT extracts were safe when appropriately self-administered.

Skoner et al. [2•] conducted a randomized, double-blind, placebo-controlled trial to identify a safe and effective maintenance dose range of sublingual, standardized, glycerinated short ragweed pollen extract in adults with ragweed-induced rhinoconjunctivitis. Patients ($n=115$) with ragweed-induced rhinoconjunctivitis were randomly assigned to placebo ($n=40$), medium-dose extract ($4.8 \mu\text{g}$ Amb a 1/d; $n=39$), or high-dose extract ($48 \mu\text{g}$ Amb a 1/d; $n=36$). Participants were administered a 1-day (rush) dose-escalation regimen in May 2006 with placebo or ragweed pollen extract in incremental doses until the maximum tolerable or scheduled dose was reached. Daily dosing was then maintained during the fall ragweed pollen season (August–October). Patient diaries were used to monitor nasal and ocular symptoms and medication use, and the primary end point was symptom score. Thirty-two of 40 individuals (80%) in the placebo group, 27 of 39 (69%) in the middle-dose group, and 23 of 36 (64%) in the high-dose group tolerated the maximum scheduled dose. The average cumulative dose administered through the entire treatment course was $498 \pm 185 \mu\text{g}$ Amb a 1/mL in the medium-dose group and $4941 \pm 1487 \mu\text{g}$ Amb a 1/mL in the high-dose group. The mean maximal tolerable doses were estimated to be $3.21 (\pm 1.64)$ and $30.54 (\pm 16.14) \mu\text{g}$ Amb a 1 in the medium-dose and high-dose groups, respectively. A 15% reduction in the total rhinoconjunctivitis symptom score was observed in both active treatment groups compared with placebo during the entire ragweed pollen season, but the difference was not statistically significant ($P>0.10$). However, an analysis of covariance that corrected for preseasonal symptoms found that mean daily symptom scores (DSS) (0.19 ± 1.16 vs 1.00 ± 2.30) and medication scores (DMS) (0.0003 ± 1.64 vs 0.63 ± 1.06) for the entire pollen season were significantly reduced in the high-dose versus placebo groups, respectively ($P \leq 0.05$). In addition to improvement in these clinical outcomes, immunologic changes were also observed. Ragweed-specific IgG, IgG₄, and IgA antibodies were increased after treatment in the medium- and high-dose groups, but not in the placebo group.

Safety was carefully evaluated in this study as well. The frequency of adverse events was similar between the placebo and active treatment groups, but oral/mucosal adverse events occurred more often with active treatment. A total of 202 adverse events (placebo, $n=67$; medium dose, $n=65$; high dose, $n=70$) were reported, with frequency ranging from 56% in the high-dose group to 73% in the placebo group. Thirteen of the 202 events (6%) were classified as severe, 4 events (2%) were considered serious, and 1 additional event was considered life-threatening. Three of the 13 severe events were reported by 2 individuals in the placebo group, and 10 of the severe events were reported by 6 individuals in the active treatment groups. The four serious events occurred in one individual in the placebo group (gallbladder surgery), one individual in the medium-dose treatment group (life-threatening blood clot in the leg), and two individuals in the high-dose treatment group (spontaneous abortion, $n=1$; sigmoid diverticulitis, $n=1$). No asthma-related events occurred. Oral/mucosal events occurred more often with medium-dose (13%) and high-dose (11%) treatment than with placebo (0%; $P=0.01$).

This study showed that standardized, glycerinated short ragweed pollen extract administered sublingually at maintenance doses of 4.8 to $48 \mu\text{g}$ Amb a 1/d was safe and induced favorable clinical and immunologic changes in ragweed-sensitive individuals. However, the study did fail to meet its primary end point, showing that additional trials will be needed to establish efficacy.

Seidenberg et al. [3] conducted a large observational study in 193 European children and adolescents with allergic rhinitis. The purpose of the study was to evaluate the safety and tolerability of an ultrarush, high-dose, sublingual-swallow immunotherapy (SLIT) regimen reaching a maintenance dose of 300 index of reactivity (IR) within 90 minutes. Children and adolescents 5 to 17 years of age with or without a history of mild asthma and with a history of allergic rhinitis caused by tree or grass pollens were studied. Standardized grass and tree pollen allergen extracts were used for ultrarush titration and co-seasonal maintenance. During ultrarush titration, 60 patients (31%) reported 117 predominantly mild and local adverse events that resolved within 150 min. During the maintenance phase, 562 adverse events were reported. The most frequent local events were oral pruritus, burning sensation, lip or tongue swelling, and gastrointestinal symptoms. The most frequent systemic events were rhinoconjunctivitis and asthma. There was one clinically significant asthma event in an 11-year old boy who was known to have asthma, in whom SLIT was resumed after an interval of 4 days. The authors concluded that ultrarush titration was safe and well-tolerated, and that pediatric patients with asthma should be monitored carefully and trained adequately to use their rescue medications during SLIT treatment.

Most of the earlier SLIT studies used single allergens, and previously, there had been no randomized, double-blind studies showing the effectiveness of SLIT with multiple allergens. Amar et al. [4•] determined whether the efficacy of SLIT with standardized Timothy extract was reduced by combining it with other allergen extracts. They conducted a single-center, randomized, double-blind, placebo-controlled trial with SLIT. After an observational grass season, SLIT was administered for 10 months to 54 patients randomly assigned to one of three treatment arms: placebo, Timothy extract (19 µg Phl p 5/d) as monotherapy, or the same dose of Timothy extract plus 9 additional pollen extracts. Symptom and medication scores were collected and a variety of mechanistic studies were conducted. First, there were no significant differences in medication or symptom scores in either treatment group compared with placebo. That could have been due to the very low grass pollen counts observed during the study season. However, compared with placebo, in the Timothy monotherapy group, thresholds for titrated nasal challenge and skin prick tests ($P=0.03$ and $P=0.001$, respectively), and serum-specific IgG₄ levels ($P=0.005$) significantly increased, and interferon (IFN)- γ levels decreased ($P=0.02$). In contrast, in the multiallergen group, significant improvement was noted only in the titrated skin prick tests ($P=0.04$), which was less than in the monotherapy group. There were no significant differences between the two active treatment groups on any outcome measure. Both active treatment groups experienced more adverse events than the placebo group. No systemic reactions were observed. The authors concluded that 1) improvement in multiple relevant outcomes suggested that SLIT with Timothy extract alone was effective and 2) the differences between multiple-allergen SLIT and placebo only in skin sensitivity to Timothy suggested a reduction in SLIT efficacy in this group. Further studies were recommended to confirm these observations, which are important because most allergen immunotherapy used in the United States is composed of multiple allergens.

In addition, several other studies have evaluated SLIT in polysensitized patients. Ciprandi et al. [5] evaluated the effect of SLIT on quality of life in a population of polysensitized patients with allergic rhinitis in a real life clinical practice setting. They prospectively evaluated 167 consecutively enrolled polysensitized patients with allergic rhinitis. They administered the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) at baseline and after 1 year of SLIT (performed in ~70% of cases using single-allergen extracts provided by the same manufacturer). The most frequent causes of allergen sensitization were grass pollen, *Parietaria* spp, and house dust mites, and the mean number of sensitizations per patient was 3.65. SLIT was performed with 1 extract in 123 patients (73.6%), with 2 extracts in 31

patients (18.6%), and with more than 2 extracts in 13 patients (7.8%). The mean values of all the quality-of-life items improved significantly ($P<0.01$ in all cases), with improvement noted in activities, sleep, general problems, practical problems, nasal symptoms, eye symptoms, and emotional aspects. The authors of this open, nonrandomized, nonblinded trial concluded that quality of life can be improved in polysensitized patients treated with SLIT, and that the use of just one or two allergen extracts was sufficient to improve quality of life.

In another study involving polysensitized individuals, Ciprandi et al. [6] evaluated the clinical effectiveness of 1 year of SLIT using an open study design. Fifty-one polysensitized Italian children (34 boys; mean age, 11.8 years; range, 5.2–17.7 years) with allergic rhinitis and/or mild to moderate asthma were studied. Forty-two children were treated with a single extract, four with two different extracts, and three with a mix of allergens. SLIT treatment resulted in a significant reduction in the number of sensitizations ($P=0.018$); significant improvements in allergic rhinitis classification and severity; and significant reductions in ocular, nasal, and bronchial symptoms ($P<0.01$ for all) and drug use ($P<0.01$ for all drugs). No systemic reactions to SLIT were reported. The authors concluded that polysensitization is not an obstacle for prescribing SLIT in children. However, future randomized, placebo-controlled trials will need to be conducted to confirm this observation.

Initial studies with SLIT in Europe and the United States focused on the use of pollen allergens. Also, very few SLIT studies enrolled participants of Asian descent. Kim et al. [7] studied 58 patients with allergic rhinitis and allergy to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. Symptom scores were significantly improved with reduced medication scores during 12 months of SLIT. In addition, specific IgE for *D. farinae* increased slightly ($P=0.019$), whereas specific IgE for *D. pteronyssinus* and total IgE did not change significantly. The authors concluded that SLIT improved the symptoms and medication scores in Korean patients with allergic rhinitis caused by house dust mites. Results from this trial are encouraging, but the study design (open, nonrandomized, lack of blinding and placebo) precludes the formulation of definitive conclusions.

Little is known about the precise onset of action of allergen immunotherapy, especially allergen immunotherapy that is delivered sublingually. Onset of action can be difficult to study in natural settings due to the unpredictability of pollen seasons. Therefore, the allergen challenge chamber was developed as a pharmacodynamic assessment tool to circumvent the problems associated with natural pollen exposure and to control the environmental allergen exposures. Horak et al. [8] used the allergen challenge chamber to evaluate the onset of action and efficacy of 300

IR of a 5-grass pollen SLIT tablet. Patients with grass pollen-induced rhinoconjunctivitis were randomly assigned to active or placebo treatment groups. A standardized grass pollen allergen challenge and symptom evaluation every 15 min was performed at baseline; after 1 week; and after 1, 2, and 4 months of treatment. In the intention-to-treat population ($n=89$), a significant treatment effect was detected after the first month ($P=0.0042$) and was maintained through the fourth month ($P=0.0007$) of therapy. In the active treatment group, the average rhinoconjunctivitis total symptom score (mean $\pm$ SD) decreased at each challenge as follows: week 1, 7.40 ± 2.682 ; month 1, 5.89 ± 2.431 ; month 2, 5.09 ± 2.088 ; and month 4, 4.85 ± 1.999 . An improvement (vs placebo) of 29.3% for the mean total symptom score was observed at the study end point. The most frequent adverse reactions were local and included oral and ear pruritus and throat irritation. The authors concluded that onset of action of the 300-IR 5-grass pollen SLIT tablets (vs placebo) was 1 month after treatment initiation.

There is evidence for disease modification when allergen immunotherapy is delivered subcutaneously. However, until recently, such evidence had been lacking for SLIT. Durham et al. [9•] investigated the sustainability of efficacy 1 year after a 3-year period of daily treatment with the SQ-standardized grass allergy immunotherapy tablet (AIT) Grazax (*Phleum pratense* 75,000 SQ-T/2,800 BAU; ALK-Abelló, Horsholm, Denmark). They conducted a randomized, double-blind, placebo-controlled, phase 3 trial including adults with a history of moderate to severe grass pollen-induced rhinoconjunctivitis that was inadequately controlled by symptomatic medication use. The results for 257 individuals at follow-up were analyzed. As expected based on the results of previous studies, significant improvements in efficacy were consistently shown during 3 years of active treatment. One year after treatment ended, the active treatment group showed sustained reductions in mean rhinoconjunctivitis symptom scores (26%; $P<0.001$) and medication scores (29%; $P=0.022$) when compared with placebo. These levels of efficacy were similar to those observed during the 3-year treatment period. Likewise, the differences in percentages of symptom- and medication-free days were significant during treatment and 1 year after treatment. Moreover, the active group reported sustained and significant improvements in quality of life. Immunologic changes paralleled the clinical changes. Importantly, no safety issues were identified. The authors concluded that the 3 years of treatment with the SQ-standardized grass AIT resulted in consistent clinical improvement and immunologic changes that were sustained for 1 year after treatment was stopped, which is consistent with disease modification and associated long-term benefits.

More recently, Marogna et al. [10] prospectively evaluated and compared the long-term effects of medical therapy alone and SLIT administered for 3, 4, or 5 years. This prospective,

open, controlled study followed up patients who were monosensitized to mites for 15 years. Seventy-eight patients were enrolled, 59 of whom completed the study. In patients receiving SLIT for 3 years, the clinical benefit as assessed by symptom scores persisted for 7 years, and for those receiving SLIT for 4 or 5 years, the benefit persisted for 8 years. Decreases in clinical reactivity and nasal eosinophils paralleled the improvements in clinical scores. The rate of new sensitizations occurred in all individuals receiving medical therapy alone and in only 15% of those receiving SLIT. The authors concluded that a 4-year course of SLIT was the optimal choice because it induced a long-lasting clinical improvement similar to that seen with a 5-year course and greater than that seen with a 3-year course. The major limitations of this study were lack of blinding and randomization.

An economic evaluation of SLIT was conducted by Ariano et al. [11]. They compared the different economic aspects of symptomatic pharmacologic therapy and SLIT in patients with allergic asthma. Seventy patients with perennial allergic asthma and sensitization to house dust mites were enrolled and treated with house dust mite SLIT ($n=50$) or with symptomatic drugs ($n=20$) for 3 years. Patients were evaluated during and for 2 years after discontinuing SLIT. Symptom scores, medication scores, and all other direct medical costs were evaluated with a specific questionnaire. Patients treated with SLIT plus drugs had a higher mean annual cost during the first year compared with patients receiving only drug treatment, but the mean annual cost of SLIT treatment became significantly lower subsequently. The authors concluded that SLIT had economic advantages that persisted after discontinuing therapy. However, the results of this open study will require confirmation in larger and better controlled studies in the future.

The optimal use of SLIT in clinical practice will require further information about the effectiveness of different treatment schedules. Sieber et al. [12] compared the effectiveness of perennial and co-seasonal high-dose SLIT treatments as well as ultrarush and classical titrations in a real world setting for pollen allergens. An individual patient data meta-analysis was performed for three open, prospective observational studies of high-dose SLIT using IR-standardized allergen extracts in patients with allergic rhinitis, both with and without asthma ($n=1052$; mean age, 24.9 years). Stratified analyses revealed consistent improvements in symptomatic score and medication score, regardless of the type of sensitization and type of treatment. Ultrarush titration resulted in considerably more pronounced improvement in symptom scores than classical titration, potentially due to better compliance of patients receiving such supervised titration. Adverse events were observed in 24% of patients during titration and in 18% during maintenance treatment. The vast majority of adverse

events (89% and 87%) were mild to moderate and predominantly local symptoms in the oral cavity. No differences were detected between the study titration or treatment schedules. Additionally, no serious adverse reactions were reported. Most of the patients (88%) decided to continue SLIT after completion of the studies. The authors concluded that high-dose SLIT with seasonal allergens given as co-seasonal or perennial treatment appears to be effective and well-tolerated in daily medical practice. Improved compliance under ultrarush titration and seasonal SLIT treatment may further enhance effectiveness. Future randomized, well-controlled trials were recommended to confirm these findings.

Noting that there are deficiencies and considerable heterogeneity in both design and data interpretation of published SLIT studies (some noted in studies discussed above), Casale et al. [13•] conducted an extensive review of these deficiencies and sources of heterogeneity and provided recommendations on the appropriate design of future SLIT trials. These recommendations included the conduct of randomized, double-blind, placebo-controlled trials in patients with all types of sensitizations (monosensitized and polysensitized) with proven clinical relevance and in whom the severity of symptoms is assessed before SLIT, both historically during the previous year and during a run-in phase. Specific recommendations on the composition of the allergen vaccine were provided, including the use of single allergens or mixtures, standardization defined based on major allergen content, and a dose of about 5 µg of major allergen/d. The authors hoped that these recommendations would result in more adequately designed SLIT trials to facilitate the appropriate placement of SLIT therapy in the treatment of patients with allergic rhinoconjunctivitis.

Most of the previous SLIT studies were conducted in Europe, and only a few controlled trials, including several discussed above [1, 2•], were conducted in the United States. Thus, experience using SLIT in North American populations was very limited until the conduct of two recent trials, one in children and one in adults. Both studies used a Timothy grass AIT. Importantly, Timothy grass is cross-reactive with Festucoideae grasses, including rye, meadow fescue, bluegrass/june, orchard/cockfoot, redtop/bent/velvet, and sweet vernal.

In the first study, Blaiss et al. [14] investigated the efficacy and safety of Timothy grass AIT in North American children with grass pollen-induced allergic rhinoconjunctivitis with or without asthma. In that study, 345 participants (5–17 years of age) were randomized to receive once-daily grass AIT (2,800 BAU, 75,000 SQ-T, ~ 15 µg Phl p 5) or placebo beginning about 16 weeks before the 2009 grass pollen season and continuing intraseasonally. Most individuals (89%) were multisensitized. The primary end point, which was the total combined score of the DSS and DMS for the

entire grass pollen season (assessed via electronic diary), improved in the grass AIT group by 26% ($P=0.001$) versus placebo. Furthermore, the DSS, DMS, and RQLQ scores versus placebo improved by 25% ($P=0.005$), 81% ($P=0.006$), and 18% ($P=0.04$), respectively. Furthermore, itchy and watery eye symptoms individually improved by 28% in the grass AIT group relative to placebo, for a combined average improvement of 28% ($P=0.003$). In parallel, the eye symptom RQLQ domain score improved significantly in the grass AIT group by 29% relative to placebo ($P=0.005$). Adverse events were largely local, mild, and transient. No investigator-assessed systemic allergic reactions were reported, but one grass AIT-treated individual experienced an event indicating a systemic reaction (lip angioedema, dysphagia, and cough). The authors concluded that once-daily Timothy grass AIT effectively treats Timothy grass pollen-induced allergic rhinoconjunctivitis in predominantly multisensitized North American children.

The second study was similar to the study conducted in children but instead enrolled adults. Nelson et al. [15•] investigated the efficacy and safety of a grass AIT (oral lyophilisate, *P. pratense*, 2,800 BAU) in allergic rhinoconjunctivitis patients with or without asthma. In that study, 439 adults with Timothy grass pollen-induced allergic rhinoconjunctivitis were randomly assigned to once-daily grass AIT or placebo beginning approximately 16 weeks before and continuing through the 2009 grass pollen season. Similar to the study in children, most individuals (85%) were multisensitized. The primary end point, which was the total combined score of the DSS and DMS for the entire grass pollen season (assessed via electronic diary), improved by 20% in the grass AIT group compared with the placebo group ($P=0.005$). Likewise and similar to the study performed in children, improvements were noted in the AIT group relative to placebo for the DSS (18%; $P=0.02$), DMS (26%; $P=0.08$), and RQLQ (17%; $P=0.02$). Furthermore, itchy and watery eye symptoms were improved in the grass AIT group by 20% and 35%, respectively, for an average improvement of 26% relative to placebo ($P<0.001$). The eye symptom RQLQ domain score was improved in the grass AIT group by 21% relative to placebo ($P=0.01$). Most adverse events were mild local reactions that were transient, with no treatment-related serious adverse events in active patients, one treatment-related serious adverse event in a placebo patient, and no reports of anaphylactic shock. The authors concluded that grass AIT was effective and well-tolerated in a predominantly multisensitized North American adult population with Timothy grass pollen-induced allergic rhinoconjunctivitis.

The safety of grass AIT in the above two trials conducted in children and adults was also carefully evaluated. The most common treatment-emergent adverse events were oral pruritus, throat irritation, and nasophar-

nginitis in the pediatric study, while they were oral pruritus, throat irritation, and upper respiratory tract infection in the adult study. The treatment-emergent adverse events asthma and urticaria were rare ($\leq 4\%$). Treatment-related adverse events (TRAEs) were reported by 122 of 175 (70%) AIT patients and 43 of 169 (25%) placebo patients in the pediatric study, and by 155 of 213 (73%) AIT patients and 62 of 225 (28%) placebo patients in the adult study. Most TRAEs were mild or moderate; less than 2% of patients had severe TRAEs. Also, most TRAEs were local application site reactions that began shortly after treatment initiation and were reported for 1 to 2 days only. The rate of development of new local application site adverse events diminished with treatment over time. Very few individuals discontinued because of adverse events (pediatric study: AIT = 13 of 175, placebo = 5 of 169; adult study: AIT = 11 of 213, placebo = 8 of 225). One patient from each study received epinephrine in response to an AIT-related reaction (pediatric study: moderate [lip angioedema/dysphagia/cough]; adult study: mild [flush/rash/chest discomfort]) at first dose. One other patient (pediatric study) reported a possible AIT-related systemic reaction (dyspnea, chest discomfort, neck pruritus, racing heart, mouth pain). No serious or life-threatening AIT TRAEs or new safety concerns were reported for either study. The authors concluded that Timothy grass AIT was generally safe and well-tolerated in North American adults and children [14, 15]. The incidence and severity of adverse events were similar across age groups, which supports use of the same dose of grass AIT in the different age groups.

Compared with subcutaneous immunotherapy, some apparent advantages of SLIT relate to the easy route of administration, especially for children, and a lower frequency of severe side effects. The apparent improvement in safety profile has led some guidelines to recommend a switch to SLIT in patients who develop severe side effects during subcutaneous immunotherapy. However, de Groot and Bijl [16] reported two cases of severe anaphylactic reactions after the first dose of high-dose standardized SLIT with 15 μg of major allergen Phl p v. Previously, both patients had experienced reactions to subcutaneous immunotherapy with grass and tree pollen, including generalized urticaria and aggravated asthma. After the first dose of SLIT taken at home, the first patient developed local irritation, swelling of the tongue, angioedema of the eyes, and generalized urticaria, and the second patient developed asthma symptoms, generalized itching, faintness, abdominal cramps, wheezing, and hypotension. The authors concluded that patients who experience systemic side effects during subcutaneous immunotherapy should not be considered ideal candidates for SLIT, and that patients treated with SLIT should be strictly advised to take the first dose under direct medical observation.

In addition to anaphylaxis, noncompliance with therapy may be an obstacle to implementation of SLIT in a real world setting. Dunskey et al. [17] prospectively investigated compliance with treatment with subcutaneous immunotherapy, SLIT, and nasal immunotherapy in 2,774 children with allergic rhinitis. Noncompliance with each route of administration was 10.9%, 21.5%, and 73.2%, respectively. Common reasons for discontinuation of treatment were cost, lack of effect, and discomfort related to administration of nasal immunotherapy. As illustrated by these results, cost and compliance may be potential barriers to adherence with SLIT in a real world setting.

Mechanisms

Although the clinical safety and efficacy of SLIT are fairly well-documented, the immunologic mechanisms of action remain relatively undefined. Multiple studies have documented that following initiation of SLIT, increases in allergen-specific IgE occur within weeks and are followed by attenuation of seasonal rises in IgE. Subsequently, there is a time- and dose-dependent increase in allergen-specific IgG, IgG₄, and IgA that rises for at least 2 years [18–20]. Several studies have documented increases in specific IgG₄ without clinical efficacy, while a few others have shown no differences in IgG levels [19, 20]. These discrepancies are most likely related to the use of suboptimal doses of SLIT. These results suggest causality but do not rule out a bystander effect. However, results from functional assays, in which sera obtained after SLIT was able to inhibit *in vitro* IgE binding and allergen-induced histamine release from basophils and mast cells, suggest causality [19, 20].

It is hypothesized that the immunologic responses mediated by SLIT occur in the oral mucosa and within regional lymph nodes [19, 20]. The oral microenvironment is regarded as a site of natural immune tolerance. Despite constant exposure to microbes and multiple foreign antigens, the oral mucosa remains free of inflammation and exhibits a paucity of effector cells as compared with other mucosal sites. Pharmacodynamic studies of SLIT uptake demonstrate that some allergen remains in the oral mucosa for several hours after dosing and that there is little systemic absorption from the mouth. The initial step in the mechanism of SLIT is hypothesized to be uptake by antigen-presenting cells. In support of this hypothesis, a recent study showed that oral mucosal Langerhans cells bind SLIT allergen in a dose- and time-dependent manner, which leads to increased production of tolerogenic cytokines, including interleukin (IL)-10 and transforming growth factor (TGF)- β 1, as well as increased migratory activity [21].

Animal studies and one recent human study have shown that oral mucosal Langerhans cells then migrate to regional

lymph nodes, where they interact with T cells. Langerhans cells may interact with naïve T cells and result in the generation of allergen-specific regulatory T cells [19, 20]. In support of this, a recent study showed increases in forkhead box P3 (FoxP3)-positive regulatory T cells in mucosal biopsies obtained from humans following SLIT [22]. It is hypothesized that the origin of these regulatory T cells is the regional lymph nodes; however, origin in the oral submucosa cannot be ruled out. Another recent human study demonstrated a strong correlation between the induction of FoxP3-positive regulatory T cells and clinical efficacy of SLIT, thereby suggesting that allergen-specific induced regulatory T cells may be a potential biomarker for the therapeutic efficacy of SLIT [23].

Interaction with memory T cells in regional lymph nodes may also result in downregulation of function and/or switching from a T-helper type 2 (Th2) to a Th1 phenotype [19, 20, 24]. Recent animal studies documented significant decreases in proliferative responses to allergen and reduced production of IL-4 and IL-5 from cells isolated from regional lymph nodes following SLIT. Similarly, decreased proliferative responses of peripheral T cells to allergen also have been observed in SLIT-treated patients and are consistent with anergy of allergen-specific T cells. SLIT also has been shown to trigger apoptosis of Th2 cells in allergen-stimulated peripheral T cells [19, 20, 24]. Several studies showed increased allergen-specific IFN- γ production during successful SLIT treatment that is consistent with Th1 skewing. These results suggested that elevations of allergen-specific IFN- γ production may be another potential biomarker for the therapeutic efficacy of SLIT [19, 20, 24].

SLIT was associated with decreased levels of conjunctival and nasal eosinophils, neutrophils, and expression of intracellular adhesion molecule-1. Some, but not all studies have shown decreases in peripheral eosinophils and eosinophil cationic protein [19, 20]. Mast cells are present within the sublingual mucosa, and tryptase is detectable within salivary secretions. These may account for local itching and swelling that may occur after SLIT administration [19, 20]. A recent animal study demonstrated significant suppression of allergen-induced eosinophil and neutrophil infiltration into the lower airway as assessed by bronchoalveolar lavage [25]. To date, no studies have examined the effect of SLIT on immune responses in the lower airways of humans.

As described above, increased production of specific anti-inflammatory cytokines may contribute to the mechanism of action of SLIT. For example, SLIT-induced production of IL-10 by T cells contributes to increased production of IgG antibodies, inhibition of T-cell responses to allergens, and the late decrease of IgE antibodies. IL-10 is also known to suppress natural killer cells and their cytolytic activity; induce IgG₄ production; and inhibit the recruitment and activation of mast cells, basophils, and

eosinophils [19, 20]. Similarly, TGF- β 1 decreases mast cells and eosinophil activation, blocks Th2 skewing, and contributes to immunoglobulin class switching toward IgG and IgA and away from IgE [19, 20]. Collectively, these responses may contribute to the development of anergy and/or tolerance that accompanies successful SLIT therapy. In support of this theory, a recent SLIT study demonstrated a reduction in proliferative responses to specific allergen that was associated with increases in IL-10 and blocked by anti-IL-10 or depletion of regulatory T cells [26]. Another recent SLIT study reported suppression of IL-5 production and T-cell proliferation mediated by TGF- β 1 [27].

Conclusions

SLIT is increasingly recognized as an effective and safe treatment for allergic rhinitis. Specifically, SLIT has been shown to reduce symptoms and requirements for rescue medication and improve the quality of life of allergic rhinitis patients. The major limitation related to previous studies evaluating the safety and efficacy of SLIT is the lack of well-designed, randomized, placebo-controlled trials. The mechanisms of SLIT are incompletely understood, but current evidence supports strong roles for oral mucosal Langerhans cells, anti-inflammatory cytokines, regulatory T cells, and induction of skewing from a Th2 to a Th1 phenotype. Areas for future study include pediatric trials, head-to-head comparisons with subcutaneous immunotherapy, and pharmacologic treatments. Other issues include assessment of long-term benefits, prevention of new allergic sensitizations, and prevention of the allergic march from rhinitis to asthma in young children. Finally, mechanisms of action need to be more fully elucidated.

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Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Esch RE, Bush RK, Peden D, et al.: Sublingual-oral administration of standardized allergenic extracts: phase 1 safety and dosing results. *Ann Allergy Asthma Immunol* 2008, 100:475–481.

2. • Skoner D, Gentile D, Bush R, et al.: Sublingual immunotherapy in patients with allergic rhinoconjunctivitis caused by ragweed pollen. *J Allergy Clin Immunol* 2010,125:660–666. *This study was significant in that it showed that standardized, glycerinated short ragweed pollen extract administered sublingually at maintenance doses of 4.8 to 48 µg Amb a 1/d was safe and induced favorable clinical and immunologic changes in ragweed-sensitive individuals.*
3. Seidenberg J, Pajno GB, Bauer CP, et al.: Safety and tolerability of seasonal ultra-rush, high-dose sublingual-swallow immunotherapy in allergic rhinitis to grass and tree pollens: an observational study in 193 children and adolescents. *J Investig Allergol Clin Immunol* 2009, 19(2):125–131.
4. • Amar SM, Harbeck RJ, Sills M, et al: Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in a multiallergen extract. *J Allergy Clin Immunol* 2009, 124:150–156. *This study was important, as it evaluated the effectiveness of SLIT with multiple allergens, the way that most allergen immunotherapy in the United States is administered.*
5. Ciprandi G, Cadario G, Valle C, et al.: Sublingual Immunotherapy in polysensitized patients: effect on quality of life. *J Investig Allergol Clin Immunol* 2010, 20 (4):274–279.
6. Ciprandi G, Cadario G, Di Gioacchino GM, et al.: Sublingual immunotherapy in children with allergic polysensitization. *Allergy Asthma Proc* 2010, 31:227–231.
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12. Sieber J, Koberlein J, Mosges R. Sublingual immunotherapy in daily medical practice: effectiveness of different treatment schedules-IPD meta-analysis. *Curr Med Res Opin* 2010, 26 (4):925–932.
13. • Casale TB, Canonica GW, Bousquet J, et al.: Recommendations for appropriate sublingual immunotherapy clinical trials. *J Allergy Clin Immunol* 2009, 124:665–670. *This is an important review that identified deficiencies and sources of considerable heterogeneity in both design and data interpretation of published SLIT studies, with the hope that recommendations provided will allow the conduct of more adequately designed SLIT trials to facilitate the appropriate placement of SLIT therapy to treat patients with allergic rhinoconjunctivitis.*
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15. • Nelson HS, Nolte H, Creticos P, Maloney J, Wu J, Bernstein DI. Efficacy and Safety of Timothy grass allergy immunotherapy tablet (AIT) in North American adults. In Press, *J Allergy Clin Immunol* 2011. *This study and that by Blaiss et al. [14] are important due in part to their large sample sizes, rigorous design, and large effect sizes detected (larger than those of many drugs currently in use to treat allergic rhinoconjunctivitis). Moreover, given its convenient administration, no dose build-up requirement, safety profile, and efficacy, this form of SLIT may become an important addition to the allergic rhinoconjunctivitis treatment armamentarium of North American adults. The cross-reactivity of Timothy grass with Festucoideae is also likely to be important.*
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