

Review of the Use of Sublingual Allergen Immunotherapy in Children

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Allergic diseases are common in pediatrics and can be caused by seasonal pollens, specifically grass, trees, and weeds. In many European countries, sublingual immunotherapy (SLIT) is an accepted form of treatment for allergic rhinitis. However, the Food and Drug Administration (FDA) has not yet approved its use in the United States. This review focuses on the use of SLIT in the form of allergen immunotherapy tablet and liquid droplet to treat allergic rhinitis and allergic conjunctivitis caused by both grass and ragweed pollens in pediatric patients.

ALLERGIC DISEASES SUCH as allergic rhinoconjunctivitis (ARC), asthma, atopic dermatitis, and food allergy are very common in pediatric populations. About 40% of children in the United States are affected by ARC.¹ ARC is an immunologic disorder with localized clinical manifestations that are mediated by an IgE antibody response.² ARC results from immune deviation from the normal response after exposure to common allergens such as molds, animal dander, pollen, or dust.³ The symptoms of ARC, including runny nose, itchy nose, sneezing, congestion, and itching and watering of the eyes, are caused by IgE-mediated mast cell degranulation resulting in release of histamine and the release of cytokines and inflammation driven by TH2 cytokines.^{2,4} ARC affects children in more aspects than the nasal and ocular symptoms, having a significant impact on a child's sleep, school performance, and behavior.⁵

The diagnosis of ARC is based on history, physical examination, and testing for the presence of allergen-specific IgE antibodies using puncture skin tests or blood tests. Treatment of ARC in children includes environmental allergen control measures to reduce exposure, and the use of a variety of medications that includes oral and inhaled antihistamines, decongestants, intranasal and systemic corticosteroids, and allergen-specific immunotherapy (IT). All of these therapies induce relief to varying degrees and, in some instances, specifically for some but not all symptoms.¹ Indeed, some of these therapies have been associated with adverse outcomes such as rhinitis medicamentosa with topical decongestants,⁴ and growth suppression with topical corticosteroids.⁶ Of these therapies, only allergen-specific IT induces immunologic tolerance via production of allergen-specific T regulatory cells, induces symptom relief and immunologic changes that are sustained long after the IT is

discontinued, and reduces the likelihood of developing new-onset asthma and new allergies.⁷ During SLIT treatment, Treg cells are primed by dendritic cells in the oral mucosa. Also during the pollen season, there is an association with IL-4 levels in peripheral blood mononucleated cells and an increase in programmed cell death ligand on both B cells and monocytes in SLIT patients.⁸ Health economic studies have shown that IT is cost-saving in comparison with pharmacotherapy.^{9,10}

Allergen-specific IT involves the use of an allergen extract as a treatment to modify an individual's immune response. Such IT can be administered subcutaneously (SCIT) or sublingually (SLIT; see Table 1). Currently, SCIT is Food and Drug Administration (FDA)-approved for ARC in adults and children in the United States, while SLIT is an off-label treatment in which the allergen extracts approved for SCIT are administered sublingually. SLIT grass and ragweed tablets have recently and extensively been studied in controlled clinical trials and are not yet FDA approved either.

In the December 2013 issue of *Pediatric Allergy Immunology and Pulmonology*, Ratajova et al. focus on grass pollen pollution from biofuels farming in the Czech Republic.¹¹ This review will focus on recent studies using SLIT to treat ARC due to grass pollen and other allergens in children.

SLIT can be used to treat allergic conditions such as allergic rhinitis, rhinoconjunctivitis, or allergic asthma.¹⁰ The patient simply places either a drop of a liquid extract or a tablet under the tongue for a short period of time, and then typically swallows the remains. The allergen is systemically absorbed through the mucosa and vascular-lymphoid network of the sublingual region, resulting in immune responses such as those seen with SCIT.¹² SLIT is very easy

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TABLE 1. COMPARISON OF SUBCUTANEOUS IMMUNOTHERAPY (SCIT) VERSUS SUBLINGUAL IMMUNOTHERAPY (SLIT)

Attribute	SCIT	SLIT
FDA approved	Yes	No
Natural extract based	Yes	Yes
Dose delivery	Subcutaneous needle injection	Drop or tablet under the tongue
Dosing location	Doctor's office	At home (after first dose in doctor's office)
Dose escalation	Yes, over months	No
Dose frequency	Every 1–4 weeks	Every day*
Dosing duration	3–5 years	3–5 years*
Number of allergens	One or multiple (typically multiple)	One or multiple (typically 1 or 2)
Patient age	≥ 8 years	≥ 4 years

*Option for non-year-round pre-coseasonal dosing.

to administer by a patient at home after initial dosing in the office. In contrast to SCIT, which is administered in increasing doses every 1–4 weeks in a doctor's office, SLIT must be given daily and no uptitrating of dose is necessary. Year-round dosing schedules for 3–5 years have been used, as well as pre- and coseasonal dosing for pollen seasons. Year-round dosing schedules have not been shown to be superior to pre- and coseasonal dosing schedules, although there is evidence for a reduction in symptoms and medication use when treatment is started ≥ 12 weeks preseasonal versus coseasonal treatment only.¹³ Adherence with daily dosing will be a concern, as is the case with any chronic disease.¹⁴

Even though SLIT is currently not approved for use by the United States FDA, it is widely used in many other countries, including Europe, South America, and Asia. Nonetheless, it is often used in clinical practice in the United States.¹⁵ According to a recent survey of U.S. practicing allergists, 11.4% of respondents had experience using SLIT,¹² but it is more commonly used than SCIT in Italy and France. In Europe, multi-allergen mixtures are not commonly used for IT, but this is a common practice in the United States.¹⁵ Most of the recent trials have focused on single allergen preparations.

Allergen-specific IT works best for patients who are monosensitized, but it can be effective for polysensitized patients as well. Emminger et al.¹⁶ studied the effective use of allergen-specific IT against grass pollen allergens. Monosensitized patients, grass pollen polysensitized patients, and patients polysensitized with other allergens besides grass pollen were treated with grass SLIT or placebo. All three groups showed a significant decrease in symptoms with SLIT compared to placebo. Thus, the benefit of single allergen SLIT is not restricted to the monosensitized subgroup of patients, and can extend to polysensitized individuals. In addition, healthcare practitioners in the United States often utilize multi-allergen SCIT. This IT consists of mixing all of the diagnosed allergens and giving this as one treatment together.¹⁶ In a study performed by Marogna et al., patients sensitized to grass and birch pollens were given the IT of each allergen either alone or together. The results showed that the allergens given together produced a greater reduction in symptoms.¹⁷ However, the clinical debate of the use of multi-allergen IT and the mixing of allergens is still ongoing.¹⁸ Nonetheless, these studies support the use of allergen-specific IT as an effective treatment plan for ARC.

SLIT has been studied in multiple clinical trials. A recent review article in *Annals of Allergy Asthma Immunology*

reviewed 28 clinical trials involving pediatric SLIT from 2009 to 2012. Most were double-blind, placebo-controlled trials using liquid extracts from European manufacturers, but four trials used tablets, and three used American manufacturers. The most common allergic symptom assessed was allergic rhinitis or rhinoconjunctivitis. From these clinical trials, it was shown that SLIT for seasonal grass pollen allergic rhinitis was effective in children as young as 5 years of age, with additional evidence to suggest that it may even be effective in those as young as 4 years of age.¹⁹

Another recent review article in *Pediatrics* examined the results of 18 studies of SLIT. Nine of the studies evaluated for allergic asthma, 12 for rhinitis or rhinoconjunctivitis, and 5 for conjunctivitis. Most of the trials used dust mite extracts, but grass mixes, tree mixes, and specific allergens were also used in several studies. Most were also placebo-controlled trials, but some were high versus low dose. They also noted three trials versus SCIT that evaluated for asthma, rhinitis, or rhinoconjunctivitis symptoms, and all used dust mite extracts. Treatment with both SLIT and SCIT were shown to be effective for allergic rhinitis in children, with a stronger evidence base for SLIT than SCIT.²⁰

Another publication compared the efficacy and safety of SLIT and SCIT when treating allergic rhinitis in both adults and children. A comparative efficacy of SCIT and SLIT in adult patients showed a 73% and 56% improvement respectively of allergic rhinitis symptoms versus controls. The pediatric comparative effectiveness of SCIT and SLIT showed significant improvement in 67% and 42% respectively in symptoms versus controls. However, there was only moderate confidence, in both the adult and pediatric SLIT studies, that these estimates reflected the true effect, and further research could change the estimate. When comparing the safety of SCIT versus SLIT, there was one report of anaphylaxis with SCIT in the adult studies, as well as one anaphylaxis event and three respiratory systemic reactions in the pediatric studies. Rarely, either severe systemic reactions or anaphylaxis are reported by pediatric patients receiving SLIT.²¹ In conclusion, there was evidence to support the safety and effectiveness of both therapies, but not enough evidence to determine which method would be superior.²²

Treatment of atopic dermatitis with SLIT was addressed in a publication by Pajno et al. Children with atopic dermatitis and sensitization only to dust mites were enrolled. The differences in the atopic dermatitis scores from baseline to treatment completion were significant. Patients with severe disease only found a marginal benefit. However, a

significant difference was found in those with mild to moderate disease severity.²³

A study by Dahl et al. evaluated the efficacy of SLIT in 351 patients with moderate to severe allergic rhinoconjunctivitis over the course of two pollen seasons. With reductions of 36% in symptom scores and 46% in medication scores, a significant efficacy was shown over the 2-year period.²⁴ A study by Durham et al. looked at the efficacy of a grass allergy immunotherapy tablet over a 3-year blinded treatment phase followed by a 2-year blinded nontreatment follow-up phase. Two hundred and thirty-eight subjects with moderate to severe rhinoconjunctivitis due to grass pollen were measured using symptom and medication scores. Over the 5 years, symptom scores were reduced by 25–36%, and medication scores were reduced by 20–45% over placebo. This study shows a lasting benefit of at least 2 years after the discontinuation of SLIT treatment.²⁵

The efficacy of SLIT in children is supported by another publication by Caffarelli et al. in which 24 children with allergies to grass pollen received either active treatment or placebo 3 months before the start of the pollen season. The active treatment group had a statistically significant reduction in total symptoms in comparison to the placebo group.²⁶

Another European study by Wahn et al. focused only on children and adolescents with allergic rhinitis caused by grass pollen. In this study, 278 children with AR induced by grass pollen, between the ages of 5 and 17 years, were given a once daily SLIT tablet or placebo. The treatment periods were started 4 months before the pollen season and continued throughout the season. Using a rhinoconjunctivitis total symptom score, it was found that the SLIT tablet group was significantly improved compared to the placebo group. The mean improvement was 28%. There was also a significant reduction in use of rescue medication between the SLIT tablet and the placebo groups.²⁷

A recent study by De Castro et al. looked at the efficacy and safety of SLIT treatment in children with allergic rhinitis and/or asthma over 3 years, involving 140 patients between the ages of 6 and 14 years. Symptom scores for rhinitis and asthma were recorded along with medication use. Improvement in the rhinitis symptom score was significant. At baseline, the SLIT treatment group had a rhinitis symptom score of 5.31 ± 2.01 versus a third-year score of 1.38 ± 1.06 . This is compared to the control group, which had a baseline of 5.00 ± 1.08 versus a third-year score of 4.68 ± 1.152 . This shows that there is a sustained reduction in rhinitis symptom scores when compared to a control group.²⁸

Bufe et al. looked at the efficacy of a grass allergen tablet in children. Two hundred and fifty-three children between 5 and 16 years of age with rhinoconjunctivitis due to grass pollen were randomized to treatment or placebo. Treatment was initiated 8 to 23 weeks prior to the start of the pollen season and continued throughout the season. The difference in the symptom scores of active treatment over the placebo group was 24% during the whole season and 28% during the highest level of seasonal pollen exposure.²⁹

Another study performed by Wahn et al. looked at efficacy and safety of high-dose aqueous SLIT treatment in 207 children between 4 and 12 years of age with allergies to grass pollen. The randomized patients took either SLIT or placebo once a day for the pre-coseasonal period. The results showed that children with allergic rhinitis due to grass

pollen in the SLIT randomization group had significantly reduced symptoms and medication use, showing SLIT to be a valid treatment option for children with grass pollen ARC.³⁰

A study by Blaiss et al. examined the efficacy and safety of Timothy grass SLIT tablets in North American children. Subjects with allergic rhinoconjunctivitis between the ages of 5 and 17 years were randomized to active treatment or placebo 16 weeks before the start of the grass-pollen season and continued throughout the season. Symptom and medication scores were recorded and showed a 26% improvement with SLIT tablets versus placebo. Specifically, the improvements of the ocular and nasal symptom scores compared to the placebo group were 28% and 23% respectively. Using quality of life questionnaires, children in the SLIT tablet group had an 18% improvement over the placebo group during the entire season and a 38% improvement during the peak of the pollen season. Safety was measured using reported adverse events. There were no reported life-threatening events, anaphylactic shock, or investigator-diagnosed systemic reactions. Oral pruritus and throat irritation were the most commonly reported adverse events in the active treatment group. The majority of adverse events in treatment-related subjects were listed as local reactions to the application site, and all but three were rated as either mild or moderate. These reactions were typically reported on the first day, but only lasted 1–2 days. No investigator-assessed systemic allergic reactions were reported. Two subjects in the grass allergy IT-treatment group received epinephrine, only one of which was due to a reaction to the tablet. This occurred in a grass allergy IT-treated subject who experienced a systemic reaction (lip angioedema, dysphagia, and cough immediately after the first dose of grass allergy IT on day 1 of the study). There was also one administration of epinephrine in the placebo group.³¹

A more recent review examined the efficacy of SLIT in several studies. The 63 randomized controlled trials enrolled patients between the ages of 4 and 74 years. Of the 63 trials, 36 trials involved rhinitis symptom scores, and 10 of those focused specifically on grass pollen, which was the most common pollen of the group. In 21 of the 36 studies, the results for symptom scores were statistically significant, with magnitude of association being moderate to strong in 14 of those studies. The findings for medication scores were similar, with 38 of 41 studies showing an improvement. The quality of life was also significantly improved in these patients.³²

A study from 2012 looked at the comparative effect of giving SLIT therapy pre-coseasonally and continuously for children with only allergic rhinitis due to grass allergy over the course of 2 years. Both of the treatment types did have a significant reduction in symptoms. However, nasal symptoms were lower in the pre-coseasonal group. Both of the treatment groups did have a significant decrease in fractional exhaled nitric oxide (FeNO) compared to the placebo group.³³

SLIT studies have now been extended to include allergens other than grass pollen. A recent study by Creticos et al. looked at allergy IT treatment in subjects with ragweed-induced allergic rhinitis/conjunctivitis. Seven hundred and eighty-four subjects were randomly assigned into a yearlong daily dosing of 1.5, 6, or 12 units of *Ambrosia*

artemisifolia allergen or placebo sublingually. Subjects were given as-needed rescue medication and filled out both daily symptom and medication scores. In peak ragweed season, total medication and symptom scores were reduced by 9%, 19%, and 24% over placebo respectively by the 1.5, 6, and 12 Amb a 1 unit doses. No serious adverse events, life-threatening events, anaphylactic shock, or systemic allergic reactions were seen in the study. Treatment-related adverse events were reported by 23%, 40%, 52%, and 54% of the subjects in the placebo, 1.5, 6, and 12 Amb a 1 unit groups respectively. Most of these were of a mild to moderate severity and consisted of application site reactions in the mouth, throat, and ear. Discontinuation due to treatment-emergent adverse events was not common. Only 3%, 5%, 8%, and 8% of the placebo, allergy IT 1.5, 6, and 12 Amb a 1 unit groups were discontinued respectively.³⁴

Another recent study looked at the safety and efficacy of ragweed allergy IT in subjects with ragweed allergy. The study by Nolte et al. focused on 6 and 12 Amb a 1 unit ragweed allergy IT doses. There was an improvement of 21% and 26% respectively over placebo. Most of the treatment-related adverse events reported were local site reactions of the mouth, throat, or ear, which only lasted a few weeks. Generally, they occurred early and were self-resolving. There were just two uses of epinephrine during the study, only one of which—in a patient in the 6 Amb a 1 unit group—was considered treatment related.³⁵

In the review by Larenas-Linnemann et al., three trials exclusively examined the safety issues regarding SLIT. There were no differences between the placebo and active treatment groups regarding adverse events during up dosing in one study focusing on SLIT of asthmatic children with allergies to tree pollen. In a dust mite SLIT trial, eight mild to moderate systemic adverse events were reported by asthmatic participants, although none was discontinued. Overall, the treatment was as equally tolerated in children under the age of 15 years as in adult subjects. The last found that the coseasonal rush build-up was well tolerated by patients with rhinitis.¹⁹

A review by Julia Kim et al. examined the safety of SLIT in children, finding that mild local reactions such as oral itching and swelling were common. Of the studies reviewed, 12 reported rates of 0.2% to 50% of patients on treatment and 6% to 25% on placebo. No deaths, life-threatening reactions, or anaphylaxis were reported, although systemic reactions were common. According to Kim et al., the least to most common reported symptoms or reactions were general, gastrointestinal, ocular, respiratory, and cutaneous. One study did report severe rhinitis and severe asthma in children above the maximum dose. However, these adverse events were no longer an issue after returning to a lower dose.²⁰

Summary

SLIT has been studied and approved for use in many countries, and recently conducted North American trials have corroborated the findings of international studies, showing that SLIT has efficacy and a good safety profile in children with ARC. Allergy in children can be caused by dust mites, ragweed, birch, perennial allergens, and grass pollen, as seen in a review by Nelson et al. This review specifically mentions the significant efficacy in the first year of treatment and acceptable safety profile for home administration after the first

dose is given in the office under observation for short ragweed and grass in U.S. studies.³⁶ Grass pollen is the most extensively studied formulation of SLIT, thus providing a specific immunologic treatment to deal with increasing ARC symptoms related to environmental changes, such as those described in this issue and related to grass pollen pollution from biofuels farming in the Czech Republic.¹¹

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