

Sublingual Immunotherapy for the Polyallergic Patient



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Allergen immunotherapy is the only disease-modifying treatment for allergic diseases. Sublingual immunotherapy (SLIT) in liquid and tablet form has been used by clinicians in Europe for years, but has only recently gained popularity and approval in the United States. In 2014, the US Food and Drug Administration approved 3 SLIT tablets for the treatment of allergic rhinitis, with or without allergic conjunctivitis. Immunotherapy treatment strategies for the polysensitized patient vary between the United States and Europe. This variation hinges upon whether the polysensitized patient is truly polyallergic. *Polysensitization* is the positive response to 2 or more allergens on skin prick testing or *in vitro* specific-IgE testing. *Polyallergy* is the symptomatic clinical response to 2 or more allergens. In this review, we discuss the use of SLIT in the United States with a focus on treating the polyallergic patient with SLIT. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:41-5)

Key words: Sublingual immunotherapy; Polyallergy; Polysensitization; Allergic rhinitis; Allergic rhinoconjunctivitis; Ragweed; Grass

CASE PRESENTATION

A 32-year-old man presents for evaluation of nasal pruritus, sneezing, rhinorrhea, and itchy, watery eyes. He lives in Chicago, Illinois. He does not have any pets, but his parents have a cat. His symptoms are worse outdoors in the spring and fall and better indoors. Skin prick testing was done to a panel of common aeroallergens in the Chicago area as well as pet dander. Results demonstrated 4+ (wheal diameter >15 mm with associated flare) responses to short ragweed (*Ambrosia artemisiifolia*), timothy grass (*Phleum pratense*), pigweed (*Amaranthus retroflexus*), and dog dander (Can f1). Upon further questioning, he does not have a dog and denied any symptoms around dogs or

during the winter months. Current medications include twice-daily intranasal fluticasone and once-daily oral cetirizine. He continues to have symptoms in the spring and fall despite his regular medication use. He asks about allergen immunotherapy, but is concerned about the time commitment and side effects. He travels frequently for work. Given short ragweed and timothy grass appear to be the 2 primary allergens causing this patient's symptoms, sublingual immunotherapy (SLIT) is recommended. The patient is started on timothy grass and short ragweed SLIT tablets, beginning each 12 weeks before the respective pollen seasons for the allergens in the tablet. When the treatment courses overlap, the patient takes one tablet in the morning and one in the evening. He is given an epinephrine autoinjector for home use.

INTRODUCTION AND BACKGROUND

Allergen immunotherapy is the only disease-modifying treatment for allergic rhinitis, conjunctivitis, and asthma and can often provide added symptom control to medications. Subcutaneous immunotherapy (SCIT) has been used around the world for over a century.¹ SLIT in liquid and tablet form has been used by clinicians in Europe for years, but has only recently gained popularity and approval in the United States. In 2014, the US Food and Drug Administration (FDA) approved 3 SLIT tablets for the treatment of allergic rhinitis, with or without allergic conjunctivitis, due to specific aeroallergens (Table 1). Two of the tablets contain grass pollen(s) and 1 contains ragweed. Oralair (Stallergenes; Antony, France) contains 5 northern grass pollens (Kentucky blue grass, orchard, perennial rye, sweet vernal, and timothy). Grastek (Merck; Whitehouse Station, NJ) contains timothy grass pollen. Ragwitek (Merck) contains short ragweed.

Approximately 50% to 80% of patients seeking treatment for respiratory allergies are polysensitized, that is, responsive to 2 or more allergens on skin prick testing or *in vitro* specific-IgE testing, as was the case with our patient.^{2,3} Physicians must use this data along with the clinical history to determine whether a patient is truly polyallergic, that is, symptomatic due to 2 or more clinically relevant allergens. Our patient had positive skin test results to ragweed, pigweed, and timothy grass, with symptoms corresponding to their pollen seasons. He also had a positive skin test result to dog allergen, but a negative exposure and symptom history. Thus, he was polysensitized to 4 allergens but clinically allergic to 2 (grass and ragweed), or perhaps 3 (grass, ragweed, and pigweed). Allergen immunotherapy treatment strategies for the polysensitized patient vary between the United States and Europe. The predominantly European approach is to treat the single or the 2 most clinically relevant allergen(s), whereas patients in the United States are usually treated for all potential clinically relevant allergens.³⁻⁵ In this review, we will

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Abbreviations used

FDA- US Food and Drug Administration

SCIT- subcutaneous immunotherapy

SLIT- sublingual immunotherapy

discuss the use of SLIT in the United States, with a special focus on treating the polyallergic patient with SLIT.

INDICATIONS FOR SLIT

Appropriate candidates for SLIT must have a documented positive response on skin prick testing or *in vitro* specific-IgE testing to the allergen(s) contained in the SLIT tablet. The first dose of each of these tablets must be administered under the supervision of a physician to monitor for local or systemic reactions and anaphylaxis, which are extremely rare. Subsequent doses can be given at home, making SLIT tablets more convenient than SCIT for some patients. The SLIT tablets are approved by the FDA for the treatment of allergic rhinitis, with or without allergic conjunctivitis.⁶⁻⁸ Allergic asthma is not an FDA-approved indication for SLIT tablets, but recent studies suggest clinical benefit in patients with asthma and a house dust mite SLIT tablet is approved for treatment of allergic asthma in Europe.⁹⁻¹²

SLIT can be given pre-coseasonally (initiated before the pollen season and continued throughout the season) or year-round. Pre-coseasonal administration is preferred because it provides the same clinical benefits while minimizing exposure.¹³ If used pre-coseasonally, SLIT is recommended to be initiated approximately 12 weeks before the start of the pollen season for the allergen(s) contained in the tablet. Grastek and Oralair are approved for use in children and adults, whereas Ragwitek is approved for use in adults only.⁶⁻⁸

POLYSENSITIZATION VERSUS POLYALLERGY

In the United States, the common practice for treating polysensitized patients is to combine multiple allergens into extracts to treat all actual or potential sensitizations.³⁻⁵ On average, SCIT extract preparations in the United States contain 8 allergens.⁴ The prevailing approach in Europe is to treat the most clinically significant allergen(s) by using extracts that contain 1, or at most 2, allergens.³⁻⁵ In line with the European view, the third United States allergen immunotherapy practice parameter update emphasizes treating only "clinically relevant allergens."¹⁴

The different treatment approaches in the United States and Europe hinge on the debate of whether the polysensitized patient is actually polyallergic. Symptom intensity and duration, ability to avoid allergen exposure, and impact on quality of life should be considered when determining which allergen(s) to treat. In some patients with multiple allergen sensitizations, the history may not completely elucidate which allergens are clinically significant. For example, in our patient skin tests were positive for 2 fall pollens, ragweed and pigweed. However, ragweed is clearly the most important cause of fall allergies in our patient's home area. Nonetheless, the significant time investment required for SCIT, due to in-office administration and monitoring after each dose, makes it difficult for US physicians to justify treating only one fall allergen if there is a possibility that the patient may remain symptomatic from another. Therefore, some may argue that our patient should also be treated for a possible pigweed

allergy. Because there are no SLIT preparations for pigweed, he would have been prescribed SCIT with ragweed, pigweed, and grass.

As mentioned previously, SLIT can be administered at home and thus is often more convenient for patients. The benefits of attempting single allergen SLIT may outweigh the risks of a theoretically less than optimal clinical response. In addition, studies demonstrate that single allergen immunotherapy is effective in polysensitized patients.^{3,15-17} Improvements in rhinoconjunctivitis symptom scores were similar for both polysensitized and monosensitized children and adults after 1 year of SLIT monotherapy with Oralair.¹⁶

Another layer to the polysensitization versus polyallergy debate involves allergen cross-reactivity or panallergens. In some polysensitized patients, responses to multiple allergens on either skin testing or *in vitro* specific-IgE testing may be explained by allergen cross-reactivity rather than true polyallergy. Molecular allergen or component-resolved diagnostics, the analysis of individual IgE-reactive biomolecules contained in allergen extracts, can be used to help determine whether clinically irrelevant cross-reactive allergens are the cause of polysensitization.^{18,19} Examples of cross-reactive allergens are tropomyosin in shrimp (*Pen a 1*) and dust mite (*Der p 10*, *Der f 10*) or peanut (*Ara h 8*) and birch pollen (*Bet v 1*).^{18,20} Panallergens in ragweed and timothy grass can account for oral allergy syndrome to certain fruits and vegetables.²¹ Procalcins and profilins are highly conserved pan-allergens that may cause ragweed and pigweed cross-reactivity.^{21,22} IgE inhibition tests can help elucidate the primary allergen in these situations, but are not currently commercially available.¹⁸ Thus, the results of component-resolved diagnostic testing must be interpreted in the context of the clinical history.

SLIT TO TREAT MULTIPLE ALLERGENS

Depending on where a patient lives, the timing of grass and ragweed pollen seasons may overlap. Currently, there is no consensus in the United States on the safety, efficacy, or mechanism for administering multiple SLIT products in combination. However, a phase 4, multicenter, open-label trial conducted in the United States and Canada found that dual administration of Ragwitek and Grastek is well tolerated. The trial reported no severe local swelling or systemic allergic reactions whether the tablets were separated by several hours (Ragwitek taken in the morning and Grastek taken at night) or only 5 minutes. The trial did note a higher number of mild to moderate local swelling events during the initial coadministration phase. This study suggests that coadministration of both grass and ragweed SLIT tablets is safe, but further clinical long-term trials are needed to determine whether there is any effect on efficacy.²³ In our patient, we opted to treat with the 2 tablets, one in the morning and the other in the evening. He did not have any significant adverse events with this regimen.

In patients sensitized and allergic to both grass and birch pollens, combination SLIT therapy with birch and grass significantly improved symptom plus medication scores over SLIT monotherapy with birch or grass, indicating that combination SLIT may be effective for polyallergic patients.²⁴ Another study reported favorable results in dually sensitized and allergic patients treated with combination grass and olive SLIT.²⁵ Conversely, another study compared SLIT with timothy grass monotherapy to timothy grass in combination with 9 other pollen allergens

TABLE I. FDA-approved SLIT tablets

SLIT product (USA)	Allergen(s)	Approved ages	Strengths	Administration instructions
Grastek (Merck)	Timothy grass	5-65 y of age	2800 Bioequivalent Allergy Unit (BAU)	Begin 12 wk before grass pollen season and continue throughout the season May be taken daily for 3 consecutive years for sustained benefits
Oralair (Stallergenes)	5 grass pollens (Kentucky blue grass, orchard, perennial rye, sweet vernal and timothy)	10-65 y of age	2 strengths: 100 IR (index of reactivity): used for treatment initiation in children 300 IR	Begin 4 mo before grass pollen season and continue throughout the season
Ragwitek (Merck)	Short ragweed	18-65 y of age	12 Amb a 1-Unit (Amb a 1-U)	Begin 12 wk before ragweed pollen season and continue throughout the season

and found that timothy-specific IgG₄ levels increased significantly only in the monotherapy group. The authors concluded that this may indicate decreased efficacy if multiple allergens are combined in SLIT.²⁶

EFFICACY OF SLIT

Several systematic reviews and meta-analyses have proven that SLIT significantly improves allergic rhinoconjunctivitis symptom and medication scores in children and adults.^{10,27-29} Grass and ragweed SLIT tablets had a greater effect on total nasal symptom scores than did montelukast and desloratidine for seasonal allergic rhinitis according to a recent pooled analysis.³⁰ In the same study, house dust mite SLIT tablets had a greater effect on total nasal symptom scores than did montelukast, desloratidine, and mometasone furoate nasal spray in perennial allergic rhinitis.³⁰ Few studies have suggested efficacy in asthma as well,^{10,11,28} but a recent Cochrane review concluded that more standardized high-quality studies are needed to fully assess the efficacy of SLIT in asthma.³¹ Liquid SLIT, used off-label in the United States, is not standardized and may not be as effective as tablets.²⁷ In Europe, liquid SLIT preparations are standardized and have been shown to be effective at the appropriate doses. However, liquid SLIT doses may be subtherapeutic, especially if multiple allergens are combined into one extract. Further evidence is needed to definitively compare the efficacy of SCIT and SLIT,³² although some studies suggest that SCIT may be superior to SLIT in controlling the symptoms of allergic rhinoconjunctivitis and asthma.^{33,34}

SAFETY OF SLIT

Side effects of SLIT are generally localized to the mouth and the gastrointestinal tract. Mouth and ear pruritus and throat irritation are the most common adverse reactions and usually resolve within 2 weeks.^{9,35} Our patient developed oral pruritus that resolved within 1 week. Because of the frequency of local reactions during SLIT, a World Allergy Organization task force proposed a 3-grade classification system, with treatment discontinuation due to a local reaction receiving the highest grade.³⁶ Two cases of eosinophilic esophagitis in association with SLIT administration are reported.^{37,38} SLIT is considered safe in mild or controlled asthma, but there is concern that it may lead to adverse events in patients with severe or uncontrolled asthma.³¹ A study of grass pollen SLIT in patients with and without mild, controlled asthma found no significant difference

in adverse events.³⁹ In a recent randomized controlled trial examining the use of house dust mite SLIT tablets in 834 adults with asthma not well controlled by inhaled corticosteroids, there were no severe systemic allergic reactions or adverse events requiring epinephrine.¹¹ All 3 FDA-approved SLIT tablets are contraindicated in patients with a history of severe uncontrolled asthma, anaphylaxis, or eosinophilic esophagitis.⁶⁻⁸

Systemic allergic reactions, including anaphylaxis,^{40,41} do rarely occur with SLIT. The rate of anaphylaxis in SLIT has been estimated to be 1 per 100 million administered doses.⁴² However, a comprehensive review of 104 SLIT studies found a systemic reaction rate of 0.056% of doses administered.⁴³ No fatalities due to SLIT have been reported after decades of use in Europe.^{28,35} The package inserts for all 3 FDA-approved SLIT tablets recommend prescribing autoinjectable epinephrine to patients for potential use during home administration. However, this is not required in Europe. In a review of 16 SLIT tablet trials (8 timothy grass, 4 short ragweed, and 4 house dust mite), the event rate of epinephrine administration was 0.1%, with 43% of administrations given for events that were determined to be unrelated to SLIT tablet use.⁴⁴

COST-EFFECTIVENESS OF SLIT

SLIT and SCIT become cost-effective as compared to symptomatic treatment approximately 6 years after treatment initiation.^{45,46} There is insufficient evidence, especially with the recent FDA approval of SLIT tablets in the United States, to compare the relative cost-effectiveness of SLIT and SCIT.^{45,47} Both SLIT and SCIT modify the immune response, resulting in lasting benefits that may further improve cost-effectiveness over a patient's lifetime. Studies of grass SLIT demonstrate 2 years of sustained clinical benefit following a 3-year course of continuous therapy.^{9,48} In a prospective study of dust mite SLIT in mono-sensitized patients, sustained clinical benefit was maintained for 8 years after 4 years of continuous therapy.⁴⁹

POTENTIAL PREVENTION OF FUTURE SENSITIZATIONS AND ASTHMA

SLIT has been shown to prevent the development of new allergen sensitizations. In a 15-year study of patients mono-sensitized to dust mite, the rate of new sensitizations among patients receiving SLIT was much lower than among the control group. New sensitizations developed in only 11% to 21% of the patients in the SLIT treatment groups, with variations depending

on the overall duration of SLIT, as compared with 100% of the patients in the control group.⁴⁹ A decreased rate of new sensitizations has also been demonstrated in children with allergic rhinitis receiving SLIT as compared with controls.⁵⁰

In children with allergic rhinitis, SLIT may have the potential to prevent the development of asthma and thus, the “atopic march.”^{9,28} In children with grass pollen allergy, the development of asthma was 3.8 times higher in the control group than in the SLIT treatment group.⁵¹ More randomized controlled trials are needed to further evaluate the preventative effects of SLIT.

FUTURE DIRECTIONS

Phase 3 clinical trials evaluating the efficacy of house dust mite SLIT tablets have been completed in Europe and the United States, but peer-reviewed results for the US trials have not yet been published. In the European study published by Demoly et al,⁵² 1-year use of house dust mite SLIT tablets resulted in an 18% to 22% reduction in total combined rhinitis scores (sum of rhinitis symptom and medication scores) over placebo ($P < .005$). These positive treatment effects were apparent by 14 weeks. Significant improvements were also noted in a number of secondary end points including combined rhinoconjunctivitis and quality-of-life scores. The treatment was well tolerated.⁵²

SUMMARY AND CONCLUSIONS

SLIT has been used by clinicians in Europe for years, but has only recently gained popularity and approval in the United States. Currently, 3 SLIT tablets are approved by the FDA, 2 grass and 1 ragweed (Table I). Clinical trials are underway for house dust mite SLIT tablets. In polysensitized and polyallergic patients, treating the most clinically relevant allergen(s) can be effective. Our patient experienced improved rhinoconjunctivitis symptoms and was able to decrease his use of intranasal corticosteroids with timothy grass and ragweed SLIT therapy, despite positive skin tests for pigweed and dog dander. SLIT tablets have an improved safety profile, with most side effects being local in nature. Our patient developed oral pruritus that resolved within 1 week. SLIT tablets can be given at home, making this mode of immunotherapy attractive for patients who are concerned about the time commitment needed for SCIT, as demonstrated in this case. Further evidence is needed to definitively compare the efficacy of SCIT and SLIT, although some studies suggest that SCIT may be superior to SLIT.

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