

Selection of patients for sublingual immunotherapy (SLIT) versus subcutaneous immunotherapy (SCIT)

Farnaz Tabatabaian, M.D. and Thomas B. Casale, M.D., FAAAAI

ABSTRACT

Allergy immunotherapy has been used to help alleviate symptoms of allergic diseases for over 100 years. In the setting of the recently approved sublingual immunotherapy, allergists are now faced with which therapeutic regimen to use in clinical practice, sublingual immunotherapy (SLIT) or subcutaneous immunotherapy (SCIT). Both SLIT and SCIT have been shown to be beneficial for the therapy of seasonal allergic rhinoconjunctivitis. Each therapeutic measure has its associated benefits. SLIT has a better safety profile with less systemic reactions and to date, no reported fatal reactions. SCIT, the primary method of allergen immunotherapy in the United States, has a slightly better efficacy profile and readily allows for treatment of polyallergic patients. This review focuses on how to incorporate SLIT into daily clinical practice and on how to choose SLIT versus SCIT.

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The United States Food and Drug Administration (FDA) recently approved three sublingual immunotherapy (SLIT) products, two grasses and one ragweed tablet. With this approval, physicians will be faced with the decision as to whether to use SLIT or subcutaneous immunotherapy (SCIT). To make a decision, several issues should be addressed. These include 1) whether it is better to use mono- versus polyallergen immunotherapy in polysensitized patients; 2) are there similar long-term clinical effects of SLIT versus SCIT; 3) which is more effective, SLIT or SCIT; 4) which is safer, SLIT or SCIT; and 5) what are the likely practical points to consider in choosing between these two treatment options. This review will address each of these issues.

IS IT BETTER TO USE MONO-VERSUS POLYALLERGEN IMMUNOTHERAPY IN POLYSENSITIZED PATIENTS?

Epidemiologic data indicate that the prevalence of polysensitization is between 51% and 82% in patients with allergic sensitivity in both Europe and the United States. The sensitization of these patients was based on skin-prick testing, serum immunoglobulin E assay or both.¹ In the United States, many allergens are simultaneously included in SCIT based on the sensitization profile. On average, United States allergists include

eight allergens per immunotherapy prescription.² It is thought that this provides an advantage by treating as many of the patient's actual or potential sensitizations/allergies. This approach is preferred because of concern of the significant time investment needed for the institution of SCIT, especially during the build-up phase. A physician might have difficulty rationalizing the use of only one allergen in a patient with both seasonal grass and ragweed symptoms along with perennial allergen-induced symptoms when the untreated allergies continue to provoke troublesome symptoms.

In contrast, the European approach typically uses a single allergen chosen according to the most clinically problematic allergy. European allergists often cite the fact that polysensitization does not necessarily mean polyallergy, and choosing a single or perhaps two most relevant allergens is the most appropriate approach.³ It is important to note that although this approach seems to be efficacious, there are no well-designed longitudinal studies comparing this approach with treating with multiple allergens, nor are there convincing data that therapy with a single allergen confers protection from symptoms from an unrelated allergen.

Let us first examine the data exploring single allergen SLIT in mono- versus polysensitized patients. In a review by Calderón *et al.*, robust, large-scale clinical trials of grass pollen SLIT showed that polysensitized patients benefited at least as much from allergy immunotherapy as monosensitized patients.¹ In a study by Emminger *et al.*, approximately 72% of patients were polysensitized, and only 28% of patients were monosensitized to grass.⁴ In the patients that were sensitized to grass plus one or more allergens, their response rates to SLIT were as good or slightly better as those that were sensitized to grass alone. This improvement was seen in both better symptoms scores and medications

Department of Internal Medicine, Division of Allergy and Immunology, University of South Florida, Tampa, Florida

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Address correspondence to Thomas Casale, M.D., USF Health, 12901 Bruce B. Downs Boulevard, MDC 19, Tampa, FL 33612

E-mail address: tbcasale@health.usf.edu

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scores. However, it is important to note that the definition of polysensitization was narrow, and individuals with confounding allergies were not included in some of these studies. Also, most of the symptom control seen in patients was within the season.

The data for SCIT, however, is not as robust. There is no single allergen SCIT trial specifically designed to compare efficacy in monosensitized and polysensitized patients. However, Frew *et al.* examined data from a large-scale, double-blinded, placebo-controlled, randomized trial examining the efficacy of single allergen SCIT featuring 77% of patients who were polysensitized and found equivalent efficacy in the poly- versus monosensitized patients.⁵

What about multiallergen immunotherapy in the polysensitized patient? Unfortunately, there is a dearth of data. In one SLIT study by Amar *et al.*, they looked at 54 subjects with grass pollen-induced rhinoconjunctivitis who either received 10 months of daily SLIT with timothy pollen extract only, the same amount of timothy extract mixed with nine unrelated pollen extracts, or placebo.⁶ The data suggested that coadministration of multiple allergens might interfere with the effectiveness of timothy grass SLIT. Similarly, there are some data in SCIT trials suggesting that multiallergen immunotherapy is less effective in polysensitized patients than single allergen immunotherapy in monosensitized patients.¹

What do the data show with the approved SLIT grass products? Grazax is a once daily sublingual tablet for patients with seasonal allergic rhinoconjunctivitis due to grass pollen. It contains a biologically standardized Timothy grass allergen extract derived from extraction and purification of *Phleum pratense* pollen. This product manufactured by Merck, Inc. only uses Timothy, because Timothy shows distinct and high cross-reactivity with Orchard, Ryegrass, Kentucky bluegrass, sweet vernal, and other Pooideae grasses. In the phase three studies used for FDA approval, pooled results indicated that 542 patients were sensitive only to grass and 2551 patients were sensitized to grass plus other allergens.^{2,7-10} The relative treatment effect was equivalent for both groups. Both had approximately 20% improvement of total combined scores relative to placebo. Oralair is a once daily sublingual tablet for patients with seasonal allergic rhinoconjunctivitis due to grass pollen produced by Stallergenes. In contrast to Grazax, it is manufactured from an allergen mixture obtained by concurrent extraction from five different grass pollens: Kentucky bluegrass, Orchard, Perennial rye, Sweet vernal, and Timothy. In the phase three pivotal trials, approximately 240 patients were monosensitized and 425 polysensitized. Equivalent efficacy was found in the monosensitized and polysensitized patients with relative least square mean differences over placebo of 24.8% and 29.8%, respectively.¹¹⁻¹³

Therefore, single allergen immunotherapy has proved to be as effective in polysensitized patients as in monosensitized patients. However, the data come mostly from studies with grass pollen. Multiallergen SLIT or SCIT in polysensitized patients needs more supporting data from large-scale clinical trials to validate it as a treatment option. Currently, choosing the most relevant allergens for optimizing allergen immunotherapy remains an art- and not science-based practice in the United States. Component-based diagnostics might ultimately help guide a better allergen immunotherapy plan.

ARE THERE DIFFERENCES IN LONG-TERM CLINICAL EFFECTS BETWEEN SLIT AND SCIT?

Allergy immunotherapy induces immune tolerance by multiple mechanisms, including regulatory T cell induction and suppression of type 2 T helper cell-mediated effects. Maintaining this tolerance might require prolonged exposure to the allergen.¹⁴ In the classic study by Durham *et al.* published in *The New England Journal of Medicine* in 1999, patients from a previous study received SCIT from 1989 to 1992 and then underwent a double-blind randomization to either receive immunotherapy or placebo for three more years.¹⁵ They found that grass SCIT administered for three years resulted in continued benefits for at least another three years. Indeed, the effects were as good as those in patients randomized to continue SCIT after the original three-year treatment. The pivotal trials leading to the approval of Grazax show that three years of treatment resulted in improved symptom scores and sustained increase in antigen-specific IgG4 throughout the three years of treatment and for two further years. Furthermore, during the posttreatment period in years four and five, patients continued to have sustained clinical benefits equivalent to what was seen in the initial three-year treatment (Fig. 1).¹⁰ Data from Oralair clinical trials also showed sustained clinical benefits for at least two more years (Fig. 2) in a preseasonal administration.¹³

Thus, both SCIT and SLIT have been shown to result in sustained benefits after three-year treatment courses.

ARE THERE DIFFERENCES IN EFFICACY?

One of the most important questions in comparing SLIT with SCIT is the comparative clinical effectiveness of these therapeutic measures. Di Bona *et al.* performed an indirect metaanalysis comparison between SLIT and SCIT to determine whether one had better efficacy.¹⁶ Treatment efficacy was determined as the standardized mean difference in symptom and medication scores obtained with active treatment, SCIT or SLIT, compared with placebo. Studies were included if they were double-blind, randomized, controlled trials com-

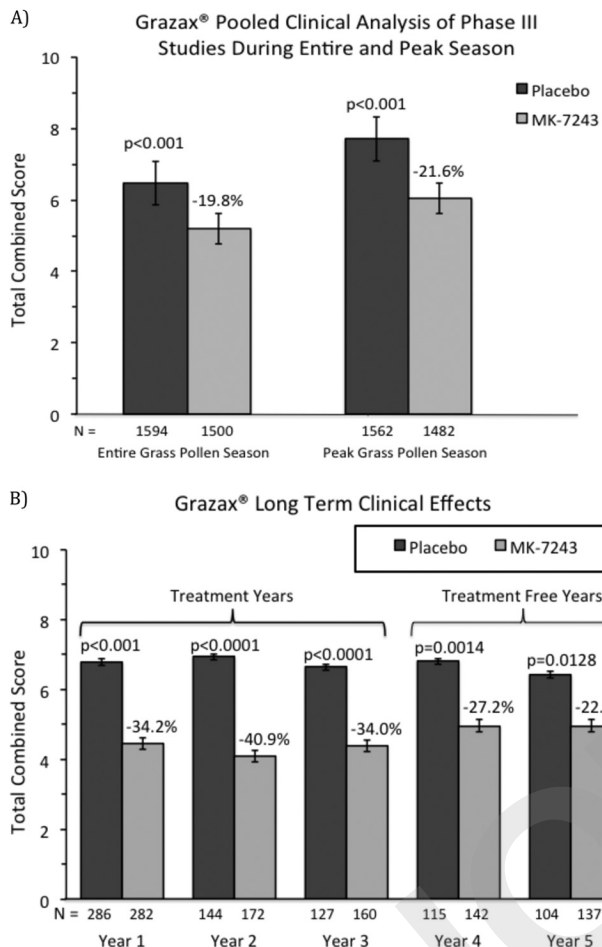


Figure 1. The effects of MK 7243 (Grazax) on total combined score (TCS), combination of the rhinoconjunctivitis daily symptom score and rhinoconjunctivitis daily medication score. (A) Pooled data from the six phase III studies done using MK 7243 compared to placebo in the entire and peak grass pollen seasons. Patients received treatment approximately 12 weeks prior to grass season and throughout the season. Verum groups showed a statistically significant decrease in the TCS. (B) Long term clinical effects on TCS comparing patients in the treatment group to placebo. In years 4 and 5, 472 subjects of 568 were observed for long term effects off SLIT. Active treatment groups in the first three years while on treatment and subsequently off SLIT had a decrease in TCS. Source: Adapted from MK-7243 Grass Allergy Immunotherapy Tablet FDA Advisory Committee Meeting Back Ground Package, Table 12 and 13 p59–65.

paring the two therapies with placebo. The authors found that the overall effect size of SCIT for symptom scores was significantly better than SLIT, administered via drops or tablets. Similar results were reported for medication scores. However, the advantage of SCIT over SLIT was small, making it difficult to assess the clinical meaningfulness of the reported differences. Dretzke *et al.* performed a metaanalysis of double-blinded, randomized controlled trials of SCIT or SLIT looking at indirect comparisons of the two.¹⁷ The re-

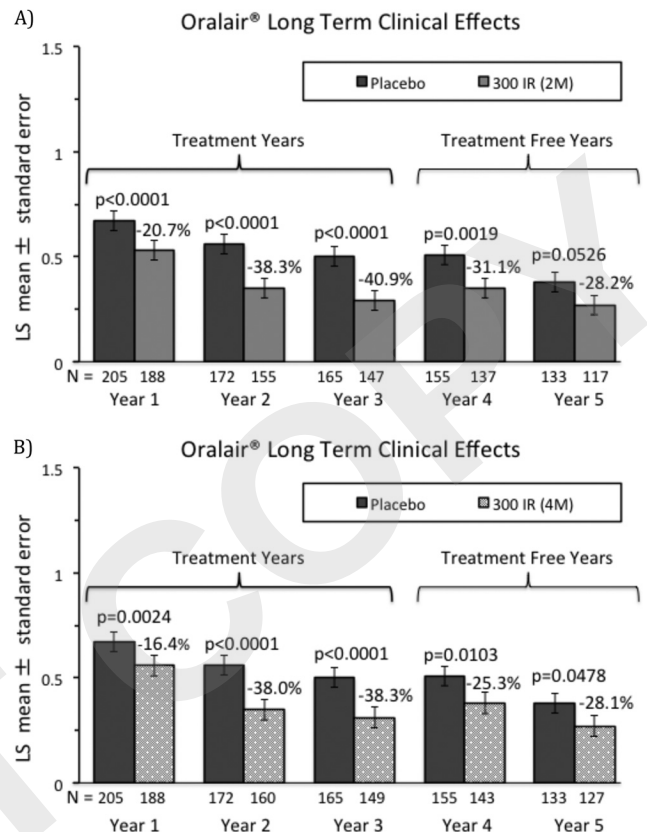


Figure 2. The long-term effects of Oralair 300 IR over the treatment period of three years with two year follow-up compared to placebo. Patients, ages 18–50, were randomized to placebo or verum for 2 (A) or 4 (B) months preseasonally and coseasonally. The primary end point was the average adjusted symptom score (AASS). (A) and (B) both demonstrate statistically significant differences in the least square means of the AASS in the SLIT treatment groups compared to placebo. Post-treatment efficacy of Oralair was observed in years 4 and 5. LS = Least square, N = number of patients evaluated for the statistical model. Source: Stallergenes S.A. Oralair Sublingual Tablets FDA Advisory Committee Briefing Document, Table 28.

sults based on symptom-medication or quality-of-life scores did not provide conclusive data favoring either SCIT or SLIT. The one head-to-head trial that met the inclusion criteria for the study also was found to be inconclusive. In a recent review by Nelson, 11 studies were identified that compared SLIT with SCIT directly.¹⁸ Four of the studies were randomized, double-blinded, double dummy studies, and seven were randomized but open. In comparing symptom scores, two of the studies showed significant improvement with SCIT compared with SLIT.^{19,20} In seven of the studies, the immunologic response in the SCIT groups was significantly prominent with a rise in IgG4 not equaled in the SLIT groups. However it is unclear whether these studies were conducted under appropriate conditions with optimal dose, frequency, and duration of

SLIT administration. Another evaluation of eight trials comparing effectiveness of SCIT versus SLIT provides evidence to support greater effectiveness of SCIT at reducing combined rhinitis symptom medication scores. There were also data supporting a greater effect for SCIT on asthma symptom reduction in this study.²¹ Thus, the data to date suggest that SCIT might be more effective than SLIT. However, it is apparent that both therapies are effective compared with placebo, but well-designed head-to-head trials are needed to truly compare the effectiveness of SCIT versus SLIT.

SAFETY OF SLIT VERSUS SCIT

The adverse effects profile of SCIT suggests that local reactions are common but not predictive of additional local reactions at the next injection or systemic reactions. Systemic reactions usually occur very rapidly, the majority within 30 minutes, but delayed reactions have been reported.^{22,23} The incidence of systemic reactions seems to have been decreasing with fairly low rates of 0.1% to 3.5% of injections.^{24,25} Deaths from SCIT are extremely rare. Between 2008 and 2012, data were gathered on 23.3 million injection visits, and only one confirmed fatality occurred in 2009.²⁵ Risk factors for systemic reactions due to SCIT include the presence of symptomatic asthma, a high degree of allergen sensitivity, the use of β -blockers, injections from new vials, cluster or rush therapies, administration during peak pollen seasons, and dosing errors.

In contrast, systemic allergic reactions from SLIT are very rare. Most associated reactions are local. Approximately 20%–25% patients have either oral pruritus or throat irritation. Another 5%–10% of patients may have ear pruritus, mouth edema, or oral paraesthesia, tongue pruritus, or lip swelling. Most of these are mild in nature. The local adverse events from SLIT occur most frequently during the first day but can average up to 5.5 days.^{10,13,26} After a week, the local adverse events from SLIT are relatively infrequent. Comparing the systemic allergic reactions occurring with Timothy grass SLIT versus SCIT, the percentage of patients having systemic allergic reactions from SLIT was 0.4% (as reported to the FDA during the approval hearing) versus 16% in a SCIT trial published by Frew *et al.*⁵ Pharmacovigilance studies comparing Timothy grass Alutard 225 versus Grazax indicate that only one patient had an episode of anaphylactic shock with an estimated 49 million tablets versus 21 patients receiving approximately 0.5 million SCIT injections. Therefore, the safety profile for SLIT is much better in regards to systemic allergic reactions. Local adverse events are to be expected with SLIT but rapidly wane in frequency after the first day. Most of these are mild in nature and do not require treatment.

CHOOSING BETWEEN SCIT AND SLIT

For grass SLIT, one sublingual tablet will be prescribed daily for both adults and children, with the first dose in the clinic. Patients should initiate dosing at least 12 weeks before the grass pollen season and continue daily until the end of the pollen season. In patients that are prescribed both a grass and ragweed SLIT product, there will be an overlap period when the patient needs to take both tablets on the same day. There is no specific guidance on how best to do this, but it makes sense to separate the two tablets by at least 30 minutes, so if there was an allergic reaction to SLIT, the physician might be better able to identify the causative product. The use of SCIT requires year-round therapy for approximately three years. SLIT data suggest that three years may also be an optimal time period for sustained immunologic and clinical benefits. Efficacy is seen for both monosensitized and polysensitized patients with both therapies.

Although the convenience of in-home dosing, avoidance of needles in patients with phobia, and overall better safety profile could favor SLIT adherence in selected patients, compliance is poor with both forms of allergen immunotherapy. Many patients may fail to take medication consistently without appropriate supervision. Precourseasonal administration (proven effective for Oralair) could increase adherence by avoiding year-round treatment. Administration of SCIT in the form of cluster therapy is a well-established approach that can provide convenience for a patient to achieve maintenance quickly.

Based on multiple studies done in the United States and Europe, allergy immunotherapy can result in cost savings over standard drug therapy.²⁷ Although SLIT costs more, this needs to be balanced by the expense and inconvenience to patients required to receive in-clinic versus in-home therapy. In a review conducted by Hankin and Cox, 24 publications were identified in the last 18 years comparing health economics of SCIT, SLIT, and standard drug therapy.²⁸ Six publications were identified that compared SLIT with SCIT directly, with only two favoring SCIT. Moreover, the adverse event profile is clearly more problematic for SCIT. The mono- versus polysensitized therapy decisions that patients and physicians must make will also enter into the equation for those patients who have multiple, clinically relevant allergies. The logistics behind doing multiple SLIT tablets for polyallergic patients remains a concern, whereas multiple allergens can readily be combined in SCIT formulations. Finally, physicians need to be cognizant of the predominant pollen seasons in their geographic location. For example, the FDA-approved grass and ragweed SLIT products are a good therapeutic option for patients residing in the Midwest United States but not in south Florida.

CONCLUSION

In the United States, we currently have two grass and one ragweed SLIT tablet products approved. The efficacy of SCIT and SLIT has been demonstrated regardless of the patient characteristics. The SLIT safety profile is better. Although comparative trials of SLIT with SCIT for efficacy are lacking, existing data suggest that SCIT might be more effective, but it is not known whether the reported differences are clinically meaningful. There are more SLIT products under development. How SLIT fits into the armamentarium for the therapy of allergic diseases will be determined by experience, local aeroallergen profiles, and patient preferences.

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