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IMMUNOTHERAPY AND IMMUNOMODULATORS (B VICKERY, SECTION EDITOR)

Sublingual Versus Subcutaneous Immunotherapy for Allergic Rhinitis: What Are the Important Therapeutic and Real-World Considerations?

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Abstract

Purpose of Review Allergen immunotherapy has been used for over 100 years in the treatment of allergic rhinitis. With two major options for administering this disease-modifying therapy, SCIT, and SLIT, what is our current understanding of the efficacy and safety of each one? How do we determine who is the appropriate candidate for each one in the real world?

Recent Findings SCIT and SLIT show significant improvement in clinical symptoms and need for medication in the treatment of allergic rhinitis. In recent meta-analyses, there is no significant difference in the efficacy between the two treatments, but SLIT has more local side effects though less systemic ones. Shared decision-making should be instituted to determine which treatment should be started in a patient with allergic rhinitis.

Summary This review provides up-to-date information on the efficacy and safety of SCIT vs SLIT in the care of children and adults with allergic rhinitis in the real world and the role of shared decision-making in the use of these modalities.

Trial Registrations Clinicaltrials.gov: NCT04145219 and NCT02478398

Keywords Subcutaneous immunotherapy · Sublingual immunotherapy · Allergen immunotherapy · Allergic rhinitis · Shared decision making

Introduction

Allergen immunotherapy (AIT) was introduced over a century ago when Leonard Noon and John Freeman performed desensitization of grass allergy in order to suppress immediate conjunctival sensitivity to grass pollen. Subsequently, they developed a protocol discussing injection intervals, effective extract dosages, and consideration of potential side effects including anaphylaxis [1, 2]. William Frankland and Rosa Augustin published the first randomized controlled trial of subcutaneous immunotherapy (SCIT) in 1954 which provided strong scientific support for the use of AIT [3, 4]. Over time, AIT use increased and ultimately extended to other allergens. SCIT continued as the only form of administration for more than 70 years until the introduction of sublingual immunotherapy (SLIT) which only received official acceptance in the 2000s [5]. The goal of AIT is to induce long-term tolerance against allergens, which in turn leads to reduction in symptoms, improved quality of life, and decreased use of medications. There has been extensive research evaluating the different mechanisms by which AIT is successful. AIT works to restore allergen tolerance via multiple pathways that serve to inhibit early- and late-phase allergic responses. These include decreased mast cell and basophil activity, increased number of regulatory T and B cells, and increased IgG4 specific for a particular allergen [6••, 7]. This review will look at recent data on the efficacy and safety of SCIT and SLIT and how to use shared decision-making in determining which type of immunotherapy is best for each patient.

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Subcutaneous Immunotherapy in Allergic Rhinitis

SCIT is available as an injection for multiple allergens, including pollens, dust mite, molds, and common household pets. Over the last several decades, multiple controlled trials have demonstrated the efficacy of SCIT for treatment of allergic rhinitis. A 2007 Cochrane Database Review of 51 randomized controlled trials including 2871 mostly adult patients treated with SCIT for 3 months to 5 years found significantly reduced symptom and medication scores among a wide range of administered allergens, including weed, grass, and tree pollens [8].

These findings have persisted through more current studies. A recent randomized, double-blind placebo-controlled trial (RDBPCT) of 56 adult patients with moderate to severe local allergic rhinitis (AR) to grass pollen showed both short-term benefit and sustained effect with significant improvements in all primary (combined symptoms medication score) and secondary endpoints (medication-free days, rhinitis severity, asthma control) as well as improved Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores when treated with timothy-grass SCIT compared with placebo [9]. Additionally, another trial of pediatric ($n = 44$) and adults ($n = 74$) treated with house dust mite SCIT over a 3-year period showed significant improvement in nasal symptom scores and quality of life measures as well as decreased medication need at the end of treatment and 2-year post-therapy [10].

Furthermore, a pediatric-specific cohort of dust mite-sensitive children ($n = 193$) was separated into dust mite SCIT ($n = 106$) and pharmacotherapy only ($n = 87$) treatment groups over a 3-year period. At the conclusion of 3 years, both groups had significantly improved their visual analogue scale (VAS) and quality of life scores; however, those patients receiving SCIT had significantly greater improvement compared with those receiving pharmacotherapy alone. Improvement was maintained for at least 2-year post-treatment [11].

In most cases, SCIT is well-tolerated and safe for children and adults. The main adverse reactions include local itching, swelling, and redness, typically occurring within 30 min at the injection site. However, systemic reactions including wheeze and anaphylaxis can occur. Multiple recent studies have evaluated the safety profile of SCIT in both pediatric and adult populations. A recent meta-analysis showed a prevalence of systemic adverse effects at 7.32% among patients receiving SCIT for house dust mite compared with placebo. The majority of these events was considered mild and well-tolerated, including local urticaria, asthma, and mild to moderate rhinitis [12]. This study included both children and adult patients, but safety profile was not compared between each group.

Recently, a retrospective case-control study was performed in patients receiving SCIT who had systemic reactions requiring epinephrine. Interestingly, administration of the highest immunotherapy doses; inclusion of cat, dog, and grass extracts; and the number of aeroallergenic groups included in the extract were associated with systemic reactions [13]. Severe systemic reactions such as anaphylaxis and death are rare with fatalities reported to be overall decreasing over time [14]. A surveillance study evaluated 28.9 million injection visits for 344,480 patients from 2008 to 2013 and found a rate of systemic reactions occurring in 1.9% of patients with a total of four fatalities in this time frame [14, 15]. An updated report indicates there were seven known SCIT-related fatalities between 2009 and 2017 with a fatality rate of 1 per every 9.1 million injection visits for years 2008–2016 [16]. The majority of these patients did have concurrent asthma and, in some cases, severe persistent asthma. Despite these potential risks, SCIT is considered to be an effective and safe option for pediatric and adult patients with AR.

Sublingual Immunotherapy in Allergic Rhinitis

In contrast to SCIT, SLIT can be provided in two different forms, either as an extract solution (SLIT-D) or a dissolvable tablet (SLIT-T). To date, FDA approval has only been granted to dissolvable tablets for ragweed, timothy grass, a combination of five northern grass species, and house dust mites. Though younger than its SCIT predecessor, SLIT has gained increasing use over time as study trials demonstrate its safety and efficacy [17, 18]. As FDA approval has been granted to SLIT-T products, allergist experience with these forms of SLIT in the USA increased to 73.5% in 2018 compared with only 5.9% in 2008 [19, 20••].

Of the seven SLIT-D RDBPCTs performed in North America to date, only two of these trials demonstrated significant improvement in medication scores and total combined symptoms scores [18]. A pilot study evaluating dual SLIT-D therapy of house dust mite and timothy grass in thirty pediatric ($n = 11$ SLIT group, $n = 3$ placebo) and adult ($n = 9$ SLIT group, $n = 7$ placebo) patients showed significantly decreased allergic rhinoconjunctivitis (ARC) and medication scores after 4 months of pre-grass pollen season treatment and an additional 8 months. Additionally, those patients receiving SLIT-D also showed increased allergen-specific IgG4, decreased allergen-specific IgE levels, and increase in T regulatory cells [21]. A larger single-allergen phase 3 clinical trial of adults ($n = 429$) with ARC with or without mild intermittent asthma treated with either ragweed SLIT-D or placebo for 8 to 16 weeks before and during ragweed season showed a 43% decrease in total combined daily rhinoconjunctivitis symptom and medication scores [22].

Furthermore, a European open-label, prospective, patient-preference, non-interventional study of a SLIT-D formulation containing different tree pollens which show high cross-reactivity (birch, alder, and hazel) evaluated efficacy in children and adults. Patients ages 2 years and older ($n = 146$) were recruited and treated for 3–8 months with initiation prior to onset of

pollen season. Before treatment, 79% of patients were categorized as having moderate to severe rhinitis based on Allergic Rhinitis in Asthma (ARIA) classification; after treatment, only 18.6% of patients retained this classification with 62.4% of patients obtaining symptom control and 34.4% of patients not requiring symptomatic medication after treatment [23].

It is important to note that all the studies showing efficacy of SLIT-D in allergic rhinitis are single or cross-reacting allergen studies. There is no conclusive data at this time that mixing more than one non-cross-reacting allergen together to be administered as SLIT-D is efficacious.

For SLIT-T, there have been eight phase 3 RDBPCTs in the USA of which 7 have met their primary endpoints in symptom and medication scores for study drug. Allergens include timothy grass, 5-grass, ragweed, and house dust mite [18]. The two earliest of these studies evaluated timothy-grass SLIT-T and included adults ($n = 439$) and children (aged 5 to 17 years, $n = 345$) with ARC with or without asthma. Patients were treated for 16 weeks before and throughout the timothy-grass season. Both studies met their primary endpoint of significant improvement in total combined symptom and medication scores compared with placebo. Additionally, they demonstrated statistically significant increases in Phl p5-specific IgG4 and IgE-blocking factor levels after SLIT-T treatment compared with placebo [24, 25]. A more recent study of children (aged 5–17 years, $n = 283$) and adults (aged 18–65 years, $n = 1218$) with AR with or without conjunctivitis and with or without asthma treated with timothy-grass SLIT-T for 12 weeks before and throughout peak season also demonstrated effectiveness of SLIT-T compared with placebo in terms of significant improvement in total combined symptom and medication scores, with a similar efficacy found between children and adults [26].

Additionally, house dust mite SLIT-T trials have also shown beneficial effect. A double-blind, randomized, multicenter trial of patients 12 years or older ($n = 1482$) with house dust mite-induced AR in the USA and Canada showed improvement in total combined symptom and medication score by 17% compared with placebo. Patients were treated for up to 52 weeks, and efficacy was determined in the last 8 weeks of treatment when house dust mite exposure was expected to be at its highest with minimal pollen interference. The demonstrated improvement was consistent between house dust mite monosensitized and polysensitized patients, and the majority of patients had not required additional symptom-relief medication by the end of the trial [27]. Similar findings of improvement in symptom and medication scores have also been found in pediatric populations treated with house dust mite SLIT-T [28, 29].

Some trials have also evaluated the long-term or disease-modifying ability of SLIT-T. Two randomized, double-blind, placebo-controlled trial in adults ($n = 633$ [30] and $n = 238$ [31]) with ARC showed sustained benefit in symptom and medication scores for up to 2 years following a 3-year treatment period with a 5-grass pollen and timothy-grass SLIT-T, respectively. Following the findings from the timothy-grass SLIT-T study, the FDA recognized this treatment as having sustained effect, and Europe allowed for its indication as disease-modifying [32].

Similar findings have also been found in pediatric populations. A double-blind, placebo-controlled trial with timothy-grass SLIT-T randomized children aged 5 to 12 years ($n = 812$) with grass-pollen ARC to receive 3 years of treatment with either SLIT-T or placebo with a total follow-up of 5 years. Results showed reduction in ARC symptoms by 22% to 30% for all 5 trial years, and the use of allergic medications was significantly reduced after 5 years from study onset [33]. Currently, house dust mite and ragweed SLIT-T are approved only for adults in the USA, but there are ongoing clinical trials to evaluate efficacy and safety for house dust mite (clinicaltrials.gov, NCT04145219) and ragweed (clinicaltrials.gov, NCT02478398) SLIT-T in children.

Findings of safety and tolerability are found in many studies evaluating either SLIT-T or SLIT-D therapies, in both adult and pediatric populations [26, 34]. In general, SLIT therapy is considered safer than SCIT as there have been no reported fatalities from SLIT and severe systemic reactions are very rare [18, 35••]. It is worth noting, however, that adverse reactions to SLIT-D are more difficult to track due to lack of FDA regulation; however, multiple studies have demonstrated that SLIT-D safety is comparable with SLIT-T [18, 36–38]. The most common reactions reported to SLIT are local application site reactions which include oral pruritus, buccal-lingual edema, throat irritation, and ear pruritus [18, 35, 39, 40]. These symptoms can occur with a rather high frequency, however, and have been reported in up to 70% of patients [40, 41]. However, most symptoms are mild and tend to resolve quickly without significant impairment in quality of life. Overall, it has been estimated that approximately 5% of patients will discontinue SLIT therapy due to these local adverse effects [42].

Comparative Studies Between SLIT and SCIT in Allergic Rhinitis

A recent systematic review and meta-analysis reviewed AIT in regard to its effectiveness for the management of ARC [43••]. AIT improved their three primary outcomes of symptom score, medication score, and combined symptom and medication scores. One hundred six studies were eligible for review, and these included 134 RDBPCTs, 19 health economic analyses, and 7 case series. From these studies, 61 evaluated SCIT in 6379 patients and 71 evaluated SLIT in 13,636 patients; a wide range of allergens were assessed including pollens (tree, grass, weed), molds, cat and dog dander, and house dust mites. Of the 160 total studies, pooled data from 58 SCIT and SLIT studies showed a moderate effect of short-term effectiveness in favor of AIT (standardized mean difference (SMD), − 0.53; 95% CI, − 0.63 to − 0.42). Subgroup analyses found this benefit in both the

SCIT studies (SMD, − 0.65; 95% CI, − 0.86 to − 0.43) and SLIT studies (SMD, − 0.48; 95% CI, − 0.61 to − 0.36). Other subgroup analyses demonstrated SCIT and SLIT efficacy in children and adults as well as seasonal and perennial allergens. In regard to medication scores, pooled data from 45 SCIT and SLIT trials showed a small-to-medium effect in favor of AIT (SMD, − 0.38%; 95% CI − 0.49 to − 0.26) with subgroup analyses further demonstrating that both SCIT and SLIT routes were effective in reducing medication scores in children and adults for seasonal and perennial allergens. Additionally, pooled data from 15 studies evaluating combined symptom and medication scores found a small-to-moderate effect in favor of AIT (SMD, − 0.49; 95% CI, − 0.69 to − 0.30). Subgroup analysis also found benefit for SCIT and SLIT in both children and adults. In terms of long-term benefit in scores, four studies found beneficial effect for long-term effectiveness in symptom scores, but there was not enough data to perform meta-analysis.

A meta-analysis of 32 studies, including 17 randomized controlled trials and 15 controlled-before-after (CBA) studies, evaluated the effectiveness of SCIT and SLIT in the prevention of development of new allergic disease in children and adults. Primary outcomes included development of first allergic disease or new allergic disease in the short term (< 2 years since AIT cessation) and long term (> = 2 years since AIT cessation). This analysis found no consistent evidence that AIT prevents short-term development of first allergic disease; however, the review did provide evidence of reduced risk of asthma development in those patients with pre-existing AR. In addition, the meta-analysis showed an overall reduction in the risk of new allergen sensitizations in the short term; subgroup analyses suggested that AIT was more likely to be beneficial for those < 18 years, in those who received SCIT, for therapy lasting 3 or more years, and for those receiving house dust mite treatment. Analysis of long-term preventative effects of AIT did not show reduction in risk of development of new allergen sensitization [44].

Ultimately, there is evidence for both SCIT and SLIT effectiveness at reducing symptom and medication scores for those with AR in short-term and some long-term studies. In addition, consensus indicates that AIT is likely beneficial for those with allergic asthma and in the prevention of asthma for those with pre-existing AR. There is also some low-quality evidence that AIT may decrease risk of new allergen sensitization [44, 45]. Overall, meta-analyses have shown that SCIT currently has greater evidence of these benefits compared with SLIT.

There have been few head-to-head studies directly comparing SCIT and SLIT, and these studies have had limited number of enrolled patients [46–48]. Four randomized double-blind controlled trials have been performed to date with three of these including placebo only arms [49–52]. Three studies evaluated seasonal allergens, including grass [49], birch [50], and cypress pollens [51] and one perennial allergen, house dust mite [52].

The earliest of these studied a 5-grass pollen extract in adolescents and adults with ARC. Patients ($n = 20$) received either active SCIT/SLIT-D placebo or active SLIT-D/SCIT placebo for a total of 12 months. At the end of the year-long period, both groups had highly significant reduction in symptom and medication scores. For combined symptom and medication scores, they found a mean percentage reduction of 50% and 51% for SCIT and SLIT-D, respectively. It was noted that laboratory parameters changed only in patients receiving active SCIT as only this group showed decreased skin sensitivity to the allergen during the first months of treatment as well as an increase in allergen-specific IgG antibodies [49].

Three further head-to-head studies including placebo only arms have also been performed to compare SCIT and SLIT therapy. A study of adult patients ($n = 48$) with birch pollen ARC randomized to active SCIT/placebo SLIT-D, active SLIT-D/placebo SCIT, or placebo SCIT/placebo SLIT-D showed reductions in symptoms and medication scores that were statistically significant for both SCIT and SLIT-D compared with placebo [50]. Another study of adult patients ($n = 40$) with cypress pollen-induced ARC randomized patients to either active SLIT-D, active SCIT, placebo SLIT-D, or placebo SCIT for 12 months. Both active treatment groups showed a reduction in symptoms compared with placebo groups. Eosinophil cationic protein and eosinophil chemotactic activity were reduced in the nasal lavage of patients treated with active SCIT and SLIT-D, which correlated with improvement of clinical symptoms in these groups [51].

The most recent placebo-controlled study randomized house dust mite monosensitized children ($n = 31$) with mild asthma to either active SCIT, active SLIT-D, or placebo for 12 months. Both active treatment groups had statistically significant differences in rhinitis and asthma symptom scores compared with the baseline year, but only SCIT was found to be statistically significant when compared with placebo. Medication scores for rhinitis and asthma were significantly decreased for the SCIT group when compared with placebo and baseline; however, only rhinitis medication scores were significantly decreased for the SLIT-D group. Overall, they found that 12 months of SCIT therapy was more effective with decreases in symptom scores for rhinitis by 28.6% and asthma by 60.9% compared with SLIT which reduced scores for rhinitis by 9.3% and asthma by 8.1% [52].

In addition to these double-blind studies, several small randomized open head-to-head studies have also been undertaken (reviewed in [47]). Taken together, the current head-to-head studies demonstrate that both SCIT and SLIT therapy are effective at reducing rhinitis symptom and medication scores, but it is difficult to draw firm conclusions from these comparative trials due to several limitations including small numbers, potential bias risk, and variable study design. Furthermore, many of these studies evaluated SLIT-D therapy which is not currently an FDA-approved route of AIT in the USA. Certainly, greater powered studies are needed for further investigation.

Shared Decision-Making

Ultimately, AIT may become part of the treatment plan for a patient with uncontrolled AR. Choosing between SCIT or SLIT treatment requires thoughtful discussion and shared decision-making between the provider and patient. This process allows for patient empowerment in therapy selection, especially when multiple options exist. Furthermore, shared decision-making leads to increased adherence and ultimately better outcomes for patients [53••]. In regard to AIT, the decision between SLIT and SCIT in terms of advantages, disadvantages, and patient preferences is a critical component of this shared decision-making process.

A patient decision aid can be helpful in guiding the discussion of shared decision-making. Three such aids have been developed specifically for AR. One of these aids, designed by the American College of Allergy, Asthma, and Immunology and the Allergy & Asthma Network, addresses the different aspects of SLIT and SCIT as a treatment for AR [54]. Important discussion points between the two types of AIT include time commitment and administration, side effects and safety profile, allergen availability, financial costs, and long-term benefit. The various aspects for each of these points and others are outlined in Table 1. Of note, SLIT-D is not FDA-approved in the USA at this time and was not included in this decision aid. As such, there is no insurance coverage or reimbursement for this therapy [17].

Conclusion

Allergic rhinitis is one of the most common chronic conditions seen in the pediatric and adult population. The typical treatment approach for these patients consists of avoidance measures to limit exposure to allergens that trigger symptoms and medications such as intranasal corticosteroids and oral antihistamines to relieve symptoms. The third leg of management is allergen immunotherapy, which has shown improvement in symptom scores and decreased need for medication in numerous studies. Presently, it is the only modality that may lead to tolerance to the particular allergens causing the patient's allergic rhinitis. Since there are few head-to-head studies between the two approaches to immunotherapy, it is not possible to state that one treatment is clearly superior to the other. Side effect profiles of each treatment show good tolerability with SCIT having a higher risk of systemic reactions such as anaphylaxis while SLIT showing more local side effects such as oral pruritus and buccal-lingual edema.

Since both types of immunotherapy show efficacy and good safety, this is an ideal treatment to use shared decision-making in determining which is best for each patient. Studies show that adherence to both SCIT and SLIT can be poor [56] and therefore having the patient share in determining the treatment that fits the best for their lifestyle can improve adherence and lead to better outcomes. Using decision aids contrasting the benefit, risk, cost, and time commitment for SCIT and SLIT gives the patient or guardian non-biased information to

Table 1 A review of shared-decision making topics for SCIT and SLIT-T

Shared decision-making Topic	SCIT	SLIT-T
Time commitment	Typically weekly injections for first 6 months and then monthly for 3 to 5 years. Thirty-minute wait at doctor's office after each injection	No obvious answer for treatment cessation. Daily dosing with first dose at doctor's office with 30-min wait period, and then all subsequent doses can be taken at home
Administration	Needle injection into arm at doctor's office only	Under the tongue, can be taken at home
Side effects and risk for severe allergic reaction	Most commonly local site reactions (swelling, itching, redness). Severe allergic reactions are very rare, but fatalities can occur	Most commonly local site reactions (oral itching, oral edema). Can also have some mild gastrointestinal symptoms (cramps, nausea, diarrhea). Severe allergic reactions extremely rare, with no reported fatalities
Allergen availability	Multiple, including animal dander, house dust mites, all grass pollens, weed pollens, tree pollens, and mold spores	Limited Two options for grass (timothy only or 5-grass combination of sweet vernal, orchard, perennial rye, timothy, and Kentucky blue grass) One option for ragweed One option for house dust mites
FDA-approved age indications (in the USA)	Recommended for ages 5 and older	Timothy grass: 5 to 65 years 5-grass combination: 5 to 65 years Ragweed: 18 to 65 years House dust mites: 18 to 65 years
Financial costs [55]	Secondary to patient insurance and copay costs. Studies show overall cost savings primarily through reduced spending on doctor visits and medications for rhinitis/asthma	Secondary to patient insurance and copay costs. Studies show overall cost savings primarily through reduced spending on doctor visits and medications for rhinitis/asthma
Long-term benefit	At least 3 years after treatment	At least 1 year after treatment with some studies showing sustained effect for up to 2 years (timothy-grass SLIT-T only)

make an informed decision in their care. Even though allergen immunotherapy has existed for over 100 years, the more recent clinical studies and meta-analyses discussed in this review clearly show that it should continue to be used in the management of children and adults with allergic rhinitis.

Compliance with Ethical Standards

Conflict of Interest Michael S. Blaiss, MD, has received honorarium for consulting for ALK and Stallergenes/Greer. No other authors have any conflict of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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