



SCIT Versus SLIT: Which One Do You Recommend, Doc?



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ABSTRACT

Allergic rhinitis is a prevalent condition that has a significant impact on the quality of life of many patients. When initial therapy fails to control the symptoms, allergen immunotherapy (AIT) has been suggested as an option by the Joint Task Force on Practice Parameters. The 2 main forms of AIT are via subcutaneous and sublingual routes, called subcutaneous immunotherapy and sublingual immunotherapy, respectively. There is debate about which is the better option for patients with each method offering its own pros and cons. We present 2 patients with allergic rhinitis/AR that were deemed good candidates for AIT and explore current evidence for both subcutaneous immunotherapy and sublingual immunotherapy. The advantages and disadvantages of each method are discussed with the goal of providing a framework for the physician when deciding on AIT for their patients. In addition, we explore the use of AIT in patients with asthma and atopic dermatitis as potential patient populations that may benefit from the treatment. We use the discussion to provide recommendations regarding which method of AIT is best suited for both our patients. [*Am J Med Sci* 2019;357(5):442–447.]

CASE PRESENTATIONS

Case #1: A 10-year-old male with a multiyear history of perennial allergic rhinitis (PAR) with mild persistent asthma and atopic dermatitis (AD). He had been prescribed intranasal corticosteroid spray, oral antihistamines and saline nasal rinses for the past 2 years, with only marginal improvement in nasal symptoms. Allergy testing was positive for timothy grass, weed pollens and dust mites. Thus, this child was considered for allergen immunotherapy (AIT) to treat his aeroallergen sensitivities and the symptoms they were causing, and a subcutaneous immunotherapy (SCIT) versus sublingual immunotherapy (SLIT) discussion ensued with the parents.

Case #2: A 36-year-old male with a history of seasonal allergic rhinitis (SAR) that was unresponsive to medical intervention with continued runny nose, sneezing and nasal obstruction. His symptoms were worse during the summer and he had positive allergy to timothy grass pollen.

INTRODUCTION

The prevalence of allergic rhinitis (AR) in the United States is 30% based on self-reported symptoms and 15% based on physician diagnosis.^{1,2} AR has been shown to substantially affect quality of life, work and school performance, sleep quality and engagement in outdoor activities.^{2,3} Initial treatment of AR consists of allergen avoidance and pharmacotherapy. According to the 2011 clinical practice guidelines on AR by the Joint

Task Force on Practice Parameters representing both the American Academy of Allergy Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology,⁴ clinicians may offer AIT for patients who have inadequate response to symptoms with pharmacologic therapy with or without environmental controls. Additionally, AIT should be considered in patients with adverse or intolerable side effects from pharmacologic therapy. The response to AIT varies among patients, and while AIT is rarely curative, it nonetheless has been shown to reduce allergic symptoms, improve quality of life and reduce the pharmacotherapy required by patients to control their symptoms. The primary forms of AIT are via SCIT or SLIT. Both involve administering small amounts of allergen regularly over a period of time (usually 3-5 years) with the aim of desensitizing the immune system to the problematic allergen. In general, the maintenance dose of SCIT involves administration of 5-20 mcg of the allergen, though different regimens exist. Currently, the only FDA approved SLIT in the United States is in tablet form for grass pollens (timothy grass or 5-grass), short ragweed pollen and house dust mites. Some practitioners offer aqueous SLIT drops, although this is not FDA-approved in the United States and is considered off-label administration.

Prior to initiating AIT, the physician will need to make sure that there are no contraindications to therapy. In general, noncompliant patients or patients with co-morbidities (significant cardiovascular disease, uncontrolled asthma) that would reduce their likelihood of surviving a systemic reaction, or treatment of a systemic reaction, should not

undergo AIT.⁵ Additional considerations should be made for patients with active diagnoses of cancer, severe psychological disorders and severe immunological diseases. AIT is not initiated in the pregnant patient, however, can be continued during pregnancy.⁶ Contraindications specific to SLIT include injury or surgical intervention in the oral cavity, acute gastroenteritis, eosinophilic esophagitis, history of severe systemic reaction to any form of immunotherapy, a severe local reaction to SLIT or history of hypersensitivity to any of the inactive ingredients of the preparation.⁷ AIT is not generally offered to patients under the age of 5, although there are no absolute age limits for SCIT. The FDA-approved SLIT tablets have a more defined age indication of 5-65 years of age.^{5,7} Our 10-year-old patient presented with mild persistent asthma which was an important consideration in the decision to undergo AIT.

When choosing between the 2 routes of AIT, the physician needs to weigh the pros and cons of each route.

SCIT ARGUMENT

Efficacy

Most studies on the efficacy of AIT have focused on the reduction of medication and symptom scores in AR and asthma. Thus far, there are 3 Cochrane meta-analyses evaluating the efficacy of SCIT and SLIT in SAR and PAR.⁸⁻¹¹ Overall assessment and indirect comparisons suggest that SCIT is more effective than SLIT; however, direct head-to-head studies comparing SLIT and SCIT are few, with limited patient enrollment (see below). For SAR, the effect size for SCIT for both symptom and medication score were about 2 times higher than that for SLIT with no overlap in the 95% confidence for symptoms and small overlap for medication use.^{9,11} For PAR, no firm conclusion can be obtained given the considerable heterogeneity in the study designs and possible nonallergic factors contributing to the perennial symptoms.

When examining further evidence derived from other systematic reviews and meta-analyses, a large meta-analysis concluded that SCIT was significantly more effective than SLIT in reducing rhinitis symptoms and medication scores in adults and children with SAR,¹² and another showed a trend favoring SCIT over SLIT.¹³ In both of these meta-analyses, SCIT and SLIT were found to be more effective than placebo. Similarly, other systematic reviews and meta-analyses found that SCIT and SLIT are effective in adults and children with SAR or PAR when compared with placebo.¹⁴⁻¹⁷ The evidence for efficacy of both modalities is higher in SAR and adults.

There are only 4 double blind randomized controlled trials that directly compare SCIT to SLIT. Three of these studies involved patients with SAR¹⁸⁻²⁰ and 1 involved patients with PAR.²¹ Although several of the studies found no differences in rhinitis symptoms and medication scores between the 2 immunotherapy treatment routes, 1 study showed a larger treatment effect of SCIT

over SLIT¹⁸ in SAR. Due to the heterogeneity in the study designs and the small number of patients recruited, it is difficult to make broad conclusions from these head-to-head comparison studies.

It is important to note that many of these studies reference aqueous SLIT and that currently there are no FDA approved products available in the United States for aqueous SLIT. The physician should recognize that, unlike SCIT, there is large variability in the effective dose range for allergens used in aqueous SLIT and most allergens have not been formally evaluated in large studies for aqueous SLIT.²² In contrast, the 3 FDA approved SLIT tablets have been rigorously tested in US populations have clearly defined dose ranges and schedules and have been shown to be effective in reducing symptoms and medication scores over placebo. This makes our second case, the 36-year-old patient, particularly difficult to advise. With evidence showing a greater efficacy of SCIT compared to SLIT, one may be quick to recommend it; however, the monosensitivity of the patient to an allergen with FDA-approved SLIT tablets provides good reason to consider SLIT. As of yet, there is still insufficient data at this point to adequately compare efficacy of SCIT to SLIT tablets.⁷

SLIT ARGUMENT

Safety

There have been no reported fatalities with SLIT and reports of anaphylaxis with this route have been sporadic and isolated.²³ On the other hand, although, generally well-tolerated severe systemic reactions and fatalities with SCIT have been reported. The most recent Annual Surveillance Study from the AAAAI reported a total of 4 fatalities resulting from SCIT administration in the survey results for years 2008-2013. This represents a decrease from the 3.4 fatalities per year that were reported in earlier surveys.^{5,24}

Because there is no standard classification of SLIT-related adverse events, comparing side effects and safety between SLIT and SCIT is difficult. Additionally, since SLIT is taken at home, there is significant potential for inaccurate accounting of SLIT adverse events, as this relies entirely on the patients' report of symptoms. Local reactions are common in both and have been reported to occur in up to 70% of patients with SLIT.²⁵ These include throat irritation, oral pruritus, oral cavity edema, oral paresthesia, stomatitis and pharyngeal edema.²⁶

Convenience to Patients

According to the most recent AIT practice parameter update by the Joint Task Force of AAAAI/American College of Allergy, Asthma and Immunology, SCIT should only be given in a physician's office. On the other hand, only the first dose of SLIT is to be given at the physician's office, and the rest taken by the patient on a daily basis at home.⁵ Reduction in travel to the physician's office, time off

work or school, avoidance of copays and parking fees, and other convenience factors are not insignificant to patients. However, these factors have to be weighed against a less well-established efficacy and potentially higher costs of SLIT.

CONFLICTING EVIDENCE

Adherence to Therapy

Adherence to therapy depends on factors related to the efficacy of treatment, cost, adverse effects and convenience. The efficacy of AIT depends on consistent exposure to the allergen and long-term tolerance is only achieved after at least 3 years of treatment.^{27,28} To the treating physician, adherence to therapy can be reliably monitored in patients receiving SCIT in the provider's office. SLIT is typically administered at home, so close monitoring of adherence is less reliable. While the convenience of SLIT may be expected to translate to better compliance, some studies evaluating compliance to immunotherapy have shown SCIT to have significantly higher compliance rates compared to SLIT.^{29,30} However, evidence remains conflicting as other studies have shown either higher compliance with SLIT³¹ or no difference.³² For SLIT, compliance can be improved in children with more frequent clinic visits.³³

For the 10-year-old patient, the issue of compliance becomes significant. Much of the burden falls on the parents to ensure that the child adheres to treatment. One might expect that a daily SLIT tablet would be easier for the parents to administer at a convenient and consistent time of day, compared to bringing the child to clinic every week for SCIT. However, the inconvenience of missing school days for the child as well as parents leaving work for SCIT appointments may not translate to better adherence. Education and monitoring of treatment seem to play the most important roles in determining adherence. Another issue with SLIT in this particular patient is that he is polysensitized and not all of the allergens he is allergic to are covered in the currently available SLIT tablets. There are currently 4 SLIT tablets approved by the FDA for use in the United States. Two for grass pollen, 1 for ragweed and 1 for house dust mite allergy. Relevant to our patient, 1 formulation called Grastek (ALK Inc.) covers timothy grass pollen and Odactra (ALK Inc.) covers dust mite allergens. There has been some evidence that using grass and ragweed SLIT tablets together, after establishing tolerability with the individual tablets, is acceptable,³⁴ however given the lack of studies supporting the use of a multiple tablet regimen, the efficacy of creating a multiple tablet SLIT regimen for this patient is unknown and not recommended.

Polysensitized Patient

Up to 80% of patients that are started on immunotherapy are polysensitized.^{35,36} In the United States, the

approach to the management of polysensitized patient is to treat for all clinically relevant allergens in SCIT,^{23,36,37} and SCIT preparations contain an average of 8 allergens.³⁷ Despite the use of multi-allergen SCIT, a large review by Nelson³⁸ concluded that there is low evidence regarding the efficacy of multi-allergen therapy, but more studies demonstrating efficacy in SCIT versus SLIT. For SLIT, several studies have demonstrated efficacy of single-allergen SLIT in polysensitized patients.³⁷ Evidence regarding efficacy of multi-allergen SLIT for polysensitized patients has been lacking.³⁹⁻⁴¹ The variability in the dosing regimens used in these studies and possibility of allergen dilution when mixing multiple allergens could explain the inconsistencies in the results.

SLIT AND SCIT IN ASTHMA AND ATOPIC DERMATITIS

The 10-year-old patient presenting with mild persistent asthma and AD provides another dimension to the discussion of AIT. Several studies have reported efficacy of AIT in reducing asthma symptoms in children and adults. SLIT has been shown with a high level of evidence to be clinically effective in improving asthma symptom scores and with a moderate level of evidence in reducing medication in children.⁴² Some studies demonstrate that SLIT may have a preventative effect on the onset of asthma in children ranging from 5 to 14 years old; there is also evidence to support that SLIT may prevent the development of new allergen sensitivities, although this is somewhat weaker.⁴³⁻⁴⁶ However, the

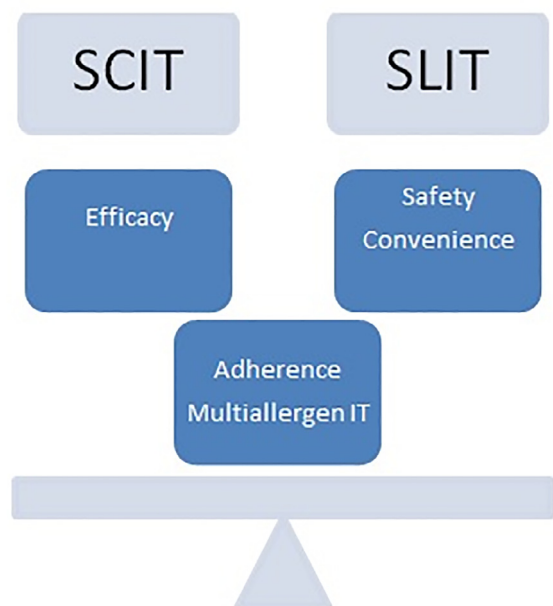


FIGURE 1. Deciding between SCIT and SLIT requires weighing the pros and cons of each method. Abbreviations: IT, immunotherapy; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

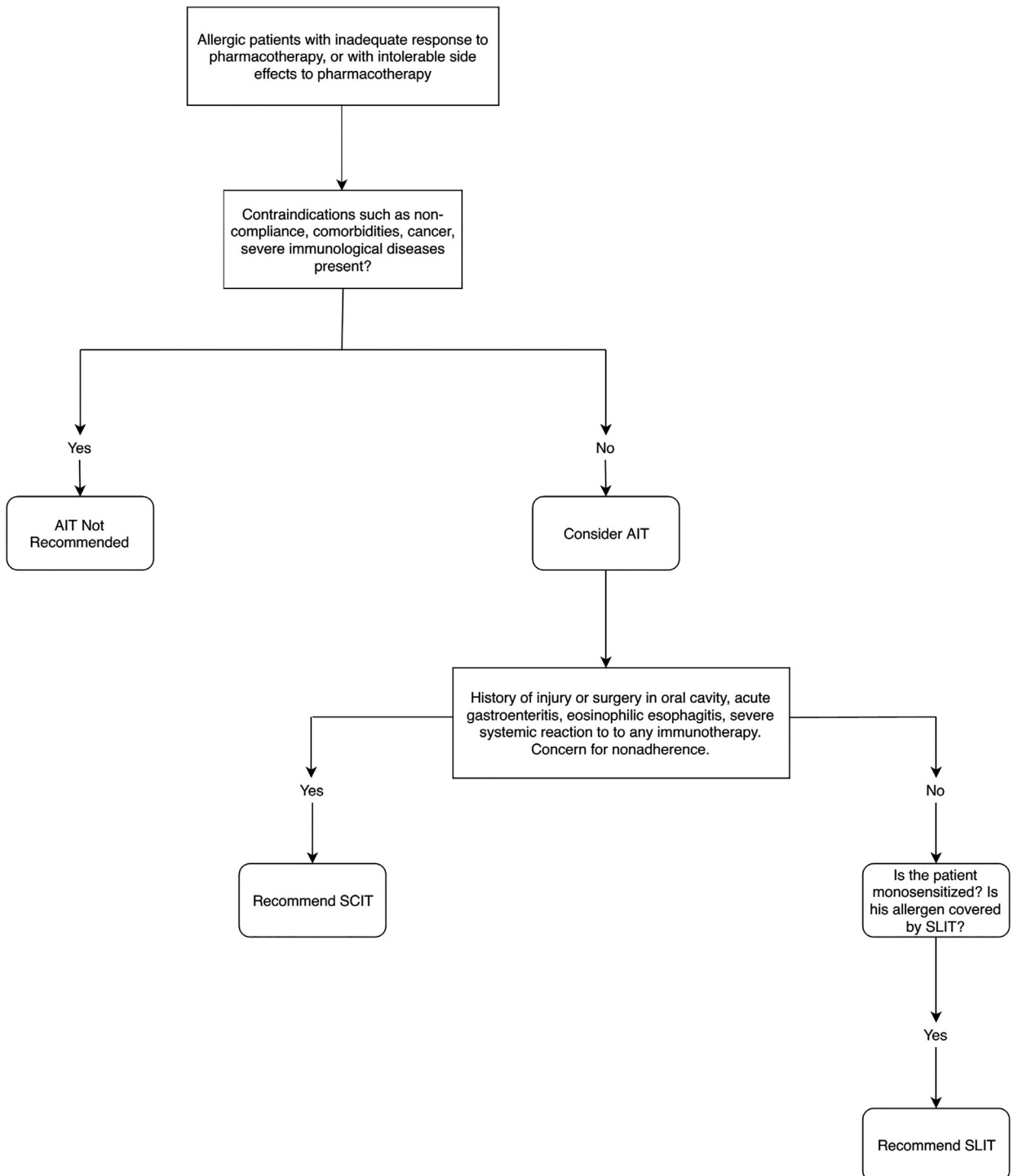


FIGURE 2. Considerations when determining to do administer AIT and SCIT vs SLIT. Abbreviations: IT, immunotherapy; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

evidence for SLIT in improving asthma symptoms in adults is lacking.

There is strong evidence for the efficacy of SCIT for both improvement and prevention of asthma in adults and children. A Cochrane review of 88 controlled

trials found evidence of improvement of asthma symptom scores, and a reduction of medication as well as bronchial hyper-reactivity in both adults and children following SCIT.⁴⁷ There is also evidence of a preventative effect on asthma in both adults and children, and a

reduction in new sensitivities in children.⁴⁸⁻⁴⁹ A 3-year course of SCIT was shown to prevent development of asthma in children for up to 7 years post treatment.⁵⁰ As mentioned previously, substantially uncontrolled asthma is considered a contraindication to AIT, thus while asthma patients may benefit from reduced symptoms with successful AIT, they may also be at risk for an adverse reaction.

Most of the research focuses on AIT with respect to AR and asthma; however, recent attention has been drawn to the potential benefits of AIT on AD. A meta-analysis of 8 different randomized controlled trials showed promising results supporting the use of AIT for AD particularly with SCIT.⁵¹ However, the results come with many caveats, including issues with heterogeneity of treatment protocols in the studies as well as small sample sizes. That being said, in the most recent AIT Practice Parameters, AD in subjects with aeroallergen sensitization was listed as a new indication for AIT.⁵ There is evidence, specifically in patients with mite allergy, that SCIT is effective for improving AD symptoms and reducing topical steroid use and thus may be a good option for our 10-year-old patient with dust mite sensitization.⁵²⁻⁵³ It is worth noting the recent approval of a SLIT tablet by the FDA for house dust mite-induced AR may offer an alternative therapy for our patient. More research is required to better understand the role of this new approved treatment in patients with AD.

CONCLUSIONS

According to the International Consensus Statement on Allergy and Rhinology: AR (ICAR-AR), both SCIT and SLIT have been given a grade A recommendation for use as AIT and have both been shown to provide significant symptom improvement, particularly in adults. In addition, there is grade A evidence to support the effectiveness of SCIT over SLIT.⁵⁴ The higher efficacy of SCIT, however, is balanced by the safety profile and at home use of SLIT (Figure 1). Head-to-head double blind randomized controlled trials to address the controversies, particularly regarding multiallergen AIT, are needed. When choosing between SCIT or SLIT, the treating physician needs to weigh the risks, benefits, cost and patient preference. Both our patients would likely see a benefit from AIT. For the 10-year-old with AR, asthma and AD we would recommend a SCIT regimen considering the relative lack of evidence for combining SLIT tablets and his polysensitivity to timothy grass, weed pollens and dust mites. He may find relief from many of his symptoms and could potentially have a significantly improved quality of life. It may also prevent his asthma from worsening down the line and prevent him from developing new sensitivities in the future. Similarly, we would recommend to our 36-year-old with a monosensitive AR a SLIT regimen covering his timothy grass allergy so that he may finally overcome the seasonal symptoms of rhinorrhea, sneezing and nasal obstruction (Figure 2).

AUTHOR CONTRIBUTIONS

Chaaban M.R. designed the paper, completed initial draft and performed revisions. Tripple J.W. contributed to the initial draft and revisions. Wise S.K. and Mansi A. performed revisions and contributed to the final draft.

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