

Evidence-Based Practice

Sublingual Immunotherapy for Allergic Rhinitis

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KEYWORDS

- Sublingual immunotherapy • Allergic rhinitis • Allergy • Antigen • Allergen • Safety
- Efficacy • Anaphylaxis

KEY POINTS

The following points provide the level of evidence based on the Oxford Center for Evidence-Based Medicine. Additional critical points are provided and the points here are expanded at the conclusion of this article.

- Sublingual immunotherapy (SLIT) reduces symptoms and medication use in allergic rhinitis. Subgroup analysis shows a benefit for seasonal and perennial antigens, adults and children, and higher antigen doses (evidence grade = 1a-).
- SLIT has shown a significant benefit for grass pollen and house dust mite antigens (evidence grade = 1a-).
- Recommended maintenance SLIT dosing for grass pollen is 15 to 25 µg major allergen per dose. Dosing for other antigens is not established (evidence grade = 1b).
- Most well-designed controlled SLIT trials have been performed with single-antigen therapy (evidence grade = 1b).
- The safety profile of SLIT for allergic rhinitis remains excellent (evidence grade = 1a-).

DISEASE OVERVIEW: ALLERGIC RHINITIS

Allergic rhinitis has a significant public health and quality-of-life impact in the United States. Using data extracted from the Agency for Healthcare Research and Quality 2007 Medical Expenditure Panel Survey, Bhattacharyya¹ recently reported that 17.8 million adults in the United States (7.9% of the US population) sought care for allergic rhinitis in 2007. In this report, patients with allergic rhinitis were older, were more commonly female, had 3 more physician office visits, filled 9 more prescriptions, and had an overall health care expenditure totaling \$1492 per person annually over

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persons without allergic rhinitis.¹ Much of the increased health care expenditure for allergic rhinitis is allocated to pharmacotherapy, including antihistamines, decongestants, topical and oral corticosteroids, and others. Antigen avoidance measures are also advocated as an adjunct to the overall treatment plan for allergic rhinitis or perhaps as the sole treatment when a single-antigen trigger can be identified and avoided appropriately.

Antigen-specific immunotherapy is frequently used as part of the treatment paradigm for allergic rhinitis. Although sublingual immunotherapy (SLIT) was first reported in the United States in 1900, the primary modality of antigen-specific immunotherapy in the United States over the last century has been subcutaneous immunotherapy (SCIT).² The benefits of SCIT for seasonal allergic rhinitis³ and perennial allergic asthma⁴ have been demonstrated in numerous randomized controlled trials and recent Cochrane reviews. However, safety concerns with SCIT remain. Systemic reactions with SCIT have been reported in 0.05% to 3.2% of injections and 0.84% to 46.7% of patients, including 23 near-fatal (5.4 per 1 million injections) and 3.4 fatal events per year (1 per 2.5 million injections).^{5–8} Concerns regarding systemic and fatal reactions with SCIT led the British Committee on the Safety of Medicines to question the safety of this immunotherapy modality in 1986.⁹ A surge of interest in alternative methods of antigen-specific immunotherapy followed. Immunotherapy methods, such as intranasal, bronchial, and oral administration, were investigated but none of these were as promising as SLIT because of the intolerable side effects or lack of efficacy.

SLIT has been a predominant immunotherapy modality in Europe for several years. However, over the last decade, clinical interest in SLIT has been growing rapidly in the United States. This increased interest and use of SLIT in clinical practice worldwide has also been accompanied by numerous randomized clinical trials assessing the efficacy of SLIT. This article reviews the evidence behind diagnostic testing for allergic rhinitis, followed by a discussion of the current evidence supporting SLIT for allergic rhinitis.

EVIDENCE-BASED CLINICAL ASSESSMENT AND DIAGNOSTIC TESTING FOR ALLERGIC RHINITIS

Allergic rhinitis is preliminarily diagnosed based on

- History
- Symptom complex
- Physical examination

Common symptoms of allergic rhinitis include intermittent clear rhinorrhea, sneezing, and pruritus of the nose. These symptoms may be accompanied by nasal congestion or obstruction and associated itching of the eyes and throat, watery eyes, and skin or pulmonary symptoms, among others. In the assessment of patients suspected of having allergic rhinitis, it is important to evaluate potential triggers by inquiring about the seasonality of symptoms; exacerbating environments or situations; family history of allergy or asthma; and other associated diseases, like rhinosinusitis, otitis media, and dermatitis.

Risk Factors for Allergic Rhinitis

Certain risk factors for developing allergic rhinitis have been described and may provide useful information as part of an allergic rhinitis history. These risk factors include a family history of atopy, first-born child or only child, cigarette smoke exposure,

higher socioeconomic status, and total immunoglobulin E (IgE) more than 100 IU/L before 6 years of age.¹⁰ Physical examination findings of allergic rhinitis are relatively nonspecific and may also be seen with several other sinonasal conditions. Edema of the nasal mucosa, inferior and middle turbinate hypertrophy, and lymphoid hypertrophy of the Waldeyer ring may be seen with allergic rhinitis but may also be present in upper respiratory infections, rhinosinusitis, and nasal obstructive conditions. In short, physical examination findings may support the diagnosis of allergic rhinitis but should not be the sole diagnostic factor for this condition.

Patient History and Environmental Triggers for Allergic Rhinitis

It is important to remember that much of the initial assessment and treatment plan for patients with allergic rhinitis depends on patient history and environmental triggers even though items necessary for a complete allergy history and physical examination vary depending on the environment and geographic location in which patients with allergic rhinitis are being evaluated and treated. A thorough history and physical examination leading to a diagnosis of allergic rhinitis is often sufficient to guide initial avoidance measures and pharmacotherapy. However, if the diagnosis is in question, specific antigen reactivity information is desired, or allergen immunotherapy is being considered, skin or in vitro allergy testing should be undertaken.

Skin Testing for Allergic Rhinitis

Skin testing for inhalant allergy is based on the principle that once an antigen crosses the intact skin or mucosal barrier, the antigen will interact with mast cells in the tissue and cross-link adjacent specific IgE molecules.¹¹ Depolarization of the mast cell ensues, and histamine is released in a dose-dependent fashion with respect to the antigen administered. This histamine release results in the classic wheal and flare reaction characteristic of the allergy skin test. Measurement of the wheal size allows a partially quantitative assessment of allergen reactivity. In vitro testing for IgE-mediated allergy may be undertaken as an alternative to skin testing. The first in vitro test for specific IgE was the radioallergosorbent test, or RAST test, reported in *Lancet* in 1967.^{12,13} Other examples of in vitro methods for the detection of allergen-specific IgE include ImmunoCAP and enzyme allergosorbent tests.^{11,14} Although the specific techniques used in each of these in vitro methods vary to some degree, a common principle involves the exposure of patients' serum to typical antigens in the test assay. The patients' IgE binds to these antigens and is then quantified via labeling and detection techniques specific to the individual assay. Quantification of allergen-specific IgE is possible because of the techniques used for in vitro allergy testing.

In the late 1980s and early 1990s, several articles were published comparing the advantages and disadvantages of skin testing and in vitro testing for inhalant allergies. In 1988, Ownby¹⁵ commented that the results of both skin and in vitro tests depend largely on the quality of the extracts used to perform the tests. Further, this article concluded that appropriately performed skin tests represent the best testing modality for the detection of allergen-specific IgE, whereas in vitro tests may be used in circumstances when the skin is not appropriate for testing, anaphylaxis is expected to occur with skin testing, or patients cannot discontinue medications that interfere with skin testing. With either skin or in vitro testing, the results of the test must be correlated with the patients' history before making a decision regarding treatment. Although in vitro allergy tests are noted to be less sensitive than skin testing methods, the use of in vitro test results for allergen-specific

immunotherapy has been shown to be safe in large clinical series.¹⁶ Further, although much of this literature dates back 20 or more years, many of the same arguments are used in comparisons of skin versus in vitro allergy testing today.

More recent evaluations of skin testing methods question certain aspects of testing protocols. In a 2008 review, Calabria and Hagan¹⁷ reported that the available literature at that time indicated that when a skin prick test is negative, a positive intradermal skin test did not correlate well with in vitro and challenge test results, therefore providing little additional information for the overall diagnosis. However, these investigators note that a negative intradermal skin test result seems to have a high negative predictive value. Krouse and colleagues¹⁸ generally agree that negative allergy screens by prick/puncture techniques are typically reliable with regard to the presence or absence of allergy. These investigators do note, however, that intradermal testing following a negative skin prick test may provide useful information if clinical suspicion for allergy remains high, especially in the case of mold antigens or unusual inhalant reactivity. Finally, special consideration should be given to skin testing for inhalant allergy when SLIT is planned. Because of the high safety profile associated with SLIT, in combination with short SLIT escalation protocols, quantification (or semiquantification) of allergy skin test reactivity is often unnecessary. Compared with skin testing for patients planning to undergo SCIT, in which intradermal dilutional testing is often performed to best determine patients' specific endpoint for each antigen and shorten the escalation period as much as possible, patients on SLIT will have short escalation protocols with all antigens typically starting at the same dilution, thus obviating extensive dilutional skin testing.

EVIDENCE-BASED MEDICAL MANAGEMENT: SLIT FOR ALLERGIC RHINITIS

Efficacy of SLIT

Beginning in 2006, multiple large, multicenter, randomized, double-blind, placebo-controlled trials of SLIT efficacy for seasonal allergic rhinitis have been published. The 2 most widely cited of these initial studies are those by Durham and colleagues¹⁹ and Dahl and colleagues.²⁰

- The 2006 study reported by Durham and colleagues¹⁹ was a multinational, multicenter, randomized, double-blind, placebo-controlled study of SLIT in which 855 patients were randomized to 3 Timothy grass tablet dosing regimens or placebo. Seven-hundred ninety patients completed this trial, which used a preseasonal and coseasonal dosing schedule. The highest dose regimen (15 µg major allergen) resulted in a significant reduction of allergy symptoms and medication use. These benefits were seen over the season and the peak season.
- Likewise, Dahl and colleagues²⁰ published a multicenter, multinational, randomized, double-blind, placebo-controlled Timothy grass SLIT trial that included 634 randomized patients (546 completed). This study also showed a significant reduction in allergy symptoms and medication use and a significant increase in well days with SLIT, as compared with placebo.
- In 2010, Durham and colleagues²¹ reported on the long-term effects of Timothy grass SLIT in patients with allergic rhinitis. In a double-blind, randomized, placebo-controlled trial of 257 participants, sustained significant benefit in symptom control and medication use were seen at the 1-year follow-up after 3 years of active SLIT treatment. Further, the sustained benefits were the same as during the active treatment phase.

Similar results have been seen for SLIT efficacy for seasonal allergic rhinitis in the pediatric population, a group in which SLIT is potentially attractive because of its safety, convenience, and avoidance of needles.

- A multicenter, randomized, double-blind, placebo-controlled study published by Bufe and colleagues²² in 2009 included 253 children aged 5 to 16 years with grass pollen allergy. With preseasonal and coseasonal administration of Timothy grass tablets, there were significant reductions in allergic rhinitis symptom and medication scores and a significant reduction in asthma symptoms. Observed immunologic changes were similar to those seen in adults.
- Similarly, Wahn and colleagues²³ showed significant reduction in allergic rhinitis symptoms and medication use in 266 children aged 5 to 17 years with a 5-grass tablet in a multicenter, multinational, randomized, double-blind, placebo-controlled trial.

Based on the availability of well-conducted, randomized, placebo-controlled trials of SLIT efficacy, it is not surprising that meta-analyses have also been undertaken in this realm.

- The most recent Cochrane systematic review and meta-analysis of SLIT efficacy for allergic rhinitis was performed by Radulovic and colleagues in 2010²⁴ and is an update of the highly cited Wilson and colleagues Cochrane review and meta-analysis initially published in 2003.²⁵ This updated analysis pooled 49 randomized controlled trials of SLIT, involving 2333 actively treated and 2256 placebo participants. Using the standard mean difference (SMD) methodology, significant symptom reduction (SMD -0.49, $P < .00001$) and significant reduction in medication requirements (SMD -0.32, $P < .00001$) were noted, favoring SLIT over placebo. A subgroup analysis revealed a benefit for seasonal and perennial allergens as well as a significant benefit for pediatric and adult patients.
- In children, a meta-analysis of SLIT for seasonal allergic rhinitis was published in 2006 by Penagos and colleagues.²⁶ This analysis included 10 randomized double-blind placebo-controlled trials and a total of 484 participants. Significant reduction was seen for allergic rhinitis symptoms (SMD 0.56, $P = .02$) and medication use (SMD 0.76, $P = .03$) with SLIT treatment. Active treatment for greater than 18 months and treatment with pollen extracts showed a benefit in subgroup analyses.

With a plethora of randomized controlled SLIT trials available, meta-analyses have also been published for specific individual antigens. In these meta-analyses, significant benefit has been shown in allergic rhinitis symptom reduction and medication reduction for seasonal grass pollen²⁷ and house dust mite²⁸ SLIT treatment.

Although systematic reviews and meta-analyses are highly regarded as representing the highest levels of evidence, one should remember that many such meta-analyses have some degree of heterogeneity among the trials that are included. On reading any of these systematic reviews or meta-analyses, it is important for the reader to determine how meaningful this heterogeneity is and to what degree it should be considered in the overall interpretation of the study conclusions.

One aspect of SLIT efficacy that is often discussed is the treatment with a single antigen versus multiple antigens. Most controlled SLIT trials are performed with single-antigen therapy (ie, grass pollen, house dust mite, or birch only). This practice occurs for several reasons.

1. Compared with practices in the United States, there is a general tendency in European countries to test and treat with fewer antigens for allergic disease, and most of the available SLIT efficacy studies are performed in European countries.
2. To perform a well-designed clinical trial, it is important to control as many extraneous factors as possible. In this vein, a trial that treats only Timothy grass allergy with SLIT is able to measure Timothy grass pollen counts and correlate patient symptoms over the course of the season without the need to account for overlapping seasonal symptoms from other tree or weed antigens or year-round symptoms from perennial antigens.
3. Designing a clinical trial that incorporates multiple-antigen treatment requires all participants to have a similar antigen reactivity and symptom pattern for multiple antigens, which may lead to substantial problems with study enrollment.

The issues with single- versus multiple-antigen SLIT intuitively make sense when considering randomized placebo-controlled trial design, but translation to clinical practice in the United States is somewhat problematic. In the United States, general immunotherapy practice incorporates testing for a panel of at least 8 to 12 (and often more) common antigens. Treatment vials are then mixed according to the patients' individual pattern of reactivity, which most often incorporates multiple antigens. However, direct translation of single-antigen efficacy studies to multiple-antigen therapy is questioned. Few studies have evaluated the efficacy of SLIT with multiple antigens and even these are often limited to only 2 antigens rather than 10 antigens, which is the mean number included on an immunotherapy prescription in the United States.²⁹

The few SLIT trials that have been performed with multiple antigens show conflicting results. For example, a 2009 US study by Amar and colleagues³⁰ was unable to demonstrate a significant benefit of multiple-antigen SLIT over single-antigen SLIT or placebo. In contrast, in a small open-label controlled study of 58 patients with grass and birch sensitization, Marogna and colleagues³¹ found that patients treated with both grass and birch antigens had significant clinical improvement over those treated with a single antigen or placebo. Based on the current available evidence, treatment with multiple-antigen SLIT clearly needs additional investigation before solid clinical treatment recommendations can be made.

Safety of SLIT

SLIT has an extremely high safety profile. The safety of SLIT, which gives rise to its tendency to be dosed at home rather than in the physician's office, is one of the reasons this modality of allergy immunotherapy is so attractive for working individuals and children.

- Among 60 trials in the 2010 Cochrane systematic review and meta-analysis by Radulovic and colleagues,²⁴ no cases of anaphylaxis occurred and no patient required epinephrine for treatment of systemic reactions. In this meta-analysis, a total of 53 participants discontinued treatment because of adverse reactions (41 out of 824 patients undergoing SLIT and 12 out of 861 placebo patients), with treatment discontinuation for local reactions being the most common.
- In children, Penagos and colleagues²⁶ also reported no lethal or severe reactions in the 2006 meta-analysis of 10 pediatric SLIT studies for allergic rhinitis, with the exception of 3 patients with an onset of severe asthma that was thought to be caused by SLIT overdose.
- In the 2009 study by Bufe and colleagues,²² 6 patients withdrew from the study because of a total of 15 adverse events. Two of these withdrawals were in the

placebo group and 3 in the active group were caused by local reactions without sequelae. There was one withdrawal caused by a serious systemic reaction that was judged as likely related to active treatment: tongue swelling and itching, shortness of breath, and tightness. This event did not require the administration of epinephrine.

- The pediatric SLIT study by Wahn and colleagues,²³ also published in 2009, reported no serious adverse events related to active treatment with the 5-grass pollen tablet, although 9 patients in the active treatment group withdrew from the study because of adverse events.

At this time, there are 11 cases of anaphylaxis reported during SLIT treatment.³² Given available information, Calderon and colleagues³² estimate that more than 1 billion SLIT doses have been taken since the year 2000 and calculate a risk of 1 case of anaphylaxis per 100 million SLIT doses. No deaths have been reported related to SLIT; nonetheless, practitioners prescribing SLIT should be aware of the potential for anaphylaxis with any form of immunotherapy. In reporting these episodes of SLIT-related anaphylaxis, some have speculated on the potential causes for the incitement of such severe reactions³²:

- Prior systemic reaction or intolerance to immunotherapy
- Noncompliance and interruptions in immunotherapy treatment
- Severe or uncontrolled asthma
- High pollen counts
- Use of nonstandardized extracts
- Little to no escalation phase

Many of these possible causes for SLIT anaphylaxis have occurred in other research or clinical situations without leading to anaphylaxis, however. At this time, *the true cause for many of these cases of SLIT anaphylaxis is unknown*. Randomized blinded research is unethical in this realm and, therefore, we remain reliant on case reports and small case series to advise us of SLIT anaphylaxis potential.

SLIT Dosing

The most advantageous SLIT dose has not yet been determined for most antigens. The authors do have evidence to support an optimal SCIT maintenance dose of 5 to 20 μ g of major allergen per injection, which is commonly defined as “the dose of an allergen vaccine inducing a clinically relevant effect in most patients without causing unacceptable side effects.”^{33,34} However, the desired SLIT maintenance dose to achieve an appropriate effect while remaining free of side effects has not been resolved, with the exception of grass pollen extract. As noted, the 2006 large-scale double-blind placebo-controlled trial of Timothy grass tablets by Durham and colleagues¹⁹ identified the 15 μ g dose to be the most efficacious in alleviating symptoms of allergic rhinitis and reducing medication use. Didier and colleagues³⁵ reported the optimum maintenance dose for a 5-grass pollen tablet to be somewhat higher at 25 μ g major allergen per dose. These SLIT per-dose recommendations for grass pollen antigen are similar to the per-dose recommendation for SCIT. However, it should be noted that SLIT maintenance is commonly dosed daily, whereas SCIT maintenance injections are typically dosed monthly.

Aside from grass pollen, maintenance doses for SLIT antigens vary greatly and do not yet have strong supporting evidence. It is clear that SLIT maintenance doses are typically larger than SCIT maintenance doses, with SLIT maintenance doses being reported up to 500 times that of SCIT maintenance doses.³⁶ Because of differing

maintenance dosing scheduled between SLIT (daily) and SCIT (monthly), it is best to compare the median monthly dose. Using this measure, the median monthly SLIT maintenance dose is distinctly higher at approximately 49 times the median monthly SCIT maintenance dose.

BOTTOM LINE: WHAT DOES THE EVIDENCE TELL US?

At this time, there is strong evidence to support certain aspects of allergic rhinitis diagnosis and SLIT treatment of allergic rhinitis. However, evidence is lacking in other aspects of this treatment paradigm.

First, available evidence supports the fact that allergic rhinitis has significant public health and economic impact, with nearly 8% of adults in the United States seeking care for allergic rhinitis and patients with allergic rhinitis spending nearly \$1500 more in health care costs than those without.¹

Secondly, when evaluating patients for possible allergic rhinitis, allergy skin testing is often undertaken in association with a thorough history and physical examination that guides the diagnosis. In proceeding through the allergy skin testing procedure, the practitioner should remain aware that with negative skin prick test results, a subsequent positive intradermal skin test does not correlate well with in vitro or challenge tests and provides little additional information in the diagnosis of allergy, whereas a negative intradermal skin test result has a high negative predictive value.¹⁷

Multiple large-scale single-antigen SLIT efficacy studies have been performed and show significant reduction in allergy symptoms and medication use.^{19,20,22,23} These studies are largely well designed, randomized, double blind, and placebo controlled. In support of the SLIT efficacy evidence from individual randomized controlled trials, several systematic reviews and meta-analyses have also been performed. The evidence supporting SLIT for seasonal and perennial allergic rhinitis, and for adults and pediatric patients, is strong.^{24,26} In addition, the clinical benefits of grass pollen SLIT beyond the active treatment period have been documented²¹ as have appropriate dose ranges for grass pollen SLIT.^{19,35} Less clear, however, is the translation of single-antigen SLIT efficacy results to clinical practice that incorporates multiple-antigen SLIT prescriptions as well as optimal dosing for antigens other than grass pollen. These areas deserve substantial future investigation before there is solid evidence to support clinical treatment decisions.

The safety of SLIT is well documented, with anaphylaxis risks distinctly lower than those historically quoted for SCIT. In addition, no lethal events have been reported related to SLIT. However, SLIT-related anaphylaxis events have been documented in case reports and small case series,³² and we must remain vigilant of the safety concerns with any form of immunotherapy.

CRITICAL POINTS WITH EVIDENCE GRADE

- Allergic rhinitis is a major public health issue with significant health care costs¹ (evidence grade = 2c).
- With negative skin prick test results, intradermal skin tests provide little additional information for overall allergy diagnosis¹⁷ (evidence grade = 4).
- SLIT reduces symptoms and medication use in allergic rhinitis. Subgroup analysis shows a benefit for seasonal and perennial antigens, adults and children, and higher antigen doses (evidence grade = 1a-).
- SLIT has shown a significant benefit for grass pollen and house dust mite antigens (evidence grade = 1a-).

- Recommended maintenance SLIT dosing for grass pollen is 15 to 25 μg major allergen per dose.^{19,35} Dosing for other antigens is not established (evidence grade = 1b).
- Most well-designed controlled SLIT trials have been performed with single-antigen therapy (evidence grade = 1b). Controlled trials of multiple-antigen SLIT are lacking. Direct translation of single-antigen SLIT efficacy studies to multiple-antigen SLIT clinical practice is difficult.
- The safety profile of SLIT for allergic rhinitis remains excellent (evidence grade = 1a-).
- Anaphylaxis has been reported with SLIT (evidence grade = 5).

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