

The role of allergen immunotherapy in the management of allergic rhinitis

Linda Cox, M.D.

ABSTRACT

Purpose: To evaluate the role of allergen immunotherapy (AIT) in the treatment of allergic rhinitis (AR).

Method: Individual studies, systematic reviews, and practice guidelines that included information on sublingual AIT (SLIT) and subcutaneous AIT (SCIT) in the treatment of AR were considered.

Results: AIT via the SLIT or SCIT route has been shown to be effective in treating AR symptoms with resultant improvements in overall quality of life, comorbid illnesses, and medication requirements. Persistent clinical benefits have been demonstrated years after AIT treatment discontinuation. AIT may prevent the progression of AR to asthma. In addition, studies that evaluated the pharmacoeconomics of AR treatment indicate that AIT may be more cost effective than pharmacotherapy. The AIT cost savings are likely underestimated in that few cost comparison studies considered AIT's long-term benefits or preventive effects.

Conclusion: Multiple individual studies and systematic reviews provide strong evidence for the clinical effectiveness of AIT in the treatment of AR. Cost-effectiveness and disease modification are additional advantages of AIT compared with standard drug treatment in the management of AR.

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Allergic rhinitis (AR) is one of the most common pediatric and adult chronic diseases. Poorly controlled AR symptoms can result in impaired sleep and resultant daytime fatigue, which can significantly impact a patient's work or school performance and overall quality of life (QOL). AR can be associated with several comorbid conditions that may further impair QOL and add to the direct and indirect treatment costs. AR has been identified as a risk factor for asthma. In a longitudinal study of 8275 children, AR was associated with a two to sevenfold increased risk of subsequent asthma in preadolescence, adolescence, or adult life.¹ In an international survey of patients and physicians on the management of AR, the three most common comorbidities were asthma, sinusitis, and conjunctivitis, which were reported in 32.7, 49.9, and 36.2% of patients, respectively.² In a birth cohort study that investigated the association of otitis media with other allergic conditions, a significant association was only seen with AR (adjusted odds ratio 3.36; $p = 0.02$).³

AR treatment includes three components: allergen avoidance measures, pharmacotherapy, and allergen immunotherapy (AIT). Each component has benefits, risks, limitations, and costs that should be considered in the context of short-term (during treatment) and long-term (after discontinuation) benefits. Evaluation of AR treatment strategies should also include the impact of the intervention on comorbid conditions and patient QOL. This review focused on the role of AIT in the management of AR. The clinical efficacy, risks, and long-term benefits of AIT were compared with environmental control measures (avoidance) and with pharmacotherapy. The cost-effectiveness of AIT compared with standard drug treatment (SDT) was also discussed in this review.

AR Prevalence, Underestimation and Costs

AR affects ~500 million people worldwide, with a higher incidence in westernized countries.⁴ It is estimated that AR affects ~113 million people in Europe⁵ and 30–60 million people in the United States.^{6,7}

These approximations likely underestimate the true incidence of AR. Studies that compared clinically confirmed AR prevalence by using questionnaire surveys indicate that AR is frequently underdiagnosed.^{8,9} In addition to being underdiagnosed, these studies indicate that AR is often undertreated and/or poorly controlled according to guideline recommendation.^{10–12} One study that aimed at investigating the prevalence of AR undertreatment found that 83% of patients with moderate-to-severe rhinitis were undertreated according to guideline recommendations.¹² Other survey studies indicate that many patients with AR remain untreated or self-treat with over-the-counter (OTC) medications. One telephone survey study found that only 50% of respondents with AR received an AR prescription.¹¹ In an Internet and telephone survey, 52.6% of respondents with rhinitis admitted to not seeing a medical professional in the past year. In this survey, medication costs were cited as the reason for not using allergy medications in 40.2% of the respondents on “homeopathic” treatment or those on “no treatment.”¹⁰

The estimated direct cost of AR in 2005 was \$11.5 billion according to the Medical Expenditure Panel Survey, a longitudinal survey that collects detailed information on health care utilization and expenditures in the United States.¹³ At the time, prescription medications accounted for the majority of the treatment costs (59%). The costs of OTC medications were not included in this survey but were estimated to be \$1.2 billion to \$1.7 billion in 2008.¹⁴ Current OTC medications likely represent a significantly higher percentage of AR management costs because many effective medications have “moved” from prescription to OTC status.

The AR indirect costs can be significantly higher than the direct costs.^{15,16} In addition to OTC medications, indirect costs include treatment of comorbid illnesses as well as lost work productivity. In a survey of U.S. employees, the total annual cost of lost productivity attributable to AR was significantly higher than the cost for any other condition assessed, including diabetes and coronary heart disease.¹⁷

AR Management

Environmental Controls and Pharmacotherapy. The “ideal” management approach to AR would be complete avoidance of the offending allergen(s). However, this is rarely achievable, and there are limited data that support the efficacy of environmental control interventions. In addition, there are limited data that any single environmental control measure will result in improved AR symptomatology or other AR-related outcomes. A Cochrane Systematic Review of randomized controlled trials that compared the effectiveness of several environmental control measures in house-dust mite (HDM) perennial AR

From the Department of Medicine, Nova Southeastern University, Davie, Florida
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L. Cox has received honoraria from Greer and Genentech, and serves on the Safety Data Monitoring Committee of Circassia and BioMay

Address correspondence to Linda Cox, M.D., 5333 North Dixie Highway, Ft. Lauderdale, FL 33334

E-mail address: lindaswolffcox@msn.com

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found that isolated use of HDM impermeable bedding did not appear to be effective.¹⁸ The investigators concluded that interventions that significantly reduced HDM load “may offer some benefit in reducing rhinitis symptoms,” but cautioned that the findings from these studies “need to be interpreted with care because of their methodological limitations.”¹⁸ In an earlier Cochrane Systematic Review that evaluated the effectiveness of environmental control measures in HDM asthma, there were no significant differences between the placebo and the intervention groups in asthma symptoms, medication use, or peak expiratory flow rate.¹⁹ The investigators concluded, “chemical and physical methods aimed at reducing exposure to house dust mite allergens cannot be recommended.”¹⁹

Similarly, there is little evidence that indicates that cat and/or dog removal from the household will improve AR or asthma symptoms. This “failure to improve” after cat and/or dog removal may be due to several factors, including persistence of airborne animal dander long after removal²⁰ and the somewhat ubiquitous nature of animal dander.²¹

One study demonstrated significant reductions in cockroach allergen levels after 6 months of a combined intervention program, which included pest management, professional cleaning, and patient education.²² Decreased exposure to indoor allergens with an individualized, home-based, comprehensive environmental intervention program correlated with reduced complications of asthma.²³ A practice guideline series on “allergen environment assessment and exposure control” recommends a multifaceted approach that uses a combination of methods to reduce indoor allergen levels.^{24–26} Restricting all activities to indoors would be the avoidance strategy for outdoor allergens, but this would counter the goal of normalizing the lifestyle of the patient with AR or asthma.

In summary, although allergen avoidance would be the optimal treatment for AR, the evidence that supports this approach is very sparse. It is likely that a combination of interventions sustained over time would be required to achieve any significant degree of clinical improvement.

There are several classes of effective allergy medication that treat different AR symptoms. The two most commonly prescribed AR medication classes, nasal corticosteroids and antihistamine pills, have several products available as OTC medications. OTC status may increase direct access to these medications, but this will also shift more of AR treatment costs to the patient. OTC medication may lessen the role of physicians and other health care professionals in AR management oversight, which may have several consequences, *e.g.*, delay in diagnosis and treatment of a frequent comorbid condition, asthma. Physician guidance may also improve adherence to therapy. Although, some patients may find intermittent allergy medication use effective, in general, effective pharmacotherapy requires regular use of medications. Also, allergy medications provide relief of symptoms during use but provide no sustained benefits after discontinuation.^{27,28}

AIT. Unlike pharmacotherapy, AIT can provide symptomatic improvement that may continue for years after therapy discontinuation.^{29,30} There is ample evidence that AIT has a disease-modifying effect through favorable immunologic changes that induce sustained tolerance. The immunologic changes associated with AIT include changes in allergen-specific T- and B-cell responses, an increase in allergen-specific immunoglobulin G₄ and suppression of allergen-specific immunoglobulin E. Reductions in mast cell, eosinophil, and basophil activation as well as end-organ sensitivity (*e.g.*, bronchial, nasal, or conjunctival) are immunologic outcomes associated with AIT. The immunologic changes take place at different time points in the AIT course. Mast cell and basophil desensitization occurs early in the treatment course, followed by induction of a generation of T- and B-regulatory cells that produce interleukin-10 and other cytokines and results in suppression of effector T-helper 1 and T-helper 2 cells.³¹ These immunologic changes can result in disease modification, which can alter the progression of the allergic disease; *e.g.*, prevent AR

progression to asthma and/or development of new allergen sensitizations.^{30,32–34}

The two most commonly prescribed routes for AIT are subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). Due to the immunologic milieu of the allergen presentation site (sublingual versus subcutaneous), the two routes differ in initial allergen uptake and processing. However, once the allergen is systemically absorbed, the immunologic responses appear to be similar.³⁵ The clinical efficacy and safety of both routes in the treatment of AR have been established in clinical trials, systematic reviews, and meta-analyses.^{36–39} The two routes appear to have comparable efficacy, with most double-blind, placebo-controlled (DBPC) trials that demonstrated 20–30% greater improvement in the combined symptom-medication score compared with placebo. Greater magnitudes of improvements have been seen in more symptomatic patient populations.^{40,41}

The first DBPC trial that demonstrated SLIT efficacy was conducted nearly 75 years after the first report that documented SCIT efficacy in the treatment of AR.⁴² Subsequently, the use of SLIT has increased significantly, such that it is prescribed at least as frequently as SCIT according to allergen extract manufacturers’ sales data and expert opinion.⁴³ In some geographic locations, such as France and Italy, it is the predominant route for new AIT prescriptions.⁴⁴ To date, the AIT route most prescribed in the United States is SCIT. This is likely because there had been no U.S. Food and Drug Administration (FDA) approved sublingual AIT formulations until 2014. Despite the absence of an FDA-approved SLIT formulations, there was a significant increase in the percentage of U.S. physicians who prescribed SLIT in 2011 (11.4%) compared with 2007 (5.9%, *p* < 0.01).^{45,46} In early 2014, the FDA approved three sublingual tablets for pollen-induced AR and/or rhinoconjunctivitis: timothy (GRASTEK; Merck & Co.),⁴⁷ 5-grass (ORALAIR; Stallergenes, Anthony, France),⁴⁸ and short ragweed (RAGWITEK; Merck & Co, Kenilworth, NJ).⁴⁹

The specific indication in the prescribing information (PI) for the three FDA-approved SLIT tablet products is treatment of ragweed or grass “pollen-induced AR with or without conjunctivitis confirmed by a positive skin test result or *in vitro* testing result for pollen-specific immunoglobulin E antibodies.”^{47–49} The majority of SLIT studies were conducted in patients with AR and/or rhinoconjunctivitis, but the pivotal trials for SLIT tablets included patients with controlled asthma. Neither the United States nor European Medicines Agency licensed SLIT PI includes asthma alone as a clinical indication. The U.S. licensed allergen extract solutions PIs list similar indications, although some include asthma, along with AR and/or rhinoconjunctivitis.⁵⁰ According to U.S. practice guidelines, the primary indications for SCIT are AR and/or rhinoconjunctivitis and asthma.⁵¹

There is emerging evidence that AIT is effective in patients with atopic dermatitis and with aeroallergen sensitivities.^{52,53} Investigations with oral AIT and SLIT for food allergy demonstrated some promising results in terms of desensitization during treatment.^{54,55} However, sustained tolerance after discontinuation has only been demonstrated in a minority of patients.⁵⁶ Many questions remain to be answered regarding long-term tolerance after discontinuation.^{57,58} At present, food AIT is considered investigational.

SLIT and SCIT Safety: How Do They Compare?

Both AIT routes can be associated with local or systemic adverse effects. Local reactions (LR) are fairly common with both routes and have been reported in >70% of patients on SCIT⁵⁹ and those on SLIT.⁶⁰ The LR clinical features vary with the route. SCIT LRs present as erythema, pruritus, and swelling at the injection site. SLIT LRs usually manifest as oromucosal pruritus and/or swelling but sometimes manifest as gastrointestinal symptoms. Most SLIT LRs occur shortly after treatment initiation and disappear within a few days to weeks without treatment or dose modification. However, some local reactions can be severe enough to cause discontinuation of treatment.

SCIT systemic reactions (SR) can range in severity from mild to

life-threatening anaphylaxis. The incidence of SCIT SRs vary, depending on several factors, including induction schedule, premedication, and the degree of patient allergen hypersensitivity. The SR rate with nonaccelerated SCIT induction schedules is ~0.1 to 0.2% of injections and 2 to 5% of patients in most studies and surveys.^{61,62} In a longitudinal AIT safety surveillance study that included more than 23.3 million injection visits, the reported SR rate was consistently 0.1% of injection visits.⁶² Almost all of the SRs (97%) were classified as mild or moderate in severity.^{62,63} The incidence of severe SR was ~1 in 1 million injections, which is similar to previous surveys.⁶⁴ There were two confirmed SCIT fatalities in this survey. In previous surveys, there were three to four SCIT-related fatalities a year, which translated into a fatality rate of 1 in 2–2.5 million I SCIT injections.⁶⁵ Identified risk factors for SCIT SRs include symptomatic asthma, previous SCIT SR, and a high degree of skin test reactivity.⁵¹

In contrast, SLIT allergic SRs are uncommon. In a comprehensive review of 104 SLIT studies published through October of 2005, the SLIT SR rate was 0.056% of doses administered.⁶⁰ To date, there have been no confirmed reports of SLIT-related fatalities. However, SLIT reactions of a severity to be categorized as anaphylaxis have been reported.⁶⁶

There are advantages and disadvantages of both routes. SLIT appears to have a clear advantage over SCIT in terms of treatment safety, which allows for home administration. In contrast, because of the risk of life-threatening anaphylaxis, practice guidelines recommend that SCIT be administered in a medically supervised setting with a 30-minute postinjection observation period.^{51,67} A SCIT treatment regimen may involve frequent visits during the initial up dosing phase, all of which requires patient time and travel to the medical clinic. This is followed by a maintenance phase, during which the injections are usually administered at monthly intervals. In contrast, SLIT is administered in the home setting, but the maintenance dosing frequency is usually daily. Thus, SLIT appears to have the advantage of greater patient convenience. Despite their very different patient time and/or travel requirements, both routes were shown to have equally poor adherence.⁶⁸ This is likely because both routes require a multiyear treatment course (usually 3–5 years). The AIT adherence rate is similar to the poor adherence reported with long-term pharmacotherapy of many diseases.⁶⁹ Interventions such as more-frequent clinic monitoring, telecommunication reminders, and educational programs may improve AIT adherence.^{69–71}

In addition to efficacy and safety, a number of factors will determine the AIT route selected, including availability of a regulatory body–approved allergen extract (e.g., FDA approved), patient's clinical allergy sensitization status (mono- versus polysensitized), treatment costs and/or insurance coverage status, and patient or physician preference.

To date, there continues to be no FDA-approved formulation for SLIT extract solution. However, FDA approval of a SLIT extract solution may be forthcoming. A large patient population study that compared a U.S. licensed ragweed extract ($N = 218$) with placebo ($N = 211$) demonstrated significant clinical efficacy, with no significant adverse events.⁷² If these findings are confirmed in a subsequent study, then the extract manufacturer may seek FDA approval for a licensed SLIT ragweed extract solution.

AIT in AR Management

How Does It Compare with SDT in Terms of Clinical Efficacy? In contrast to AR pharmacotherapy trials, virtually all AIT trials allow for rescue medications use. In essence, the placebo group in AIT clinical trials represents a pharmacotherapy only group. Thus, there are no randomized placebo-controlled trials that compared AIT against a truly “untreated” control group. Despite the allowance for rescue allergy medications, virtually all of the systematic reviews and meta-analyses of SCIT and SLIT for AR and asthma demonstrated significant clinical efficacy over the placebo group, in which the subjects were allowed allergy medications.³⁶ A review of meta-anal-

yses that included five or more randomized DBPC trials of SCIT or SDT for seasonal AR, provided indirect evidence that SCIT was at least as “potent” as SDT in controlling AR symptoms in the first treatment year.⁷³ There was a significantly greater improvement in nasal symptom scores with SCIT (relative clinical impact [RCI], $-34.7 \pm 6.8\%$), compared with three different medication classes: nasal corticosteroids, antihistamine, and a leukotriene antagonist, ($p < 0.0001$) as mometasone (RCI, $-31.7 \pm 16.7\%$), montelukast (RCI, $-6.3 \pm 3.0\%$), and desloratadine (RCI, $-12.0 \pm 5.1\%$).

Pharmacoeconomics. In evaluating the pharmacoeconomics of the different AR management options, consideration needs to be given to the long-term benefits of AIT, which may persist for years or decades after treatment completion. The AIT treatment costs can be offset by the reduction in the need for long-term symptomatic drug treatment and disease-modifying effect of AIT, which can prevent the development of asthma or new allergen sensitivities. These combined outcomes may translate the clinical efficacy of AIT into a significant economic benefit. This economic benefit has been confirmed in a number of studies that compared SCIT and/or SLIT with SDT from several different perspectives, including societal, health care system, patient, and third-party payers.⁷⁴ The analysis designs used in these studies varied and included review of retrospective claims data and theoretical economic modeling. The outcome assessed included “real-life” total health care costs to theoretical quality-adjusted life year gained or the number of asthma cases prevented. In some studies, cost-effectiveness was based on the presumption of persistent efficacy for years after discontinuation or prevention of asthma. There was some variability across the studies in the AIT cost-effective or break-even time point. In a 6-year prospective study that compared a 3-year course of SCIT with SDT, the cost savings became significant in the third treatment year.⁷⁵ AIT cost savings reached 80% in the fourth year and were maintained through the 3 posttreatment years. In some studies, the cost-effective “time point” was reached several years after discontinuation, which likely reflects the time required for the sustained benefits of AIT to outweigh the AIT treatment costs.⁷⁴

Two systematic reviews that evaluated the cost-effectiveness of SLIT and SCIT found evidence that favored both over SDT. One systematic review that identified 14 economic evaluations published through April 2011, concluded that both SCIT and SLIT may become cost effective compared with SDT at ~6 years after beginning treatment.⁷⁶ The review found limited evidence that indicated that SCIT may be more beneficial and less costly than SLIT, but the investigators noted the challenges in comparing and combining results across studies that used different outcome measures and encouraged further research to “establish the comparative effectiveness of SCIT compared with SLIT and to provide more robust cost-effectiveness estimates.”⁷⁶ All of the studies in this systematic review used a single allergen.

The other systematic review identified 24 studies that reported health economic outcomes associated with AIT that compared SLIT and/or SCIT with SDT or SCIT versus SLIT.⁷⁷ The review found that 23 of the 24 comparative cost studies provided “compelling evidence for the cost savings of AIT.”⁷⁷ The review found that, in four of the six studies that compared SLIT and SCIT cost outcomes, the cost-savings favored SLIT. With the exception of three Florida Medicaid retrospective claims analyses studies; all of these studies used single-allergen AIT.^{78–80}

Unmet Needs. There are a number of unmet needs regarding SLIT and SCIT.³⁶ Some unmet needs are more pertinent to one route, but, in general, they apply to both:

- **Multiallergen AIT.** There are limited data on the effective of multiallergen AIT with either route.⁸¹ Almost all of the SCIT and SLIT randomized-controlled DBPC trials used single allergens.⁸² Further studies are needed to determine the efficacy of multiallergen SCIT and SLIT.⁸³

- **Optimal up dosing and maintenance regimen.** Further research is needed to determine optimal dosing regimen for both routes.
- **SCIT.** The conventional up dosing schedule for SCIT involves a single-dose increase per administration visit. Accelerated schedules, *e.g.*, cluster and rush, reduce the number of injection visits by administering multiple dose increases each visit, but they may be associated with a higher risk of SR.⁸⁴ The optimal maintenance dosing frequency has not been studied in any controlled trials.
- **SLIT.** Many trials used no up dosing schedule and began treatment at the maintenance dose. No up dosing schedules appear to have comparative safety as multi-week up dosing SLIT protocols. A daily dosing regimen was used in the most recent clinical trials but comparative studies with less frequent dosing regimens are lacking. Unmet needs more pertinent to SLIT include when to initiate treatment in terms of the allergy season and whether to treat year round or pre-coseasonal.
- **Gaps in scheduled treatment.** The unmet needs for the two routes differ in terms of addressing gaps in treatment:
 - **SCIT.** Is a dose reduction needed if there is a gap in treatment? If so, how much of a dose reduction is needed after how long of a gap in treatment?
 - **SLIT.** How many daily doses can a patient miss before an intervention is recommended, such as contacting the health care professional?
- **Effective allergen dose.** There have been very few SCIT or SLIT allergen dose-response studies. Further research is needed to determine the effective dose for many allergens.
- **Optimal duration of AIT.** The optimal treatment duration for both routes has been suggested to be 3 years, but there are limited data to support this recommendation.^{29,85} The optimal duration may vary, depending on allergen seasonal versus perennial and infrequent versus frequent intermittent exposure.⁸⁶

The FDA PI of the approved SLIT tablets provides information and guidance on some of these issues. The Allergen Immunotherapy Practice Parameter also provides some consensus-based guidance on some of the unmet needs identified for SCIT.⁵¹

CONCLUSION

AIT is a well-established proven effective treatment for AR. It is unique in that it treats both AR symptoms and the underlying cause by inducing immunologic changes that produce allergen-specific immune tolerance. In addition to improvement in AR symptoms and medication requirements, AIT has been shown to improve overall QOL. The two most commonly prescribed AIT routes, SCIT and SLIT, have demonstrated comparable clinical efficacy. The safety profile of SLIT is superior to SCIT, but both have been shown to have fairly poor adherence in “real-life” studies. The cost-effectiveness of both SCIT and SLIT compared with SDT has been demonstrated in a number of studies and two systematic reviews. There is no conclusive evidence that one route is more cost effective or clinically effective. More research using standardized outcomes and reporting measures is needed to establish the comparative effectiveness of SCIT and SLIT as well as to assess the long-term cost-effectiveness of both AIT routes in terms of disease control and modification.

Key Points:

- AR is one the most common chronic conditions worldwide. It can require years of symptomatic treatment.
- There are considerable direct and indirect consequences and costs of poorly controlled AR.
- The clinical efficacy of AIT in AR management appears to be at least equivalent if not superior to pharmacotherapy.

- AIT results in immunologic changes that can induce long-term allergen-specific tolerance.
- In contrast to pharmacotherapy, AIT can provide long-term clinical benefits after discontinuation, which can translate into significant cost savings.
- AIT has been shown to prevent the progression of AR to asthma and the development of new allergen sensitivities.

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