



Cost-effective Analysis of Subcutaneous vs Sublingual Immunotherapy From the Payor's Perspective

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Abstract

Objective. Compare the cost-effectiveness of subcutaneous immunotherapy (SCIT) and aqueous sublingual immunotherapy (SLIT) as treatment modalities for adult patients with allergic rhinitis and conjunctivitis who undergo testing and qualify for allergen immunotherapy (AIT).

Methods. A systematic review was performed to identify key statistics for analysis, including the compliance and efficacy rates for each treatment. The body of literature on this topic is highly heterogeneous, so ranges were obtained and assumptions stated clearly where they were made. Charges were derived from average commercial payor charges from a single hospital institution. A hypothetical 100 patients are examined for the study.

Results. A cost-effectiveness sensitivity analysis was then performed using a decision tree model to compare the modalities. A sensitivity and threshold analysis was then performed to assess the strength of recommendations after identifying results at baseline.

Discussion. Assuming an 80% compliance rate with allergen immunotherapy and an estimated efficacy (assumed to be clinically significant improvement in symptoms) of 70% for SLIT and 80% for SCIT, at the 12-month mark, the baseline total cost to the payor of SLIT per successful treatment outcome is \$1196 while the charge of SCIT per successful treatment outcome is \$2691. Our analysis favors SLIT as the more cost-effective modality per successful outcome.

Implications for Practice. When compared to SCIT, SLIT is economically favorable and should be considered the financially conscious option for patients with >40% adherence to therapy.

Keywords

SCIT, SLIT, cost-effectiveness, systematic review, allergen, immunotherapy, allergic, rhinitis, conjunctivitis, PS/QI

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Implications for Practice

An estimated 20% to 40% of the US population has allergic rhinitis.¹ Medical management of this prevalent disease includes allergen avoidance, pharmacotherapy, and immunotherapy. Allergen immunotherapy is typically reserved for patients whose asthma and allergic rhinitis symptoms are not adequately controlled by medication and environmental controls, for patients who are intolerant of pharmacotherapy, or for patients who do not comply with chronic medication regimens.² There are 2 major forms of allergen immunotherapy clinically used in the United States: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT).

The efficacy of both SLIT and SCIT modalities has been well established in the literature, although most studies for both modalities use single or pauci antigen therapy. SCIT has been illustrated as an effective treatment for allergic rhinitis in adults and asthma in adults and children.^{3–5} There is strong evidence that SCIT improves rhinoconjunctivitis-specific quality of life; it has been shown to reduce rhinitis, asthma, and conjunctivitis symptoms, as well as asthma and rhinoconjunctivitis medication use. The strength of evidence is high that SLIT reduces asthma symptoms, and the strength of evidence is moderate that SLIT reduces rhinitis/rhinoconjunctivitis symptoms, symptom scores, and conjunctivitis symptoms, as well as improves allergy-specific quality of life.⁶ SLIT efficacy has been studied for allergic rhinitis in adults and children, asthma in adults and children, and conjunctivitis, house dust mites, and grass allergens in adults and children.^{5,7} Meta-analyses suggest

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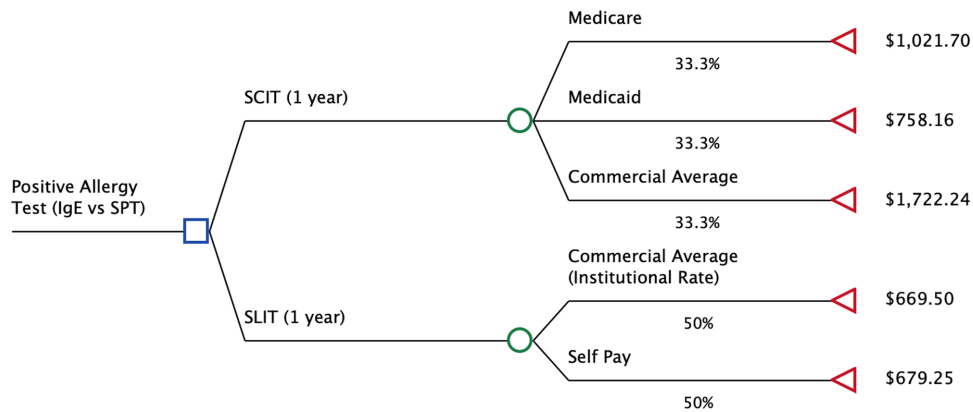


Figure 1. Cost-effective analysis of subcutaneous vs sublingual immunotherapy from the payor's perspective. A decision tree illustrating the fundamental components of this cost-effective analysis. Squares represent decisions (binary), circles represent chance (probabilities), and the triangles represent terminal payoffs. SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SPT, skin prick test.

that the size of treatment effect for allergen immunotherapy and pharmacotherapy for allergic rhinitis is comparable.³

Broadly addressing the current literature, there are a limited number of randomized, head-to-head comparison studies for the relative clinical efficacy of SCIT and SLIT. These have suggested greater clinical and immunologic responses from SCIT. There have been a broad range of effective doses and considerable variation in design and power of these studies. In 2013, Chelladurai et al⁸ published moderate-grade evidence favoring SCIT in symptom score reduction and no difference in treatment effectiveness between SCIT and SLIT with respect to medication scores. The same year, Kim et al⁹ found low-grade evidence favoring SCIT with respect to both symptom and medication scores.

Indirect study comparisons of SLIT vs SCIT have been inconsistent with significant clinical and methodological heterogeneity. In several studies comparing each modality to placebo, meta-analysis suggests that SCIT has greater efficacy.¹⁰ One such indirect study in 2013 by Dretzke et al¹¹ favored SCIT over SLIT with respect to both symptom and medication score reductions. The overall consensus is that the body of evidence consistently provides moderate to high support for the efficacy and safety of both SCIT and SLIT for treatment of allergic rhinitis and asthma. However, the definitive clinical superiority of one modality over the other remains unknown.⁷ Internationally, direct and indirect examinations of SCIT and SLIT therapies have found variations in terms of the more clinically or cost-effective option.^{10,12} The variations may be related to study heterogeneity or the variation in country-specific coverage of these treatment modalities. These studies have, for SLIT, primarily focused on tablets including Oralair (ALK-Abelló, Inc; freeze-dried allergen extracts of 5 grasses) and Grazax (ALK-Abelló, Inc; standardized extract of allergen from timothy grass, *Phleum pratense*).¹³

The US Food and Drug Administration (FDA) has approved the use of allergen extracts for SCIT for treatment of seasonal and perennial allergic rhinitis and asthma, resulting in most insurance companies providing coverage for this treatment, although they may limit the number of injections they will cover. Some insurance companies will limit doses of

allergenic extracts per calendar year. At this time, most insurance companies do not cover charges for sublingual immunotherapy as it is labeled by the FDA as “off-label” use; however, at the authors’ institution, there is an unusual situation where benefits contracts have been negotiated in advance where payors will knowingly cover charges for SLIT. Given the unique situation of payor coverage of both SLIT and SCIT, this study aims to evaluate the cost-effectiveness from the payor perspective for patients undergoing SCIT vs SLIT treatment. Of important note, the insurance payor patterns described in this study are specific to the US health care system omitting the wide variations in practice patterns and payment plans observed in other countries.

Methods

A decision tree was thoughtfully constructed following recently published technique guidelines^{14,15} to study the cost-effectiveness of the 2 modalities in a population of 100 theoretical patients with clinical diagnoses of allergic rhinitis (**Figure 1**). The purpose of this decision model was to address the mean objectives of demonstrating the cost-effectiveness of SLIT from the payor’s perspective and promoting widespread insurance coverage for this service. The tree is designed to represent cost of each arm of immunotherapy under the stipulations outlined in **Table 1**. The decision tree was constructed via TreeAge Pro Healthcare Version 2021 R2.0.

The hypothetical patients had positive allergy test results, whether in vitro specific IgE testing or skin prick testing, with appropriate controls and skin prick results considered positive if they were 3 mm or greater than the negative control. The decision would then be made to treat only the positive test allergens that correlated with patient symptoms. One treatment vial was created per 10 weeks of SCIT treatment, with SCIT patients receiving 5 vials per year for their therapy. In contrast, for SLIT patients, there would be 3 vials mixed annually. This model was produced and manipulated to determine the relative charge per successful outcome of SCIT vs aqueous SLIT. Several assumptions were made in the construction of this decision tree, which are highlighted in **Table 1**. The values of the variables in the model demonstrate

Table 1. Baseline Case Scenario Assumptions for Decision Tree Construction.

- 100 hypothetical patients with complaints fitting AAO-HNS guidelines for diagnosis with allergic rhinitis
- Adherence to treatment defined as continued enrollment in therapy for SCIT and daily administration of SLIT at the 12-month mark of treatment
- Nonadherent patients at the 12-month mark are not considered successful treatment outcomes
- Effectiveness of sublingual and subcutaneous immunotherapy, ranges estimated based on breadth of literature. Effective or successful treatment defined as clinical improvement in symptoms after 12 months of treatment
- Charges of 1 year of sublingual immunotherapy vs subcutaneous immunotherapy based on charges to the insurance payer, obtained from a single institution

Abbreviations: AAO-HNS, American Academy of Otolaryngology–Head and Neck Surgery; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

Table 2. Detailed Breakdown of the Values Used to Determine Cost in US Dollars for Each Leg of Treatment and the Absolute Cost Difference Between the Commercial Average of SCIT vs SLIT.

Characteristic	SCIT			SLIT			
	Medicare	Medicaid	CA	Medicare	Medicaid	CA	Self-pay
Reimbursement							
Per 10-dose vial	118.40	68.50	175.60	0	0	206.00	209.00
Vial test	7.24	4.23	4.92	—	—	—	—
Per shot visit	7.81	7.73	15.56	—	—	—	—
Reimbursement per unit							
Actual dose per vial	11.84	6.85	17.56	—	—	12.88	13.06
Per shot (1-shot assumption)	7.81	7.73	15.56	—	—	—	—
Annual (52 doses)							
Vial	615.58	356.20	913.12	—	—	669.50	679.25
Shots	406.12	401.96	809.12	—	—	—	—
Total	1021.70	758.16	1722.24	—	—	669.50	679.25
Absolute cost difference	1052.74						

Abbreviations: AAO-HNS, American Academy of Otolaryngology–Head and Neck Surgery; CA, commercial average; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; —, Data unavailable.

a range obtained from results of meta-analyses, as well as individual randomized controlled trials, and is reflected in **Table 2**.^{13,16-19} The range for patient compliance from 10% to 90% was chosen to apply the scenario to target a wide range of potential situations and to appropriately mirror the wide variation of patient compliance between practices and the reported data. Institutional review board approval was not indicated given the hypothetical nature of the study design and analysis.

The hypothetical patients were set forth as qualifying patients with symptoms of allergic rhinitis incompletely controlled by 1 or more medications with positive allergy testing who wished to pursue immunotherapy. Sublingual and subcutaneous immunotherapy modalities were compared for this population, with varying compliance rates and effectiveness for each. The literature reports a range of compliance and effectiveness rates; therefore, we similarly used a range of values to most closely examine the cost-effectiveness and maximize generalizability. The charges to the payor for the sublingual and subcutaneous therapies were obtained from a single institution with a contractual agreement for the payment of either SCIT or SLIT across a single year of

immunotherapy—these charge values were \$1722.24 for SCIT and \$669.50 for SLIT.

The “payor” refers to the health insurance company. Therefore, the charges used are the charges to insurance companies and the contracted rates (at a single institution). The SCIT charges include the *Current Procedural Terminology (CPT)* 95165 code, as well as the 95115 and 95117 (shot) codes. Conversely, there is no designated *CPT* code for aqueous SLIT, and while some practices may bill the unlisted code (95199), this is not recommended. SLIT charges at this institution, which mimicked those in this study, include mixing the vial and administration of the first dose in the office. Neither the estimated SCIT or SLIT charges in this study include physician follow-up visits.

Results

The results of the analysis are highlighted in **Table 3**, which illustrates that for an assumed 80% efficacy of SCIT compared to 70% efficacy for SLIT, at all adherence rates, SLIT is the more cost-effective option per successful outcome to the payor. SCIT only becomes the more cost-effective option if, for instance, adherence rate is <40% to SLIT and the patient

Table 3. Parameters Used in Decision Tree Analysis.

Parameter	Baseline value	Range	References
Charge of SCIT to payer, per 12 months of therapy	1722.24	NA	NA
Charge of SLIT to payer, per 12 months of therapy	669.50	NA	NA
Adherence to SCIT	80	10-90	9
Adherence to SLIT	80	10-90	9
Effectiveness of SCIT	80	60-90	11, 12, 13
Effectiveness of SLIT	70	60-90	14, 15

Abbreviations: NA, Not applicable; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

is >90% adherent to the SCIT treatment plan. When comparing head-to-head 80% adherence to either therapy, for a range of efficacy levels (60%-90% effective for each, as these values vary in the literature), SLIT is the more cost-effective modality.

The results were relatively consistent despite changes in efficacy and compliance rates, within clinical reason.

Discussion

Several studies evaluate the adherence to SLIT vs SCIT. In 2005, Pajno et al²⁰ published the results of a prospective study (performed from 1998 to 2003) that found significantly more patients were treated with SLIT than SCIT, and 22% of SLIT patients discontinued treatment prematurely compared to 11% of SCIT patients who did so. However, Hsu and Reisacher¹⁶ in 2012 retrospectively examined patients in the United States receiving immunotherapy (IT) from 2007 to 2010 and found that 45% of SLIT patients prematurely discontinued therapy in comparison to 41% of SCIT patients. In 2013, a retrospective analysis examined pharmacy claims of 6486 Dutch adults who received SCIT or SLIT and completed 3 years of treatment—by this measure, 93% of SLIT patients had discontinued therapy prematurely, compared to 77% of SCIT patients who did so as well.¹⁷ A 2016 study published noncompliance rates of 11% to 50% for SCIT and 3% to 25% for SLIT.¹⁸

There is a range of values in the literature for SCIT efficacy. Klimek et al¹⁹ performed a randomized double-blind placebo-controlled (RDBPCT) trial for SCIT in allergic rhinitis, which revealed a reduction in symptoms of 34% ($P = .004$) and 40% reduction in medication use (.004). Meadows et al,⁵ in 2013, performed a systematic review revealing a standardized mean difference (SMD) of -0.65 favoring SCIT. Another RDBPCT in 2012 by Rajakulasingam²¹ revealed improvement from baseline year in symptoms for 65% of the active arm vs 35% in placebo. With regard to SLIT efficacy, there is a similar range of values, although the general consensus is that SCIT may be more effective than SLIT.²²

The charges of SCIT and SLIT were previously compared in 2012 by Seiberling et al,²³ who evaluated a total of 9 insurance groups, including 8 preferred provider organizations (PPOs) and Medicare for the charges to the patients. Their evaluated charges included coverage for injections, vial fees, weekly copays, and deductibles. They found that the charge

for SCIT varied significantly depending on insurance plan, and the charges for SLIT varied between clinical practices. SLIT was overall more expensive to patients due to lack of insurance coverage, but indirect costs associated with SCIT made plans with less than 80% coverage or high-weekly copays more expensive and closer in cost to SLIT than anticipated.

One international study examining SCIT vs SLIT cost-effectiveness in Austria, Spain, and Switzerland patient populations determined that SCIT was superior to SLIT in terms of quality-adjusted life years and costs. The model in this study is specific to the health care systems in these aforementioned countries, in contrast to the model that currently exists in the United States. In this study, SCIT was described as the modality with lower drug costs and slightly higher patient compliance.¹² Another study, published from Canada, indirectly compared SLIT to SCIT, with the SLIT options including Oralair and Grazax. This study included a systematic review for double-blind placebo-controlled randomized trials involving Oralair, Grazax, or SCIT for grass-induced seasonal allergic rhinitis, specifically. Oralair was found to be associated with cost savings in comparison to year-round SCIT (\$2471), seasonal SCIT (\$948), and Grazax (\$1168) in a single year of therapy.¹³

Given that this study evaluates the charges to the insurance payor rather than the patient, indirect costs of immunotherapy such as travel cost or lost productivity—which affect the patient rather than payor—were not considered. Generally, higher costs would be anticipated for the SCIT patient population. For sublingual and subcutaneous immunotherapy, treatment is recommended for a period of 3 to 5 years. The fixed annual costs of SCIT and SLIT used in this study were taken from the charges to a payor seen at a single institution, calculated from the average contractual rates across a 12-month period of time. The unique circumstance surrounding the contractual rate offered at this institution may not represent the general populous, but it may serve as a benchmark for future efforts in promoting widespread coverage of this meaningful service. Furthermore, recent studies estimate that despite variable pricing structure, the average yearly cost for SLIT is \$500 to \$1200 for vials containing <10 antigens for most practices.²⁴ This estimates an average yearly cost of ~\$850, which is reasonably comparable to this institution's contractual rate of \$669.50. Ideally, all patients would receive the

same number of doses in a calendar year. However, this study is based on 100 hypothetical patients with varying compliance rates, while, in reality, some patients may require more than 1 vial for treatment (whether SCIT or SLIT modality) either due to the number of antigens being treated or lack of compatibility between antigens. This hypothetical study is limited to single vials. Each vial is mixed with 10 doses, which does not vary with the number of antigens included; the number of doses per vial is always the same for aqueous sublingual therapy. For SCIT, each patient generally requires 5 to 6 vials mixed per year of treatment, while for SLIT, most patients require 3 vials per year. Ultimately, many patients continue with therapy for more than 1 year.

Although SCIT is a more effective therapy, our analysis favors SLIT as the more cost-effective treatment because it has a lower cost per successful outcome. This holds true for a wide range of therapy compliance levels. From an insurance payor standpoint, SLIT is a favorable option for first-line treatment when able to emulate our cost structure. Assuming 80% adherence to allergen immunotherapy and 70% efficacy for SLIT vs 80% efficacy for SCIT at the 12-month mark, the baseline total cost to payor per successful treatment outcome is \$1196 for SLIT and \$2691 for SCIT, respectively. In total, this is a savings of \$1495 per year of treatment, per patient when assuming the pricing algorithm outlined in **Table 2**. Sensitivity analysis revealed that SCIT becomes the more cost-effective option for compliance rates less than 40% with SLIT therapy, assuming the adherence to SCIT is 90% and the effectiveness for each is set at 70% and 80%, respectively.

The findings from our analysis are in agreement with a study published in 2008 by Pokladnikova et al.²⁵ They performed an economic evaluation of SLIT vs SCIT in a European patient population and found that SLIT was less expensive than SCIT from all perspectives—including both patient and insurance payor. To the payor, the total average direct medical cost per patient for 3 years of SLIT was 416 euros vs 482 euros for SCIT.

It is difficult to compare noncompliance rates between the 2 modalities because noncompliance in SCIT is defined by withdrawal from therapy, whereas in SLIT, it is considered poor adherence to daily administration. In addition, rates of efficacy for SCIT and SLIT were obtained from the literature; these studies tend to be somewhat heterogeneous in dosing and protocols, while frequently involving treatment with single-antigen therapy. It is worth noting that there has been concern internationally regarding the long-term adherence to SLIT, which may decrease the cost-effectiveness of this modality if its benefits are not conferred with treatment continued over time.^{17,26} There are few studies evaluating or supporting the efficacy of multiantigen immunotherapy, although that is the most common method of immunotherapy used by allergists in the United States. Regardless of whether multi-, pauci-, or monoantigen therapy is used, most providers will not adjust the charge per vial related to the number of antigens in the vial. In general, the charge for a vial (whether SLIT or SCIT) is the same, regardless of the number of antigens being treated. The purpose of this study is not to delineate between

single- or pauciantigen therapy and multiantigen therapy, but rather, it is critical to acknowledge that they exist and note that the number of antigens included in an aqueous vial may be reflected in a varied profit margin for the practice. Another limitation of the study is the variation in effectiveness rates for adults with allergic rhinitis undergoing immunotherapy—for this reason, we used a range of values in a sensitivity analysis. In addition, values in a decision tree are static with respect to time, which may also limit the generalizability of this study as costs may vary per practice and over time.¹⁴

At this point, the analysis is limited to immunotherapy treatment of allergic rhinitis in adults. Future directions include cost-effective analysis of SLIT vs SCIT for asthma and allergic conjunctivitis, as well, with additional studies aimed at pediatric populations rather than adults. Most immunotherapy randomized controlled trials are single-antigen studies, and future directions may address how these translate to multiantigen clinical practice.

Implications for Practice

The results of this study indicate that for the insurance payor, cost of SLIT per successful outcome, as determined by clinically significant reduction in allergic rhinitis symptoms, is favorable when compared to cost of SCIT per successful outcome per 1 year of immunotherapy treatment. This study demonstrates that payor coverage of SLIT may be the economically sound option for cost reduction in the allergic rhinitis adult patient population. SCIT becomes the more cost-effective option in certain scenarios, for instance, if a patient is at least 90% adherent to SCIT and less than 40% adherent to SLIT therapy. Adherence to a given immunotherapy treatment is therefore a major factor in cost per successful treatment outcome.

Author Contributions

Frances Mei Hardin, design, conduct, analysis, presentation of the research; **Peter N. Eskander**, design, conduct, analysis; **Christine Franzese**, design, conduct, analysis.


Disclosures

Competing interests: Christine Franzese has the following conflicts: speakers bureau (ALK, Renegeron/Sanofi, AstraZeneca, Optinose, GSK), advisory board (ALK), and research support (ALK, Novartis, Genetech/Roche, GSK, Merck, Optinose).

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