

The Cost-Effectiveness of Allergen Immunotherapy Compared with Pharmacotherapy for Treatment of Allergic Rhinitis and Asthma



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KEYWORDS

- Allergen immunotherapy • Asthma • Allergic rhinitis • Subcutaneous immunotherapy
- Sublingual immunotherapy • Atopic dermatitis • Pharmacoeconomics

KEY POINTS

- After an extensive search of the PubMed and Medline databases was performed, the authors concluded that SCIT and SLIT were cost-effective compared with SDT from around 6 years after treatment initiation (with most treatments being 3 years). There was no strong evidence indicating superior cost-efficacy of SCIT or SLIT over SDT in either of these systematic reviews.
- There is strong evidence in the collective literature, which included individual studies and systematic reviews, that AIT is cost-effective in the management of allergic rhinitis and asthma as compared with SDT alone.
- The magnitude of AIT's cost-effectiveness is likely underestimated because most of the studies considered during-treatment costs and not AIT's long-term benefits or preventive/prophylactic effects.

INTRODUCTION

Allergic rhinitis (AR) affects approximately 20% to 30% of the United States and European populations.^{1–4} Symptoms include rhinorrhea, sneezing, congestion, and nasal pruritis.⁵ According to the American Academy of Allergy, Asthma and Immunology and American College of Allergy, Asthma and Immunology's Joint Task Force on Practice Parameters, Allergen Immunotherapy, AR treatment may include appropriate environmental control measures directed at reducing the allergen load,^{6–9}

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pharmacotherapy,⁵ and allergen immunotherapy (AIT).¹⁰ Among these treatments, only AIT induces immunologic tolerance to the specific allergens responsible for allergy symptoms.¹¹

There is a tendency toward underdiagnosis and undertreatment of AR by health care professionals.^{12–15} The burden of poorly controlled AR is borne by patients, caregivers, employers, and health care systems.^{16,17} Patients whose AR is poorly controlled are at increased risk for asthma, recurrent otitis media, chronic rhinosinusitis, and other comorbid conditions.^{1,18,19} These patients also face decrements in health-related quality of life, which can manifest as disturbed sleep, poor school and work performance, decreased energy, depressed mood, and low frustration tolerance.^{20–25}

The economic costs of poorly controlled AR include those for over-the-counter medications to treat symptoms; prescription medications; and medical care for treatment of comorbid complications, such as asthma and acute sinusitis.^{16,26–29} The indirect costs of poorly controlled AR include absenteeism and “presenteeism” from work or school, reduced productivity, lost wages, and fatigue-related injuries.^{4,17,20,26,30} This article examines published literature regarding the pharmacoeconomics of AIT versus standard drug treatment (SDT) for the treatment of AR. Where possible, we also considered studies that examined outcomes of AIT versus SDT for the treatment of allergic asthma, atopic dermatitis, and other allergic conditions.³¹ The review includes research specifically designed to evaluate the pharmacoeconomics of AIT and studies that provided sufficient secondary data for pharmacoeconomic analyses.

BACKGROUND: THE ECONOMIC IMPACT OF POORLY CONTROLLED ALLERGIC RHINITIS

In addition to pharmacotherapy, management of AR must include allergy diagnostic testing to identify the specific causative allergens so that appropriate avoidance measures are recommended and initiated.^{6,8,9,32} Pharmacotherapy includes topical nasal and oral antihistamines, topical nasal corticosteroids, nasal ipratropium, and leukotriene modifiers.⁵ These medications are used regularly to control symptoms or on an as-needed basis. It is worth noting that pharmacotherapy generally provides only partial symptomatic relief: approximately 33% of children and 60% of adults report a suboptimal response to medications.³³ Furthermore, none of these medications have a disease-modifying effect.

AIT is distinguished from avoidance measures and pharmacotherapy because it modifies the allergic disease.^{11,34} AIT has also been shown to mitigate the development of asthma and the development of new allergen sensitivities.^{35–38} Furthermore, AIT can induce long-term tolerance, which translates into clinical efficacy and cost savings that persist years after AIT is discontinued.^{4,39,40} According to US and international guidelines, AIT is indicated as a treatment option for patients with AR and/or asthma with^{10,41,42}

- Symptoms unresponsive to pharmacotherapy
- Troublesome medication side effects
- Patient preference, that is, patients who are reluctant to take medications indefinitely to control or “mask” rather than cure their allergic disease

There are currently two Food and Drug Administration–approved forms of AIT that are commercially available in the United States: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). Each route has its advantage and disadvantages.³⁴ Although SCIT is a well-established effective treatment of seasonal and

perennial allergic diseases,^{25,35–37} its disadvantage is that it must be administered in a physician's office or clinic with appropriate emergency equipment and personnel equipped to recognize and manage serious allergic reactions, such as anaphylaxis.^{25,38} SLIT has emerged as an alternative form of effective AIT that provides the advantage of home administration because of its superior safety compared with SCIT.³⁹

SUBCUTANEOUS IMMUNOTHERAPY PHARMACOECONOMIC STUDIES

In 2005, estimated total direct US costs of AR exceeded \$11 billion, with 60% of expenditures for prescription medications.^{17,18,26} Treatment of the comorbid conditions associated with AR (eg, asthma, otitis media, and recurrent sinusitis) are estimated in the billions of dollars.^{1,19,20} Several studies have examined the cost-effectiveness of AIT versus pharmacotherapy alone. In general, most of these studies found the AIT was associated with significant cost-savings either during treatment or after treatment completion. The explanation for the delayed cost-effectiveness related to the AIT treatment costs being offset by AIT's post-treatment clinical efficacy, which translated into reduced health care utilization and costs, medications, and so forth.

In the most compelling study demonstrating the cost-effectiveness of AIT, Ariano and colleagues⁴⁰ examined the pharmacoeconomics of SCIT with SDT compared with SDT alone among 30 patients with an at least 2-year history of *Parietaria*-induced AR and asthma. Patients were treated for 3 years and followed for an additional 3 years after treatment discontinuation. In addition to tracking symptom scores and medication use, the investigators calculated patients' health care costs, which included scheduled and unscheduled clinic visits and prescription medications. Within the first year of the study, those receiving SCIT experienced significant improvements in symptoms and reductions in medication use compared with patients receiving SDT alone. In the second year of treatment, SCIT conferred a 48% cost savings compared with SDT alone. At study end, researchers reported that SCIT conferred a net per patient annual savings of \$830, which represented an 80% cost reduction compared with the SDT group. Although this was a small study, it was well designed because it captured not only the direct costs of SCIT, but also the total health care costs (ie, all prescribed medications, scheduled and unscheduled medical clinic visits, and so forth). This study provides strong support for AIT in terms of reduction in direct and indirect costs compared with SDT alone.

In a 2-year double blind placebo-controlled trial (DBPC) comparing ragweed allergen extract administered by SCIT with placebo for the treatment of 77 adolescents and adults with ragweed-induced asthma, researchers reported a significant improvement in clinical and economic outcomes in the patient population receiving SCIT compared with the placebo group.⁴³ The costs of asthma medication and allergen extracts used over the 2-year study period were considered. Over the course of the study, asthma medication costs for those receiving SCIT were \$840 versus \$1194 for those receiving placebo; this represented a 30% cost savings benefit conferred by SCIT. However, these cost savings were offset by the \$527 expended for SCIT-related supplies and administration costs. Of note, the study did not examine costs of AR-associated comorbid conditions, nor did investigators consider the long-term efficacy of AIT after discontinuation.

A 2005 Danish study that examined the direct and indirect costs of AIT for seasonal grass pollen allergic and house dust mite (HDM) allergic patients revealed significant savings associated with AIT.⁴⁴ Before AIT initiation, the direct per patient annual costs of allergy treatment were 2580 Danish Krone (DKK). In the years following AIT

discontinuation, direct per patient annual costs fell to DKK 1072, representing a 60% savings. When direct and indirect cost were considered, the per patient annual costs were significantly less from SCIT than SDT. This study further supports the cost savings benefits of SCIT for patients with allergic respiratory conditions.

In a multinational study that included Austria, Denmark, Finland, Germany, the Netherlands, and Sweden, Keiding and Jorgensen⁴⁵ evaluated the pharmacoeconomics of SCIT versus SDT among adult patients with grass pollen-induced seasonal AR that was not controlled by SDT (oral antihistamines, topical steroids, or sodium cromoglycate). This analysis was based on the UK Immunotherapy Study Group's (UKIS) 1-year randomized multinational European randomized, DBPC, parallel-group trial, which included an economic analysis evaluating 3 years of SCIT treatment and 6 years of follow-up after SCIT discontinuation.⁴⁶ From the health care system perspective, SCIT was found to be cost-effective in comparison with SDT with the estimated cost savings to be €10,000 to €25,000 per quality-adjusted life year (QALY). A QALY is a generic measure of disease burden, which includes the quality and the quantity of life lived. It is used in economic evaluations to assess the value of medical interventions. One QALY is equal to 1 year in perfect health.² If an individual's health is lower than this maximum, QALYs are accrued at a rate of less than 1 per year. To be dead is associated with 0 QALY. From a societal and patient perspective and the indirect costs, which included days lost from work, productivity, lost wages, and other factors, SCIT was found to be considerably more cost-effective than SDT.

A 2008 study examined 15 years of German health care systems claims. Investigators found that compared with SDT alone, SCIT was associated with a significant reduction in new cases of asthma.⁴⁷ Furthermore, the total per-patient costs in the SDT-alone group were approximately €2100 higher than costs among those receiving SCIT (€26,100 SDT vs €24,000 SCIT). Investigators estimated that the annual per-patient cost benefit for SCIT was approximately €140. From a societal point of view the SCIT reached an incremental cost-effectiveness ratio (ICER) of -€19,787 per additional QALY, which implies that SCIT and standard treatment were more effective and less costly than symptomatic treatment alone. The ICER is a statistical figure for determining the value of a health care intervention. It is defined by the difference in cost between two possible interventions, divided by the difference in their effect. It represents the average incremental cost associated with one additional unit of the measure of effect. There was variation in the ICER with adults being the largest beneficiary most likely reflecting a more significant reduction in indirect costs.

In a claims-based analysis of Florida Medicaid patients, Hankin and associates⁴⁸ compared direct costs (pharmacy, outpatient and inpatient services for any reason) incurred by pediatric patients newly diagnosed with AR in the 6 months before SCIT initiation with parallel direct costs these patients incurred in the 6 months following SCIT discontinuation. Investigators found significant ($P<.001$) cost reductions in the 6-month period following SCIT, even after the costs of SCIT were included. In an extension of the previously mentioned data, Hankin and colleagues⁴⁹ conducted a retrospective, matched-cohort analysis of 10 years of claims data (1997–2007) to examine whether children with newly diagnosed AR who received SCIT incurred less health care utilization and fewer costs during an 18-month follow-up period compared with a matched group of children with AR who did not receive SCIT. Children treated with SCIT incurred significantly lower 18-month median per-patient total health care costs even after including the costs associated with allergen immunotherapy (IT) (\$3247 vs \$4872), outpatient costs exclusive of SCIT-related care (\$1107 vs \$2626), and pharmacy costs (\$1108 vs \$1316) compared with the matched control subjects ($P<.001$ for all). Consistent with the previous study, the significant

difference in total health care costs was evident within the first 3 months of initiating immunotherapy. This study demonstrated that the early cost savings associated with SCIT persisted and, more importantly, increased through the 18-month study period.

In a large-scale retrospective, matched cohort, claims analysis that evaluated 12 years of Florida Medicaid data, Hankin and colleagues¹⁶ found comparable cost savings in adults with newly diagnosed AR treated with SCIT. In this study, investigators compared the mean 18-month health care costs (pharmacy, outpatient and inpatient services) of adult and pediatric patients with newly diagnosed AR who received SCIT with those who did not. Overall, SCIT-treated patients demonstrated a 38% reduction in 18-month total (pharmacy, outpatient and inpatient services, including costs associated with SCIT) mean health care costs (\$6637 vs \$10,644; $P < .0001$). Specifically, SCIT treatment was associated with the following cost savings:

- Adults: 30% total 18-month health care cost reduction (\$10,457 SCIT vs \$14,854 matched control subjects; $P < .0001$)
- Children: 30% total 18-month health care cost reduction (42%; \$5253 AIT vs matched \$9118 control subjects; $P < .0001$)

These health care cost savings, which included costs associated with SCIT, were evident within the first 3 months of treatment and continued throughout the 18 months of follow-up. Together, these three studies provide strong support for the cost saving benefits of AIT for adults and pediatric patients with AR.

A 2000 German study compared the cost-effectiveness of SCIT in addition to standard therapy versus the use of SCIT alone.⁵⁰ The combination of SCIT with SDT was associated with a cost-savings of €140 per patient. From a society perspective, the ICER for SCI was €19,787 per additional QALY, indicating that SCIT plus SDT was more effective and less costly compared with SDT only. In some European countries, an ICER up to €50,000 per QALY is considered cost-effective. Against this background SCIT was again reported to be a cost-effective treatment.

A study investigated the cost-effectiveness of SCIT in children with allergic asthma.⁵¹ In this study, patients were treated with HDM SCIT for 3 years or pharmacotherapy alone. In the first year of treatment, the investigators found no difference between the two groups in terms of medication costs. However, they found a significant reduction in total medications cost in the SCIT-treated group versus the SDT group after 3 years of SCIT (€193 vs €498, respectively; $P < .001$). This included a reduction in allergy medication costs (€168 vs €453, respectively; $P < .002$). The study was not powered to evaluate the effect of SCIT on outpatient visit costs or hospitalizations. This cost-effectiveness analysis (CEA) study provides further support that SCIT provides significant cost savings compared with SDT alone. Presumably, this is because of SCIT's disease modifying effect.

PHARMACOECONOMICS OF SUBLINGUAL IMMUNOTHERAPY

One of the initial studies analyzing the cost-effectiveness of SLIT was an Italian retrospective study of 135 pediatric patients with season and perennial AR and/or asthma (Table 1).⁵² The investigators analyzed data related to health care costs 1 year before SLIT and during the 3 years during SLIT therapy. The outcomes measured included: number of exacerbations, clinic visits, absence from school, direct cost (medications, specialist visits, and SLIT), and indirect cost (costs associated lost time at school and parental lost time from work). Treatment with SLIT resulted in fewer exacerbations, medical visits, and lost days from school and work. Direct costs decreased 56%

Study	Comparators	Type	Perspective	Results
Berto et al, ⁵² 2005	1 y of SDT before SLIT; SLIT for 3 y	CEA	Health care system, society	Cost-savings with SLIT per health care system and society: Year before SLIT: mean annual health care costs/annual total costs per patient were €506 and €2672, respectively During SLIT: €224 (health care costs) and €629 (total cost) d
Berto et al, ⁵⁷ 2006	Pollen SLIT for 3 y plus SDT as needed; SDT	CCA	Health care system, society	SCIT compared with SDT: Greater 6-y mean savings from payer and societal perspective More asthma cases avoided and patients improved
Bachert et al, ⁵⁴ 2007	Grass SLIT for 3 y plus SDT as needed; SDT	CUA	Society	SLIT cost-effective cost per QALY; average 0.0287 QALYs per season compared with SDT
Beriot-Mathiot, ⁶⁹ 2007	Grass SLIT for 3 y continuous or seasonal; SDT	CUA	Societal	Per ICER seasonal SLIT was cost- effective Continuous SLIT was cost-effective if sustained effect for ≥ 2 y after treatment
Canonica et al, ⁵⁵ 2007	Grass SLIT for 3 y plus SDT as needed; SDT	CUA	Society	SLIT cost-effective per QALY: average 0.0167 QALYs per season compared with SDT
Berto et al, ⁵⁸ 2008	Grass SLIT for 1 y; SDT for 1 y	CCA	3rd-party payer	Mean annual direct costs for SLIT greater than SDT €311.4 and €179.8, respectively
Nasser et al, ⁵⁶ 2008	Grass SLIT for 3 y plus SDT as needed; SDT	CUA	Society	SLIT "very cost-effective" per QALY gained QALY gained at 9 y = 0.197; equivalent to an extra "72 d of perfect health" for patients treated with SLIT when compared with those receiving placebo
Ariano et al, ⁴⁰ 2009	SLIT for 3 y plus SDT as needed; SDT	CCA	Health care system	Health care costs greater for SLIT plus SDT in Year 1, same in Years 2 and 3, and significantly lower in Years 4 and 5, compared with SDT
Ruggeri et al, ⁵⁹ 2013	SLIT for 3 y plus SDT as needed; SDT	CEA	3rd-party payer, society	SLIT cost-effective per ICER; benefit of 0.127 QALYs in patients with medium AAdSS and 0.143 QALYs in patients with high AAdSS

Abbreviations: AAdSS, adjusted average symptom score; CCA, cost-consequence analysis; CUA, cost-utility analysis.

^a Included in the Meadows et al, systematic review.⁴¹

^b Included in the Hankin et al, systematic review.⁵⁸

^c Included in both systematic reviews.

From Cox L. Pharmacoeconomics of allergic diseases. In: Akdis CA, Agache I, editors. Global Atlas of Allergy. European Academy of Allergy and Clinical Immunology; 2014; with permission.

from €506 to €224 and indirect costs decreased 81% from €2166 to €406 during treatment with SLIT. Overall costs decreased 76% from €2672 pre-SLIT to €629 during SLIT treatment. The investigators only examined health care cost in patients with seasonal or perennial AR. It is presumed that the overall health care cost-savings would be even greater in patients with AR and asthma.

Several studies evaluated the health care economics of a randomized trial of SLIT grass-pollen tablets in adult patients with allergic rhinoconjunctivitis.⁵³ These studies considered the societal perspective over a 9-year horizon. In the Northern European cohort of this SLIT study, there was a significant improvement in QALY in the SLIT group (0.976 vs 0.947; $P < .001$), with annual treatment costs less than €2200.⁵⁴ Similarly in the Southern European cohort, SLIT was cost-effective at an annual cost in the range of €1500 to €1900.⁵⁵ For reference, to be considered cost-effective it was calculated that a drug must generate one QALY for less than €29,200. Finally, an analysis of the study data from the United Kingdom demonstrated that the cost of QALY gained was €6380, again suggesting that SLIT treatment provided pharmacoeconomic benefit.⁵⁶

The Sublingual Immunotherapy Pollen Allergy Italy (SPAI) study evaluated the costs of using SLIT in association with standard therapy compared with standard treatment alone among 2200 adults with pollen-induced AR and asthma.⁵⁷ SLIT was associated with a 20.6% reduction in direct costs (-€626) and 43.7% reduction in indirect costs (-€1487). SLIT conferred a 32.8% reduction in direct and indirect costs.

The Sublingual Immunotherapy in Allergic Patients (SIMAP) study was a 1-year observational study of 102 Italian children and adults with grass-pollen-induced AR that evaluated the efficacy and safety of SLIT compared with SDT alone.⁵⁸ The mean annual treatment costs were higher in the SLIT versus SDT groups (€311 vs €180; $P < .0001$). The higher costs were caused by the costs of SLIT itself. The study also found that in both groups, patients with AR and asthma generated more costs than those with AR alone.

Ruggeri and colleagues⁵⁹ evaluated the cost-effectiveness of a five-grass pollen tablet in adults with grass pollen-induced AR. In this study, cost-effectiveness was stratified by low, medium, and high burden of disease based on average adjusted symptom score (AAdSS). Their analysis demonstrated that low AAdSS patients did not benefit from use of five-grass pollen SLIT, whereas patients with medium to high AAdSS did benefit. The five-grass pollen SLIT was found to cost €1024/QALY for patients with medium AAdSS and €1035/QALY for patients with high AAdSS. These numbers were lower than the critical threshold €30,000/QALY indicating that for patient with medium to high AAdSS, SLIT was a cost-effective treatment. In patients with low AAdSS, SLIT was not found to be cost-effective. To the contrary, the use of SLIT added to the cost of treatment without providing any significant clinical benefits, thus illustrating the importance of proper patient selection for AIT treatment.

Ronaldson and colleagues⁶⁰ performed a cost-utility analysis (CUA) in a model that follows two hypothetical cohorts of 1000 children with grass pollen allergic rhinoconjunctivitis, with or without asthma, who are treated with SLIT and symptomatic medications or SDT only. Their analysis demonstrated that the SLIT-treated group obtained an ICER of 0.10 QALYs per patient. The cost of SLIT treatment was €1202 higher than the SDT group. However, the ICER for the SLIT-treated group was €12,168/QALY, which fell lower than the threshold of €20,000 to €30,000/QALY that is used in the United Kingdom to deem a product cost-effective. This study again supports the cost-effectiveness of grass pollen AIT.

Hahn-Pederson and colleagues⁶¹ evaluated the cost-effectiveness of an HDM SLIT tablet in the treatment of adults with HDM-induced allergic asthma. This was

a CUA based on a phase III randomized controlled trial comparing the efficacy of ACARIZAX (ALK-Abello, Horsham, Denmark) with placebo. Both groups received conventional asthma pharmacotherapy. SLIT treatment resulted in an additional 0.66 QALY at an incremental cost of €2673. This equates to an ICER of €4041, which fell lower than the cost-effective threshold of €40,000. This study's results suggest that HDM SLIT is cost-effective in the treatment of adults with HDM-induced allergic asthma.

A German study compared the cost-effectiveness of HDM SLIT versus SDT alone in patients with moderate to severe HDM-induced AR.⁶² The investigators performed a pharmacoeconomic analysis that examined a 9-year time horizon. They found that SLIT resulted in an additional QALY of 0.31 at an incremental cost of €2276. This resulted in an ICER of €7516 indicating that HDM SLIT in addition to pharmacotherapy is more cost-effective than pharmacotherapy alone.

PHARMACOECONOMICS OF SUBCUTANEOUS IMMUNOTHERAPY VERSUS SUBLINGUAL IMMUNOTHERAPY

Pokladnikova and colleagues⁶³ performed an economic evaluation of SCIT versus SLIT in adults with grass-induced rhinoconjunctivitis. Their analysis included the perspectives of third-party payers, patients, and society. After 3 years of treatment, SLIT and SCIT resulted in significant reductions in symptom scores and medication use. However, in the third year of study, SCIT demonstrated greater improvements in the visual analog scale and antihistamine use versus SLIT. From an economic perspective, SLIT proved to be less expensive. However, from a patient perspective SCIT was financially preferable to SLIT, particularly if the patient did not incur loss of income or travel expenses to receive SCIT. From the third-party payer perspective, the 3-year direct medical costs were €416 versus €482 for SLIT and SCIT groups, respectively. When both direct and indirect costs were considered, 3 years of treatment was €684 versus €1004 in the SLIT versus SCIT groups, respectively ($P < .001$). If patients in the SCIT group incurred no loss of income or productivity from receiving SCIT in a medically supervised setting then SCIT was overall financially preferable to SLIT.

A Danish study evaluated the budget impact of grass pollen-induced rhinoconjunctivitis comparing SQ-standardized grass AIT (Grazax; *Phleum pratense*, 75,000 SQ-T/2800 BAU, ALK) with SCIT (Alutard; *P. pratense*, 100,000 SQ-U/mL, ALK).⁶⁴ The total direct and indirect costs associated with SLIT was €3789. This was €3460 less expensive than the company's SCIT product (Alutard). The authors suggested this cost-savings would allow for a health care system to treat an additional 600 patients with SLIT at no additional cost.

Westerhout and colleagues⁶⁵ evaluated the cost-effectiveness of grass pollen AIT (Oralair, Grazax, Anthony, France; Alutard SQ) in grass pollen-allergic rhinoconjunctivitis patients versus SDT alone. Patients were treated for 3 years and the assessment used a Markov model and a 9-year timeframe. The cost-utility ratio of Oralair versus SDT was €14,728 per QALY. When estimated incremental costs and incremental QALYs were considered, Oralair was determined to be the dominant strategy.

In 2014, Dranitsaris and Ellis⁶⁶ performed an indirect comparison of DBPC trials to evaluate the efficacy, safety, and cost between Oralair, Grazax, and grass pollen SCIT for the treatment of AR.⁵⁵ Twenty trials met their inclusion criteria.⁶⁶ Their analysis indicated that Oralair was less expensive than Grazax or SCIT. In the first year of treatment, Oralair use resulted in a cost savings of:

- \$948 versus seasonal SCIT
- \$1168 versus Grazax

- \$2471 versus perennial SCIT

Most of the increased costs associated with SCIT were related to indirect costs caused by lost productivity and travel because of the requirement that SCIT be administered in a medically supervised setting. In the second and third years the pattern was similar with Oralair offering a cost savings of \$868 versus perennial SCIT, \$1883 versus seasonal SCIT, and \$2344 versus Grazax. This model assumes that SCIT results in decreased productivity caused by lost hours from work for administration. If one were to make SCIT administration available, such that it required no lost work time (eg, an onsite medical clinic), then the total cost for perennial SCIT would be \$1721 versus \$1889.6 for Oralair. Thus, Oralair would be 9% more expensive than SCIT. This indicates that the cost differential between SLIT and SCIT could be reduced if administration of SCIT did not require lost time from work.

Verheggen and colleagues⁶⁷ using a Markov model and a 9-year time horizon evaluated the cost-effectiveness of Oralair (five-grass tablet) versus subcutaneous allergoid component for the treatment of grass pollen-induced allergic rhinoconjunctivitis. Oralair SLIT was associated with higher overall patient cost-savings of €458 per patient. Additionally, it was shown to be superior to SCIT in terms of clinical efficacy. SLIT resulted in an increased QALY of 0.036 and an ICER of €12,593 compared with allergoid SCIT. According to this study, there was 76% probability that the SLIT tablet was the most cost-effective treatment option.

Rheinhold and Bruggenjurgen⁶⁸ compared the cost-effectiveness of SCIT with Allergovit (Allergopharma, Germany) with Oralair SLIT using a Markov model with a timeframe of 9 years. Over the 9-year treatment period, the total per-person cost for SLIT was approximately 14% greater than for SCIT (€1159 for Allergovit vs €1322 for Oralair, respectively). In addition, SCIT treatment resulted in a per QALY gain of €11,000 compared with a €41,405 QALY gain for SLIT. As a reference, cost-effective therapy is considered to be less than €40,000 to €50,000 per QALY gained. In this study, SCIT was more cost-effective than SLIT for treatment of grass pollen-induced rhinoconjunctivitis.

ALLERGEN IMMUNOTHERAPY PHARMACOECONOMICS IN SYSTEMATIC REVIEWS

In a review paper examining the efficacy of AIT for AR, Cox²⁷ summarized two systematic reviews that specifically examined AIT cost-effectiveness (Table 2). The most comprehensive review to date on AIT cost-efficacy was a systematic review and meta-analysis of studies that provided data on costs and clinical efficacy of SCIT and/or SLIT with SDT alone.⁴ The systematic review was conducted by the National Institute for Health Research Health Technology Assessment (HTA) program.⁴ The purpose of an HTA program is to produce high-quality research information on the effectiveness, costs, and broader impact of health technologies for those who use, manage, and provide care in the National Health Service. This HTA review used the electronic databases and trial registries (from inception up to April 2011).⁴ They applied the standard systematic review methods for study selection, data extraction, and quality assessment of DBPC trials of SCIT or SLIT, SCIT compared with SLIT. Economic evaluations, meta-analysis, and indirect comparison meta-analysis were presented. The authors identified 14 economic evaluations and 2 reviews of economic evaluations (Table 3).⁴ Four different types of cost-analyses were used in the 14 identified economic evaluation studies:

- 4 cost-consequences analyses
- 2 CEA

Table 2
Systematic reviews evaluating allergen immunotherapy health economics

Author, Year ^a	Economic Outcome Conclusion ^b	SCIT vs SDT ^b	SLIT Tablets vs SDT ^b	SLIT Drops vs SDT ^b	SCIT vs SLIT vs SDT ^b
Meadows et al, ⁴ 2013	14 Both SCIT and SLIT may be cost-effective from around 6 y	6 Cost-effective but varied in terms of payer perspective and timepoint	3 Cost-effective at ~ 6 y and various ICER	2 All favored SLIT	3 SCIT more cost-effective over time
Hankin & Cox, ²⁹ 2014	23 Favored AIT over SDT	10 All favored SCIT	8 1 found higher costs with SLIT	1 Reduced costs by Year 4	4 All favored SLIT SLIT 48% cost-savings from healthcare system (HCS) perspective

^a Included 3 studies that evaluated the actual total health care cost via claims analyses not included in the Meadows review.

^b Number of studies evaluated.

From Cox L. The role of allergen immunotherapy in the management of allergic rhinitis. Am J Rhinol Allergy 2016;30(1):48-53; with permission.

Table 3
Studies comparing SCIT with SDT

Study	Comparators	Type	Perspective	Results
Schadlich & Brecht, ⁵⁰ 2000	Pollen or HDM SCIT for 3 y plus SDT as needed; SDT	CEA	Society, health care system, 3rd-party payer	SCIT < SDT over 10 y Break-even point reached in the 7th y
Petersen et al, ⁴⁴ 2005	Grass or HDM SCIT for 3–5 y plus SDT as needed; SDT	CEA	Society	Direct cost: SCIT > SDT If indirect costs of sick days included in the economic evaluation, SCIT costs < SDT
Ariano, ⁷⁰ 2006	<i>Parietaria</i> SCIT for 3 y plus SDT as needed; SDT	CCA	Health care system, society	SCIT < SDT; 80% cost reduction found 3 y after stopping SCIT
Keiding & Jorgensen, ⁴⁵ 2007	Grass SCIT for 3 y plus SDT as needed; SDT	CEA CUA	Health care system, society	SCIT cost-effectiveness per QALY; in the range of €10,000–€25,000 per QALY from perspective of the health care system
Omnes, ⁷¹ 2007	HDM or pollen SCIT 3–4 y plus SDT as needed; SDT	CEA	Society	Cost-effective per incremental cost of asthma cases avoided (ICER)
Bruggenjurgen et al, ⁴⁷ 2008	SCIT for 3 y plus SDT as needed; SDT	CUA	3rd-party payer, society	Break-even point = 10 y After 15 y, annual cost savings of €140 per SCIT-treated patient
Hankin et al, ⁴⁸ 2008	Costs 6 mo before and 6 mo after SCIT	CCA	Health care system	Weighted mean 6-mo savings/patient: \$401
Hankin et al, ⁴⁹ 2010	SCIT for 18 mo plus SDT as needed; SDT as needed for 18 mo	CCA	Health care system	SCIT 18-mo total health care costs 33% reduction compared with SDT
Hankin et al, ¹⁶ 2013	SCIT plus SDT as needed for 18 mo; SDT as needed for 18 mo	CCA	Health care system	SCIT 18-mo total health care costs compared with SDT: children = 42% reduction; adults = 30% reduction

Abbreviation: CCA, cost-consequence analysis.

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- 5 CUA
- 1 CEA and CUA
- 1 CEA and cost–benefit analyses
- 1 CEA and cost–consequences analyses

These cost-analyses differ in the way outcomes were measure or expressed, with CEAs, cost–benefit analyses, and CUAs typically reporting outcomes as the ICER. The ICER is calculated from QALY with the following formula:

$$ICER = \frac{\text{Cost of SCIT} - \text{Cost of ST}}{\text{QALYs for SCIT} - \text{QALYs for ST}}$$

The authors concluded that based on £20,000 to £30,000 per QALY, AIT became cost-effective in comparison with SDT alone 6 years of treatment initiation from the patient. From the National Health Services perspectives AIT was cost-effective after 7 years. Using the same threshold, SCIT was found to be cost-effective compared with SLIT after 5 years. The authors concluded that “... SCIT and SLIT may be cost-effective compared with SDT from around 6 years at a threshold of £20,000 to 30,000 per QALY.”⁴ Limited evidence indicated SCIT may more beneficial and less costly than SLIT. The authors did note that the studies used different outcome measures making it difficult to compare and combine results. They encouraged further research to “establish the comparative effectiveness of SCIT compared with SLIT and to provide more robust cost-effectiveness estimates.”⁴ All of the studies in this systematic review used single-allergen AIT.

Another systematic review of published studies that reported health economic outcomes associated with AIT conducted by Hankin and Cox²⁹ evaluated 23 studies that compared SLIT and/or SCIT with SDT (SCIT, 9; SLIT liquid drops, 2; SLIT tablets, 8; SCIT and SLIT, 4) and one directly comparing SLIT with SCIT (see [Table 1](#)). Only one early study comparing SCIT with SDT in adults with ragweed-allergic asthma failed to demonstrated significant cost-savings.⁴³ The review concluded that the remaining 23 comparative cost studies provided “compelling evidence for the cost savings of AIT (whether delivered subcutaneously or sublingually).” Four of the six studies comparing cost outcomes of SLIT with SCIT reported cost-savings favoring SLIT. All of the studies, except the three retrospective claims analyses studies of the Florida Medicaid reviewed previously in this paper, used single-allergen AIT.^{16,48,49}

SUMMARY

The preponderance of the data suggests that AIT, with either SLIT or SCIT, is a cost-effective treatment option for patients with AR and/or asthma. One of this review’s limitations is that most of the studies used one or two allergens. Additionally, most of the studies in this review were performed in European centers. Thus, the applicability to US patients may be limited. This is particularly relevant for the SCIT versus SLIT comparison in the United States because the typical US allergy-trained physician prescribes multiallergen AIT.⁵⁷ The cost of multiallergen SLIT using effective doses could be considerable.^{58,59} SCIT in the United State is reimbursed by private and third-party payers with the definition of a dose being the volume administered (eg, 1 mL = dose). This reimbursement formula does not consider the number of allergens that are required to effectively treat the patients with AR. Thus, single-allergen SCIT is reimbursed the same multiallergen SCIT. In contrast, SLIT tablets only provide treatment of a single allergen and multiallergen allergic patients would have to take multiple

tablets, which could be cost-prohibitive.^{34,58} Clearly, in these patients, multiallergen SCIT would be less expensive than SLIT.

One of the arguments for SLIT over SCIT is that safe administration requires that SCIT is administered in a medically supervised setting, which is associated with indirect costs because of lost work time and reduced productivity. Most studies on SCIT cost-effectiveness assume that all patients will receive SCIT in a medical facility during usual business hours. Additionally, no study collected data directly from patients regarding the economic impact that SCIT had on them. However, in the United States, patients can receive SCIT outside of standard business hours and this would reduce the indirect costs of SCIT that is, “lost time from work.” Another consideration is that many patients can continue their work electronically (eg, computer, smart phone) during the time they spend in medical clinic for SCIT treatment.

Overall, SLIT and SCIT are clinically efficacious and cost-effective treatment options for patients with AR and asthma. Whether SCIT is more cost-effective than SLIT or vice versa remains to be determined and requires more detailed pharmacoeconomic analysis that includes the direct and indirect costs of patients with AR, particularly multiallergen patients in the United States.

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