



Allergy immunotherapy: what is the evidence for cost saving?

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Purpose of review

Given the widespread prevalence of allergic disease, its substantially associated clinical and economic burden, the unique disease-modifying benefits of allergy immunotherapy (AIT), and increased availability of sublingual immunotherapy (SLIT), a critical update of the evidence for AIT-related cost savings [for both subcutaneous immunotherapy (SCIT) and SLIT] is particularly relevant and timely. The present article reviews the evidence for SCIT-related and SLIT-related cost savings derived from a systematic review of the published literature.

Recent findings

Examined were 24 publications pertaining to the health economics of AIT. Except for one early study comparing the costs of AIT to symptomatic drug treatment (SDT), the remainder provide compelling evidence for AIT cost savings (whether SCIT or SLIT) over SDT. Furthermore, of the six studies comparing cost outcomes of SLIT to SCIT, four reported cost savings favoring SLIT.

Summary

This review, spanning research from Southern Europe, Scandinavia, Northern Europe, North America, and the Czech Republic, encompasses a range of perennial and seasonal allergic conditions, including allergic asthma, allergic rhinitis with or without asthma, and rhinoconjunctivitis with or without allergic rhinitis due to house dust mite, grass or ragweed pollen, or a mixture of various allergens. All but one study compellingly demonstrate cost savings conferred by AIT over SDT.

Keywords

allergy immunology, cost analyses, health economics, systematic literature review

INTRODUCTION

The global prevalence of allergic disease, in general, and allergic rhinitis, allergic conjunctivitis, allergic asthma, and atopic dermatitis, specifically, is increasing dramatically, especially within the developed countries [1]. Allergic rhinitis alone affects approximately 500 million people worldwide [2], including an estimated 113 million in Europe [3] and 30–60 million in the United States (USA) [4].

Allergy immunotherapy (AIT) is indicated for the treatment of allergic rhinitis, allergic conjunctivitis, and allergic asthma in patients whose symptoms are not adequately controlled by symptomatic drug treatment (SDT) and avoidance measures, those experiencing unacceptable adverse effects from SDT, or patients who wish to reduce the long-term use of SDT [5].

In contrast to SDT, which offers temporary symptomatic relief, AIT holds unique distinction as the only allergy treatment known to alter the clinical course of allergic disease. AIT has the potential to halt the progression from allergic rhinitis to

asthma [6–11], prevent the development of new allergies [11–19], and reduce the need and use of SDT [19–34,35[■]]. Improved symptoms, reduced SDT use, and favorable immunological changes (per skin prick test and serum allergen-specific antibodies) have been sustained for up to 12 years after discontinuation of a 2–5-year course of AIT [19–21,23,25–34,35[■],36].

Sublingual immunotherapy (SLIT) has garnered growing attention since three products were recently awarded approval by the U.S. Food and Drug Administration (FDA). Oralair, a once-daily SLIT dissolving tablet, became the first SLIT product to be approved for the U.S. market [37]. Oralair is

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KEY POINTS

- Three SLIT products recently were FDA approved, and the U.S. economic viability of AIT, in general, and SLIT, in particular, are drawing attention from allergy specialists, payers, public policy decision-makers, and patients.
- With the exception of one early study [42] that compared costs for AIT to costs for SDT, the remaining 23 comparative cost studies provide compelling evidence for the cost savings of AIT (SCIT or SLIT) over SDT.
- Of the six studies [61,62[■],63–66] comparing the cost outcomes of SLIT to SCIT, the preponderance of findings favored SLIT [62[■],64–66].

indicated for the seasonal treatment of grass-pollen-induced allergic rhinitis with or without allergic conjunctivitis confirmed by positive skin test or in-vitro testing for pollen-specific IgE antibodies (for Sweet Vernal, Orchard, Perennial Rye, Timothy, or Kentucky Blue Grass Mixed Pollens) in persons aged 10 through 65 years [37]. Next to become FDA approved was Grastek, indicated for the seasonal treatment of grass-pollen-induced allergic rhinitis with or without allergic conjunctivitis confirmed by positive skin test or in-vitro testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens [38]. FDA approval was most recently awarded for Ragwitek, indicated for use as immunotherapy for the treatment of short ragweed-pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in-vitro testing for pollen-specific IgE antibodies in patients aged 18–65 years [39]. Given the widespread prevalence of allergic disease, its substantially associated clinical and economic burden, the unique disease-modifying benefits of AIT, and increased availability of SLIT, a critical update of the evidence for AIT-related cost savings [for both subcutaneous immunotherapy (SCIT) and SLIT] is particularly relevant and timely. The present article reviews the evidence for SCIT-related and SLIT-related cost savings derived from our systematic review of the published literature.

SYSTEMATIC LITERATURE REVIEW: METHODOLOGY

We conducted a systematic literature review of the published studies indexed in MEDLINE through 31 March 2014 that reported health economic outcomes associated with AIT. We also conducted a hand search to identify whether there were

additional relevant publications not captured in this search. The following MEDLINE database search query identified 445 publications: ‘cost) OR costs) OR economics) OR economic) OR cost-effectiveness) OR pharmacoeconomics) OR pharmacoeconomic) OR health economic) OR health economics) OR health-economic) OR health-economics) AND ((immunotherapy) AND (allergy) AND effectiveness (sb)’. The strategy for identification of relevant publications for in-depth review is shown in Fig. 1. A complete list of the 445 identified publications and their selection determinations are available upon request.

Identified were 27 publications that span 18 years (1996 to 31 March 2014). We conducted an in-depth review of each identified publication and abstracted information in Microsoft Word text tables (see Appendix I which is available online at <http://links.lww.com/COAI/A8>). Among the 27 publications, 12 pertain to the health economics of SCIT [40–45,46[■],47–51]; 8 to the health economics of SLIT tablets [52–58,59[■]]; 2 pertain to the health economics of SLIT liquid drops [60,61]; 4 publications compared the economic outcomes of SLIT, SCIT, and SDT [62[■],63–65]; and 1 compared the health economic findings of SCIT versus SLIT [66].

THE HEALTH ECONOMICS OF SUBCUTANEOUS IMMUNOTHERAPY

Ten of the 12 studies pertaining to the health economics of SCIT compared the cost outcomes of SCIT with or without SDT to SDT alone [40–42,44–46[■],47,49–51].

A comparative cost analysis (CCA) was based upon a 2-year, prospective, randomized, double-blind study of 77 adolescents and adults with asthma sensitized to ragweed. Investigators compared the use and costs of asthma medications during two allergy seasons (July 1 through October 31) among participants who were randomized to receive a seasonally administered regimen of SCIT versus those who received placebo injections [42]. Costs of asthma medications during seasons 1 and 2, total combined costs for both seasons, and costs of allergen extracts were examined. Investigators found a lower 2-year mean cost of asthma-related medication in the SCIT-treated group compared with the placebo group (\$840 vs. \$1,194 in 1987 dollars, statistical significance not provided). The savings conferred by SCIT offset its 2-year cost outlay (\$527).

In 2000, German investigators published a decision-tree cost model based on a review of the literature [51]. This CEA examined the economic effects of 3 years of SCIT and 7 years of follow-up.

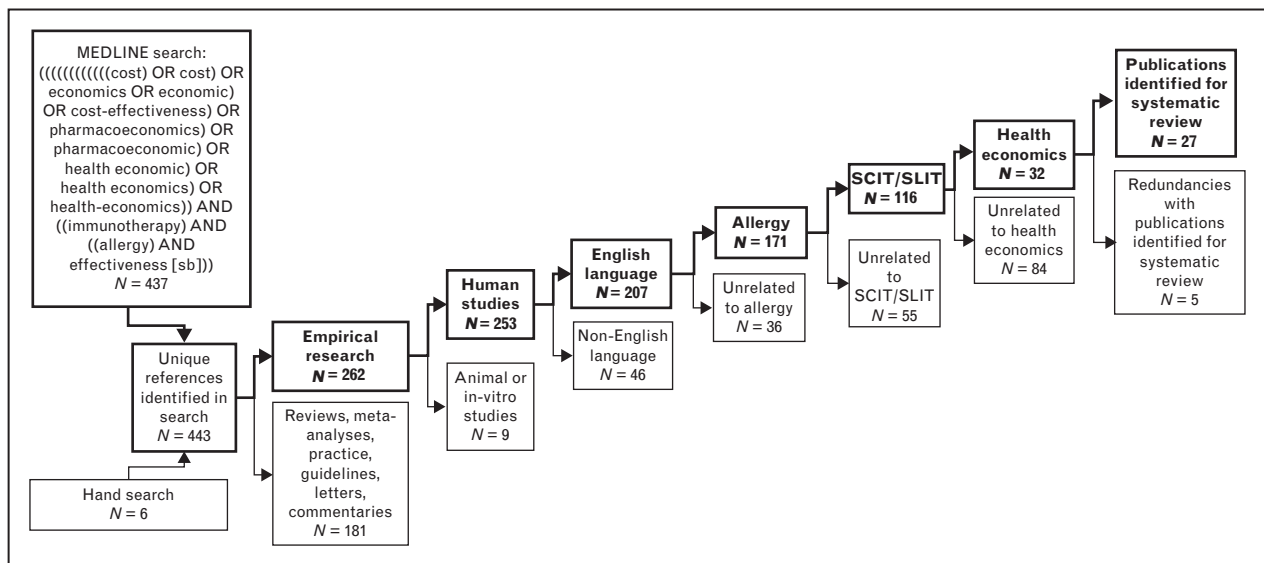


FIGURE 1. Selection of publications for review.

Investigators found that the advantages of a 3-year SCIT regimen was achieved within 6 years of treatment initiation, and resulted in a final net savings of 590–650 Deutsche Marks (€302–€332) from the third-party payer perspective, 580–670 Deutsche Marks (€296–€343) from the healthcare system perspective, and 1100–1190 Deutsche Marks (€562–€608) from the societal perspective.

In 2005, an economic analysis of Danish patients with seasonal grass pollen or perennial house dust mite (HDM) allergy found that direct costs per patient per year were 2580 Danish Krone (DKK) (€347) during the year before SCIT and 1072 DKK (€144) during the year after SCIT [49]. Four years of SCIT were associated with additional direct costs of 13 676 DKK (€1841) per patient. When indirect costs were included, SCIT was expected to result in net positive savings of 19 849 DKK (€2672) over 4 years of treatment and 11 838 DKK (€1592) per year in the subsequent years.

A prospective observational study [40] examined the outcomes of patients with allergic rhinitis and asthma caused by *Parietaria* pollen who received either 3 years of SCIT plus SDT or SDT alone. A significant reduction in the symptom scores and SDT use was achieved within the first year of treatment with SCIT. The reduction in costs was approximately 15% within the second year of SCIT and 48% within the third year of treatment. The statistically significant difference between groups was maintained through the sixth year of follow-up (i.e. 3 years after stopping SCIT), at which point an 80% reduction was realized. The net savings for each patient at the final year 6 follow-up evaluation corresponded to €623 (approximately \$830) per year. The authors note that the savings realized with

SCIT may be important for individuals and socially relevant when considering the number of people undergoing AIT.

In 2007, a study [47] examined the cost-effectiveness of SCIT versus SDT in adults with grass-pollen-induced allergic rhinoconjunctivitis who did not respond adequately to SDT. The clinical efficacy of SCIT was based on the findings from the UK Immunotherapy Study Group (UKIS) trial, a 1-year, randomized, double-blind, single-controlled trial [67]. Results from this 1-year study were extended to 3 years of SCIT and an additional 6 years of follow-up. The cost-effectiveness of SCIT plus SDT versus SDT when considered in terms of symptom-free days (SFDs) or well days fell within the range of €10 000–€25 000 per quality adjusted life year (QALY) from the perspective of the healthcare systems of Austria, Denmark, Finland, Germany, the Netherlands, and Sweden. SCIT was even more effective and less expensive from the societal perspective, for which indirect costs were included.

In 2008, an economic analysis based on a Markov model compared the cost-effectiveness of SCIT plus SDT versus SDT for the treatment of allergic rhinitis and allergic asthma from the perspectives of the German healthcare system and society [41]. Total societal cost after 15 years amounted to €26 100 with SDT and €24 000 with SCIT plus SDT, with an annual cost savings of €140 per SCIT-treated patient. The break-even point of cumulative costs between treatment alternatives was achieved in the 10th year. From the healthcare system perspective, a patient treated with SCIT and SDT incurred annual costs of approximately €750 compared with €690 for those receiving only SDT.

Hankin *et al.* [44,45,46^{***}] conducted three economic studies comparing the cost consequences of SCIT versus SDT by examining healthcare utilization and costs of patients enrolled in Florida Medicaid. The first study compared healthcare utilization and costs of children newly diagnosed with allergic rhinitis who initiated de-novo AIT. Investigators compared the utilization and costs incurred during the 6 months before SCIT initiation to utilization and costs incurred by these children in the 6 months following SCIT discontinuation [44]. Inpatient, outpatient, pharmacy utilization and costs, and total healthcare costs (\$1635 versus \$1850, $P < 0.0001$) were significantly lower in the post-SCIT versus pre-SCIT phases. The second study [45] was a retrospective matched cohort analysis comparing 18-month healthcare utilization and costs between children with newly diagnosed allergic rhinitis who received de-novo SCIT to matched controls with newly diagnosed allergic rhinitis who did not receive SCIT. Children who received SCIT incurred significantly lower 18-month median per-patient total healthcare costs (\$3247 versus \$4872), outpatient costs exclusive of immunotherapy-related care (\$1107 versus \$2626), and pharmacy costs (\$1108 versus \$1316) compared with the matched controls ($P < 0.001$ for all). The significant difference in total healthcare costs was evident 3 months after initiating immunotherapy and increased through study end. In a similarly designed study [46^{***}], investigators found that results previously identified for children similarly extended to adults: children and adults with newly diagnosed allergic rhinitis who received de-novo SCIT incurred, respectively, 42% ($P < 0.0001$) and 30% ($P < 0.0001$) lower 18-month total healthcare costs than matched controls with newly diagnosed allergic rhinitis who did not receive SCIT. Again, significant differences between SCIT and matched control groups were evident within the first 3 months of SCIT initiation and were maintained throughout the 18-month study follow-up.

Longitudinal drug cost, break-even, and cost-effectiveness analyses from the perspective of the German healthcare system were conducted to examine the effects of SCIT on children and adolescents with HDM-induced allergic asthma [50]. Total drug costs achieved a significant difference in the year 3 following SCIT initiation. Break-even was expected in year 7 (4 years after the completion of a 3-year course of SCIT). In the CEA, superior efficacy (in terms of mean annual adjusted morning peak flow) was achieved for patients receiving SCIT. Investigators concluded that there was a 90% probability that SCIT leads to superior efficacy compared with controls.

The remaining two studies pertaining to SCIT do not specifically examine the cost-saving evidence of treatment.

The first of these studies compared the costs of an accelerated (3-week) cluster schedule to the costs of a traditional (13-week) up-dosing schedule [48]. Only costs for allergen extract (at €5.75 per injection) and patient wait time spent following each clinic visit (at €17.3/h) during the up-dosing period were included in this highly idiosyncratic analysis [48]. It is, therefore, not surprising that investigators found the cluster schedule to yield significantly greater cost savings than the traditional up-dosing schedule.

The other study [43] examined the retrospective claims of health maintenance enrollees with allergic rhinitis or allergic asthma due to a range of allergy sensitivities who were classified as having 'completed' (defined as having received ≥ 61 SCIT injections within a parallel 3.5-year period from SCIT initiation) versus not having completed (defined as having received < 61 injections during a parallel period) SCIT. The duration of follow-up after SCIT discontinuation was highly variable, with a mean duration of 7 months. Investigators found that enrollees who did not complete SCIT incurred lower costs during treatment than counterparts who had completed 3.5 years of treatment. This stands to reason, given that treatment completers had more severe allergic illness and used more services at baseline, and no adjustments for baseline illness severity were made.

THE HEALTH ECONOMICS OF SUBLINGUAL IMMUNOTHERAPY TABLETS

Eight studies [52–58,59^{***}] examined the health economics of SLIT tablets.

The first was a retrospective analysis of 135 Italian children and adolescents with allergic rhinitis [54]. Patients' medical records during the year preceding and 3 years during SLIT were examined to determine the healthcare utilization and school days absent because of allergic rhinitis. Mean annual healthcare costs per patient were 56% (€282) lower during SLIT than before SLIT. When indirect costs attributable to lost school or work days were included, mean annual total costs per patient were 76% lower (€2043) during SLIT compared with before SLIT. A second analysis compared a subgroup of 41 children with allergic asthma who received SLIT with a matched control group extracted from a network database of pediatricians of 35 children with allergic asthma who had not received SLIT. The direct cost per patient over 4 years of

follow-up was €1182 for SLIT-treated patients and €1100 for controls.

Four economic evaluations based on the same randomized controlled trial assessed the cost-effectiveness of SLIT (Grazax) for treating grass-pollen-induced allergic conjunctivitis in Northern Europe [52], Southern Europe [57], the UK [58], and for seasonal and perennial allergic conjunctivitis in Sweden [53]. All the four studies adopted a societal perspective. The three European studies had a 9-year time horizon; the seasonal and perennial study [52] applied a time horizon of up to 15 years. SLIT was cost-effective (i.e. cost per QALY gained < €29 200) at a cost of less than €2200 in seven Northern European countries. Similarly, SLIT was cost-effective at a cost of less than €1900 in four Southern European countries [57]. In the UK, the cost per QALY gained with SLIT versus SDT was £4319 (€6380) [58]. The analysis of seasonal versus perennial SLIT found that the most cost-effective outcome occurred with persistent daily use over 3 years when the time horizon was 6.3 years or more [53].

The Sublingual Immunotherapy Pollen Allergy Italy (SPAI) study [55] was designed to evaluate the costs and consequences of using SLIT in association with SDT compared with SDT alone in 2200 young adults with allergic rhinitis because of pollen allergy. From both the healthcare system and societal perspectives, SLIT plus SDT was more effective and less costly than SDT alone, with 21% (€507) lower direct costs and 33% (€2113) lower total costs over 6 years (3 years of SLIT or SDT and 3 years of follow-up).

The Sublingual Immunotherapy in Allergic Patients (SIMAP) study [56] was a 1-year observational evaluation of efficacy, safety, and cost in 102 Italian children and adults with grass-pollen-induced allergic rhinitis who had received SLIT or SDT. Mean annual cost of treatment was higher in the SLIT versus SDT group (€311 versus €180, $P < 0.0001$). The difference in total costs was mainly because of costs of SLIT. Patients with allergic rhinitis and asthma generated more cost than those with allergic rhinitis alone in both groups.

Ruggeri *et al.* [59^{***}] examined the cost-effectiveness of five grass pollen tablets for the treatment of grass-pollen-induced allergic rhinitis in adults. Effectiveness data were based on findings from two randomized controlled trials; healthcare resource use was derived from a retrospective claims analysis. A clinically significant improvement was defined by a gain of at least 1.45 points in the Adjusted (for rescue medication use) Average Daily Symptom Score (AAdSS). From the third-party payer perspective, SLIT was found to cost €1024/QALY for

patients with a medium AAdSS and €1035 for patients with a high AAdSS. Multivariate probabilistic sensitivity analysis indicated that the incremental cost-effectiveness ratio (ICER) remained below €30 000 in 99% of scenarios tested.

THE HEALTH ECONOMICS OF SUBLINGUAL IMMUNOTHERAPY DROPS

Ariano *et al.* [60] conducted a cost-consequence analysis based on a prospective, randomized, single-center trial of 50 clinic-treated patients aged 8–50 years with allergic asthma due to HDM. Patients were randomized to receive a 3-year course of SLIT liquid drops plus SDT or SDT alone. Patients in both groups completed daily diaries to document symptom severity, medication use, and health services utilization. Clinic visits, which occurred at 6-month intervals, assessed lung function (e.g. spirometry) as well as atopic status (including skin prick tests), and to review patient diaries. The study spanned 5 years to include 2-year outcomes following SLIT discontinuation. Compared with patients receiving SDT alone, mean, annual per-patient costs (SLIT plus allergy-related medications) incurred by the patients receiving SLIT plus SDT were higher in year 1, equivalent in years 2 and 3, and significantly lower in years 4 and 5. Annual, per-patient incremental costs in year 5 were €3881 for patients who received SLIT plus SDT, and €5020 for those who received SDT; this represented a net saving of 23%. The year 5 savings, in terms of annual per-patient incremental costs that were achieved by patients receiving SLIT plus SDT increased with disease severity and reached 34% for severe asthmatic patients.

Investigators interviewed Medicare and eight preferred party payers in the USA to identify reimbursement practices for SLIT drops and SCIT injections from the patient's perspective. Investigators found that no U.S. insurers covered the costs for SLIT [61]. Based purely on insurance coverage, the authors concluded that SCIT can be more cost-effective than paying out-of-pocket for SLIT. Investigators acknowledged that this conclusion does not take into account indirect costs and expenses as well as time and effort saved from weekly 30-min injection appointments for SCIT, which may be required for several years.

THE HEALTH ECONOMICS OF SUBLINGUAL IMMUNOTHERAPY TABLETS VERSUS SUBCUTANEOUS IMMUNOTHERAPY WITH OR WITHOUT SYMPTOMATIC DRUG TREATMENT

Four publications compared the outcomes among SLIT, SCIT, and SDT [62^{***}, 63–65], and one compared

the health economic findings of SCIT versus SLIT [66].

A CEA was performed using a decision-tree model from the societal perspective, comparing SCIT, SLIT, and SDT in French adults and adolescents with HDM and pollen allergy [63]. Adults were assumed to have received AIT for 4 years and adolescents for 3 years. In adults, the incremental cost per asthma case avoided with SCIT versus SDT was €393 for HDM and €1327 for pollen allergy over a 6-year period. In adolescents, the incremental cost per asthma case avoided with SCIT versus SDT was €583 for HDM and €597 for pollen allergy over a 7-year period. The ICER per additional improved patient ranged from €349 (in adolescents with HDM allergy) to €722 (in adults with pollen allergy). The model presents at least two notable limitations. First, the model excludes costs for allergy-related and asthma-related hospitalizations; the authors, therefore, acknowledge that the cost benefits of AIT may be underestimated. Second, and most importantly, model parameters and assumptions are not clearly explicated, and the reader is unable to confirm the authors' conclusions that AIT (whether delivered subcutaneously or sublingually) is a cost-effective treatment option in allergic rhinitis and asthma due to pollen and house dust mite, and that SLIT is an attractive option in pollen-induced allergic rhinitis, particularly in children.

Pokladnikova *et al.* [64] evaluated the cost-effectiveness of SLIT compared with SCIT and SDT over 3 years from third-party payer and societal perspectives in the Czech Republic. Total direct medical costs after 3 years of AIT were higher in the SCIT compared with the SLIT group (€416 versus €482, $P < 0.001$). From a societal perspective, SLIT was 32% less expensive than SCIT (€684 versus €1004, $P < 0.001$).

Westerhout *et al.* [65] evaluated the cost-effectiveness of 3 years of treatment with Oralair compared with Grazax (SLIT), Alk Depot SQ (SCIT), or SDT for the treatment of grass-pollen-induced allergic rhinitis from the German healthcare system perspective over a time horizon of 9 years. A meta-analysis of randomized controlled trials of the three active treatments was conducted to determine the effectiveness of each treatment compared with placebo for reducing rhinoconjunctivitis symptom scores and improving the number of SFDs during the pollen season. The incremental cost per QALY and SFD gained with Oralair compared to SDT was €14 728 and €28, respectively. Oralair was the dominant strategy compared with Grazax and Alk Depot SQ.

A budget-impact analysis comparing grass SLIT (Grazax; ALK) and SCIT (Alutard; ALK-Abello) from the perspective of the Danish healthcare system

found that SLIT was associated with a total cost savings of €3450 per patient (48%) relative to SCIT [66]. This analysis suggests that, if 1500 patients were treated with grass pollen SLIT instead of SCIT, it would be possible to treat approximately 600 more patients per year without increasing the current cost to the healthcare system.

In the most recently published health economic study [62²²], investigators conducted a cost-minimization analysis based on a systematic literature review of double-blind, randomized, placebo-controlled trials that compared four treatments from the Canadian healthcare perspective: Oralair (seasonally administered) and Grazax (perennially administered) SLIT tablets and perennially administered and seasonally administered SCIT. There were 20 trials that satisfied the selection criteria. The indirect analysis suggested improved efficacy in terms of allergic rhinitis symptom control with Oralair over SCIT [standardized mean difference (SMD) = -0.21; $P = 0.007$] and Grazax (SMD = -0.18; $P = 0.018$). There were no significant differences in the risk of discontinuation because of adverse events among therapies. In the first year of treatment, Oralair was associated with significant cost savings compared with SCIT administered throughout the year (\$2471), SCIT administered seasonally (\$948), and Grazax administered throughout the year (\$1168). It is likely that the seasonal administration of Oralair contributed to the product's favorable cost savings when compared to perennially administered Grazax and SCIT. However, the significant cost benefits reported for Oralair versus seasonally administered SCIT remain noteworthy.

CONCLUSION

We examined 27 publications pertaining to the health economics of AIT. These publications span 18 years of research conducted across Southern Europe, Scandinavia, Northern Europe, North America, and the Czech Republic, and encompass a range of perennial and seasonal allergic conditions, including allergic asthma, allergic rhinitis with or without asthma, and rhinoconjunctivitis with or without allergic rhinitis due to house dust mite, grass or ragweed pollen, or a mixture of various allergens. Of the 27 publications originally identified, 3 were disqualified (one compared the duration of AIT [43], another examined cluster versus traditional SCIT up-dosing [48], and a third study compared the economic outcomes between SCIT with inhaled corticosteroid (ICS) versus ICS alone) [50]. Among the remaining 24 published studies meeting the selection criteria, 9 pertained to the health economics of SCIT

[40–42,44,45,46[■],47,48,51]; 8 to the health economics of SLIT tablets [52–58,59[■]]; 2 pertained to the health economics of SLIT liquid drops [60,61]; 4 publications compared the economic outcomes of SLIT, SCIT, and SDT [62[■],63–65]; and 1 compared health economic findings of SCIT versus SLIT [6].

One study [43] compared the outcomes of patients who completed versus who did not complete at least 3.5 years of AIT; a second study [49] compared the outcomes between patients who received SCIT cluster versus traditional SCIT up-dosing; and a third compared the outcomes of patients who received SCIT with ICS versus ICS alone [50].

We found that with the exception of one early study [42] that compared the costs for AIT to costs for SDT, the remaining 23 comparative cost studies provide compelling evidence for the cost savings of AIT (whether delivered subcutaneously or sublingually) over SDT. This early study reported findings from the first 2 years of treatment; it is possible that a more prolonged observation period would have yielded results that are more consistent with the remaining body of literature. Furthermore, of the six studies [61,62[■],63–66] comparing the cost outcomes of SLIT to SCIT, only two reported cost savings in favor of SCIT [61,63]. The first idiosyncratically included costs only incurred by the patient [61] and the second relied extensively upon expert opinion [63].

The worldwide prevalence of allergic disease is accelerating in concert with its growing clinical and economic burden. AIT is the only currently available treatment that has the potential to modify the immune system and thereby halt disease progression, mitigate disease severity, and prevent the development of new allergies. Given the burgeoning availability of SLIT, concerns regarding the economic viability of AIT in general, and SLIT specifically, are quite relevant. Among the 27 publications identified for the current systematic review, there were 24 that were most germane to our investigation. Nearly all compellingly demonstrate the cost savings conferred by AIT over SDT.

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Conflicts of interest

Cheryl Hankin, PhD, is a consultant for Stallergenes. There are no relevant conflicts of interest for Linda Cox, MD.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Schoenwetter WF. Allergic rhinitis: epidemiology and natural history. *Allergy Asthma Proc* 2000; 21:1–6.
2. Ozdoganoglu T, Songu M. The burden of allergic rhinitis and asthma. *Ther Adv Respir Dis* 2012; 6:11–23.
3. Valovirta E, editor. EFA book on respiratory allergies. Brussels, Belgium: European Federation of Allergy and Airways Diseases Patients Associations; 2011. Available at <http://www.theipcr.org/download/attachments/689587/EFABookonRespiratoryAllergiesFINAL.pdf?version=1&modificationDate=1332965739000>. [Accessed 6th May 2014]
4. Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol* 2008; 122 (2 Suppl.):S1–S84.
5. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011; 127 (1 Suppl.):S1–S55.
6. Moller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002; 109:251–256.
7. Novembre E, Galli E, Landi F, et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2004; 114:851–857.
8. Polosa R, Li Gotti F, Mangano G, et al. Effect of immunotherapy on asthma progression, BHR and sputum eosinophils in allergic rhinitis. *Allergy* 2004; 59:1224–1228.
9. Niggemann B, Jacobsen L, Dreborg S, et al. Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. *Allergy* 2006; 61:855–859.
10. Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007; 62:943–948.
11. Marogna M, Tomassetti D, Bernasconi A, et al. Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. *Ann Allergy Asthma Immunol* 2008; 101:206–211.
12. Des Roches A, Paradis L, Menardo JL, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol* 1997; 99:450–453.
13. Pajno GB, Barberio G, De Luca F, et al. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy* 2001; 31:1392–1397.
14. Purello-D'Ambrosio F, Gangemi S, Merendino RA, et al. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not: a retrospective study. *Clin Exp Allergy* 2001; 31:1295–1302.
15. Marogna M, Falagiani P, Bruno M, et al. The allergic march in pollinosis: natural history and therapeutic implications. *Int Arch Allergy Immunol* 2004; 135:336–342.
16. Gulen F, Zeyrek D, Can D, et al. Development of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. *Asian Pac J Allergy Immunol* 2007; 25:7–11.
17. Inal A, Altintas DU, Yilmaz M, et al. Prevention of new sensitizations by specific immunotherapy in children with rhinitis and/or asthma monosensitized to house dust mite. *J Investig Allergol Clin Immunol* 2007; 17:85–91.
18. Reha CM, Ebru A. Specific immunotherapy is effective in the prevention of new sensitivities. *Allergol Immunopathol (Madr)* 2007; 35:44–51.
19. Marogna M, Spadolini I, Massolo A, et al. Long-lasting effects of sublingual immunotherapy according to its duration: a 15-year prospective study. *J Allergy Clin Immunol* 2010; 126:969–975.
20. Hedlin G, Heilborn H, Lilja G, et al. Long-term follow-up of patients treated with a three-year course of cat or dog immunotherapy. *J Allergy Clin Immunol* 1995; 96 (6 Pt 1):879–885.
21. Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999; 341:468–475.
22. Grammer LC, Shaughnessy MA, Suszko IM, et al. Persistence of efficacy after a brief course of polymerized ragweed allergen: a controlled study. *J Allergy Clin Immunol* 1984; 73:484–489.
23. Mosbech H, Osterballe O. Does the effect of immunotherapy last after termination of treatment? Follow-up study in patients with grass pollen rhinitis. *Allergy* 1988; 43:523–529.
24. Des Roches A, Paradis L, Knani J, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. V. Duration of the efficacy of immunotherapy after its cessation. *Allergy* 1996; 51:430–433.
25. Musarra A, Bignardi D, Troise C, Passalacqua G. Long-lasting effect of a monophosphoryl lipid-adjuvanted immunotherapy to parietaria: a controlled field study. *Eur Ann Allergy Clin Immunol* 2010; 42:115–119.

26. James LK, Shamji MH, Walker SM, *et al.* Long-term tolerance after allergen immunotherapy is accompanied by selective persistence of blocking antibodies. *J Allergy Clin Immunol* 2011; 127:509–516; e501–e505.
 27. Tabar AI, Arroabarren E, Echechipia S, *et al.* Three years of specific immunotherapy may be sufficient in house dust mite respiratory allergy. *J Allergy Clin Immunol* 2011; 127:47–63.
 28. Ariano R, Kroon AM, Augeri G, *et al.* Long-term treatment with allergoid immunotherapy with Parietaria: clinical and immunologic effects in a randomized, controlled trial. *Allergy* 1999; 54:313–319.
 29. Eng PA, Borer-Reinhold M, Heijnen IA, Gnehm HP. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. *Allergy* 2006; 61:198–201.
 30. Eng PA, Reinhold M, Gnehm HP. Long-term efficacy of preseasonal grass pollen immunotherapy in children. *Allergy* 2002; 57:306–312.
 31. Di Rienzo V, Marcucci F, Puccinelli P, *et al.* Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. *Clin Exp Allergy* 2003; 33:206–210.
 32. Durham SR, Emminger W, Kapp A, *et al.* Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. *J Allergy Clin Immunol* 2010; 125:131–138; e131–e137.
 33. Durham SR, Emminger W, Kapp A, *et al.* SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol* 2012; 129:717–725; e715.
 34. Tahamiler R, Saritzali G, Canakcioglu S. Long-term efficacy of sublingual immunotherapy in patients with perennial rhinitis. *Laryngoscope* 2007; 117:965–969.
 35. Didier A, Malling HJ, Worm M, *et al.* Posttreatment efficacy of discontinuous treatment with 300IR 5-grass pollen sublingual tablet in adults with grass pollen-induced allergic rhinoconjunctivitis. *Clin. Exp Allergy* 2013; 43:568–577.
- In this double-blind, placebo-controlled trial, adults with allergic rhinitis due to grass pollen were randomized to receive 4 months of Oralair 300 IR prior to the expected start of pollen season and throughout the season; 2 months of placebo, then 2 months of Oralair 300 IR prior to the expected start of pollen season and continued through the season; or placebo for 4 months prior to the expected start of pollen season and through the season. These regimens were continued for 3 years. Results were obtained in the 4th year (1 year posttreatment discontinuation). Both regimens of Oralair continued to show significantly improved efficacy in the posttreatment year over placebo. Note that the FDA approval supports only the 4-month preseasonal and co-seasonal regimen based on these and the findings published elsewhere.
36. Marogna M, Bruno M, Massolo A, Falagiani P. Long-lasting effects of sublingual immunotherapy for house dust mites in allergic rhinitis with bronchial hyperreactivity: a long-term (13-year) retrospective study in real life. *Int Arch Allergy Immunol* 2007; 142:70–78.
 37. Stallergenes. Oralair [Product Insert]. Antony, France: Stallergenes S.A.; 2014.
 38. Merck. Grastek [Product Insert]. Whitehouse Station, NJ: Merck & Co.; 2014.
 39. Merck. Ragwitek [Product Insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2014.
 40. Ariano R, Berto P, Tracci D, *et al.* Pharmacoeconomics of allergen immunotherapy compared with symptomatic drug treatment in patients with allergic rhinitis and asthma. *Allergy Asthma Proc* 2006; 27:159–163.
 41. Bruggenjurgen B, Reinhold T, Brehler R, *et al.* Cost-effectiveness of specific subcutaneous immunotherapy in patients with allergic rhinitis and allergic asthma. *Ann Allergy Asthma Immunol* 2008; 101:316–324.
 42. Creticos PS, Reed CE, Norman PS, *et al.* Ragweed immunotherapy in adult asthma. *N Engl J Med* 1996; 334:501–506.
 43. Donahue JG, Greineder DK, Connor-Lacke L, *et al.* Utilization and cost of immunotherapy for allergic asthma and rhinitis. *Ann Allergy Asthma Immunol* 1999; 82:339–347.
 44. Hankin CS, Cox L, Lang D, *et al.* Allergy immunotherapy among Medicaid-enrolled children with allergic rhinitis: patterns of care, resource use, and costs. *J Allergy Clin Immunol* 2008; 121:227–232.
 45. Hankin CS, Cox L, Lang D, *et al.* Allergen immunotherapy and healthcare cost benefits for children with allergic rhinitis: a large-scale, retrospective, matched cohort study. *Ann Allergy Asthma Immunol* 2010; 104:79–85.
 46. Hankin CS, Cox L, Bronstone A, Wang Z. Allergy immunotherapy: reduced healthcare costs in adults and children with allergic rhinitis. *J Allergy Clin Immunol* 2013; 131:1084–1091.
- The authors found that the significant benefits of AIT (SCIT) they previously reported for children enrolled in Florida Medicaid also extended to adult enrollees. Children and adults with newly diagnosed allergic rhinitis who received de-novo SCIT incurred, respectively, 42% ($P < 0.0001$) and 30% ($P < 0.0001$) lower 18-month total healthcare costs compared with matched controls with newly diagnosed allergic rhinitis who did not receive SCIT. Significant differences ($P > 0.001$) between patients who received SCIT and matched controls were demonstrated as early as 3 months for the child, adult, and combined (child and adult) samples.
47. Keiding H, Jorgensen KP. A cost-effectiveness analysis of immunotherapy with SQ allergen extract for patients with seasonal allergic rhinoconjunctivitis in selected European countries. *Curr Med Res Opin* 2007; 23:1113–1120.
 48. Mauro M, Russello M, Alesina R, *et al.* Safety and pharmacoeconomics of a cluster administration of mite immunotherapy compared to the traditional one. *Eur Ann Allergy Clin Immunol* 2006; 38:31–34.
 49. Petersen KD, Gyrd-Hansen D, Dahl R. Health-economic analyses of subcutaneous specific immunotherapy for grass pollen and mite allergy. *Allergol Immunopathol (Madr)* 2005; 33:296–302.
 50. Reinhold M, Willich S, Brüggengjürgen B. Subcutaneous specific immunotherapy: economic implications from the perspective of statutory health insurance – a population based cost-effectiveness estimation. *Allergologie* 2012; 35:539–550.
 51. Schädlich PK, Brecht JG. Economic evaluation of specific immunotherapy versus symptomatic treatment of allergic rhinitis in Germany. *Pharmacoeconomics* 2000; 17:37–52.
 52. Bachert C, Vestenbaek U, Christensen J, *et al.* Cost-effectiveness of grass allergen tablet (GRAZAX(R)) for the prevention of seasonal grass pollen induced rhinoconjunctivitis: a Northern European perspective. *Clin Exp Allergy* 2007; 37:772–779.
 53. Beriot-Mathiot A, Vestenbaek U, Bo Poulsen P. Influence of time horizon and treatment patterns on cost-effectiveness measures: the case of allergen-specific immunotherapy with Grazax. *J Med Econ* 2007; 10: 215–228.
 54. Berto P, Bassi M, Incorvaia C, *et al.* Cost effectiveness of sublingual immunotherapy in children with allergic rhinitis and asthma. *Allergy Immunol (Paris)* 2005; 37:303–308.
 55. Berto P, Passalacqua G, Crimi N, *et al.* Economic evaluation of sublingual immunotherapy vs symptomatic treatment in adults with pollen-induced respiratory allergy: the Sublingual Immunotherapy Pollen Allergy Italy (SPAI) study. *Ann Allergy Asthma Immunol* 2006; 97:615–621.
 56. Berto P, Frati F, Incorvaia C, *et al.* Comparison of costs of sublingual immunotherapy and drug treatment in grass-pollen induced allergy: results from the SIMAP database study. *Curr Med Res Opin* 2008; 24:261–266.
 57. Canonica GW, Bousquet J, Mullol J, *et al.* A survey of the burden of allergic rhinitis in Europe. *Allergy* 2007; 62 (Suppl. 85):17–25.
 58. Nasser S, Vestenbaek U, Beriot-Mathiot A, Poulsen PB. Cost-effectiveness of specific immunotherapy with Grazax in allergic rhinitis co-existing with asthma. *Allergy* 2008; 63:1624–1629.
 59. Ruggeri M, Oradei M, Frati F, *et al.* Economic evaluation of 5-grass pollen tablets versus placebo in the treatment of allergic rhinitis in adults. *Clin Drug Investig* 2013; 33:343–349.
- This cost-effective analysis stratified results by high, medium, and low burden of allergic rhinitis according to the Average Adjusted Symptom Score (AAdSS). The findings demonstrated cost-effectiveness for patients with medium and high allergic-rhinitis-related burden.
60. Ariano R, Berto P, Incorvaia C, *et al.* Economic evaluation of sublingual immunotherapy vs. symptomatic treatment in allergic asthma. *Ann Allergy Asthma Immunol* 2009; 103:254–259.
 61. Seiberling K, Hiebert J, Nyirady J, *et al.* Cost of allergy immunotherapy: sublingual vs subcutaneous administration. *Int Forum Allergy Rhinol* 2012; 2:460–464.
 62. Dranitsaris G, Ellis AK. Sublingual or subcutaneous immunotherapy for seasonal allergic rhinitis: an indirect analysis of efficacy, safety and cost. *J Eval Clin Pract* 2014; 20:225–238.
- This Canadian study examined the published literature of placebo-controlled trials to identify the lowest first year cost of AIT for grass-pollen-induced allergic rhinitis among four treatments: Oralair SLIT tablets, which are administered once-daily 4 months before and 1 month during allergy season; Grazax SLIT tablets, which are administered daily throughout the year; and perennially administered and seasonally administered SCIT. There were 20 trials that satisfied the selection criteria. Investigators found that Oralair had at least noninferior efficacy and comparable safety against SCIT and Grazax at a lower annual cost.
63. Omnes LF, Bousquet J, Scheinmann P, *et al.* Pharmacoeconomic assessment of specific immunotherapy versus current symptomatic treatment for allergic rhinitis and asthma in France. *Allergy Immunol (Paris)* 2007; 39:148–156.
 64. Pokladnikova J, Krcmova I, Vlcek J. Economic evaluation of sublingual vs subcutaneous allergen immunotherapy. *Ann Allergy Asthma Immunol* 2008; 100:482–489.
 65. Westerhout KY, Verheggen BG, Schreder CH, Augustin M. Cost effectiveness analysis of immunotherapy in patients with grass pollen allergic rhinoconjunctivitis in Germany. *J Med Econ* 2012; 15:906–917.
 66. Ronborg SM, Svendsen UG, Michélsen JS, *et al.* Budget impact analysis of two immunotherapy products for treatment of grass pollen-induced allergic rhinoconjunctivitis. *Clinicoecon Outcomes Res* 2012; 4:253–260.
 67. Frew AJ, Powell RJ, Corrigan CJ, Durham SR. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006; 117:319–325.