



Allergy immunotherapy in reducing healthcare cost

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Purpose of review

To evaluate the cost-effectiveness of allergen immunotherapy (AIT) in the treatment of allergic rhinitis and asthma. Individual studies and systematic reviews that included information on AIT economic outcomes as compared with symptomatic drug treatment (SDT) were evaluated.

Recent findings

One systematic review that included 14 studies concluded that subcutaneous and sublingual immunotherapy may be cost-effective compared with SDT from around 6 years. Another systematic review of 24 studies comparing economic outcomes of subcutaneous allergy immunotherapy and/or sublingual allergy immunotherapy with SDT found compelling evidence for cost-savings with both forms of AIT over SDT. There was no strong evidence indicating superior cost-efficacy of subcutaneous allergy immunotherapy or sublingual allergy immunotherapy over SDT in either of these systematic reviews. Individual studies have demonstrated AIT cost-savings as high as 80% compared with SDT. Significant cost-savings were reported as early as 3 months after AIT initiation. In some studies, cost-efficacy time-point was not established until after treatment discontinuation – presumably due to time required for the clinical benefits to outweigh the AIT treatment costs. Although some economic modeling studies included the costs of ‘asthma prevented’, the collective literature of AIT economics provides very little to no information about the cost benefits of the preventive aspect of AIT.

Summary

Overall, individual studies and systematic reviews provide strong evidence for the cost-effectiveness of AIT over SDT. The magnitude of cost-efficacy is likely underestimated in that few studies consider the cost-savings due to AIT’s long-term benefits or preventive effect.

Keywords

allergen immunotherapy, allergic rhinitis, asthma, cost-comparativeness, cost-efficacy, pharmacoeconomics, sublingual immunotherapy

INTRODUCTION

Allergic rhinitis and asthma are chronic, common conditions that can result in significant costs to patients, healthcare systems, and society. Multiple studies have demonstrated the superior clinical efficacy of allergen immunotherapy (AIT) as compared with symptomatic drug treatment (SDT) in reducing disease symptomatology. However, other outcomes, such as improved quality of life and cost-effectiveness, are becoming more important to patients, payers, and other healthcare decision-makers [1]. It is likely in the near future that it will no longer be sufficient for new therapies to demonstrate efficacy and safety. But rather, they likely may be required to demonstrate that the improved clinical outcome was associated with cost-savings as compared with standard treatment. Few AIT studies have included cost comparison in their outcome assessment. This review will examine the cost-effectiveness of AIT in the

published studies, as well as two systematic reviews examining the pharmacoeconomics of AIT. The review will also consider the economic burden of allergic rhinitis and asthma.

BURDEN OF ALLERGIC DISEASE

Allergic rhinitis and asthma are amongst the most common and costliest chronic conditions worldwide. The overall prevalence of physician-diagnosed asthma in the Global Health Survey was 4.3%, but

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KEY POINTS

- Allergic asthma and allergic rhinitis carry considerable direct and indirect costs. Both conditions are associated with a number of comorbid illnesses that can compound these costs. Both conditions can require years of symptomatic treatment. All of these factors need to be considered when considering treatment cost-effectiveness.
- In contrast to pharmacotherapy, AIT can provide long-term clinical benefits after discontinuation. The sustained benefits of AIT can translate into cost-savings as high as 80% as compared to SDT in one study.
- Two systematic reviews evaluating the economics of AIT concluded that SLIT and SCIT were cost-effective compared with SDT with no strong evidence favoring either route.
- The cost-effective time-point was determined to be about 6 years after AIT initiation in one systematic review, but was seen as early as 3 months in a large retrospective claim analysis.

varied by as much as 21-fold amongst the 70 countries surveyed [2]. In the United States, asthma prevalence was reported at its highest level in 2010 at 8.4% (25.7 million persons) [3].

Global estimates suggest that allergic rhinitis affects approximately 500 million people [4]. Developed countries have higher allergic rhinitis incidence. It is estimated that 113 million people in Europe [5] and 30–60 million in the United States are affected by allergic rhinitis [6,7]. Studies comparing allergic rhinitis prevalence in patient-reported questionnaires with subsequent clinically confirmed allergic rhinitis suggest that allergic rhinitis is frequently underdiagnosed [8,9]. In some studies, 43–70% of the undiagnosed allergic rhinitis patients had longstanding symptoms before the clinical diagnosis was established [8,9]. In addition to underdiagnosis, these studies indicate that allergic rhinitis and asthma are often undertreated and/or poorly controlled [10–12]. In a study aimed at determining ‘... the extent of unawareness and undertreatment of asthma and allergic rhinitis’ in a Danish adult and adolescent population using standardized questionnaires, skin prick tests, and pulmonary function tests, 50% of asthmatic patients and 32% of rhinitis patients had not been previously diagnosed with these conditions [12]. In the diagnosed patients, 76% of asthmatic patients and 83% of patients with moderate to severe rhinitis were undertreated according to guideline recommendations. Many allergic rhinitis patients remain untreated or self-treat with over-the-counter (OTC) medications. In a random sample survey of European adults, only 50% of the

936 respondents with diagnosed allergic rhinitis had received an allergic rhinitis prescription [11]. The remainder of the diagnosed allergic rhinitis patients were untreated (28%) or pursued OTC self-treatment (21%). In an internet and telephone survey of 2966 adults with allergies, 52.6% of the respondents admitted to not seeing medical professionals in the past year for their rhinitis symptoms [10]. In this survey, the ‘nontreaters’ and ‘homeopathic treaters’ combined represented 26.2% of the respondents, 40.2% of whom cited medication costs as a reason they did not use allergy medications.

COSTS OF ALLERGIC DISEASE: DIRECT AND INDIRECT

There is convincing evidence that allergic rhinitis is a risk factor for developing asthma. One longitudinal study of 8275 children examining the association between allergic rhinitis and subsequent asthma found that children with allergic rhinitis had a 2–7-fold increased risk of incident asthma in preadolescence, adolescence, or adult life [13]. Aeroallergens can play a significant role in asthma pathogenesis and disease activity. Published guidelines and expert reviews recommend allergy testing to an appropriate panel of perennial and seasonal allergens in patients with persistent asthma to characterize their asthma phenotype and potential triggers [14–16].

Asthma and allergic rhinitis are frequent comorbid conditions. Both can be associated with symptoms and other comorbid illnesses, such as presenteeism, impaired sleep with subsequent daytime fatigue, otitis media, and sinusitis. These consequent symptoms and associated conditions can significantly impair quality of life, as well as add to the direct and indirect costs of treatment.

Data from the Medical Expenditure Panel Survey – a longitudinal survey that collects detailed information on healthcare utilization and expenditures in the United States – estimated the direct costs of allergic rhinitis to be \$11.5 billion in 2005, with prescription medications (59%) accounting for the majority of the costs [17]. Direct cost estimates in this survey did not take into account the costs of OTC allergy medication, which were estimated at \$1.2–1.7 billion in 2008 [18]. In the United States, indirect costs related to OTC medications will likely increase as more prescription allergy medications become OTC.

The total indirect costs associated with allergic rhinitis can be considerable and may be greater than the direct costs [19,20]. In addition to costs of OTC medications, indirect costs include lost work productivity. In a survey of US employees, the total

annual cost of lost productivity attributable to allergic rhinitis was about \$600 per employee (2002 value) [21]. This was significantly higher than the cost for any other condition assessed, including diabetes and coronary heart disease. In Europe, the annual loss to employers related to untreated allergic rhinitis-related presenteeism has been estimated to be approximately €100 billion (2011 value) [22].

Asthma is the leading chronic illness of children in the United States. With a prevalence of approximately 8%, asthma currently affects over 7 million US children and 16 million US adults [23]. Total US direct medical care costs for asthma in 2010 were estimated at \$15.6–18 billion [23,24]. In the United States, a substantial portion of asthma direct medical costs are borne by the US public healthcare system – Medicaid. Approximately 30% of the adult asthma population is covered by Medicaid, whereas only 10% of the general population was covered by Medicaid [24]. In a US study that examined the incremental direct medical costs and productivity losses due to asthma, the estimated total direct and indirect costs to society combined was \$56 billion in 2007 [25].

ALLERGIC DISEASE TREATMENT PHARMACOECONOMICS

The management of allergic respiratory diseases is often multifaceted, and treatment recommendations may include environmental control measures, pharmacotherapy, and AIT. Ideally, the optimal approach would be complete allergen avoidance, but this is rarely achievable. Medications can be very effective in controlling allergy symptoms, but they are only effective when they are taken. Allergy medications provide no sustained benefits after discontinuation [26,27]. In contrast, AIT can provide symptomatic improvement during and years after discontinuation, as well as prevent the progression of the allergic disease [28,29]. Currently, the primary indications for AIT are allergic rhinitis/rhinoconjunctivitis and asthma [30], but there is evidence that it may be effective in some patients with atopic dermatitis and aeroallergen sensitization [31]. Food immunotherapy investigations have shown promising results in terms of desensitization during treatment, but many questions remain to be answered regarding long-term tolerance after discontinuation [32,33]. The two most commonly prescribed routes for aeroallergen AIT worldwide are subcutaneous [subcutaneous allergy immunotherapy (SCIT)] and sublingual [sublingual allergy immunotherapy (SLIT)]. The frequency of the prescribing route varies with

geographic location, but depends on a number of factors, such as availability of a regulatory body-approved extract [e.g. US Food and Drug Administration (FDA) or European Medical Agency], patient preference, and costs. In 2014, the US FDA approved three sublingual tablets for pollen-induced allergic rhinitis/rhinoconjunctivitis – 5-grass (Oralair, Stallergenes, Antony, France), short ragweed (Ragwitek, Merck & Co, Kenilworth, New Jersey, USA), and timothy (Grastek, Merck & Co). Prior to this, there were no US FDA-approved SLIT formulations and, to date, there continues to be no US FDA-approved formulation for SLIT drops. However, US FDA approval of a SLIT extract solution may be forthcoming. A large patient population phase III study that compared a US licensed ragweed extract ($N=218$) with placebo ($N=211$) demonstrated significant clinical efficacy with no significant adverse events [34]. If these findings are confirmed in a subsequent study, it is anticipated that the extract manufacturer will seek US FDA approval for a licensed SLIT ragweed extract solution.

In contrast to pharmacotherapy trials, virtually all AIT trials allow rescue medication use; thus, there is no true ‘untreated’ placebo group in these studies. In essence, the AIT placebo group is equivalent to a pharmacotherapy-alone group (e.g. SDT). Despite the allowance for rescue allergy medications, virtually all of the systematic reviews and meta-analyses of SCIT and SLIT for allergic rhinitis and asthma have demonstrated significant clinical efficacy over placebo [35]. A review of meta-analyses that included five or more randomized, double-blind, placebo-controlled (DBPC) trials of SCIT or ‘anti-symptomatic’ treatment provided indirect evidence that SCIT was at least as ‘potent as’, if not greater, than pharmacotherapy, in controlling symptoms of allergic rhinitis ‘as early as the first season of treatment’ (relative clinical impact: SCIT, $-34.7\% \pm 6.8\%$; mometasone, $-31.7\% \pm 16.7\%$; and montelukast, $-6.3\% \pm 3.0\%$; all $P < 0.00001$) [36].

Economic outcomes were not directly assessed in most of the randomized, DBPC AIT clinical trials. Thus, AIT’s resultant impact on treatment costs can only be estimated through medication scores and the secondary clinical outcomes reported (e.g. hospitalizations, or unscheduled clinic or emergency visits). Many clinical trials do not provide outcome information related to comorbid illnesses or the indirect costs of allergic rhinitis. Some of the studies that have compared the costs of pharmacotherapy with both forms of AIT have demonstrated substantial healthcare cost-savings during treatment [37,38]. This economic benefit would be even greater if one factors the persistent clinical improvement after treatment discontinuation and the potential preventive effect of

AIT outcomes that are not seen with pharmacotherapy [27]. One 6-year prospective study demonstrated 80% lower healthcare costs in the patients who received SCIT compared with SDT, 3 years after discontinuation [39]. The economic benefit of AIT over SDT has been confirmed from several different perspectives, for example, societal, healthcare system, third-party payer, or some combination of perspectives, which have included various outcomes in addition to direct costs (Tables 1 and 2). The analysis designs employed in these comparative studies varied and included 'real-life' retrospective claim reviews and theoretical economic modeling (e.g. cost-consequence analysis). The outcomes assessed also ranged from 'real-life' total healthcare costs to theoretical quality-adjusted life-years (QALYs) gained or number of asthma cases prevented. In some studies, cost-effectiveness was based on the presumption of

persistent efficacy for years after discontinuation or prevention of asthma. The QALY is a '... measure of the state of health in which the benefits, in terms of length of life, are adjusted to reflect the quality of life' [40]. QALYs are calculated by estimating the years of life remaining following a particular treatment or intervention, and weighting each year with a quality-of-life score (on a 0–1 scale), with one QALY equal to 1 year of life in perfect health [40].

ALLERGEN IMMUNOTHERAPY PHARMACOECONOMICS IN SYSTEMATIC REVIEWS

A systematic review and meta-analysis of studies that evaluated the costs and benefits of SCIT and/or SLIT with SDT published through April 2011 identified 14 economic evaluations and 2 reviews of economic evaluations (Table 1) [41].

Table 1. Studies comparing subcutaneous allergy immunotherapy with standard drug treatment

Study	Comparators	Type	Perspective	Results
Schadlich and Brecht, 2000 [42] ^c	Pollen or HDM SCIT for 3 years + SDT as needed; SDT	CEA	Society, healthcare system (HCS), third-party payer	SCIT < SDT over 10 years. Break-even point reached in the 7th year
Petersen <i>et al.</i> , 2005 [43] ^a	Grass or HDM SCIT for 3–5 years + 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 <i>et al.</i> , 2006 [39] ^c	<i>Parietaria</i> SCIT for 3 years + SDT as needed; SDT	CCA	Healthcare system, society	SCIT < SDT; 80% cost reduction found 3 years after stopping SCIT
Keiding and Jorgensen, 2007 [44] ^c	Grass SCIT for 3 years + SDT as needed; SDT	CEA CUA	Healthcare system, society	SCIT cost-effectiveness per QALY; in the range of €10 000–25 000 per QALY from perspective of the healthcare system
Omnes <i>et al.</i> , 2007 [45] ^c	HDM or pollen SCIT 3–4 years + SDT as needed; SDT	CEA	Society	Cost-effective per incremental cost of asthma cases avoided (ICER)
Bruggenjurgen <i>et al.</i> , 2008 [46] ^c	SCIT for 3 years + SDT as needed; SDT	CUA	Third-party payer, society	Break-even point = 10 years. After 15 years, annual cost-savings of €140 per SCIT-treated patient
Hankin <i>et al.</i> , 2008 [47] ^b	Costs 6 months before and 6 months after SCIT	CCA	Healthcare system	Weighted mean 6-month savings/patient: \$401
Hankin <i>et al.</i> , 2010 [48] ^b	SCIT for 18 months + SDT as needed; SDT as needed for 18 months	CCA	Healthcare system	SCIT 18-month total healthcare costs 33% reduction compared with SDT
Hankin <i>et al.</i> , 2013 [38 [■]] ^b	SCIT + SDT as needed for 18 months; SDT as needed for 18 months	CCA	Healthcare system	SCIT 18-month total healthcare costs compared with SDT: children: 42% reduction, adults: 30% reduction

CCA, cost-consequence analysis; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; HDM, house dust mite; SCIT, subcutaneous allergy immunotherapy; SDT, standard drug treatment; QALY, quality-adjusted life-year.

^aIncluded in the Meadows *et al.* [41] systematic review.

^bIncluded in the Hankin and Cox [59[■]] systematic review.

^cIncluded in both systematic reviews.

Table 2. Studies comparing sublingual allergy immunotherapy with standard drug treatment

Study	Comparators	Type	Perspective	Results
Berto <i>et al.</i> , 2005 [49] ^c	1 year of SDT before SLIT; SLIT for 3 years	CEA	Healthcare system, society	Cost-savings with SLIT per healthcare system and society: Year before SLIT: mean annual healthcare costs/annual total costs per patient were €506 and €2672, respectively During SLIT: €224 (healthcare costs) and €629 (total cost)
Berto <i>et al.</i> , 2006 [50] ^c	Pollen SLIT for 3 years + SDT as needed; SDT	CCA	Healthcare system, society	SCIT compared to SDT: Greater 6-year mean savings from payer and societal perspective More asthma cases avoided and patients improved
Bachert <i>et al.</i> , 2007 [51] ^c	Grass SLIT for 3 years + SDT as needed; SDT	CUA	Society	SLIT cost-effective cost per QALY; average 0.0287 QALYs per season compared with SDT
Beriot-Mathiot <i>et al.</i> , 2007 [52] ^c	Grass SLIT for 3 years continuous or seasonal; SDT	CUA	Societal	Per ICER seasonal SLIT was cost-effective. Continuous SLIT was cost-effective if sustained effect for ≥2 years after treatment
Canonica <i>et al.</i> , 2007 [53] ^c	Grass SLIT for 3 years + SDT as needed; SDT	CUA	Society	SLIT cost-effective per QALY: average 0.0167 QALYs per season compared with SDT
Berto <i>et al.</i> , 2008 [54] ^b	Grass SLIT for 1 year; SDT for 1 year	CCA	Third-party payer	Mean annual direct costs for SLIT greater than SDT €311.4 and €179.8, respectively
Nasser <i>et al.</i> , 2008 [55] ^c	Grass SLIT for 3 years + SDT as needed; SDT	CUA	Society	SLIT 'very cost-effective' per QALY gained. QALY gained at 9 years = 0.197; equivalent to an extra '72 days of perfect health' for patients treated with SLIT when compared with those receiving placebo
Ariano <i>et al.</i> , 2009 [56] ^b	SLIT for 3 years + SDT as needed; SDT	CCA	Healthcare system	Healthcare costs greater for SLIT + SDT in year 1, same in years 2 and 3, and significantly lower in years 4 and 5, compared with SDT
Ruggeri <i>et al.</i> , 2013 [57] ^a	SLIT for 3 years + SDT as needed; SDT	CEA	Third-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.

AAdSS, adjusted average symptom score; CCA, cost–consequence analysis; CEA, cost-effectiveness analysis; CUA, cost–utility analysis; HCS, healthcare system; HDM, house dust mite; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SCIT, subcutaneous allergy immunotherapy; SDT, standard drug treatment; SLIT, sublingual allergy immunotherapy. Adapted from [58].

^aIncluded in the Meadows *et al.* [41] systematic review.

^bIncluded in the Hankin and Cox [59[■]] systematic review.

^cIncluded in both systematic reviews.

The review was part of the National Institute for Health Research Health Technology Assessment (HTA) program. The purpose of a 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 (NHS). This HTA review used standard systematic review methods for study selection, data extraction, and quality assessment of DBPC trials of SCIT or SLIT, SCIT compared with SLIT, and economic evaluations. Meta-analysis and indirect-comparison meta-analysis were carried out. Four different types of cost analyses were used in these 14 identified economic evaluation studies:

- (1) Four cost–consequence analyses (CCA).
- (2) Two cost-effectiveness analyses (CEA).
- (3) Five cost–utility analyses (CUA).
- (4) One CEA and CUA.
- (5) One CEA and cost–benefit analyses (CBA).
- (6) One CEA and CCA.

These cost analyses differ in the way outcomes were measure or expressed, with CEAs, CBAs, and CUAs typically reporting outcomes as the incremental cost-effectiveness ratio (ICER). The ICER is calculated from QALY with the following formula:

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

On the basis of £20 000–30 000 per QALY, AIT became cost-effective as compared with SDT after 6 years of treatment initiation from the patient and NHS perspectives, and 7 years from NHS perspective only. Using the same threshold, SCIT was found to be cost-effective compared with SLIT after around 5 years. The review concluded that ‘... SCIT and SLIT may be cost-effective compared with SDT from around 6 years at a threshold of £20 000–30 000 per QALY’ [41]. Limited evidence indicated SCIT may be more beneficial and less costly than SLIT. However, the authors noted the challenges in comparing and combining results across studies utilizing different outcome measures and encouraged further research to ‘establish the comparative effectiveness of SCIT compared with SLIT, and to provide more robust cost-effectiveness estimates’ [41]. All of the studies in this systematic review employed single allergen AIT.

Another systematic review of published studies that reported health economic outcomes associated with AIT identified 23 studies that compared SLIT and/or SCIT with SDT: SCIT (9), SLIT liquid drops (2), SLIT tablets (8), SCIT and SLIT (4), and directly comparing SLIT with SCIT (1) (Table 3) [59[■]]. Only one early study comparing SCIT with SDT in adults with ragweed-allergic asthma failed to demonstrated significant cost-savings [62]. The review concluded that the remaining 23 comparative cost studies provided ‘compelling evidence for the cost-savings of AIT (whether delivered subcutaneously or sublingually)’. In the six studies comparing cost outcomes of SLIT to SCIT, four reported cost-savings favoring SLIT. With the exception of three retrospective claim analyses of the Florida Medicaid [38[■],47,48] population, all of these studies employed single allergen AIT.

ALLERGEN IMMUNOTHERAPY
PHARMACOECONOMICS IN ‘REAL LIFE’:
CLAIMS DATA ANALYSIS

There is variability across the studies in terms of the AIT cost-effective or break-even time-point. In some studies, the cost-effective ‘time-point’ was reached several years after discontinuation, which likely reflects the time required for the sustained benefits of AIT to outweigh the AIT treatment costs. However, studies that calculated cost through claims data, generally, have demonstrated significant cost-savings during the treatment period. In the previously mentioned 6-year prospective study comparing a 3-year course of SCIT with SDT, cost calculations based on monthly patient diaries that registered medications, clinic visits, and medical tests, significant cost-savings were seen in the second treatment year [39]. Cost-savings increased to 80% by the end of the 3-year AIT course and were maintained at this level through the subsequent 3 post-treatment years. In a 12-year retrospective claims analysis of the Florida Medicaid population (1997–2009), which included approximately 7.5 million people, there was an 18-month total health-care cost-savings of 30% in adults and 42% in children with newly diagnosed allergic rhinitis, compared with a matched control population who did not receive AIT [38[■]]. This study confirmed the findings of a similarly designed pediatric study that found significant cost-savings with AIT, beginning at 3 months and progressively increased through 18-month evaluation period [48]. The reason(s) for this early treatment economic benefit can only be speculated, but are likely multifactorial and include the benefits of specialty care, as well as the AIT treatment effect [71]. These ‘real-life’ retrospective studies lend strong support for the cost-effectiveness of AIT.

Table 3. Systematic reviews evaluating allergen immunotherapy health economics					
Author (number of studies included in economic analyses)	Economic outcome	SCIT vs. SDT	SLIT tablets vs. SDT	SLIT drops vs. SDT	SCIT vs. SLIT vs. SDT
Meadows <i>et al.</i> , 2013 [14,41]	Both SCIT and SLIT may be cost-effective from around 6 years	6 [39,42–44,46]; cost-effective from 3, 6 and 10 years, but varied with perspective	4 [51–55]; cost-effective at ~ 6 years and various ICER	2 [49,50]; all favored SLIT	3 [45,60,61]; SCIT more cost-effective over time
Hankin and Cox, 2014 [24,59 [■]] ^a	23 favored AIT over SDT	10 [39,42–44, 46–48,62–64]; all favored SCIT	8 [49,50,52,54, 55,57,65,66]; 1 found higher costs with SLIT	1 reduced costs by year 4	4 [67–70]; all favored SLIT; SLIT 48% cost-savings from HCS perspective [67]

SCIT, subcutaneous allergy immunotherapy; SDT, standard drug treatment; SLIT, sublingual allergy immunotherapy. ^aIncluded three studies that evaluated the actual total healthcare cost via claims analyses not included in the Meadows *et al.* review [38[■],47,48].

CONCLUSION

Allergen immunotherapy has well established proven efficacy in reducing allergic rhinitis and asthma symptomatology, and medication requirements. Studies that have included validated general and disease-specific quality-of-life measurement tools have also demonstrated a significant positive effect of AIT on overall quality of life. A limited number of studies have included cost comparisons between AIT and SDT. There is considerable variability in the way the economic outcomes were expressed and/or measured in these studies, with some of the assessed outcomes being theoretical and others directly calculated. Despite this variability, systematic reviews have concluded that AIT is cost-effective in comparison to SDT. Individual studies have demonstrated cost-savings as high as 80% and as early as 3 months after treatment initiation. However, there was a considerable variation in the 'cost-effective' time-point. One systematic review suggested that both SCIT and SLIT may become cost-effective compared with SDT at around 6 years after beginning treatment [41]. There is no conclusive evidence that one route is more cost-effective, and more research using standardized outcome and reporting measures is needed to establish the comparative effectiveness of SCIT and SLIT, as well as to assess the long-term cost-effectiveness of both AIT routes in terms of disease control and modification.

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Conflicts of interest

There are no conflicts of interest.

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

- of special interest
- of outstanding interest

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