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Cost-effectiveness of grass pollen SCIT compared with SLIT and symptomatic treatment

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Abstract
Background Whereas specific immunotherapy (SIT) has already been shown to be cost-effective in the treatment of allergic rhinitis compared with symptomatic treatment, only a small number of investigations have compared sublingual (SLIT) and subcutaneous (SCIT) immunotherapeutic approaches. This analysis discusses the cost-effectiveness of SCIT compared with SLIT and a symptomatic treatment modality. At the same time, particular attention is paid to preparation-specific characteristics.
Methods The investigation is based on a previously published health economic model calculation. A Markov model, with predefined disease stages and a time period of 9 years, formed the basis of the analysis. The data on specific SCIT (Allergovit®) and SLIT (Oralair®) preparations required for the calculation were adjusted for the present analysis. Quality-adjusted life years (QALYs) based on symptom scores were calculated as the endpoint for effectiveness. Furthermore, the total costs and cost effectiveness of SCIT were determined. Model uncertainties were estimated by means of additional sensitivity analyses.
Results With regard to effectiveness, both the SCIT and SLIT preparations proved superior compared to symptomatic treatment. Although more expensive, SIT seem to be cost-effective. A direct comparison of SCIT (Allergovit®) and SLIT (Oralair®) showed lower total costs for SCIT treatment over the study period (SCIT 1159 € versus SLIT 1322 €) and improved effectiveness (SCIT 7.112 QALYs versus SLIT 7.060 QALYs).
Discussion SIT represents a cost-effective treatment option for patients with allergic rhinitis compared with symptomatic treatment. The comparison of SCIT (Allergovit®) and SLIT (Oralair®) showed SCIT to be predominant and cost-effective, due in particular to somewhat greater patient compliance and lower drug costs. It also became evident that, as far as possible, product-specific model variables are required for an economic evaluation of SIT treatment.

Keywords Specific immunotherapy · Cost effectiveness · Allergic rhinitis · Model calculation

Abbreviations

AA	Allergic asthma
AR	Allergic rhinitis
QALY	Quality-adjusted life year
SIT	Specific immunotherapy
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy

Background

Allergic rhinitis (AR) is a common chronic disease associated with numerous symptoms that impair quality of life [1]. In addition to the possibility of symptomatic treatment, specific immunotherapy (SIT) has proven to be a promising – and indeed the sole – causal treatment option. Studies have already proved the effectiveness and cost-effectiveness of SIT compared with symptomatic treatment [2, 3]. What has not been sufficiently investigated to date, however, is how an estimate of effectiveness, and in particular cost-effectiveness, would look if sublingual (SLIT) and subcutaneous (SCIT) immunotherapy approaches were compared with each other. A 2012 review was unable to

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provide a clear answer to this question at that time [4]. The subject of cost and cost-effectiveness was not addressed until 2015, when Verheggen et al. [5] published an analysis of a five-grass tablet (Oralair®) compared with a SCIT treatment mixture. This investigation was based on a health economic model calculation over a 9-year time period. Such models are widely used in health economics and are particularly well suited to extrapolating existing findings over a long time period and combining a range of different data sources [6–8]. The authors concluded that, while SLIT using Oralair® was associated with higher overall costs at 458 €/patient over the study period, it also proved to be superior in terms of effectiveness compared with SCIT. On combining the benefit in quality-adjusted life years (QALYs) and the cost difference between treatment approaches, the additional costs generally deemed cost-effective for Oralair® were 12,593 € per QALY gained. However, the results of model calculations such as this depend strongly on the underlying data and assumptions. Bearing this in mind, a significant limitation of this analysis lies, in our view, in the selection of the comparative therapy. The comparison of a mix of SCIT treatment preparations, including Depiquick®, Allergovit®, Pollinex®, and Purethal®, in the study by Verheggen et al. [5] does not take the heterogeneity of the various individual preparations sufficiently into consideration, given that the individual drugs differ in terms of manufacturer-specific composition and clinical data. For this reason, the current guideline on specific immunotherapy (SIT) focuses on an individual consideration of each SIT preparation [9].

The aim of the present analysis is to determine the cost-effectiveness of SCIT using specific and adequately documented grass-pollen immunotherapy (Allergovit®) compared with SLIT using Oralair® or symptomatic treatment in patients with grass pollen-associated AR or rhinoconjunctivitis.

Definition of terms: what is a QALY?

The term QALY stands for "quality-adjusted life year." It is a parameter frequently used in international health economic studies to reflect treatment effectiveness from a patient view. The basic concept of the QALY is an assessment of length of life in a state of health in relation to the quality of life perceived by the patient. According to the theoretical concept of the QALY, quality of life is assigned a value between 1 (perfect health) and 0 (death). QALYs are arrived at by multiplying the quality-of-life value with the quantity-of-life value in this state of health. For example, if patients live for 1 year with their quality of life reduced by half, this year of life corresponds to only 0.5 QALYs (quality of life 0.5 × 1 year). In addition to permitting a consideration of the patient's perspective, QALYs also make it possible to compare various treatments with each other, including those for different indications.

Methods

The analysis was closely based on the model calculation published by Verheggen et al. [5], which was essentially already published in an earlier publication by Westerhout et al. 2012 [10]. In contrast to these earlier calculations, the present analysis used specific model variables that applied to the preparation Allergovit®.

Model assumptions

The Markov model underlying the calculation is based on predefined disease stages which, once combined with corresponding transition probabilities, make it possible to predict the course of disease in a patient cohort (Fig. 1). The treatment arms considered included:

- SCIT with Allergovit®,
- SLIT with Oralair®,
- Symptomatic treatment alone.

The underlying Markov model has a 1-year cycle length and a time horizon of 9 years. At the start of the model calculation, patients had a mean age of 29 years and were affected by grass pollen-related AR or rhinoconjunctivitis, but not allergic asthma (AA). During the model duration, patients could develop AA. For these patients a higher mortality and reduced quality of life were assumed in the calculation. The model also assumed that incident asthmatics during the pollen season are affected by this disease over the entire model period.

The possibility of additional symptomatic treatment was allowed for in both SIT arms. SIT duration was assumed to be 3 years. The transition probabilities of the Markov model were adjusted accordingly to the relevant treatment arm. For example, Verheggen et al. [5] assumed a relative risk reduction of annual AA incidence of 0.505 [11, 12], which was also adopted in the present calculation. It was assumed that there were no differences in risk reduction between SCIT and SLIT. For those patients who discontinued SIT before the end of the 3-year period, it was assumed that no quality of life-enhancing results or risk-reducing effects on AA incidence would be seen following SIT discontinuation. The percentage of patients that discontinued SIT prematurely was determined on the basis of the study results obtained by Kiel et al. [13]. It was also assumed that patients did not re-initiate SIT following discontinuation. The grass pollen season lasts 4.5 months per year [14, 15].

Costs and use of resources

Costs for all treatment arms of the model were determined from a health insurance perspective. Drug costs for 3 years under Allergovit® were firstly ob-

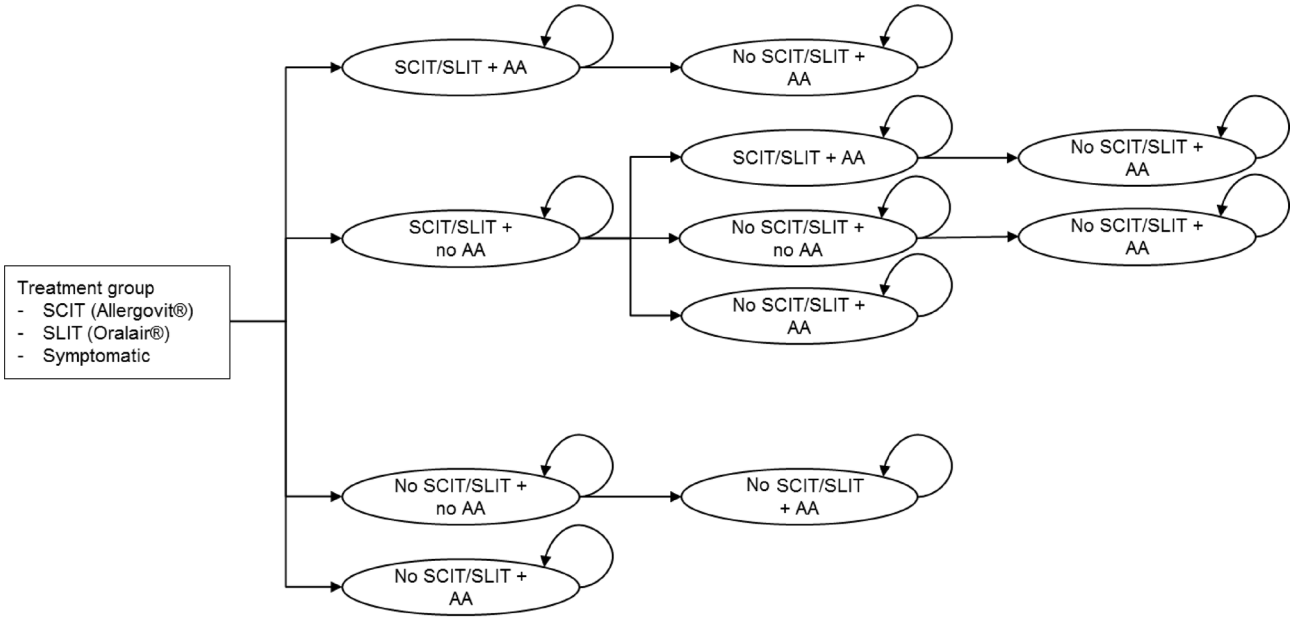

Fig. 1 Basic structure of the underlying Markov model [5, 10] (all patients are at risk of death. This is not shown in order to simplify representation). *AA* allergic asthma, *SCIT* subcutaneous immunotherapy, *SLIT* sublingual immunotherapy

tained on the basis of the required prescription quantities specified in the prescribing information [16]. The number of packs required for the entire treatment period was then calculated according to the time period covered by each pack. At 119–175 days, this yielded a total number of packs of Allergovit® of one per year. A similar approach was taken to establish drug costs for Oralair®. According to the prescribing information, treatment with Oralair® should be initiated 4 months prior to, and continued throughout the pollen season [17]. According to the information on initiation and continued treatment, it was assumed that two packs à 90 tablets, as well as two packs à 31 tablets, were required per treatment year. The number of required packs for both drugs was then multiplied by the pharmacy retail price, including VAT and deducting mandatory rebates [18]. On balance, this yielded SIT drug costs of 1095 € for Allergovit® and 2669 € for Oralair® for the entire 3-year treatment period, with the costs distributed equally over the 3 treatment years. For those patients who discontinued SIT, drug costs were reduced by 50% for the year in which treatment was discontinued.

The cost of additional symptomatic treatment was calculated on the basis of costs previously estimated by Verheggen et al. [5] for loratadine or budesonide. The same applied to the costs of contact with medical specialists, SCIT injections, diagnostic costs, and treatment costs upon onset of AA (Table 1). In addition to this, seven injections, as well as seven related contacts with medical specialists, were annually assumed for patients under Allergovit® (preseasonal treatment). Contact with a medical specialist was assumed to take place on a quarterly basis among patients using Oralair®. As with Verheggen et al. [5], 1.9 contacts with medical specialists were assumed for all SIT patients for the time following the 3-year treatment period. Likewise, allergy diagnostic workup was performed in the first year in all SIT patients prior to treatment initiation.

Effectiveness parameters

QALYs, which can be interpreted as length of life with no impairments to quality of life, were the primary outcome for therapeutic effectiveness. In a first step, utility values reflecting impairment to quality of life during the pollen season were determined based on standardized symptom scores. Therefore the data of a meta-analysis published in 2012 [19] were taken. The symptom scores reported in that meta-analysis adapted from a study by Corrigan et al. [20] were used for the preparation Allergovit®, while the symptom scores adapted from Didier et al. [21, 23], Wahn et al. [22], and Cox et al. [24] were used for Oralair®. Since the instruments used to determine symptoms differed between these studies, a standardized mean difference was firstly arrived on the basis of symptom score information, and a standardized symptom score then determined [25], as with the approach taken by Verheggen et al. ([5]; Table 2). It was assumed that symptoms were not present outside the pollen season. QALYs were then calculated on the basis of utilities determined in this way. As a further gauge of treatment effectiveness, the number of new-onset cases of AA was determined. All prognosed effects and costs were discounted at a rate of 3%.

Table 1 Model calculation input data

Model assumptions	Mortality rate for allergic asthma p. a. [5]	0.07%		Min-max variation in sensitivity analyses (%)
	Background mortality rate p. a.[5]	0.05%		±30
	Dropout rate for SCIT Allergovit®[13]	Year 1	20%	±30
		Year 2	49%	±30
		Year 3	44%	±30
	Dropout rate for SLIT Oralair®[13]	Year 1	62%	±30
		Year 2	53%	±30
		Year 2	61%	±30
	Asthma incidence p. a. [5]	0.46%		±30
	Relative risk reduction in asthma incidence with SIT [5]	50.5%		±30
	Pollen season duration [14, 15]	4.5 Months		±30
Cost and resource assumptions	Costs for SCIT with Allergovit® over 3 years	1095.33 €		±10
	Costs for SLIT with Oralair® over 3 years	2668.86 €		±10
	Costs for loratadine per season [5]	SIT	5.14 €	±10
		ST	7.54 €	±10
	Costs for budesonide per season [5]	SIT	2.19 €	±10
		ST	3.83 €	±10
	Costs per contact with a medical specialist [5]	13.29 €		±10
	Costs per SCIT injection [5]	5.11 €		±10
	Diagnostic work-up [5]	20.61 €		±10
	Costs attributable to allergic asthma p. a. [5]	186.30 €		±50
	Number of annual physician contacts for SCIT with Allergovit® [16]	7		±30
	Number of injections p. a. for SCIT with Allergovit® [16]	7		±30
	Discount rate p. a.	3%		±30

SCIT subcutaneous immunotherapy, *SLIT* sublingual immunotherapy, *ST* standard treatment

Table 2 Determination of standardized symptom scores and derivation of utility values during the pollen season in order to determine QALYs*

Study	SIT symptom score	SD	Placebo symptom Score	SD	Standardized mean difference	New standardized symptom score (0–18)	Pollen season utility value (0–1)
Allergovit®							
Corrigan et al. [20]	166.5	114.93	218	135.39	–0.410	*3.0245*	*0.832*
Oralair®							
Didier et al. [21]	3.58	2.976	4.93	3.229	–0.431	–	–
Wahn et al. [22]	3.25	2.86	4.51	2.93	–0.435	–	–
Didier et al. [23]	2.67	3.63	4.03	3.71	–0.370	–	–
Cox et al. [24]	3.21	4.54	4.16	4.51	–0.210	–	–
–					–0.343 (pooled)	*3.26*	*0.819*
Symptomatic treatment							
Verheggen et al. [5], additional file: meta-analysis [25]						*4.48*	*0.751*

* Verheggen et al. [5], additional file: meta-analysis [25]
QALY quality-adjusted life year, *SD* standard deviation, *SIT* specific immunotherapy

Model calculation outcomes

Total costs per treatment group, QALYs, and the expected number of AA cases were considered as model outcomes over the time period of 9 years. Incremental cost-effectiveness results are also reported (costs per QALY gained) in the case of additional costs – but greater therapeutic benefit – compared with the comparative treatments.

Sensitivity analysis

Sensitivity analyses are commonly used instruments in health economics to estimate assumption-related

Table 3 Per-patient costs over 9 years according to treatment type taking into account all patients in a treatment arm (including those that dropped out from SIT)

Type of cost	Allergovit®	Oralair®	Symptomatic treatment
SIT	652 €	959 €	–
Symptomatic treatment	79 €	85 €	91 €
Asthma costs	20 €	25 €	29 €
Visits to a medical specialist	323 €	232 €	202 €
Injections	64 €	–	–
Allergy diagnostic work-up	21 €	21 €	–
Total costs per patient	*1159 €*	*1322 €*	*322 €*

SIT specific immunotherapy

uncertainties in model results. Both probabilistic and deterministic sensitivity analyses were performed in the present investigation in order to estimate that inaccuracy.

The particular feature of a probabilistic sensitivity analysis is that a number of input data (from the value ranges listed in Table 1) are drawn simultaneously and at random. This procedure was repeated 1000 times in the present analysis. Thus, by performing multiple repetitions of the calculations, alternative analysis results were obtained that graphically represent the extent of uncertainty.

The deterministic sensitivity analysis, in contrast, varied individual influencing factors in the model consecutively with minimum and maximum values and documented the main analysis result after each variation. In this way, it was possible to deduce the influence of individual parameters on the uncertainty of the model.

Results

Costs

Over the 9-year time period, the total per-patient cost of treatment with Allergovit® was 1159 €, the average total per-patient cost with Oralair® 1322 € (Table 3). The majority of these costs are accounted for by the drug costs associated with SIT treatment. This becomes particularly apparent when one considers the comparatively low total costs in the patient group receiving symptomatic treatment alone. Total costs per patient in this group were 322 €. Based on our assumptions on the SIT dropout rates used in the model, only 228 of the 1000 patients initially treated completed the entire 3-year treatment period with Allergovit® and only 70 with Oralair®. The full SIT drug costs used in the model applied only in these patients (over 3 years: 1095 € for Allergovit®; 2669 € for Oralair®). On the other hand, if one takes all patients into consideration (including those that dropped out), one arrives at average SIT-specific drug costs of 652 € for Allergovit® and 959 € for Oralair®. Treatment costs for AA were comparatively modest due to the low AA incidence of 0.46% per year.

Effectiveness

With regard to patient quality of life, both SIT groups showed effects that were superior to symptomatic treatment. This becomes evident from the number of QALYs determined. While 7036 QALYs over the modeling period were determined for patients receiving symptomatic treatment alone, treatment with Allergovit® and Oralair® achieved 7112 and 7060 QALYs, respectively. This differencees are primarily accounted for by the varying number of AA cases occurring in the SIT treatment groups and the differences in the percentage of patients that completed the entire 3-year SIT treatment period, and thereby profited from the quality of life-enhancing and AA incidence-lowering effects of SIT. While AA occurred in 39 of 1000 patients receiving symptomatic treatment only, the number of incident asthmatics is lower at 31 cases (Allergovit®) and 36 cases (Oralair®). Thus, the reduction in quality of life associated with the presence of AA comes more relevant in the symptomatic treatment group and results in fewer QALYs.

Cost-effectiveness

A comparison of Allergovit® with Oralair® revealed SCIT to be economically superior, resulting in a saving of 163 € (1159 € vs. 1322 €). Since Allergovit® also showed better effectiveness in terms of QALYs determined and the number of asthmatics, it predominates over SLIT and is thus cost-effective.

A direct comparison of Allergovit® with symptomatic treatment revealed additional costs of 837 € for SIT patients andbetter effects, both in terms of QALYs gained and the number of new-onset AA cases. However, QALY differences in relation to additional costs also support the cost-effectiveness of Allergovit® treatment. Thus, the costs per QALY gained are 11,000 €, thereby putting them in the range considered as cost-effective (according to internationally accepted threshold values of maximally 50,000 € per QALY gained).

Although Oralair® also showed better effects compared with purely symptomatic treatment, the addi-

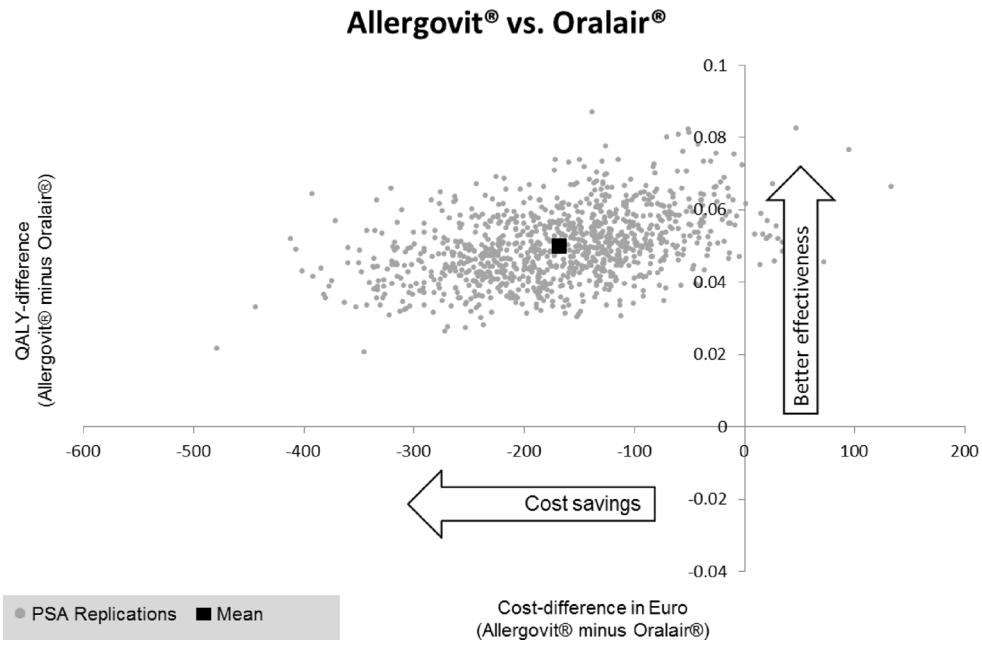

Fig. 2 Results of the probabilistic sensitivity analysis (PSA) on the cost-effectiveness of SCIT versus SLIT. *QALY* quality-adjusted life year, *SCIT* subcutaneous immunotherapy, *SLIT* sublingual immunotherapy

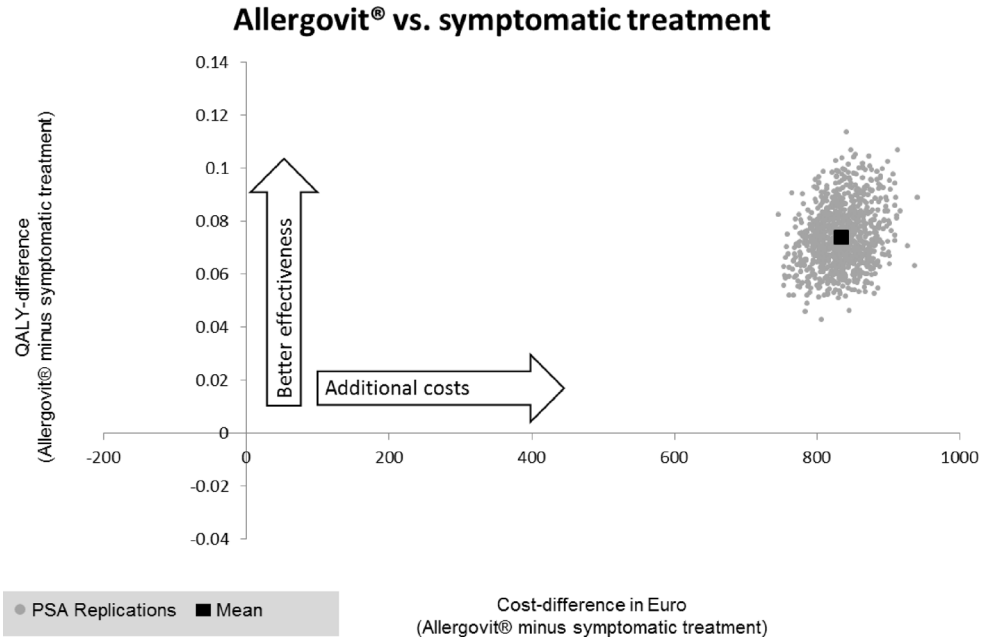

Fig. 3 Results of the probabilistic sensitivity analysis (PSA) on the cost-effectiveness of SCIT versus symptomatic treatment. *QALY* quality-adjusted life year, *SCIT* subcutaneous immunotherapy

tional costs here as well as the smaller effect difference lead to increased cost per QALY gained of 41,405 €.

Sensitivity analysis

Cost and effectiveness results were largely robust in the sensitivity analysis. The replicated results demonstrate that, compared with Oralair®, Allergovit® shows the superior effectiveness of SCIT in virtually all cases, both in terms of additional QALYs determined and Allergovit®-related savings (Fig. 2). The robustness of the results becomes even more apparent when one compares Allergovit® with symptomatic treatment. Here, the replicated results show only low scatter around the mean value of QALY-differences. The same applies to the cost differences (Fig. 3). The deterministic sensitivity analysis revealed the assumptions on SIT dropout rates, as well as the assumed SIT drug costs, to be the model input variables that give rise to the greatest degree of uncertainty in terms of the cost results of the analysis. With regard to QALYs determined in the treatment groups, these were the assumptions set in the model calculation about achievable symptom scores and pollen season duration.

Table 4 Cost-effectiveness evaluation of SCIT versus SLIT under different assumptions relating to patient compliance

	Dropout rate in year 1 (%)	Dropout rate in year 2 (%)	Dropout rate in year 3 (%)	Costs	QALYs	Cost-effectiveness evaluation
Dropout rate in the baseline calculation						
SCIT	20	49	44	1159 €	7.112	*SCIT dominates SLIT*
SLIT	62	53	61	1322 €	7.060	
Scenario 1						
SCIT	62	53	61	838 €	7.065	*SCIT still dominates SLIT*
SLIT				1322 €	7.060	
Scenario 2						
SCIT	20	49	44	1159 €	7.122	*SCIT still dominates SLIT*
SLIT				1960 €	7.100	

QALY quality-adjusted life year, *SCIT* subcutaneous immunotherapy, *SLIT* sublingual immunotherapy

Discussion

The results based on the present analysis suggest that the treatment of patients with pollen-induced rhinoconjunctivitis or AR using SCIT with Allergovit® is both effective and cost-effective compared with SLIT using Oralair® or purely symptomatic treatment. This finding is based on an adaption of an existing health economic model calculation previously published by Verheggen et al. [5] and Westerhout et al. [10]. These two studies drew conflicting conclusions; however, they compared SLIT using Oralair® with a SCIT treatment mix, which appears to be an unsuitable comparison given the heterogeneity of individual SCIT preparations available on the market. Therefore, for the purposes of this investigation, essentially only those changes to the underlying model variables required to illustrate treatment with a specific SCIT preparation (Allergovit®) were made.

However, a number of the differing input variables used in this analysis require more detailed explanation. For example, Verheggen et al. [5] and Westerhout et al. [10] assumed an average pollen season duration of 3 months in their model calculations. However, since the current figures issued by the Meteorological Institute at the Free University of Berlin suggest that the grass pollen season appears to be effectively longer, the present analysis differed in that it assumed an average duration of 4.5 months [14].

Deviations from the model calculation published by Verheggen et al. [5] also arose in terms of the percentage of patients that discontinued their SIT during the treatment period. This appears to be particularly relevant, since the deterministic sensitivity analysis identified those dropout rates as model input variables that gave rise to a comparatively high degree of uncertainty in the present analysis. The data used in the study by Verheggen et al. [5] on treatment discontinuation before the end of the 3-year period were based on an investigation by Sieber et al. 2011 [26], whereas the present analysis used data from Kiel et al. [13]. There are two main reasons for this: Firstly, the data published by Sieber et al. [26] appear overly optimistic against the background of the recommendations for use of Oralair®, since one single prescribed drug pack per year was considered sufficient to fulfill the compliance criterion. A further reason is the detailed and indeed more realistic representation of patient compliance in the publication by Kiel et al. [13]. Whereas Sieber et al. [26] assumed 100% compliance in the first year of therapy, Kiel et al. already showed dropout figures for the corresponding phase of their study. The validity of this assumption is also supported by a further publication [27]. Nevertheless, it should be noted at this point, that an alternative calculation of the model on the basis of comparable dropout rates for the SIT treatment arm does not fundamentally change the results of the present calculation. If one assumes the same dropout rates for SCIT as for SLIT (and vice versa), the number of achievable QALYs in the two treatment arms moves closer together – albeit with SCIT still showing a slight superiority (Table 4). However, due to the differences in the price of SIT preparations the cost saving benefit of the SCIT will increase.

However, the costs of 3-year SIT are a further uncertainty variable in the present model calculation. Here again, the data used by Verheggen et al. [5] (Oralair®, 2100 € versus SCIT treatment mix, 1450 €) differ from those used in the present calculation (Oralair®, 2669 € versus Allergovit®, 1095 €). These differences can be explained firstly by differing assumptions on the duration of the pollen season, as well as by the use of real prices in the current analysis, whereby it is assumed that cost levels seen from the perspective of the health insurance schemes are reflected more realistically. Nevertheless, it should be borne in mind when considering these results that, since the SIT drug costs account for a high proportion of total patient costs, they strongly influence the cost results of the analysis. Therefore, a future price change could result in a reevaluation of costs and cost-effectiveness.

Besides SIT drug costs, other cost factors are also included in the model calculation; for the purposes of

better comparability, however, these costs are largely aligned with the data already used by Verheggen et al. [5]. Here again, however, limitations are evident, e. g., in terms of the costs attributable to the manifestation of AA, which were put at 186 € per season in the calculation. This appears to be extremely low compared with other investigations. For example, a 2003 study concluded that the annual cost of treatment for adults with AR increases from 1543 € to 9287 € as a result of the additional presence of AA (costs attributable to AA, 7744 €) [28]. Although, according to the authors, 58% of these total costs are accounted for by indirect costs (which are not taken into consideration from the health insurance perspective in our analysis), the remaining direct costs of 3252 € are still significantly higher compared with the present calculation. This is particularly relevant when one considers the low number of incident AA cases in the SCIT treatment group. If higher costs had be set for all AA cases that occurred, the difference in total costs would have been more markedly in SCIT's favor.

The non-consideration of indirect costs also has other limitations, since, e. g., patients' time costs are omitted. It should be noted in this context that, unlike SLIT, further indirect costs are incurred due to the additional visits to medical professionals associated with SCIT administration.

In terms of the effects of SIT on the relative risk reduction for the manifestation of AA, the model calculation assumes comparability between SCIT and SLIT. Since no studies directly comparing SLIT and SCIT in large patient cohorts have been published to date, this assumption also represents a possible limitation. A number of publications suggest the stability of this assumption [29], while other studies comparing SCIT and SLIT demonstrate slightly superior efficacy compared with placebo – accompanied, however, by a greater potential for side effects [30]. The current data seem to justify the assumption that the treatment effects of SCIT, at least, are more sustained. Whereas only study results spanning a few years are available for SLIT [31], SCIT analyses with Allergovit® demonstrate a sustained clinical effect even at 12 years following the completion of treatment [32].

Conclusion

Using preparation-specific variables in a health economic model calculation, SCIT therapy with Allergovit® was shown to be cost-effective in the treatment of patients with AR. Although the two SIT treatments exhibit essentially similar effectiveness in terms of AA incidence, a cost-effectiveness benefit is seen for SCIT compared with SLIT due, in particular, to the lower dropout rates and lower drug costs. It also becomes apparent that the results of health economic model calculations can be strongly influenced by the underlying model assumptions, which in turn underlines the need to use model variables that are as product-specific as possible in order to perform an economic assessment of SIT. It is precisely this type of product-specific consideration that needs to be implemented more rigorously in future medical comparisons and economic evaluations of SIT.

Conflict of interest T. Reinhold receives honoraria for lectures from Allergopharma GmbH & Co. KG. B. Brüggenjürgen has received honoraria for lectures, workshops, and commissioned research from Allergopharma GmbH & Co. KG, ALK-Abelló, and Stallergenes. This study was sponsored by Allergopharma GmbH & Co. KG.

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