

Economic Evaluation of Specific Immunotherapy Versus Symptomatic Treatment of Allergic Rhinitis in Germany

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Abstract

Objective: To use published data to compare the economic consequences of specific immunotherapy (SIT) lasting 3 years with those of continuous symptomatic treatment in patients with either pollen or mite allergy.

Design and setting: The evaluation was conducted from the following 3 perspectives in Germany: (i) society; (ii) healthcare system; and (iii) statutory health insurance (SHI) provider. A modelling approach was used which was based on secondary analysis of existing data. The follow-up period was 10 years. The break-even point of cumulated costs, their difference per patient and the additional cost per additional patient free from asthma symptoms [incremental cost-effectiveness ratio (ICER)] were used as target variables, each from the viewpoint of SIT. The types of costs were direct and indirect (society), direct (healthcare system) and those incurred by SHI (i.e. expenses). In the base-case analysis, the average values of the clinical parameters and average case-related costs/expenses were applied.

Main outcome measures and results: The break-even point was reached between year 6 and year 8 after the start of therapy, resulting in net savings of between 650 and 1190 deutschmarks (DM) per patient after 10 years. The ICERs of SIT were between –DM3640 and –DM7410, depending on study perspective and nature of the allergy (1990 values for symptomatic treatment and treatment of asthma, 1995 values for SIT; DM1 ≈ \$US0.58). The sensitivity analysis demonstrated the robustness of the model and its results. First, all the independent variables of the model were varied. Secondly, the influence of the model variables was quantified using a deterministic model. SIT was more likely to result in net savings than in additional costs. An economic parameter (cost for symptomatic treatment) had the highest influence on the results.

Conclusions: This evaluation showed that SIT for 3 years is economically advantageous in patients who are allergic to pollen or mites and whose symptoms are inadequately controlled by continuous symptomatic treatment. After 10 years, the administration of SIT leads to net savings from the perspectives of society, the healthcare system and SHI (third-party payer) in Germany.

Up to about 20% of the population in industrialised countries have type I allergic conditions of the respiratory tract, especially seasonal allergic rhinitis (pollen allergy, 'hay fever'), perennial allergic rhinitis (most often caused by house dust mites) and allergic asthma.^[1-3] The estimates of the lifetime prevalence of these rhinitis-type syndromes in the UK, Germany, Switzerland and Finland range between 14 and 20%.^[1,4] In the case of asthma, about 30% of adult patients have exogen-allergic asthma.^[5] Conversely, approximately 20% of patients with allergic rhinitis also have asthma.^[6]

Suitable treatment of allergic rhinitis consists of the following alternatives: (i) avoidance of the offending allergens; (ii) pharmacotherapy using antihistamines, decongestants and corticosteroids; (iii) specific immunotherapy (SIT) [hyposensitisation]; and (iv) surgery.^[1] In patients with high intensity of allergic symptoms, proven sensitisation to definite allergens, insufficient allergen avoidance and inadequate response to drug treatment, SIT over a period of 3 years is indicated.^[7-10] SIT is the practice of gradually administering increased quantities of an allergen extract to a patient with the allergy to ameliorate the symptoms associated with subsequent exposure to the causative allergen.^[10]

The clinical effectiveness of SIT has been documented in a wealth of controlled clinical trials and observational studies. Two position papers (one by the European Academy of Allergology and Clinical Immunology^[7] and the other by the WHO,^[10] as well as a meta-analysis of randomised controlled trials of SIT in asthma,^[11] are cited here. However, resources for medical care of the population are limited and therefore make it necessary to base the decision for a specific treatment alternative not only on proven clinical effectiveness but also on economic consequences. This is even more true as costs for SIT in the 3-year treatment period are higher than those for symptomatic treatment (pharmacotherapy).

Therefore, the purpose of our study was to estimate and compare the long term economic consequences of the treatment alternatives, SIT and symptomatic treatment, in patients with seasonal (pollen) and perennial (mite) allergic rhinitis over a period

of 10 years in Germany. For SIT, the cost for SIT from year 1 up to year 3 plus allergy- and asthma-related treatment costs from year 1 up to year 10 were evaluated. For symptomatic treatment, the costs from year 1 up to year 10 were evaluated. The following perspectives were chosen: (i) society with direct medical and indirect costs; (ii) German healthcare system with direct medical costs; and (iii) statutory health insurance (SHI). This last perspective includes expenses for ambulatory and hospital treatment (except rehabilitation), calculated as direct medical costs minus patient charges minus the discount received from public pharmacies in an outpatient drug treatment setting.

In this analysis, a group of allergen extracts from 3 German manufacturers was evaluated. In pollen allergy, Allergovit® A/B, Tyrosin-Allergoid® and Purethal® were taken. In mite allergy, Novo-Helisen® Depot, ADL-Depot® and Depot-HAL AU® were investigated.

The following target variables were chosen, each from the perspective of SIT: (i) the break-even time of cumulated costs/expenses between the 2 treatment alternatives; (ii) the difference in cumulated costs/expenses per patient after 10 years; and (iii) the additional costs/expenses per additional patient free from asthma symptoms after 10 years.

Methods

Estimation of Economic Consequences

This economic evaluation of SIT versus pharmacotherapy in seasonal and perennial allergic rhinitis, respectively, was conducted according to the recommendations of the German Society for Clinical Pharmacology and Therapy for performing and assessing pharmacoeconomic studies.^[12]

The retrospective approach of the investigation used an economic model which incorporated: (i) empirical effectiveness data of SIT and pharmacotherapy; (ii) secondary analysis of epidemiological information and of structural data; (iii) regulations; (iv) an additional survey in the outpatient sector to assess resource consumption during SIT; and (v) expert knowledge.

The proportion of patients with asthma at the

initiation of treatment, the cumulative incidence of asthma, the cumulative remission of asthma symptoms, the excess mortality of patients with asthma and the reduction in the need for anti-allergic pharmacotherapy were used as clinical (effectiveness) parameters for both alternatives. The frequency of adverse events needing treatment was considered for SIT exclusively.

Diagnostic measures, allergen extracts, medical outpatient services and treatment costs of adverse events, symptomatic anti-allergic comedication and treatment of asthma in the case of SIT, as well as anti-allergic treatment and treatment of asthma in the case of symptomatic pharmacotherapy, were used as economic parameters.

Modelling

Modelling in the course of the investigation was based on a decision-tree technique and comprised 3 steps. First, the disease course of the target patients assigned to either of the treatment alternatives was described over a period of 10 years using the clinical parameters described above, except remission of allergic rhinitis symptoms. Secondly, average case-related costs/expenses were applied per patient per year according to the cumulative prevalence of all the clinical parameters. In the third step, these interim results were summed year by year over the whole period of 10 years for each of the treatment alternatives. This process gave a stochastic model for quantification of the target variables using a functional correlation between the target variables and the exogenous parameters (independent variables) of the model.

The target variables, break-even point of cumulated costs/expenses and difference in cumulated costs/expenses per patient after 10 years between the 2 alternatives were assessed using a cost-consequence analysis (CCA). Therefore, the year X of the break-even point was derived from:

$$(CSIT_{1-X}) = (CP_{1-X})$$

where $CSIT_{1-X}$ is the cumulated cost in the SIT group from year 1 to X and CP_{1-X} is the cumulated cost in the group which receives anti-allergic phar-

macotherapy from year 1 to X. The difference in cost per patient after 10 years, $\Delta C_{1-10}/\text{patient}$, was estimated as:

$$DC_{1-10}/\text{patient} = (CSIT_{1-10} - CP_{1-10})/\text{patient}$$

where $CSIT_{1-10}$ is the cumulated cost in the SIT group from year 1 to 10 and CP_{1-10} is the cumulated cost in the group which receives anti-allergic pharmacotherapy from year 1 to 10. The difference per patient, $\Delta C/\text{patient}$, is negative (savings) if the break-even point is reached before year 10.

Additional costs/expenses incurred by SIT per additional patient free from asthma symptoms after 10 years were quantified in an incremental cost-effectiveness analysis (ICEA). Therefore, the incremental cost-effectiveness ratio (ICER) of using SIT instead of anti-allergic pharmacotherapy was estimated as:

$$ICER = \Delta C_{1-10}/\Delta SFA$$

where ΔC_{1-10} is the incremental cost of using SIT instead of anti-allergic pharmacotherapy and is given by $CSIT_{1-10} - CP_{1-10}$ and ΔSFA is the number of additional patients free from asthma symptoms gained by SIT instead of anti-allergic pharmacotherapy.

Information Sources

The following sources were used to estimate the economic consequences of SIT versus pharmacotherapy in seasonal and perennial allergic rhinitis, respectively:

- clinical trials, observational studies and epidemiological information^[6,7,13-53]
- the price of allergen extracts in public pharmacies for outpatient care,^[54] regulations governing patients' prescription charges^[55] and discounts received by SHI^[56]
- the Uniform Assessment Standard (UAS) [*Einheitlicher Bewertungsmaßstab (EBM)*] of the Federal Union of Panel Doctors (*Kassenärztliche Bundesvereinigung*) governing the tariffs of the different outpatient medical services for which panel doctors are remunerated by SHI in Germany^[57]

- cost-of-illness studies on allergic rhinitis and asthma in Germany.^[58-60]

Valuation of the Cost Parameters

The economic valuation of the cost parameters was performed using average case-related costs/SHI expenses. Costs/expenses were based on 1997 prices for the allergen extracts and their administration in outpatient care. Costs/expenses for allergic rhinitis and for asthma were based on different years, according to the available sources. All costs/expenses are given in deutschmarks (DM; DM1 = \$US0.5764, 1997 values).

Discounting

The economic evaluation of SIT versus symptomatic treatment of allergic rhinitis covered a treatment period of more than 1 year. Therefore, a common discount rate of 5% annually^[61-63] was applied to determine the current value of future costs/SHI expenses and savings at the time of this investigation.

Base-Case and Sensitivity Analyses

The base-case results were derived from average values of the clinical (effectiveness) parameters and from average case-related treatment costs and SHI expenses, respectively. A sensitivity analysis was conducted to test the robustness of the model. This was achieved by the application of 2 different methods. First, the range of base-case results that had to be expected was described in a best-case/worst-case scenario from the perspective of SIT. Numerical variation of the exogenous parameters of the model was used. Secondly, the impact of the exogenous parameters on the target variables was investigated in a deterministic model.

Results

Disease Model

The disease course of patients with allergic rhinitis who were treated with either SIT or continuous symptomatic pharmacotherapy is given in figure 1. This decision tree summarises the devel-

opment which is given at the end of the 10-year observation period. Therefore, the p-values represent cumulative prevalence rates of patients without asthma symptoms and patients with asthma, respectively. The tree was based on the average values of: (i) the proportion of patients with asthma at start of treatment; (ii) the annual incidence and remission rates of asthma, according to the treatment alternatives; and (iii) the excess mortality of patients with asthma per year. A detailed description of the stochastic process and the sources used is given in Appendix A. Figure 1 demonstrates the decrease in the proportion of patients with asthma in the group assigned to SIT from 30% at treatment start to about 19% after 10 years, whereas more patients in the group who were assigned to symptomatic treatment developed asthma, with an increase from 30% up to approximately 35% over the 10-year period. In the incremental cost-effectiveness analysis, there were 161 additional patients without asthma symptoms in the SIT group compared with the group assigned to symptomatic treatment. This refers to a hypothetical cohort of 1000 patients each at start of treatment. Therefore, 0.161 additional patients free from asthma symptoms were gained by SIT per patient initially treated in a population encompassing on average 30% of patients with asthma.

The reduction in the need for anti-allergic pharmacotherapy over the 10-year observation period was estimated from secondary analysis of clinical trials, observational studies and epidemiological information. Details are given in Appendix B, according to the respective treatment alternatives.

Treatment Costs

Specific Immunotherapy (SIT)

Resource use in ambulatory SIT was collected from a survey among specialist healthcare providers. The frequencies of injections per patient-year and thereby the number of packages of allergen extract, depending on the nature of the allergy, were assessed in expert interviews with the members of the Medical Advisory Committee. Costs were determined by multiplying utilised resource

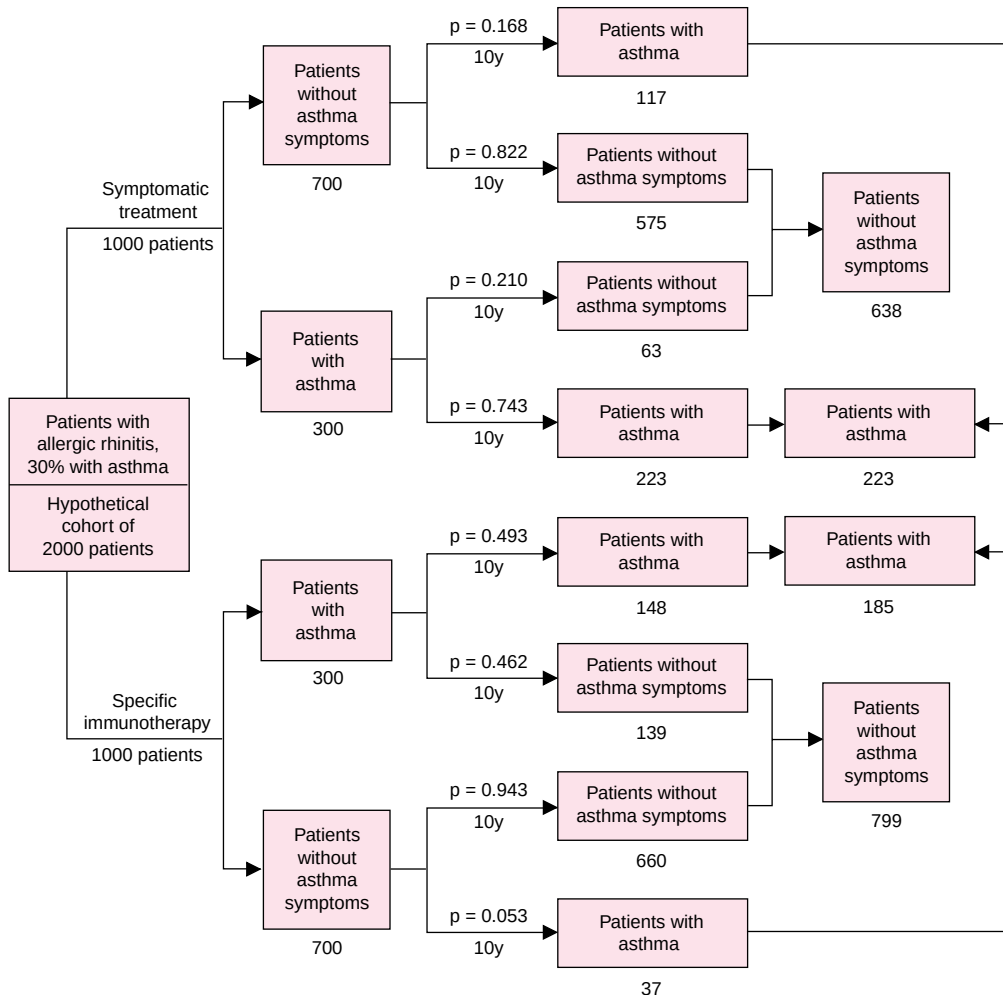


Fig. 1. Disease course of patients with allergic rhinitis after a period of 10 years. Patients were assigned to either specific immunotherapy or symptomatic treatment (anti-allergic pharmacotherapy). Transition probabilities (p) were based on average values of the cumulative incidence and remission rates of asthma, respectively, and therefore were cumulative prevalence rates at the end of the 10-year period. These p -values for patients with and without asthma symptoms did not add up to 1, respectively, because of the excess mortality of patients with asthma compared with patients without asthma. In the case of symptomatic treatment, 22 patients with asthma out of the initial 1000 patients had died. In the case of specific immunotherapy, 16 patients with asthma out of the initial 1000 patients had died.

items according to the UAS list^[57] by the tariff of each item (number of points and point value). Costs of medical services are given by SHI expenses. However, in the case of SHI expenses for the allergen extracts, patient charges^[55] and a dis-

count of 5% received from the pharmacies^[56] had to be subtracted from the prices.^[54]

The frequency of systemic adverse events needing treatment during the 3-year administration of SIT was derived from the secondary analysis of

clinical trials and observational studies. There is an average of 0.0312^[24] (0.007 to 0.08)^[24,53] events per patient-year during SIT with allergoids and 0.0102^[52] (0.01 to 0.17)^[52,53] events per patient-year during SIT using depot extracts in mite allergy, respectively.

In the case of pollen allergy and preseasonal SIT, there were 7 injections per year, giving a total of 21 injections in 3 years. This equals 3 treatment sets of the allergoids. Average costs/expenses are given by the average of the evaluated group of allergen extracts, the lower limit by the lowest priced and the upper limit by the highest priced preparation. Diagnostic measures per patient in year 1 were given by 1 prick test, 0.175 (0.15 to 0.2) provocation tests and 1.08 (0.5 to 1.67) assessments of allergen-specific immunoglobulin E. Medical services per patient for 3 years encompassed 6 administrative charges, 21 consultations and 21 hyposensitisation treatments, equally distributed over each year. Resource consumption per systemic adverse event needing treatment was estimated as 1 treatment of shock plus DM100 (DM50 to DM150) for drugs. All these medical services totalled 7460 (7271 to 7699) points and were valued at DM0.07 (DM0.06 to DM0.08) per point.

In the case of mite allergy and perennial SIT, there were 19 injections per patient in year 1, and 10 in year 2 and 3, each giving a total of 39 injections in 3 years. This equals 1 treatment set and 3

continuation sets of the depot extracts. Average costs/expenses are given by the average of the evaluated group of depot extracts, the lower limit by the lowest priced and the upper limit by the highest priced preparation. Diagnostic measures per patient in year 1 were given by 1 prick test, 0.175 (0.15 to 0.2) provocation tests and 1.08 (0.5 to 1.67) assessments of allergen-specific immunoglobulin E. Medical services per patient in year 1 encompassed 4 administrative charges, 19 consultations and 19 hyposensitisation treatments. In years 2 and 3, there were 4 administrative charges, 4 consultations and 10 hyposensitisation treatments per year. Resource consumption per systemic adverse event needing treatment was estimated as 1 treatment of shock plus DM100 (DM50 to DM150) for drugs. All these medical services totalled 9711 (9569 to 10 166) points and were valued at DM0.07 (DM0.06 to DM0.08) per point.

Patient-related direct medical costs/SHI expenses for SIT over the 3-year treatment period, encompassing the acquisition cost for allergen extracts, diagnostic measures, medical services during administration of SIT and treatment of systemic adverse events are given in table I according to the nature of the allergy.

Cost of Allergic Rhinitis and Asthma

Disease costs and SHI expenses incurred by patients with allergic rhinitis and asthma in Germany were selected according to the perspectives of this evaluation. All the relevant costs/expenses were obtained from secondary analysis of published cost-of-illness studies in Germany.^[58-60] Table II summarises these costs/SHI expenses in Germany per year for patients with seasonal allergic rhinitis, perennial allergic rhinitis and asthma, respectively.

Direct medical and indirect costs (perspective of society) comprise direct costs incurred by outpatient medical services, outpatient drug treatment, inpatient treatment and rehabilitation treatment, as well as indirect costs incurred by loss of productivity caused by absence from work, premature retirement and premature death.^[58-60]

Direct medical costs (perspective of healthcare system) are incurred by outpatient medical services,

Table I. Cumulated direct medical cost and SHI expenses per patient for SIT over 3 years in Germany [rounded to the nearest deutschmark (DM); 1995 values]^a

Type of cost and limits	Cost (DM) of SIT in	
	seasonal (pollen) allergy	perennial (mite) allergy
Direct medical cost		
Lower limit	1124	2007
Average	1491	2200
Upper limit	1933	2720
SHI expenses		
Lower limit	1078	1927
Average	1431	2119
Upper limit	1866	2636

a Discount rate used was 5% annually.

SHI = statutory health insurance; **SIT** = specific immunotherapy.

Table II. Costs and SHI expenses in Germany per year for patients with seasonal (pollen) allergic rhinitis, perennial (mite) allergic rhinitis and asthma, respectively, according to cost-of-illness studies^[58-60] [rounded to the nearest deutschmark (DM)]^a

Type of cost and limits	Cost (DM) for symptomatic therapy		
	seasonal allergy (1990 values)	perennial allergy (1990 values)	asthma (1990 ^[58] and 1992 ^[59,60] values)
Direct medical and indirect cost			
Lower limit	368 ^b	739 ^c	1420 ^[59]
Average	739 ^d	1055 ^[58]	1643 ^[58]
Upper limit	1055 ^[58]	1210 ^e	2979 ^[60]
Direct medical cost			
Lower limit	330 ^b	697 ^c	873 ^[59]
Average	697 ^d	1013 ^[58]	1064 ^[58]
Upper limit	1013 ^[58]	1168 ^e	1155 ^[60]
SHI expenses			
Lower limit	330 ^b	682 ^c	692 ^[59]
Average	682 ^d	998 ^[58]	997 ^[58]
Upper limit	998 ^[58]	1168 ^e	1095 ^[60]

a Discount rate used was 5% annually.

b Calculated from the published figures,^[58] assuming no hospital and no rehabilitation treatment as well as no premature retirement.

c Calculated from the published figures,^[58] assuming less resource consumption incurred by medical services.

d Calculated from the published figures,^[58] assuming less resource consumption incurred by medical services.

e Calculated from the published figures,^[58] assuming 50% more resource consumption in drug treatment but no hospital and no rehabilitation treatment.

SHI = statutory health insurance.

outpatient drug treatment, inpatient treatment and rehabilitation treatment.^[58-60]

SHI expenses are given by direct medical cost for outpatient medical services, outpatient drug treatment minus patient charges and pharmacy rebate, as well as for inpatient treatment minus patient charges.^[58-60]

Direct and indirect nonmedical costs to the patient were not considered in the course of the evaluation and are therefore not part of the values given in table II.

Economic Consequences of SIT

Base-Case Analysis

In the base-case analysis, average values of the clinical parameters and average case-related treatment costs/expenses were applied.

Costs/expenses per surviving patient and year incurred by the SIT group were calculated from (i) costs/expenses for hyposensitisation therapy in years 1, 2 and 3, plus (ii) costs/expenses for anti-allergic comedication in patients with allergic rhinitis symptoms only, according to their cumulative

prevalence and corrected by the extent of cumulative reduction in the need for this comedication in year 1 up to year 10, plus (iii) costs/expenses for treatment of asthma in patients with asthma, according to their cumulative prevalence in year 1 up to year 10.

The costs/expenses per surviving patient and year incurred by the symptomatic treatment group were calculated from (i) costs/expenses for anti-allergic pharmacotherapy in patients with allergic rhinitis symptoms only, according to their cumulative prevalence and corrected by the extent of cumulative remission in the need for this medication in year 1 up to year 10, plus (ii) costs/expenses for treatment of asthma in patients with asthma, according to their cumulative prevalence in year 1 up to year 10.

Figure 2 depicts the comparison of annual direct medical costs in the case of seasonal (pollen) allergy. Figure 3 represents the cumulative difference from the perspective of SIT over the whole observation period of 10 years. As can be seen from figure 3, the break-even point between the treatment alternatives is reached in the seventh

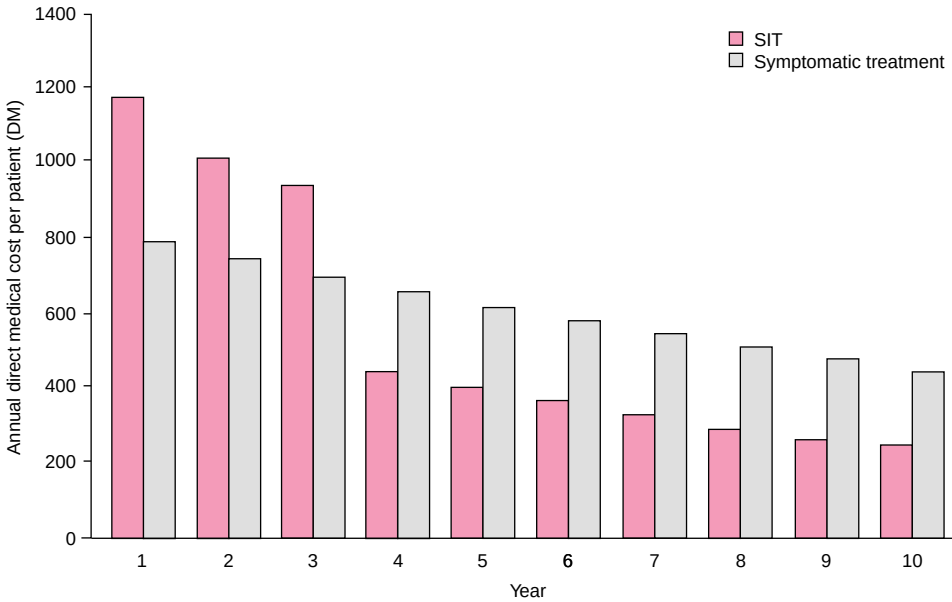


Fig. 2. Base-case analysis. Annual direct medical cost per patient with seasonal (pollen) allergy during the observation period of 10 years. The discount rate used was 5% annually. Patients were assigned to either specific immunotherapy (SIT) or symptomatic treatment (anti-allergic pharmacotherapy). The decrease in cost in the group treated with anti-allergic pharmacotherapy is mainly caused by discounting. **DM** = deutschmarks.

year. From this point in time, the cumulative difference is in favour of SIT, ending up with savings of DM673 per patient after 10 years. During the same time, 161 additional patients free from asth-

ma symptoms were gained through SIT compared with symptomatic treatment per 1000 patients in the treating population at the start. This corresponded to an increment of 0.161 per patient and, therefore, to an ICER of –DM4180 (net savings) per additional patient free from asthma symptoms (–DM673/0.161).

The quantified target variables are summarised in table III. These base-case results indicate an economic advantage of SIT over symptomatic treatment at the end of the 10-year observation period.

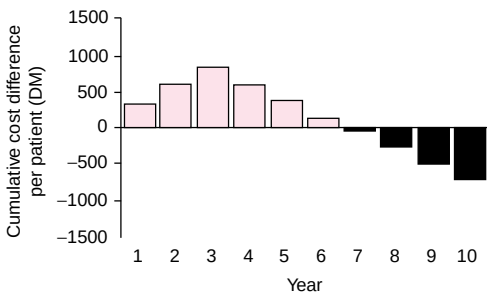


Fig. 3. Base-case analysis. Cumulative difference in direct medical cost per patient with seasonal (pollen) allergy from the perspective of specific immunotherapy (SIT) over the observation period of 10 years. After 7 years, there were already net savings because the cumulated cost in the SIT group was lower than that in the group assigned to symptomatic treatment. After 10 years, there were net savings of DM670 per patient through SIT as opposed to symptomatic treatment. The discount rate used was 5% annually. **DM** = deutschmarks.

Sensitivity Analyses

Results of economic analyses are more dependent on temporal and local changes in basic conditions than are the results of controlled clinical trials. Therefore, the extent to which the different model variables influence the base-case results was investigated. As the correlation between the target variables and the exogenous parameters (independent variables) of the model can be described by equations, the variability of results can be investigated in a best-case/worst-case scenario via numerical variation

Table III. Base-case results for the long term economic consequences of SIT compared with symptomatic treatment in Germany [rounded to the nearest 10 deutschmarks (DM); 1997 values for allergoids and depot extracts, 1990 values for symptomatic treatment of pollen and mite allergy, and for treatment of asthma]^a

Target variables	Perspective		
	society ^b	healthcare system ^c	SHI ^d
Break-even point			
SIT in pollen allergy using allergoids	Year 6	Year 7	Year 7
SIT in mite allergy using depot extracts	Year 7	Year 8	Year 8
Difference per patient after 10y (DM)^e			
SIT in pollen allergy using allergoids	-1190	-670	-650
SIT in mite allergy using depot extracts	-1100	-580	-590
ICER after 10y (DM per additional patient free from asthma symptoms)^f			
SIT in pollen allergy using allergoids	-7410	-4180	-4070
SIT in mite allergy using depot extracts	-6850	-3640	-3640

a Discount rate used was 5% annually.

b Direct medical and indirect costs.

c Direct medical cost.

d Expenses of SHI for ambulatory and inpatient treatment.

e Negative value indicates net savings per patient through SIT.

f Negative value indicates net savings per additional patient free from asthma symptoms through SIT.

ICER = incremental cost-effectiveness ratio; **SHI** = statutory health insurance; **SIT** = specific immunotherapy.

of all the exogenous parameters. In addition, the extent of impact of the exogenous parameters on the target variables is described by the method of the total differential (deterministic model).^[64,65]

The perspective of the healthcare system (i.e. direct medical cost) was chosen as it is best suited to describe possible net savings or additional costs for the cost carriers in Germany, encompassing SHI and retirement insurance.

Scenario Analysis

Table IV depicts the combination of limits of the independent variables for use in the best-case/worst-case scenario. Table V summarises the results of this scenario analysis together with the base-case results for all the target variables from the perspective of direct medical cost. In the best case, SIT was superior. The break-even point was reached very early, net savings per patient after 10 years were high and the ICER reflected considerable net savings per additional patient free from asthma symptoms after 10 years. In the worst case, symptomatic treatment was superior over the observation period of 10 years. The break-even point was not reached and SIT incurred additional costs per patient. Con-

sequently, SIT no longer yielded net savings per additional patient free from asthma symptoms.

The range in cost from the scenario is large, indicating that individual patients may end up with outcomes quite different from the average represented by the base-case analysis. The scenario analysis reveals the upper and lower limits of the base-case results for single cases that may be expected under day-to-day practice. But in total, these limits contribute to the base-case results. According to this scenario, SIT is much more likely to be superior than inferior to symptomatic treatment of appropriate patients with seasonal and perennial allergic rhinitis.

Impact Analysis

The impact analysis is described in detail in Appendix C. The deterministic model showed that the determinant with by far the greatest impact on the target variable is the economic parameter direct medical cost for anti-allergic pharmacotherapy (symptomatic treatment), irrespective of the nature of the allergy. The first effectiveness parameter to appear in the rank order, average increase of asthma prevalence with symptomatic treatment, took second place in the case of SIT in pollen allergy using

Table IV. Scenario analysis. Combination of limits of the exogenous parameters of the model from the perspective of SIT, irrespective of the nature of the allergy

Exogenous parameters	Best-case combination		Worst-case combination	
	SIT	APT	SIT	APT
Cumulative incidence of asthma	Lower limit	Upper limit	Upper limit	Lower limit
Cumulative remission of asthma	Upper limit	NR ^[30,31]	Lower limit	NR ^[30,31]
Prevalence of patients with asthma at the start of treatment	Lower limit	Lower limit	Upper limit	Upper limit
Cost for SIT	Lower limit	NA	Upper limit	NA
Cost for APT	Upper limit	Upper limit	Lower limit	Lower limit
Reduction in the need for APT	Upper limit	Lower limit	Lower limit	Upper limit
Cost for the treatment of asthma	Upper limit	Upper limit	Lower limit	Lower limit
Excess mortality of patients with asthma	Lower limit	Lower limit	Upper limit	Upper limit

APT = anti-allergic pharmacotherapy; **NA** = not applicable; **NR** = natural remission of asthma (remission without treatment); **SIT** = specific immunotherapy.

allergoids, and third place in the case of SIT in mite allergy using depot extracts. The cost for SIT, another economic parameter, has more impact on the target variable than the second effectiveness parameter, average decrease of asthma prevalence with SIT, which appears for both pollen and mite allergy. The clinical parameter asthma prevalence at treatment start also has a minor impact, together with the economic parameter cost for treatment of asthma. The elasticities are summarised in table VI.

Discussion

This evaluation of economic consequences of SIT versus symptomatic treatment used a model-

ling approach. The model combined retrospective and historical prospective techniques to quantify the target variables. The selection of the data input was based on the necessity to reflect day-to-day practice in the care of patients with allergic rhinitis and to provide meaningful results according to the perspectives of this analysis: society, the healthcare system and SHI in Germany.^[66,67]

Data Input

The model approach consisted of synthesising clinical, epidemiological and economic data from the following sources: (i) clinical trials, observational studies and epidemiological information from

Table V. Sensitivity analysis with direct medical cost via numerical variation. Best-case/worst-case scenario of long term economic consequences of SIT in Germany [rounded to the nearest 10 deutschmarks (DM); 1997 values for allergoids and depot extracts, 1990 and 1992 values for symptomatic treatment of pollen and mite allergy, and for treatment of asthma]^a

Target variables	Variability		
	best case	base case	worst case
Break-even point			
SIT in pollen allergy using allergoids	Year 1	Year 7	> Year 10
SIT in mite allergy using depot extracts	Year 5	Year 8	> Year 10
Difference per patient after 10y (DM)^b			
SIT in pollen allergy using allergoids	-3 620	-670	1 420
SIT in mite allergy using depot extracts	-2 740	-580	2 210
ICER after 10y (DM per additional patient free from asthma symptoms)^c			
SIT in pollen allergy using allergoids	-17 020	-4 180	16 060
SIT in mite allergy using depot extracts	-6 850	-3 640	24 900

a Discount rate used was 5% annually.
b Negative value indicates net savings per patient through SIT.
c Negative value indicates net savings per additional patient free from asthma symptoms through SIT.

ICER = incremental cost-effectiveness ratio; **SIT** = specific immunotherapy.

Germany and comparable countries to estimate the prevalence of patients with asthma at the start of treatment, the cumulative incidence and remission of asthmatic symptoms and the excess mortality of patients with asthma; (ii) additional surveys in outpatient care in Germany to estimate the nature and frequency of medical services during SIT in patients with seasonal and perennial allergic rhinitis, respectively; and (iii) cost-of-illness studies to quantify costs/expenses for symptomatic treatment of allergic rhinitis and of asthma in Germany.

In order to reflect the situation in Germany as closely as possible, the prevalence of patients with asthma at the start of treatment was exclusively drawn from those clinical trials and observational studies that were conducted in Germany.^[13-26] In addition, cumulative incidence and remission of asthmatic symptoms were derived from studies^[7,22,27-30] that reported from Germany and from countries that are similar to Germany with respect to allergen exposure (i.e. Scandinavia, Switzerland, the UK and the US). This was done so as not to overestimate the effect in favour of SIT. For example, in the Mediterranean area, it is reported that patients with allergic rhinitis develop asthma in 43.1% of cases after a mean period of 8.2 years if treated with symptomatic pharmacotherapy.^[68] In our analysis, the upper limit of the cumulative incidence of asthma with symptomatic pharmacotherapy was 31.1% after 10 years,^[22] which is considerably lower.

The results of the additional survey in outpatient care in Germany to estimate the nature and frequency of medical services during SIT in patients with seasonal and perennial allergic rhinitis, respectively, were discussed and confirmed with the members of the Medical Advisory Committee. It was not intended to develop guidelines or recommendations of how the target patients should be treated, nor was it intended to obtain a best educated guess on the resource consumption in question. Therefore, we do not feel that our estimates are prone to the shortcomings of consensus methods and expert panels in pharmacoeconomic studies that have recently been discussed.^[69] Despite the extreme lack of data for indication-related costs/expenses in outpatient care in Germany, the

Table VI. Impact of main determinants on the target variable (difference in direct medical cost per patient after 10 years) in SIT in allergic rhinitis: total differential method

Independent variables	Elasticity (%) of the target variable when altering the independent variable by 1%	
	SIT in pollen allergy using allergoids	SIT in mite allergy using depot extracts
Cost for symptomatic treatment (economic parameter)	7.17	12.32
Average increase of asthma prevalence with symptomatic treatment (effectiveness parameter)	5.39	6.40
Cost for SIT (economic parameter)	4.55	8.94
Average decrease of asthma prevalence with SIT (effectiveness parameter)	3.87	4.60
Asthma prevalence at the start of treatment (clinical parameter)	1.52	1.80
Cost for treatment of asthma (economic parameter)	1.52	1.80
Discount rate (economic parameter)	0.64	1.12
SIT = specific immunotherapy.		

necessary information could be ascertained and valued.

The costs/expenses for treatment of asthma could be obtained directly from different sources,^[58-60] resulting in the average values and the limits necessary for such a modelling study. In the case of symptomatic treatment of allergic rhinitis, no differentiation of costs/expenses according to the nature of the allergy was available.^[58] The assumptions made to create variability for the analysis are given in table II. It is important to note that in none of the cases were the published figures taken as lower limits in order to prevent the analysis from being *ex ante* favourable to the treatment alternative SIT.

Choice of Methodology and Consequences

This retrospective analysis of the long term economic consequences of SIT was performed from the perspectives of society, the healthcare system

and SHI in Germany. With respect to society, the types of costs examined are limited. In particular, direct nonmedical costs are not included, according to the approach of this investigation. These direct nonmedical costs involve patients' expenses relating to transportation, tissues, high efficiency particulate air filter vacuums and carpet removal. However, exclusion of these costs does not affect the validity of our analysis, as net savings obtained with SIT would have been even higher if direct nonmedical costs had been included in the analysis.

A modelling study was chosen because of the ability to estimate economic consequences during an observation period of 10 years.^[12] The financial resources that would be necessary for an empirical investigation of this duration with a sample size large enough to assure adequate depiction of the variance, especially of economic parameters, precludes such a study. Two aspects of a modelling study are pivotal. First, the input into the model must be collected to ensure quality of the model itself.^[70] This has already been discussed. Secondly, the robustness of the model has to be investigated.^[12] This was achieved by comprehensive sensitivity analyses encompassing a scenario based on numerical variation and by an impact analysis. The latter showed that economic parameters had a higher impact on the target variable than clinical and effectiveness parameters, such as cumulative remission and incidence of asthma symptoms. This is important with respect to the sometimes controversial debate about the role of SIT in asthma.^[11,71,72] Therefore, we also tested the robustness of the base-case results under the assumption that there are no differences in the cumulative incidence and remission of asthma between SIT and symptomatic treatment. The averages of the incidence under SIT and the natural remission under symptomatic treatment were applied equally. The values of the remaining parameters were kept unchanged, according to the base-case analysis. This scenario was clearly in favour of the alternative, symptomatic, treatment. Even under these very unlikely assumptions,^[11] SIT was superior from all 3 perspectives of the analysis. The break-even point was reached between year 8 and 9, and with SIT there were net

savings per patient in both seasonal and perennial allergic rhinitis.

Direct medical costs/expenses for treatment of adverse events were exclusively considered for SIT, although it is well known that anti-allergic pharmacotherapy also causes adverse events.^[1] Once again, this approach is not *ex ante* favourable to SIT. The frequencies of nonfatal systemic allergic reactions applied in our analysis are confirmed by a recent literature review of 10 000 patients with SIT that was published in 1998.^[73]

Other Studies of the Economic Consequences of SIT

In a controlled clinical trial in the US investigating the efficacy of ragweed immunotherapy in adult asthma, the costs of medication and immunotherapy over a 2-year treatment period were recorded.^[74] The reduced medication costs were counterbalanced by the cost of immunotherapy (1987 values).

Another economic evaluation of an SIT drug in Germany revealed net savings with SIT after a 10-year observation period.^[75] This analysis also used a modelling approach. However, the results are not comparable with those of our evaluation because of various methodological differences. For example, 2 patient groups were evaluated separately in that analysis, namely those with allergic rhinitis or with allergic asthma.^[75] These 2 groups were not mixed according to the prevalence of patients with asthma at the start of treatment in real-life conditions in Germany. Remission of asthma symptoms was not incorporated in that analysis and there was no differentiation between seasonal and perennial allergic rhinitis. Direct and indirect costs were considered, but no expenses of SHI. In addition, no sensitivity analysis testing the robustness of the model is given in the publication.

Economic Implications

This integrative study led to transparent and reproducible results. The analysis revealed an economic advantage of SIT over anti-allergic pharmacotherapy of both seasonal and perennial allergic

rhinitis in patients whose rhinitis symptoms were not adequately controlled for by allergen avoidance and symptomatic treatment. Net savings obtained with SIT after the 10-year observation period are independent of the perspectives chosen, thus leading to net savings for the cost carriers in Germany. These results are based on the broad information content of the study, on careful selection of the data input which prevented *ex ante* preference for SIT and on comprehensive sensitivity analyses. Even with variation of the basic assumptions, SIT is more likely to result in net savings than in additional costs/expenses, while at the same time improving patients' state of health.

Although the patient's perspective was not taken in this analysis, it may be concluded that their investment in time and charges during SIT will be counterbalanced by an improved state of health, better quality of life, and fewer expenses for drugs and nonmedical devices in the long term.

Conclusions

The prevalence of seasonal and perennial allergic rhinitis as well as allergic asthma is high. SIT is a well tolerated form of therapy and will result in net savings for SHI, the healthcare system and society in Germany as long as patients who are eligible for SIT are properly selected and treated according to current recommendations. As is the case with every specific treatment, SIT is a well tolerated and cost-saving therapy if given to the appropriate patient.

Appendices

Appendix A

Asthma: Prevalence, Incidence, Remission and Excess Mortality

Table VII summarises the clinical parameters related to asthma for use in the decision tree derived from the secondary analysis of clinical trials, observational studies and epidemiological information.

The prevalence of patients in the categories 'asthmatic' and 'without asthma symptoms' at the end of each interval was calculated in 2 steps be-

Table VII. Clinical parameters related to asthma for use in the decision tree

Parameters	Lower limit (%)	Average (%)	Upper limit (%)
Prevalence of patients with asthma at the start of treatment ^[13-26]	9	30	44
Cumulative incidence rate of asthma per year			
SIT	0.46 ^[27]	0.74 ^[27]	1.02 ^[7]
symptomatic treatment	1.90 ^[28]	2.52 ^[7]	3.65 ^[22]
Cumulative remission rate of asthma per year			
SIT	4.35 ^[29]	6.41 ^[27]	7.64 ^[27]
symptomatic treatment (natural remission)		2.45% ^[30]	
Excess mortality of patients with asthma per year	0.25 ^[31]	0.48 ^[32]	0.70 ^[30]

SIT = specific immunotherapy.

cause of the different disease courses. In the first step, they were estimated on the basis of each subpopulation at the start of treatment, patients with asthma and patients without asthma symptoms, according to the parameter values given in table VII.

In the initial subpopulation (patients with asthma), the decreasing prevalence of patients with asthma was given by:

cumulative survival of asthmatic patients × cumulative prevalence after remission

The increasing prevalence of patients without asthmatic symptoms was given by:

cumulative survival of patients with asthma × cumulative remission

In the initial subpopulation (patients without asthma symptoms), the increasing prevalence of patients with asthma was given by:

cumulative incidence of asthma × cumulative survival of patients with asthma × cumulative prevalence after remission

The decreasing prevalence of patients without asthma symptoms was given by:

(1 – cumulative incidence of asthma) + (cumulative incidence of asthma × cumulative survival of patients with asthma × cumulative natural remission)

Table VIII. Reduction in the need for anti-allergic pharmacotherapy with symptomatic treatment

Reduction	Lower limit (%)	Average (%)	Upper limit (%)
Remission rate per year	1.26 ^[6]	1.93 ^[51]	4.00 ^[50]

In the second step, these interim results were combined according to the prevalence of patients with asthma and patients without asthma symptoms, respectively, that are given at the start of treatment.

Appendix B

Reduction in the Need for Anti-Allergic Pharmacotherapy

The reduction in the need for anti-allergic pharmacotherapy after SIT was derived from secondary analysis of 23 clinical trials and observational studies^[19,20,24-27,33-49] using 3 steps: (i) the proportion of patients without anti-allergic pharmacotherapy was sorted by interval from 1 year after initiation of SIT up to 6.5 years, according to the available sources; (ii) these empirical proportions were each weighted by the difference between the total number of patients and the number of patients without anti-allergic comedication as observed in each publication; and (iii) logarithmic regression with regard to the value and weight of each empirical proportion led to the following exponential function which describes the average cumulative reduction:

$$Cr_i = 1 - e^{(n_i \times a - b)}$$

where Cr_i is the average cumulative reduction in the number of patients with any anti-allergic comedication after i years, e is Euler's number, n_i is the number of the year, $a = -0.062905$ and $b = 0.439544$. The limits of this average were based on the range of the empirical proportions. The lower limit is given by:

$$Cr_i = 0.805 - e^{(n_i \times a - b)}$$

The upper limit is given by:

$$Cr_i = 1.1435 - e^{(n_i \times a - b)}$$

The reduction in the need for anti-allergic pharmacotherapy in the group assigned to symptom-

atic treatment is given in table VIII. The values of the remission rates per year were obtained from secondary analysis of epidemiological information.^[6,50,51]

Appendix C

Total Differential: Impact Analysis

Because of the analytic depiction of the target variable (difference in direct medical cost per patient after 10 years) in the form of a functional correlation with the exogenous parameters (see the Methods section), the extent of the correlation between these parameters and the target variable can be described by the total differential method.^[64,65]

In the first step, the correlation between the target variable and the independent variables (effectiveness and economic parameters) was modelled via curve adaptation using a quadratic function. The total differential revealed the relative weight of each independent variable in the second step. The correlation between the relative weight of each independent variable and the value of the target variable can then be described as an elasticity under *ceteris-paribus* conditions, i.e. the amount of percentage alteration of the target variable after altering 1 independent variable by 1% while the remaining independent variables are kept constant with their average values at the same time. Table VI summarises this procedure for SIT in seasonal (pollen) and perennial (mite) allergy, respectively, for those independent variables with the highest impact.

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