

Budget impact analysis of two immunotherapy products for treatment of grass pollen-induced allergic rhinoconjunctivitis

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Background: Grass pollen-induced allergic rhinoconjunctivitis constitutes a large burden for society. Up to 20% of European and United States (US) populations suffer from respiratory allergies, including grass pollen-induced allergic rhinoconjunctivitis. The majority of patients are treated with symptomatic medications; however, a large proportion remains uncontrolled despite use of such treatments. Specific immunotherapy is the only treatment documented to target the underlying cause of the disease, leading to a sustained effect after completion of treatment. The aim of this study was to compare the economic consequences of treating patients suffering from allergic rhinoconjunctivitis with either a grass allergy immunotherapy tablet (AIT) or subcutaneous immunotherapy (SCIT).

Methods: A budget impact analysis was applied comparing SQ-standardized grass AIT (Grazax[®]; *Phleum pratense*, 75,000 SQ-T/2,800 BAU; ALK, Denmark) with SCIT (Alutard[®]; *P. pratense*, 100,000 SQ-U/mL; ALK, Denmark). Budget impact analysis included health care utilization measured in physical units based on systematic literature reviews, guidelines, and expert opinions, as well as valuation in unit costs based on drug tariffs, physician fees, and wage statistics. Budget impact analysis was conducted from a Danish health care perspective.

Results: Treating patients suffering from allergic rhinoconjunctivitis with grass AIT instead of grass SCIT resulted in a total reduction in treatment costs of €1291 per patient during a treatment course. This cost saving implies that approximately 40% more patients could be treated with grass AIT per year without influencing the cost of treatment.

Conclusion: Budget impact analysis showed that grass AIT is a cost-saving alternative to SCIT when treating patients with grass pollen-induced allergic rhinoconjunctivitis.

Keywords: grass pollen, allergic rhinoconjunctivitis, allergy immunotherapy tablet, subcutaneous immunotherapy, health economics, budget impact analysis

Introduction

Allergic rhinoconjunctivitis is a common allergic respiratory disorder caused by allergens such as grass or tree pollens and house dust mites. The prevalence of allergic rhinoconjunctivitis is increasing and is a major health issue worldwide. In Europe and the US, up to 20% of the adult population suffers from this condition.¹⁻⁴ Allergic rhinoconjunctivitis is associated with symptoms such as a runny, blocked and/or itchy nose, sneezing, a gritty feeling in the eyes, and red/itchy/watery eyes, has a considerable impact on quality of life, and indirect costs arising from absenteeism from work and school, impaired sleep quality, and decreased productivity.⁵⁻⁹ Furthermore, allergic rhinoconjunctivitis is an independent risk factor for asthma or sinusitis.⁵ This increases the societal and economic impact of allergic rhinoconjunctivitis.

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Treatment strategies for allergic rhinoconjunctivitis are largely symptomatic, and include oral antihistamines, nasal corticosteroids, and eye drops.¹⁰ However, the underlying allergic disease remains unaffected and symptomatic treatment offers only short-term relief.

Allergen-specific immunotherapy is the only treatment capable of activating immunomodulatory mechanisms and modifying the underlying course of the disease, thereby providing sustained relief of symptoms.¹¹ Allergen-specific immunotherapy can be administered in different formulations, such as subcutaneous immunotherapy (SCIT) and allergy immunotherapy tablets (AIT).

SCIT has been widely used throughout Europe for decades. Treatment is initiated by a up-titration phase, during which the patient is given subcutaneous injections with increasing doses of allergen over a period of several weeks. This is followed by a maintenance phase during which the patient is given the maximum tolerated dose of allergen with each injection. More recently, AIT, a new and convenient form of immunotherapy, has been approved and marketed. AIT can be self-administered at home without up-titration.

The magnitude of and similarity in efficacy between these two treatment concepts has been and is still widely discussed. SCIT is documented to be efficacious and well tolerated in patients with grass pollen-induced allergic rhinoconjunctivitis.¹² Sustained effectiveness of SCIT has also been demonstrated.¹³ Several trials have likewise confirmed the benefits of AIT treatment, with sustained efficacy and a favorable safety profile in patients with grass pollen-induced allergic rhinoconjunctivitis.^{14–21}

Direct comparisons between SCIT and AIT in clinical trials are still lacking, mainly because of the use of different treatment regimens and thereby difficulties in designing proper and ethical head-to-head comparisons. However, the efficacy of grass AIT and grass SCIT has recently been compared in a meta-analysis,²² which concluded that the clinical effect of grass AIT is similar in magnitude to that observed for SCIT in patients with grass pollen-induced allergic rhinoconjunctivitis of the same severity.

The international economic crisis has led to an increased demand for evaluations of potential cost savings to health care systems without impacting the quality and safety of treatment, and budget impact analyses showing the economic consequences of different treatments may be highly relevant or even warranted for health care decision-makers. This study compared the economic consequences of treating patients with grass pollen-induced allergic rhinoconjunctivitis using either grass AIT or grass SCIT.

Materials and methods

Health economic analysis

A model was constructed to compare the budget impact of two standard immunotherapy treatments, ie, SQ-standardized grass AIT (Grazax®; *Phleum pratense*, 75,000 SQ-T/2,800 BAU; ALK, Denmark) and grass SCIT (Alutard; *P. pratense*, 100,000 SQ-U; ALK, Denmark). The model was developed based on clinical data²¹ and a recently published meta-analysis,²² and all calculations were performed using Microsoft Office Excel 2007 (Microsoft, Redmond, WA).

The methodology for developing the budget impact analysis followed international health economic guidelines for budget impact analyses.²³ According to these guidelines, a budget impact analysis should define scenarios relevant to health care decision-makers, the perspective should be that of the budget-holder, and the outcome of the analysis should reflect scenarios of interest to the decision-maker rather than assumptions intended to be generally applicable. Therefore, our budget impact analysis included calculation of all marginal costs from a Danish health care perspective to estimate possible annual savings to health care budgets resulting from implementation of grass AIT instead of grass SCIT. The analysis also included patient and societal costs, and reported these costs separately.

General model assumptions

The economic evaluation was conducted from a Danish health care perspective and included allergy treatment for adults in both the primary and secondary sector in Denmark. The analysis included direct treatment costs (cost of medication and physician visits), direct patient costs (travel expenses), and indirect patient costs (time lost). In accordance with Danish guidelines,²⁴ a discount rate of 3% per year was applied to account for treatment duration of 3–5 years. General model assumptions are outlined in Table 1.

Resource use

Resources in terms of medication use, physician visits, and patient time were calculated and are outlined in Table 2. Health care utilization was calculated based on data collected from a review of clinical trials and standard treatment in Denmark (according to the Summary of Product Characteristics), and where data were limited, these were validated by medical experts. Expert validation was obtained from two structured workshops with Danish physicians. The wide variability in the participating physicians' specialties is considered to contribute to the robustness of the analysis.

Table 1 General model assumptions

Overall assumptions	Details
Grass AIT	
Duration of treatment	Patients are treated for 3 years according to Summary of Product Characteristics.
Immunotherapy treatment and visits	Year 1: treatment is initiated by two consultations, ie, administration of first tablet in the clinic, and investigation of desired treatment effect approximately one month later. Initial consultations are followed by an additional follow-up consultation. Years 2 and 3: two follow-up consultations per year. In total, seven consultations per treatment course (3 years).
Treatment setting	Initiation of treatment takes place either at the general practitioner's office, at medical specialist in private clinic or at medical specialist in hospital setting. All follow-up consultations take place at the general practitioner's office.
Additional medical supervision	No peak flow measurements are performed.
Compliance	Compliance is set to 80%. ^a
Package size	Treatment is based on packs with 100 tablets and packs with 30 tablets.
Grass SCIT	
Duration of treatment	Duration of treatment differs between hospitals (3 or 5 years). It is assumed that 80% of patients are treated for 3 years and 20% are treated for 5 years.
Immunotherapy treatment and visits	Treatment is initiated with weekly injections at the clinic for 15 weeks (uptitration). This is followed by a transition phase with one injection 2 weeks after last uptitration injection and an additional injection 4 weeks after the first transition injection. Maintenance injections with 8 weeks interval. In total, 33 consultations in a 3-year treatment course; 47 consultations in a 5-year treatment course.
Treatment setting	Uptitration of treatment takes place at the general practitioner's office, at a medical specialist's private clinic or with a medical specialist in a hospital setting. In the maintenance phase, 1/5 of patients uptitrated by a medical specialist are referred back to their own general practitioner. Treatment at medical specialists in private clinic is performed by internal medicine specialists, dermatologists, or ear, nose and throat specialists.
Additional medical supervision	Peak flow measurements are performed before and after each injection.
Compliance	Compliance in uptitration phase is set to 100%. Compliance in maintenance phase is set to 90%. ^a
Vials	Vials are personal and cannot be shared between patients. A maintenance vial (5 mL) contains 4.7 injections. All liquid in vials is used. If extra liquid is left after end of treatment, patients will receive extra injection at an additional visit.

Note: ^aBased on experiences from daily practice in Denmark.

Abbreviations: AIT, allergy immunotherapy tablets; SCIT, subcutaneous immunotherapy.

Costs

Cost estimates are outlined in Table 3. Unit costs were obtained from established Danish public sources, including the Danish federal statistical office (Statistics Denmark), fees for service remuneration, and product list prices.^{25–29} All costs are reported in 2010 prices except when otherwise stated. Costs were obtained in Danish kroner and exchanged to Euro using the average 2010 exchange rate (1 Euro = 7.447366 DKK).

Sensitivity analysis

The robustness of the budget impact analysis was investigated using a one-way sensitivity analysis. The most sensitive resource costs were systematically calculated to investigate the sensitivity of the overall result. The sensitivity analysis was based on direct treatment costs.

Results

Treatment-related costs

The result of the budget impact analysis is shown in Table 4. Direct treatment costs for treatment with grass SCIT were

estimated to be €4555 per patient for a treatment course. In comparison, the direct treatment costs for treatment with grass AIT were estimated to be €3264 per patient for a treatment course, representing a cost saving of €1291 per patient. Estimated direct and indirect patients costs were €2694 for treatment with grass SCIT and €525 for treatment with grass AIT, representing a cost saving in total patient costs of €2169. Total savings (treatment costs and patient costs) amounted to €3460. This corresponds to a decrease of 28% in direct treatment costs, a decrease of 81% in direct and indirect patient costs, and a decrease in total costs of 48%, if treatment with grass AIT is used instead of grass SCIT (Figure 1).

The cost savings gained by prescribing grass AIT instead of grass SCIT may be utilized to treat more patients with immunotherapy. In Figure 2, the relationship is shown between the number of subjects treated with grass AIT instead of grass SCIT, cost savings when using grass AIT instead of grass SCIT, and the number of new patients who could possibly be started on grass AIT without any additional cost as compared with the current costs for grass SCIT. As shown, it is

Table 2 Resource use (health care utilization)

Resource category	Resource type	Year 1	Year 2	Year 3	Year 4	Year 5
Grass AIT						
Medication	Number of tablets (tablet/day × compliance) ^a	292	292	292	–	–
Physician	Number of initial visits (visit/year) ^b	2	–	–	–	–
	Treatment by general practitioner	0.2	–	–	–	–
	Treatment in private clinic	1.6	–	–	–	–
	Treatment in hospital setting	0.2	–	–	–	–
	Number of follow-up visits (visit/year) ^c	1	2	2	–	–
	Treatment by general practitioner	1	2	2	–	–
Patient	Treatment in private clinic	–	–	–	–	–
	Treatment in hospital setting	–	–	–	–	–
	Travel distance (km/visit) ^d	30	20	20	–	–
	Time lost (hours/visit) ^e	6	4	4	–	–
Grass SCIT						
Medication	Number of up-titration kits	1	–	–	–	–
	Number of maintenance vials needed (actual) ^f	1.06	0.34	0.83	1.11	0.60
	Number of maintenance vials needed (rounded) ^g	2	1	1	2	1
	Remaining injections in opened vial at the end of the year ^h	4.4	3.1	0.8	4.2	1.9
Physician	Uptitration visits	15	–	–	–	–
	Maintenance visits	5	6	7	6	8
	Number of peak flow measurements ⁱ	10	12	14	12	16
Patient	Travel distance (km/visit) ^d	200	60	70	60	80
	Time lost (hours/visit) ^e	40	12	14	12	16

Notes: ^aOne tablet/day; compliance = 80%; ^btwo initial visits; ^cOne follow-up visit 1st year; 2 follow-up visits the following years; ^d10 km/visit based on experiences from daily practice in Denmark; ^e2 hours/visit based on experiences from daily practice in Denmark; ^fnumber of maintenance visits (injections)/no of injections per maintenance vial; ie, no of maintenance visits (injections)/4.7; ^gnumber of maintenance vials rounded to nearest whole vial; ^h[number of maintenance vial needed (rounded) – number of maintenance vials (actual)] × number of injections per maintenance vial. Remaining injections in opened vial at the end of the year are used in the following year; ⁱpeak flow measurements are performed before and after each injection. Peak flow measurements are included in medical specialist costs (private clinic/hospital setting), but not in general practice costs. Because general practitioners perform part of the maintenance visits, peak flow measurements are calculated based on number of maintenance visits.

Abbreviations: AIT, allergy immunotherapy tablets; SCIT, subcutaneous immunotherapy.

Table 3 Cost input (in €)

Cost category	Cost type	Unit	Cost/unit
Medication			
Grass AIT	Pack with 30 tablets	Per tablet	3.78
	Pack with 100 tablets	Per tablet	3.40
	Average price, model assumption ^a	Per tablet	3.48
Grass SCIT	Uptitration kit	Per up-titration	233.80
	Maintenance	Per vial (5 mL)	224.40
Physician visits			
General practitioners	Visit	Per visit	17.38
	Peak flow measurement	Per measurement	4.87
Medical specialists in private clinic ^b	First visit	Per visit	78.86
	Second visit	Per visit	52.43
	Consecutive visit	Per visit	19.34
	First visit including fees ^c	Per visit	113.49
	Second visit including fees ^c	Per visit	87.05
	Consecutive visit including fees	Per visit	53.97
Medical specialists in hospital setting	Outpatient visit	Per visit	170.66
	Additional costs, uncomplicated allergy treatment	Per visit	384.03
	Additional costs, complicated allergy treatment	Per visit	528.11
Patient costs			
Work	Lost working hours ^d	Per hour	36.16
Travel	Travel by private car	Per km	0.48

Notes: All costs are based on 2010 prices unless otherwise stated; medication costs²⁹ physician visit costs;^{27,28} patient costs.^{25,26} ^aTreatment based on packs with 100 tablets (80%) and pack with 30 tablets (20%); ^bmedical specialist costs (private clinic) are based on a weighted average of consultation fees for internal medicine specialists, dermatologists and ear, nose and throat specialists; ^cfees include peak flow measurements and fee for injection; ^dlost working hours are based on the mean salary/hour for the general population aged 18–65 years in Denmark including the unemployed.

Abbreviations: AIT, allergy immunotherapy tablets; SCIT, subcutaneous immunotherapy.

Table 4 Costs (in €) in relation to treatment with grass AIT and grass SCIT

Cost category	Resource type	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Grass AIT							
Direct treatment costs	Medication (tablets)	1014	985	956	–	–	2955
	Physician visits	242	34	33	–	–	309
	Treatment by GP	21	34	33	–	–	88
	Treatment in private clinic	110	–	–	–	–	110
	Treatment in hospital setting	111	–	–	–	–	111
Direct treatment costs, total		1256	1019	989	–	–	3264
Direct patient costs	Travel expenses	14	9	9	–	–	32
Direct treatment + patient costs, total		1270	1028	998	–	–	3296
Indirect costs	Patient productivity (time lost)	217	140	136	–	–	493
Total costs		1487	1168	1134	–	–	3789
Grass SCIT							
Direct treatment costs	Medication (uptitration kits)	234	–	–	–	–	234
	Medication (maintenance vials)	449	218	212	82	40	1001
	Physician visits	2027	504	571	95	123	3320
	Uptitration visits	1594	–	–	–	–	1594
	Maintenance visits	433	504	571	95	123	1726
Direct treatment costs, total		2710	722	783	177	163	4555
Direct patient costs	Travel expenses	96	28	32	5	7	168
Direct treatment + patient costs, total		2806	750	815	182	170	4723
Indirect costs	Patient productivity (time lost)	1446	421	477	79	103	2526
Total costs		4252	1171	1,292	261	273	7249
Cost reduction (grass AIT – grass SCIT)		–2765	–3	–158	–261	–273	–3460

Note: Costs include 3% discount.

Abbreviations: AIT, allergy immunotherapy tablets; SCIT, subcutaneous immunotherapy.

possible to treat a substantial number of new patients on grass AIT without any additional cost to the health care system. For example, if 1500 subjects were treated with grass AIT instead of grass SCIT, it would be possible to treat approximately 600 more patients per year without increasing the current costs to the health care system. This corresponds to an increase in the number of treated patients of approximately 40%.

Sensitivity analysis

The results of the one-way sensitivity analysis are shown in Table 5. The basic treatment cost saving was €1291. Resource

costs were varied in both directions and, regardless of variation/adjustment, all costs were in favor of grass AIT with incremental costs for grass SCIT. Notably, variations between the general practice and hospital settings resulted in major changes in direct treatment costs, whereas the discount rate and duration of treatment had no or at least less impact on the analysis.

Discussion

A budget impact analysis compares the costs of different treatment options seen from a health care decision-maker

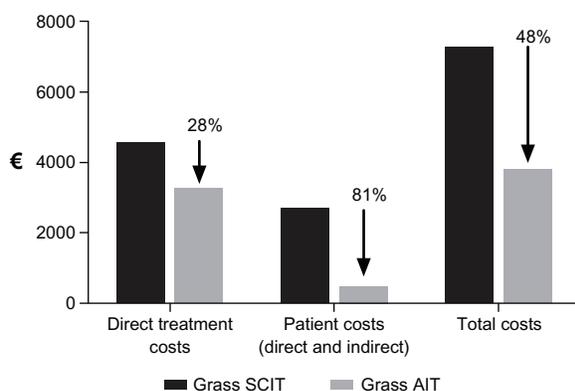


Figure 1 Decrease in direct treatment costs, patients costs and total costs in relation to treatment with grass AIT as compared with grass SCIT.

Abbreviations: AIT, allergy immunotherapy tablets; SCIT, subcutaneous immunotherapy.

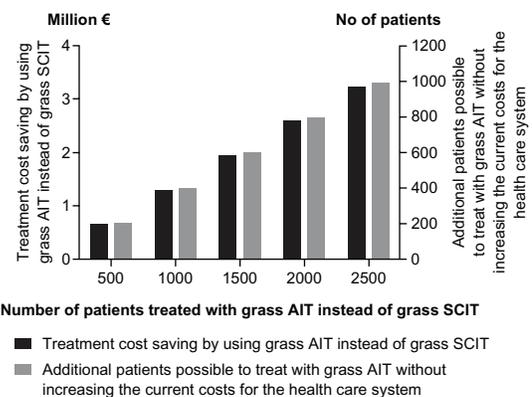


Figure 2 Relationship between number of patients treated with immunotherapy, treatment costs savings and possibility to initiate additional patients on grass AIT without increasing the current health care budget.

Abbreviations: AIT, allergy immunotherapy tablets; SCIT, subcutaneous immunotherapy.

Table 5 One-way sensitivity analysis (direct treatment costs, in €)

Sensitivity analysis	Mean direct treatment costs (€), grass AIT	Mean and incremental direct treatment costs (€), grass SCIT (difference from grass AIT)
General		
Base case	3264	4555 (+1291)
Discount rate		
0%	3354	4660 (+1306)
5%	3207	4489 (+1282)
Grass AIT		
Base case	3264	4555 (+1291)
Initiation of treatment		
100% hospital setting	4148	4555 (+407)
100% general practice	3074	4555 (+1480)
Follow-up treatment		
As for grass SCIT	3490	4555 (+1065)
100% general practice	3264	4555 (+1291)
Number of visits/year		
4 + 3 + 3	3314	4555 (+1241)
2 + 1 + 1	3213	4555 (+1342)
Compliance		
100%	4002	4555 (+553)
60%	2525	4555 (+2030)
Duration of treatment		
As for grass SCIT	3688	4555 (+867)
3 years	3264	4555 (+1291)
Grass SCIT		
Base case	3264	4555 (+1291)
Injections extracted per vial		
+20%	3264	4515 (+1251)
-20%	3264	4836 (+1572)
Uptitration visits		
100% hospital setting	3264	11,280 (+8016)
100% general practice	3264	3366 (+102)
Maintenance visits		
100% hospital setting	3264	13,891 (+10,627)
100% general practice	3264	3369 (+105)
Number of weeks between injections		
10 weeks	3264	3996 (+732)
6 weeks	3264	5301 (+2037)
Compliance, uptitration		
100%	3264	4555 (+1291)
80%	3264	4250 (+986)
Compliance, maintenance		
100%	3264	4557 (+1293)
70%	3264	4233 (+969)
Duration of treatment		
0% treated for 5 years ^a	3264	4214 (+950)
40% treated for 5 years	3264	4894 (+1630)

Note: ^aAll patients treated for 3 years.

Abbreviations: AIT, allergy immunotherapy tablets; SCIT, subcutaneous immunotherapy.

perspective. Therefore, the focus of this budget impact analysis was to compare the economic consequences of treating patients with grass pollen-induced allergic rhinitis using either grass AIT or grass SCIT.

The analysis showed that overall direct treatment costs as well as patient costs were lower for treatment with grass

AIT than for treatment with grass SCIT. The main cost difference between the two treatments was the result of fewer physician visits being needed for grass AIT as compared with grass SCIT. The cost of medication per patient was higher for grass AIT as compared with grass SCIT, whereas the costs of physician visits, travel expenses, and lost working hours

were considerably lower for grass AIT. The overall impact was reduced costs for the health care system and society (reduced physician visits and resources) as well as for individual patients (reduced travel expenses and less lost working hours). The robustness of these results was confirmed by the one-way sensitivity analysis.

The total treatment cost saving to the health care system amounted to €1291 per patient per treatment course when using grass AIT instead of grass SCIT. In 2010, approximately 1200 patients were initiated on grass SCIT treatment in Denmark (data on file). Assuming a similar continuous number of patients initiating immunotherapy treatment per year in the future, the implication for Danish society will be a treatment cost saving of more than €1,500,000 on a yearly basis if grass AIT is used as treatment instead of grass SCIT. Cost saving in this range implies that more than 450 additional patients per year could be treated with grass AIT without influencing costs. An increase in the number of patients treated per year may have additional beneficial outcomes for the health care system both in terms of additional cost savings as well as in terms of improved health status for patients. Allergic rhinitis is an independent risk factor for development of asthma.⁵ Because asthma is a disease with considerable burden and substantial costs to both the public and private health care systems,³⁰ the potential cost savings to the health care system may be even more pronounced if patients with grass pollen-induced allergic rhinitis are treated with grass immunotherapy. In addition, having more patients on immunotherapy may decrease the use of other kinds of medication used for treatment of allergic rhinitis and/or asthma, thereby decreasing costs to the health care system in relation to these medications. Grass AIT also has a number of other advantages which may be beneficial for the health care system, but which are not included in the budget impact analysis per se.

Grass AIT is generally considered to have a significantly lower risk profile than SCIT.^{31,32} The potentially lower costs for treatment of adverse events resulting from AIT are not considered in this analysis. The main cost related to side effects and seen from a health care decision-maker perspective is for hospitalization. Hospital admissions due to side effects of immunotherapy are considered to be uncommon but, because no firm documentation on the extent of these admissions is available, they have not been addressed in this study.

Treatment with grass AIT is also simpler and more convenient than for grass SCIT because tablets can be administered at home instead of injections at a clinic. Home administration

will, as mentioned above, result in fewer physician visits as compared with grass SCIT, and thereby lead to cost savings to the health care system. However, home administration is often perceived to be related to lower compliance than that achieved when treatment is given in a specialist office, leading to lower efficacy of treatment. However, a recent study evaluating compliance with grass AIT and grass SCIT indicated that compliance with both treatments was high and comparable ($\geq 80\%$).³³

Grass AIT has also been shown to have a sustained and disease-modifying effect.^{14,21} This may lead to additional cost savings for both the individual patient and for society as a whole in terms of improved quality of life and lower costs related to absenteeism from work and decreased productivity.

Because several of the aforementioned factors are not included in the budget impact analysis due to limited data, a more comprehensive economic evaluation may be warranted to evaluate the overall health economic consequences of using grass AIT instead of grass SCIT. Further evaluation may include a cost-utility analysis to obtain data on quality of life for patients and a cost-benefit analysis to obtain data on willingness to pay.

Conclusion

In conclusion, this budget impact analysis shows that grass AIT is a cost-saving alternative to grass SCIT when treating patients with grass pollen-induced allergic rhinitis. Seen from a health care perspective, grass AIT represents an efficient use of cost and resources. Further analyses may be warranted to evaluate the overall health economic consequences of implementation of grass AIT instead of grass SCIT.

Disclosure

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