

Economic studies of immunotherapy: a review

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Purpose of review

To analyse and discuss the growing body of evidence on the economic advantages offered by immunotherapy for allergic rhinitis and asthma, in the various perspectives (society, national healthcare system, patients, etc) and according to the various types of standardized economic evaluations.

Recent findings

This review shows that the economic studies of allergic rhinitis and asthma focus on three main research areas: studies aimed at determining the cost of illness and studies focused either on a simple cost comparison amongst available therapeutic alternatives, or directly comparing alternatives using full economic evaluations (cost-effectiveness, cost-utility measures, etc).

Summary

Studies exploring the full cost of allergic rhinitis and asthma are still lacking; on the contrary, studies on immunotherapy (in its many administration forms, subcutaneous, sublingual, tablet, etc) in comparison with standard pharmaceutical treatment, have shown that immunotherapy may be very beneficial to the healthcare systems, in that either it could bring more clinical outcome at a reduced cost, versus standard therapy alone, or it could bring extra benefit at a very acceptable extra cost. This is even more correct under the societal perspective, that is, when indirect costs of lost productivity are considered and included in the economic analysis.

Keywords

allergens, asthma, costs, economics, immunology, immunotherapy, rhinitis

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Introduction

Allergic rhinitis and its principal comorbidity, atopic asthma, represent a growing public health concern: their interconnection – with allergic rhinitis often preceding asthma – and the need for a stepwise approach in medical treatment in order to improve patient life expectancy and quality of life, is established by Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [1,2]. Recently, an official statement by the American Thoracic Society (ATS) has included ‘cost’ and the concept of ‘best estimate of benefits, harms, burden and costs for relevant populations’ amongst factors that should be considered by panels in deciding on the grade of recommendation for medical interventions [3]. According to the International Society of Pharmacoeconomics and Outcomes Research (ISPOR): ‘pharmacoeconomics is the scientific discipline that assesses the overall value of pharmaceutical healthcare products, services and programs. Of necessity, it addresses the clinical, economic, and humanistic aspects of healthcare interventions in the prevention, diagnosis, treatment and management of disease (... thus providing) information critical to the optimal allocation of healthcare resources’ [4]. Most readers may have already encountered the main terms used in pharmacoeconomic

research; cost effectiveness, cost benefit, cost-of-illness: these sometimes are used interchangeably as, according to pharmacoeconomic theory, each of them actually represents a specific type of economic analysis to be applied to healthcare decisions and interventions [5,6].

Hence, it may be worth reporting a simple description and classification of the methods of pharmacoeconomic analysis to inform the results of this review. A first categorization regards the so called completeness of the economic evaluation: indeed pharmacoeconomic studies are firstly divided into evaluations that analyse only costs (and therefore are called incomplete pharmacoeconomic analyses) and evaluations that analyse both costs and outcomes of different therapeutic interventions (and for this reason are called complete or full pharmacoeconomic evaluations): each of these is briefly discussed below.

Economic studies focused solely on costs

In this category two main types of studies can be found, cost-of-illness (COI) studies and cost-to-cost analyses (CCA). COI is deemed at reflecting the economic impact of a disease: by assessing all the resources used (visits, drugs, hospital admissions, working days – lost or gained), each of them valued by its unitary cost in

monetary terms (euros, dollars, etc.), it is possible to quantify the economic burden of a disease on the local payer (for example, an insurance company in the USA, a local healthcare unit in England or Italy), on the global healthcare provider (for example Medicare in the USA, the National Health Service (NHS) in England or Italy), or on the society as a whole (especially the case when productivity and disability losses are quantified alongside with the medical costs). CCA is used to compare the costs of two or more alternative interventions only focusing on cost, that is, not considering at all the clinical (or quality of life) outcome of the interventions. Thus, it should be evident why both COI and CCA are incomplete analyses: neither of them is deemed at investigating the outcome in association with the cost as they solely focus on the monetary value generated by the consumption of resources.

Economic studies focusing on both costs and outcomes of treatments

This category groups cost-effectiveness (CEA), cost-minimization (CMA), cost-utility (CUA) and cost-benefit (CBA) analyses. All of these types of economic evaluation examine at the same time (in the same study/analysis) both costs and outcomes of alternative therapeutic regimes or interventions: this directly refers to the essence of economics, that is the concept of efficiency which determines how much we have to pay for a better outcome, or which alternative provides the best outcome at the lowest cost. Full description of each of these types of economic analyses is beyond the scope of the present paper, however, we can briefly point out that all of them value costs in monetary terms, as they differ for the evaluation of outcome: CBA is used when outcomes (as well as costs) are valued in monetary terms; CMA is applied when, because the interventions have shown the same clinical efficacy (such as in randomized clinical trials), only their respective costs need to be analysed and compared (it must be noted that although they may look similar, CMA and CCA are remarkably different from the other: in CMA the alternatives have already been demonstrated equal in terms of clinical efficacy so it is appropriate to compare only costs, in CCA efficacy is not assessed at all and the comparison is limited to the cost); CEA is used when outcomes are quantified in physical units of efficacy (such as for example, asthma exacerbations, number or percentage of disease-free patients, years of life gained or lost); CUA is to be applied when there is enough data to value, in the outcome, not only the effect of the alternative interventions on life expectancy [life years gained (LYG)] but also the utility measure of that life expectancy for patients [which in most cases translates into the well known measure of Quality Adjusted Life Years (QALYs)].

As 'pharmacoeconomics is a relatively recent discipline whose use has been spread by the necessity of decision

makers in most industrialized countries, to gain understanding of the economic effect of medical technologies, in parallel with their clinical performance' [7[•]], it is of much relevance to the medical community, to develop the understanding of the significance and applicability of the different types of pharmacoeconomic analyses, alongside with the capability to require specific economic studies in order to inform their own decision-making process.

Text of the review

The main source of this review was a PubMed search which was performed in two separate subsets: firstly using the terms 'immunotherapy' and 'allergic rhinitis' and 'asthma' and 'cost' (limit '10 years') and secondly using the terms 'rhinoconjunctivitis' and 'cost' (limit '10 years'). These two searches yielded a total (without duplicates) of 52 abstracts. All abstracts were reviewed in order to discard: reviews, or papers that actually did not report pharmacoeconomic data, or were published in a language other than English. This phase produced a total of 14 original papers that were subsequently analysed in detail. The selected papers were classified into three main categories: papers that report on COI [8–10]; papers that report on CCA [11–13,14[•],15^{••}]; papers that really compare alternative strategies using CEA or CUA measures [16–21]. General summary features of the selected papers are reported in Table 1. The differences amongst these main types of economic analyses prompt for the need to a separate review, so to draw homogeneous considerations and conclusions that may be truly supportive of the clinical decision-making process.

Cost-of-illness studies of allergic disease

As in previous COI studies from the USA [22–24], the 1999 study by Ray *et al.* [8] was based on national healthcare surveys' data from the National Center for Health Statistics, which were extracted in accordance to the decisions of a double round Delphi Panel of expert clinicians. The global burden of allergic rhinoconjunctivitis (rhinitis+conjunctivitis) was estimated at US\$ 5.9 billion (in 1996 dollars), of which child care represented 38% and adult care 62%; the distribution between outpatient services, medications and inpatient services was respectively 63, 25 and 12%. More importantly, it appeared that 68% of the total calculated cost of the disease was generated by rhinitis and conjunctivitis being the secondary diagnosis to inner ear-related disorders, acute and chronic sinusitis and asthma, and 32% when rhinitis and conjunctivitis was the primary diagnosis. According to the authors, it is possible that their calculations were actually underestimating the true cost of disease, both because this illness is often unreported and self-treated, and as such may have not been fully captured by the survey methodology, and because the

Table 1 Summary of the general features of the studies discussed in the review

Author, Year [Ref.]	Type	IT	Population	Disease	Allergen	Data source	Country
Ray <i>et al.</i> , 1999 [8]	COI	—	Ad + Ch	R + C	Seas + Per	rDB	USA
Pitt <i>et al.</i> , 2004 [9]	COI	—	Ad	C	Seas	pST	UK
Smith <i>et al.</i> , 2005 [10]			Ad + Ch	C	Seas	pST	Spain
Donahue <i>et al.</i> , 1999 [11]	CTC	Sc	Ad + Ch	R + C + A	Seas + Per	rDB	USA
Berto <i>et al.</i> , 2005 [12]	CTC	SI	Ch	R + A	Seas + Per	rDB	Italy
Ariano <i>et al.</i> , 2006 [13]	CTC	Sc	Ad	R + A	Seas	pST	Italy
Berto <i>et al.</i> , 2008 [14 ^a]	CTC	SI	Ad	R + A	Seas	pDB	Italy
Hankin <i>et al.</i> , 2008 [15 ^{**}]	CTC	Sc	Ch	R + C + A	Seas + Per	rDB	USA
Schadlich and Brecht, 2000 [16]	CEA	Sc	Ad	R + A	Seas + Per	Mod	Germany
Berto <i>et al.</i> , 2006 [17]	CEA	SI	Ad	R + A	Seas	Mod	Italy
Omnes <i>et al.</i> , 2007 [21]	CEA	Sc + SI	Ad	R + A	Seas + Per	Mod	France
Bachert <i>et al.</i> , 2007 [18]	CUA	Tb	Ad	R + C + A	Seas	pST	North-EU ^a
Canonica <i>et al.</i> , 2007 [19]	CUA	Tb	Ad	R + C + A	Seas	Mod	South-EU ^b
Keiding and Jorgensen, 2007 [20]	CUA	Sc	Ad	R	Seas	Mod	Selected ^c

A, asthma; Ad, adults; C, conjunctivitis; CEA, cost effectiveness; Ch, children; COI, cost-of-illness; CTC, cost-to-cost; CUA, cost-utility; IT, immunotherapy; Mod, economic model; pDB, prospective database; Per, Perennial allergen; pST, prospective study; R, rhinitis; rDB, retrospective database; rST, retrospective study; Sc, Subcutaneous IT; Seas, Seasonal allergen; SI, Sublingual IT; Tb, Tablet IT.

^a North-Europe, includes: UK, Germany, Netherlands; Sweden; Denmark, Norway and Finland.

^b South-Europe, includes: Spain, France, Italy and Austria.

^c Selected Countries includes: Austria, Denmark, Finland, Germany, Netherlands and Sweden.

estimates were based only on the medical cost, thus not considering the cost of lost work and school attendance, which may be substantial.

The two studies by Pitt *et al.* and Smith *et al.* [9,10] were based on the same methodology, but applied to two different settings (the UK Oxfordshire and five cities in Spain). By interviewing patients enrolled by general practitioners or through the local hospital-based eye-clinics, they were able to measure resources consumption and quality-of-life (QoL) of 160 and 201 patients respectively, with seasonal allergic conjunctivitis (SAC), in the two areas. In the UK study the cost per patient/year varied between £64.61 and £123.69 (€96 to 186), as in the Spanish study it was estimated as €348.5; noteworthy the authors point out a major difference in the design of the studies with the Spanish one being based on private patients and the UK one on public attendances, as to conclude 'we expect that our sample of private patients is simply willing to spend more time and money alleviating their SAC symptoms than was the Oxfordshire sample'. QoL data were broadly comparable between the two datasets, with both populations being more impaired by symptoms, than their respective controls across a variety of QoL instruments.

Cost-to-cost studies of immunotherapy in allergic disease

The 1999 study by Donahue [11] represented probably one of the very first attempts to measure and compare the cost of individuals treated with immunotherapy (brands not specified), versus patients managed with only symptomatic treatments, in a cost-to-cost approach. This was a retrospective database analysis from the records of a large Health Maintenance Organisation (HMO) in the USA, with 2 to 6 years follow-up. The main findings of this early piece of research were the realization that patients with rhinitis and asthma cost more than patients with

rhinitis only, and that premature immunotherapy interruption carries lower costs vs. longer immunotherapy treatment 'which is consistent with more severe disease in this group' [11].

Although it comprised the wording cost-effectiveness in the title, the first Italian study was indeed a cost-to-cost evaluation of SLIT in children with allergic rhinitis and asthma [12], from one allergy centre. 135 patients with 1-year pre-sublingual immunotherapy (SLIT) (Staloral, Stallergenes) data and 3-year SLIT data, were extracted from existing records, direct costs (€ spent on drugs, specialists visits, and SLIT) and indirect costs (costs resulting from children's schools and parental work loss) were analysed. Secondary analysis compared a subgroup of allergic asthmatic children from the same database, with a control group for costs, based on records of patients not SLIT-treated, extracted from a network-database of geographically matched paediatricians. Of the 135 analyzed patients, 46 had perennial and 89 seasonal allergies with comparable age and gender distribution. A substantial reduction was found in all outcome measures during SLIT versus the pre-SLIT period. The average annual cost/patient was €2672 pre-SLIT and €629/year during SLIT. Similar results were found for allergen subgroups. This was confirmed in the asthma subanalysis (41 SLIT children and 35 controls), where the direct cost/patient over the whole follow-up (4 years) was €1182 for SLIT-treated children and €1100 for controls. This was the first study to document that high dose SLIT may be effective in reducing the cost of allergic rhinitis and asthma and comparably expensive to conventional treatment in children with allergic asthma over a 4 year follow-up.

Similar results were found in adults treated with high dose SCIT for Parietaria (Alustal, Stallergenes), in a

6-year follow-up prospective observational study also conducted in Italy [13], which demonstrated a significant difference in favour of SCIT (3 year treatment) versus drug treatment alone, with a cost reduction that started at the second year and increased to 48% at the third year, with highly statistical significance maintained up to the sixth year (3 years after SCIT interruption), and to a global net saving of €623/patient/year.

Another Italian study confirmed the economic advantage of SLIT (Staloral, Stallergenes) in adults with seasonal allergic rhinitis and asthma, from the prospective longitudinal observational database SIMAP of a network of allergy centres [14^{*}]. On 102 patients, the yearly cost/patient of treatment was higher in SLIT patients, both in the whole sample (€ 311 vs. 180/patient), in the rhinitis (€ 288 vs. 116) and rhinitis and asthma (€ 362 vs. € 230) subgroups. Patients with rhinitis and asthma generated more costs than rhinitis alone in both groups. Nevertheless, considerable savings were obtained in the cost of symptomatic drugs (−22% for rhinitis, −34% for rhinitis and asthma) and corticosteroids in SLIT patients, thus highlighting the use of symptomatic drugs as an important indicator of effective allergy control. Notably, this survey was the first to show this outcome in a routine care population in the medical practice environment of an observational study, and yet at the first year of treatment. More recently, Hankin *et al.* [15^{**}] extracted the consumption of resources and calculated the cost for children affected by seasonal and perennial allergic disease with/without SCIT treatment (brands not specified), from the Florida Medicaid claim database: this paper further confirmed the results of the Italian studies, that is, both the resources sparing effect (less pharmacy claims, less inpatient and outpatient admissions) and the significant cost reductions for immunotherapy patients. One final paper (already published, but not yet indexed on PubMed, at the time this review was written) showed that SLIT (Staloral) represents a less expensive treatment than SCIT (Phostal) (both Stallergenes-Antony, France) from all study perspectives (society, patient and NHS) [25^{*}].

Cost effectiveness studies of immunotherapy in allergic disease

Six pertinent studies are found in the area of CEA–CUA studies: specifically three were CEAs [16,17,21] and three were CUAs [18,19,20]; two of them evaluated Alustal, Staloral (Stallergenes-Antony, France), or both [17,21], two evaluated Grazax one Alutard (both of ALK-Abellø, Hørsholm, Denmark) [18,19], one finally analysed a mixture of different SCIT brands (these were: in pollen allergy: Allergovit A/B, Tyrosin-Allergoid and Purethal; in mite allergy: Novo-Helisen Depot, ADL-Depot and Depot-HAL AU) [16]. This latter was probably the very first attempt to evaluate cost effectiveness of immunotherapy: it was basically a model fed with efficacy data

from clinical trials of the different allergen extracts and prices and tariffs from available sources in Germany, to estimate the cost per patient free of asthma symptoms over the 10-year horizon of the analysis [16]. The study concluded that it was very likely for immunotherapy to be cost-effective versus symptomatic treatment alone, both for seasonal and perennial allergic disease, with a break-even point (BEP) of costs vs. savings at the seventh year and with an incremental cost per patient without asthma strongly in favour if immunotherapy in both seasonal and perennial disease (in economics, specifically cost accounting, the BEP is the point at which cost or expenses and revenue are equal: there is no net loss or gain, and one has ‘broken even’) [26].

The other two CEAs were very similar in design, being based on the same epidemiological model, and again, evaluated the cost per patient without asthma at the end of an observation period of 6 years in Italy [17] and France [21]. The Italian study was limited to SLIT Staloral (Stallergenes-Antony, France) in adults with seasonal rhinitis and asthma, as the French one was much broader including children and adults, treated with SLIT or SCIT (Alustal and Staloral, Stallergenes-Antony, France), in both seasonal and perennial rhinitis and asthma. Both of them concluded in favour of immunotherapies cost effectiveness: for France, SIT was found to be comparatively more cost effective in dust mite allergy in adults and pollen allergy in children [21]; for Italy break-even is achieved at the fourth year in the perspective of the National Healthcare System, and at the second year in the societal perspective, with SLIT being dominant vs. the alternative [17]; notably, in pharmacoeconomics, a treatment or intervention is defined as dominant when it produces more health effect at the same time saving costs in comparison with the alternative. Also the work by Keiding and Jorgensen [20] was based on a modelling approach, on SCIT for seasonal rhinitis and asthma with the QALY as the main outcome measure, in a number of selected countries (for details, see note in Table 1): in most of the countries (except the Netherlands and Sweden) immunotherapy was found dominant when indirect costs (productivity losses) were considered; for all countries the cost/QALY gained was judged to be acceptable also when only direct costs (conservative assumption) were taken into account. The two papers from Canonica *et al.* [19] and Bachert *et al.* [18] evaluated the CUA of Grazax (a grass allergen tablet for treatment of rhinitis and asthma from *Phleum pratense*) in the perspective of a selection of countries of northern and southern Europe (for details, see note in Table 1). QALYs’ calculation was possible because the source trial [27] included measurement of utilities using the EQ-5D questionnaire. Over the 9-years time horizon, the cost/QALY of this immunotherapy was found acceptable (below NICE threshold value) for a tablet price of €6

(annual cost of €2190) in northern EU countries [18]; for the southern EU countries this was confirmed at a tablet price of €1500 to €1900 per year of treatment [19]. These results were also confirmed for Denmark in a recent study, of which only the abstract is in English language (full paper is in Danish) [28].

Conclusion

Much work still needs to be done in the field of pharmacoeconomics applied to the disease area of seasonal and perennial allergy, especially when considering the cost of disease itself, which has only been investigated in a few studies and for a very limited number of countries around the world. There is a large potential for new and interesting data to be produced in order to fully appreciate the economic burden of allergic rhinitis, asthma and conjunctivitis, considering both direct and indirect costs in different patient populations and healthcare systems.

Concerning immunotherapy, its role in the management of allergic disease has been already assessed from the clinical point of view [2], but now this could also be stated for the economic perspective: the many studies summarized in this review have shown that immunotherapy may be very beneficial to the healthcare system, in that either it could bring more clinical outcome at a reduced cost versus standard therapy alone, or it could bring extra benefit at a very acceptable extra cost, thus fully accomplishing the inner significance of the term cost effectiveness. So is this all about the economics of immunotherapy? This author believes it's not, because with the growing expectations of prescribers and payers alongside with the spread of use of this new technology, more studies will be needed to account for the different types of immunotherapy, patients, management processes and healthcare settings in which immunotherapy can be used in many countries around the world.

Acknowledgements

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References and recommended reading

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

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 596).

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