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"Pharmacoeconomics of allergen specific immunotherapy"

THE ROLE OF HEALTH TECHNOLOGY ASSESSMENT IN THE COMPREHENSIVE EVALUATION OF THE IMPACT OF IMMUNOTHERAPY ON REAL PRACTICE

F. Frati (1), R. Ariano (2), G. Cadario (3), C. Ortolani (4), G. Passalacqua (5)

SUMMARY: The increasing development of new health care technologies, along with the ageing of the population and the increasing patients' expectations, cause a significant raise in medical costs, inducing in policy makers the need for well-funded information to support their decisions. The development of Health Technology Assessment (HTA), which is the systematic evaluation of properties, effects or other impacts of health technology and can be considered as a bridge between the world of research and the world of policy-making, reflects this high level of demand. HTA requires a multidisciplinary approach, that covers many different disciplines, in order to assess various aspects of health technologies, as technical properties, safety, efficacy/effectiveness, economic aspects, social, legal, ethical and political impacts.
Allergic diseases show a worldwide increasing prevalence and consequent increasing costs, which result very high in recent evaluations. Specific immunotherapy is the only treatment able to alter, differently from drugs, the natural course of allergic diseases, exerting a long-lasting therapeutic effect, that persists also after stopping the therapy. This has a potential great impact in the cost of disease, which only recently was considered in properly designed studies. These issues claim for a larger use of HTA, which may provide a more comprehensive approach to the evaluation of the impact of immunotherapy on allergic patients.
Key-words: Allergic diseases - Health Technology Assessment - Specific immunotherapy.

The increasing development of new health care technologies, along with the ageing of the population and the increasing patients' expectations, cause a significant raise in medical costs, inducing in policy makers the need for well-funded information to support decisions regarding the adoption of such technologies, including not only devices but also pharmacological treatments, clinical procedures, equipments, prevention programs and organizational-managerial systems. The development of health technology assessment reflects this high level of demand and "contributes in many ways to the knowledge base for improving the quality of health care, especially to support development and updating of a wide spectrum of standards, guidelines and other health care policies" (1).

Health technology assessment (HTA) is the systematic evaluation of properties, effects or other impacts of health technology and can be considered as a bridge between the world of research and the world of policy-making. HTA requires a multidisciplinary approach, that covers many different disciplines, in order to assess various aspects of health technologies, as technical properties, safety, efficacy/effectiveness, economic aspects, social, legal, ethical and political impacts. Consequently, different types of experts are to be involved in the process of HTA, such as health professionals, patients, epidemiologists, economists and lawyers.

HTA supports health decision-making at all the levels, that are the micro level, including decisions made by clinicians for individual patients, the meso level, referred to those decision made in institutions and organizations, and the macro level, concerning those decisions made by health authorities.

HTA is usually carried out by non profit organizations, linked to regional or national governments. In Italy, differently from other Developed Countries, HTA activity tends to be scarce and uncoordinated, and it is hoped that, prompted from the local availability of databases together with the Regionalization of healthcare governance instituted by the National Legislation, Regional level organizations and groups take the lead of HTA development and implementation in the Country.

As previously mentioned, an important section of HTA is represented by the economic analysis, that

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provides decision-makers with essential information to best allocate healthcare resources. Scope of pharmacoeconomics (PE), in fact, is to analyse, measure and compare costs and outcomes of alternative healthcare programs from different perspectives.

The identification of the study perspective, intended as the addressee for whom the analysis results are needed in order to make decisions (e.g. National Health System, society), is a fundamental step in PE analysis, as it clearly influences many aspects of the study, including the type of analysis to be applied and the types of costs to be analyzed.

Costs included in PE analysis can be either direct or indirect: the first includes all those resources consumed because of the illness (e.g. drug treatment, hospitalization), while the second is referred to those resources that can't be produced because of the illness (e.g. lost workdays). The decision on what costs to include in a PE study is very important, as it can significantly influence the results of the analysis.

When necessary information to properly conduct a PE analysis is not available, models can be used as an approximation of reality. As the adoption of a model could introduce some uncertainty in the study, variables and assumptions should be the subject of sensitivity analysis and maximum transparency should be provided in order to allow the reader to make reasonable self-judgement on the hypothesis as well as on the study results.

The four types of economic analysis have in common the determination of costs whilst they differ in the measurement of outcome: Cost-Benefit Analysis (CBA) measures outcome in monetary terms, Cost-Utility Analysis (CUA) by utility scores, Cost-Effectiveness Analysis (CEA) and Cost-Minimization Analysis (CMA) in physical health units. CMA, differently from CEA, compare costs among alternative programs with equal efficacy. An other type of PE analysis, Cost of Illness Analysis (COI), only evaluates the costs deriving from a specific illness, without comparing outcomes resulting from alternative programs. From a PubMed search resulted that almost 80% of economic analysis is represented by CEA, that, together with CUA, may be the best types of analysis for allergy and immunotherapy. The most useful outcome measurements should be long-term hard end-points, as life expectancy or cases avoided (CEA), and Quality-Adjusted Life-Years, QALY (CUA), that also take into account patients' quality of life, as allergic diseases strongly affect patients activities. The selection of costs to be included, as for all other PE analysis, will depend on the perspective taken by the analysis.

Allergic rhinitis represents a growing global health problem: the prevalence of this pathology, in fact, is increasing up to 20%, and current evidence indicates that co-morbid allergic rhinitis may have clinically relevant effects on asthma. Asthma and allergic rhinitis frequently occur concomitantly and the presence of AR often precedes the development of asthma and is a known risk factor for asthma (2). Apart from asthma, allergic rhinitis may also coexists with other disorders, such as otitis media, Eustachian tube dysfunction, sinusitis, nasal polyps, allergic conjunctivitis, and atopic dermatitis. Allergic rhinitis may also contribute to cognitive effects, sleep disorders, mood disturbances and fatigue. The impact of allergic rhinitis on functional, physical and psychological activities decreases not only worker productivities but also patient quality of life (3).

The economic burden of these pathologies is becoming very relevant: in Europe, the average annual cost per patient for allergic rhinitis is €1543, of which 50% is represented by indirect costs. Including also asthma and atopic dermatitis, this amount would result significantly higher.

As drug treatment accounts for a relevant part of allergy costs, a preventive strategy as immunotherapy, that has demonstrated to reduce the use of symptomatic drugs, can be a significant support in reducing this economic burden.

Specific immunotherapy was first introduced in 1911, while the sublingual route of administration was introduced in 1986. In 1998, the World Health Organization and the European Academy of Allergology and Clinical Immunology (EAACI) affirmed the clinical effectiveness of immunotherapy by injections or local nasal or sublingual administration (4), defining that "allergen immunotherapy is the administration of gradually increasing quantities of an allergen vaccine to an allergic subject, reaching a dose which is effective in ameliorating the symptoms associated with subsequent exposure to the causative allergen". In 1995, a meta-analysis including 54 clinical trials and assessing the efficacy of immunotherapy in asthma led to the conclusion that immunotherapy significantly reduces asthma symptoms, medication, and worsening of asthma (5).

Moreover, differently from drugs, immunotherapy has the capacity to alter the natural course of allergic diseases, exerting a long-lasting therapeutic effect, that persists also after stopping the therapy.

In 2001, the ARIA guidelines affirmed that "allergen immunotherapy is the only treatment that can modify the immune response to allergens and alter the course of allergic diseases" (6).

More recently, in August 2007, the US National Institute of Health issued the Guidelines for the Diagnosis and Management of Asthma, meaningful part of the National Asthma Education and Prevention Program. The Expert Panel, that had the responsibility of preparing this important document, decided to

expand the paragraph dedicated to allergen immunotherapy in respect to the previous version of this guidelines (1997) and to explicitly recommend immunotherapy for those patients that present an evident relationship between asthma symptoms and exposure to a specific allergen (7).

Many studies demonstrated the health economic advantage of immunotherapy over drug treatment, deriving from lower need, for those patients treated with immunotherapy, of rescue medications (antihistamines and corticosteroids) and less productivity losses. In a recent study conducted in France, the savings with subcutaneous immunotherapy were €1327 for pollen allergy in adults over a 6-year period, in respect to standard treatment. Considering sublingual immunotherapy, savings resulted to be higher (€1708 for pollen allergy), as administration does not require any visits for injections (8).

A recent study conducted in Lombardy, evaluated three groups of patients, treated with sublingual immunotherapy, with subcutaneous immunotherapy or with standard treatment. The results of this study confirmed that sublingual immunotherapy can not only decrease the mean number of treatment days per patient in respect to the other two groups of patients, but also reduce costs in adults with allergic rhinitis and/or asthma (9).

Another Italian study compared the costs of sublingual immunotherapy associated with standard treatment versus standard treatment alone, in young adults suffering from allergic rhinitis with or without asthma. Both direct and indirect costs were included in the analysis and, beginning from the fourth year of treatment, the overall cost of sublingual immunotherapy resulted to be lower than for patients receiving standard treatment alone (10).

As detailed in the following articles, it is apparent that HTA in immunotherapy is currently thoroughly investigated and real advances in a more complete appreciation of such treatment are likely to be achieved in next years.

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HEALTH TECHNOLOGY ASSESSMENT (HTA): DEFINITION, ROLE AND USE IN THE CHANGING HEALTHCARE ENVIRONMENT

D. Gallio (1), P. Berto (1)

SUMMARY: The increasing availability of health care technology – boosted by considerable advances in areas like biotechnology, biomaterials, surgical techniques and computer technology - has accompanied burgeoning health care costs, and for this reason an increasing number of subjects (clinicians, health product makers, regulators, patients, hospitals, managers, payers, government leaders) demand for well-founded information to support decisions about development, adoption, acquisition and use of new and existing technologies. Technology assessment is a form of policy research that identifies policy issues, assesses the impact of alternative courses of action, and presents findings. This article is aimed at describing the historical development, reviewing the various definition and classifications, illustrating the purposes and actors of Health Technology Assessment and its possible applications in the current healthcare scenario.
Key-words: Health Care Technology - Health Care Costs - Health Technology Assessment.

INTRODUCTION

Technological innovation has entailed considerable advances in health care, especially during the last three decades. Progress in areas like biotechnology, biomaterials, surgical techniques and computer technology has notably improved health care delivery and patient outcomes (1, 2), both in terms of diagnostic capability and therapeutic efficacy. The proliferation of health care technology has accompanied burgeoning health care costs (3-5), and, for this reason, an increasing number of subjects (clinicians, health product makers, regulators, patients, hospitals, managers, payers, government leaders) demand for well-founded information to support decisions about development, adoption, acquisition and use of new and existing technologies. The growth and development of health technology assessment (HTA) in governmental and private sector reflects this high level of demand (table 1).

- Advances in science and engineering
- Intellectual property, especially patent protection
- Aging population
- "Cascade" effects of unnecessary tests, unexpected results, or patient or physician anxiety
- Emerging pathogens and other disease threats
- Third-party payment
- Inability of third-party payers to limit coverage
- Financial incentives of technology companies, clinicians, and others
- Clinician specialty training at academic medical centers
- Malpractice avoidance
- Provider competition to offer state-of-the-art technology
- Public demand driven by consumer awareness, direct-to-consumer advertising, and mass media reports
- Strong economies, high employment

Table 1: Factors that reinforce the market of Health Technologies (1).

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ORIGINS OF TECHNOLOGY ASSESSMENT

In the Fifties, in the United States of America, decision makers started requesting for appropriate methods to fully assess consequences of those projects that required a remarkable investment of public resources. The emerging issue was not only to evaluate the quality of these projects, but moreover to compare them to alternative ones in order to best allocate the limited available financial resources.
In the Seventies, the epochal technological innovation contributed to enhance that demand, which started involving the health care area: in this setting, HTA was established to support decisions in health policy (6).

DEFINITIONS OF HEALTH TECHNOLOGY

Health Technology (HT) is the practical application of knowledge with the aim of preventing, diagnosing and treating illness. Thus, this term is not only concerned to devices and equipments but also to clinical procedures, prevention programs, pharmacological treatments and organizational-managerial systems (2). Health care technology can be classified on the basis of its material

nature, its purpose, and its stage of diffusion These classifications present some limits, as not all technologies univocally fit into single categories: in fact, certain "hybrid" technologies, as implantable drug pumps and drug inhalers, combine characteristics of drugs and devices; many tests and other technologies used for diagnosis also are used for screening and some technologies are used for diagnosis as well as treatment (e.g. coronary angiography to diagnose heart disease and to monitor coronary angioplasty); moreover, a technology may be investigational for certain indications, established for others, and outmoded or abandoned for still others (e.g. thalidomide) (table 2).

A. MATERIAL NATURE:	
Drugs	Aspirin, beta-blockers, antibiotics
Biologics	Vaccines, blood products, cellular and gene therapies
Devices, equipment and supplies	Cardiac pacemakers, surgical gloves
Medical and surgical procedures	Psychotherapy, coronary angiography
Support systems	Electronic patient record systems, drug formularies, blood banks
Organizational and managerial systems	Prospective payment using diagnosis-related groups, alternative health care delivery configurations, clinical pathways
B. PURPOSE OR APPLICATION	
Prevention	Protect against disease by preventing it from occurring, reducing the risk of its occurrence, or limiting its extent or sequelae (e.g. immunization, hospital infection control program, fluoridated water supply)
Screening	Detect a disease, abnormality, or associated risk factors in asymptomatic people (e.g. mammography, serum cholesterol testing)
Diagnosis	Identify the cause and nature or extent of disease in a person with clinical signs or symptoms (e.g. electrocardiogram, x-ray for possible broken bone)
Treatment	Designed to improve or maintain health status, avoid further deterioration, or provide palliation (e.g. antiviral therapy, psychotherapy, drugs for cancer pain)
Rehabilitation	Restore, maintain or improve a physically or mentally disabled person's function and well-being (e.g. exercise program for post-stroke patients, assistive device for severe speech impairment, incontinence aid)
C. STAGE OF DIFFUSION:	
Future technology	In a conceptual stage, not yet developed, or in the earliest stages of development.
Emerging technology	Prior to adoption, undergoing bench or laboratory testing using animals or other models.
New technology	In the phase of adoption, undergoing initial clinical evaluation.
Accepted technology	In general use.
Obsolete technology	Superseded by other technologies or demonstrated to be ineffective or harmful, should be taken out of use.

Table 2: Classification of health technologies (1).

DEFINITIONS OF HTA

In 1967, an American congressman said: *"Technical information needed by policy makers is frequently not available, or not in the right form (…) technology assessment is a form of policy research (…) it identifies policy issues, assesses the impact of alternative courses of action, and presents findings"* (7, 8).

The US Institute of Medicine (9), in 1985, presented the following definition: *"We shall use the term assessment of a medical technology to denote any process of examining and reporting properties of a medical technology used in health care, such as: safety, efficacy, feasibility and indications for use, cost and cost-effectiveness, as well as social, economic, and ethical consequences, whether intended or unintended"* (10).

Technology assessment requires a multidisciplinary approach, as it ranges through multiple disciplines, including also critical evaluation and measurement of the effective improvement in terms of patients' quality of life (2).

Battista (7) affirms that *"HTA is not simply more research*" and suggests four key features that distinguish it from research: the first is its policy orientation, since its aim is to support policy-makers' decisions; the second feature is interdisciplinary content and process; thirdly, HTA is produced through synthesizing information, examining data-base and generating primary data; fourth, results of the assessment are disseminated and communicated to different target audiences, differently from research findings that are usually published in specialized journals.

Thus, HTA becomes a bridge between the world of research and the world of policy-making (11).

More specifically, in HTA are assessed different aspects: firstly, technical properties, as for example performance characteristics and conformity with specifications for design, composition, tolerances, reliability, ease of use, maintenance; secondly, safety, intended as judgment of the acceptability of risk associated with using a technology in a specific situation; thirdly, efficacy and/or effectiveness, meant as benefits derivable from using a technology for a particular problem under ideal conditions (efficacy, e.g. in a randomized controlled trial) or under general or routine conditions (effectiveness, e.g., by a physician in a community hospital); then, economic aspects, that, at the microeconomic level, include costs, prices, charges and reimbursement modalities while, at the macroeconomic level, refer, for example, to the impact of the new technologies on national health care costs or to the effect of technologies on resource allocation; lastly, social, legal, ethical and political impacts, since a variety of technologies (e.g. genetic testing, fertility treatments, expensive or non-curative technologies) raise social and ethical concerns.

Basic HTA Orientations

HTA can be conducted with three different orientations (1), that can overlap and complement one another, to produce a technology-, a problem- or a project-oriented assessment; the first type of HTA is intended to determine the clinical, economic, professional, scientific and/or industrial impacts of particular technologies. The second is focused on managing a particular problem for which alternative or complementary technologies might be used, with the aim of examining the impact of different technologies in the same health condition. The third, instead, is focused on the usage of a technology at the institutional level (e.g. when a particular hospital have to decide whether or not to purchase a specific technology), integrating assessments with local economic, professional and social aspects.

Of course, these three different orientations can't be considered as unambiguous, since HTA can present aspects from all these categories: for example, a problem-oriented assessment, evaluating effects and impacts of alternative technologies on a specific problem, may compare results obtained by multiple technology-oriented assessments.

Purposes of HTA

The main aim of HTA is to support decision-making, advising or informing technology-related policymaking, at all the levels in the health care system (12):

- Micro level - health practice based on evidence: micro decisions are made by health professionals about care of individual patients, as a clinician who require an assessment to support the introduction of a test in the laboratory practice.
- Meso level - "management" based on evidence: meso decisions are made in institutions and organizations, as for example the allocation of resources within a hospital budget. Even if made in direct response to policy decisions, meso decisions are conceptually distinct from macro policy since they take into account local aspects and can vary among institutions and organizations, even when made in response to the same policy direction.
- Macro level - health policy based on evidence: macro decisions, as those regarding the implementation of screening programs, are typically made by health authorities.

The production of evidences and the availability of multiple databases represent a key point in the realization of an HTA process, that can be useful to support decisions when a technology is rather complex and presents numerous uncertainties, when a treatment or a diagnostic test is very innovative or contro-

versial, when a well-established technology is involved in remarkable changes of use or outcomes or when a technology carries significant cost burden (2).

Evidences in HTA

Good quality evidence of efficacy should be at the base of decisions regarding health technologies and decisions should embrace a model of evidence-based medicine, defined as the conscientious and judicious use of current best evidence from clinical care research in the management of individual patients and population (13).
Battista (7) suggests that "*effective assessment requires recognizing and gathering 3 conceptually distinct types of evidence: the scientific, the contextual and the historical".* The first is defined as the raw material of HTA, the second refers to those factors that could influence policy decision (e.g. who makes decisions? how?) whilst the third one is related to patients' history, an issue that strongly affects patient's compliance and, thus, the success of a therapy (14,15).

TEN BASIC STEPS OF HTA

A correct and complete HTA process would ideally follow (1) ten basic steps, although not all assessment programs conduct all the steps, or conduct them in sequence:
➢ Identify assessment topics.
➢ Specify the assessment problem.
➢ Determine locus of assessment: determination of the most appropriate organization to conduct the assessment.
➢ Retrieve evidence: e.g. through databases, grey literature.
➢ Collect new primary data: e.g. clinical trials.
➢ Interpret evidence, to critically appraise the quality of the available studies.
➢ Synthesize or consolidate the available findings: e.g. meta-analysis
➢ Formulate findings, intended as results or conclusions of an assessment, and recommendations, meant as suggestions and advices that follow from the findings.
➢ Disseminate findings and recommendations.
➢ Monitor impact: e.g. adoption of a new technology, attributable to its HTA.

ACTORS OF HTA

As HTA requires a multidisciplinary approach, different types of experts are needed: physicians, nurses and other health operators involved in clinical researches; policy makers, managers of hospitals and other health care organizations; patients and citizens for socio-cultural aspects; epidemiologists, biostatisticians, economists, lawyers, social scientists, ethicists and many other figures.
As the aim of health technology assessment is to support decision-makers to best allocate available resources, HTA is usually carried out by non profit organizations (figure 1).

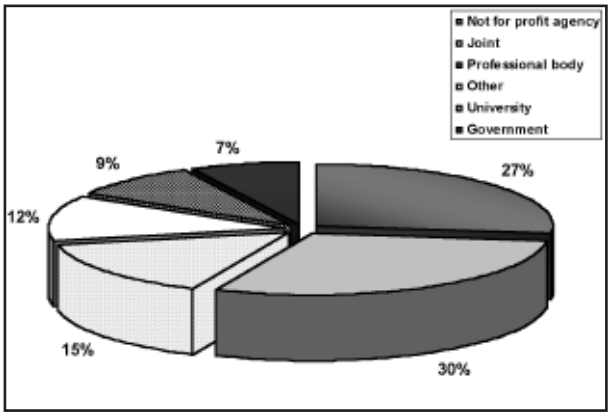

Figure 1: Type of organizations that conduct HTA (16).

The most relevant international network of HTA agencies is INAHTA(17), a non-profit organization that was established in 1993 to coordinate the international HTA activity and to promote a shared and appropriate assessment method. INAHTA gathers 45 member agencies from 23 countries including North and Latin America, Europe, Australia, and New Zealand. All members are non-profit organizations (e.g. NICE in UK) that produce HTA and are linked to regional or national governments.
Until few years ago, Italy had no national agency responsible for conducting, promoting, and financing HTA (18): in fact, HTA activity was limited and tended to be *"untargeted, uncoordinated, and without priorities"* (19). In 2003, the Ministry of Health funded a project to create an Italian Network to coordinate the existing HTA agencies (NI-HTA): however, HTA' impact on health policy is still scarce and it's impossible to quantify with any precision the volume of HTAs being carried out to date. With the reform of Title 5 of the Italian Constitution (Legge Costituzionale n. 3/2001), Italian health policy has been decentralized from national authorities to the Regions (20): firstly this boosted the emergence of a bunch of new decision makers based at the local (regional) level: secondly it has empowered these decision makers to redesign local provision and distribution of medical services together with the allocation of resources to obtain centrally assigned objectives. As a matter of fact, the most appropriate HTA agencies in Italy are, in our opinion those represented by Regional organiza-

tions, who could best benefit from the availability of local databases and data sources, to target local needs and regional policy-makers requests.

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PHARMACOECONOMICS AND IMMUNOTHERAPY

P. Berto (1)

SUMMARY: : Pharmacoeconomics is a relatively new discipline whose scope is to describe, measure and compare costs and outcomes of alternative healthcare programmes from a variety of perspectives. This article is aimed at describing the various types of pharmacoeconomics analyses, indicating what types of costs and outcomes could be measured within each type of study, summarising the value of modelling techniques in pharmacoeconomics studies and finally suggesting what kind of pharmacoeconomic research can usefully be conducted in order to appreciate the burden of respiratory allergic disease and to evaluate the economic impact of health technologies that can effectively be used to manage it. Pharmacoeconomics is a relatively recent discipline whose use has been spread by the necessity of decision makers in most industrialised countries, to gain understanding of the economic effect of medical technologies in parallel with their clinical performance: only a wider use of the techniques of pharmacoeconomics analysis, together with an increasing willingness of the scientific community to understand the mechanics and appreciate the added value of pharmacoeconomics analysis, can help the discipline to proceed and provide further improvement to the healthcare system and to the society.
Key-words: Pharmacoeconomics - Cost of health care - Health technology - Allergic diseases.

INTRODUCTION AND DEFINITIONS

The term pharmacoeconomics (PE) is a neologism. This word did not exist in English language until the need for application of economic analysis to the pharmaceutical sector arose, as a response to the increasing burden that the production of much and better health was placing on the healthcare systems and on the societies around the world, that is, in the years after the second world conflict.

A simple definition was provided by Townsend, "scope of pharmacoeconomics is to analyse, measure and compare costs and outcomes of different healthcare programmes from a variety of perspectives"(1), whilst other authors prefer to use the expression "economic evaluation of healthcare programmes"(2), which indeed is more precise and purports that economics can effectively be applied to all healthcare technologies and not necessarily only to drugs, but on the other hand, is longer and less immediate.

The International Society of Pharmacoeconomics and Outcomes Research (ISPOR) in its 2003 edition of the ISPOR Book of terms(3), provides a clear description of pharmacoeconomics, and according to this: *"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"*(3).

Since its introduction, PE has been increasingly used: every year more papers are published (see figure 1 for an illustration of the number of papers published in PubMed, through retrieval by single MESH (Medical Subjects Headings) citation of the term cost-effectiveness analysis), and an increasing number of healthcare agencies and regulatory bodies currently require PE data in support to the application for the registration/reimbursement of new technologies (4, 5).

This prompted the need for some sort of standardisation of the methods to be used in the economic analysis of healthcare technologies and much has been written and published on this topic, because this was and indeed still is relevant for researchers as well as editors and decision makers(5-39) (figure 1).

Detailed analysis of the contents and application of PE analysis is beyond the scope of this paper; nevertheless, for better understanding of the following chapters, a brief discussion on the major topics of the discipline will be presented here, together with some considerations on the application of PE studies to the area of allergy and immunotherapy.

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TYPES OF PHARMACO-ECONOMIC ANALYSIS

The first issue to be addressed is the type of PE study to be performed in order to support the decision making process; four types of economic analysis have indeed been described and applied in the past decades, namely: Cost-Benefit Analysis (CBA), Cost-Effectiveness Analysis (CEA), Cost-Minimization Analysis (CMA) and Cost-Utility Analysis (CUA). These are recognised as full (or complete) PE analyses, since they all address the efficiency of a medical technology by comparing its costs and outcomes to those of an appropriately chosen reference therapy. Another type of PE that is labelled as an incomplete one, is Cost Of Illness Analysis (COI) as this type of study focuses solely on the analysis of costs of a certain illness and thus, not addressing measurement of outcomes, nor making comparison among different strategies, it cannot be enumerated among complete PE studies(12).

As to what regards full PE analyses, all of them basically address the question on whether or not a specified medical technology provides good value for the money spent in its delivery: all of them require that cost of the alternatives under study is measured by means of some monetary unit (dollars, euros, etc.) but they all differ as to what regards the measurement of outcome. In CBA the outcome is measured in monetary terms (as it is for the cost), in CEA and CMA the outcome is measured in physical health units (such as the typical clinical end-points resulting from clinical trials, i.e. pulmonary function, asthma exacerbations, life-years lost or gained etc.), in CUA the outcome is measured by a utility score (that is a measure of patients' preference towards specified health states; typical unit measure of CUA is the Quality Adjusted Life Year - QALY, a combination of the number of years of life expectancy provided by medical treatments, combined by their relative utility scores).

Finally the main difference between CEA and CMA relies on the fact that CMA can only be applied when the efficacy of the comparators under study has been demonstrated equal in the frame of well conducted clinical studies: indeed, being efficacy between comparators the same, this type of analysis relies only on the comparison of costs among the different alternatives.

To provide the reader with a simple measurement of the use of the described types of analysis, we undertook a simple PubMed search using the above indicated terms as single MESH citations; results are reported in figure 2: out of 9105 articles retrieved, almost 80% use cost-effectiveness analysis which is indeed the most applied type of PE study, followed by CBA, CUA, COI and CMA.

COSTS AND PERSPECTIVE OF PE ANALYSES

Costs to be considered in PE studies can be broken into two main categories: direct and indirect costs, where the first includes the value of all the goods, services, and other resources that are consumed in the provision of an intervention or in dealing with the side effects or other current and future consequences linked to it, whilst indirect costs include the value of lost or impaired ability to work or to engage in leisure activities due to morbidity (morbidity costs) and lost economic productivity due to death (mortality costs) (40). Obviously the decision on what costs to include in any PE study is of extreme relevance as it can significantly effect the results of the analysis in terms of size and quality of the economic effect: in this respect, study perspective must be used as the driving force. In fact, perspective of the economic analysis must be decided upfront, whenever a PE study is undertaken, because identification of the study perspective, that is, who will use the results of the analysis in order to make allocation decisions (i.e. the society as a whole, the National Healthcare System - NHS, a single institution, etc.),

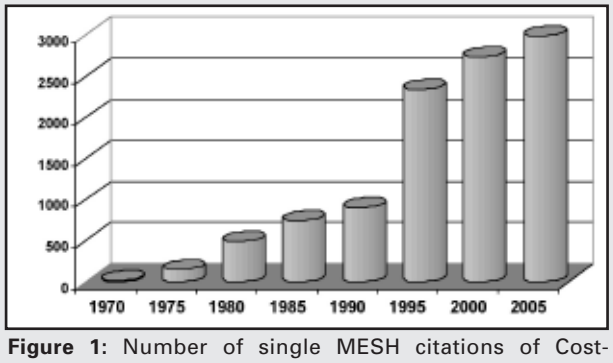

Figure 1: Number of single MESH citations of Cost-Effectiveness Analysis in PubMed (as of August 2007).

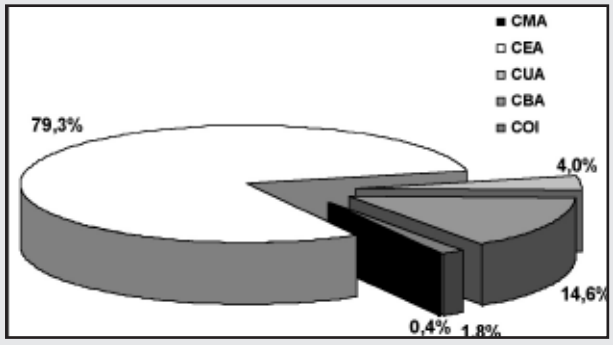

Figure 2: Number of PubMed publications using single MESH citations (as of August 2007).

drives the selection of study comparators, types of costs and outcomes to be analysed, type of analysis to be applied and ultimately affects any conclusion that may be derived from the specific study.
A detailed description of the types of cost to be included in PE studies in the frame of the Italian healthcare environment is presented in table 1, that illustrates what costs should be included according to the perspective of the society, of the Italian NHS or of an hospital institution and provides suggestions on the sources from which each cost may be derived, especially for those costs for which a specified National Tariff is available according to Italian sources.

THE USE OF MODELS IN PE ANALYSES

Because not always all the necessary information to fill the gaps of a properly conducted PE study is available, researchers have increasingly used modelling techniques. *"Models of various types are routinely used in a wide variety of scientific disciplines. They are a way of representing the complexity of the real world in a more simple and comprehensible form. Where true experiments are infeasible or impracticable, models can be used to simulate experiments and to explore alternative scenarios"*(41).
Models are an approximation of reality that allow the researcher and the user of PE analysis to figure out what could be efficiency of a certain medical intervention in comparison with one (or more) alternative(s) under a set of specified conditions, applying data derived from different sources and/or introducing estimates instead of measurements. According to Buxton *et al.*, PE models can be used to: extrapolate beyond the data observed in a trial; link intermediate clinical endpoints to final outcomes; generalize results to other settings; synthesize head-to-head comparisons where relevant trials do not exist; inform decisions in the absence of hard data (41).
A typical modelling study could for example estimate what would be the cost-effectiveness of a new treatment for asthma in comparison with standard care in a population of severe asthmatic patients, in the perspective of the Italian NHS. Because the new technology has not been used previously in the Italian medical practice, the use of registration studies (typically double-blind, placebo controlled studies of selected patient populations) would in itself introduce some sort of uncertainty in the conclusions derived from CEA: this is why the study variables should be subject to sensitivity analysis in order to test the robustness of conclusions and recommendations. In summary, due to the intrinsic uncertainty associated with PE studies in general and modelling studies in particular, conclusions and recommendations derived from modelling studies should always be handled with care: by the researcher, in that a full description of the model structure, variables and assumptions should be given and extensive sensitivity analysis should be provided; by the reader who should carefully analyse study results and conclusions and ultimately search for sufficient transparency and applicability to support the decision for adoption of the new technology in his/her own institutional setting.

APPLICATION OF PHARMACO-ECONOMICS TO ALLERGY AND IMMUNOTHERAPY

Other Authors in the following papers will address in detail some of the most interesting and relevant economic studies of allergy and immunotherapy, their results and limitations. Here, the key issues for performing economic studies of allergy and immunotherapy are briefly discussed, in view of the principles presented in the previous paragraphs.
CEA and CUA studies may represent the best tools to compare between alternative anti-allergic treatments; both of them address at the same time costs and outcomes, both of them report outcomes that are based on clinical efficacy/effectiveness; outcome unit measurement in CEA should be based on long-term hard end-points (life expectancy, asthma cases avoided, patients clinically improved), rather than intermediate or soft end-points (like morning peak expiratory flow or other laboratory parameters); in CUA the use of QALYs may be of particular help, in that it would allow contemporary consideration of the effect of treatment on life expectancy together with the utility (or preference) attributed by patients to health states. For example, a recent paper published the results of a validation study to derive utility scores for Italy, France, and the United Kingdom from the Asthma Symptom Utility Index (ASUI), a preference-based outcome measure used in the US, and suggested that the ASUI may be a complementary patient-reported outcome for clinical studies and may be useful for applications in cost-utility studies comparing different asthma treatments (42). As to what costs should be measured in PE analysis of this therapeutic area, they will depend on the perspective taken by the analysis, for instance, in the perspective of the Italian NHS for each study alternative direct medical costs should be identified and measured, including the cost of medical visits, of laboratory tests and examinations used to diagnose the disease, of treatments used to control symptoms as well as of any preventive treatment (including immunotherapy), the cost of hospital admissions for asthma exacerbations, the cost of

rehabilitation following any disease or treatment related event that may severely affect patient's functioning. Out-of-pocket expenditures, such as for example some symptomatic drugs that are not reimbursed by the Italian NHS, should conversely be included in a study that analyses economics of alternative treatments in the perspective of the society as a whole, together with indirect costs including days off work (for both the patient and the caregiver) resulting from increased morbidity or mortality.

CONCLUSIONS

Allergic rhinitis and its principal co-morbidity, 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 ARIA guidelines(43). 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(44). Pharmacoeconomics is a relatively recent discipline whose use has been spread by the necessity of decision makers in most industrialised countries, to gain understanding of the economic effect of medical technologies in parallel with their clinical performance: only a wider use of the techniques of PE analysis, together with an increasing willingness of the scientific community to understand the mechanics and appreciate the added value of PE analysis can help the discipline to proceed and give further contribution to the healthcare system and to the society (table 1).

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RESOURCE ITEM	Study Perspective			Type of price to be applied	Source
	Hospital	NHS	Society		
GP visit	NO	YES	YES	National ambulatory Tariff	Ministero Salute. Nomenclatore Tariffario delle prestazioni ambulatoriali DM 22.7.96; GU n° 216, 14.9.96
Out-patient (ambulatory) specialist visit	NO	YES	YES	National ambulatory Tariff	Ministero Salute. Nomenclatore Tariffario delle prestazioni ambulatoriali DM 22.7.96; GU n° 216, 14.9.96
Out-patient drug prescription (NHS charge)	NO	YES	YES	National Drug Formulary (public price)	Informatore Farmaceutico OEMF Milano (or) www.giofil.it
Out-patient drug prescription (non-reimbursed)	NO	NO	YES	Retail price	Informatore Farmaceutico OEMF Milano (or) www.giofil.it
Out-patient medical device	NO	YES	YES	Retail price	Manufacturer
Out-patient immunotherapy	NO	YES	YES	Retail price	Manufacturer
Out-patient laboratory tests, diagnostics & exams	NO	YES	YES	National ambulatory Tariff	Ministero Salute. Nomenclatore Tariffario delle prestazioni ambulatoriali DM 22.7.96; GU n° 216, 14.9.96
Out-patient (ambulatory) procedures	NO	YES	YES	National ambulatory Tariff	Ministero Salute. Nomenclatore Tariffario delle prestazioni ambulatoriali DM 22.7.96; GU n° 216, 14.9.96
Rehabilitation	NO	YES	YES	National Hospital Tariff (DRG for rehabilitation)	Ministero Salute. Ricognizione e primo aggiornamento delle tariffe massime per la remunerazione delle prestazioni sanitarie; DM 12.09.06 - SO Gazzetta Ufficiale n° 289 13.12.06
Hospital admission (day-hospital or acute care)	NO	YES	YES	National Hospital DRG Tariff	Ministero Salute. Ricognizione e primo aggiornamento delle tariffe massime per la remunerazione delle prestazioni sanitarie; DM 12.09.06 - SO Gazzetta Ufficiale n° 289 13.12.06
Hospital in-patient drug prescription	YES	NO	NO	National Drug Formulary (50% of public price)	Informatore Farmaceutico OEMF Milano (or) www.giofil.it
Hospital hotel costs	YES	NO	NO	Hospital accounting costs	To be determined at the local hospital level
Hospital in-patient visits & consultations	YES	NO	NO	Hospital accounting costs	To be determined at the local hospital level
Hospital in-patient laboratory tests, diagnostics & exams	YES	NO	NO	Hospital accounting costs	To be determined at the local hospital level
Hospital in-patient procedures	YES	NO	NO	Hospital accounting costs	To be determined at the local hospital level
Hospital in-patient medical device	YES	NO	NO	Hospital accounting costs	To be determined at the local hospital level
Indirect costs (due to short term production losses	NO	NO	YES	Friction cost or human	According to the type of indirect cost and available

Table 1: Study perspective and costing of resources in the Italian Healthcare System.

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PHARMACOECONOMICS OF SUBCUTANEOUS ALLERGEN IMMUNOTHERAPY

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SUMMARY: The current burden of allergic diseases, estimated by both direct and indirect costs, is very relevant. In fact the cost estimation for rhinitis amount globally to 4-10 billion dollars/year in the US and to an average annual cost of 1089 euros per child/adolescent and 1543 euros per adult in Europe. The estimated annual costs in Northern America for asthma amounted to 14 billion dollars. Consequently, preventive strategies aimed at reducing the clinical severity of allergy are potentially able to reduce its costs. Among them, specific immunotherapy (SIT) joins to the preventive capacity the carryover effect once treatment is discontinued. A number of studies, mainly conducted in the US and Germany demonstrated a favourable cost-benefit balance. In the nineties, most surveys on patients with allergic rhinitis and asthma reported significant reductions of the direct and indirect costs in subjects treated with SIT compared to those treated with symptomatic drugs.
This is fully confirmed in recent studies conducted in European countries: in Denmark the direct cost per patient/year of the standard care was more than halved following SIT; in Italy a study on Parietaria allergic patients demonstrated a significant difference in favor of SIT plus drug treatment for three years versus drug treatment alone, with a cost reduction starting from the 2nd year and increasing to 48% at the 3rd year, with a highly statistical significance which was maintained up to the 6th year, i.e. 3 years after stopping immunotherapy, corresponding to a net saving for each patient at the final evaluation of 623 euros per year; in France a cost/efficacy analysis comparing SIT and current symptomatic treatment in adults and children with dust mite and pollen allergy showed remarkable savings with SIT for both allergies in adults and children.
Key-words: Rhinitis - Asthma - Allergen immunotherapy - Drug treatment - Pharmacoeconomics.

INTRODUCTION

Allergic diseases, with particular importance for allergic rhinitis, asthma, and atopic dermatitis, show in developed countries an increasing prevalence, currently estimated in figures up to 20% (1-4) which attributes them a growing importance as medical problems. As a consequence, the economic burden of allergic diseases is becoming very relevant. Concerning allergic rhinitis, in the United States a rising number of billion dollars per year was estimated for direct and indirect costs (5-12). Direct costs derive from drug treatment, physician visits and, especially for asthma, from hospital admission, while indirect costs are related to reduced productivity (9), and include patient's quality of life, cognitive and learning functions, decision making, and self-perception (10).

At the European level, data from the European Lung White Book showed that the total financial burden of asthma in Europe, including all costs (drugs, ambulatory care, inpatient care, lost work days) and excluding mortality and rehabilitation costs, is estimated in 17.7 total billions of euros (11). Therefore, taking into account that the prevalence of clinical asthma across the European region is ranging between 10% and 2.5% of proportion population with asthma, with the exception of UK in which more higher percentage of population (>10%) is affected, the European burden of asthma is really impressive and more strengthened actions must be done to face the increasing economic impacts.
A study conducted in the nineties calculated that two-thirds of the total cost of allergic rhinitis in the US - estimated in 1.8 billion dollars - were due to direct medical costs and one third was due to indirect costs (12). In 1997 much higher costs were approximated, with 4.5 billion dollars for direct and 3.4 billion dollars for indirect costs (6).
More recent papers outline a further increase of the economic burden: a study on only direct costs, based on the US Medical Expenditure Panel Survey, calculated an amount of 4.4 billion dollars, with medication accounting for 47% and physician visits accounting for 52% of cost (13), while in 2001 about 10 billion dollars of indirect costs for allergic rhinitis were estimated, higher than the direct costs of the disease (14).
An European study reported an average annual cost of 1089 euros per child/adolescent and 1543 euros per adult (15); indirect costs amounted to about 50% in adults but only to 6% in children, in whom nevertheless the calculation was based on time lost by parents/caregivers but not on school absences.
Obviously, the figures are bigger considering also asthma and atopic dermatitis (16). For asthma, the estimated costs in Northern America in the nineties amounted to 14 billion dollars (17, 18), and a recent study in the US calculated an average per person annual cost of asthma of 4912 dollars, of which 3180 for direct costs – with drugs and hospitalizations as major causes - and 1732 for indirect costs (19). Also in Europe the distribution of asthma costs shows that the total amount of lost work days is more than the sum of both drugs and ambulatory care, emphasizing the high level of social-economic burden of the disease (11).
Concerning atopic dermatitis, studies conducted in the nineties on children, who suffer from such skin disorder much more than adults, found that moderate disease was associated to an average cost per year of 1700 dollars, while severe disease was associated to a cost of over 2500 dollars (20). A global estimation in such time calculated in 364 million dollars the annual cost for treating atopic dermatitis in the US (21). A study in the UK which considered also indirect costs such as work loss by parents nearly doubled that figure, reporting a cost of 700 million dollars per year (22). A recent investigation dealt with the costs of treatment of asthma and atopic dermatitis in a birth cohort of children in Germany, which averaged 627 and 219 dollars/year per person, respectively (23). Considering a prevalence of 10% of these conditions in German population, this correspond to an annual cost of about 8 billion dollars.
As hinted above, drug treatment accounts for a significant part of the costs - direct and indirect - of allergy. For example, first generation antihistamines (because of their sedating effects) impair the mental performances more than untreated rhinitis does (24) and thus increase the indirect cost, but recent generations antihistamines are more expensive and increase the direct cost (25). Also most drugs introduced in the latest decade to treat asthma (such as inhaled corticosteroids especially in association with long acting beta2-agonists) and atopic dermatitis (such as tacrolimus and pitecrolimus) are more costly than the preceding agents. On the other hand, in a literature review lack of treatment, undertreatment, or nonadherence were seen to increase both direct and indirect costs of allergic rhinitis (26). In addition, no estimations of expenditure due to alternative medicine such as homeopathy are available.
On this ground, any preventive strategy aimed at reducing the clinical severity of respiratory allergy is potentially able to reduce its costs.

COST EFFECTIVENESS OF ALLERGEN IMMUNOTHERAPY

Specific immunotherapy (SIT) is the practice of administering increasing doses of the allergen to which the subject is sensitised. It modifies the immune response to allergens at early stages and, therefore, is capable of reducing the symptoms under allergen exposure and of modifying the natural history of the disease (27). From a clinical point of view, the special mechanisms of action of SIT result in symptomatic improvement, long lasting effects after cessation of the treatment, and prevention of the evolution of the disease. SIT can be administered either subcutaneously or sublingually. A number of studies showed that in the long term subcutaneous IT is associated to a lower expenditure compared to drug treatment.
The first studies conducted in Germany in the nineties showed very good results: Buchner *et al*. reported in a retrospective 10-year analysis that the direct and indirect costs in patients with allergic rhinitis and asthma were reduced by 54% in subjects treated with SIT compared to those treated with symptomatic drugs, and estimated that in such 10-year period the cost savings per patient should amount to 9500 deut-

schmarks (DM) for asthma and 5000 DM for rhinitis (28). In another study, Fischer *et al*. estimated that the use of immunotherapy could save respectively 500 and 1000 DM per year in subjects with allergic rhinitis and allergic asthma (29). In the same years, data from the US showed that in patients with allergic rhinitis SIT reduced the cost of care by 180 dollars after two years of treatment, along with a significant improvement of quality of life (30), and that in patients with ragweed-induced asthma a cost reduction of about 30% was reported during the performance of a placebo controlled study (31). On the other hand, another contemporary study from the US on asthmatics found a mean cost about 20% higher in subjects treated with immunotherapy, however the same authors argued that the greater severity of asthma, and consequently the greater drug use, in patients admitted to immunotherapy could account for such observation (32). Moreover, the short duration of the study - seven months - seems unable to achieve the cost reduction, which we know from the other studies generally occurring after 2-3 years.

A German retrospective study still concerning the nineties examined the economic effects of three years of subcutaneous SIT by a follow-up of 10 years and found that the advantage on drug treatment started after six years and resulted in final net savings of between 650 and 1190 DM per patient (33); a sensitivity analysis with direct medical costs via numerical variations showed that SIT was more likely to result in net savings than in additional costs. In this study the economic benefit was clear but the break-even point was reached only three years after discontinuing SIT, while in a French study a significant reduction of the direct costs of the allergic disease after already two years of immunotherapy was reported (34).

Three studies conducted in different European countries were published in recent years. In 2005, an health-economic analysis performed in Denmark on a large group of patients with grass pollen or mite allergy and including direct and indirect costs revealed that the direct cost per patient/year of the standard care before SIT was 2580 Danish kroner (DKK), while was 1072 DKK per patient/year after SIT (35); in the long term, introduction of SIT incurred additional direct costs of 13.676 DKK per patient, but when indirect costs were included in the economic evaluation SIT showed a net benefit. In 2006, an Italian study addressed rhinitis and asthma caused by Parietaria pollen, treated with subcutaneous SIT by a Parietaria judaica extract (Alustal, Stallergénes, Antony, France) by a conventional build-up schedule in 12 weeks and a maintenance treatment every 4 weeks for 3 years, or with antiallergic drugs (36). Each patient was evaluated before starting the treatment and annually for six years in the pollen period of Parietaria by means of nose, eye, and lung symptom scores, and drug consumption registered in diary cards. In other specifically designated cards general practitioner's or specialist's visits, the number of desensitizing injections, and the number of boxes of antiallergic drugs were registered.

A significant difference in favour of SIT plus drug treatment versus drug treatment alone was observed, reaching a reduction of cost of about 15% at the 2nd year, and of 48% at the 3rd year, with a highly statistical significance which was maintained up to the 6th year, i.e. 3 years after stopping immunotherapy, when a 80% reduction was found. The net saving for each patient at the final evaluation corresponded to 623 euros per year.

The latest study was conducted in France in 2007: a cost/efficacy analysis was performed using a decision tree model by the perspective of the French Social Security, comparing SIT and current symptomatic treatment in adults and children with dust mite and pollen allergy (37). In adults, the savings with subcutaneous SIT were 393 euros for dust mite and 1327 euros for pollen allergy over a 6-year period. In children, the savings were 583 euros for dust mite and 597 euros for pollen allergy over a 7-year period. In such study was considered also sublingual immunotherapy, which showed – as expected because of no need of visits for injections – higher savings, corresponding to 3158 euros for dust mite and 1708 euros for pollen allergy in adults, and to 3938 euros for dust mite and 824 euros for pollen allergy in children.

CONCLUDING REMARKS

Among treatment options for respiratory allergy, SIT has unique characteristics, such as the capacity to change the natural history of the disease and, differently from drugs, to extend its effectiveness to many years after stopping therapy. Considering this, it is surprising that SIT is largely less used than drugs. For example, it has been reported that in the nineties in Spain the expense for anti-asthmatic drugs rose by three times, while the expense for SIT was dwarfed to one third than that of the eighties (38). The data reported by the numerous studies cited above, demonstrating a clear health economic advantage of SIT over drug treatment, should lead to carefully reconsider the optimal choice when deciding to treat a patient with allergic rhinitis or asthma.

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ECONOMIC EVALUATION OF SUBLINGUAL IMMUNOTHERAPY: AN ANALYSIS OF LITERATURE

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SUMMARY: Allergic rhinitis and asthma constitute a global health problem because of their very high prevalence and the consequent burden of disease, concerning medical and economical issues. Among the treatments of allergy, specific immunotherapy has the capacity to favourably alter the natural history of the disease both during and after its performance and thus to reduce the direct and indirect costs of allergic rhinitis and asthma. A number of studies reported such cost reduction for traditional, subcutaneous immunotherapy and recent data demonstrate that also sublingual immunotherapy (SLIT) is associated to economic advantages and/or monetary savings, specifically in terms of reduction of disease economic burden. Only few formal economic assessments of SLIT have been carried out so far, this article will present and discuss the published studies addressed to this issue. The data obtained, although the number of studies is still limited, provide preliminary evidence supporting a SLIT effect on sparing costs for respiratory allergy.
Key-words: Allergic rhinitis - Allergic asthma - Cost of disease - Specific immunotherapy - Sublingual immunotherapy.

INTRODUCTION

Allergic rhinitis and asthma constitute a global health problem as the prevalence is very high (up to 25% of general population) (1). Respiratory allergies may be a severe disease, present several co-morbidities, alter the social life of patients, affect school performance and work productivity. Therefore, the costs incurred by them are substantial.

Specific immunotherapy (IT), together with allergen avoidance and pharmacological treatment, is a cornerstone of the management of respiratory allergic diseases, and its clinical indications are well established (2). The sublingual route of administration (SLIT) was introduced in 1986 (3) and today its efficacy is supported by numerous randomized controlled trials (4) and meta-analyses conducted in both allergic rhinitis and asthma (5-7). In addition to clinical studies, some post-marketing surveys (8-10) including also very young children, confirmed the optimal safety profile of the treatment. SLIT is used in many European countries and in the ARIA guidelines it is considered as a viable alternative to injection IT (11). Similarly to subcutaneous IT, SLIT can modify the natural course of respiratory allergic disease (12;13) and exerts a long-lasting therapeutic effect (14). Although confirmatory studies on preventive and

long-term effects are needed, it is reasonable to expect that SLIT is associated to economic advantages and/or monetary savings, specifically in terms of reduction of the economic burden of allergic disease.
The economic performance of treatments is of primary relevance: the optimal treatment needs to be clinically effective but should also have a measurable impact on the costs of disease. It has been suggested that, being self-managed by the patient at home, SLIT can carry substantial savings over subcutaneous IT (15). Nevertheless, only few structured economic assessments of SLIT have been carried out so far. Therefore, this article will present and discuss them.

ANALYSIS OF THE LITERATURE

The first published study concerned the evaluation of cost effectiveness of SLIT in children with allergic rhinitis and asthma (16). This study involved one allergy center located in Italy (north of Milan). From the existing records of patients seen for allergic disease, all children and adolescents with allergic disease, who had 1-year data prior to receive SLIT and 3-year data on SLIT, were evaluated. Outcome measures were the number of exacerbations, visits, absence from nursery or school. Moreover, direct costs (€ spent on drugs, specialists visits, and SLIT) and indirect costs (costs resulting from children school and parental work loss) were considered. A second analysis compared a sub-group of allergic asthmatic children with a control group for costs, based on records of patients not SLIT-treated, extracted from a network-database of pediatricians.
Globally, 135 patients were analyzed, 46 of which had perennial and 89 seasonal allergy with comparable gender and age distribution. A substantial reduction was found in all outcome measures during SLIT compared with the previous period. The average annual cost/patient was € 2672 before SLIT initiation and € 629/year during SLIT. Similar results were found for allergen subgroups. The asthma sub-analysis involved 41 children with SLIT and 35 controls. Again, SLIT patients showed a substantial reduction in outcomes. The direct cost/patient over the whole follow-up (4 years) was € 1182 for SLIT-treated children and € 1100 for controls.
Therefore, this study evidenced 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.
The second study concerned a large cohort of adult with pollen allergy and was conducted with rigorous methodology (17).
This study (SPAI: SLIT Pollen Allergy Italy) was designed to assess the costs and consequences of using SLIT in association with standard treatment compared to standard treatment alone (No-SLIT) in young adults with pollen-induced allergic rhinitis and asthma. The study was specifically designed for the Italian environment, based on a cost-effectiveness model originally developed for France (18), and considered both the perspective of the National Healthcare System (NHS) and of the society.
This study compared costs, clinical outcomes and cost-effectiveness ratios of two strategies in the management of allergic rhinitis and asthma, namely SLIT associated with pharmacotherapy and pharmacotherapy alone (No-SLIT). Drug therapy for rhinitis and asthma was that recommended in international guidelines. The study was performed from the perspective of the NHS (only direct medical costs) and of the Society (direct and indirect costs). Target population were young adults suffering from pollen-induced rhinitis with or without asthma. Time horizon was established at 6 years in order to incorporate long term effectiveness of SLIT. Patients' data were collected in 25 Italian centers and analyzed through a decision tree model, based on medical and economic assumptions that represent real-life observations.
Retrospective Observation Physician Panel (ROPP), including 27 physicians from 25 allergy centers, carried out data collection on epidemiology and consumption of resources. Each physician was responsible for collecting by clinical records retrospective data of approximately 100 consecutive young adults (range 16-45 years), with ascertained allergic rhinitis with/out asthma due to pollens. In particular, ROPP was asked to provide information on how much patients had rhinitis and/or asthma and how much improved/worsened or remained unchanged with/without SLIT and data collected were used to "populate" the economic model.
Main assessment criteria for the two different strategies were: a) costs, including the direct medical costs assessed in the NHS perspective and the direct plus indirect costs and patient out-of-pocket expenses assessed in the societal perspective; b) effectiveness end-point, including: number of patients improved and number of asthma cases avoided; c) incremental cost per improved patient and incremental cost per asthma case avoided. The economic incremental cost-effectiveness ratio (ICER) represents the difference between SLIT and No-SLIT based on their difference of cost and effect.
Direct costs included visits, diagnostic procedures, drugs, SLIT and hospitalizations. Indirect costs included lost working days. From the societal perspective also the cost of drugs not reimbursed by the NHS (paid by the patient) were considered. The cost of medications (based on the recommended daily dose) and reimbursement rates were retrieved from the Italian National Drug Price List. The cost of SLIT was

based on the dosing schedule recommended by the manufacturer (Stallergénes SA, Antony, France). The number of follow-up visits per year by disease severity was retrieved from the ROPP, and the relative cost (20.66 €) was obtained from the National Ambulatory Tariff List. The costs of diagnostic tests, according to international guidelines was based on the current NHS tariffs. Finally, the yearly number of hospital admissions, was obtained from the ROPP data analysis. In order to adopt a conservative approach, we attributed the same rate of hospitalization to both SLIT and No-SLIT groups. Cost of hospital admissions was based on the current NHS tariffs.

Working days losses were obtained from the ROPP data analysis and no working day loss was attributed to rhinitis, whatever its level of severity. According to published Italian economic literature indirect costs were valued on the basis of 2002 gross salary of individuals with paid occupation in Italy divided by 220 working days/year. Direct and indirect costs were discounted at 3% yearly rate.

Twenty-five questionnaires were completed and returned. These questionnaires summarized the data of 2230 patients (age range 16-45 year, mean age 28.2 years, 58% female). According to ROPP data analysis, 60.2% of patients had rhinitis only and 39.8% rhinitis with asthma. Rhinitis was severe in 31.9% and moderate in 68.1% of patients, whereas asthma was mild in 66.3 % and moderate in 33.7 % of patients

Cost analysis was performed in order to define the lowest cost strategy. A mean cost per patient treated over a period of 6 years was calculated for each therapeutic strategy and for each of the two perspectives studied. SLIT strategy resulted in less expense in term of both direct and indirect costs. The break-even point of SLIT, such as the time in which the overall cost of treatment for SLIT patients becomes lower than for patients receiving only drugs for the societal perspective is reached at year 4, as shown in figure 1.

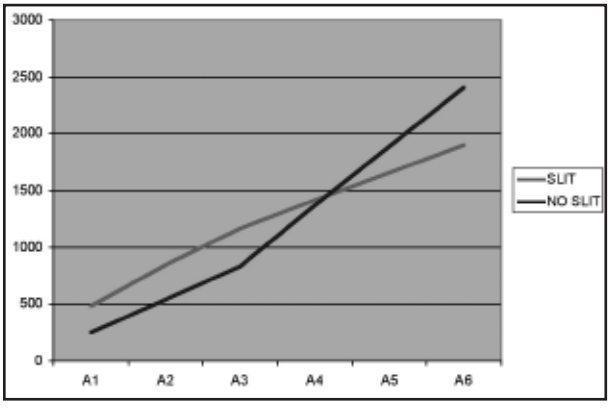

Figure 1: Break-even point for Immunotherapy (SLIT) versus controls (No-SLIT)(17).

This study evidenced that SLIT is more effective and less costly than No-SLIT from both the NHS and the societal perspective and these results remain stable over a realistic range of sensitivity analyses. However, the main limit of this approach is that the analysis is not prospective, but is based on a mathematical model "populated" with retrospectively collected data. On the other hand, the model is rigorous, retrospective data come from a large population in real life setting, and this approach allows to calculate the results in the best and worst cases (sensitivity analysis).

In conclusion, this study demonstrated that SLIT is a cost-effective strategy, a "dominant" strategy, compared to symptomatic treatment.

A third study concerned a population of ragweed-allergic patients from Lombardia, Northern Italy (19). The aim of this study was to provide the Regional decision makers with real world information on the use and impact of immunotherapy in terms of efficacy on symptoms, use and cost of drugs in ragweed-allergic patients. This observational study evaluated three groups of patients: treated with pre-co-seasonal SLIT, with pre-seasonal subcutaneous immunotherapy or with drugs alone. Patients were enrolled by a network of specialist centers from Lombardia and were randomly assigned to one of the study groups. Drug cost was calculated by applying Italian NHS prices.

The analysis of results showed that the mean number of drug treatment days/patient was lower for SLIT patients in comparison with patients treated with drugs alone. Similarly, the mean cost/patient of drug treatment was lower with SLIT versus subcutaneous immunotherapy and drug therapy alone. In conclusion, this study evidenced that SLIT can effectively reduce use and cost of drug treatment in adults with rhinitis and/or asthma caused by ragweed.

Another study regarded the long-term economic evaluation of SLIT in adults with dust-mite allergic asthma (20). The purpose of this study was to evaluate the long-term economic burden of symptomatic asthma treatment and SLIT in adults affected by allergic asthma. Seventy adult asthmatic patients with allergy to Dermatophagoides and asthma severity (according to GINA guidelines) corresponding to 1,2 or 3 degree were evaluated. Fifty of them were treated with SLIT for 3 years and 20 were kept on their standard drug therapy. All of them were followed up for 5 years (i.e. 2during the SLIT and 2 years after its discontinuation). Specific weekly cards allowed to collect subjective symptom scores and data regarding the use of medical resources along the whole study period: consumption of medical resources was translated into NHS costs using published prices and tariffs.

The total NHS cost per patient over the 5 year follow-up was € 3881 for SLIT-group and €5126 for control group. Difference in favour of SLIT was maintained

for each asthma level. Therefore, this long-term observational study demonstrated that SLIT allows to reduce the costs of allergic asthma.

Another study considered the economics of SLIT in patients with pollen allergy and suffering from allergic rhinitis alone or associated with asthma compared with standard case controls (21). This study (sublingual immunotherapy in allergic patients, SIMAP) was made by a longitudinal observational database operated by a network of Allergy centers. Patients were randomly assigned to SLIT (plus drugs as needed) or to treatment with drugs alone. The outcome measures included use of: drugs, SLIT, visits and exams. Costs were assessed in the perspective of the Italian NHS. However, the relevance of this study is based on a new paradigm: the application of technologies in real practice, measures taken for improvement and subsequent reappraisal, in other words, the spirit of health technology assessment (HTA). According to the definition of the National Health Service it is an internationally recognised term that covers any method used to promote health, prevent and treat disease and improve rehabilitation or long-term care (www.hta.ac.uk). HTA answers questions on whether a health technology (intervention) works, for whom does it work and at what cost, and how does it compare with the alternatives. HTA can effectively be produced from systematic literature reviews, experimental studies, observational studies and economic models. Therefore, this study aimed at producing an HTA report on SLIT.

Globally, 102 patients were evaluated. Overall per patient yearly cost of treatment was higher in SLIT patients, both in the whole sample (€ 311 vs 180/patient), in the rhinitis (€ 288 vs 116) and rhinitis associated with asthma (€ 362 vs € 230) sub-groups. Patients with rhinitis plus 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 plus asthma) in SLIT patients, as shown in Figure 2, thus highlighting the use of symptomatic drugs as an important indicator of effective allergy control. Even though other studies provided evidence that SLIT can reduce the use of drugs, this survey is the first that demonstrates 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 importantly this study confirmed the inhaled corticosteroids sparing effect of SLIT thus, highlighting the use of symptomatic drugs as an important indicator of effective allergy control. Even though other studies provided evidence that SLIT can reduce the use of drugs, this survey is the first that demonstrates this outcome in a routine care population, in the medical practice environment of an observational study, and yet at the first year of treatment.

Two very recent studies concerned the evaluation of economic aspects of immunotherapy performed with oral tablets for grass pollen allergen in Northern (22) and Southern Europe (23). Aim of the first study this study was the assessment of cost-effectiveness of grass allergen tablet compared with use of symptomatic drugs in seven Northern European countries. A societal perspective was adopted, and the analysis had a 9-year time horizon. Main outcome measure was Quality Adjusted Life Years (QALYs). QALYs measure patients' health-related Quality of Life on a scale from 0 (dead) to 1 (perfect health), and are a multi-attribute utility scale that can generate a single numeric index of health-related QoL.

Results of this study showed that grass allergen tablet was clinically superior to symptomatic treatment, producing statistically significant differences for all efficacy end-points, including the number of QALYs gained – 0.976 vs. 0.947 QALYs gained. There was a significantly higher usage of rescue medications (antihistaminics and corticosteroids), and more hours missed from work (productivity losses) in the symptomatic group. The cost per QALY gained in the grass allergen tablet group was similar in the 7 countries (€ 12930 to 18263 for an annual cost of the grass allergen tablet of € 1500). The analysis showed that the grass allergen tablet was cost-effective for all countries for an annual cost below € 2200.

This pharmacoeconomic analysis showed that this immunotherapy is a cost-effective intervention for the prevention of grass pollen induced rhinoconjunctivitis in Northern European countries, for a tablet price below € 6. For example, in Germany the price of the tablet is € 2.95 corresponding to a yearly treatment cost of € 358 – based on a 9-year time horizon.

The second study assessed the cost-effectiveness of grass pollen oral tablets in patients suffering from grass pollen induced allergic rhinitis living in four Southern European countries (Spain, France, Italy, and Austria) (23). Thus, a prospective pharmacoeconomic analyses was carried out alongside a multina-

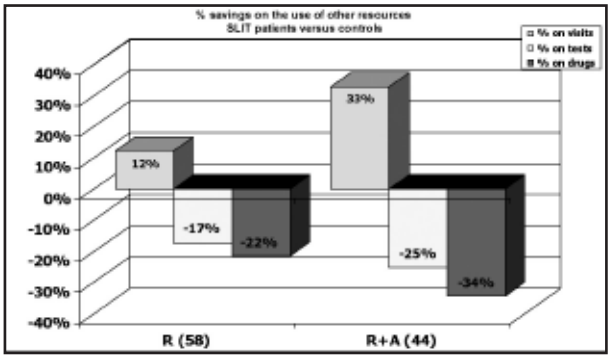

Figure 2: Percentage savings on the use of other resources in patients affected by asthma alone (A) or asthma plus rhinoconjunctivitis (R+A) (21).

tional, clinical trial measuring the efficacy of grass pollen tablets. Pooled data on resource use and health outcomes were collected. A societal perspective was adopted, and the analysis had a nine-year time horizon. The primary outcome measure was quality adjusted life years (QALYs). Allergen specific immunotherapy was superior to standard care for all efficacy endpoints, including QALYs gained, and resulted in significantly less use of rescue medication and fewer hours missed from work. Oral grass allergen tablet was cost-effective for all countries for an annual price in the range of euro 1500-euro1900. The result was improved by inclusion of future costs of asthma and exclusion of Spanish trial centres which experienced an exceptionally low pollen season.

Finally, recent meta-analyses were published on SLIT efficacy in treating allergic rhinitis and asthma in children and adults (5-7, 24). Although these meta-analyses were primarily performed to evaluate effects on symptoms and use of medications, some pharmacoeconomic information may be derived from the second parameter. As outcome data analysed was continuous but authors used a wide variety of scoring systems and scales for medication use, the analysis was performed by applying the method of standardized mean differences (SMD), expressing the difference in means between immunotherapy and placebo recipients in units of pooled standard deviations. As a result, the meta-analysis on rhinitis provided evidence that the combined SMD for medication scores following SLIT was –0.43 indicating a significant reduction in medication use (p=0.00003). Sub-group analyses were conducted: for pollen allergies (significant), for perennial allergens (not significant), for studies involving children only (not significant), for adult/adult and children studies (significant), for duration <6 months (significant), duration 6-12 months (significant) and duration >12 months (not significant). Also in children the medication scores after SLIT showed a significant decrease (SMD, 0.76; p = 0.03) and in the subgroup analysis for allergens a significant reduction with pollens compared with mite was found.

The meta-analysis on asthma (7) showed that in 10 studies with 488 patients there was a significant reduction in the use of medication for asthma and rhinitis. However, in 6 studies with 254 patients there was no significant reduction in the need for medication for asthma alone. There was also a significant heterogeneity in these two outcomes. In the meta-analysis on children (24) there was a highly significant reduction in medication use (SMD – 1.92 95%CI -3.19 to - 0.64; p = 0.003) following immunotherapy, and also in the subgroup analyses of patients that received SLIT for less than 18 months and those that received low doses of immunotherapy, a significant effect on symptom scores was found, allowing to conclude that SLIT is an effective treatment of allergic asthma in children. Still, it is necessary to conduct further studies, and such conclusion has been confirmed by the most recent update review on this issue (25).

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