Comparison of costs of sublingual immunotherapy and drug treatment in grass-pollen induced allergy: results from the SIMAP database study

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\textbf{Key words:} Costs – Economic evaluation – Respiratory allergy – Sublingual immunotherapy

\textbf{ABSTRACT}

\textbf{Objectives:} This analysis is focused on the comparison of costs of allergic rhinitis (R) alone or with allergic asthma (R + A) in grass pollen allergy, for subjects treated with sublingual immunotherapy (SLIT) and symptomatic drugs, versus standard care controls.

\textbf{Methods:} The SIMAP (Sublingual Immunotherapy in Allergic Patients) study is a longitudinal observational database operated by a network of Allergy centers. Patients suffering from grass pollen allergy were included in this analysis and assigned to SLIT (plus drugs as needed) or to treatment with drugs alone. Outcome measures included use of medications, SLIT, visits and tests. Costs were assessed from the perspective of the Italian National Health Service; unit costs were obtained from published sources to produce an average cost/patient for the first year after enrolment.

\textbf{Results:} One hundred and two patients were analyzed. Demographics were comparable in the two groups. Overall per patient yearly cost of treatment was higher in SLIT patients, both in the whole sample (€311 vs. €180/patient), in the R (€288 vs. €116) and R + A (€362 vs. €230) subpopulations, with R + A patients generating more costs than R patients in both groups. Nevertheless considerable savings were obtained in the cost of symptomatic drugs (–22% for R; –34% for R + A) in SLIT patients.

\textbf{Conclusions:} Other studies have shown that SLIT can reduce the use of drugs for asthma and rhinitis, but this is the first time this outcome has been demonstrated in a routine care population (in the medical practice environment of an observational study) within the first year of treatment.
Introduction

Health Technology Assessment (HTA) answers questions regarding whether a health technology (intervention) works, for whom it works 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. Examples of application of HTA in many different therapeutic areas are available on the National Health Service (NHS)-HTA website.

Currently, no studies are available on HTA concerning allergen-specific immunotherapy (SIT) in allergic disease. The role of SIT as a valuable health technology has been investigated in two Cochrane reviews, the latter being focused specifically on sublingual-immunotherapy (SLIT). The efficacy of SLIT has been assessed by several studies and meta-analyses, and its preventive role in respiratory disease was confirmed by the ARIA Workshop Report endorsed by the World Health Organization (WHO).

These studies and reviews have so far assessed the effect of SLIT on the consumption of medical resources (particularly on symptomatic drugs) mostly as measured within clinical trials; nevertheless the economic role of SLIT, and as such the answers to the HTA questions ‘for whom does it work, at what cost, and how does it compare with the alternatives’ are yet to be provided by studies conducted in a real life model in significant numbers of patients.

To meet such need, we designed a real-life study on patients with allergic rhinitis and asthma treated with SLIT, with the primary outcome measure of cost saving for standard drug treatment. This study, called SIMAP (Sublingual Immunotherapy in Allergic Patients) is a longitudinal observational evaluation using a specific database for pharmacoeconomic studies whose general aim is to describe and analyze the clinical management in terms of efficacy, safety and costs of allergic rhinitis, with or without asthma, in a population of children and adults followed up by allergy centers in Italy. This first analysis is focused on the economic evaluation of rhinitis and asthma in grass pollen allergy, for adolescent and adult subjects treated with SLIT plus drugs, recruited and managed by allergy centers in the form of an observational study.

Methods

The SIMAP database is a network of six Allergy centers located in five regions from the North, Center and South of Italy. By the end of 2003 all centers uploaded specially designed software (Società Servizi Telematici, Padova, Italy). The aim of the network was to collect longitudinal information on the clinical management of all patients affected by allergic respiratory disease. Clinicians were fully free to adopt any measure and apply any diagnostic and treatment protocol, according to their personal preference; no pre-defined tests, prescriptions or treatments were to be implemented. In summary, this was designed as a fully observational study.

Patients

The original database included 382 patients with hypersensitivity to various allergens, such as house dust mites, tree pollens, and Parietaria pollen. Regular interim analyses of this ongoing database study were planned, so after 1 year the database was stopped and patient data were extracted according to the following inclusion criteria: males and females, adults and adolescents (i.e. aged less than 18 years) affected by grass pollen allergy, diagnosis documented by allergy tests, patient treated with high dose SLIT or only with standard care drugs as recommended by ARIA and GINA guidelines. Accordingly, 122 patients were included in the evaluation. SLIT was performed by a high dose grass mix extract (Storalor 300, Stallergénes, Antony, France) by the schedule suggested by the manufacturer for pre-coseasonal treatment (from 16 weeks before to the end of grass pollen season, i.e. from January to June). The allergen extract is standardized in index of reactivity (IR), includes five grasses (Phleum pratense, Dactylis glomerata, Lolium perenne, Anthoxanthum odoratum, and Poa pratensis) and the cumulative dose administered during a pre-coseasonal treatment course corresponds to near 22,000 IR. Drug treatment involved standard anti-allergic medications (controls) including antihistamines (such as cetirizine, levocetirizine, loratadine, desloratadine, ebastine, and others), and topical nasal steroids (such as fluticasone, budesonide, and mometasone) for rhinitis, and beta2-agonists (such as salbutamol, salmeterol, and formoterol) and inhaled steroids (such as fluticasone, budesonide, and others) for asthma. In order to be included in this analysis, patients had to be registered in the database and provide data for 1 year of follow-up (± 30 days).

Variables for evaluation

Among the variables included in the SIMAP database the following were extracted for the purpose of this economic study: demographics (sex, age, length of follow-up in days), use of medications (drugs used to manage allergic disease, respiratory disease and any other possibly correlated disease), SLIT, medical visits (including consultations to allergist, otolaryngologist, pneumologist and ophthalmologist), instrumental and laboratory tests, and hospital admissions.
Cost analysis

Costs were assessed from the perspective of the Italian National Health Service (NHS), and as a result included only direct costs; unit costs were obtained from published sources, in particular national tariffs were applied to visits and tests and market prices to drugs and immunotherapy. For each treatment arm the average cost/patient for each medical resource used and the total direct medical costs in the first year after enrolment was produced.

Statistical analysis

Differences for the two groups of patients, SLIT and controls (in total and by rhinitis alone [R] and rhinitis with asthma [R + A]), for age and total follow-up, which are parametric data, were analyzed by one sample t-test. Differences for the calculated cost/patient, which are generally highly skewed, were analyzed by the Mann–Whitney test for non-parametric estimates. The distribution of R and R + A in SLIT and control patients was analyzed by the Chi-squared test. For all analyses a difference was considered significant with a p-value < 0.05. Statistical analysis was performed using GraphPad Prism 4 for Windows (GraphPad Prism, GraphPad Software Inc., San Diego, CA, USA).

Results

Descriptive variables

Of the 122 patients included in the evaluation, 20 did not complete the follow-up, thus the analysis was carried out on data from 102 patients. Patients were divided into two groups according to treatment, i.e. those receiving SLIT plus other drugs (study patients) and those receiving only drugs (controls).

Demographics are presented in Table 1. There were 54 study patients (24 males and 30 females) with mean age 28.3 ± 13.0 years and mean follow-up 377.8 ± 31.4 days. There were 48 controls patients (32 males and 16 females) with mean age 31.5 ± 13.7 years and mean follow-up 375.8 ± 27.0 days.

With respect to the distribution among the different diagnoses, the ratio R/R + A was 58/44 in the whole population, 37/17 in the SLIT group and 21/27 in the control group. These differences were not statistically significant.

Cost analysis

As shown in Table 2 the overall yearly cost of treatment per patient was higher in SLIT patients, both in the whole sample (311.4 vs. 179.8 €/patient), in the R subgroup (287.9 vs. 115.8 €/patient) and in the R + A subgroup (362.4 vs. 229.6 €/patient), these differences being highly significant.

R + A patients generated more costs than R patients in both groups. Figure 1 shows that the difference in total cost was mainly due to SLIT. Nevertheless the cost per patient was lower for use of drugs (~22% for R; ~34% for R + A) in SLIT patients as shown by Figure 2. Figures 2 and 3 also show that the cost of other resources (i.e. excluding the cost of immunotherapy itself) was lower in R patients than in R + A patients (irrespective of the treatment group), and that there was less use of tests and drugs, but not of medical visits, in the SLIT group versus controls.

Table 1. Patient demographics

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Males, n (%)</th>
<th>Age, years, mean ± SD</th>
<th>Length of follow-up, days, mean ± SD</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>102</td>
<td>56 (55)</td>
<td>28.3 ± 13.0</td>
<td>377.8 ± 31.4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>SLIT</td>
<td>54‡</td>
<td>24 (44)</td>
<td>29.8 ± 13.8</td>
<td>369.2 ± 27.9</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Controls</td>
<td>48†</td>
<td>32 (67)</td>
<td>31.5 ± 13.7</td>
<td>375.8 ± 27.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>58</td>
<td>33 (61)</td>
<td>31.5 ± 13.7</td>
<td>375.8 ± 27.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>SLIT</td>
<td>37</td>
<td>19 (51)</td>
<td>29.8 ± 13.8</td>
<td>369.2 ± 27.9</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Controls</td>
<td>21</td>
<td>14 (82)</td>
<td>24.5 ± 9.5</td>
<td>367.6 ± 28.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Rhinitis + asthma</td>
<td>44</td>
<td>23 (48)</td>
<td>24.5 ± 9.5</td>
<td>367.6 ± 28.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>SLIT</td>
<td>17</td>
<td>5 (24)</td>
<td>25.0 ± 10.7</td>
<td>396.7 ± 32.4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Controls</td>
<td>27</td>
<td>18 (67)</td>
<td>37.0 ± 14.1</td>
<td>382.2 ± 24.3</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*p-value measured by one sample (two tailed) t-test
†adults 48; adolescents 6
‡adults 44; adolescents 4
SD = standard deviation; SLIT = sublingual immunotherapy
**Discussion**

As stated in the preliminary version of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Real World Task Force Report\(^2\), ‘data from randomized controlled studies remain the critical foundation for almost all coverage and reimbursement decisions’ … ‘yet, efficacy evidence in a particular group or subgroup is typically insufficient to project the size of the effectiveness impact in the population.

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**Table 2. Total cost per patient (total population and disease subgroups) in euros**

<table>
<thead>
<tr>
<th></th>
<th>Yearly cost, euros, mean ± SD</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SLIT group</td>
<td>Control group</td>
</tr>
<tr>
<td>Total population</td>
<td>311.4 ± 85.24</td>
<td>179.8 ± 161.1</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>287.9 ± 55.44</td>
<td>115.8 ± 35.49</td>
</tr>
<tr>
<td>Rhinitis + asthma</td>
<td>362.4 ± 114.5</td>
<td>229.6 ± 200.1</td>
</tr>
</tbody>
</table>

SD = standard deviation; SLIT = sublingual immunotherapy
that would actually use a product’. As a matter of fact, no one questions that demonstration of efficacy and safety must be derived through experimental studies, but all physicians know that what is demonstrated in experimental studies is only a first step along the road of knowledge for a particular medical technology, and decision makers also know that what is proven in clinical studies may be fully understated or overstated when translated into a real world setting.

This is why observational studies are becoming so important in the lifetime development of medical technologies, and this is the reason why we focused this research on medical records of patients managed and treated in the real world setting of a relatively small number of allergy centers located in Italy.

Recently another Italian study has shown the economic impact of immunotherapy\(^{13}\); this study was a prospective open-label observational study on adult allergic patients treated with injective immunotherapy for pollinosis to *Parietaria judaica* plus symptomatic drugs or with drugs alone. There was a 15% reduction in the cost of treatment from the second year after initiation of immunotherapy and the size and magnitude of this positive effect was increased in the following years – reaching a 50% reduction at the third year – and maintained for at least 3 years after SIT discontinuation.

The few previously published studies were conducted in Germany and in France in the nineties. Buchner and Siepe\(^{14}\) reported in a retrospective 10-year study that the direct and indirect costs in patients with allergic rhinitis and asthma were reduced by 54% in subjects treated with specific immunotherapy compared to those treated with symptomatic drugs, and Fischer\(^{15}\) estimated that the use of immunotherapy could save respectively 500 and 1000 deutschmarks (DM) per year in subjects with allergic rhinitis and allergic asthma. A French study introduced the issue of time-dependence, reporting a significant reduction of the direct costs of the allergic disease after 2 years of immunotherapy\(^{16}\).

More recently, a retrospective study examined the economic effects of 3 years of immunotherapy by a follow-up of 10 years and found that the advantage from drug treatment started after 6 years and resulted in final net savings of between 650 and 1190 DM per patient\(^{17}\).

The literature regarding SLIT is very scant. A first study in 2005 was addressed at children with allergic rhinitis and asthma followed for 4 years, and showed that SLIT achieved substantial reductions of costs\(^{18}\). The other study was a model, using a decision tree populated with epidemiologic and resource utilization data, concerning about 2000 patients; the sum of direct and indirect costs per patient considering a 6-year period were 4313 euros for SLIT added to drug treatment compared to 6426 euros for drug treatment alone\(^{19}\).

The present real-life study is limited to only 1 year of observation and, as such, our results must be cautiously considered; nevertheless we can state that the magnitude of the effect measured goes in the same direction, with considerable savings in the cost of symptomatic drugs (–22% for R; –34% for R + A) in SLIT patients.

Indeed, a particularly important issue is the effect of SIT (SLIT in the present study) on drug sparing, critical with regard to inhaled corticosteroids, which have systemic adverse effects clearly demonstrated by meta-analysis studies\(^{20}\), and recently were found to lack the capacity to influence the natural history of asthma in children\(^{21}\). Use of anti-allergic drugs is an important indicator of effective allergy control. Meta-analysis studies have shown that SLIT can reduce the use of symptomatic drugs for asthma and rhinitis\(^{5,7}\), but the present study demonstrates that such effect...
achieves a cost reduction. In addition, the grass pollen season in the considered year was a mean pollen season regarding both duration (7 weeks) and pollen counts over 30 grains/m$^3$ in Northern, Central and Southern Italy\textsuperscript{22}. Pollen seasons more intense in this regard are likely to be associated with higher drug consumption.

Another aspect to be taken into account is the effect on quality of life, which is not measurable in terms of costs but is the most important factor from the patient’s point of view. Such a parameter was not included in the SIMAP database, but the ability of SLIT to improve quality of life was demonstrated in both placebo-controlled\textsuperscript{23} and real-life studies\textsuperscript{24}.

Conclusions

SLIT was introduced relatively recently but has accumulated ample evidence of efficacy and safety in the treatment of allergic rhinitis and asthma. The efficacy of anti-rhinitic treatments is generally assessed by symptom scores and consumption of drugs, but the estimation of the effect of treatment on costs has received less attention. Our study suggests that SLIT can reduce the cost of drugs (in a routine care population in the medical practice environment of an observational study) within the first year of treatment. The results may thus have important implications for the management of respiratory allergy in general practice.

Acknowledgements

Declaration of interest: This study was funded by an unrestricted grant from Stallergenes Italy.

The Authors wish to thank Antonio Scamarcia from the Società Servizi Telematici, Padova, Italy for his contribution in this research.

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http://www.cmrojournal.com

Paper CMRO-4166_1, Accepted for publication: 01 November 2007
Published Online: 00 MMM 2007
doi:10.1185/030079908X253726