Economic evaluation of sublingual immunotherapy vs symptomatic treatment in allergic asthma

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Background: The worldwide increased prevalence of allergic diseases, and especially of respiratory allergy, is paralleled by increased health costs. This requires consideration of the cost to efficacy ratio of the available treatment to identify the optimal choice.

Objective: To compare the different economic relevance, over a long evaluation time, of symptomatic pharmacologic therapy and sublingual immunotherapy (SLIT) in patients with allergic asthma.

Methods: Seventy patients with perennial allergic asthma, sensitized to dust mites, were enrolled; 50 of these patients were treated with SLIT against house dust mites and 20 were treated with symptomatic drugs. The patients were evaluated for 2 years after discontinuing immunotherapy, which was performed for 3 years, to obtain a more complete follow-up. Symptom scores, medication scores, and all other direct medical costs were evaluated with a specific questionnaire.

Results: Patients treated with SLIT plus drugs had a higher mean annual cost in the first year of SLIT treatment compared with patients only receiving drug treatment, but the mean annual cost became significantly lower since the end of SLIT both in the whole population and in the subgroups defined by disease severity.

Conclusion: The economic advantage measured alongside this prospective observational study was long lasting and still present at the fifth year of the follow-up (2 years after discontinuing SLIT) and could positively be related to the persistent good clinical control of patients.


INTRODUCTION

The worldwide increased prevalence of allergic diseases, and especially of respiratory allergy, is well-known and is associated with an increase of health costs, which is clearly recognized by the National Healthcare System (NHS). Considering that the economical aspects have an impact on health status and treatment choices, physicians and prescribers are increasingly asked to take into account the cost-effectiveness ratio of every medical treatment, to identify the most efficient solutions to improve patient’s health status while balancing the management of health cost.

This is especially important for new emerging therapies for allergy, such as specific sublingual immunotherapy (SLIT). The clinical efficacy of SLIT is clearly demonstrated in a number of studies by using scores measuring clinical symp- toms and drug intake. In particular, several studies have shown a significant reduction of drug use during SLIT, both in allergic rhinitis and in asthma, but did not consider the advantage in terms of costs.

Specifically addressed pharmacoeconomic studies on subcutaneous immunotherapy (SCIT) in patients with rhinitis and asthma have been available since the mid-1990s; recently, some studies, mostly conducted on patients with seasonal allergy, also analyzed the effects of SLIT on health expenditures.

The aim of the present study was to estimate, during a long period, the economic value of symptomatic drug therapy and SLIT in adult patients with rhinitis and asthma, sensitized to house dust mites. The main goal of the study was to evaluate the effectiveness and the use of health resources for SLIT vs drug therapy during a 5-year follow-up (3 years of SLIT and 2 years after its discontinuation). A secondary goal was to evaluate the efficacy and tolerability of SLIT.

METHODS

Patients

Seventy patients from the Allergy Center of Bordighera Hospital, Bordighera, Italy, were enrolled in the study. All patients had allergic rhinitis and allergic asthma, with a level of 1 to 3 according to the Global Strategy for Asthma Management and Prevention classification, and were sensitized to house dust mites. Patients were randomized by the program...
(detailed at http://www.randomization.com) into 2 groups: 20 were treated only with symptomatic drugs (group 1), and 50 were treated with SLIT to house dust mites plus drugs as needed (group 2). This proportion was chosen to minimize the number of patients receiving the less favorable treatment while maintaining a sufficient number for statistical analysis. The inclusion criteria were as follows: age of 8 to 50 years, persistent allergic asthma for at least 2 years, skin prick test result positive to Dermatophagoides (wheat diameter >5 mm), and positive radioallergosorbent test result for Dermatophagoides (at least class 2). Exclusion criteria were as follows: systemic immunological disease, congenital immunodeficiency, severe systemic disease, neoplastic diseases, severe psychological or neurologic disorders, treatment with SCIT or SLIT in the preceding 5 years, treatment with systemic steroids or β-blockers, pregnancy or lactation, and sensitization to other perennial or prolonged seasonal allergens (such as Parietaria pollen) able to interfere with the study. Sensitization to pollens with a short seasonal duration in our area, such as cypress (11 patients), olive (10 patients), Betulaceae (9 patients), mugwort (6 patients), and beech (4 patients), was not an exclusion criterion.

The study was approved by the Ethical Committee of Bordighera Hospital, and all patients gave their informed consent to the study.

Study Design
The study was prospective: at visit 1, the patients were evaluated and included in the study; at visit 2, the randomization and the start of SLIT, with delivery of clinical diaries, were scheduled. Further visits every 6 months, with evaluation of clinical diaries, were performed. After discontinuing SLIT, the visits were every 6 months, with accurate checking of clinical diaries, but the mean costs were evaluated on an annual basis to the purpose of the study. Patients included in the SLIT group were treated for at least 3 years. The study was performed between January 2002 and December 2006 and lasted for 2 years after discontinuing SLIT, with an annual follow-up. Score cards were used to collect symptoms and costs (ie, resources consumed). Symptom scores were coded as follows: 0, no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms. The drug intake score was measured, attributing 1 point for each administration. The cost was calculated, at each follow-up visit, by the general practitioner or the specialists and by the number of drug boxes purchased. The mean annual cost per patient was the sum of visits, specialist’s testing (such as spirometry and skin prick tests), specific immunotherapy, and all drugs related to asthma treatment drugs (at NHS charge). Patients could purchase the drugs allowed during the study in any pharmacy, the price being the same because in Italy it is under government control. Each resource or drug was assigned a unitary cost, according to the actual NHS rate lists or market prices.28

Table 1. Demographic Data at Baseline

<table>
<thead>
<tr>
<th>Category</th>
<th>SLIT plus drugs</th>
<th>Drugs only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
<td>27 (54)</td>
<td>23 (46)</td>
</tr>
<tr>
<td>Female</td>
<td>27 (54)</td>
<td>23 (46)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>27.98 (12.89)</td>
<td>28.20 (11.75)</td>
</tr>
<tr>
<td>Symptom score, mean (SD)</td>
<td>14.00 (3.56)</td>
<td>13.70 (4.04)</td>
</tr>
</tbody>
</table>

Abbreviation: SLIT, sublingual immunotherapy.
(5.2%) of 250 group 2 patients; this difference was not significant. The comparison between groups at T0 and at T3 is shown in Figure 1. At T0, there was no significant difference between group 1 and group 2, whereas at T3, those treated with SLIT had significantly lower scores for each indicator. Furthermore, a statistically significant difference for bronchial, nasal, and total symptom scores was detected between T0 and T3 in group 2, but not in group 1.

The mean patient cost per year for the whole studied population is reported in Figure 2. Patients in group 2 (SLIT plus drugs) had a significantly higher mean annual cost only in the first year of treatment compared with patients in group 1. At year 2, there was no difference; and at year 3, the mean annual cost per patient was insignificantly lower in group 2. At years 4 and 5, the mean annual cost per patient was significantly lower in group 2 when compared with group 1 (Fig 2).

When the incremental annual costs per patient were estimated for the asthmatic patients (Table 2), the total cost at year 5 of €3,881 for those treated with SLIT plus drugs represented a 22.7% savings with regard to the total cost at year 5 of €5,020 for those treated with drugs only. Such savings tended to increase with disease severity, reaching a value of 33.8% for severe asthmatic patients.

The evaluation of the efficacy of the intervention, through VAS scores, is reported in Table 3. At T0, the study and control groups did not differ by VAS score. Patients treated with SLIT plus drugs had a statistically significant reduction in their mean VAS score (−67.5%) between T0 and T3. At T3, their mean VAS score was significantly lower than that of patients treated only with drugs. The patients treated only with drugs did not show any significant trend with time.

The use of allergen extracts, as evaluated by checking the returned boxes, was regular in all patients. Adverse reactions in the SLIT-treated group were mild and transient, with 5 class 1 reactions (local itch or edema) and 3 class 2 reactions (rhinitis or conjunctivitis) in 5 patients; the other 45 patients had no adverse events.

**DISCUSSION**

The main health outcome of the present study on patients with dust mite–induced rhinitis and asthma is the significant reduction of symptom scores after 3 years of SLIT. Along the same lines, the patients’ evaluation of treatment by VAS was undoubtedly more favorable in the SLIT group when compared with the drug-only group. Indeed, it is known that the VAS score is correlated to symptom severity both in adults and children and to more complex and demanding tools, such as Juniper’s quality of life questionnaires.

From the pharmacoeconomic point of view, the total annual cost evaluation for the first 2 years was higher in patients treated with SLIT plus symptomatic drugs, but since the third year of treatment, this trend was reversed, with a higher cost for patients treated only with drugs. Such an advantage increased after the third year, at the end of SLIT treatment, because the cost of SLIT itself was no longer present, whereas its clinical benefits persisted for at least another 2 years (which was the total follow-up of the study).
Although pharmacoeconomic studies focusing on SLIT are still few, recent data have underlined the usefulness of this approach’s strategy in the global long-term care of patients and health care service.30 Our current results show a substantial reduction in all outcome measures during SLIT compared with the previous period. Similarly, in a population sample of 135 children with asthma, rhinitis, and/or conjunctivitis,22 there was a positive effect on all the clinical variables evaluated as outcome measures (number of exacerbations, visits, and absence from nursery or school) and also on the direct costs (Euros spent on drugs, specialists’ visits, and SLIT) and indirect costs (costs resulting from children’s school and parental work loss). The average annual cost per patient was €2,672 before SLIT initiation and €2,200 after SLIT treatment, corresponding to €1,550 to €1,900 found in recent SLIT studies performed with oral tablets for grass pollen in northern Europe31 and southern Europe.32 In the first study, a societal perspective was adopted, and the evaluation of cost-effectiveness of SLIT compared with use of symptomatic drugs in a 9-year time horizon analysis was performed in 7 northern European countries.31 In this study, the main outcome measure was quality-adjusted life years as an index of health-related quality of life, whereas we used a simpler measure (VAS, recently validated in its evaluation capacity),20 but the 2 pharmacoeconomic evaluations are in agreement. In fact, our data support the cost-effective evidence that SLIT is better than symptomatic treatment, either producing statistically significant differences for all efficacy end points or reducing the annual cost. Interestingly, our results shown in Figure 2 point out the lowest annual price of SLIT treatment, corresponding to €1,532 (±333.8) and €1,769.1 (±74.83) in the first and third years, respectively, compared with an annual price of €1,550 to €1,900 found in a prospective pharmacoeconomic analysis of the tablet SLIT preparation in patients with grass pollen–associated rhinitis living in 4 southern European countries (Spain, France, Italy, and Austria).32

The economic aspects of SLIT have also been evaluated in 2 recent SLIT studies performed with oral tablets for grass pollen in northern Europe31 and southern Europe.32 In the first study, a societal perspective was adopted, and the evaluation of cost-effectiveness of SLIT compared with use of symptomatic drugs in a 9-year time horizon analysis was performed in 7 northern European countries.31 In this study, the main outcome measure was quality-adjusted life years as an index of health-related quality of life, whereas we used a simpler measure (VAS, recently validated in its evaluation capacity),20 but the 2 pharmacoeconomic evaluations are in agreement. In fact, our data support the cost-effective evidence that SLIT is better than symptomatic treatment, either producing statistically significant differences for all efficacy end points or reducing the annual cost. Interestingly, our results shown in Figure 2 point out the lowest annual price of SLIT treatment, corresponding to €1,532 (±333.8) and €1,769.1 (±74.83) in the first and third years, respectively, compared with an annual price of €1,550 to €1,900 found in a prospective pharmacoeconomic analysis of the tablet SLIT preparation in patients with grass pollen–associated rhinitis living in 4 southern European countries (Spain, France, Italy, and Austria).32

Our results are very close to those of a study recently conducted in France concerning a cost-efficacy analysis on the comparison of immunotherapy (subcutaneous and sublingual) and current symptomatic treatment in adults and children with dust mite and pollen allergy.25 As expected, SLIT, because of no need of visits for injections, yielded a higher cost savings with regard not only to SCIT but also to drugs, especially in pollen-allergic patients (both adults and chil-

### Table 3. Patient’s Global Evaluation (VAS Score)

<table>
<thead>
<tr>
<th>Variable</th>
<th>SLIT plus drugs (n=50)</th>
<th>Drugs only (n=20)</th>
<th>( P ) value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>7.38 (1.12)</td>
<td>7.75 (1.07)</td>
<td>.77</td>
</tr>
<tr>
<td>After 3 y</td>
<td>2.40 (1.81)</td>
<td>6.35 (1.81)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>( P ) value*</td>
<td>&lt;.001</td>
<td>.45</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; SLIT, sublingual immunotherapy; VAS, visual analog scale.

*Obtained via Mann-Whitney test for independent groups.

### Table 2. Incremental Annual Cost Throughout 5 Years for Asthmatic Patients, by Severity

<table>
<thead>
<tr>
<th>Year*</th>
<th>Total</th>
<th>Asthma 1</th>
<th>Asthma 2</th>
<th>Asthma 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SLIT plus drugs</td>
<td>Drugs only</td>
<td>SLIT plus drugs</td>
</tr>
<tr>
<td></td>
<td>( E )</td>
<td>(n=50)</td>
<td>(n=20)</td>
<td>(n=10)</td>
</tr>
<tr>
<td>1</td>
<td>1.532 (49)</td>
<td>2.584 (48)</td>
<td>3.353 (48)</td>
<td>3.629 (48)</td>
</tr>
<tr>
<td>2</td>
<td>1.008 (19)</td>
<td>2.012 (17)</td>
<td>3.001 (17)</td>
<td>4.012 (17)</td>
</tr>
<tr>
<td>3</td>
<td>1.239 (19)</td>
<td>2.097 (19)</td>
<td>2.825 (19)</td>
<td>3.083 (19)</td>
</tr>
<tr>
<td>4</td>
<td>735 (9)</td>
<td>1.469 (8)</td>
<td>2.204 (8)</td>
<td>2.943 (8)</td>
</tr>
<tr>
<td>5</td>
<td>3.057 (8)</td>
<td>1.934 (7)</td>
<td>2.704 (7)</td>
<td>3.433 (7)</td>
</tr>
</tbody>
</table>

Abbreviation: SLIT, sublingual immunotherapy.

*All costs are given in Euros. Numbers in parentheses indicate the number of patients at each time point.
REFERENCES
We thank Giovanni Viegi, MD, for his advice.

ACKNOWLEDGMENT
We thank Giovanni Viegi, MD, for his advice.

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