

COST EFFECTIVENESS OF SUBLINGUAL IMMUNOTHERAPY IN CHILDREN WITH ALLERGIC RHINITIS AND ASTHMA

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SUMMARY:

Background: Economic evaluations are increasingly relevant in order to provide support for decision makers when judging about alternative ways to allocate public funds. Aim of this study was to evaluate the economic effect of treatment with high dose sublingual immunotherapy (SLIT) in children.

Methods: The study involved one allergy center, located in the north of Milan, Italy. From the existing records of patients seen for allergic disease, we extracted all children and adolescents with allergic disease, who had 1-year data prior to receiving SLIT and 3-year data on SLIT. Outcome measures (number of exacerbations, visits, absence from nursery or school), direct costs (euros spent on drugs, specialist visits, SLIT) and indirect costs (costs resulting from children school and parental work loss) were analysed. 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 paediatricians.

Results: 135 patients were extracted, of which 46 had perennial, and 89 had seasonal allergy with comparable gender and age distribution. A substantial reduction was found in all outcome measures during SLIT compared with the before 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 outcome measures; the direct cost/patient over the whole follow-up (4 years) was _1182 for SLIT patients and _1100 for controls.

Conclusion: 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 years follow-up.

Key-words: Sublingual immunotherapy - Cost-analysis - Economic analysis - Outcomes.

Abbreviations: IT: immunotherapy; SLIT: sublingual immunotherapy; NHS: national health service; ICD: international classification of diseases.

INTRODUCTION

Allergic rhinitis represents a global health problem. It is a common disease affecting worldwide at least 10 to 25% of the population and its prevalence is increasing (1). Although allergic rhinitis is not usually a severe disease, it alters the social life of patients and affects school performance and work productivity. Moreover, the costs incurred by rhinitis are substantial. Asthma and rhinitis are

common co-morbidities, as indicated by epidemiological studies, consistently showing that they often co-exist in the same patients and by pathophysiological studies, suggesting a strong relationship between rhinitis and asthma, with upper and lower airways sharing a common, and probably evolving inflammatory process, which may be sustained and amplified by interconnected mechanisms (2).

Allergen immunotherapy (IT) is the only treatment acting on the cause and not only on symptoms of rhinitis and asthma (2). Traditionally, IT is administered by subcutaneous route but other routes were recently introduced, mainly for safety reasons. Among these, sublingual immunotherapy (SLIT) is now accepted as a viable alternative (2), and its use is increasing, especially in European countries and particularly in children (3). As reported by a recent Cochrane Review, SLIT is a safe treatment which significantly reduces symptoms and medication requirements in allergic rhinitis, though the size of this benefit compared to that of other available therapies is not clear, having been assessed directly in very few studies (4).

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Recently an excellent revision of the economic literature reported that most estimates of the annual cost of allergic rhinitis range in the area of \$US 2-5 billion at 2003 values (5); calculations based on the studies published thus far suggest a cost of rhinitis per patient per year ranging from €52 to €266 for direct costs and from €4 to €970 for indirect costs (6-13). This large variability could be due to a number of reasons, such as the different patient populations and data sources on which the studies are based and the different methodologies applied to collect and analyse direct and indirect costs. Nevertheless this prompts the need for studies which could provide useful and meaningful information to decision makers.

Since no studies are published to describe the cost of allergic rhinitis and co-morbid conditions in Italy and in view of subsequent prospective data collection studies, this research was carried out with the objective of providing an initial assessment of the cost of treatment with SLIT in children.

MATERIAL AND METHODS

This economic evaluation was based on a retrospective database chart review which involved one allergy center, and a group of paediatricians both located in the north of Milan (Lombardia, Italy).

The first part of the study concerned the existing records of patients seen for allergic disease at the allergy center, all children and adolescents with allergic rhinitis and/or allergic asthma, who had at least 1 year data prior to receiving SLIT and 3 year data on SLIT, were extracted. SLIT was performed by high-dose allergen extracts (Staloral®, Stallergenes, Antony, France). For each patient, outcome measures and consumption of resources were recorded. In particular, outcome measures included: number of asthma and rhinitis exacerbations, visits, absence from nursery or school; consumption of resources included: concomitant pharmacologic treatment for allergic disease, specialist visits, SLIT; nursery/school days lost were also used as a proxy in order to calculate the number of working days lost by parents. Demographic data, outcome measures and data on consumption of resources were tabulated into an excel spread-sheet; each resource was subsequently multiplied by its cost to produce a cost per patient in the year before SLIT initiation and an average annual cost during treatment with SLIT.

According to study perspective, resources consumed were attributed a monetary cost which was retrieved from national published sources, as follows: for spe-

cialist visits, the Italian NHS reference tariff currently in use was applied (14); for each drug, the published official NHS price was applied, as indicated in the Italian Official Price List (15); for SLIT the individual per patient quantity of the prescribed allergens was retrieved from the Manufacturer's database and subsequently valued according to its price (16); the value of a working day lost for parents was imputed according to a previously published methodology (17), based on the average income of Italian workers in 2002 (18) divided by an estimate of 220 working days per year, i.e. a daily cost of _138.54; for the value of a school/nursery day lost we also applied a value based on existing methodology (19) including the cost of a baby sitter, at an hourly cost of €7.75.

In order to provide a meaningful comparison for costs, a second (case-control) analysis was developed that involved a sub-group of subjects with allergic asthma from the same initial patients' selection in the specialist database, and a control group which was based on records of patients with identical characteristics but not treated with SLIT, which were extracted from Pedianet, a network-database of paediatricians located in the same geographical area, i.e. Lombardia (20). The same type of resources consumed was then retrieved and valued using the same costing approach, as previously described. For this second analysis indirect costs were not considered since this type of resource was not retrievable from the control group database. Similarly, cost of hospitalizations, which was available for the control group but not for SLIT treated patients, was not included in our analysis. The average cost per patient was calculated over a total follow-up of 4 years which corresponds to the 1 year period before SLIT and the 3 years period during SLIT, in SLIT-treated patients, and to 4 years of follow-up for controls (non-SLIT-treated patients). For these reasons cost analysis had to be limited to the analysis of direct costs over 4 years and in the average year of treatment in the two subsamples analysed.

RESULTS

A total of 135 children and adolescents were extracted from the centre database: their demographics and kind of allergies are shown in table 1. Mean (SD; median) age at database extraction was 12.10 years (3.63; 11.00); mean age at SLIT initiation was 7.37 years (3.63; 6.73). Similar figures were obtained when analysing patients by kind of allergen (Table 1). Grass pollen was the most frequent type of allergen (52.6% of patients) followed by house dust mites (34.1%) (table 2). The most frequent clinical diagnosis at database inclusion was a combination of

rhinitis and asthma (44.4% of patients) followed by asthma alone (30.4%) and by a combination of asthma, rhinitis and conjunctivitis (16.3%) as illustrated in table 2.

Clinical outcomes as measured by exacerbations, medical visits and school/nursery days lost in the before-SLIT (1 year) and during-SLIT (average annual value over 3 years) periods are reported in table 3. For each of these outcomes, substantial reductions were seen both in the whole population and in the perennial and seasonal subsamples, the mean number of exacerbations being 5 times lower; the number of school/nursery days lost about 4 times

lower and the number of medical visits being about 3 times lower during one average year under SLIT treatment, than the corresponding figures in the year before SLIT initiation.

As illustrated in table 4, the mean cost per year per patient also strongly decreased during SLIT in comparison with the before-SLIT period: mean direct cost per patient/year was 506 and 224 respectively before and during SLIT for the whole population, with small variations for perennial allergens €518/patient/year (before) and €232/patient/year (during SLIT) and for seasonal allergens €500/patient/year (before) and €219/patient/year (during SLIT). Indirect cost per patient per year showed even a more substantial decline in the before-during SLIT comparison with the mean cost per patient falling from €2166 to €406 in the whole group and similar figures for the allergens sub-populations (table 4). Finally, the total (direct plus indirect) cost per patient per year fell by as much as 3 times (from €2672 to €629 per patient per year) in the before SLIT versus during-SLIT periods for the whole group, again with comparable results for the perennial vs. seasonal sub-groups.

The case-control analysis was based on 41 asthmatic children treated with SLIT in the specialist practice and 35 asthmatic children not treated with SLIT from the Pedianet network. Age at SLIT initiation (for SLIT patients) was comparable to age at database extraction in the control group, as indicated in table 5. Outcome measures again declined in the period before SLIT and during SLIT for the SLIT patients: the per patient mean number of exacerbations declined from 46.1 to 7.2/patient/year; school/nursery days lost from 37.5 to 7.2/patient/year and medical visits from 9.6 to 2.5/patient/year respectively (table 6).

As shown in table 7, direct costs per patient were comparable in size between asthmatic SLIT-treated patients (€1182 per patient) and controls (€1100 per patient) both over 4 years of follow-up, and as average per patient/year cost i.e. €296 vs. €275, respectively.

DISCUSSION

Although there is abundant literature on the economic impact of allergic rhinitis, there are relatively few empirical analyses, particularly outside the US (5). Even scarcer is the body of evidence regarding the costs and consequences of different treatment regimens, which are currently available for management of this condition, and this is particularly true for Italy.

This retrospective and partly cross-sectional study shows that high-dose sublingual immunotherapy

	N	Mean (SD)
Total sample	135	
Male/Female	89/46	
Age at database extraction		12.10 (3.63)
Age at SLIT initiation		7.37 (3.63)
Perennial Allergen	46	
Male/Female	32/14	
Age at database extraction		12.13 (3.58)
Age at SLIT initiation		7.39 (3.60)
Seasonal Allergen	89	
Male/Female	57/32	
Age at database extraction		12.08 (3.60)
Age at SLIT initiation		7.37 (3.62)

Table 1: Demographics.

	N	%
Total sample	135	100
Kind of allergen		
Perennial (mites)	46	34.1
Seasonal	89	65.9
Alternaria	9	6.7
Ragweed pollen	7	5.2
Grass pollen	71	52.6
Parietaria pollen	2	1.4
Clinical diagnosis at database inclusion		
3 diagnoses (A+R+C)	22	16.3
2 diagnoses (A+R)	60	44.4
2 diagnoses (A+C)	11	8.2
2 diagnoses (R+C)	1	0.7
1 diagnosis (A)	41	30.4

Table 2: Distribution of allergens and clinical diagnosis (all patients N=135).

Notes: A = Asthma; R = Rhinitis; C = Conjunctivitis.

	Before SLIT	During SLIT	Before SLIT	During SLIT	Before SLIT	During SLIT
	All (N=135)		Perennial (N=46)		Seasonal (N=89)	
Exacerbations						
Mean (SD)	45.0 (12.0)	6.9 (3.2)	44.1 (12.3)	6.2 (1.9)	45.5 (11.9)	7.3 (3.6)
Median	45.0	6.0	45.0	6.0	45.0	6.7
School/nursery days lost						
Mean (SD)	37.9 (12.4)	7.3 (3.5)	37.2 (12.9)	6.5 (1.9)	38.3 (12.3)	7.6 (4.1)
Median	36.3	7.0	38.9	7.0	36.3	7.0
Medical visits						
Mean (SD)	9.9 (3.7)	2.3 (1.1)	10.6 (3.9)	2.4 (1.1)	9.6 (3.6)	2.3 (1.2)
Median	9.0	1.8	9.0	1.8	8.8	1.8

Table 3: Outcomes (exacerbations, visits and school losses) in the before and during SLIT periods (all patients N=135). Notes: "Before SLIT" 1 year record analysis before SLIT initiation; "During SLIT" average per year over 3 years of SLIT treatment.

	Before SLIT	During SLIT	Before SLIT	During SLIT	Before SLIT	During SLIT
	All (N=135)		Perennial (N=46)		Seasonal (N=89)	
Direct Cost (Euros)						
Mean (SD)	506 (111)	224 (51)	518 (102)	232 (42)	500 (115)	219 (55)
Median	479	226	491	229	465	219
Indirect Cost (Euros)						
Mean (SD)Median	2166 (2652) 403	406 (512) 71	2057 (2523) 417	370 (443) 70	2222 (2722) 403	424 (544) 71
TOTAL Cost (Euros)						
Mean (SD)	2672 (2664)	629 (514)	2575 (2543)	602 (438)	2723 (2730)	643 (549)
Median	926	342	941	339	896	342

Table 4: Cost per patient in the before and during SLIT periods (Euros). Notes: "Before SLIT" 1 year record analysis before SLIT initiation; "During SLIT" average per year over 3 years of SLIT treatment.

	SLIT patients		Controls	
	N	Mean (SD)	N	Mean (SD)
Patients	41		35	
Male/Female	26/15		26/9	
Age at database extraction		11.88 (3.63)		7.94 (2.70)
Age at SLIT initiation		7.29 (3.67)		---

Table 5: Asthma sub-sample - Demographics.

	SLIT patients N=41	Controls N=35
Direct Cost (Euros) per patient over 4 years		
Mean (SD)	1182 (198)	1100 (608)
Median	1183	914
Direct Cost (Euros) average per patient per year		
Mean (SD)	296 (49)	275 (152)
Median	296	228

Table 7: Asthma sub-sample. Direct Cost per patient (Euros).

	Before SLIT	During SLIT
	Asthma sub-sample (N=41)	
Exacerbations		
Mean (SD)	46.1 (12.4)	7.2 (3.2)
Median	45.0	6.7
School/nursery days lost		
Mean (SD)	37.5 (13.7)	7.2 (3.4)
Median	37.0	7.0
Medical visits		
Mean (SD)	9.6 (3.1)	2.5 (1.3)
Median	8.8	1.8

Table 6: Asthma sub-sample. Outcomes (exacerbations, visits and school losses) in the before and during SLIT periods. Notes: "Before SLIT" 1 year record analysis before SLIT initiation; "During SLIT" average per year over 3 years of SLIT treatment.

may be effective in reducing the burden of disease as measured by number of exacerbations, need for medical visits and school/nursery time losses, with a considerable reduction of annual management costs. Also when considering only direct medical costs (NHS costs), the reduction is clear and appreciable in the whole population considered, as well as in the allergen type sub-samples and in the case-control sub analysis of allergic asthmatic patients.

Several aspects of the present analysis limit the strength of the economic data generated. First, the fact that analysis of the consumption of resources, and consequently costs, could not include diagnostic tests and hospitalization costs, which in particular may be substantial: an analysis of the hospital admission data for 2002 retrievable from the NHS web-site (21) demonstrates that in Italy there are as many as 3.6 million standard hospital admissions and 1.9 million Day hospital stays for the ICD-IX codes (493.0 Allergic Asthma; 477.0-477.9 Allergic Rhinitis) for children-adolescents below 15 years of age, at a cost to the NHS in the area of £5.5 million. We believe that ours is actually an underestimation of the true effect of SLIT on costs, given the significant reductions that were seen in the other resources included in our analysis.

Other studies have demonstrated that immunotherapy provides greater economic benefit in the long term: Buchner's model estimated that immunotherapy becomes cost-saving versus symptomatic treatment for asthma at the 6th year and for rhinitis at the 4th year of follow-up (22); similarly Kumar showed that the progressive reduction in traditional treatment costs for allergic rhinitis becomes statistically significant as compared with no-ITS after the 3rd year of immunotherapy (23), and Schädlich demonstrated that between the 6th and 8th year of follow-up, immunotherapy provides significant economic benefits (24).

Therefore, a second limitation concerns the fact that our analysis was not extended to the after-SLIT period; as a matter of fact, the "after-SLIT period data collection" is still ongoing for some of the patients and more suitable prospective studies are also ongoing, which will hopefully provide an estimation of the magnitude of the economic benefit that could be obtained with SLIT over the longer term.

Finally, another study limitation is that the case-control sub-analysis was not conducted on all patients (i.e. the initial 135 patients' population retrieved from the specialist centre database) but only on the sub-sample of asthmatic patients: this is in part due to the retrospective nature of the study and in part to the difficulty of finding a control group, for

which sufficient retrospective data were retrievable. Given the paucity of good and reliable electronic database information in Italy, we believe this analysis, although partial and limited in size, may be indicative of the amount of resources that should be allocated to the effective management of this condition.

We can conclude that high dose SLIT may be effective in reducing both the clinical and economic burden of allergic disease in children. Further studies should be conducted to validate these results in populations possibly enrolled in a prospective observational fashion, with particular attention in performing cost-effectiveness analyses in order to match the comparison of costs with the assessment of the clinical effects of standard treatment versus SLIT.

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