Pharmacoeconomics of allergen immunotherapy compared with symptomatic drug treatment in patients with allergic rhinitis and asthma

Renato Ariano, M.D.,* Patrizia Berto, Ph.D.,# Daniela Tracci, M.D.,* Cristoforo Incorvaia, M.D.,§ and Franco Frati, M.D.¶ (Italy)

ABSTRACT

Only a few studies analyzed the pharmacoeconomics of allergen immunotherapy compared with drug treatment in subjects with allergic rhinitis and asthma. This study was aimed at evaluating whether allergen immunotherapy has an economic advantage on standard antiallergic drugs in patients with pollen-induced rhinitis and asthma. Thirty patients with rhinitis and asthma caused by Parietaria *pollen were included in the study, 20 (11 men and 9 women; mean age, 35.45 ± 10.45 years) were treated with subcutaneous immunotherapy 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, and 10 (6 men and 4 women; mean age, 31.90 ± 10.97 years) were treated with antiallergic drugs. Each patient was evaluated before starting the treatment and annually for 6 years in the pollen period of* Parietaria *by means of nose, eyes, and lung symptom scores, along with 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 favor of immunotherapy plus drug treatment versus drug treatment alone was observed, reaching a cost reduction of ~15% the second year and 48% the third year, with a highly statistical significance that was maintained up to the sixth year,* i.e., *3 years after stopping immunotherapy, when an 80% reduction was found. The net saving for each patient at the final evaluation corresponded to €623 ($830)/year. These findings confirm some previous observations in studies from Germany and the United States that subcutaneous immunotherapy has significant economic advantages over antiallergic drug treatment in the long term.* (Allergy Asthma Proc 27:159–163, 2006)

In developed countries, allergic disorders and, particularly, the diseases concerning the airways such as allergic rhinitis and asthma, are showing an increased prevalence[1–4] and, consequently, a growing importance as medical problems. Recent investigations attribute to allergic rhinitis and asthma a very relevant economic burden, estimated in the United States in the range of $2–5 billion/year.[5–8] Such assessments generally consider the direct costs deriving from drug treatment and physician visits, but the indirect costs related to reduced productivity also are of the utmost importance, with a recent study estimating the economic burden of allergic rhinitis at ~$10 billion, higher than the direct costs of the disease.[9]

*From the *Allergy and Clinical Immunology Unit, General Hospital, Bordighera, Italy, #Pbe Consulting, Verona, Italy, §Allergy/Rheumatology Unit, ICP Hospital, Milan, Italy, and ¶Department of Obstetric, Gynecologic and Pediatric Sciences, University of Perugia, Italy*

Address correspondence and reprint requests to Cristoforo Incorvaia, M.D., Allergy/Rheumatology Unit, ICP Hospital, Via Bignami 1, 20100 Milan, Italy

E-mail address: cristoforo.incorvaia@fastwebnet.it

Consequently, any preventive strategy aimed at reducing the clinical severity of respiratory allergy is potentially able to reduce its costs. Some studies reported that allergen-specific immunotherapy—a treatment that reduces the allergic symptoms by increasing the tolerance to the specific allergen and modifying the natural history of the disease[10]—in the long term is associated with a lower expenditure compared with drug treatment.[11–13] This study aimed at evaluating whether allergen immunotherapy, compared with standard antiallergic drugs, may result, along with its efficacy, in an economic advantage with respect to drug treatment in patients with allergic rhinitis and asthma caused by sensitization to *Parietaria* pollen.

METHODS

Patients

Thirty subjects suffering from seasonal allergic rhinitis and asthma caused by sensitization to *Parietaria* pollen and referring to the Allergy Center of the Bordighera Hospital were included in this study. The fol-

Table 1 **Antiallergic Drugs Used in the Study**

Drug Class	Agent
Antihistamines	Cetirizine
Nasal decongestants	Oxymethazoline spray
Corticosteroids	Fluticasone, nasal or bronchial spray
	Budesonide Turbohaler
	Methylprednisolone, oral or parenteral
	Betamethasone, oral or parenteral
β2-Agonists	Salbutamol spray
	Salmeterol spray
	Formoterol spray
Association of corticosteroids and β2-agonists	Fluticasone-salmeterol
	Budesonide-formoterol
Membrane stabilizers	Cromones, nasal and bronchial
	Spaglumic acid, eyedropper
Anticholinergic	Oxytropium bromide, nasal or bronchial
Methylxantines	Anihydrated theophylline

lowing were the inclusion criteria: must be between 18 and 50 years of age, have a history of allergic rhinitis and asthma (classified as level 2 or 3 according to the GINA criteria 1998) for at least 2 years, have a positive skin-prick test to *Parietaria* extract with a wheal of at least 5 mm in diameter, a radioallergosorbent test positive to *Parietaria* of at least class 2, and have adequate collaboration and comprehension.

The exclusion criteria were an age of $<$18 years and $>$50 years, the presence of systemic immunologic diseases or immunodeficiencies or of diseases such as chronic obstructive pulmonary disease, ischemic cardiopathy, renal or hepatic failure, malignancies, neurological or psychiatric disorders, chronic treatment with corticosteroids or β-blockers, pregnancy, and previous specific immunotherapy in the preceding 5 years. Each subject was randomly assigned to specific immunotherapy with a *Parietaria* extract or to drug treatment with a 2:1 ratio. Thus, 20 subjects underwent specific immunotherapy and 10 subjects were treated only with symptomatic drugs.

Treatment

Specific immunotherapy was performed by subcutaneous route with an alum absorbed *Parietaria judaica* extract (Alustal; Stallergńes, Antony, France) standardized to the index of reactivity (IR)[14] by a conventional schedule in 12 weeks with a top dose of 8 IR and subsequent maintenance treatment of this dose with a 4-week interval. During the pollen period of *P. judaica* the maintenance dose was halved to 4 IR. The treatment was continued for 3 consecutive years.

Drug treatment was performed by the pharmacologic agents reported in Table 1, according to the prescription of general practitioners or specialists. Each patient was evaluated before starting treatment and then annually for 6 years in the pollen period of *Parietaria*, *i.e.*, the months from March to June, by symptom scores registered in diary cards according to the following score: 0 = absent, 1 = slight, 2 = moderate, and 4 = severe. Each symptom of nose (sneezing, itching, rhinorrhea, and blockage), eyes (itching, redness, tear dropping, and edema), and lungs (cough, wheezing, dyspnea, and catarrh) had to be reported. Drug consumption was registered in the same diary card, according to a score of 1 for a single assumption and 2 for two or more assumptions for each drug used.

The safety of immunotherapy also was evaluated because of the possible influence on costs by adverse reactions requiring interventions from physicians or from emergency room visits. Side effects were classified as follows: 0 = absent, 1= local reactions such as itching and edema around the site of injection, 2 = slight systemic reaction such as rhinitis or conjunctivitis, and 3 = moderate/severe systemic reactions such as asthma, urticaria, angioedema, and/or anaphylactic shock.

A control visit was scheduled with 6-month intervals for all the duration of the study, *i.e.*, the 3 years of immunotherapy and the 3 years after its discontinuation. At the end of immunotherapy, each patient had to state his/her subjective satisfaction of the results obtained by the following scale: 0 = bad, 1 = good, 2 = very good, and 3 = excellent results.

Economic Analysis

All patients received a specifically designated card in which they must register each month the general practitioner's or specialist's visits, the number of desensitizing injections, and the number of boxes of antialler-

Table 2 **Differences in Symptom Scores and Drug Consumption between the Group Treated by Immunotherapy Plus Drug Treatment and the Group Treated by Drug Treatment Alone**

Category	Year	Mean ± SD in Immunotherapy Plus Drug Treatment Group	Mean ± SD in Drug Treatment Alone Group	Significance (p)
Symptom score	0	13.45 ± 2.42	12.90 ± 2.02	NS
	1	9.30 ± 1.84	11.80 ± 1.75	0.004
	2	6.30 ± 1.38	11.20 ± 1.75	<0.001
	3	2.80 ± 1.28	10.90 ± 1.52	<0.001
	4	2.55 ± 1.32	10.80 ± 1.55	<0.001
	5	2.50 ± 1.32	10.60 ± 1.58	<0.001
	6	2.55 ± 1.32	10.70 ± 1.57	<0.001
Drug consumption	0	8.10 ± 1.12	8.40 ± 1.35	NS
	1	5.80 ± 1.32	8.10 ± 1.45	<0.001
	2	3.85 ± 1.04	7.80 ± 1.23	<0.001
	3	2.50 ± 1.32	7.80 ± 1.23	<0.001
	4	2.15 ± 0.99	7.80 ± 1.23	<0.001
	5	2.15 ± 0.99	7.70 ± 1.16	<0.001
	6	2.15 ± 0.99	7.70 ± 1.16	<0.001

NS = not significant.

Table 3 **Final Evaluation by the Patients of the Results of Treatment**

Kind of Treatment	Bad (no. and %)	Good (no. and %)	Very Good (no. and %)	Excellent (no. and %)
Immunotherapy plus drugs	0	7 (35%)	8 (40%)	5 (25%)
Drugs alone	0	5 (50%)	5 (50%)	0

gic drugs. The cards were withdrawn at each control visit to calculate the expenditure due to medical visits, specialist examinations (*e.g.*, spirometry or skin tests), and the costs of immunotherapy and antiallergic drugs. All costs were calculated according to the price list of the Liguria region, and an overall annual cost per patient was established.

Statistical Analysis

Differences in the two groups of patients respectively treated by immunotherapy plus drugs and by only drugs according to symptom scores and drug consumption were analyzed by the Mann-Whitney test. The same test was used to analyze differences in costs of the two groups. The difference was considered significant with a value of $p < 0.05$.

RESULTS

Clinical Effectiveness

The 20 patients treated by immunotherapy with the *P. judaica* extract plus drug treatment were 11 men and 9 women, with a mean age of 35.45 ± 10.45 years (range, 18–50); the 10 patients treated only by drug treatment were 6 men and 4 women, with a mean age of 31.90 ± 10.97 years (range, 18–46 years). Table 2 shows the results of the analysis of symptom scores and drug consumption, with a significant difference in favor of immunotherapy plus drug treatment starting from 1 year of treatment and maintaining the significance after discontinuation of immunotherapy. The patient's satisfaction at the final assessment is reported in Table 3, with the majority of patients (65%) rating the results of immunotherapy as very good or excellent.

Economic Analysis

Table 4 reports the mean annual cost in patients treated with immunotherapy plus drug treatment versus patients treated with drug treatment alone, which shows a significantly lower cost starting from 3 years of treatment and, as with effectiveness parameters, a maintained significance after discontinuation of immunotherapy.

Table 4 **Differences in Overall Annual Cost between the Group Treated by Immunotherapy Plus Drug Treatment and the Group Treated by Drug Treatment Alone**

Year	Annual Cost in US$ (mean ± SD) in Immunotherapy Plus Drug Treatment Group	Annual Cost in US$ (mean ± SD) in Drug Treatment Alone Group	Significance (p)
1	1165.21 ± 213.89	1075.44 ± 233.00	NS
2	895.69 ± 174.86	1045.11 ± 249.39	NS
3	542.84 ± 42.57	1047.24 ± 262.16	<0.001
4	216.66 ± 63.41	1038.07 ± 262.68	<0.001
5	215.19 ± 59.29	1039.79 ± 254.80	<0.001
6	209.01 ± 60.91	1038.33 ± 249.83	<0.001

NS = not significant.

DISCUSSION

Allergen immunotherapy is an accepted treatment of allergic rhinitis and asthma,[10,15] which has the peculiar ability to modify the natural history of these diseases. Consequently, the effects of immunotherapy on allergic symptoms, contrary to drugs that act only when they are administered, persist for a long time after its discontinuation.[16,17]

A possible criticism of this apparent clinical advantage is that the natural history of allergic diseases may lead, by itself, to spontaneous disappearance or decrease of symptoms with time[18] and therefore it is important to compare groups of patients with similar characteristics undergoing allergen immunotherapy or drug treatment.

In this study we compared two groups of patients with rhinitis and asthma due to allergic sensitization to *Parietaria* pollen, following them for 6 years. All subjects had standard drug treatments with common agents used for lung, nose, and eye symptoms, but two-thirds also had allergen immunotherapy by conventional subcutaneous route for the first 3 years. At baseline, the two groups were homogeneous according to age, symptom score, and drug consumption; however, after the first year, the two parameters of efficacy were significantly lower in patients treated with immunotherapy. After 2 years a higher significance was reached and then maintained over the observation period of the study. One may argue that a placebo-treated control group would have increased the strength of the observations; however, a placebo effect is unlikely to persist for such a long time. Nevertheless, the superiority of immunotherapy associated to drug treatment compared with drug treatment alone is well known[10,15] and was not the main objective of the study; instead, we compared the cost of the two kinds of treatment. Our findings show an expected higher cost in immunotherapy-treated patients in the first year because of the fact that the cost of immunotherapy added to the cost of standard treatment with antiallergic drugs. At the second year a cost reduction of ~15% was observed in the immunotherapy group, and at the third year the cost reduction was 48%, with a highly statistical significance that was maintained up to the sixth year, *i.e.*, 3 years after stopping immunotherapy, when an 80% reduction was found. The decrease of cost in the immunotherapy group was progressively lower at each year of observation, indicating that the need of symptomatic drugs was continuously diminishing with time, whereas in patients not treated with immunotherapy the need for symptomatic drugs was unchanged for all 6 years. This suggests that, at least in the small group we studied, no spontaneous decrease of allergic symptoms related to natural history occurred.

The comparison of the cost of immunotherapy and drug treatment must be discussed regarding the few available studies, conducted in Germany and in United States in the 1990s. Buchner 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 with those treated with symptomatic drugs,[19] and Fischer estimated that the use of immunotherapy could save, respectively, DM500 ($610) and DM1000 ($1220) per year in subjects with allergic rhinitis and allergic asthma;[11] 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 on drug treatment started after 6 years and resulted in final net savings of between DM650 ($784) and DM1190 ($1452)/patient.[13]

The data from studies in the United States are somewhat contrasting; in a randomized, placebo-controlled study on immunotherapy in patients with ragweed-induced asthma, a cost reduction of ~30% was reported,[12] and a survey on asthmatic patients found a mean cost ~20% higher in subjects treated with immunother-

apy; however, the same authors argued that the greater the severity of asthma and, consequently, the higher the drug use in patients admitted to immunotherapy could account for such an observation.[20] Moreover, the short duration of the study—7 months—seems unable to achieve the cost reduction, which we know from the other studies generally occur after 2–3 years.

Such time dependence is confirmed in a French study reporting a significant reduction of the direct costs of the allergic disease after 2 years of immunotherapy.[21] This is in line with our observations, indicating a significant cost reduction in patients treated with immunotherapy at the third year, with an ~50% lower cost with respect to drug-treated subjects and a further decrease after stopping immunotherapy, although with the same statistical significance, which reached an 80% reduction at the sixth year. The net savings for each patient at the final evaluation corresponds to €623/year (~$830), an amount of money certainly important for individuals and socially relevant when transferred to the number of people undergoing allergen immunotherapy.

REFERENCES

1. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema. Lancet 351:1225–1232, 1998.
2. Sly RM. Changing prevalence of allergic rhinitis and asthma. Ann Allergy Asthma Immunol 82:233–248, 1999.
3. Upton MN, McConnachie A, McSharry C, et al. Intergenerational 20 year trends in the prevalence of asthma and hay fever in adults: The Midspan family study survey of parents and offspring. BMJ 321:88–92, 2000.
4. Linneberg A, Nielsen NH, Madsen F, et al. Increasing prevalence of specific IgE to aeroallergens in an adult population: Two cross-sectional studies 8 years apart; the Copenhagen Allergy Study. J Allergy Clin Immunol 106:247–252, 2000.
5. Malone DC, Lawson KA, Smith DH, et al. A cost of illness study of allergic rhinitis in the United States. J Allergy Clin Immunol 99:22–27, 1997.
6. Mackowiak JI. The health and economic impact of rhinitis. Am J Manag Care 3:S8–S18, 1997.
7. Ray NF, Baraniuk JN, Thamer M, et al. Direct expenditures for the treatment of allergic rhinoconjunctivitis in 1996, including the contributions of related airway illnesses. J Allergy Clin Immunol 103:401–407, 1999.
8. Law AW, Reed SD, Sundy J, et al. Direct costs of allergic rhinitis in the United States: Estimates from the 1996 Medical Expenditure Panel Survey. J Allergy Clin Immunol 111:296–300, 2003.
9. Kessler RC, Almeida DM, Berglund P, et al. Pollen and mold exposure impairs the work performance of employees with allergic rhinitis. Ann Allergy Asthma Immunol 87:289–295, 2001.
10. Bousquet J, Lockey RF, and Malling HJ. WHO Position Paper. Allergen immunotherapy: Therapeutic vaccines for allergic diseases. Allergy 53(suppl 44):4–30, 1998.
11. Fischer P. Therapie des allergisches Asthma. Die spezifische Hyposensibilierung kann helfen Kosten in Milliardenhohe einzusparen. Laryngorhinootologie 74:28, 1995.
12. Creticos PS, Reed CE, Norman PS, et al. Ragweed immunotherapy in adult asthma. N Engl J Med 334:501–506, 1996.
13. Schadlich PK, and Brecht JG. Economic evaluation of specific immunotherapy versus symptomatic treatment of allergic rhinitis in Germany. Pharmacoeconomics 17:37–52, 2000.
14. Wutrich B, Gumowski PL, Fah J, et al. Safety and efficacy of specific immunotherapy with standardized extracts adsorbed on aluminium hydroxide. J Invest Allergol Clin Immunol 11: 149–56, 2001.
15. Bousquet J, and van Cauwenberge P (Eds). Allergic rhinitis and its impact on asthma (ARIA). Position Paper endorsed by WHO. J Allergy Clin Immunol 108(suppl 5):147–334, 2001.
16. Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 341:468–475, 1999.
17. Di Rienzo V, Marcucci F, Puccinelli P, et al. Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: A 10-year prospective study. Clin Exp Allergy 33:206–210, 2003.
18. Settipane GA, Greisner WA, and Settipane RJ. Natural history of asthma: A 23-year followup study of college students. Ann Allergy Asthma Immunol 84:499–503, 2000.
19. Buchner K, and Siepe M. Nutzen der Hyposensibilierung unter wirtschaftlichen Aspekten. Allergo J 4:156–163, 1995.
20. Donohue J, Greneider DK, Connor-Lake L, et al. Utilization and cost of immunotherapy for allergic asthma and rhinitis. Ann Allergy Asthma Immunol 82:339–347, 1999.
21. Le Pen C, Rumeau-Pichen C, and Lillin H. L'impact de l'immunothérapie specifique sur le couts directs de la maladie allergique: Une etude pragmatique. Rev Franc Allergol Immunol Clin 37:11–14, 1997. □