Effects of allergic diseases, concomitant with allergic rhinitis, on the clinical efficacy and costs of allergen-specific immunotherapy in Poland

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Abstract

Aim: Evaluation the clinical efficacy of allergen-specific immunotherapy (SIT), while assessing its effects on direct cost reduction in the symptomatic therapy of allergic disease, depending on the concomitance of allergic bronchial asthma (BA), oral allergy syndrome (OAS) and/or atopic dermatitis (AD) in patients with allergic rhinitis.

Material and methods: The study comprised 76 subjects above 16 with allergic rhinitis, qualified for SIT (Allergopharma-Nexter, Reinbeck, Germany).

Results: Among 30 female and 46 male subjects in the study group, BA was the allergic disease most often concomitant with allergic rhinitis. The OAS syndrome was identified in 29 and AD in 15 patients. The pre-SIT index of disease symptoms in the study group was 23.1 (21.7-24.5) points, while the after-SIT index decreased considerably, down to 5.3 (4.3-6.4) points (p = 0.000001). During the pre-SIT year, the mean annual costs of symptomatic treatment, assessed from the social perspective, amounted to PLN 967.4 (737.5-1197.4) (EUR 1 = PLN 4.0; year 2008). Following the 3-year SIT therapy, the mean annual cost of symptomatic therapy fell to PLN 306.8 (176.4-437.1) (p = 0.000001). Significant positive correlations were observed in patients with coexisting allergic rhinitis and allergic BA and the rate of saving in symptomatic therapy after SIT.

Conclusions: Clinical efficacy of SIT is higher in patients with allergic rhinitis and concomitant BA or the OAS than in cases of allergic rhinitis concomitant with AD.

Key words: allergy, allergic rhinitis, atopic dermatitis, bronchial asthma, the oral allergy syndrome, specific immunotherapy.

Introduction

Allergic diseases are a serious health and social-economic problem in highly industrialised countries. It is estimated that specific IgE antibodies against aeroallergens, identifiable in blood serum by skin tests, are present in almost half of the population in Europe, the United States of America, Australia and New Zealand [1]. Allergic rhinitis (AR) affects approximately 500 million people worldwide [1]. Allergic diseases significantly deteriorate the quality of patient life, while also being the cause of considerable burdens for the healthcare funding system [2, 3]. Specific-allergen immunotherapy (SIT) is the only effective method, giving a chance of persistent elimination of allergic symptoms [4-7]. In the reported study, the clinical efficacy of SIT and SIT impact on direct cost reduction in the symptomatic allergy treatment were evaluated in patients with allergic rhinitis, depending on concomitant bronchial asthma (BA), the oral allergy syndrome (OAS) and atopic dermatitis (AD).

Material and methods

The study comprised patients above 16 with allergic, seasonal rhinitis, qualified for allergen-specific immuno-

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therapy (SIT) at the Department of Allergology and Clinical Immunology of the Military Institute of Medicine, who had never been treated before by the method of specific immunotherapy. In each subject qualified for the study, disease diagnosis was determined, following detailed allergological diagnostics, performed at least a year before the study and including history taking, medical examination, skin tests and measurements of allergen-specific antibodies in IgE class (sIgE) in blood serum. Skin prick tests were performed with a standardized panel (Allergopharma-Nexter, Reinbeck, Germany) of allergens including grass, tree, and weed pollens, moulds, *Dermatophagoides pteronyssinus*, *D. farinae*, cat dander, dog dander, cockroach, milk, and egg white. Histamine dihydrochloride (10 mg/ml) and 0.9% physiological saline diluents were used as positive and negative controls, respectively. After 20 min, the mean diameters of wheals were calculated. The sensitivity of skin tests was estimated by wheal sizes, calculated by the following formula: (DA + dA)/2, where DA is the largest wheal diameter and dA is the mid-orthogonal wheal diameter. Wheal size above 3 mm was considered as a positive result. Skin test results were confirmed by assessment of specific anti-IgE antibodies in blood serum. Specific IgE concentrations were analysed with a Pharmacia CAP System (Pharmacia Diagnostics AB, Uppsala, Sweden), according to the manufacturer's instructions. The level of specific IgE ≥ 0.7 kU/l was considered positive.

Allergen-specific immunotherapy was administered by the subcutaneous, perennial method, using commercially available Allergovit vaccines (of the Allergopharma-Nexter Company, Reinbeck, Germany), following the manufacturer's recommendations.

Combined symptom + medication score was used for assessment of the clinical status of patients before and after SIT. The 4-point rating scale (from 0 = absent to 3 = severe) was applied to each of the following clinical symptoms: nasal itching, nasal obstruction, sneezing, rhinorrhoea, ocular itching, lacrimation, red eye symptom, chest tightness, shortness of breath, cough and wheezing. Additionally, if administered, one point was attributed to each dose of nasal, ocular, oral antihistamines or bronchodilator drugs, 2 points for inhaled or nasal corticosteroids, and 3 points for the use of oral corticosteroids [8].

Direct annual costs (including the costs of medications and doctor visits) of treatment of allergic rhinitis and concomitant allergic diseases were calculated, covering the year before and the year after SIT. The calculations were carried out from the social perspective. The costs of drugs were estimated on the basis of used packaging units, taking into account the prices, specified in the National Specification of Reimbursed Drugs for the year 2008. The costs of doctor visits were calculated from the number of visits and their appraisal by the payer, i.e., the National Healthcare Fund. All costs were expressed in PLN for the year 2008 (1 PLN = 0.25 Euros).

The Wilcoxon test was applied in statistical analysis for comparisons of the clinical efficacy of SIT and of the differences in costs of symptomatic treatment before and after immunotherapy. The Kruskal-Wallis test was used for comparisons of groups with unrelated data. Multiple regression analysis was applied to evaluate the relationships among selected variables, the obtained clinical improvement and differences in direct costs of treatment before and after SIT. The following dependent variables were taken into consideration in multiple regression equations: the difference (Δ) in the degree of allergic symptoms before and after SIT and the difference (Δ) in the annual costs of symptomatic SIT treatment in each examined patient. Independent variables included patient age and gender and concomitant allergic diseases (bronchial allergy, OAS, AD). The 95% confidence interval was computed for statistically significant differences.

Results

In total, 79 subjects were qualified for the study. A 3-year specific immunotherapy programme was completed by 76 subjects (30 female and 46 male) of that group, including 20 subjects allergic to tree (birch, alder, hazel) pollens, 32 subjects allergic to grass and corn pollens, and 24 subjects allergic to both grass and tree pollens.

Two subjects (1 female and 1 male) withdrew from SIT after a few months due to inefficacy of the therapy, while 1 male subject discontinued the SIT programme for an unknown reason.

The mean age of the patients who completed the 3-year therapy programme was 31.7 (min-max 17-59) years. Among patients in the study group, bronchial asthma was the disease most frequently concomitant to allergic rhinitis, including 52 subjects, while OAS was present in 29 and AD in 15 patients.

The cumulative dose of administered vaccine was, on average, 162 098.2 (95% CI: 151 046.4-173 150.0) TU/ml in the entire study group, including 165 673.8 (95% CI in patients with bronchial asthma (152 401.6-178 946.0)) TU/ml, 168 167.1 (95% CI: 147 494.1-188 840.1) TU/ml in patients with OAS, and 159 492 (95% CI: 134 172.6-174 811.5) TU/ml in those with AD. No statistically significant differences were found in the cumulative dose of the vaccine received by patients with asthma, OAS and/or AD ($p > 0.5$). The index of symptoms in the whole study group before SIT was 23.1 (21.7-24.5) points, while after SIT it considerably decreased, to 5.3 (4.3-6.4) points ($p = 0.000001$). The use of symptomatic drugs in the study group diminished, on average, by 78.8% (95% CI: 64.5-93.2). The mean annual costs of symptomatic treatment, calculated from the social perspective, were PLN 967.4 (737.5-1197.4), EUR 241.85 (184.37-299.35) in the SIT preceding year. After the applied 3-year immunotherapy programme, the mean annual cost of symptomatic treatment

Table 1. Multiple regression equation. The correlation between gender, age and allergic diseases concomitant with allergic rhinitis and SIT efficacy (expressed as Δ difference in the degree of allergic symptoms). *R* coefficient of the regression model = 0.55; *p* = 0.0001* (the coefficients marked with * are statistically significant)

Parameters	β	β SE	*r*	*p*
Gender	–0.08	0.10	–0.004	0.3
Age	–0.16	0.11	–0.02	0.4
Bronchial asthma	0.43	0.10	0.38*	0.00008*
Atopic dermatitis	–0.34	0.11	–0.19*	0.002*
Oral allergy syndrome	0.26	0.10	0.25*	0.02*

β – β *coefficient,* β *SE – standard error of* β, *r – coefficient of partial correlation, p – p value*

Table 2. Multiple regression equation. The correlation between gender, age, allergic diseases concomitant with allergic rhinitis and the saving rate in the symptomatic treatment after SIT (expressed as Δ difference between the average annual costs of symptomatic therapy during the year before and the year after SIT termination). *R* coefficient of the regression model = 0.47; *p* = 0.003* (the coefficients marked with * are statistically significant

Parameters	β	β SE	*r*	*p*
Gender	–0.07	0.11	–0.08	0.5
Age	0.02	0.11	0.02	0.9
Bronchial asthma	0.46	0.11	0.44*	0.00009*
Atopic dermatitis	0.05	0.11	0.05	0.7
Oral allergy syndrome	–0.03	0.11	–0.03	0.8

β – β *coefficient,* β *SE – standard error of BETA, r – coefficient of partial correlation, p – p value*

demonstrated a triple reduction, falling to merely PLN 306.8 (176.4-437.1), EUR 76.7 (44.1-109.27) (*p* = 0.000001). In the performed multiple regression analysis, a statistically significant, positive relationship was found between the concomitance of bronchial asthma and of the oral allergy syndrome with allergic rhinitis and the clinical efficacy of specific immunotherapy. The presence of AD in patients with allergic rhinitis was significantly, but negatively, correlated with the clinical efficacy of SIT (Table 1).

In the analysis of the effects of selected variables on the costs of symptomatic treatment, a positive correlation was observed between the reduction of the annual costs of symptomatic treatment and the presence of bronchial asthma (Table 2).

Discussion

According to the standards defined by a group of international experts in collaboration with the World Health Organisation and concerning the therapy of allergic rhinitis (ARIA – Allergic Rhinitis and its Impact on Asthma), subcutaneous specific immunotherapy is the basic therapeutic method, ensuring permanent reduction or total elimination of allergic disease symptoms [1].

The efficacy of immunotherapy in eliminating allergic symptoms varies, according to different authors, between 50% and 97%, while the use of symptomatic medications decreases by 33% to 82% [8].

Specific immunotherapy is used in the treatment of allergic, IgE-dependent diseases [1, 6]. The SIT is an effective treatment method of atopic asthma, allergic rhinitis and allergy, induced by venoms of hymenoptera [6]. Its efficacy with regards to atopic dermatitis is still the subject of discussions [9, 10]. Currently, it is recommended only in patients with AD and with additionally diagnosed IgE-dependent allergy to pollens [11, 12]. In this group of patients, SIT suppresses skin changes and decreases the degree of allergic symptoms in other organs [11, 12]. In the reported study, a performed regression analysis revealed a positive correlation between the occurrence of bronchial asthma or OAS and the decrease of the degree of allergic symptoms, unlike in the patients with AD, in whom the correlation coefficient was significant but negative. It can then be concluded that patients with allergic rhinitis, with additionally concomitant bronchial asthma or OAS, derive more clinical benefit from ST than patients who simultaneously suffer from allergic rhinitis and AD.

It is estimated that allergic rhinitis affects approximately 25% of the population in Europe (from 17% in Italy to 28.5% in Belgium) [1].

In the Świdnica 2003 and EACP (Epidemiology of Allergic Diseases in Poland) 2006, performed in conformity with ECRHS (European Community Respiratory Health Survey II) standards in selected regions of Poland, it has been documented that allergic rhinitis is the most frequent allergic disease in Poland, affecting approximately 25% of the population [13, 14]. Allergic rhinitis often coexists with other allergic diseases, such as allergic bronchial asthma, the oral allergy syndrome or atopic dermatitis/allergic eczema.

Bronchial asthma is the least cost-effective allergic disease. According to the European Book of Lung Diseases, the costs of its treatment in Europe amount to EURO 17.7 billion a year [15]. Unlike allergic rhinitis, asthma requires hospitalisation much more often plus additional doctor counselling and is, out of all the allergic diseases, most burdened with the risk of death [16].

Therefore, regarding the treatment of allergic patients, a health cost avalanche is very likely, where SIT may effectively diminish the expenses incurred for the therapy of allergic diseases [17-19]. Ariano *et al*. [20] have demonstrated that SIT, administered in patients with allergy to *Acarina* allergens, reduces the costs of symptomatic therapy by 15% in the 2nd year of desensitisation, by 48%

in the 3rd year and by as much as 80% in the 6th year of SIT application.

In the reported study, after 3 years of SIT application in patients allergic to grass and/or tree pollens, the annual costs of symptomatic treatment decreased almost by 70% and the use of symptomatic medications was reduced by 80%. In the multiple regression equation, a statistically significant, positive correlation was found between the occurrence of bronchial asthma in desensitised patients and the rate of saving in symptomatic treatment (Table 2). This means that, when SIT is administered to patients with allergic rhinitis concomitant with allergic bronchial asthma, the obtained rate of savings is higher than in the case of desensitisation of patients with OAS or AD. No exacerbations of asthma were observed among the study participants. It seems that the obtained savings in the therapy of asthmatic patients resulted, first of all, from the lower use of post-SIT, very expensive inhalatory glucocorticosteroids and long-acting β_2-mimetics, which are regarded as the "golden standard" in the disease control. The obtained saving rate, as perceived from the social perspective, which result from SIT application in patients with allergic rhinitis and allergic bronchial asthma, can be an argument in favour of total reimbursement of expenses in this group of patients by a third-party payer.

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