EFFECTS OF ALLERGEN SPECIFIC IMMUNOTHERAPY ON THE ALLERGENS EXCLUDED FROM THE TREATMENT

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Aim:Specific immunotherapy is one of the alternative treatments of the allergic diseases. The efficacy of specific immunotherapy was investigated in patients receiving allergen specific immunotherapy with the diagnosis of allergic rhinitis and/or asthma.

Methods: Six child and 11 adult pollen sensitive patients were included in the study. Patients were treated with specific immunotherapy at least 24 months and more. All patients challenged with the mixed inhalant allergen extracts. Some of them were not selected for the specific immunotherapy.

Results: The challenge procedure was tolerated in all patients. Adverse reactions and systemic allergic reactions were not occured.

Conclusion: Allergen specific immunotherapy may alter the natural course of the allergic diseases, and we can treat allergic rhinitis and/or asthma with specific immunotherapy.

Key words: Specific immunotherapy, allergens, challenge

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INTRODUCTION

Specific immunotherapy (SIT) is an effective treatment modality for allergic diseases when properly implemented. Standard allergen extracts have been shown to be beneficial in the treatment of allergic rhinitis and asthma. It has been shown in many studies that immunotherapy is the only therapeutic approach that may alter the natural course of allergic diseases if administered in appropriate dosages and durations (1-10).

In this study, we tried to find out an answer for the question whether allergen specific immunotherapy is truly specific for allergens? The data verified in our study may guide to new opinions on either the clinical effects or probable mechanisms of immunotherapy.

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MATERIAL AND METHODS

Patients

This study includes six children and 11 adult pollen sensitive patients who were under allergen specific immunotheraphy for at least 24 months and more. These patients were evaluated at Gulhane Military Medical Faculty (GATA) Allergy Clinic, Ankara, Turkey. Our study population comprised all patients who applied to the outpatient clinic of our department and involved in immunotherapy owing to the allergical analyses performed in our unit between October and December 2003. The etiology of allergic rhinitis and/or asthma was evaluated by medical history, physical examination and laboratory tests. The onset and the duration of clinical symptoms along with precipitating factors were investigated. After a thorough physical examination, laboratory analyses including chest radiography, complete

Table 1. Demographic and clinical characteristics of the study group

	Adult group %		Children group (<14 age) %	
n	11		6	
Female	5	46 %	2	33 %
Male	6	54 %	4	67 %
Mean age, years	30.8±9.55		10.2±1.16	
Allergic rhinitis, n	9	81 %	5	83 %
Allergic rhinitis and asthma, n	2	19 %	1	17 %
Mean SIT duration (month)	34.8±10.2		35.17±7.88	

blood count, differential sedimentation rate, total serum IgE, respiratory function tests, skin prick tests (SPT), and allergen-specific IgE were performed to define allergic rhinitis and/or asthma.

All patients challenged with the mixed allergen extract, which contains allergens that were neither involved in the treatment nor were strong cross-reactive with therapeutic allergens involved. Six child (<14 age) and 11 adult patients were included in the study in which systemic reactions were not detected both in building and maintenance periods.

Specific immunotherapy

SIT indication, which is approved recently according to international standards were applied to patients. Before SIT indication is maintained, chronic illness of the immune system was checked with laboratory tests and the cases with these disorders were excluded from the study. Patients found to be sensitive to the allergens with the prick test were administered these allergens (Greer Lab, Lenoir, USA).

At the beginning of the treatment, 0.05 ml solution with 10 w/v was given twice a week and the dosage gradually increased to 1.000 w/v in 0.5 ml of the solution. Experienced physicians in our allergy clinic performed SIT. All patients waited at least 30 minutes after injections.

Evaluation of patients receiving immunotherapy

a) Initial assessment: The initial investigation included the recording of full clinical history, skin tests with a standardized panel of allergens, and the measurement of allergen-specific IgE.

b) Assessment of newly developed sensitization: Each patient involved in the study was followed up for not less than 24 months and the results of skin tests and allergen-specific IgE were studied by using the same allergen panel. The diagnostic tests were performed as described previously.

Design of the study

The study was planned as clinical based and included patients suffering from allergic rhinitis and/or asthma. The cases were followed up as outpatients during the immunotherapy period. All patients were informed about the study protocol and the effects and side effect of the challenge. All patients were asked to sign an informed consent preceding the treatment.

The patients in the study were underwent SPT. SPTs were performed in the patient's asymptomatic period and at least 7 days antihistamine-free period following the last dose of antihistaminic drugs. Fifty-six common aeroallergens (pollens found in Turkey's atmosphere, molds, house dust mites and animal dander) were used (Greer Lab, Lenoir, USA). SPT was performed using disposable lancets and the reactions were recorded 15 minutes after the test. Reactions with a wheal diameter greater than 3 mm with surrounding erythema were considered positive. The wheal without erythema was accepted as irritant reaction and was excluded. In addition, test with negative control solution (diluents with 0.9% saline and 0.4% phenol) was particularly performed to all patients to differentiate dermographic and irritant reactions.

All patients who were sensitized to different allergens and suffering from respiratory symptoms in our study have

been submitted to prick tests at the beginning and at the end of the study.
Allergen-specific IgE: A sample of blood was taken from each patient for allergen-specific IgE for the in vitro determination of allergen-specific IgE according to a routine procedure followed in our centre. Serum specific IgE was measured by using the ELISA method (Dr. Fooke, Neuss, Germany).

Challenge

All patients challenged with the mixed allergen extract (Bermuda grass and Timothy grass, 1.000 w/v in 0.5 ml, Greer Lab, Lenoir, USA)

Study protocol

Immunotherapy was given to the patients who were provided to have a minimum time period (24 months) for clinical healing. The challenge was maintained to the cases with standard mixed allergen solutions comprising allergens either excluded from the therapeutic program initially or those without cross reactions with the included allergens.

The challenge was provided after establishing standard conditions to interfere systemic reactions. The cases were evaluated with physical examination and respiratory function tests preceding the challenge and were excluded from the study when underlying respiratory pathologies were detected. If the patients were using antihistamines, the therapy was postponed owing to the probability of the suppression of the reactions. All the injections were administered out of pollen season.

RESULTS

Characteristics of the patients

The average of child patients' age was 10.17$\pm$1.16, and adult patients' age was 30.82$\pm$9.55 years. Fourteen patients had allergic rhinitis and 3 patients had both allergic rhinitis and asthma. Demographic and clinical characteristics of the patients and prick test results are summarized in Table 1 and 2 respectively.

Specific IgE results

The results of specific IgE were not concordant with in-vivo test (prick test). Although the skin testing was positive in all cases, sIgE was negative in 10 applicants.

Challenge

The challenge procedure was tolerated in all patients and systemic reaction was observed in none of them. The second SPT results were concordant with the pretreatment SPTs, except one patient who developed house dust mite sensitivity during the therapeutic course. In just one patient, 4 cm of local reaction was developed. But in the subsequent injections, injection reactions were tolerated despite the unchanging dosage. Challenge test results are summarized in Table 3.

DISCUSSION

SIT has been widely used for many years. Numerous studies have demonstrated the safety and the efficacy of SIT in allergic patients. Large-scale studies on efficacy of the subcutaneous immunotherapy with inhalant allergens have been undertaken in patients with pollen allergy. Double-blind placebo-controlled studies using standardized vaccines have shown that immunotherapy has beneficial effects on allergic symptoms and/or decreases the need for allergic diseases' medications for both pollen and house dust mite atopy (11,12).

SIT has a different mechanism. This mechanism of action has been unique, and different from any other pharmacological treatment in many respects. First, SIT can modify the natural history of allergic disease, as confirmed in rigorously conducted trials (13,14). Second, SIT can prevent the onset of new sensitizations, as demonstrated clearly in children in several studies (15,16). Third, SIT even maintains its clinical efficacy years after discontinuation. This latter fact is supported by different studies using subcutaneous SIT for a variety of allergens (17-19).

Venoms and pollens (grass and tree) represent the most extensively tested allergens in immunotherapy. Venom immunotherapy shows more than 90 % efficacy (20) and most double blind, placebo-controlled studies using pollens show significant improvement in clinical symptoms. A study by Durham et al. (18) showed long term clinical efficacy of grass-pollen immunotherapy after the discontinuation of treatment in a

Table 2. Prick test results and allergens used in the immunotherapy

Patient No.	First prick	Second prick test	Using allergens in SIT
1	H.D.mites, Aspergillus fumigatus, Alternaria alternate, Bermuda grass	-	H.D. mites
2	H.D. mites, Timothy grass, Pine, Dog epithelia, Sweet wernal	-	H.D. mites, Pine, Sweet wernal
3	Bermuda grass, Timothy grass, Candida albicans, Betula lenta, Olive pollen, Cockroach	-	Olive pollen, Betula lenta
4	Alternaria alternate, Maple, Dandelion, Penicillum notatum, Bermuda grass, Timothy grass, Cockroach, Sweet wernal	-	Sweet wernal, Maple, Dandelion
5	H.D. mites, Bermuda grass, Sunflower, Hazelnut, Quack grass, Linden, Wheat pollen	-	H.D. mites, Linden, Sunflower, Quack grass
6	Bermuda grass, Rye cultivated, Wheat pollen, Quack grass, Mucor plumbeus, Alternaria alternate, Candida albicans, Cockroach	-	Rye cultivated, Wheat pollen, Quack grass
7	Penicillum notatum, Bermuda grass, Timothy grass, Olive pollen, Cat epithelia, Quack grass	H.D. mites	Olive pollen, Quack grass
8	H.D. mites, Bermuda grass, Timothy grass, Cockroach, Aspergillus fumigatus, Penicillum notatum, Rose, Zea mays	-	H.D. mites, Rose, Zea mays
9	H.D. mites, Bermuda grass, Avena fatua, Orchard grass, Lolium perenne, Barley	-	Avena fatua, Orchard grass, Lolium perenne, Barley, H.D. mites
10	H.D. mites, Bermuda grass, Timothy grass, Trichopyton rubrum, Linden, Quack grass	-	H.D. mites, Linden, Quack grass
11	Wall pellitory, Bermuda grass, Timothy grass, Cockroach, Orchard grass, Poa pratensis, Sweet wernal, Rye grass, wheat pollen	-	Orchard grass, Poa pratensis, Sweet wernal, Rye grass, wheat pollen
12	Poa pratensis, Sweet wernal, Rye grass, Bermuda grass	-	Sweet wernal, Rye grass
13	H.D. mites, Penicillum notatum, Pine	-	H.D. mites
14	Cockroach, Olive pollen, Poa pratensis, Rye grass, Avena fatua, Pine	-	Olive pollen, Poa pratensis, Rye grass, Avena fatua, Pine
15	Bermuda grass, Poa pratensis, Rye grass, Avena fatua	-	Poa pratensis, Rye grass, Avena fatua
16	Rose, Cockroach, Bermuda grass, Timothy grass, Aspergillus fumigatus, Populus alba, Corn pollen, Pine	-	Rose, Populus alba, Corn pollen
17	H.D. mites, Cockroach, Cat epithelia	-	H.D. mites

H.D.Mites: House dust mites

randomized, double blind, placebo-controlled trial. During the 3 years of this trial, scores for seasonal symptoms and medication and the late skin response remained low after the discontinuation of immunotherapy, and there was no significant difference between patients who continued therapy and those who discontinued it.

Jacopsen et al. (14) studied the long term effects of tree pollen extract immunotherapy by following up the symptom scores and skin tests in 36 patients in 6 years after a 3 year course of immunotherapy. The data showed that 86 % of the patients with rhinitis and 68 % of the patients with asthma maintained improvement after the termination of the treatment. The skin sensitivity of the patients decreased significantly during therapy, and the skin reactions six years after the treatment were still significantly

Table 3. Challenge tests results

Patient No.	Age	Gender	Diagnosis(*)	Antigens of Challenge (**)	Local reactions	Systemic reactions	Additional allergens
1	43	Female	AR	B + T	_	_	_
2	22	Male	AR+BA	B + T	_	_	_
3	37	Male	AR	B + T	_	_	_
4	31	Male	AR	B + T	_	_	_
5	36	Female	AR	B + T	> 4 cm	_	_
6	31	Female	AR	B + T	_	_	_
7	16	Male	AR	B + T	_	_	Mite
8	9	Female	AR	B + T	_	_	_
9	9	Male	AR+BA	B + T	_	_	_
10	40	Male	AR	B + T	_	_	_
11	11	Female	AR	B + T	_	_	_
12	12	Male	AR	B	_	_	_
13	40	Female	AR+BA	B	_	_	_
14	10	Male	AR	B	_	_	_
15	10	Male	AR	B	_	_	_
16	16	Male	AR	B + T	_	_	_
17	27	Female	AR	B + T	_	_	_

(*)AR: Allergic rhinitis, BA: Bronchial asthma
(**) The sensibility of patient to the illnesses but it is not taken to the immunotherapy program and allergens which in the applying and low cross reactive or middle degree allergens
(B) Bermuda grass (low cross reactivity)
(T) Timothy grass (middle degree cross reactivity)

lower than the pretreatment levels.

One significant aspect of the long-term effect of allergen immunotherapy is the prevention of progression of allergic rhinitis to asthma. A link between allergic rhinitis and atopic asthma has been demonstrated in numerous epidemiological studies. It is reported that 25 to 43 % of the patients experiencing rhinitis naturally develop asthma within 10 years (21,22), whereas in the study by Jacobsen et al., (14) none of the patients with allergic rhinitis developed asthma over a six-year period following the termination of immunotherapy.

There are lots of immunological changes following allergen immunotherapy. The first observed parameter indicating immunological changes caused by immunotherapy is the striking rise in IgG or blocking antibodies, which is postulated by some to prevent allergen from combining with mast cell-and basophile-bound IgE and degranulation of these cells (23,24). Allergen specific IgE is the most typical antibody in allergic diseases. Decreases in allergen-specific IgE responses are observed in some studies. But more studies do not show significant alteration in IgE responses following allergen immunotherapy, even when significant improvement in clinical symptoms and medication scores are observed (11,12,25).

Atopic allergy is associated with active T cell responses to common environmental allergens that are skewed towards TH_2 cytokine production, in contrast to the TH_1 skewed responses in normal individuals (23). TH_2 cytokines especially interleukin IL-4, IL-5 and IL-13 have been found to be critical in the development of immediate hypersensitivity. IL-4 is essential for IgE switch and IL-13, in many cases, plays a similar role to IL-4. IL-5 is crucial for the respiratory tract eosinophilia observed in asthma and rhinitis and IL-13 appears important for bronchial mucus production. Allergen immunotherapy affects the cytokine profile of allergen-specific T cells and switches TH_2-type immune responses in patients with atopy towards TH_0 - or TH_1-type immune responses (26-29). Allergen immunotherapy can significantly inhibit eosinophilic inflammation in the airways

of patients with asthma. In addition to inhibiting TH_2 cytokine production, which enhances eosinophilia, allergen immunotherapy is able to suppress the production of factors inducing eosinophil adhesion thus inhibiting eosinophil recruitment in allergic inflammation (30). Medicinal effects due to allergy drugs have not been shown on the natural courses of allergic diseases up to now. When the early and late clinical effects of SIT were observed, it can be concurred that this mode of treatment is a proper option especially when the selection of the patients are made on a suitable basis (8,9,10,31).

Purello and his friends (16) practiced 7182 patients who have allergy of respiratory systems and they gave only medicine core to 1214 patients. Both groups were appraised at the end of 4 and 7 years. In the group of immunotherapy, end of the 4 years is 23 %, in the group of medicine is 68 %, at the end of 7 years in the group at immunotherapy is 26 % and in the group of medicine is 76 % has been established new sensibility developments.

A lot of data demonstrating the effects of SIT on the natural courses of allergy has been found in children. Des Roches et al. (15) has been studied in children with allergic asthma. In this study 22 child with asthma monosensitized to house dust mite and these children younger than 6 years of age who received SIT were evaluated prospectively and compared with 22 children monosensitized to house dust mite who were not treated with SIT. Children who received SIT had less new sensitivity to inhalant allergens than those who did not received SIT. Forty-five percent of monosensitized children who received SIT did not have new sensitization as compared with 0 % in the control group. This study suggests that allergen immunotherapy can alter the natural course of allergy in children sensitized to allergen by preventing the development of new sensitivities.

The aim of this study is to show the efficacy of treatment whether the effects are maintained over the atopic immune system or the allergens included. If the effects of immunotherapy were attributed to the selected allergen extracts, then the decreasing sensitivities for these allergens would be expected. In this situation, some of the symptoms would persist due to other allergens, which either cross-react with those included in SIT or the patient is known to be sensitive. Similarly, when this low cross reactivity presenting allergens are given in high doses to the patients, specific IgE antibodies bound on the mast cells and the basophiles would react with the allergen and extensive local or systemic reactions would occur.

Allergen specific immunotherapy is one of the treatment alternatives of the allergic diseases. In this study, the truth of the theory of “immunotherapy is not only effective on the targeted allergens, but also may directly affect the immune system” was investigated in patients receiving allergen specific immunotherapy with the diagnosis of allergic rhinitis and/or asthma. In addition, additional sensitizations with new allergens during the immunotherapy course were investigated.

In conclusion, allergen specific immunotherapy may alter the natural course of the allergic diseases. In addition to known mechanisms, it has been widely accepted that there are some unknown ones related to effects of the immunotherapy on the immune system. In this study, we tried to find an answer for question of “allergen specific immunotherapy is truly allergens specific?”, and obtained some results that may be guide to the new opinions about clinical effects and probable mechanisms of immunotherapy.

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