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Development of New Sensitizations in Asthmatic Children Monosensitized to House Dust Mite by Specific Immunotherapy

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SUMMARY It has been hypothesized that specific immunotherapy (SIT) significantly decreases the development of new allergen sensitizations in mono-sensitized patients. In this study, we evaluated the effect of SIT on the development of new allergen sensitizations in 129 asthmatic children mono-sensitized to house dust mite. SIT was accepted by only 70 of them (SIT group). The remaining 59 children were treated only with medication (control group). At the end of the study we found that 33% of all patients developed new sensitizations. Surprisingly, the prevalence of new sensitizations was significantly higher in the SIT group (45.5%) than in the control group (18.1 %). Ash tree (*Fraxinus excelsior*), Olive and Meadow fescue (*Festuca elatior*) were the most common allergens responsible for the new sensitizations. We conclude that SIT did not prevent the onset of new sensitizations in asthmatic children mono-sensitized to house dust mite.

Allergen specific immunotherapy (SIT) has been in use since the beginning of the 20th century and is still one of the most important therapeutic approaches in the treatment of allergic respiratory diseases. The benefits and the effects of SIT have been mentioned in the *WHO Position Paper* and the *EAACI Position Paper* as well as in many other articles.[1-4] Besides the positive effect on the allergic disease, SIT is suggested to prevent the development of asthma in patients with allergic rhinitis and development of new allergen sensitizations in mono-sensitized patients.[5-8] The hypothesis that SIT could prevent the development of new allergen sensitizations especially in mono-sensitized patients was first reported by Des Roches *et al*.[9] This theory was then confirmed by other investigations.[10,11] Although it is now widely accepted, some authors reported that SIT did not prevent the development of new allergen sensitizations in mono-sensitized patients.[12] As there is still no conclusion on this subject, this study aimed to show the effect of SIT on the development of new allergen sensitizations in asthmatic children mono-sensitized to house dust mite (HDM).

MATERIAL AND METHODS

Patients

One hundred twenty-nine patients of the Aegean University Pediatric Allergy Outpatient Clinic aged 6-10 (8.1 ± 1.3) years were included in the study on the basis of the following criteria: 1)

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clinical history: at least one year of mild to moderate persistent asthma (according to the criteria of the GINA report);[13] 2) a positive skin prick test against a biologically standardized HDM (*Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae)* extract; 3) a positive *in vitro* test for serum IgE specific to HDM (Pharmacia Diagnostics AB, Uppsala, Sweden). All parents agreed by written informed consent for their children to participate in the study.

Study groups

Patients who were included in the study were divided into two groups. SIT was proposed to all the children's parents, but was accepted by only 70 (SIT Group). The remaining 59 children were treated with medication only (mainly for economical, compliance reasons, fear of injections or fear of adverse reactions), and accepted as control group. The choice of treatment was left to their parents. Randomization was not performed because the majority of the parents refused a blind choice with the perspective of a possible long, invasive, and demanding treatment as required with SIT.

Injective SIT with mite mix was administered to the SIT Group during the first four years and all patients were followed up to 6 years. Allergic sensitizations were investigated using skin prick test and serum-specific IgE at the end of the follow-up period.

Diagnosis of allergy

Skin prick test

All skin prick tests were done by specialists in pediatric allergy in our clinic and the results were evaluated by the same physicians. The standard respiratory allergen panel included tree pollens, grass pollens, dust mite, fungus, animal dander, grains pollen, wild grass, flower pollens and latex (Stallergenes S. A., France). First allergens were applied on the anterior side of the forearm, and then pierced by stallerpoint. After 20 minutes, the test was evaluated. Histamine was used as positive control and physiologic saline was used as negative control. Results were evaluated according to the European Academy of Allergology and Clinical Immunology (EAACI) criteria.[14]

Specific IgE

The Pharmacia CAP system was used to determine the inhalant allergens sensitization in the sera (dust mite, fungi, animal epithelia, grass pollens, tree pollens, flower pollens, wild grass pollens and latex). 0.35 kU/l of specific IgE were accepted as positive.

SIT

A depot calcium phosphate-adsorbed preparation of mite mix (*D. pteronyssinus* and *D. farinae*, 50% of each; Stallergenes, France) was used for the SIT Group. Children in the SIT group received immunotherapy during the first four years of the study. Immunotherapy was administered subcutaneously according to the perennial schedule of the SIT group. Dosages were adjusted on an individual basis, according to the following criteria: 1) the dose was repeated at the next visit if a local reaction was greater than 6 x 6 cm; 2) injections were postponed if other diseases were present on a given visit.

After the induction phase, a maintenance dose of 50,000 SQU (standard quality units) was administered once a month for four years. The patients were kept under observation for 1 hour after each administration.

Drugs

Both groups were followed up regularly and received their drugs according to the GINA report.[13] All patients, whether treated with SIT or not, were prescribed and instructed to use the same antiallergic drugs to control their respiratory symptoms. Antihistamine tablets, inhaled β-2 adrenergic agonists, and topical and systemic steroids were administered to the patients.

Statistical analyses

Statistical analysis was performed using "SPSS 11.0 software for Windows". The mean ages of both groups were compared by student t test. Other comparisons were evaluated by Pearson's chi-square test and calculating odds ratios (OR). A "*p*" value < 0.05 was considered significant.

RESULTS

Characteristics of the patients

One hundred twenty-nine patients diagnosed with asthma bronchiale, with a single sensitization to mite allergen were included in this study. Ages varied from 6 to 10 years. A total of 123 out of 129 children (95.3%) completed the 6-year study period. Two patients in the SIT group and 4 in the control group were excluded from the study. Both groups were comparable in terms of age and sex. Median age at the beginning of the study was 9 years (range 6-10) in the SIT group and 8 years (range 6-10) in the control group. Fifty-eight percent of the SIT group and 54% of control group were boys, and there was no statistically significant difference in the sexual distribution of patients between the groups (p = 0.65). In addition, there was no difference between the two groups in terms of family history of atopy (p = 0.88) (Table 1).

Evolution of sensitization

At the end of the 6-year study period, thirty-three percent of the patients (n = 41) had developed new sensitizations. Surprisingly, the prevalence of new sensitizations was significantly higher in the SIT group (31/68; 45.5%) than in the control group (10/55; 18.1%) (χ^2 = 10.28, OR : 3.77, 95% CI = 1.52- 9.5, p = 0.001). The most prevalent sensitivities were the same in children who were polysensitized, whether or not they had received SIT. Ash tree (*Fraxinus excelsior*), Olive and Meadow fescue (*Festuca elatior*) were the most common allergens responsible for the new sensitization(s) (Table 2).

There was no statistically significant difference in the development of new allergen sensitizations between the two groups in terms of family history of atopy (p = 0.07, OR = 0.87 [0.3-2.3]).

DISCUSSION

A number of studies have established the efficacy and long-term effect of allergen-specific immunotherapy in patients with airborne allergies.[1,5,15,16] Sensitization to mites is a known risk factor for early and late onset of asthma,[16] and sensitivity to perennial allergens such as mites and animal dander seems to appear at an earlier age than sensitivity to seasonal allergens.[17,18] In asthmatic children sensitized to mites, SIT was shown to reduce both bronchial hyper-responsiveness,[19] and the late asthmatic reaction.[20]

In recent years it has been suggested that SIT, which has been used for a long time as treatment of atopic diseases, significantly decreases the development of new allergen sensitizations compared to pharmacotherapy. The mechanisms to explain the lower rate of new sensitizations in children given SIT are still unclear. The clinical success of SIT may depend on two main immunological mechanisms: (a) immune deviation, *i.e.* a shift in the balance of Th1/Th2 responses in favor of the former one, possibly mediated by IL-12, the strongest inducer of Th1 responses known,[21] and (b) Immune tolerance, induced by the immunosuppressive cytokine IL-1.[22,23] Together, these events lead to a reduction in the production of cytokines by allergen-specific Th2 cells,[24] which profoundly influence the production of specific IgE, priming and recruitment of mast cells, activation of eosinophils, and lymphoproliferative responses.[25]

Des Roches *et al.*[9] proposed that SIT pre-

Table 1 Demographic data of the patients

	SIT group	Control group	*p*
Age in years (mean ± SD, range)	8.42 ± 1.3 (6-10)	7.83±1.2(6-10)	0.71
Sex			0.63
M (%)	28 (41.2)	25 (45.5)	
F (%)	40 (58.8)	30 (54.5)	
Family history of atopy	38 (55.9)	30 (54.5)	0.88

vents the development of new allergen sensitizations especially in mono-sensitized patients. Many articles supported that idea.[10,11] However, Asero[12] did not find any effect of SIT on the development of new allergen sensitizations. Recently, studies on SIT were increased and different results have been announced on new sensitizations.[26,27] Since this issue is still under debate and is important for the prognosis of immunotherapy, we evaluated the effect of SIT on the development of new allergen sensitizations in asthmatic children mono-sensitized to house dust mite using objective tests such as the skin prick test and the in vitro detection of specific IgE.

We planned our study as an open-controlled study. The choice of treatment was left to the parents. Moreover, we believe that a randomized or double-blinded placebo-controlled study in which a large number of children are enrolled and treated for several years is neither ethical nor practically feasible.

In this study, surprisingly, the prevalence of new sensitizations was significantly higher in the SIT group (45.5%) compared to the control group (18.1%). Ash tree (*Fraxinus excelsior*), Olive and Meadow fescue (*Festuca elatior*) were the most common allergens responsible for the new sensitizations.

A family history of atopy is one of the major risk factors in the development of atopic diseases.[28] It may also effect the development of new allergen sensitization. However, we did not find any association between family history of atopy and development of new allergen sensitization in patients who underwent SIT.

In conclusion, according to our data, SIT did not prevent the onset of new sensitizations in asthmatic children mono-sensitized to house dust mite. It has been suggested that the function of regulatory T cells which are supposed to play a major role in the effect of SIT is under genetic control and a defect in the function of these cells can present different clinical pictures.[29-31] For this reason, individual or regional variations may be seen as a result of SIT administration.

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Table 2 Development of new sensitizations and drop-outs of the two groups

Patients	SIT group	Control group
Number of patients enrolled	70	59
Drop-outs	2	4
Patients followed-up for 6 years	68	55
New sensitizations*	31	10
Olive	20	8
Meadow fescue (*Festuca elatior*)	18	7
Ash tree (*Fraxinus excelsior*)	16	6
Grass	14	5
Cat	3	1
***Alternaria* spp.**	3	2
Dog	2	0

*$p = 0.001$

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