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The Effect of Allergen Immunotherapy on the Development of New Sensitization in Children

Şükrü Çekiç[1], Yakup Canıtez[1], Fatih Çiçek[1], Gökhan Ocakoğlu[2], Nihat Sapan[1]

[1]Division of Pediatric Allergy, Uludağ University School of Medicine, Bursa, Turkey
[2]Department of Biostatistics, Uludağ University School of Medicine, Bursa, Turkey

What is already known on this topic?

- *The improving effect of allergen immunotherapy on clinical findings has been demonstrated in many meta-analyses, but its protective effect against new allergen sensitivity is controversial.*

What this study adds on this topic?

- *Sensitivity to weed pollen and a diagnosis of asthma were found to be risk factors for the development of new sensitivity.*

ABSTRACT

Aim: The protective effect of allergen immunotherapy against a new allergic sensitization is controversial. This study aimed to investigate the effect of allergen immunotherapy on new allergic sensitization in children.

Materials and Methods: The study included 50 patients who received immunotherapy for at least 3 years, and whose skin prick tests were repeated at intervals of at least 3 years (31 patients for house dust mite immunotherapy, 19 patients for pollen immunotherapy), and 69 controls with similar characteristics.

Results: The number of patients who developed a new sensitization was similar both in the groups of patients who received house dust mite and pollen immunotherapy, and the control group. There was no significant difference between the first and last skin prick tests of the patients who received house dust mite and pollen immunotherapy; however, in the control groups, a significant increase in sensitivity to tree pollens ($n = 2$, 5.4%; $n = 8$, 21.6%) and weed pollens ($n = 7$, 26.9%; $n = 14$, 53.8%) was detected ($P = .031$ and $P = .039$). While allergen sensitivities in the first tests of the pollen immunotherapy group and the control group were similar, weed pollen sensitivity was significantly higher in the last tests of the control group ($n = 14$, 53.8%; $n = 4$, 21.1%, $P = .027$). It was determined that the presence of weed pollen sensitization (OR: 8.1, 95% CI: 1.5–42.4) and having asthma (OR: 3.5, 95% CI: 1.3–10.8) increases the risk of new sensitization in all groups.

Conclusion: Allergen immunotherapy has been found to protect against new sensitization to tree and weed pollens. However, this effect was insignificant in the multivariate analysis. Weed pollen sensitization and the presence of asthma are related to the development of new sensitization.

Keywords: Asthma, immunotherapy, new sensitization, weed pollen

INTRODUCTION

Allergen immunotherapy is a treatment method that aims to develop immune tolerance against the sensitized allergen by administering it at increasing doses in regular intervals.[1] It was first used in the treatment of allergic rhinitis by Noon and Freeman in 1911.[2,3] This treatment is the only method that can change the natural course of allergic diseases. The main areas of application are allergic rhinitis/rhinoconjunctivitis, allergic asthma, and bee (venom) allergy treatments.[1]

Data show that in addition to the therapeutic properties, allergen immunotherapy protects against the development of asthma in patients with allergic rhinitis and prevents the development of new allergen sensitivity in patients.[4-8] However, contrary to this information, published

Corresponding author:
Nihat Sapan
✉nihatsapan@yahoo.com.tr
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studies also report that it does not protect against new sensitivity development, or causes sensitivity to increase.[9-11] As a result, more evidence is needed on whether allergen immunotherapy protects against new sensitizations.[12]

Our aim in this study was to evaluate the effect of allergen immunotherapy on the development of new allergen sensitivity.

METHODS

The study was conducted by retrospectively examining the patients who received immunotherapy for respiratory allergic diseases between 2010 and 2018 in Uludağ University Faculty of Medicine, Division of Pediatric Allergy. Approval for the study was obtained from the Uludağ University Faculty of Medicine Clinical Research Ethics Committee with the decision number 2017/10-27. The study was conducted following principles outlined in the Declaration of Helsinki.

Patients

The immunotherapy group consisted of patients who received house dust mite (HDM) or pollen (weed pollens or weed-cereal pollens) immunotherapy for at least 3 years, and patients whose skin prick test was repeated at an interval of at least 3 years after immunotherapy. Controls for both immunotherapy groups consisted of patients with similar age, gender, allergic disease, and allergen sensitivity, who did not receive immunotherapy, and whose skin prick test was repeated at intervals of at least 3 years. Among the screened patients, 31 cases who received HDM immunotherapy and 19 cases who received pollen immunotherapy, and 69 controls (42 cases for the HDM immunotherapy group, 27 cases for pollen immunotherapy) were included in the study. The ages of the patients receiving immunotherapy (10.8 ± 3.1 years) and the ages of the control group (10.1 ± 2.7 years) and the time between 2 tests in both groups (4.2 ± 1 year for the immunotherapy group and control 4.25 ± 1 year) were similar (P = .165 and P = .690, respectively).

Skin Prick Test

Skin prick tests were applied at Uludağ University Faculty of Medicine Pediatric Allergy Division Laboratory using ALK-Abello (Horsholm, Denmark) standard allergen kits and disposable plastic lancets (Stallergenes, Antony, France). After the allergens were dropped on the volar surface of both forearms at intervals of at least 2 cm, different lancets were used for each allergen, allowing the allergens to reach a depth of approximately 1 mm. Histamine 0.1% (1 mg/mL) was used for positive control and saline solutions were used for negative control. The result was considered positive for the relevant allergen when edema of 3 mm or more was detected compared to the negative control, 15 minutes after the allergen was administered. Dermatophagoides farinae, Dermatophagoides pteronyssinus, grass pollen mix (Dactylis, Festuca, Lolium, Phleum, Poa), cereal pollen mix (Avena, Hordeum, Triticum, Secale), weed pollen mix (Artemis, Chenopodium, Parieteria, Planta) in the skin prick test panel), Plantago pollen, olive tree pollen, tree pollen mix (Alnus, Betula, Corylus), Alternaria, cat allergen, dog allergen, and cockroach allergens were used. House dust mite sensitivity was accepted as any mite sensitivity, grass pollen sensitivity as any sensitivity to grass pollen, cereal pollen sensitivity as sensitivity to any cereal pollen, tree pollen sensitivity as sensitivity to any tree pollen, and sensitivity to weed pollen as the presence of sensitivity to any weed pollen.

Immunotherapy Protocol

Subcutaneous immunotherapy was applied with the classical method in all patients. Aluminum hydroxide or calcium phosphate-adsorbed standardized extracts or allergoid preparations (NovoHelisen Depot, Allergovit, Allergopharma, Reinbek, Germany; Alutard SQ, ALK Laboratories, Hoersholm, Denmark; APSI Retard, Stallergenes, Antony, France) were used for subcutaneous immunotherapy. Immunotherapy injections were administered in increasing doses weekly in the first 2-6 month period, which is the initial-dose-increase period; after reaching the maximum tolerated concentration, the maintenance period was initiated and the same dose was administered at intervals of 4 weeks for 3-5 years.

Statistical Analysis

Variables are expressed as mean ± standard deviation and median (minimum, maximum) values. The compliance of continuous variables to normal distribution was examined using the Shapiro–Wilk test. Independent samples *t*-test or Mann–Whitney *U*-test was used to compare quantitative data according to normality test results. Categorical variables were expressed as *n* (%),the McNemar test was used for the comparison of dependent time measurements within the patient group, and the Pearson's chi-square test or Fisher exact test was used for independent variables. Analyses were made with the SPSS (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0, IBM Corp., Armonk, NY) program, and the type I error level was accepted as $\alpha = 0.05$ in statistical analysis.

RESULTS

The immunotherapy and control groups were similar in terms of gender, age, the time between two tests, allergic diseases, and sensitization rates to a single allergen (Table 1). The mean immunotherapy duration of the patients who received allergen immunotherapy was 4.2 ± 0.8 years. The most common disease in patients receiving house dust mite immunotherapy was asthma (n = 27, 87.1%), and the most common allergic disease in the pollen immunotherapy group was allergic rhinoconjunctivitis (n = 17, 89.5%).

When the patients who developed new sensitivity in the allergen immunotherapy and control group were evaluated, no significant difference was found between the groups in terms of the number of patients who developed new sensitivity (Table 2).

Allergen sensitivity was similar between the first tests of the patients who received HDM immunotherapy and pollen immunotherapy, and the first tests of the control group. However, in the last tests of the patients who received pollen immunotherapy and the control group, weed pollen sensitivity (n = 14, 53.8%) was significantly increased in the control group compared to those who received pollen immunotherapy (n = 4, 21.1%) (P = .027) (Figure 1).

The allergen sensitivity in the first tests of the patients who received immunotherapy and the allergen sensitivity in the last tests, and the allergen sensitivity in the first tests of the

Table 1. General Characteristics of the Immunotherapy Groups and Control Groups

	HDM IT [*n* (%)]	Control [*n* (%)]	*P*	Pollen IT [*n* (%)]	Control [*n* (%)]	*P*
Female/male	18/13 (58.1/41.9)	23/19 (54.8/45.2)	.779†	8/11 (42.1/57.9)	12/15 (44.4/55.6)	.875†
Age (year) mean ± SD (median, the smallest-the largest)	11 ± 3.1	10.3 ± 2.9	.295‡	10.5 ± 3.3	9.9 ± 2.5	.523‡
The time between 2 tests (year) mean ± SD (median, the smallest-the largest)	4.1 ± 1	4.4 ± 0.9	.294‡	4.3 ± 1.1	4.1 ± 0.9	.575‡
Asthma	27 (87.1)	35 (83.3)	.750§	14 (73.7)	18 (66.7)	.611†
Allergic rhinoconjunctivitis	25 (80.6)	32 (76.2)	.649†	17(89.5)	23 (85.2)	>.99§
Sensitivity to a single allergen (*n*, %)	23 (74.2)	25 (59.5)	.192†	9 (47.7)	8 (29.6)	.220†

†Pearson's chi-square.
‡Independent samples *t*-test.
§Fisher's exact test.
HDM, house dust mite; IT, immunotherapy; SD, standard deviation.

control groups and the allergen sensitivity in the last tests, were compared. This comparison showed no significant difference between allergen sensitivity in the tests performed at an interval of at least 2 years in the patients who received HDM immunotherapy, whereas, in the control group, tree pollen sensitivity was found to be significantly higher in the last test compared to the first test ($n = 2$, 5.4%; $n = 8$, 21.6%, $P = .031$). Comparison within the series of pollen immunotherapy results for each patient showed no significant difference found between the first and last tests. Weed pollen sensitivity in the last tests of the control group ($n = 14$, 53.8%) was significantly higher than in the first tests ($n = 7$, 26.9%) ($P = .039$). The changes between the first and last tests of the patients who received immunotherapy and control groups are shown in Table 3.

An examination of the effects of age, gender, immunotherapy, allergic diseases, and allergen sensitivities on new sensitization in all patients who received immunotherapy, and in the controls, revealed that the presence of weed pollen sensitivity and a diagnosis of asthma were associated with the development of new sensitivity (odds ratios: 8.1 and 3.8, respectively). Allergen immunotherapy did not show a significant effect on the development of new sensitivity (OR: 0.72, 95% CI: 0.3-1.7, $P = .455$). Univariate and multivariate analyses of factors affecting the development of new sensitivity are shown in Table 4.

DISCUSSION

The argument that allergen immunotherapy protects against new sensitization was first put forward by Roches et al.[4] in 1997. In their prospective study with 22 asthmatic children with HDM sensitivity and the same number in the control group, they found that the development of sensitivity to cat allergens, dog allergens, Alternaria, and grass pollen was less in patients who received immunotherapy. In another prospective study, Cengizlier et al.[13] found that the development of new sensitivity in children who received HDM and grass pollen immunotherapy was significantly lower than the control group. Similarly, it has been shown in various studies that immunotherapy protects against the development of new sensitivity.[5-8,14] In contrast, there are also studies showing that it does not protect against new sensitization and even increases new sensitization.[9-11,15,16] In a meta-analysis evaluating 32 studies, evidence was presented that allergen immunotherapy reduces the risk of new sensitization in the short term, while no clear evidence of a long-term reduction in sensitization risk was presented.[17] In our study, the number of patients who developed new sensitivity with HDM and pollen immunotherapy was similar to those in the control group. When the sensitivity developments were evaluated separately in each allergen group, there was a significant increase in tree pollen sensitivity in the HDM immunotherapy control

Table 2. Patients with New Sensitivity in Allergen Immunotherapy and Control Group

	Immunotherapy, *n* (%)	Control, *n* (%)	*P*
In immunotherapy ($n = 50$) and control groups ($n = 65$)	21 (42)	25 (38.5)	.701†
Between IT ($n = 32$) and control ($n = 33$) groups with sensitivity to a single allergen	17 (53.1)	12 (36.4)	.174†
New sensitivity in house dust mite immunotherapy group			
All IT ($n = 31$) and control ($n = 42$) groups	12 (38.7)	15 (35.7)	.793†
IT ($n = 23$) and control ($n = 25$) groups with sensitivity to a single allergen	11 (47.8)	8 (32)	.263†
New sensitivity in pollen immunotherapy recipients			
All IT ($n = 19$) and control ($n = 27$) groups	9 (47.4)	13 (48.1)	.958†
IT ($n = 9$) and control ($n = 8$) groups with sensitivity to a single allergen	6 (66.7)	4 (50)	.637‡

Pearson's chi-square.
‡Fisher's exact test.
IT, immunotherapy.

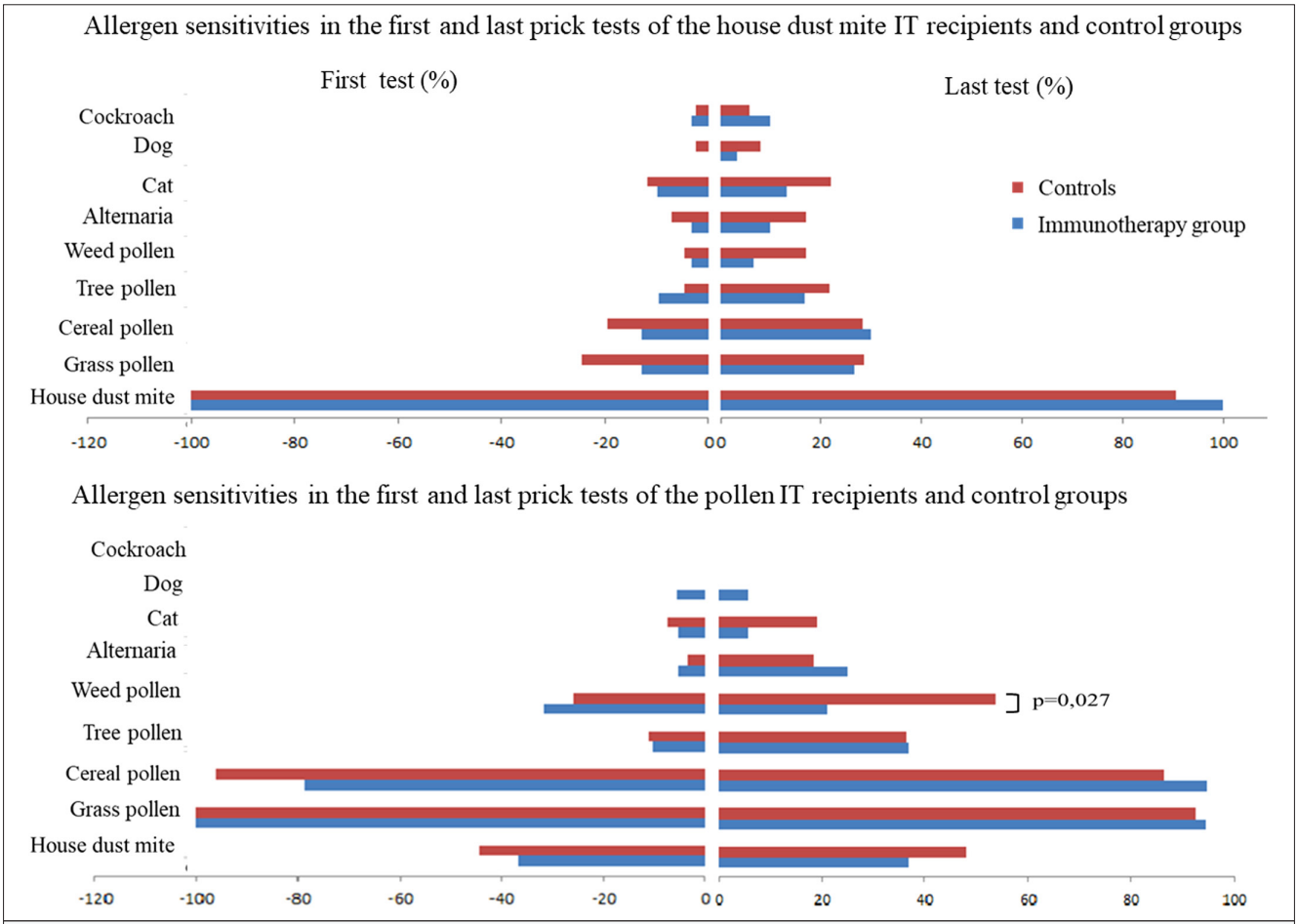

Figure 1. Changes in allergen sensitivities in Receiving Allergen IT and control groups.
The details of the data in the Figure 1 are shown in Table S1.
IT, immunotherapy.

group, and in the weed pollen sensitivity in the pollen immunotherapy control group.

The protective effects of house dust mite immunotherapy against pollen and mold sensitivity are controversial. In addition to studies showing that pollen sensitivity develops less in patients who received house dust mite immunotherapy compared to control, studies show that sensitivity develops at a similar or higher rate than in the control group.[4,8,11,13,14] A similar situation is also valid for the development of new sensitivity to mold spores in patients receiving HDM immunotherapy.[6,8,11,14] However, most of the studies statistically analyze these increases and decreases. In our study, while tree and weed pollen sensitivity increased significantly in control groups, it was observed that this increase was not significant in immunotherapy groups. We think that in patients receiving house dust mite immunotherapy, the protection against the development of new sensitivity to tree pollen compared to the control groups can be explained by the effect of allergen immunotherapy on the natural course of allergic sensitization, rather than by prevention of the development of sensitivity to allergens with similar structures.

In the study conducted by Karaman et al.[14], while none of the patients who received pollen immunotherapy developed new HDM sensitivity, it developed in 13% of the control group. In our study, HDM sensitivity did not change in patients who received pollen immunotherapy.

Inal et al.[8] reported that HDM immunotherapy containing aqueous and adsorbed extract reduced new allergen sensitivity by 3- and 4-fold, respectively. In the meta-analysis conducted by Kristiansen et al.[17] although there is evidence that allergen immunotherapy reduces the risk of new sensitization in the short term, this cannot be confirmed in the sensitivity analysis, and no change was found in the sensitivity risk in the short term (OR: 0.72; 95% CI: 0.24-2.18) and long term (OR: 0.47; 95% CI: 0.08-2.77). Similarly, in our study, it was found that allergen immunotherapy had no significant effect on the risk of new sensitization.

Allergic sensitivity occurs as a result of the interaction of many different factors. Some of these factors are genetic, exposure time to allergens, amount of allergens one is exposed to, air pollution, socioeconomic status, and diet.[18] However, data on the factors affecting new sensitization are limited. In our study, when the factors affecting the development of new sensitivity were examined, it was found that being diagnosed with asthma and having weed pollen sensitivity increased the risk of new sensitization.

Table 3. Comparison of Allergic Sensitization in the First and Last Skin Prick Tests of Patients Receiving Allergen IT and Control Groups

	IT Group			Control Group		
Sensitized Allergens	**First Test, *n* (%)**	**Last Test, *n* (%)**	***P*†**	**First Test, *n* (%)**	**Last Test, *n* (%)**	***P*†**
House Dust Mite IT Recipients and Control Group						
House dust mite	31 (100)	31 (100)	-	42 (100)	39 (90.5)	-
Grass pollen	4 (13.3)	8 (26.7)	.219	10 (24.4)	12 (29.3%)	.727
Cereal pollen	4 (13.3)	9 (30)	.125	8 (21.1)	11 (28.9%)	.375
Tree pollen	3 (10)	5 (16.7)	.500	2 (5.4)	8 (21.6%)	**.031**
Weed pollen	1 (3.3)	2 (6.7)	>.99	2 (4.9)	7 (17.1%)	.063
Alternaria	1 (3.3)	3 (10)	.500	3 (7.3)	7 (17.1%)	.219
Cat	3 (10.3)	4 (13.8)	>.99	5 (9.1)	10 (18.2)	.063
Dog	-	1 (4)	-	1 (2)	4 (7.8)	.250
Cockroach	1 (3.4)	3 (10.3)	.500	1 (2)	2 (4.1)	>.99
Pollen IT recipients and control group						
House dust mite	7 (36.8)	7 (36.8)	>.99	12 (44.4)	13 (48.1)	>.99
Grass pollen	18 (100)	17 (94.4)	-	27 (100)	25 (92.6)	-
Cereal pollen	15 (78.9)	18 (94.7)	.375	21 (95.5)	19 (86.4)	.500
Tree pollen	2 (10.5)	7 (36.8)	.180	3 (13.6)	8 (36.4)	.063
Weed pollen	6 (31.6)	4 (21.1)	.727	7 (26.9)	14 (53.8)	**.039**
Alternaria	1 (6.3)	4 (25)	.250	1 (3.7)	5 (18.5)	.125
Cat	1 (5.6)	1 (5.6)	>.99	2 (7.7)	5 (19.2)	.375
Dog	1 (5.9)	1 (5.9)	>.99	-	-	-
Cockroach	-	-	-	-	2 (11.1)	-

†McNemar test.
IT, immunotherapy.

The natural course of allergic sensitization is not yet fully understood. Sensitivity to HDM and pet allergens, which are among the respiratory allergens, usually precedes the development of sensitivity to fungal and pollen allergens.[19,20] As in the general population, many studies investigating the development of new sensitivity in patients receiving allergen immunotherapy in our country have also found that new sensitivity developed is especially against pollens.[8,11,13,14,16] In our study, similar to the literature, the most frequent new sensitivity developed was against pollen.

Our study has some limitations, namely, the retrospective nature of the study, the small number of patients, the evaluation of allergen sensitivity by the skin prick test alone, and the exclusion other factors that may affect sensitization.

CONCLUSION

Allergen immunotherapy is currently the only treatment method that can change the natural course of allergic diseases and has long-term effects on pathophysiology. The improving effect of allergen immunotherapy on clinical findings has been demonstrated in many meta-analyses, but its protective effect against new allergen sensitivity is controversial. In our study, it was determined that allergen immunotherapy protected against new sensitizations to tree and weed pollens compared to control groups, but its protective effect against new sensitization was not significant in multivariate analysis. Sensitivity to weed pollen and a diagnosis of asthma were found to be risk factors for the development of new sensitivity.

Table 4. Univariate and Multivariate Analyses of Factors Affecting New Sensitization

	Single Variable Model				Multivariate Model			
	OR	**95% CI**		*P*	**OR**	**95% CI**		*P*
Immunotherapy	0.724	0.3	1.7	.455				
Age	0.978	0.85	1.1	.749				
Gender	0.79	0.3	1.8	.584				
Asthma	3.806	1.2	11.9	**.021**	3.8	1.3	10.8	**.013**
Allergic rhinitis	0.933	0.3	2.8	.902				
Grass pollen sensitivity	0.546	0.1	2.9	.481				
Cereal pollen sensitivity	1.308	0.2	8.5	.779				
Tree pollen sensitivity	0.954	0.2	4.4	.952				
Weed pollen sensitivity	11.17	1.9	66.3	**.008**	8.1	1.5	42.4	**.013**
HDM sensitivity	1.319	0.3	5.4	.699				
Cat sensitivity	1.818	0.4	8.5	.448				

HDM, house dust mite; OR, odds ratio.

Ethical Committee Approval: Ethical committee approval was received from the Uludağ University School of Medicine Clinical Research Ethics Committee (2017/ 10-27).

Informed Consent: Patient consent was not obtained due to the retrospective design of the study.

Peer-review: Externally peer-reviewed.

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