



Does Allergen-Specific Immunotherapy Prevent New Sensitizations in Childhood Allergic Airway Diseases?

Allerjen Spesifik İmmünoterapi Allerjik Hava Yolu Hastalığı Olan Çocuklarda Yeni Duyarlanmaları Önler mi?

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ABSTRACT

Objective: Specific immunotherapy (SIT) is a well-established treatment method that is suggested to alter the natural course of the disease. Although the mechanisms remain unclear, recent studies have shown that allergen-specific immunotherapy may reduce the risk of new sensitizations. The aim of this study was to evaluate new sensitizations in children who underwent SIT for allergic airway diseases: allergic rhinitis, allergic asthma or both.

Materials and Methods: This retrospective observational study was conducted at Behçet Uz Children's Hospital, among children with an allergic airway disorder due to monosensitization. The SIT group consisted 67 patients who had been offered, and accepted, and thus underwent SIT regularly during four years while the control group consisted of 57 patients who had been offered but refused SIT, and thus had not undergone SIT and were treated with medications only. The allergens that were negative at the first skin prick test but positive at the second prick test were accepted as 'new sensitization'.

Results: The SIT group consisted of 67 (mean age \pm SD: 15.27 \pm 3.15; Male /Female: 42/25) while the control group included 57 (mean age \pm SD: 12.61 \pm 2.69; Male /Female: 35/22) monosensitized patients with allergic airway disorder. There was no significant difference between SIT group and controls considering age and gender, current airway disease and current responsible allergen ($p>0.05$). The rate of new allergen sensitization in the immunotherapy group was 26/67 (38.8%) and slightly higher than control group (14/57;

ÖZ

Amaç: Spesifik immünoterapi (SIT) allerjik hastalıkların tedavisinde yer alan ve hastalığın doğal gidişini değiştirme potansiyeli olan bir tedavi yöntemidir. Mekanizması tam olarak bilinmemekle birlikte, son yıllarda yeni allerjik duyarlanmaları önleyebileceği yönünde çalışmalar bildirilmektedir. Çalışmanın amacı, allerjik hava yolu hastalığı olan çocuk hastalarda, SIT sonrası yeni duyarlanma gelişimi arasındaki ilişkinin değerlendirilmesidir.

Gereç ve Yöntem: Bu retrospektif kesitsel araştırma, Dr. Behçet Uz Çocuk Hastanesinde allerjik rinit ve/veya astım nedeniyle izlenmekte olan monosensitize çocuk olgular ile planlandı. İzlemede, SIT önerilen ve kabul ederek uygulanmış olan olgular SIT grubunu (n:67), kabul etmeyerek medikal tedaviyle izlenmiş olan olgular ise kontrol grubunu (n:57) oluşturdu. Tanı sırasında deri testinde saptanmayan ve tedavi sonunda gelişmiş olan allerjik duyarlanmalar 'yeni duyarlanma' olarak kabul edildi.

Bulgular: SIT grubu (yaş ortalaması: 15.27 \pm 3.15; E/K: 42/25) ile kontrol grubu (yaş ortalaması: 12.61 \pm 2.69) yaş, cinsiyet ve allerjik hava yolu hastalığının dağılımı ve mevcut hava yolu allerjisi açısından benzerdi ($p>0.05$). İzlem süresi sonunda saptanan yeni duyarlanma oranı SIT grubunda (26/67)%38.8 olarak saptanırken, kontrol grubunda (14/57) %24.6 olarak tespit edildi. Bu fark istatistiksel olarak anlamlı değildi ($p:0.12$). Çalışma grubunda en sık gelişen yeni duyarlanmanın ot polenleri (12/40), hayvan tüyü(7/40) ve zeytin polenine (6/40) karşı olduğu görüldü. Yeni duyarlanma

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24.6%) but the difference was not significant, statistically ($p=0.12$). The most common allergens causing new sensitization were pollens of grass (12/40), animal dander (7/40) and olive tree (6/40). When newly sensitized patients were evaluated, the atopy incidence was significantly higher than patients with no new sensitizations (32/40 vs 8/40).

Conclusion: We suggest that SIT may not prevent new sensitizations in childhood allergic airway diseases in monosensitized patients. The most important risk factor in developing new sensitization is presence of atopic disease in the parents.

Key words: Childhood, asthma, allergic rhinitis, immunotherapy, new sensitizations

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gelişimi ile ilgili en önemli faktörün ailede atopi öyküsü olduğu saptandı.

Sonuç: SIT, allerjik hava yolu hastalığı olan monosensitize çocuklarda yeni duyarlanma gelişimini önlemiyor olabilir. Yeni duyarlanma saptanan olguların ise en önemli risk faktörü ailede atopi öyküsü olmasıdır.

Anahtar kelimeler: Çocukluk çağı, allerjik, astım, allerjik rinit, immünoterapi, yeni duyarlanma

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INTRODUCTION

It has been over than 100 years since allergen specific immunotherapy (SIT) was first described in 1911 (1). Then, in 1998, SIT was affirmed to have a clinical effect on allergic rhinitis and asthma by injections or local nasal or sublingual administration by the World Health Organization (2) and the European Academy of Allergology and Clinical Immunology (EAACI) (3). Today, it is a well-established treatment method in allergic diseases (2-4). Moreover, it is the only method suggested to alter the natural course of allergic disorders (2,5,6). The mechanism of SIT is mainly to switch the Th 2- response to the Th 1-type, by increased IFN γ and IL-2 production (7). Although the mechanisms remain unclear, recent studies have shown that allergen-specific immunotherapy may reduce the risk of new sensitizations (8-11). The aim of this study was to evaluate the new sensitizations in children who underwent subcutaneous immunotherapy (SCIT) for allergic airway diseases: allergic rhinitis, allergic asthma or both.

PATIENTS and METHODS

Study Group

The study group included 124 monosensitized patients with allergic airway diseases followed up at the Department of Allergy of our hospital, a tertiary care hospital for pediatric patients. The SIT group consisted 67 patients who had been offered, and accepted, and thus underwent SIT regularly during four years while the control group consisted of 57 patients who had been offered but refused SIT and thus had not undergone SIT and were treated with

medications only. The SIT group had concluded the SIT schedule within the last year, while the control group had been under follow up for the last 5 years at the time of the study. The data collection including age, gender, family history of atopy, eosinophil count, total Ig E level, skin prick test results and immunotherapy schedules was performed retrospectively after the patient had given informed consent. The patients who had started immunotherapy but given up at any time during treatment.

Skin Prick Tests

The patients were evaluated with skin prick tests twice by pediatric allergists; the first, to diagnose the current responsible allergen of the allergic disease, and the second, to diagnose the sensitizations at the end of the follow-up period. For each patient, the allergens that were negative at the first skin prick test but positive at the second prick test were accepted as a 'new sensitization'. The standardized allergen solutions of Allergopharma (Allergopharma Joachim Ganzer KG, Germany) and Stallergenes SA (Antony Cedex, France) were injected by the prick method to the forearm of the patients with a standardized polymethylacrylate needle separately for each allergen (Stallerpoint, Stallergenes SA, Antony Cedex, France). The positive and negative controls were performed with histamine and 0.9% NaCl solution, respectively. The results were evaluated by a milimetric ruler 20 minutes later and considered positive if the mean wheal diameter was 3 mm compared with the negative control. The patients were allowed to stop antihistamines and systemic corticosteroids before prick testing. The results were evaluated according to the EAACI position paper (13).

Specific Immunotherapy

The patients sensitized to a single allergen and believed to have an allergic airway disorder due to this sensitization with clinical history and physical examination were offered SIT after the informed consent process. Allergen extracts of Allergopharma (Allergopharma Joachim Ganzer KG, Germany) and Stallergenes SA (Antony Cedex, France) conforming to the diagnosed allergen by skin prick testing were administered subcutaneously in the clinic. The immunotherapy schedule conducted included an induction phase (weekly injection for 12 weeks) starting with 0.2-0.8 ml and a maintenance phase (every 3-4 weeks for 3-5 years) (14). The patients were monitored for an hour following administration in order to recognize short-term complications.

Statistical Analysis

The data were analyzed using a statistical software package (SPSS version 18.0). The Chi-square test or Fisher’s exact test, where appropriate, was used to compare the percentages in the different groups. Factors were considered statistically significant if the *p* value was <0.05.

RESULTS

The SIT group consisted of 67 (age range: 9-22 years; mean age ±SD: 15.27±3.15; Male /Female: 42/25) while the control group included 57 (age range: 8-19 years; mean age ± SD: 12,61 ± 2,69; Male /Female: 35/22) monosensitized patients with allergic airway disorder. There was no significant difference between the SIT group and controls regarding the age and gender (*p*>0.05). The frequency

of allergic rhinitis, allergic asthma and both in the study group were 20.1%, 44.3% and 34.4%, respectively. The most frequent allergen of both study group was house dust mite (75%). Although, one of the most common allergen in Mediterranean region is pollens of the olive tree, its frequency was only 6.5% in our study group as it is usually observed as polisensitization in our population. Table I shows the demographic data and the distribution of the diagnoses and current allergens of the patients. There was no statistical difference between the groups regarding the diagnosis and current allergens, either (*p*>0.05).

We evaluated the sensitizations of the study group at the end of the follow-up period. The mean follow up period of patients in immunotherapy group was 5.21±0.94 years, while it was 4.95±0.99 years in the control group (*p*>0.05). The rate of new allergen sensitization in the immunotherapy group was 26/67 (38.8%) and slightly higher than the control group (14/57; 24.6%) but the difference was not significant, statistically (*p*=0.12) (Table II). A total of 40 patients had acquired new sensitizations and the most common allergens causing new sensitization were pollens of grass (12/40), animal dander (7/40) and olive tree (6/40). The distribution of new sensitizations in the study group is also presented on Table II. Figure 1 presents the patients with new sensitizations in the SIT group (26/67) and control group (14/57).

When newly sensitized patients were evaluated, the atopy incidence was significantly higher than patients with no new sensitizations. Eosinophilia and elevated Ig E levels (at the beginning and during follow-up) were similar between the two groups. The type of current allergen was not associated with developing a new sensitization, either. The risk factors that influence developing a new sensitization are presented on Table III.

Table I. The properties of the study group

	SIT Group (n=67)	Control Group (n=57)	<i>p</i>
Age*	15.27 ± 3.15	12.61 ± 2.69	0.19
Gender (M/F)	42/25	35/22	0.47
Current airway disease			
Allergic rhinitis (n,%)	11 (16.4)	14 (24.6)	0.45
Asthma (n,%)	33 (49.2)	23 (40.3)	
Both (n,%)	23 (34.3)	20 (35)	
Responsible allergen			
House-dust mite(n,%)	47 (69.1)	28 (50)	0.39
Grass mix (n,%)	14 (27)	22 (39)	
Tree mix (n,%)	4 (6)	6 (10)	
Others (n,%)	2 (3)	1 (1.7)	

SIT: Specific immunotherapy, *mean ±SD.

Table II. The new sensitizations of the immunotherapy group and control group at the end of the follow-up period

	SIT Group	Control group	<i>p</i>
New sensitizations	26/67	14/57	0.12
House-dust mite	0	2	
Tree mix	3	1	
Olive tree	4	2	
Grass mix	7	5	
Animal dander	5	2	
Alternaria spp.	3	1	
Polisensitization	4	1	

Table III. The risk factors associated with getting new sensitizations of the study group at the end of the follow-up period (n=40)

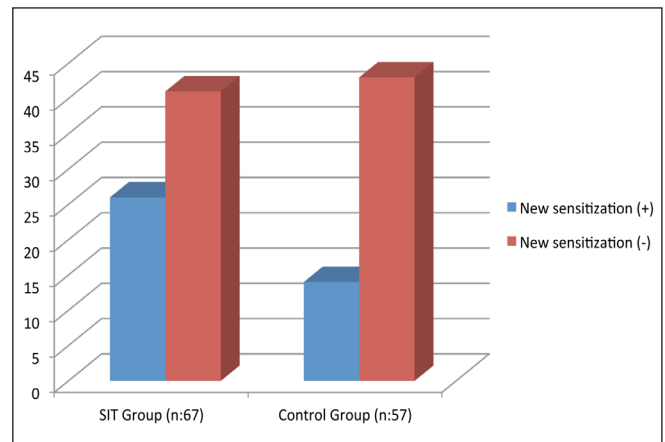
	Yes	No	p
Atopic disease in parents	32	8	0.03
Eosinophilia			
At the beginning	18	22	0.12
During follow-up	16	24	0.08
Elevated serum Ig E			
At the beginning	17	23	0.09
During follow-up	14	26	0.06
Responsible allergen			0.13
House-dust mite		22	
Grass mix		12	
Tree mix		2	
Others		4	

At the end of the immunotherapy schedule, the patients were evaluated regarding the necessity of medication. The frequency of daily medication or bronchodilator requirement was significantly lower in the immunotherapy group than control group.

DISCUSSION

The current study has been conducted among children and adolescents with allergic airway disorders due to single allergen and our results indicate that SIT may not prevent new sensitizations. Only the patients with a history of atopy in the parents were prone to developing new sensitizations.

Although the efficacy and long term effect of SIT in reducing symptoms, medication, and bronchial reactivity have been well established (1-3, 15,16), there are conflicting reports on the preventive effect of SIT against sensitization to different inhalant allergens. The preventive effect of SIT on the onset of new allergen sensitizations was reported in many reviews, position papers and the consensus conference but the findings of only a few observational studies performed on children and adults were evaluated in these reports. Des Roches et al. (9) were the first to report that SIT prevents the development of new allergen sensitizations, especially in mono-sensitized patients. Pajno et al. (10) and Purello-D'Ambrosio et al. (11) supported these findings in both adults and children. Inal et al. also reported that SIT has the potential to prevent the onset of new sensitizations in children with rhinitis and/or asthma monosensitized to house dust mite in their report from our country (12). In contrast, Asero (17) reported that SIT did not prevent the development of new allergen sensitizations

**Figure 1.** Patients with new sensitizations in the SIT group (26/67) and control group (14/57).

to two novel airborne allergens, birch and ragweed pollen, in adult monosensitized patients. In this report, the authors suggested that the key determinant in the development of a new sensitization is the genetic predisposition of an individual towards developing a type 2 helper T cell (Th_2) response to specific allergens. It is also reported that SIT did not prevent the onset of new sensitizations in asthmatic children monosensitized to house dust mite and they suggested that individual or regional variations may be seen as a result of SIT administration due to the fact that regulatory T cells are under genetic control (18). Our results support this idea as the rate of new allergen sensitizations in the immunotherapy group was 38.8% and slightly higher than the control group (24.6%) but the difference was not significant, statistically ($p=0.12$). Moreover, according to our results, the individuals who developed new sensitizations were the patients with a family history of atopy. Eosinophilia and elevated Ig E levels (either at the beginning or during follow up) and the type of current allergen were not associated with developing new sensitizations, either. Thus, we suggest that the genetic predisposition is the most prominent factor in developing new sensitizations. A recent review has already reported that the available evidence supporting the notion that SIT is effective in reducing the development of new allergen sensitizations in allergic mono- or polysensitized patients is low in strength (19).

When we evaluated the new sensitizations (40/124), the most common allergens were pollens of grass (12/40), animal dander (7/40), pollens of olive (6/40), and *Alternaria* spp.(4/40), respectively (Table II). House dust allergy was only detected in 2 patients in the control group.

At the end of the immunotherapy schedule, the frequency of daily need for medication or bronchodilators was significantly lower in the SIT group than in the control group. The clinical success of SIT is known to depend on two main immunological mechanisms: (a) immune deviation, with a shift in the balance of Th1/Th2 responses, possibly mediated by IL-12, and (b) immune tolerance, induced by the immunosuppressive cytokine IL-1(20). However, the mechanisms that explain the lower rate of new sensitizations in children administered SIT are unclear. It has been reported that SIT has effects of decreasing the production of IL-4 and IL-5(21-22) and increasing the production of interferon- γ (22). Tolerance to the allergen and the development of a specific anergy against an allergen are important immunological changes mediated by peripheral T cells and IL-10 associated with SIT. It was suggested that these actions may modify or at least delay the natural course of respiratory allergic diseases.

In conclusion, we suggest that SIT is effective in reducing symptoms and the need for medical drugs and bronchodilators in childhood allergic airway diseases in monosensitized patients but it may not prevent new sensitizations. Due to the retrospective design, the current study lacks randomization and placebo control but we suggest that the study group was comparable, in terms of age, gender and homogenous distribution of the diseases. Prospective, double blinded and placebo-controlled studies may elucidate the mechanisms of the new sensitizations in patients with allergic disorders.

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