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The Prevention of New Sensitizations by Specific Immunotherapy: A Long-Term Observational Case Control Study

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Abstract

Some studies have indicated that allergen specific immunotherapy (SIT) may prevent new sensitizations to other inhalant allergens; however, there are only a few longitudinal observations that have explored this event. The aim of this study was to perform a 20 year post-SIT observational analysis to assess the appearance of new sensitizations in SIT patients compared with non-SIT patients.

Material and methods: In total, 1,420 atopic bronchial asthma or/and allergic rhinitis patients (701 women and 719 men) with a mean age of 21.2 ± 9.2 years (at the time when the SIT concluded) were evaluated twenty years after their immunotherapies. New sensitization cases were determined by evaluating skin prick tests, allergen specific IgE and the clinical symptoms that were evaluated prior to and 5, 10, 15 and 20 years after SIT. The SIT group was compared with a control group consisting of 1,254 allergic patients who had never received SIT and had only received symptomatic treatments.

Results: After 20 years, 301 (21.2%) patients in the 4-5 year SIT group showed a new sensitization compared with 509 (40.6%) control group patients (p=0.004). In monosensitized SIT patients (n=886), there were significantly more new sensitizations in the control group (n=624): 69 (7.8%) vs. 195 (31.3%) (p=0.001). The odds ratio of the post-SIT new sensitization incidence in the whole group was 0.76 (95% CI: 0.55-0.92), whereas it was 1.32 in the control group (95% CI: 1.22-1.45).

Conclusion: The obtained data suggests a preventive role for specific immunotherapy in new sensitizations, especially in monosensitized patients.

Keywords: Sensitization; Immunotherapy; Allergy; Alergic rhinitis; IgE

Background

Allergen-specific immunotherapy (SIT) involves the administration of allergen extracts to achieve clinical tolerance to the allergens that cause symptoms in patients with allergic conditions. SIT has been shown to be effective in patients with allergic disease [1]. Existing data suggest that the effects of SIT take longer to achieve, but once established, SIT provides long-lasting allergic symptom relief, whereas the benefits of drugs only last as long as they are taken. Some studies suggest that SIT may also modify the course of allergic diseases by reducing the risk of developing new allergic sensitizations and by also inhibiting the development of clinical asthma in patients treated for allergic rhinitis. This last observation is controversial, however [2,3]. Some studies have confirmed that SIT in monosensitized patients could have an effect on preventing sensitizations to other airborne allergens [4].

We aimed to investigate the development of new sensitizations in 1,420 patients with rhinitis and/or asthma that were mono or polysensitized to pollen allergens, Alternaria or house dust mites 4-5 years post-SIT. These patients were compared with a parallel group that was only treated with medication. Additionally, these subjects were monitored for new sensitizations by the skin prick test, allergen specific IgE and the clinical symptoms that occurred during 20 years after SIT was completed as compared with the control group.

Materials and Methods

Patients

For this prospective study, 1,586 patients qualified. The inclusion criteria were: allergy to house dust mites or pollen, allergic rhinitis and/or asthma and the completion of at least a 4-5 year SIT course to these allergens. Some patients dropped out during twenty-year prospective observation (about 10%); thus, 1,420 patients (701 women and 719 men) were analyzed for the study. The mean age of the experimental group was 21.2 ± 9.2 years at the start of the prospective observation study (after they completed SIT). They had a mean age of 45.1 ± 8.2 at the end of the study. All patients signed an informed consent to participate in the study.

The patients were divided into the following subgroups:

A. Perennial allergic rhinitis (PAR) and/or bronchial asthma patients who received a four-five-year perennial immunotherapy course to treat house dust mite allergies using the Novo-Helisen Depot (composition: 708 *D. farinae* -50%, 725-*D. pteronyssinus* 50%; Allergopharma, Reinbek, Germany). These patients were mono-sensitized with *D. pteronyssinus* and *D. farinae* or were SPT poly-sensitized, but these patients only had house dust mite allergy symptoms.

B. Patients with seasonal allergic rhinitis (SAR) and bronchial

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asthma who received a four-five-year seasonal immunotherapy course to treat grass pollen allergies using Allergovit (composition: 015 grass/cereals-100%; Allergopharma, Reinbek, Germany). These patients were mono-sensitized to grass and cereals or were SPT poly-sensitized, but these patients only had grass allergy symptoms.

C. SAR and/or bronchial asthma patients who received a four-five-year seasonal immunotherapy course to treat allergic rhinitis to trees using Allergovit (composition: 108 Birch -35%, 115 Alder-30%, 129 Hazel-35%, Allergopharma, Reinbek, Germany). These patients were mono-sensitized to trees or were SPT poly-sensitized, but these patients only had tree allergy symptoms.

D. SAR and/or bronchial asthma patients who received a four-five-year perennial immunotherapy course to treat allergic rhinitis to Alternaria with the Novo-Helisen Depot (composition: 400-Alternaria-100%; Allergopharma, Reinbek, Germany). These patients were mono-sensitized to Alternaria or were SPT poly-sensitized, but these patients only had Alternaria allergy symptoms.

E. A control group of patients with house dust mite allergies, PAR and/or bronchial asthma that only received symptomatic treatments and not SIT.

F. A control group of patients with pollen allergies, SAR and/or bronchial asthma who only received symptomatic treatments and not SIT.

All detailed information is included in Table 1.

The control group (n=1254, 668 women and 586 men) inclusion criteria were: a comparable house dust mite or pollen allergy duration to the study group at the start of the prospective observational period, only 4-5 years of symptomatic therapy without SIT (lack of patient consent for such treatment) at the same time when immunotherapy was administered to the study group. The mean age of the control group was 19.7 ± 6.3 years at the start of the observational period. More detailed data are shown in Table 1.

Protocol

All patients were subjected to the following procedures:

1. A retrospective diagnostic procedure analysis (allergy history, skin prick test and specific IgE) and a cumulative Allergovit or Novo-Helisen Depot dose assessment of the total SIT period (which were performed between 1984 and 1993).

The mean post-SIT prospective observation time was 20.9 ± 2.7 years. The following procedures were performed between 1993 and 2013:

2. New sensitization monitoring was provides every 12-24 months during outpatient clinic visits. Skin prick tests, allergen specific IgE assessments, allergy symptom medical history assessments (rhonoconjunctivitis symptoms, bronchial asthma episode, skin manifestation) and overall examinations were conducted. However, only 5 year interval data were used in the final analysis.

All patients were diagnosed with asthma based on the ECRHS II questionnaire [5], physical examinations and with positive reversibility test (Lungtest 1000, MES and Krakow, Poland). For a positive result, a ≥ 12% increase in the forced expiratory volume in one second (FEV1) or a 200 ml increase was necessary, which is in accordance with the ATS and ERS criteria [6]. Additionally, the patients stopped using short-acting beta 2 agonists for 8 hours, ipratropium and theophylline derivatives for 24 hours and long-acting beta 2 agonists for 48 hours or tiotropium for 72 hours prior to testing. Current smokers refrained from smoking for 1 hour before testing. Testing was delayed for 4 weeks in respiratory tract infection cases. Asthma severity and disease control were determined based on patient history and spirometry and assessed according to the Global Initiative for Asthma (GINA) criteria [7].

A new sensitization was defined as a new positive skin prick test result and a positive IgE concentration (a minimum class I allergy of >0.35 U/l) and clinical symptoms that appeared after SIT termination. The following allergens (Alleropharma, Reinbek, Germany) were tested: *D. pteronyssinus, D. farinae,* hazel, birch, alder, grass pollen, *Alternaria, Cladosporium*, cat, dog, and *Artemisia.* These extracts were used in all patients at the start of study and during follow up.

The study was approved by the District Medical Board of Silesia Bioethical Committee, Katowice, Poland (NN-2468/90).

Statistical analysis

The data that met normal distribution criteria, such as age and

Characteristics	Group A	Group E	P	Group B	Group C	Group D	Group F	P
Number (%)	508 (35.8)	429 (34.2)	NS	370	345	197*	-	<0.05*
				912 (64.2) (B+C+D)			825 (65.8)	NS
Mean age at the end of the study	40.5 ± 5.3	42.7 ± 4.2	NS	41.7 ± 6.5			42.5 ± 5.2	NS
Female (%)	248 (17.5)	233 (18.7)	NS	453 (31.9)			435 (34.7)	NS
Monosensitized (%)	317 (26.7)	298	NS	489			385	-
Total IgE (U/l) ± SD	145 ± 87	195 ± 33	NS	206 ± 76			231 ± 54	NS
Mean duration of the disease (± SD) at the start of treatment (SIT)	4.9 ± 3.1	-	-	3.3 ± 2.8			-	-
Mean duration of SIT (± SD) in years	5.2 ± 2.2	-	-	3.8±1.4			-	
Mean cumulative SIT dose in TU (± SD)	36667* ± 8222	-	-	20130* ± 2341	16310* ± 3850	35920* ± 6292	-	-

NS: Not Significant; TU: Therapeutic Units,

* -the cumulative doses are not comparable due to different types of SIT (natured HDM-mixture and chemically modified allergens)

Table 1: The analyzed patient characteristics at the beginning of the observational period.

	Total	Mites	Grass	Trees	Artemisia	Cat	Dog	Alternaria	other
SIT group n	301	37	58	50	52	32	7	32	20
mean specific IgE U/l ± SD	-	18 ± 11	27 ± 13	22 ± 12	16 ± 9	32 ± 10	8 ± 2	9 ± 4	-
Control group n	509	55	81	72	76	55	17	83	77
mean specific IgE U/l ± SD	-	24 ± 5	32 ± 18	26 ± 11	14 ± 11	39 ± 21	11 ± 5	12 ± 7	-

Table 2: New sensitization profiles that developed in the study groups with concentration of specific IgE.

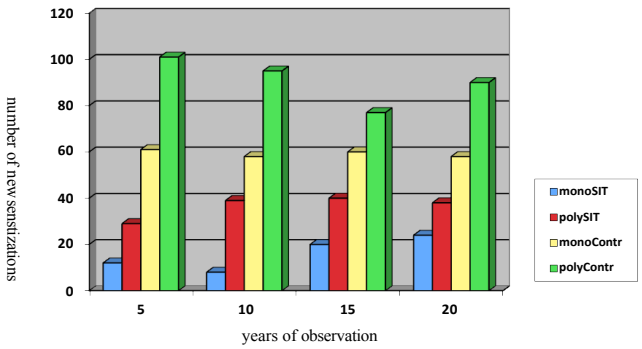

Figure 1: Distribution of new sensitization during twenty years monitoring.

disease duration, were analyzed using Student's t-test, for independent variables. Other non-parametric data were compared with the chi-square test. The summary odds ratio, 95% confidence intervals and standard errors using random-effects models were also computed.

Results

At the end of the 20 year post-SIT observation period, 301 (21.2%) post-SIT patient showed new sensitizations compared with 509 (40.6%) control group patients (p=0.004). The detailed data are presented in Table 2.

In patient subgroup that was monosensitized before SIT, new sensitizations were significantly lower than in the polysensitized group: 64 (7.9%) vs. 237 (38.6%) (p=0.001). In the control group, the same differences between the mono- and polysensitized subjects were observed: 146 (30.2%) vs. 363 (63.5%). The most frequent new sensitization type in the post-SIT group at the end of the study was grass pollen (which was independent of the immunotherapy type). Moreover, grass pollen sensitizations were observed in 58 post-SIT subjects and in 81 control group. The detailed data are shown in Table 2. Overall, in the SIT group, 189 patients developed at least one sensitization. However, it was predominant in the monosensitized patients compared with the polysensitized patients (53 (82.8%) vs. 165 (69.6%) (p=0.03) in the SIT group and 113 (77.4%) vs. 218 (60.1%) (p=0.01) in the control group, respectively).

The new sensitization dynamics that occurred during the 20 year observation period are shown in Figure 1.

The new sensitization allergen profile was independent of the allergy and SIT types.

However, there was a positive correlation between the incidence of new sensitizations and the coexistence of two or three atopic disease types (asthma, allergic rhinitis and atopic dermatitis) in one patient (p=0.02). In study patients the total mean IgE was not statistically changed during all observations however it was increased in control group from 196 ± 45 U/l at the start to 278 ± 59 U/l at the end. The high total serum IgE concentrations also correlated with a greater tendency for new sensitizations to occur: odds ratio 2.56 (95% CI: 2.12-2.76) if total IgE>185 U/l.

Discussion

The induction of new allergies throughout life is an interesting phenomenon. There are studies that suggest that the predisposition to respiratory allergies is both allergen-specific and life-long lasting in each individual patient. In other words, subjects prone to becoming allergic to a certain allergen will not develop any allergy until the "appropriate" allergen is encountered [4,5].

Allergen-specific immunotherapy has been used widely for many years. The efficacy and long-term effect of SIT in reducing symptoms, medication, and bronchial reactivity has been well established. Some studies have focused on the prevention of new allergies after SIT administration [1]; however, the data are differential. Most of results suggest a positive role of SIT in reducing new allergy instances [4,8-10]. Unfortunately, many observations are still too short and evaluate relatively small populations. On the other hand, some studies suggest that SIT therapies are not effective in the prevention of new sensitizations [11]. One study reported that SIT did not exert any preventive effect against de novo airborne allergen sensitization in mono-sensitized adult patients. In that study, the author suggested that genetic predisposition of an individual towards developing a type 2 helper T-cell response to specific allergens is a key determinant in the development of new sensitizations [11].

The positive effects of SIT in mono-sensitized children with rhinitis and asthma are well documented [12-17]; however, there is not enough information about patients who are poly-sensitized after SIT. Our data reveal that there are also benefits from SIT in the reduction of new allergies; however, there was no such significance observed in the mono-sensitized patients. It is important that the same effect of SIT in the prevention of new sensitizations is also observed in children who have been better documented.

The mechanisms that explain the lower new sensitization rate in the SIT patients is unclear. It has been reported that SIT has a regulatory effect on the balance between Th1 and Th2 cells and has been shown to decrease the production of interleukin (Il) 4 and 5, increase the production of interferon gamma, and decrease the number of inflammatory cells in target organs. The induction of peripheral T-cell tolerance plays a crucial role in SIT and is initiated by the action of Il-10 and tumor growth factor beta, which are increasingly produced by antigen specific regulatory cells. Tolerance to allergens and the development of a state of specific energy in peripheral T cells by Il-10 are important immunological changes associated with SIT [18-20]. It was suggested that these actions might modify or at least delay the natural course of respiratory allergy diseases. Some author suggest that the SIT-related modifications of the peripheral and mucosal Th2 responses to allergens in favor of Th1 responses may significantly contribute to the prevention of new sensitization development in patients after specific immunotherapy courses.

Our results show that reducing new sensitizations is not dependent

upon the initial allergy types and from the time SIT was administered. Some longitudinal studies, however, have reported an increase in the sensitization rate as children grow into adults. One study conducted in children concluded that the evolution form mono- to poly-sensitization was age related. In another study, the same authors reported that the poly-sensitization development rate was 43.4% in previously mono-sensitized children 2 to 10 years after their first diagnosis.

Our data shows similar results to other studies; however, a 20 year observational study is unique.

A limitation of the study is that it was not a randomized and double blind placebo controlled trial but the study start 20 years ago. However the aim was primarily to explore whether SIT had the potential to reduce new sensitization development by using an objective parameter.

In conclusion, we suggest that SIT has a preventive role in new airborne allergies in patients who were previously mono-sensitized, and less so in poly-sensitized patients. Further investigation is required to clarify the immunologic mechanisms by which SIT reduces the development of new sensitizations.

References

1. Passalacqua G, Canonica GW (2011) Specific immunotherapy in asthma: efficacy and safety. Clin Exp Allergy 41: 1247-1255.
2. Cappella A, Durham SR (2012) Allergen immunotherapy for allergic respiratory diseases. Hum Vaccin Immunother 8: 1499-1512.
3. Petalas K, Durham SR (2013) Allergen immunotherapy for allergic rhinitis. Rhinology 51: 99-110.
4. Inal A, Altintas DU, Yilmaz M, Karakoc GB, Kendirli SG, et al. (2007) Prevention of new sensitizations by specific immunotherapy in children with rhinitis and/or asthma monosensitized to house dust mite. J Investig Allergol Clin Immunol 17: 85-91.
5. Janson C, Anto J, Burney P, Chinn S, de Marco R, et al. (2001) The European Community Respiratory Health Survey: what are the main results so far? European Community Respiratory Health Survey II. Eur Respir J 18: 598-611.
6. Brusasco V, Crapo R, Viegi G; American Thoracic Society; European Respiratory Society (2005) Coming together: the ATS/ERS consensus on clinical pulmonary function testing. Eur Respir J 26: 1-2.
7. Gina report (2008) Global Initiative for asthma. Global strategy for Asthma Management and Prevention.
8. Asero R (2004) Analysis of new respiratory allergies in patients monosensitized to airborne allergens in the area north of Milan. J Investig Allergol Clin Immunol 14: 208-213.
9. Yang X (2001) Does allergen immunotherapy alter the natural course of allergic disorders? Drugs 61: 365-374.
10. Jacobsen L, Valovirta E (2007) How strong is the evidence that immunotherapy in children prevents the progression of allergy and asthma? Curr Opin Allergy Clin Immunol 7: 556-560.
11. Asero R (2004) Injection immunotherapy with different airborne allergens did not prevent de novo sensitization to ragweed and birch pollen north of Milan. Int Arch Allergy Immunol 133: 49-54.
12. Silvestri M, Oddera S, Rossi GA, Crimi P (1996) Sensitization to airborne allergens in children with respiratory symptoms. Ann Allergy Asthma Immunol 76: 239-244.
13. Barbee RA, Kaltenborn W, Lebowitz MD, Burrows B (1987) Longitudinal changes in allergen skin test reactivity in a community population sample. J Allergy Clin Immunol 79: 16-24.
14. Purello-D'Ambrosio F, Gangemi S, Merendino RA, Isola S, Puccinelli P, et al. (2001) Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. Clin Exp Allergy 31: 1295-1302.
15. Eng PA, Borer-Reinhold M, Heijnen IA, Gnehm HP (2006) Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. Allergy 61: 198-201.
16. Pajno GB, Barberio G, De Luca F, Morabito L, Parmiani S (2001) Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. Clin Exp Allergy 31: 1392-1397.
17. Des Roches A, Paradis L, Menardo JL, Bouges S, Daurés JP, et al. (1997) Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. J Allergy Clin Immunol 99: 450-453.
18. Durham SR, Till SJ (1998) Immunologic changes associated with allergen immunotherapy. J Allergy Clin Immunol 102: 157-164.
19. Secrist H, Chelen CJ, Wen Y, Marshall JD, Umetsu DT (1993) Allergen immunotherapy decreases interleukin 4 production in CD4+ T cells from allergic individuals. J Exp Med 178: 2123-2130.
20. Akdis CA, Blaser K (1999) Immunologic mechanisms of specific immunotherapy. Allergy 54: 31-32.