ORIGINAL ARTICLE

Prevention of New Sensitizations by Specific Immunotherapy in Children With Rhinitis and/or Asthma Monosensitized to House Dust Mite

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Abstract

Background: Previous studies have suggested that single-allergen–specific immunotherapy (SIT) may prevent sensitization to other airborne allergens in monosensitized children. We aimed to assess the prevention of new sensitizations in monosensitized children treated with single-allergen SIT injections in comparison with monosensitized patients given appropriate pharmacologic treatment for their disease.

Methods: A total of 147 children with rhinitis and/or asthma monosensitized to house dust mite were studied; 45 patients underwent SIT with adsorbed extracts and 40 patients underwent SIT with aqueous extracts for 5 years. The control group was comprised of 62 patients given only pharmacologic treatment for at least 5 years. Skin prick tests, medication scores for rhinitis and asthma, and atopy scores according to skin prick tests were evaluated at the beginning and after 5 years of treatment.

Results: All groups were comparable in terms of age, sex, and disease characteristics. At the end of 5 years, 64 out of 85 (75.3%) in the SIT group showed no new sensitization, compared to 29 out of 62 children (46.7%) in the control group ($P = .002$). There were no differences between the SIT subgroups with regard to onset of new sensitization ($P = .605$). The patients developing new sensitizations had higher atopy scores ($P = .002$) and medication scores for both rhinitis ($P = .008$) and asthma ($P = .013$) in comparison to patients not developing new sensitizations after 5 years of SIT.

Conclusion: According to our data, SIT has the potential to prevent the onset of new sensitizations in children with rhinitis and/or asthma monosensitized to house dust mite.

Key words: Asthma. House dust mite. Immunotherapy. New sensitization. Rhinitis.

Resumen

Antecedentes: Estudios previos han sugerido que la inmunoterapia específica (ITE) con un único alérgeno puede prevenir la sensibilización a otros aeroalérgenos en niños monosensibilizados. Nuestro objetivo fue valorar la prevención de nuevas sensibilizaciones en niños monosensibilizados y tratados con inyecciones de ITE de un sólo alérgeno comparado con pacientes monosensibilizados con un tratamiento farmacológico apropiado para la enfermedad.

Métodos: Estudiamos a un total de 147 niños con rinitis o asma, monosensibilizados al ácaro del polvo doméstico; 45 pacientes se sometieron a ITE con extractos adsorbidos y 40 pacientes a ITE con extractos acuosos durante 5 años. El grupo control estaba integrado por 62 pacientes a quienes sólo se administró tratamiento farmacológico durante cinco años como mínimo. Al inicio del tratamiento y pasados cinco años, se realizaron evaluaciones de las pruebas cutáneas, de los resultados de los medicamentos para la rinitis y para el asma, e índices de atopia basados en las pruebas cutáneas.

Resultados: Todos los grupos eran comparables en cuanto a edad, sexo y características de la enfermedad. Transcurridos los cinco años, 64 de los 85 pacientes (75,3%) del grupo ITE no presentaban nuevas sensibilizaciones, frente a 29 de los 62 niños (46,7%) del grupo control ($P = 0,002$). No hubo diferencias entre los subgrupos del tratamiento ITE en cuanto a la aparición de nuevas sensibilizaciones

(*P* = 0,605). Los resultados de atopia (*P* = .0,002) y de medicamentos para la rinitis (*P* = 0,008) y el asma (*P* = 0,013) en los pacientes que desarrollaron nuevas sensibilizaciones fueron más elevados que los de los pacientes que no presentaron nuevas sensibilizaciones tras cinco años de ITE.

Conclusión: Según nuestros datos, la ITE puede potencialmente prevenir la aparición de nuevas sensibilizaciones en niños con rinitis o asma sensibilizados únicamente al ácaro del polvo doméstico.

Palabras clave: Asma. Ácaro del polvo doméstico. Inmunoterapia. Nueva sensibilización. Rinitis.

Introduction

Specific immunotherapy (SIT) was first introduced in 1911 [1]. In 1998, the World Health Organization [2] and the European Academy of Allergology and Clinical Immunology (EAACI) [3] affirmed the clinical effectiveness of SIT by injections or local nasal or sublingual administration in the management of allergic rhinitis and asthma when standardized extracts are used in adequate amounts. A meta-analysis including 54 clinical trials and assessing the efficacy of SIT in asthma led to the conclusion that SIT significantly reduces asthma symptoms, medication, and worsening of asthma [4]. SIT has also proven able to reduce specific bronchial reactivity and prevent the development of asthma in patients with allergic rhinitis [5-13]. Whether SIT in monosensitized patients could have an effect of preventing sensitization to other airborne allergens has also been investigated [14-16], and it was recently demonstrated that the reduction of onset of new sensitization after discontinuation of preseasonal grass pollen immunotherapy was sustained 12-years later in a prospective controlled follow-up study [17].

We aimed to investigate the development of new sensitizations in 147 children with rhinitis and/or asthma who were monosensitized to house dust mite. One group of children were treated with SIT injections for 5 years. They were compared to a parallel group treated with medication only. We recorded the results of skin prick tests and medication use for rhinitis and asthma.

Methods

Patients and Study Design

The study was planned as a parallel group open study including patients suffering from allergic rhinitis and/or asthma who were monosensitized to house dust mite. The patients were followed from 1995 to 2005 in our department. Inclusion criteria were as follows: a) age between 6 and16 years; b) a clinical history of allergic rhinitis and/or mild-to-moderate asthma as defined by the Global Initiative for Asthma (GINA) report [18], with symptoms lasting at least 1 year; c) monosensitization to house dust mite (*Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae*); d) a positive finding of specific immunoglobulin (Ig) E to *D pteronyssinus* and/or *D farinae* (Pharmacia CAP system, Pharmacia Diagnostics AB, Uppsala, Sweden) and/or a positive skin prick test to *D pteronyssinus* and/or *D farinae* (Allergopharma, Reinbeck, Germany); e) complete follow-up in our department for at least 5 years.

Eighty-five patients underwent SIT and 62 were treated only with medication. The SIT group was further subdivided into 2 subgroups of patients who underwent SIT with adsorbed extracts (SIT-ad) and patients who underwent SIT with aqueous extracts (SIT-aq). Different SIT regimens were used because aqueous extracts were used more commonly than adsorbed extracts in our clinic at the beginning of the study period and in the following years, the patients on that SIT regimen prefered to continue with the same extract.

SIT was recommended to all patients after diagnosis, but patients who did not accept SIT (mainly because of its cost, inconvenience, or travel difficulties) were treated with medication only and included as a control group.

Skin Prick Tests

Skin prick tests were performed on the volar surface of the forarm according to EAACI recommendations [19] at the beginning and end of SIT. We used a standard panel of respiratory allergens including mites (*D pteronyssinus* and *D farinae*), grass mix, tree mix, mold mix, *Alternaria* species, *Cladosporium* species, eucalyptus pollen, olive pollen, cat and dog dander and certain food allergens (milk, egg, cocoa, wheat, and peanut) (Allergopharma). Histamine hydrogen chloride 10 mg/mL was used as the positive control and physiologic saline as the negative one. A mean wheal diameter greater than 3 mm in diameter was considered positive if no dermographism and/or positivity of the negative control was recorded. All patients were instructed not to take medications during the 2 weeks before the test.

SIT

Biologically standardized depot preparations of mite mix (*D pteronyssinus* and *D farinae*) were used for 5 years in the SIT-ad group. The preparations were aluminium hydroxide or calcium phosphate adsorbed extracts (Alutard SQ, ALK Laboratories, Hoersholm, Denmark; NovoHelisen Depot, Allergopharma; or APSI Retard, Stallergenes, Antony, France). The ALK preparations were supplied as 4 biologically standardized allergen concentrations of 100, 1000, 10 000, and 100 000 standard quality units per milliliter; the Stallergenes preparations were supplied as having indices of reactivity (IR) of 0.01, 0.1, and 1. The Allergopharma preparations were

of 5, 50, 500, and 5000 therapeutic units per milliliter. The induction phase was performed according to the manufacturer's recommendations and was followed by a perennial schedule with maintenance injections (0.8 mL, the maximum individual dose tolerated by all patients at 4-week intervals).

The patients in the SIT-aq group were given treatment with aqueous extracts prepared from solutions of 5000 allergy units (AU) per milliliter (Greer Laboratories, Lenoir, North Carolina, USA). Dilutions were prepared for concentrations of 1, 10, 100, 1000, 5000 AU/mL and given at weekly intervals for 5 years. Dosages were adjusted on an individual basis. Specifically, injections were postponed if other diseases were present and the dose was lowered to the preceding dose at the next visit if a local reaction greater than 3 cm in diameter appeared or it was halved if a systemic reaction occurred. Patients were kept under observation for 30 minutes after each administration.

Environmental Avoidance Measures

All patients were instructed to take standard environmental measures to decrease exposure to mites (ie, removal of carpets, soft toys and plants from the patient's bedroom, frequent vacuum cleaning, washing sheets with water >55-60°C at least once a week, no use of humidifiers). Although mattress encasings were recommended to all patients, they were too expensive for the patients to acquire.

Drugs

For control of symptoms related to asthma and/or rhinitis, all patients, whether undergoing SIT or not, were treated according to the guidelines of the Global Initiative for Asthma [18], the consensus statement of the EAACI for allergic rhinitis [20], or the Allergic Rhinitis and Its Impact on Asthma workshop report [21].

Atopy Scores, Medication Scores of Asthma and Rhinitis

Atopy scores were evaluated at the beginning and after 5 years of treatment in all patients according to skin prick test results in the following way: a) the atopy score was negative if the result of the skin prick test was not different from the negative control; and b) it was assessed as 1+, 2+, 3+, or 4+ if the wheal diameter was equal to 25%, 50%, 100%, or 200% of the size of the histamine wheal. The total atopy score of the patient was calculated as the sum of the positive results for *D pteronyssinus* and *D farinae*.

All patients, whether treated with SIT or not, were seen regularly and their required medication was recorded by a medication score modified according to the system of Bousquet et al [22]. For asthma, taking inhaled salbutamol 200 μg/day counted 1 point, and regular use or 600 μg/day counted 2 points; inhaled cromolyn or nedocromil or oral ketotifen counted 3 points; and inhaled steroids counted 4 points (200-400 μg/day) or 5 points (400-800 μg/day). For rhinitis, regularly taken antihistamines (oral or nasal) counted 1 point, topical corticosteroids counted 2 points, and requirement of both topical steroid and antihistamines counted 3 points.

Statistical Analysis

All data were analyzed using a standard statistical software package (SPSS for Windows, version 11.0). A χ^2 test was used for the comparison of groups in terms of sex, diagnosis, and the development of new sensitization. One-way analysis of variance was used for comparison of age groups. The correlation between development of new sensitization and atopy scores or medication scores of rhinitis and asthma was analyzed with a Mann–Whitney U test. Changes within each treatment group were tested using a Wilcoxon signed rank test. A P value less than .05 was considered statistically significant.

Results

Patients

There was no statistically significant difference between groups in terms of age ($P = .07$) or sex ($P = .473$). Demographic data of all patients are shown in Table 1. No statistically significant difference between the groups was detected with regard to diagnosis of asthma and/or rhinitis upon enrollment ($P = .984$).

Development of New Sensitizations

At the end of 5 years, 64 out of 85 (75.3%) children in the SIT group showed no new sensitization, compared to 29 out of 62 children (46.7%) in the control group ($P = .002$). There was no statistically significant difference between the SIT-aq and SIT-ad subgroups in terms of development of new sensitization ($P = .605$). The risk of development of new sensitization was 3-fold higher in the control group than in the SIT-aq group (95% confidence interval [CI], 1.28-7.04; $P = .012$) and 4-fold higher in the control group than in the SIT-ad group (95% CI, 1.68-9.43; $P = .002$). In the SIT group overall, 15 out of the 21 patients developing at least 1 new sensitization developed only 1 and 6 patients developed 2 or more new sensitizations; in the control group, on the other hand, 1 new sensitization was seen in 22 out of 33 patients and 2 or more new sensitizations were seen in 11 patients at the end of 5 years. The most frequent new sensitizations at the end of the study were to grass pollens. The next most frequent were to animal danders and olive pollens (Table 2).

There was a statistically significant correlation between the development of new sensitizations and final atopy scores ($P = .002$), final medication scores of rhinitis ($P = .008$), and asthma ($P = .013$) evaluated after 5 years of treatment. The patients developing new sensitivities had higher atopy scores and medication scores for both rhinitis and asthma in comparison to patients not developing new sensitizations after 5 years of treatment.

Table 1. Patient Characteristics Over a Period of 5 Years*

	SIT Group		
	SIT, Adsorbed Extracts	SIT, Aqueous Extracts	Control Group
No. of patients	45	40	62
Gender, female/male	23/22	23/17	28/34
Age, y	13.88 ± 2.81	14.95 ± 2.75	13.5 ± 3.56
Asthma, n (%)	21 (46.7%)	18 (45%)	26 (41.9%)
Asthma and rhinitis, n (%)	19 (42.2%)	18 (45%)	28 (45.2%)
Rhinitis, n (%)	5 (11.1%)	4 (10%)	8 (12.9%)
Patients with no new sensitizations at the end of the study, n (%)	35 (77.7%)	29 (72.5%)	29 (46.7%)

* Data are mean ± SD unless otherwise indicated.

Table 2. Distribution of New Sensitizations Developed in the Study Groups*

	Total	None	Grass	Dog	Cat	Olive	Pine	*Cladosporium* species	*Alternaria* species	Cockroach	Eucalyptus
SIT group	85	64									
SIT-ad	45	35	4	0	1	4	1	2	0	0	0
SIT-aq	40	29	4	2	2	3	4	1	1	0	0
Control group	62	29	12	12	9	3	3	0	1	2	1

* SIT-ad indicates specific immunotherapy with adsorbed extracts; SIT-aq, with aqueous extracts.

Patients who underwent SIT who developed new sensitization after 5 years tended to have higher atopy scores (5.52 ± 1.75) at the beginning when compared to patients who were still monosensitized at the end of the study (4.70 ± 2.04), although this difference was not statistically significant ($P = .103$).

We found no correlation between the onset of new sensitizations and diagnosis (rhinitis and/or asthma) ($P = .610$).

Atopy Scores and Medication Scores for Asthma and Rhinitis

Atopy scores and medication scores of rhinitis and asthma of all patients are shown in Figures 1 and 2. Five years of SIT with adsorbed extracts led to a significant improvement in atopy scores ($P = .05$) (Figure 1) and medication scores for asthma ($P = .001$) (Figure 2); decreased drug intake for relief of rhinitis symptoms was observed in the SIT-ad group, but it was not statistically significant ($P = .167$). In the SIT-aq group, there was significant improvement only in the medication scores for asthma ($P = .004$) (Figure 2). We found no statistically significant difference for atopy scores ($P = .357$) or medication scores for rhinitis ($P = .298$) in the SIT-aq group after 5 years. There was no significant difference in the medication scores for rhinitis ($P = .421$) or asthma ($P = .818$) in the control group after 5 years of treatment, whereas atopy scores were found to be significantly increased ($P = .008$) (Figure 1).

Progression From Rhinitis to Asthma

The 5 patients having only rhinitis in the SIT-ad group did not develop asthma during the 5 years of the treatment. Two of the 4 patients in the SIT-aq group and 4 of the 10 patients in the control group who had only rhinitis developed asthma in the second and third years of treatment.

Discussion

In the present study, 85 children with asthma and/or rhinitis aged between 6 and 16 years, monosensitized to house dust mite, received SIT for 5 years with adsorbed or aqueous extracts and were evaluated and compared with 62

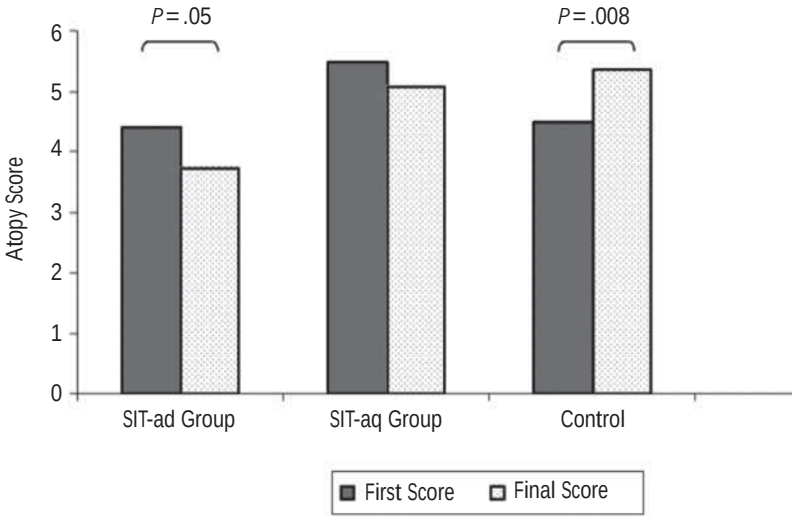

Figure 1. Atopy scores. Specific immunotherapy (SIT) with adsorbed extracts (SIT-ad) reduced atopy scores significantly whereas the atopy scores of the control group increased after 5 years of treatment. SIT-aq indicates SIT with aqueous extracts.

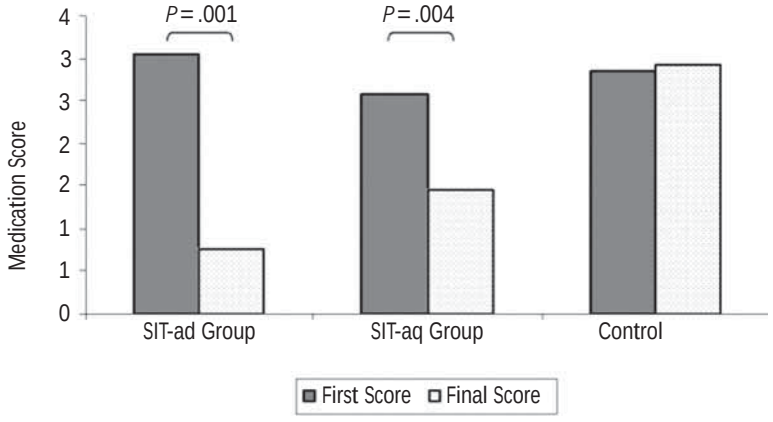

Figure 2. Medication score of asthma. Specific immunotherapy with adsorbed (SIT-ad) and aqueous (SIT-aq) extracts reduced the asthma medication score significantly after 5 years of treatment.

children monosensitized to house dust mite who received only pharmacologic treatment. The comparison was based on the development of new sensitization. New sensitizations to inhalant allergens developed less frequently (24.7%) in children who received SIT than those who did not (53.3%). The patients developing new sensitizations had higher atopy scores and medication scores of rhinitis and asthma than did those who did not develop new sensitizations.

Allergen-specific immunotherapy has been widely used for many years. The efficacy and long term effect of SIT in reducing symptoms, medication, and bronchial reactivity have been well established [4-13]. It has been less well documented that SIT with a single allergen has a preventive effect against sensitization to different inhalant allergens [14-17]. Previously, 2 studies were carried out on a pediatric population allergic to house dust mite [14,15]. In a double-blind placebo-controlled trial, 10 out of 22 children monosensitized to house dust mite in the active treatment group developed new sensitization as compared to all children in the control group [14]. In another trial in children sensitive to house dust mite, 24.6% of patients treated with SIT for 3 years developed a new sensitization in comparison to 66.7% of children in the control group [15]. In a retrospective study of pollen- or mite-sensitive adults, the rate of new sensitizations developing after 4 years of SIT was found to be 23.75% in comparison to 68.03% in the control group [16]. In our study the prevalence of new sensitizations in the SIT group was consistent with the findings from those studies, but the rate in our control group was lower. A single study reported that SIT did not exert any preventive effect against de novo sensitization to airborne allergens in monosensitized adult patients [23]. In that study, the author suggested that genetic predisposition of an individual towards developing a type 2 helper T cell (T_H2) response to specific allergens is a key determinant in the development of new sensitization.

Some longitudinal studies have reported an increase in the sensitization rate from childhood to adulthood [24-26]. One of them was carried out on children and concluded that the evolution from mono- to polysensitization was age-related [25]. In another study the same authors reported that the rate of development of polysensitization was 43.6% in previously monosensitized children after 2 to 10 years from the first diagnosis [26]. They found that 45.4% of the patients who were monosensitized to house dust mite became polysensitized. We found a slightly higher rate of polysensitization (53.3%) in our control group.

Our observation that patients developing new sensitizations also have higher atopy scores than those who did not develop new sensitizations supports the probability that genetic predisposition influences the onset of new sensitizations. Additionally, although it was not statistically significant, the atopy scores of the patients who developed new sensitization in the SIT-group were higher than those who did not. Therefore, transition from mono- to polysensitization is inevitable as the child grows toward adulthood. Nevertheless, we also demonstrated that SIT, especially with adsorbed extracts, has a significant effect on both the development of new sensitizations (77.7%) and decreasing atopy scores. We suggest that SIT has a significant preventive effect on the development of new sensitizations in children monosensitized to house dust mite, but our interpretation is that such therapy is able to decrease the absolute rate but not the normal trend towards new sensitizations.

The mechanisms that explain the lower rate of new sensitizations in children given SIT are unclear. It has been reported that SIT has an effect on the regulation of the balance between T_H1 and T_H2 cells [27] and has been shown to decrease the production of interleukin (IL) 4 and IL-5 [28,29], increase the production of interferon-γ [30], and decrease the number of inflammatory cells in the nose [31]. 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 ß, which are increasingly produced by antigen-specific regulatory T cells. Tolerance to the allergen and the development of a state of specific anergy in peripheral T cells by IL-10 are important immunological changes associated with SIT [32]. It was suggested that these actions may modify or at least delay the natural course of respiratory allergic diseases. In our opinion, these SIT-related modifications of peripheral and mucosal T_H2 responses to allergens in favor of T_H1 responses may contribute significantly to preventing the development of new sensitizations in patients who are monosensitized to house dust mite.

One study reported that new sensitizations were significantly more likely to occur in patients suffering from asthma and rhinitis as compared to patients with only rhinitis [16]. Our results are not consistent with this report; we found no correlation between the development of new sensitizations and diagnosis. This discrepancy may be related to the small number of the patients with only rhinitis in our study.

A limitation of our study is that it was not a randomized or placebo-controlled trial. However, our aim was primarily to explore whether SIT had the potential to reduce the development of new sensitizations by using an objective parameter, namely skin prick testing. A strength of our study is that data from a large sample of patients were analyzed and both SIT and non-SIT groups had homogenous distributions with respect to gender, age, and diagnosis. Furthermore, to our knowledge, this is the first study to compare SIT with aqueous extracts to SIT with adsorbed extracts with regard to the development of new sensitizations. In comparison to the control group, SIT with both extracts had a significant preventive effect on the onset of new sensitizations and led to a reduction of asthma medication scores in monosensitized patients.

We believe that SIT should begin at earlier ages, especially in children with rhinitis who are monosensitized to house dust mite to prevent polysensitization. We also suggest that adsorbed extracts should be preferred to aqueous ones because of the greater preventive effect on the development of new sensitization, decreased number of injections, and earlier achievement of maintenance. Further investigation is required to clarify the immunologic mechanisms by which SIT reduces the development of new sensitizations in monosensitized children.

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