

Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children

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Background: The natural history of allergic sensitization is complex and poorly understood. A prospective nonrandomized study was carried out in a population of asthmatic children younger than 6 years of age whose only allergic sensitivity was to house dust mites (HDMs).

Objectives: The study was designed to determine whether specific immunotherapy (SIT) with standardized allergen extracts could prevent the development of new sensitizations over a 3-year follow-up survey.

Methods: We studied 22 children monosensitized to HDM who were receiving SIT with standardized allergen extracts and 22 other age-matched control subjects who were monosensitized to HDM. The initial investigation included a full clinical history, skin tests with a panel of standardized allergens, and the measurement of allergen-specific IgE, depending on the results of skin tests. Children were followed up on an annual basis for 3 years, and the development of new sensitizations in each group was recorded.

Results: Ten of 22 children monosensitized to HDM who were receiving SIT did not have new sensitivities compared with zero of 22 children in the control group ($p = 0.001$, chi square test).

Conclusions: This study suggests that SIT in children monosensitized to HDM alters the natural course of allergy in preventing the development of new sensitizations. (J Allergy Clin Immunol 1997;99:450-3.)

Key words: Allergy, IgE, immunotherapy, natural course

Specific immunotherapy (SIT) is an effective treatment for allergic diseases when properly implemented. When standard allergen extracts are used, it has been shown to be beneficial in the treatment of allergic rhinitis and asthma. Although this form of treatment was introduced in 1911,¹ indications for its use still require clear definition. In particular, it is not yet known whether SIT should be administered to young children. On one hand, it has been suggested that SIT should be introduced early in the course of

Abbreviations used

BU:	Biologic units
HDM:	House dust mite
RIT:	Rush immunotherapy
SIT:	Specific immunotherapy

the disease^{2,3} because allergic inflammation occurs rapidly after onset. It may therefore be easier to turn off the allergen-specific IgE immune response in young children, and SIT given to children with rhinitis may prevent the onset of asthma. In contrast, subcutaneous SIT is poorly tolerated by young children. It has been demonstrated that SIT with standardized extracts causes a higher incidence of systemic reactions in children younger than 5 years of age than in older subjects,⁴ and when a bronchial reaction occurs it may be more difficult to control in children younger than 5 years of age.² Finally, it is not clear whether SIT with a single allergen can prevent the onset of other allergic sensitivities, although some pediatricians have proposed that SIT in young children may prevent the development of new sensitivities.

A case-control prospective study was carried out involving 44 children with asthma younger than 6 years of age, monosensitized to house dust mite (HDM) who were followed up for 3 years to determine whether SIT with a standardized *Dermatophagoides pteronyssinus* extract could prevent the onset of new sensitizations. Twenty-two children received SIT, and 22 children served as a control group.

METHODS

Patients

Forty-four patients ranging in age from 2 to 6 years and attending the asthma clinic of the hospital were included in the study on the basis of the following criteria.

1. A clinical history of asthma was clearly established.⁵ Asthma was defined according to the criteria of the National Asthma Education Program Expert Panel Report.⁶
2. A positive skin prick test response to *D. pteronyssinus* (Stallergènes Laboratories, Fresnes, France) was demonstrated.
3. A positive Phadebas RAST or CAP system score in response

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to Der p (Pharmacia Diagnostics AB, Uppsala, Sweden) was observed.

4. No previous or ongoing immunotherapy of any form was administered.

The study was approved by the Ethical Committee of the Clinic. The parents gave informed consent for their children to participate in the study.

Extracts

SIT was performed with a standardized *D. pteronyssinus* extract (Stallergenes Laboratories), the preparation and shelf-life of which have been previously described in detail.⁷

Diagnosis of allergy

Skin prick tests. Skin prick tests were carried out as previously described, and results were considered to be positive if the wheal size induced by the allergen extract was at least 70% of the size of that elicited by a 9% codeine phosphate positive control.^{7,8} A battery of extracts consisting of the common food and aeroallergens found in the Montpellier area was used. When possible, standardized allergen extracts were used. The following allergens were tested: *D. pteronyssinus*, *D. farinae*; *Alternaria*, *Cladosporium*, and *Aspergillus* species; cat and dog dander; cockroach; orchard grass, *Parietaria*, olive, and cypress pollen; and food allergens (milk, egg, fish, peanut, shrimp, and wheat).

Allergen-specific IgE. Serum-specific IgE was measured by using the Phadebas RAST or CAP System. Specific IgE was selected on the basis of a positive skin test result.

Specific immunotherapy

Rush immunotherapy protocol. Rush immunotherapy (RIT) was administered according to methods used in previous studies with Der p RIT.⁷ The RIT consisted of a rapid increase in allergen doses, allowing the optimal maintenance dose to be reached under hospital supervision in 2 days. All patients received the same biologic maximal dose (1500 biologic units [BU], i.e., 2 µg of Der p 1).

Maintenance injections. Maintenance injections (1500 BU) were given every week for the first 6 weeks after the RIT protocol, then every 2 weeks for 1 year, and then every month over the next 2 years.

Evaluation of patients receiving immunotherapy

Initial assessment. The initial investigation included the recording of a full clinical history, skin tests with a standardized panel of allergens, and the measurement of allergen-specific IgE.

Assessment of newly developed sensitization. Each patient involved in the study was followed up for at least 3 years, and results of skin tests and allergen-specific IgE were studied annually by using the same allergen panel and tests as described previously.

Design of the study

When a child with asthma was found to be allergic to HDM, we gave the parents the option of various forms of treatment: either SIT and pharmacologic intervention or pharmacologic intervention alone. Moreover, we asked the parents to use the same allergen and irritant avoidance measures (in particular avoidance of tobacco smoking). The choice of treatment was left to the 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 treat-

ment as required with SIT. The study was not double-blind, placebo-controlled because the aim was not to characterize the efficacy of SIT but simply to determine whether SIT could reduce the onset of new sensitizations.

Statistical analysis

Statistical analysis was performed by using S.A.S./STAT software package running on VAX/VMS. Quantitative outcomes are expressed with medians because they are not normally distributed. A Mann-Whitney rank U test was used for comparison between groups. The main outcome measurement (occurrence of new sensitization) was compared by means of a chi square test. A significance level of 0.05 was used.

RESULTS

Characteristics of the patients

Forty-four children younger than 6 years of age who were monosensitized to HDM were enrolled in the study. Twenty-two patients received SIT, and a second group of 22 patients who did not receive SIT served as a control group. Both groups were comparable in terms of age and sex. The median age at the beginning of the study was 5 years (range, 4 to 6 years) in the SIT group and 4 years (range, 3 to 5 years) in the control group. Sixty-eight percent of members of the SIT group were boys as compared with 64% in the control group.

Clinically, the SIT group was composed of 16 patients (73%) who were first seen with both asthma and rhinitis and six patients (27%) who were first seen with asthma only. In the control group 17 patients (77%) had asthma and rhinitis, and five (23%) had asthma alone.

Evolution of sensitization

At the end of the study, the most prevalent sensitivities were the same in children who became polysensitized, whether or not they had received SIT. Fifty-three percent of the children became sensitized to cat dander, 35% to dog dander, 24% to *Alternaria* species, and 20% to pollen.

The occurrence of new sensitizations was significantly less in monosensitized children who received SIT than in children in the control group ($p < 0.001$, chi square test). Ten of 22 monosensitized children (45%) who received SIT did not have any new sensitivity as compared with zero of 22 children (0%) in the monosensitized control group.

DISCUSSION

In this study 22 children with asthma monosensitized to HDM and younger than 6 years of age who received SIT were evaluated prospectively and compared with 22 children monosensitized to HDM who were not treated with SIT. Children who received SIT had fewer new sensitivities to inhalant allergens than those who did not receive SIT. Forty-five percent of monosensitized children who received SIT did not have new sensitization as compared with 0% in the control group.

SIT has been widely used for many years. Despite this, the usefulness of SIT in children younger than 6 years of age remains to be determined. Numerous studies have

TABLE I. Development of new sensitivities

Initial sensitivity	No. of patients	New sensitivities				
		None	Cat	Dog	Alt	Grass
SIT group	22	10	6	4	2	1
Control group	22	0	12	8	6	6

Alt, *Alternaria* species.

demonstrated the safety and efficacy of SIT in older children and adults, but few studies have evaluated SIT in young children; and, to our knowledge, no study has attempted to evaluate the evolution of sensitivities during SIT in young children.

The natural history of allergic sensitization is complex and poorly understood in young children. On the basis of skin testing, it seems that infants are preferentially sensitized to foods and later have allergies to aeroallergens. In general, molds and danders give rise to early sensitizations; whereas mite sensitivity appears later in life, and pollen sensitivity is the last allergy to develop.⁹⁻¹⁷ However, this general scheme is not always followed, and all scenarios are possible. In particular, pollen allergy may appear very early in life in children born just before the pollen season.¹⁸⁻²⁰ The second difficulty in charting the natural history is the course of allergic diseases. It appears that sensitivities occur sequentially, but some sensitizations may later disappear, at least clinically as has been shown in the case of some food allergies.^{21, 22} The effect of SIT on the natural course of allergen sensitization is presently unknown.

In children who did not receive SIT, the evolution of sensitization was similar to that reported in the literature.¹⁵ It is known that in the first 18 months of life, food allergy predominates, and later, sensitization to inhalants develops.^{15, 16} Sensitivity to perennial allergens (HDM, animal danders) seems to appear at an earlier age than sensitivity to seasonal allergens (pollen, grass). In comparison with food sensitivity, inhalant sensitivities tend to persist and increase with time.¹⁵ Sensitivity to animal danders, *Alternaria* species, and grass pollen were the major allergic responses that developed during the follow-up period of the study. It seems that HDM sensitivity appears early in life and tends to persist. On the other hand, pollen and animal dander sensitivities appear to develop later in life. These findings are similar to those of previous reports.^{15, 23}

This study is the first, to our knowledge, to show that SIT may prevent the onset of new sensitizations in patients who are allergic only to HDM. However, these results cannot be extended to polysensitized children because we have found that the rate of sensitization of these children is unaltered by the administration of SIT.²⁴ The reasons for the lack of new sensitizations in monosensitized children are unclear, but several hypotheses can be put forward. SIT has been shown to decrease IL-4 release from peripheral blood mononuclear cells,²⁵

and IL-4 is critical for the differentiation of a T_{H2}-like phenotype. Thus it is possible that a decrease in IL-4 induced by SIT could lead to a decreased propensity for the development of new allergen-specific IgE. On the other hand, patients who are polysensitized usually have a greater IL-4 response to nonspecific stimuli than those who are monosensitized,²⁶ and their total and specific serum IgE levels are higher.²⁷ In these patients, with the doses of allergens used, SIT may not be able to alter the ongoing IL-4 response.

The absence of randomization could have introduced some bias in the results. Effectively, it is possible that the group treated with SIT was different from the group without SIT. The motivation required for SIT could be associated with a higher level of interest in environmental control, which could prevent the appearance of new sensitization. However, new sensitivities had appeared in 55% of the group of children who received SIT. We asked parents to use the same allergen and irritant avoidance measures (in particular avoidance of tobacco smoking), and although we did not control it with objective measures, it seems that parents of children in both groups were very careful in avoidance measures. However the majority of new sensitivities in this group were related to cat and dog danders, which could be easily avoided by strict environmental control, but unfortunately, cats and dogs were introduced for the most part indirectly in the environment of children in both groups. Another bias may be attributed to the medications used. The non-SIT group received more pharmacologic treatment than the SIT group, and the airways of patients using bronchodilators may have been exposed to more allergens. However, because patients should have remained, as much as possible, symptom-free, there should have been no major difference in the exposure of the respiratory tract to allergens. This study was not a double-blind, placebo-controlled trial. However, the aim of the study was simply to determine whether SIT could reduce the onset of new sensitizations by using an objective parameter such as skin prick testing, which decreases the risk of a placebo effect.

This study highlights an interesting and new concept in SIT in young children because it is the first to show a significant prevention of new sensitivities in monosensitized children undergoing SIT. However, it requires confirmation by a multicenter prospective study involving a greater number of monosensitized children.

REFERENCES

1. Noon L. Prophylactic inoculation against hay fever. *Lancet* 1911;1:1572-3.
2. Malling H, Weeke B. Immunotherapy. Position Paper of the European Academy of Allergy and Clinical Immunology. *Allergy* 1993;48(suppl 14):9-35.
3. Ownby DR, Adinoff AD. The appropriate use of skin testing and allergen immunotherapy in young children. *J Allergy Clin Immunol* 1994;94:662-5.
4. Hejjaoui A, Dhivert H, Michel FB, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. IV. Systemic reactions according to the immunotherapy schedule. *J Allergy Clin Immunol* 1990;85:473-9.
5. Delacourt C, Labbe D, Vassault A, Brunet-Langot D, de-Blic J, Scheinmann P. Sensitization to inhalant allergens in wheezing infants is predictive of the development of infantile asthma. *Allergy* 1994;49:843-7.
6. Expert panel report to provide clinical guidelines for diagnosis and treatment of asthma. *J Sch Health* 1991;61:249-50.
7. Bousquet J, Calvayrac P, Guerin B, Hejjaoui A, Dhivert H, Hewitt B, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. I. In vivo and in vitro parameters after a short course of treatment. *J Allergy Clin Immunol* 1985;76:734-44.
8. Bousquet J, Guerin B, Dotte A, Dhivert H, Djoukhar F, Hewitt B, et al. Comparison between rush immunotherapy with a standardized allergen and an alum adjuved pyridine extracted material in grass pollen allergy. *Clin Allergy* 1985;15:179-93.
9. Calkhoven PG, Aalbers M, Schilte PP, Yntema BJ, Griffioen RW, van-Nierop JC, et al. Newly generated IgE antibodies to *Dermatophagoides pteronyssinus* in children are directed against components distinct from *Der p* I and *Der p* II. *J Allergy Clin Immunol* 1991;88:265-71.
10. Sigurs N, Hattveig G, Kjellman B, Kjellman NI, Nilsson L, Bjorksten B. Appearance of atopic disease in relation to serum IgE antibodies in children followed up from birth for 4 to 15 years. *J Allergy Clin Immunol* 1994;94:757-63.
11. Croner S, Kjellman NI. Natural history of bronchial asthma in childhood. A prospective study from birth up to 12-14 years of age. *Allergy* 1992;47:150-7.
12. Guillet G, Guillet MH. Natural history of sensitizations in atopic dermatitis. A 3-year follow-up in 250 children: food allergy and high risk of respiratory symptoms. *Arch Dermatol* 1992;128:187-92.
13. Kjellman B, Dalen G. Long-term changes in inhalant allergy in asthmatic children. *Allergy* 1986;41:351-6.
14. Kjellman NI. Atopic allergy and serum IgE concentrations in randomly selected children followed up from 8 to 12 years of age. *Allergy* 1984;39:443-50.
15. Kjellman N. Natural course of asthma and allergy in childhood. *Pediatr Allergy Immunol* 1994;5(suppl 1):13-8.
16. Rowntree S, Cogswell JJ, Platts-Mills TA, Mitchell EB. Development of IgE and IgG antibodies to food and inhalant allergens in children at risk of allergic disease. *Arch Dis Child* 1985;60:727-35.
17. van-Asperen PP, Kemp AS. The natural history of IgE sensitisation and atopic disease in early childhood. *Acta Paediatr Scand* 1989;78:239-45.
18. Bjorksten F, Suoniemi I, Koski V. Neonatal birch-pollen contact and subsequent allergy to birch pollen. *Clin Allergy* 1980;10:585-91.
19. Korsgaard J, Dahl R. Sensitivity to house dust mite and grass pollen in adults. Influence of the month of birth. *Clin Allergy* 1983;13:529-35.
20. Businco L, Ziruolo MG, Ferrara M, Benincori N, Muraro A, Giampietro PG. Natural history of atopic dermatitis in childhood: an updated review and personal experience of a five-year follow-up. *Allergy* 1989;9:70-8.
21. Bock SA, Atkins FM. The natural history of peanut allergy. *J Allergy Clin Immunol* 1989;83:900-4.
22. Dannaeus A, Inganas M. A follow-up study of children with food allergy. Clinical course in relation to serum IgE- and IgG-antibody levels to milk, egg and fish. *Clin Allergy* 1981;11:533-9.
23. Van-Asperen PP, Kemp AS, Mellis CM. A prospective study of the clinical manifestations of atopic disease in infancy. *Acta Paediatr Scand* 1984;73:80-5.
24. Des Roches A, Paradis L, Knani J, Hejjaoui A, Dhivert H, Michel FB, et al. Specific immunotherapy prevents the onset of new sensitizations in monosensitized children [abstract]. *J Allergy Clin Immunol* 1995;95:309.
25. Secrist H, Chelen CJ, Wen Y, Marshall JD, Umetsu DT. Allergen immunotherapy decreases interleukin 4 production in CD4+ T cells from allergic individuals. *J Exp Med* 1993;178:2123-30.
26. Pene J, Rivier A, Lagier B, Becker WM, Michel FB, Bousquet J. Differences in IL-4 release by PBMC are related with heterogeneity of atopy. *Immunology* 1994;81:58-64.
27. Bousquet J, Becker WM, Hejjaoui A, Chanal I, Lebel B, Dhivert H, et al. Differences in clinical and immunologic reactivity of patients allergic to grass pollens and to multiple-pollen species. II. Efficacy of a double-blind, placebo-controlled, specific immunotherapy with standardized extracts. *J Allergy Clin Immunol* 1991;88:43-53.