

Immunotherapy in children with allergic asthma: Effect on bronchial hyperreactivity and pharmacotherapy

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Background: Immunotherapy has been shown to reduce allergen sensitivity to allergens such as cat and dust mite. The aim of this study was to investigate the effect of cat or dust mite immunotherapy on bronchial hyperreactivity and the need for inhaled corticosteroids in children with asthma, cat or dust mite allergy, and hay fever.

Subjects: Twenty-nine children, 7 to 16 years old, completed the 3-year study. They were randomly allocated to receive cat/dust mite or placebo and birch/timothy immunotherapy.

Methods: Before immunotherapy was begun and then once each year, bronchial histamine challenges were performed. Bronchial allergen challenge with the perennial allergen was done before and after the 3-year study. Pharmacotherapy was given according to a standardized protocol.

Results: PC₂₀ allergen increased significantly in both the active immunotherapy group ($P < .001$) and in the placebo-pollen group ($P < .05$). PC₂₀ histamine increased continuously in the active immunotherapy group ($P < .05$ and $P = .002$ after 1 and 3 years, respectively) and had also increased after 3 years in the placebo-pollen group ($P < .05$). The difference between the 2 groups was significant for PC₂₀ allergen ($P = .001$) but not for PC₂₀ histamine. There was no significant change in the dose of inhaled budesonide needed for symptom control in either of the groups.

Conclusion: Pollen immunotherapy combined with inhaled corticosteroids results in improvement of both cat/dust mite bronchial sensitivity and hyperresponsiveness to histamine. The combination of cat or dust mite, pollen immunotherapy, and inhaled budesonide enhances this improvement. Cat immunotherapy also induces cat allergen tolerance. (*J Allergy Clin Immunol* 1999;103:609-14.)

Key words: Immunotherapy; children; asthma; cat, dust mite, and pollen allergy; bronchial hyperreactivity; budesonide

Abbreviations used

BHR: Bronchial hyperreactivity
LAR: Late-phase allergen reaction
PEF: Peak expiratory flow
SQU: Standard quality units

In children with asthma, cat allergy is common. A Swedish study reports a positive skin test response to cat allergen in 53% of a group of schoolchildren with asthma of varying severity.¹ Cats are abundant, and cat allergen is ubiquitous.² Therefore exposure of children to cat allergen cannot be avoided. Cat allergen is a major cause of persisting airway inflammation and entails a risk of deterioration of asthma in children. Allergy to dust mite allergen plays a similar role in children with asthma and dust mite allergy.

In a previous study of immunotherapy in children and adults with mostly mild asthma caused by cat and/or dog allergy, we found not only the expected decrease of allergen sensitivity but also a continuous improvement in bronchial hyperreactivity (BHR), measured by repeated histamine challenges during 3 years of immunotherapy in the cat allergen-treated group.³ At the time of the study, inhaled steroids were still used with caution, particularly in children, and few participants received steroids on a regular basis. Today, inhaled corticosteroids are often the first-line treatment in children with moderate asthma. There is still, however, some concern about sideeffects, particularly on growth when continuous therapy is needed for years.⁴ There is reason to keep the dose as low as possible. Immunotherapy might help to achieve this goal.

This study was designed to investigate the effect of 3 years of cat or dust mite immunotherapy in children with moderate asthma. In particular, we wished to study the effect of immunotherapy on long-term BHR. A secondary objective was to study whether immunotherapy would influence the need for inhaled corticosteroids required to maintain symptom control and normal lung function. To motivate the children for 3 years of blinded placebo-controlled cat or dust mite immunotherapy, the children were simultaneously treated with 1 pollen extract.

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TABLE I. Subjects

	N	Age (y)*	Sex (F/M)	Allergy (n)			
				Cat	<i>D pteronyssinus</i>	Birch	Timothy
Group A (perennial and pollen immunotherapy)	15	11.7 (7-16)	8/7	13	2	10	5
Group P (placebo and pollen immunotherapy)	14	11.9 (10-16)	6/8	13	1	9	5
Drop outs	3	10.7 (7-14)	1/2	2	1	2	1

*Mean (range).

METHODS

Subjects

Thirty-eight children were recruited. Four children (2 children with dust mite allergy and 2 children with cat allergy) changed their mind about participating in the study for personal reasons at the first visit after randomization. One child had been randomized without fulfilling the inclusion criteria and was excluded at the start of the study, as was another child who had a bicycle accident before starting therapy. Thirty-two children (age range, 7 to 16 years; mean, 11.5 years) were finally included (Table I). Twenty-eight of them were allergic to cat allergen, and 4 of them were allergic to dust mite allergen; they all had tree and/or grass pollen allergy as judged by history and positive skin prick test responses. The perennial allergy was confirmed by allergen bronchial challenge. Of the children with allergic reactions to cat allergen, 26 of 28 were allergic also to dog and/or horse allergen.

The children were eligible for enrollment in the study if they had asthma for more than 2 years and had required corticosteroids by inhalation for symptom control and normal lung function during more than 3 months preceding recruitment. Children with an allergic reaction to cat allergen with a positive skin test or RAST response to molds and/or dust mite allergen and children with an allergic reaction to dust with a positive skin test or RAST response to molds and/or animal dander were excluded, as were children with furry pets at home.

The study was approved by the Ethics Committee at the Karolinska Institutet. Parents and children gave their consent after oral and written information about the study.

Study design

The study included 2 groups, and the design was double blind and placebo controlled for the perennial allergen, cat or dust mite allergen, and open for the seasonal allergen, birch or timothy. On the basis of age, sex, and the result of the bronchial allergen and histamine challenges, the children were matched into pairs, and the 2 treatment alternatives were allocated randomly within the pairs. Group A received 1 pollen extract and cat or dust mite immunotherapy; group P received 1 pollen extract and placebo. Bronchial histamine challenge was done before the study began and then once a year. A bronchial allergen challenge with cat or dust mite allergen was performed before therapy was started and after the last immunotherapy injection 3 years later. Serum was obtained in connection with the challenges for antibody analyses.

Before challenges and immunotherapy, daily symptom scores and peak expiratory flow (PEF) rates were recorded for a run-in period of 3 to 6 months to ensure optimal pharmacotherapy. Spirometry was recorded on 2 or 3 occasions. During the study, PEF

was recorded daily during the build-up phase and during a minimum of 2 weeks before each immunotherapy injection. Spirometry was performed at every visit to the clinic.

Pharmacotherapy

After the run-in period, the dose of budesonide was adjusted every sixth week. An increase in the dose of budesonide was required if symptoms occurred more than twice a week, if the FEV₁ was less than 75% of predicted value at the visit, or if PEF was less than 80% of the child's optimal PEF for 14 days or more during the 6 weeks preceding the visit. Reduction of the dose of budesonide was recommended when patients were symptom-free and had normal lung function. If a child had no symptoms for 6 weeks and the dose of budesonide was less than 300 µg per day, budesonide could be omitted. If 400 µg per day or more of steroids were required, either oral theophylline or a depot β₂-agonist could be added to the therapy. When improvement was established, the oral bronchodilator could be omitted before the budesonide dose was reduced to less than 400 µg.

Allergen extracts

Partly purified and standardized extracts of cat dander, *Der-matophagoides pteronyssinus*, timothy pollen, and birch pollen were provided by ALK (Hørsholm, Denmark). Extracts from the same batch were used for the skin prick tests, bronchial allergen challenges, and antibody analyses. For treatment, aluminum hydroxide-adsorbed extracts (Alutard SQ) were used. The cat dander extract contained 15.0 µg Fel d 1 per 100,000 standard quality units (SQU). The dust mite extract contained 7.0 µg Der p 1 per 100,000 SQU; the timothy extract contained 20 µg Phl p 5 per 100,000 SQU, and the birch extract contained 23 µg Bet v 1 per 100,000 SQU. The placebo extracts contained histamine chloride to ensure blinding.

Immunotherapy

The build-up dose of the depot extracts was administered once each week, starting with 0.2 mL of 100 SQU/mL. The individual maximum dose (ideally 1 mL of 100,000 SQU/mL) was administered every sixth week. The duration of the treatment was 3 years, including the build-up phase.

Systemic and local side-effects were registered after each injection. PEF recordings were performed before and 30 minutes after each injection and again in the evening of the same day to detect early-phase reactions and LAR in the airways.

Bronchial allergen challenge

Bronchial sensitivity to cat and dust mite allergen was measured by inhalation of cat dander or dust mite extracts from a demand-

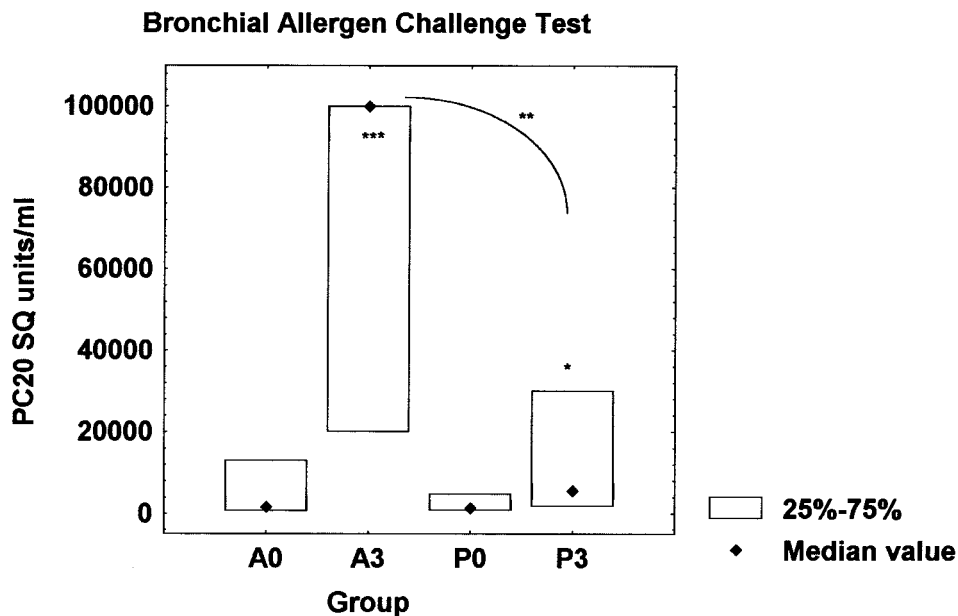


FIG 1. Bronchial allergen challenge test. Results are presented as medians with the 25 to 75 percentiles. A0, A3, P0, and P3 represent before and after 3 years. The challenge was done before the study and after 3 years when immunotherapy was stopped. * $P < .05$, ** $P < .01$, and *** $P < .001$ indicate change from the start of the study or the difference between the groups. The difference between group A and P after 3 years of immunotherapy was significant ($P = .001$).

type nebulizer (Pari inhaler boy; Paul Ritzau Pari Werk, Starnberg, Germany) that was driven by compressed air (5 L/min). The challenge was started by inhalation of 1 mL of saline solution and was continued by 10-fold stepwise-increasing doses of allergen every 15 minutes. PEF was recorded 5 and 15 minutes after each inhalation. The starting dose of allergen was 1 SQU, and the maximum dose was 100,000 SQU (15 μ g Fel d 1 or 7 μ g Der p 1). The challenge was stopped when PEF decreased by 20% from the PEF recording after the saline solution. The concentration of allergen inducing a 20% fall in PEF (PC_{20} allergen) was calculated by linear interpolation from the log dose-response curve. PEF recordings were done every hour for 8 hours after the challenge to detect any LAR.

Bronchial histamine challenge

BHR was evaluated by histamine challenge according to the protocol of Cockcroft et al.⁵ The same equipment was used and the same preconditions were applied as with the allergen challenge. Histamine hydrochloride was inhaled, starting with 0.03 or 0.06 mg/mL; the concentration was doubled at each dose step. The maximum concentration used was 16 mg/mL. PC_{20} histamine was calculated from the log dose-response curve. Histamine challenge was performed 1 to 2 weeks before the allergen challenge.

Specific IgE and IgG4 levels

Specific IgE and IgG4 were measured with a chemiluminescence immunoassay, including monospecific antibodies to Fel d 1, Der p 1, Bet v 1, and Phl p 5.^{6,7} Serum samples obtained before therapy began, after the maintenance dose had been reached, 1 year thereafter, and at the end of the study were analyzed in the same assays. Results of specific IgE were expressed as standard quality units per milliliter; specific IgG4 was expressed as percent of total activity added in the immunoassay.

Statistics

The number of subjects was based on the results of previous immunotherapy studies because the intention was to use nonparametric statistics. The Wilcoxon paired signed-rank test was used to evaluate changes related to therapy, and the Mann-Whitney U test was used to compare groups. ANOVA for log-transformed regression coefficients was also applied to compare PC_{20} histamine between groups.

RESULTS

Patients

Twenty-nine children completed the 3-year study period. Three children dropped out, 2 children from the active group and 1 child from the placebo group. One child allergic to cat allergen in group A dropped out because of systemic side-effects of immunotherapy. The other dropped out for reasons not related to the study, including 1 of the children from group A allergic to dust mite allergen. Data for the children are presented in Table I.

Immunotherapy

All but 3 patients reached the targeted maintenance dose of 100,000 SQU of the respective extracts. Two children in the active group had 80,000 SQU as their maintenance dose of cat allergen, and 1 child in the placebo group received 50,000 SQU of both extracts as her maintenance dose because of periods of asthma deterioration. The mean cumulated doses of the major allergens were 298 μ g and 151 μ g for Fel d 1 and Der p 1, respectively.

Side-effects

Mild systemic side-effects occurred in 5 children in group A who received cat immunotherapy. None of the reactions was severe or life-threatening. One child allergic to cat and timothy allergens who had recurrent urticaria and asthmatic reactions in connection with the injections in spite of dose reductions, however, was excluded from the study.

Bronchial allergen challenge

Fig 1 shows the result of the 2 allergen challenges. Before the study, median PC₂₀ allergen was comparable (1900 and 1400 SQU/mL) in groups A and P. After 3 years of therapy, the improvement in group A was highly significant, with the median PC₂₀ allergen 100,000 SQU ($P < .001$). In group P, there was an increase in PC₂₀ allergen to 5600 SQU/mL ($P < .01$). The difference between the groups was highly significant ($P = .001$) after 3 years. Eight of 15 children in group A had become nonresponders. LAR occurred in 3 children in group A before therapy, but in none of them after completed immunotherapy. In group P, 4 children experienced LAR after the first provocation; in 2 children the LAR remained. The significance levels were of the same magnitude if the children with allergic reactions to dust mite allergen were excluded.

Bronchial histamine challenge

Fig 2 shows the change in PC₂₀ in the groups during the 3 years. In group A, PC₂₀ histamine increased significantly from median 0.18 mg/mL to 0.50 mg/mL when the children had reached their maintenance dose ($P < .05$). After the second and third year, PC₂₀ was 0.58 mg/mL and 1.68 mg/mL ($P = .01$ and $P = .002$ compared with before therapy; $P = .006$ after 3 years if the children treated for allergic reaction to dust mite allergen were excluded). In group P, PC₂₀ at the start of the study was 0.28 mg/mL, which was not significantly different from group A. In this group, PC₂₀ had also increased significantly after the second and third year (median, 0.7 mg/mL and 0.54 mg/mL; $P < .05$ vs before immunotherapy; $P = .06$ if the child with an allergic reaction to dust mite allergen was excluded). The difference between PC₂₀ in group A and group P was not significant, nor did the changes of PC₂₀ in the respective groups differ significantly.

Pharmacotherapy

We found that 1 child in group A and 3 children in group P could discontinue corticosteroids without worsening the asthma. There was no significant difference between the groups; the median dose of budesonide in the week before the histamine challenges was 400 µg through the study in both groups. All children used oral terbutaline daily before the study, but only 1 and 2 children in the respective groups still used it at the end of the study.

Antibody levels

Specific IgE to Fel d 1, Der p 1, Phl p 5, and Bet v 1 during the study are illustrated in Table II. The changes

of specific IgE levels were generally not significant. Specific IgG4 increased during the first year of treatment in response to allergen therapy and remained high throughout the treatment period, although in those children given placebo, IgG4 remained low (Table II).

Global assessment

At the end of the study before children or investigators had broken the code, a questionnaire was given to the children. They were asked about seasonal allergic symptoms, about symptoms on exposure to cat allergen, and about their overall assessment of the severity of asthma. All but 1 child allergic to cat allergen in group A reported to be free of symptoms on exposure to cat allergen. In group P, 6 of 13 children had improved and had fewer symptoms on exposure, which was significantly different from group A ($P < .05$). Seasonal symptoms were generally milder but had not disappeared completely in any child in groups A and P. Subjective assessment of overall asthma severity demonstrated improvement in 12 children in each group.

DISCUSSION

In this study we found a general reduction in the severity of asthma after 3 years of immunotherapy, combined with regular treatment with inhaled corticosteroids. We have previously reported that cat immunotherapy in patients with mild asthma, mostly without corticosteroid therapy, favorably affects both BHR and bronchial sensitivity to allergen.³ The development of BHR during immunotherapy was similar in this study of children with more severe asthma, and there was a continuous decrease in histamine sensitivity during the 3 years of therapy. The difference between those who had received pollen, cat, and dust mite immunotherapy and those who only had received a pollen extract was not significant, however, which might be due to the number of patients being too small. In view of the results of our previous study, it still seems probable that the positive effect on BHR can partly be attributed to immunotherapy with the perennial extract. However, pollen immunotherapy may also affect BHR. Birch immunotherapy attenuates the increase in BHR that accompanies a period of pollen exposure.⁸ Thus the positive development of asthma in both immunotherapy groups could partly result from immunotherapy per se.

The well-known anti-inflammatory properties of inhaled corticosteroids also ameliorate BHR. The change in histamine sensitivity in our immunotherapy pollen-placebo group was comparable to the change seen over the same period in a study of BHR during continuous treatment with budesonide for 2 years.⁹ It therefore remains difficult to separate the importance of regular corticosteroid therapy from the effects of immunotherapy. The decrease in allergen sensitivity to perennial allergen in the pollen-placebo group must be attributed mainly to the anti-inflammatory effects of topical corticosteroids. They have been shown to affect immediate

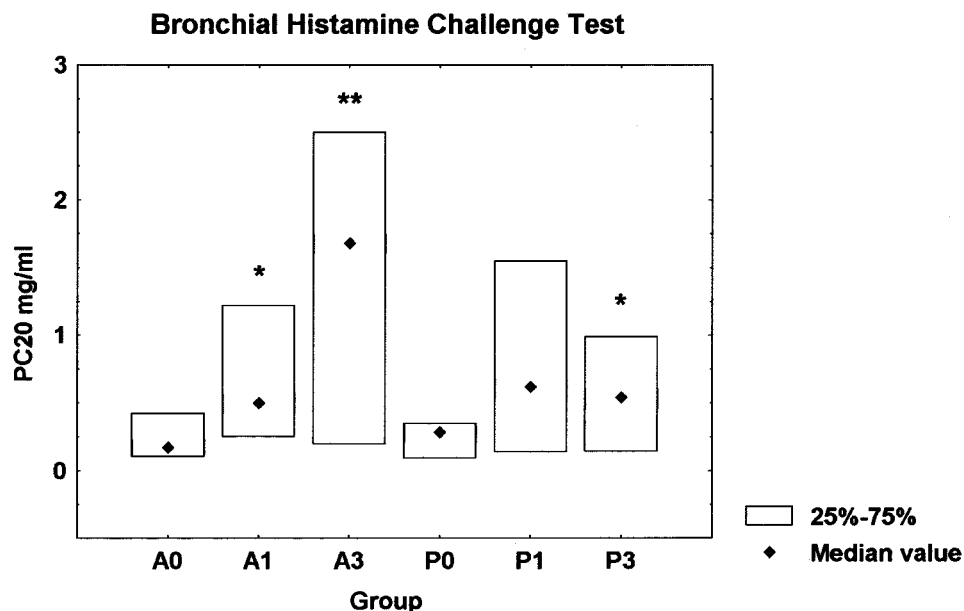


FIG 2. Bronchial histamine challenge test. Results are presented as medians with the 25 to 75 percentiles. The challenge was done before the study and then once each year for 3 years until immunotherapy was stopped. The 2-year results can be found in the text. A0, A1, and A3 represent group A before and after 1 and 3 years of immunotherapy. P0, P1, and P3 represent group P at the same time points. A3 and P3 were not significantly different. * $P < .05$ and ** $P < .01$ indicate change from before therapy.

TABLE II. IgE and IgG₄-antibody levels* in serum before and after immunotherapy

	Bet v 1		Ph p 5		Fel d 1		Der p 1	
	IgE SQU/ mL (b/a)	IgG ₄ (%; b/a)†	IgE SQU/ mL (b/a)	IgG ₄ (%; b/a)†	IgE SQU/ mL (b/a)	IgG ₄ (%; b/a)†	IgE SQU/ mL (b/a)	IgG ₄ (%; b/a)†
Group A	14.7/12.2	2.5/34.6‡	7.2/8.3	0.17/57.4‡	288/106	3.7/68.3‡	69.7/57	4.6/61§
Group P	45.4/23.9	4.7/36.4‡	17.2/27.1	0.48/56.4‡	110/49	1.6/1.6	132/133	0.59/0.57§

b, Before; a, after.

*Analyses for pollen IgE and IgG₄ were done in those children who received the respective extracts in group A and P. Results are presented as medians.

†IgG₄ levels are expressed in percent of total activity added to the immunoassay.

‡ $P < .05$.

§Der p 1 antibody was measured in 2 children in group A and 1 child in group P.

reactions after a period of regular therapy, most probably as a result of improvement of airway inflammation.¹⁰ So far as we know, there have been no previous reports that immunotherapy with 1 extract could bring about a significant improvement in other allergies than those included in the therapy. However, the anti-allergic/anti-inflammatory effects of pollen immunotherapy⁸ may also have influenced general allergen sensitivity.

Immunotherapy failed to affect the need for regular corticosteroid therapy. One reason for the failure could be that 12 of the 13 children in group A were also allergic to dog and/or horse allergen. With current knowledge of the amount of dog allergen in dust from schools and other public places¹¹ and the importance of low-dose exposure in chronic inflammation,¹² it appears probable that this allergen exposure maintains the need for steroids also in those whose allergic reaction to cat allergen has

been successfully treated. Other mechanisms, like airway inflammation caused by various nonspecific triggers (eg, viral airway infections and environmental tobacco smoke), are also of importance for the triggering of symptoms.

There is a risk of overmedication in a study like this because this will not be detected on PEF recordings or other lung function tests. This problem has previously been discussed by Adkinson et al¹³ in their multiple allergen-immunotherapy study.

In conclusion, 3 years of pollen immunotherapy combined with daily treatment with inhaled corticosteroids reduces bronchial allergen sensitivity and hyperresponsiveness to histamine. The combination of cat/dust mite and pollen immunotherapy and regular use of inhaled budesonide enhances this effect, and cat immunotherapy in addition induces cat allergen tolerance.

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