

Long-term follow-up of patients treated with a three-year course of cat or dog immunotherapy

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Background: A 5-year follow-up study was conducted to investigate the duration of the effects of a 3-year course of immunotherapy with standardized cat or dog extracts in 32 children and adults with asthma caused by animal dander.

Methods: Thirty of the subjects could be reached with a questionnaire, 19 underwent bronchial allergen and histamine challenges, and four had only a histamine challenge. Specific IgE and IgG₄ levels in serum were measured in those who underwent challenges.

Results: Almost all subjects (26 of 30) reported no change (17 subjects) or increased tolerance (9 subjects) on exposure to cats or dogs. In contrast, 17 of the 19 who underwent allergen challenges had increased allergen sensitivity compared with when therapy was stopped ($p < 0.01$), and the results were no longer significantly different from before therapy was started. Mean provocative concentration of histamine causing a 20% fall in peak expiratory flow was, however, still higher than before therapy in the cat immunotherapy group ($p < 0.01$) and had not changed significantly during the follow-up period. In the dog immunotherapy group there was no significant change during or after therapy. Specific IgG₄ had decreased, and specific IgE in serum had remained low and was comparable to the levels measured at the end of the study period.

Conclusions: Five years after stopping immunotherapy, objectively measured bronchial allergen sensitivity had increased and had approached pretreatment conditions. Asthma symptoms, according to patients' subjective evaluations, had continued to be mild in most patients, and bronchial histamine sensitivity had remained stable. These observations could reflect remaining effects of immunotherapy or the natural history of mild asthma. (*J ALLERGY CLIN IMMUNOL* 1995;96:879-85.)

Key words: Immunotherapy, cat, dog, asthma, bronchial challenge

Since standardized extracts were introduced, a number of controlled studies of the effects of immunotherapy have been done. Overall, the efficacy has been shown to be good in patients with asthma and rhinitis treated with pollen,^{1,2} dust mite,^{3,4} and animal dander.^{5,6} However, fairly few

Abbreviations used

BHR:	Bronchial hyperreactivity
LAR:	Late asthmatic response
PC ₂₀ :	Provocative concentration (of allergen or histamine) causing a 20% fall in PEF
PEF:	Peak expiratory flow

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attempts have been made to determine how long the effect of the therapy remains after the treatment has been stopped. Those involved in venom immunotherapy studies have so far been the pioneers in this field by reporting results of sting challenges year after year, after therapy has been stopped.^{7,8} Golden et al.⁸ reported in 1991 that after 5 years without therapy, only 10% of their

TABLE I. Number of patients who participated in follow-up study

Follow-up participation	Cat IT group		Dog IT group		Total	
	Adults	Children	Adults	Children	Adults	Children
Answered questionnaire	6	13	6	5	12	18
Allergen challenge	4	9	3	3	7	12
Histamine challenge	5	11	3	4	8	15
Antibody levels in serum	3	10	3	4	6	14

IT, Immunotherapy.

subjects had systemic reactions, none of which were serious, after a sting challenge. Other follow-up studies have focused on the patients' subjective evaluations of any remaining effect of the therapy. Mosbech and Osterballe⁹ returned to their grass-treated patients 6 years after therapy and found that most of them reported symptoms to have stabilized or decreased further. This finding was in contrast to the fact that the immunoglobulin-binding patterns were similar to patterns observed in the patients' sera before therapy had been started.¹⁰ Wihl et al.¹¹ recently presented a 5-year follow-up of tree pollen-treated patients with rhinitis, and like Mosbech and Osterballe,⁹ they reported the majority of patients to have mild or no symptoms during a pollen season.

The aim of our study was to investigate, by objective and subjective means, any remaining effects of 3 years of immunotherapy with standardized cat and dog extracts in children and adults with asthma. Our follow-up was performed 4 to 5 years after the immunotherapy study had been completed.

METHODS

Twenty children and 20 adults with asthma caused by allergy to cat or dog started in a 3-year study of the effects of cat or dog immunotherapy. Thirty-two of the participants received immunotherapy with standardized cat or dog extracts (Alutard SQ; ALK, Horsholm, Denmark) for 3 years. The first year of the study was performed in double-blind, placebo-controlled fashion. The results have been reported elsewhere.^{12, 13} In summary, active treatment resulted in decreased specific bronchial sensitivity to allergen and decreased nonspecific bronchial sensitivity to histamine. Those who belonged to the placebo group were then transferred to active treatment. Immunotherapy was administered for 3 years in a total of 32 patients. The results of 3 years of therapy have also been published.⁶

Four to five years after therapy had been stopped, those who completed the study were approached with a questionnaire. They were also asked to undergo bronchial challenges with allergen (cat or dog) and histamine. In connection with the visits, serum was obtained

for antibody analysis. Table I gives an overview of the number of patients participating in the different parts of the follow-up procedure. All but two children answered the questionnaire. The study was approved by the Ethics Committee at the Karolinska Institutet.

Questionnaire

The questionnaire included seven questions. The first three concerned animal exposure: (1) "Have you been exposed to cats or dogs during the last year?"; (2) "Have you been exposed to other animals?" (a. frequently, b. occasionally, c. not at all); (3) "Do you have a pet of your own?" Questions 4 and 5 were: (4) "Have your asthma symptoms on exposure to cats or dogs changed?" (improved, no change, worse during the last years); (5) "Have your symptoms in cold weather, after exercise, etc. changed during the last years?" Question 6 concerned smoking habits (ongoing, quit, started). Finally, the subjects were asked to give detailed information about their current pharmacotherapy, including medications taken as needed and on a regular basis.

Bronchial challenges

Bronchial allergen challenge was performed as described previously⁵ with cat or dog extracts (Aquagen SQ, ALK), starting with a potency of 10^{-3} HEP (1 HEP cat extract = 2.15 μ g Fel d 1/ml, 1 HEP dog extract 76.0 μ g dog albumin/ml) and then increasing the dose 10-fold at each dose step until peak expiratory flow (PEF) had decreased by more than 20%. Results are expressed as provocative concentration causing a 20% fall in PEF (PC_{20}), which was calculated from the log-dose-response curve.

Bronchial histamine challenge was performed according to the method described by Cockcroft et al.¹⁴ Histamine hydrochloride was inhaled by means of a De Vilbiss nebulizer (De Vilbiss Medizinische GmbH, Langen, Germany) in doubling concentrations, starting with 0.06 mg/ml, until the PEF rate dropped 20%. PC_{20} (in milligrams per milliliter) was then calculated from the dose-response curve. The method was identical to that used at the start and the end of the immunotherapy study.

Antibody levels in serum

Specific IgE and IgG₄ were measured with a chemiluminescence immunoassay,^{15, 16} including monospecific

TABLE II. Symptoms reported by subjects ($N = 30$) at different stages of the study

	Symptoms								
	Improved (no.)			No change (no.)			Worse (no.)		
	1 yr*	3 yr†	f-u‡	1 yr*	3 yr†	f-u‡	1 yr*	3 yr†	f-u‡
On exposure									
Cat IT group	9a/3p	15	6	4a/5p	6	12	0	0	3
Dog IT group	4a/1p	4	3	2a/2p	5	5	0	0	1
BHR									
Cat IT group	4a/2p	9	5	8a/5p	11	13	1a/1p	1	3
Dog IT group	4a/1p	3	2	2a/2p	6	6	0	0	1

The first year of the study was placebo-controlled; patients treated with placebo were then transferred to active treatment for 3 years. IT, Immunotherapy; a, active IT; p, placebo IT.

*After 1 year of the study.

†After subjects had completed 3 years of active immunotherapy.

‡Follow-up 4 to 5 years after therapy had been stopped.

antibodies to Fel d 1 and Can f 1. Samples obtained from before therapy was started, at the end of 3 years of therapy, and from the 5-year follow-up visit were analyzed with the same assays. Results of Fel d 1-specific IgE are expressed as standardized units per milliliter, and Can f 1-specific IgE and Fel d 1- and Can f 1-specific IgG₄ are expressed as percent of total activity added in the immunoassay.

Statistics

Nonparametric tests were used. Wilcoxon paired signed-rank test was used to evaluate changes during immunotherapy and the follow-up period. Spearman's rank correlation coefficient was applied to evaluate correlations between results of tests. Chi square analysis was used to evaluate differences between groups.

RESULTS

Questionnaire

According to the answers to the questionnaire about animal exposure, two children (treated with cat extract) had acquired dogs of their own, and one adult (treated with dog extract) reported that he had three cats. Eight other subjects reported frequent exposure to cats and dogs. The remaining 19 had little or no contact with cats, dogs, or other pets.

The subjective evaluations of symptoms on exposure to cats and dogs and symptoms of bronchial hyperreactivity (BHR) are presented in Table II; also included in the table are the subjective evaluations of the effect of immunotherapy after 1 year (the placebo-controlled year) and after 3 years of immunotherapy by the 30 subjects who participated in the follow-up study.

Five years after study completion, 17 of 30 subjects who answered the questionnaire had not noted any change in symptoms on exposure to cats or dogs. Symptoms of BHR were perceived as

unchanged in 19 subjects. Three patients in the cat immunotherapy group and one in the dog immunotherapy group reported deterioration. The rest reported improvement (Table II). Twenty of 28 subjects who answered questions about pharmacotherapy were taking only β_2 -agonists as needed. Three subjects used inhaled steroids daily, and five used inhaled steroids periodically. Two of the regular users did not agree to participate in the challenges. Only one subject had had steroids added to her pharmacotherapy during the follow-up years.

Bronchial challenges

Thirteen of 21 subjects in the cat immunotherapy group agreed to undergo an allergen challenge. In all but one, PC₂₀ had decreased, as shown in Fig. 1, since the end of therapy (from a median of 1.6 HEP to 0.1 HEP; $p < 0.01$). Median PC₂₀ was still higher than before therapy (median, 0.03 HEP); however, the difference was not significant ($p = 0.1$).

Sixteen subjects treated with cat immunotherapy took part in histamine bronchial challenges (Fig. 1). Median PC₂₀ after 5 years without therapy was not significantly different from median PC₂₀ when therapy was stopped (4.8 mg/ml and 5.4 mg/ml, respectively), and there was still a significant difference compared with PC₂₀ before therapy (median, 0.9 mg/ml; $p < 0.01$).

The response to both challenges was not significantly different in those who reported frequent exposure to cats and dogs compared with those who were rarely exposed.

Six of 11 subjects in the dog immunotherapy group returned for bronchial allergen challenge. Five of them were more sensitive as determined by PC₂₀ than at the end of the study; median PC₂₀ was 0.04

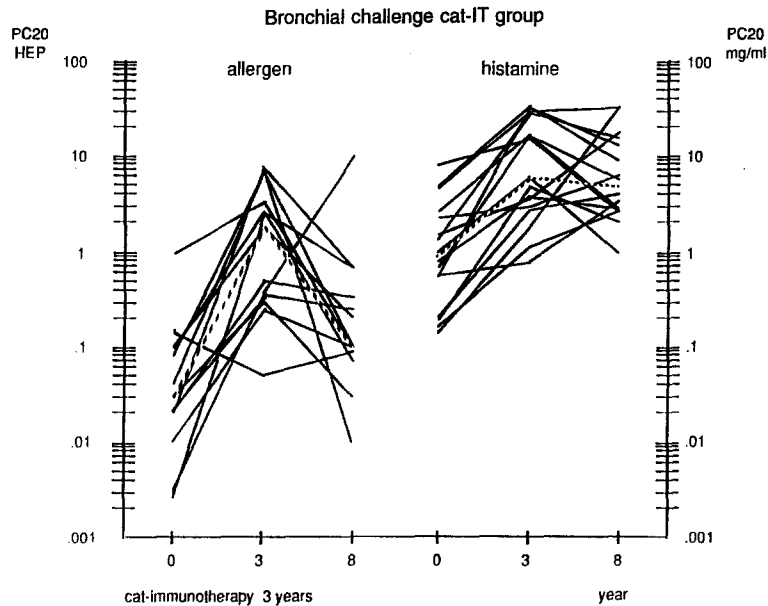


FIG. 1. Results of cat allergen challenges and histamine bronchial challenges before therapy, after 3 years of cat immunotherapy, and 5 years after immunotherapy had been stopped in the subjects who received cat immunotherapy. Median is indicated. 1 HEP cat/ml = 2.15 μ g Fel d 1/ml.

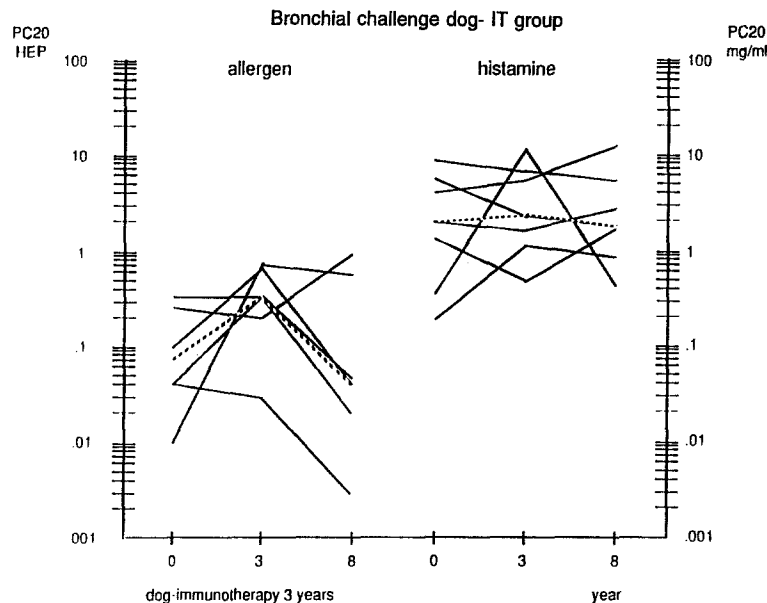


FIG. 2. Results of dog allergen challenges and histamine bronchial challenges before therapy, after 3 years of dog immunotherapy, and 5 years after immunotherapy had been stopped in the subjects who received dog immunotherapy. Median is indicated. 1 HEP dog = 76.0 μ g dog albumin/ml.

HEP at follow-up, which was not significantly different from the value before the study (median, 0.07 HEP). Seven subjects underwent histamine challenges; median PC₂₀ values were 2.0, 2.1, and 1.8 mg/ml before treatment, after immunotherapy, and at the follow-up challenge, respectively (Fig. 2).

Antibody levels

Specific IgE to Fel d 1 had decreased during treatment from a mean of 138.9 SU/ml to 84.8 SU/ml (Table III). The IgE levels were still low (mean, 74.0 SU/ml) at follow-up. The Can f 1-specific IgE levels were low at all three points of

TABLE III. Specific antibody levels before and after immunotherapy and at the 5-year follow-up visit

	Before IT	After IT	5-year follow-up
Cat IT group (13)*			
Fel d 1 IgE (SU/ml)	138.9 ± 43.3	84.8 ± 32.7	74.0 ± 26.8
Fel d 1 IgG ₄ (%)	8.5 ± 4.4	68.3 ± 1.2	22.1† ± 5.1
Dog IT group (7)*			
Can f 1 IgE (%)	1.7 ± 0.6	1.0 ± 0.4	1.2 ± 0.5
Can f 1 IgG ₄ (%)	3.8 ± 0.7	39.2 ± 4.8	6.5‡ ± 1.8

Values are expressed as means ± SEM.

IT, Immunotherapy.

*Number of subjects for whom three serum samples were available.

†*p* = 0.02 compared with before therapy.

‡*p* = 0.05.

measurement: mean values were 1.74%, 1.02%, and 1.21%. Specific IgG₄ to Fed d 1 increased during treatment from a mean of 8.5% to 68.3% and fell to 22.1% at follow-up, still significantly higher than before therapy (*p* < 0.01). Can f 1-specific IgG₄ changed in a similar way from a mean of 3.8% to 39.2% after 3 years of therapy and had decreased to 6.5% 5 years later (*p* = 0.05 vs before therapy).

Correlations

There was no significant correlation between the change in PC₂₀ histamine and symptoms of BHR or between the change in PC₂₀ allergen and symptoms on exposure (chi square). This could partly be explained by the small number of subjects who underwent bronchial challenges. Five reported fewer BHR symptoms; of these, two had not undergone the histamine challenge, two had PC₂₀ higher than that after 3 years of therapy, and one had a decreased PC₂₀. Six subjects had improved further on exposure to the offending animal; of these, two had not been challenged, and the other four had increased bronchial allergen sensitivity. There was, however, a significant correlation between change in PC₂₀ histamine and PC₂₀ allergen (*r* = 0.47, *p* < 0.05). There was no further correlation between change in specific IgE or IgG₄ and the challenge results. IgG₄ Fel d 1 was not higher in those who had improved further, according to subjective evaluations, on exposure to cat.

DISCUSSION

This follow-up study is based on objective measurements and subjective evaluation of probable remaining effects of immunotherapy 5 years after the treatment was stopped. Immunotherapy is a demanding and expensive treatment of long duration. It is therefore reasonable to require that the

effects of immunotherapy should last for some time after the treatment has been stopped. So far there are few follow-up studies after immunotherapy with standardized extracts. In our study the clinical effects, as judged by the patients, are in agreement with the Danish grass pollen immunotherapy follow-up results¹; thus, 26 of our 30 subjects reported further improvement or no change in symptoms on exposure to cats or dogs. This is somewhat surprising because 17 of 19 subjects who had a bronchial challenge had an increase in allergen sensitivity. We did not, however, make any attempt to measure a possible late-phase reaction after the bronchial allergen challenges. The association between the late asthmatic response (LAR) and BHR is by now well established. Van Bever and Wim¹⁷ and others have shown immunotherapy to attenuate the LAR, and a remaining effect of immunotherapy on LAR could be associated with a sustained improvement of BHR and concurrent mild symptoms of allergy to cats or dogs. This hypothesis could further be supported by the fact that the improvement of BHR achieved by cat immunotherapy remained in 14 of the 16 histamine-challenged subjects in our cat immunotherapy group. According to Van Bever and Wim,¹⁷ however, LAR did recur 1 year after stopping a 1-year course of mite immunotherapy in children. In studies by Hejjaoui et al.¹⁸ the effects of mite immunotherapy are reported to last for more than 3 years if the duration of therapy has been more than 3 years. Thus it is probable that the longer the duration of the therapy, the more lasting are the clinical effects. Another possible explanation for the stable result of the histamine challenges in our study is the introduction of antiinflammatory pharmacotherapy, but only three subjects had started to use inhaled steroids during

the follow-up period, and two of these did not undergo histamine challenges. Therefore the result of the bronchial histamine challenge could not be explained by addition of antiinflammatory drugs. Most children and adults considered their asthma to be mild at the end of the study, and only four subjects answered that they were worse at the follow-up, which was in agreement with the fact that 20 of 28 still did not need any medication other than β_2 -agonists as needed.

The answers to the questionnaire can be difficult to interpret because so much time had elapsed between the end of immunotherapy and the follow-up study. It would have been preferable to have approached the subjects once a year to get a clearer picture of the course of the disease.

Furthermore, differences in the natural history of animal dander allergy when subjects were or were not exposed have, as far as we know, not been addressed in any published study. Kjellman and Pettersson¹⁹ investigated the prevalence of allergy to furred pets in a cohort of children with asthma. Eight years later, Kjellman and Dalen²⁰ performed a follow-up study in the same children. According to this study, skin prick test results continued to be positive in the majority of children (74% of the subjects with cat, horse, and dog sensitivity), and symptoms on exposure remained in 92% of these children after 8 years. However, their study did not include any information about how often the children were exposed to furred animals.

Two follow-up studies have dealt with pollen immunotherapy. Osterballe¹ reevaluated severity of symptoms in grass-treated patients 6 years after termination of treatment. The patients' subjective evaluations by symptom scores during a season indicated increased symptoms, although the season had higher pollen counts than the last season during the treatment period. The authors adjust for this difference and conclude that symptom scores on the whole remain low after 6 years without therapy. Antibody levels of specific IgE had increased, specific IgG had decreased, and both had returned to pretreatment levels.¹⁰ Wihl et al.¹¹ reported similar results from their follow-up study of adults with rhinitis who were treated with tree pollen. Thus the impression is that in subjects with rhinitis or mild to moderate asthma, immunotherapy could contribute to a mild course of the disease. We did not, however, include a control group not treated with immunotherapy, and the influence of the natural course of asthma could therefore not be evaluated.

Overall, our results may reflect the effects of exposure or avoidance rather than the remaining

effects of the therapy. None of the subjects had cats or dogs during the immunotherapy part of the study. Three subjects had pets: two children who received cat immunotherapy had dogs, and one adult who received dog immunotherapy had three cats at follow-up. Eight patients reported that they were exposed to dogs and cats often outside of their homes. Thus 19 of 30 patients continued to avoid direct exposure. There was, however, no general tendency for those exposed to have more symptoms, lower PC₂₀ allergen or histamine, or higher specific IgE levels or IgG levels than those who were exposed rarely or not at all. Two of four subjects who considered themselves worse at follow-up did not undergo challenges, which could have affected the overall results. The other two had improved PC₂₀ histamine but increased sensitivity as determined by allergen bronchial challenge.

The persistent low levels of cat-specific IgE could reflect a remaining immunologic effect of immunotherapy. The low levels of IgG₄ further confirm the lack of relationship between specific IgG and clinical effects of immunotherapy, also reported in the grass pollen immunotherapy follow-up.¹⁰ Finally, one of the most thorough long-term follow-up studies has concerned the safety of stopping venom immunotherapy. For up to 5 years after stopping therapy, 90% of the subjects who were sting-challenged were protected from systemic reactions.⁸ Also in this study, specific IgE levels did remain low for up to 4 years after stopping therapy.

In summary, five years after a 3-year course of immunotherapy with standardized cat or dog dander extracts, symptoms of asthma, according to patients' subjective evaluations, had not increased in general or on exposure to the previously offending animal. Contrary to the patients' reports, the sensitivity to cat or dog allergen had increased as measured by bronchial allergen challenge. However, specific serum IgE levels were still low, and the improvement in BHR gained during immunotherapy in the subjects treated with cat extract was still present.

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