

Immunotherapy in patients allergic to cat and dog dander

I. Clinical results

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Twenty-four asthmatics allergic to cat and/or dog dander were included in a study to examine the efficacy and safety of immunotherapy (IT) with partially purified, standardized extracts of cat or dog dander. In the first placebo controlled, double-blind part of the study, 10 patients were treated with extracts of both cat and dog, 12 with cat extracts and 2 with dog extracts. Fifteen patients received active IT and 9 placebo injections. Patients treated with both extracts received active extracts only, or placebo only. Bronchial allergen challenge after 5 months demonstrated a significant fall in sensitivity to cat ($P = 0.04$) in patients treated with cat extracts. No significant changes were found in sensitivity to dog after treatment with dog dander extract or in the placebo groups. During this period, bronchial sensitivity to histamine did not change significantly in any of the groups. To examine the effect of more prolonged IT, 19 patients allergic to cat (17) and/or dog (9) were treated for 12 months. Bronchial sensitivity to cat decreased further ($P = 0.003$), while no significant change was found in dog extract-treated patients. In cat extract-treated patients a significant decrease in bronchial histamine sensitivity developed ($P = 0.02$). Systemic side effects were few, but in some cases, local side effects were a dose-limiting factor. This study demonstrated that IT with cat extract may benefit cat-allergic asthmatics, whereas no influence of IT with dog extract was detected in dog-sensitive asthmatics.

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In patients with allergic asthma, allergy to cat and dog has been detected in about 50%, characterized by a positive skin prick test (SPT) and history of clinical sensitivity to animal danders (9, 22, 23). Dogs and cats are kept as pets in 50% of homes of Swedish schoolchildren, and in 25% of homes of asthmatic children with known animal dander allergy (9). Although avoidance of contact with the offending animal is the preferred treatment, this is in many cases impossible and has great impact on the social and working life of the asthmatic. Indirect exposure may occur at school, working places or other public places, and animal dander proteins have been found in significant amounts in dust samples from homes where no pets were kept (22), possibly causing symptoms in highly sensitive individuals. The results of immunotherapy (IT) for animal dander allergy have varied (3, 18). The introduction of well-characterized extracts with a known content of major allergens has been promising (14, 17). We present the clinical results of a double-blind placebo controlled study of

IT with standardized extracts of cat and dog dander in asthmatics. Our purpose was to examine the efficacy of this treatment regarding the bronchial sensitivity to animal dander and to investigate the occurrence of adverse reactions during IT.

Material and methods

Patients

Twenty-seven patients were selected for the study (15 female and 12 male with a mean age of 28 years (range, 13 to 48 years)). The inclusion criteria to be fulfilled were: 1) a positive history of asthma provoked by contact with cat or dog, 2) a positive skin prick test (wheal ≥ 3 mm diameter) with cat or dog dander extracts in a concentration of 10000 biological units (BU), 3) a positive bronchial challenge test (BCT) with extracts of cat or dog dander in a concentration of 100000 BU or less, 4) a positive RAST (Phadebas® RAST, Pharmacia AB, Uppsala, Sweden) defined as $\geq$ RAST class 1.

The study was approved by the Ethics Committee of Aarhus County. All patients gave their consent to participate after written and oral information.

Study design

The patients were allocated to treatment with extracts of cat and/or dog dander or placebo. Allocation was based on sex, age and bronchial sensitivity to allergen according to a prepared scheme. Patients allergic to both cat and dog were treated with extracts of both cat and dog dander injected separately, or given subcutaneous placebo injections on the extensor side of the forearms. The study consisted of two parts. Part one lasted for 5 months and was a double-blind, placebo controlled period, where patients were allocated to 2 groups. Group A received injections with extracts of cat and/or dog dander and Group P received placebo injections. To examine the effect of more prolonged IT, the study was continued with the patients in Group P switched to active treatment. Active treatment was continued in all patients for 12 months. Diagnostic tests were performed during the run-in period, after the placebo period and, for all patients, after 5 and 12 months of active treatment (Fig. 1).

Allergen extracts

Extracts used for diagnosis and treatment were Pharmalgen[®] cat epithelium extract and dog dander extract (Pharmacia AB, Uppsala, Sweden. ALK, Hørsholm, Denmark). These were partly purified and standardized by quantitative immunoelectrophoresis and RAST inhibition to determine composition and potency. Biological strength was defined in biological units by skin prick testing a group of known allergic patients. Extracts giving the same wheal size as histamine chloride 10 mg/ml were defined to have an allergen concentration of 10 000 BU/ml. According to the manufacturer, the quantity of Fel d 1 in the cat extract was 200 µg/ml (8 Ohman U/ml) in the vials containing 100 000 BU/ml (4). For diagnostic use and primary up dosing, freeze-dried extracts were reconstituted in albumin diluent (0.03%

human albumin in saline). The same batch of extracts was used for diagnostic tests and IT throughout the study. For final up dosing and maintenance therapy a depot diluent (0.2% Al(OH)₃ and 0.4% phenol in saline) was used. Placebo preparation was histamine chloride containing burned glucose to ensure blinding.

Immunotherapy protocol

The injections were given every 2nd week with 2 injections on the same day for the first 8 injections and then one injection on each occasion. The first 8 injections were given with aqueous extracts and the remaining injections with depot extract (Table 1). Maintenance dose was administered every 4–6 weeks, and was the maximum tolerated dose, or 1 ml of depot extract with an allergen concentration of 100 000 BU/ml.

Diagnostic tests

Skin prick tests were performed as titration with cat and/or dog dander in concentrations of 1000, 10 000, 100 000 BU/ml. The procedure and results of this and *in vitro* immunological results will be reported elsewhere. SPT was also made with a panel of common inhalant allergens including horse dander, timothy, birch, house dust mite (*Dermatophagoides pteronyssinus*), *Cladosporium herbarum* and *Alternaria tenuis* in concentrations of 10 000 BU/ml. Histamine chloride 10 mg/ml was used as control.

Bronchial challenge with histamine dihydrochloride was performed as a modification of the method described by Cockcroft et al. (5). The patients inhaled for 2 min from a Pari-nebuliser (Pari Ritzau Pari Werk, Starnberg, Germany), driven by compressed air (flow 5 l/min) giving a mean output of 0.57 ml/min. The aerosol was delivered via a facemask. Isotonic saline was first inhaled. Peak expiratory flow

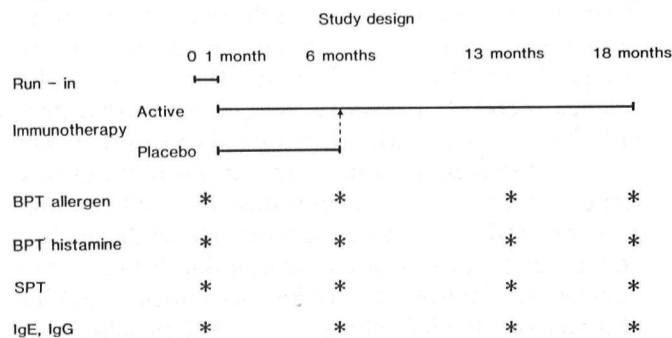


Fig. 1. Study design.

Table 1. Dose schedule for immunotherapy with animal dander extracts

Injection No.	Day	Diluent used	Dose injected (BU)
1	1	Albumin	10
2	1	Albumin	100
3	15	Albumin	200
4	15	Albumin	400
5	29	Albumin	1000
6	29	Albumin	2000
7	43	Albumin	2000
8	43	Albumin	3000
9	57	Depot	20000
10	71	Depot	40000
11	85	Depot	70000
12	99	Depot	100000

(PEF) measured 3 min after this was used as baseline value. Doubling concentrations of histamine dihydrochloride were then inhaled, starting with 0.03 mg/ml until a fall in PEF of at least 20% had been obtained. The highest concentration used was 8 mg/ml. The concentration of histamine dihydrochloride producing a fall in PEF of 20% (PC₂₀ histamine) was calculated by linear interpolation on the log dose-response curve (6).

Bronchial challenge test with allergen was a modification of a procedure previously described (8). The same Pari-inhaler as used for histamine challenge nebulised the extract. Inhalations were taken via a facemask at tidal breathing, with 5 inhalations of diluent as control. PEF was recorded 5 and 10 min after inhalation. Allergen BCT began with 2 inhalations of the allergen dilution giving a 2–3 mm wheal at SPT. If there was a fall in PEF of <10%, 4 inhalations of the same concentration were taken. If PEF fell between 10 and 20%, the last dose was repeated, and if the fall after 4 inhalations was <10%, 8 inhalations were taken. The next step was a 10-fold increase in allergen concentration, continuing increasing doses until a 20% fall in PEF occurred. The cumulated dose of allergen producing a 20% fall in PEF (PD₂₀ allergen) was calculated by linear interpolation on the log dose-response curve.

Statistics

Nonparametric statistical tests were used and logarithmic transformation of data was made before analyses. For changes within groups during time Wilcoxon matched-pairs, signed-ranks sum test was used, and for comparison between groups the Mann-Whitney U test. For correlation analyses Spearman or Kendall tests were used. Tests were performed with the SPSS package (13).

Side effects

Local wheal and flare at the site of injection was recorded after 30 min by the investigator, and during the next 48 h by the patients. Systemic side effects were recorded in the same manner, and the patients measured PEF twice daily 48 h after each injection.

Results

Patients

Skin prick tests were positive to horse dander in 6 patients, to timothy in 5, to birch pollen in 2 and to house dust mite (*D. pteronyssinus*) in 2, while no patients had a positive SPT to moulds. Three of the patients withdrew in the interval between diagnostic

tests and the start of injections. Since these patients had all been allocated to placebo treatment, 15 patients received active IT, and 9 patients placebo injections. Of these 24 patients, 10 had a diagnosis of allergy to both cat and dog, 12 were allergic to cat only, and 2 allergic to dog only. The patients were treated as follows: active cat extract 14 patients, active dog extract 8 patients, placebo cat 8 patients and placebo dog 4 patients. After completing the 5 months of placebo controlled IT, 4 patients dropped out for reasons unrelated to the study, and during the second part of the study one patient who did not want to continue the study after a severe systemic side effect was withdrawn. The 12 months of active IT were completed by 19 patients, of whom 7 were allergic to both cat and dog, 10 allergic to cat only, and 2 allergic to dog only.

Bronchial challenge test with allergen

After 5 months of IT the patients treated with cat allergen had a significantly decreased PD₂₀ to cat extract ($P=0.04$), while no significant change was demonstrated in the placebo group. A comparison of the change in PD₂₀ between the placebo group and the group of patients treated with cat extract showed no significant difference after 5 months of IT ($P=0.13$). For the patients treated for 12 months, the decrease in PD₂₀ to cat was more pronounced ($P=0.003$). Patients treated with dog allergen demonstrated no significant decrease in PD₂₀ to dog extracts after 5 and 12 months, and neither did the placebo group. No significant difference between placebo and dog extract-treated patients was found (Fig. 2).

Patients' assessment

After 5 months, before any tests were performed, patients were asked by questionnaire about their symptoms when exposed to the offending animal(s). Less symptoms than before treatment were reported by 12/15 patients in the active-treated group, while no remarkable difference was reported by the patients in the placebo group ($P<0.01$).

Bronchial challenge with histamine

Patients treated with cat allergen increased their PC₂₀ histamine after 5 months ($P=0.08$) and after 12 months this increase was significant ($P=0.01$) (Fig. 3). After 5 months the placebo group of dog-allergic patients showed a decrease in PC₂₀ histamine ($P=0.02$). After 12 months a significant ($P=0.01$) correlation between the increase in PD₂₀ cat and the increase in PC₂₀ histamine was found in patients treated with cat extract.

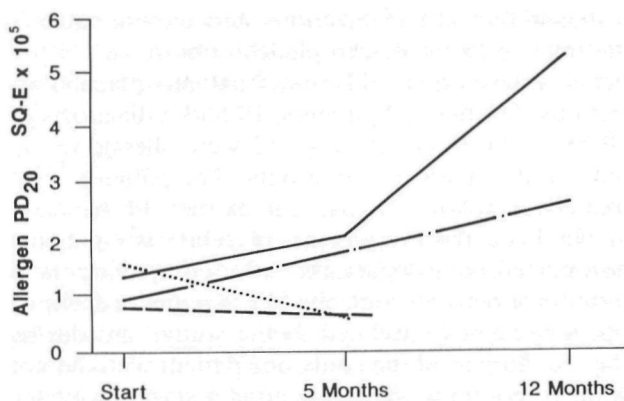


Fig. 2. Changes in $\log_{10}$ PD_{20} to cat and dog extracts during immunotherapy (active cat: —; active dog: - - -; placebo cat: --, placebo dog: ···).

Side effects

After 8–12 h a local swelling of 5–10 cm in diameter was reported after 19% of the injections, and a swelling > 10 cm after 6% of the injections. Moderate asthma 8–12 h after an injection was reported 10 times in 2 patients in the placebo group and 5 times in 2 patients given allergen injections. An attack of severe asthma occurred in one patient 5 min after injection, during the dose increment phase at a dose of 70 000 BU where depot diluent was used, and one patient had an immediate anaphylactic reaction also during the dose increment phase with depot diluent at a dose of 40 000 BU. Apart from this, minor asthmatic attacks within 30 min after injection occurred in 2 patients during maintenance treatment, treated efficiently by inhalation of β_2 -agonists.

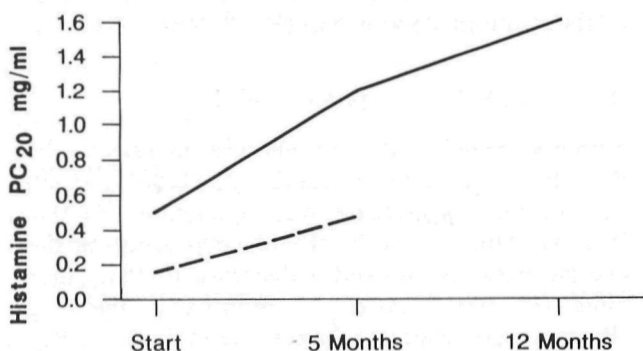


Fig. 3. Changes in $\log_{10}$ PC_{20} histamine during immunotherapy in the group of cat-allergic patients (active: —; placebo: --).

Table 2. Maintenance doses of allergen

	5 months	12 months
Cat		
mean	43,700 BU	60,900 BU
range	15,000–100,000 BU	20,000–100,000 BU
Dog		
mean	42,800 BU	65,000 BU
range	20,000–100,000 BU	20,000–100,000 BU

Table 3. Cumulated doses of allergen

	5 months	12 months
Cat		
mean	229,000 BU	676,000 BU
range	63,710–418,710 BU	198,810–1,338,710 BU
Fed d 1		
mean	458 μ g	1352 μ g
range	127–837 μ g	398–2677 μ g
Dog		
mean	185,000 BU	667,000 BU
range	63,710–418,710 BU	198,810–1,338,710 BU

Allergen dosage

The mean maintenance dose after 5 months was 91428 BU for patients given placebo cat and 100 000 BU for placebo dog. Due to occurrence of local side effects the mean maintenance dose in the group of patients treated with cat extract was 43 700 BU (range, 20 000 to 100 000 BU) after 5 months, and 60 937 BU (range, 20 000 to 100 000 BU) after 12 months. Corresponding figures for patients treated with dog extract were 42 778 BU (range, 20 000 to 100 000 BU) after 5 months and 65 000 BU (range, 20 000 to 100 000 BU) after 12 months (Table 2). The cumulated dose expressed in BU after 5 and 12 months was similar in the groups treated with cat and dog allergen (Table 3).

Discussion

In patients with specific sensitivity a specific treatment should always be considered. In animal dander allergy it is possible in most cases to reduce allergen exposure, but keeping furred pets is so common that some degree of exposure is inevitable. A major factor in the decision whether to start IT is the documentation of the efficacy of IT. We found a significant increase in our patients' tolerance to BCT with cat extract, and the patients reported fewer symptoms

when exposed to cat. The protection became more pronounced when the period of treatment was extended from 5 to 12 months and the number of patients who tolerated significantly higher amounts of allergen at BCT increased. These results indicate that the duration of treatment is important when investigating the efficacy of IT. Our results are in accordance with those of other investigators using purified extracts in IT of cat asthma (14, 16, 17, 20). In contrast, we were not able to demonstrate any significant increase in the PD₂₀ to dog extract. This was probably due to the relatively small number of patients included, but other studies have also had difficulties in demonstrating the efficacy of IT in dog asthma using BCT for evaluation (16, 19). A significant increase in PD₂₀ dog has only been reported in a Scandinavian study (7, 10) where there was evidence that the dog extract was less potent than cat extract as the number of side effects was lower in patients treated with dog extracts. In the present study we found no difference between cat and dog extracts in the number and size of local side effects, we had very few systemic side effects, and in the patients treated with both dog extract and cat extract, we were unable to discriminate between systemic side effects caused by cat or dog extracts. In our patients, maintenance and cumulated doses of cat and dog extract, expressed in BU, were absolutely comparable. Thus, although it may be possible, our data produces no direct evidence indicating that the dog extract used was less potent than the cat extract.

In vitro studies have shown some cross-reactivity between cat and dog extracts (2) but clinical and *in vitro* sensitivity restricted to either cat, dog or both is well recognized. That there is a much higher frequency of sensitivity to cats than to dogs (12) is also reflected in our study population. Many of our patients were allergic to both cat and dog and we chose to treat such patients with extracts of both allergens, and used specific BCT as the parameter of evaluation. Two of our patients who were sensitive only to cat and with a positive BCT to cat failed to react to dog extract at BCT before the study. Equivalent doses of Fel d I inhaled during BCT and at natural exposure to cat have been shown to induce a comparable drop in lung function in sensitive asthmatics, making BCT a possible model of natural exposure (21). We did not examine the influence of IT with cat extracts on the sensitivity to dog, or vice versa, but others have found no development of new allergies as a result of prolonged IT (11, 24). The influence of IT in asthma on non-specific bronchial hyperresponsiveness has not been clarified. Our patients receiving cat extract showed a decrease in specific as well as non-specific bronchial responsiveness. The significant correlation between the improvement in

PD₂₀ cat and PC₂₀ histamine indicates that this may be due to a beneficial effect on bronchial inflammation. In another study a decrease in non-specific bronchial responsiveness has been demonstrated (7, 10, 16), while others have not been able to detect any change in non-specific bronchial responsiveness (14, 17, 20).

The occurrence of side effects in the present study seems acceptable, although large local reactions were a dose-limiting factor in many patients not reaching the intended maintenance dose. Systemic side effects were limited, but their occurrence stresses the importance of keeping the patients under observation immediately after allergen injections. Late reactions were found mostly as local reactions at the site of injection.

In conclusion, we have demonstrated IT to be effective in reducing both specific and non-specific bronchial sensitivity in patients with asthma and allergy to cat, while no significant effect of IT could be demonstrated in patients allergic to dog dander. IT was safe with the doses of allergen extract administered in the present study.

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