

Original article

Sublingual immunotherapy with a standardized cat dander extract: evaluation of efficacy in a double blind placebo controlled study

Background: Little information is available on the clinical efficacy of sublingual immunotherapy (SLIT) using extracts derived from mammalian epithelia.

Objectives: To assess clinical efficacy of cat SLIT based on natural exposure challenge test (NCT).

Material and methods: Fifty cat allergic patients with rhinoconjunctivitis with or without asthma were included in a randomized double blind placebo controlled clinical trial of cat SLIT during 1 year. Twenty-five patients received active treatment and 25 placebo. Sublingual immunotherapy efficacy was assessed by natural exposure challenge to a cat in a cat-room and by skin tests. Airborne Fel d 1 levels, symptom scores and peak expiratory flow (PEF) values were monitored.

Results: Thirty-three (66%) out of 50 patients completed the treatment. Fel d 1 content of the maximum concentration was 0.51 µg per ml. During the build up phase, the accumulated dose was 1.7 µg of Fel d 1 and during the entire length of the study was 17.1. No adverse reports were reported. The active group showed a marked reduction (62%) in symptoms during the NCT ($P < 0.001$) with no changes in placebo group. Active group also showed a reduced PEF response to cat exposure ($P < 0.05$), and an improvement in skin test reactivity to a standardized cat extract ($P < 0.05$), without significant changes in placebo group. Mean Fel d 1 exposure during the NCT was 6.2 ± 2.21 ng/m³.

Conclusions: The results suggest that the cat SLIT used in this study was able to improve cat allergy based on natural exposure challenge.

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Key words: cat allergic rhinitis and asthma; Fel d 1; immunotherapy; sublingual immunotherapy.

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In many industrialized countries, several factors such as the increasing frequency of cats in homes or the presence of significant levels of cat allergen in cat-free areas (homes, schools, day-care centres and workplaces without a cat) have contributed to increase the frequency of cat allergy (1–6). In some areas, the frequency of asthmatic children sensitized to domestic pets has been reported to be up to 50–70% (7).

Fel d 1 is a major cat allergen (8) and more than 80% of cat allergic patients are sensitized to Fel d 1. Fel d 1 is able to inhibit more than 80% of cat specific immunoglobulin E (IgE) binding in the serum of cat allergic individuals (8). Based on these facts, cat allergy emerges as an interesting model for allergy research. Today, immunological advances permit the development of specific monoclonal antibodies and recombinant allergens

to better assess cat exposure by monitoring airborne levels of Fel d 1. Luczynska et al. (9) analysed Fel d 1 levels in a cat vivarium housing 12 cats, and determined a concentration of 40 ng Fel d 1/m³. A wide range of airborne Fel d 1 concentrations has been reported from homes with cats, oscillating between 0.7 and 468.5 ng/m³ (10). In addition, cat allergens have also been detected in homes without cats (10–13), recording smaller levels in these cat free homes (0.24–1.78 ng/m³) (10). Most of the authors have concluded that low levels of airborne Fel d 1 (ng quantities per m³) are capable of eliciting symptoms in cat sensitized patients (3, 14, 15).

The first-line therapeutic measure in cat allergic patients is to remove cats from the domestic environment. However, in many cases, patients reject this possibility, or, when adopted, the removal of the cat is insufficient to achieve complete allergen avoidance. Cat immunotherapy (IT) is the only treatment able to alter the natural course of cat allergy. Several studies have demonstrated the efficacy of s.c. IT in the treatment of cat respiratory allergy (16–23). Other routes of IT administration have been analysed for safety. Among them, the sublingual

Abbreviations: AUC, area under the curve; CI, confidential interval; CL, confidence limits; CL, confidential limit; HEP, histamine equivalent prick; IQ, interquartile; IT, immunotherapy; NCT, natural challenge test; PEF, peak expiratory flow; SLIT, sublingual immunotherapy.

route is the most frequent alternative to s.c. IT (24). In 1993, Nelson et al. (25) reported a double blind placebo controlled study, which concluded that cat sublingual IT was no more effective than placebo. Bousquet et al. (26) pointed out some methodological problems in this study. Both reports agreed that further studies would be justified to fully assess the efficacy of cat sublingual immunotherapy (SLIT). The aim of this study was to evaluate efficacy of SLIT as a treatment of cat allergic patients based on natural challenge test (NCT) in a cat room.

Material and methods

Patient population

Fifty patients (13 males and 37 females, mean age 27 years of age) with persistent rhinitis moderate-severe symptoms according to ARIA guidelines (27), with or without asthma, caused by exposure to cats were enrolled in this study. The diagnosis of cat allergy was made by clinical history, positive skin prick test (SPT) with a standardized cat extract [30 histamine equivalent prick (HEP)/ml, containing 70 µg of Fel d 1/ml; Laboratorios LETI, S.L., Tres Cantos, Madrid, Spain] and serum specific IgE measured by the CAP System (Pharmacia Diagnostics AB, Uppsala, Sweden). All patients had at least a history of 1 year of known allergic symptoms when in contact with cats. The medication used by these patients consisted of antihistamines (Loratadine; Clarytine, Schering-Plough, SA, Madrid, Spain), local corticosteroids (nasal and bronchial budesonide; Pulmicort, Rhinocort 64, AstraZeneca, Spain), nedocromil and salbutamol. The use of β -blockers was strictly prohibited. All patients were skin tested with a battery of standardized allergen extracts (Laboratorios LETI, S.L.). Regular environmental prophylactic measures were recommended (28) and patients were advised to avoid cat exposure. However, they continued having direct or indirect contact with cat allergen. The study was reviewed and approved by both the Independent Ethics Committee of the University Hospital 'Ramón y Cajal' and by the Spanish Health Authorities (Agencia Española del Medicamento). The study was conducted in accordance with the Declaration of Helsinki.

The inclusion criteria were: positive clinical history of allergy to cats and monosensitization to cat allergens, from 14 to 55 years of age; positive SPT results (wheal ≥ 7 mm²) with a standardized cat dander extract and specific IgE to cat dander; positive clinical history of respiratory allergic symptoms related to cat exposure. The exclusion criteria were: use of IT during the last 5 years; any contraindication for the IT according to criteria of European Allergy and Clinical Immunology Immunotherapy Subcommittee, including treatment with β -blockers, immunopathological diseases and serious psychiatric/psychological disturbances. In addition, the following conditions were considered as exclusion criteria: pregnancy or lactation and intolerance to aspirin.

Sample size calculation

To determine the sample size, the results of the study by Varney et al. (29) were used. In the active group, they measured a mean symptom score of 61.6 (SE 9.1) before treatment and of 17.1 (SE 7.6) at the end of the study. In the placebo group the values were 64.7 (SE 13.6) and 62.1 (10.0). We expected to observe a difference of 30 points in symptom scores between the active and the placebo groups. Therefore, the number of patients necessary for an $\alpha = 0.05$

and $\beta = 80\%$ was of 20 per group. We considered the possibility of a 20% of withdrawals, thus the final sample size settled at 25 patients per group. However, at the end of the study, <20 concluded per arm. We, therefore, calculated the power of the results obtained with the natural provocation tests with the patients who concluded the study. When the results of both groups were compared at the end of the study, the power was 0.7821 (78.21%). When the results of the active group were compared at baseline and at the end, the power was 0.9967 (99.67%).

Study design

The design of the study was randomized, double blind and placebo controlled. Patients were randomly allocated into two groups (one group received the active treatment and the other placebo) and treated for 12 months. Because of small sample size, we did not use the minimization method of allocation of patients to the arms of the study (30). At the end of the study and when the code was opened, we confirmed that the distribution of patients by disease and severity was homogeneous and no significant differences were observed. Each patient was evaluated before IT (time T0) and 1 year after commencement of the IT. Efficacy was assessed by natural exposure to cat in a cat-room scoring symptoms (conjunctival, nasal and bronchial symptoms) and peak expiratory flow (PEF) values. Allergen levels were assessed by quantitation of airborne Fel d 1 levels several times during the NCT. Patients were also skin tested before the start of specific IT and after 12 months of treatment. Side effects were assessed at every time after initiating SLIT.

Treatment protocol

The active treatment consisted of an aqueous solution of standardized semi-purified cat dander extract (Fig. 1). The extract also contained NaCl 0.9%, phenol 0.4% and glycerol 50%. The patients were instructed to keep the liquid for at least 2-min under the tongue before swallowing it. The qualitative and quantitative composition of the placebo was identical to the experimental

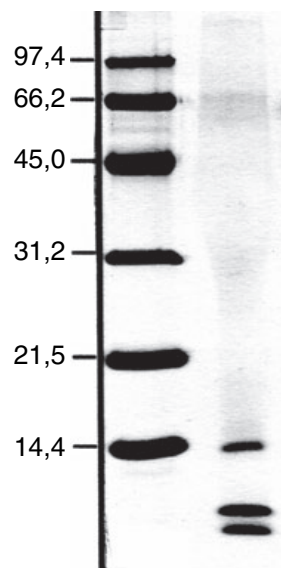


Figure 1. Sodium dodecyl sulphate-polyacrylamide gel electrophoresis of the cat extract used in the study for skin testing and sublingual immunotherapy.

product, but without active ingredients. The active and placebo treatments were supplied by Laboratorios LETI, S.L. Seven consecutively numbered vials were used. Fel d 1 content of the maximum concentration was 0.51 µg per ml. During the build up phase, the accumulated dose was 1.7 µg of Fel d 1. The total accumulated dose during the entire length of the study was 17.1 µg of Fel d 1. Patients received the corresponding dosage daily, starting the first day with one drop of the more diluted vial 1, two drops the second day, three drops the third, until the fifth day in which the patient received five drops. When this level was reached, vial 2 was started, following the same scheme until a maximum of five drops were reached, following with the next vial. This schedule was followed until the intake of five drops of vial 6. Afterwards, a maintenance dose of two drops of vial 7 were taken daily.

Dose response skin test

Patients were skin tested before the start of specific IT and after 12 months of treatment. The SPTs were conducted in duplicate, on the volar surface of the forearm using four 10-fold dilutions of freeze-dried extract of cat dander. The maximum concentration was 30 HEP/ml, containing 70 µg of Fel d 1/ml). The extract was supplied freeze-dried and vacuum closed to be reconstituted just before use. Histamine HCl 10 mg/ml and glycerinated saline solution were used as positive and negative controls, respectively. The same batch of allergen extract was used throughout the trial. The same trained allergist performed the test to avoid variations. Skin tests were performed between 9:00 and 11:00 AM to avoid circadian differences in skin reactivity. None of the patients was pretreated with drugs that could have affected the results of the test. All the reactions were recorded after 15 min of application (31). Wheal areas were outlined with a fine tip marker and transferred, with transparent tape, to the corresponding sheet of a case report form. The area of each wheal was measured by planimetry using a Wacom palette (Wacom Technology Co., Vancouver, WA, USA) and the computer program Mac Draft (Microspot Inc., Boca Raton, FL, USA). For each patient, the individual 10 HEP was calculated, which is the bio-equivalent dose of allergen extract to achieve a wheal of the same size as the wheal produced by the positive control (32).

Cat exposure and NCT

Cat sensitivity was assessed by NCT. Patients were challenged between 8 AM and noon to avoid circadian variations. Patients were asked to discontinue medication that could interfere with the results of the test. Patients were exposed to cat allergens in a cat room, which was designed based on the previous reported experience (15, 23, 33). Exposures were performed before initiating the treatment (baseline) and after 1 year of treatment in a 21 m³ room housing a female cat. The room was cleaned daily and was kept between 21 and 24 °C. Serial Fel d 1 determinations in the ambient air were carried out before and after exposure to the cat took place. Air samples were collected using an Air sentinel (Quantechair Inc., Rochester MN, USA) at a flow of 9 m³/h. Airborne allergens were collected on PTFE filters (ESW Inc., Concord, Canada) and extracted in PBS overnight. Fel d 1 levels were analysed using monoclonal antibodies (Indoor Biotechnologies Ltd, Charlottesville, VA, USA).

All subjects were asked to record the severity of symptoms and perform a peak flow reading before entering the room and after 5, 10, 15, 30, 60 and 90 min. Symptoms were subdivided into three categories: ocular (itchy, watery), nasal (running, sneezing, blockage and pruritus) and asthma symptoms (cough, wheeze and shortness of breath). Severity of symptoms was recorded according to the

following score: 0, absent; 1, mild; 2, moderate; and 3, severe. Subjects were not allowed to undergo challenge if forced expiratory volume at one second (FEV₁) was <70% of predicted. Subjects remained in the room for 90 min, unless they had intolerable symptoms. Those who left the room were treated and observed until symptoms resolved.

Safety

All patients received their immunotherapy vials from the Allergy Clinic. At regular intervals, the patients were evaluated by the investigator to assess the safety of the treatment which was evaluated recording all side-effects related to the administration of specific IT. Systemic reactions were defined and evaluated according with the criteria of the Position Paper of the European Academy of Allergy and Clinical Immunology (34). Patients were asked to contact the investigators immediately if an adverse event (related or not to the treatment) occurred. Symptoms and medication use was also discussed, but not evaluated as an outcome measure in the study.

Statistical analyses

The software SamplePower (SPSS Inc., Chicago, IL, USA) was used for power calculation with the patients who concluded the study and spss software package (SPSS Inc.) was for statistical analysis. The value of the mean and the 95% confidence intervals (CI), and the median and the interquartile (IQ) range was used for descriptive statistics. The area under the curve (AUC) of each patient obtained during the NCT at baseline and after the 12 months of treatment was calculated for the symptom score and the PEF values.

Nonparametric tests were used for comparative statistics: Mann–Whitney *U* test for intergroup and Wilcoxon signed rank test for intragroup. The Hodges–Lehmann estimator [with the 95% lower and upper confidence limits (CL)] was used to measure the effect size of the differences in symptom score during the NCT between the two groups. The per cent of improvement of active group at the end was calculated referred to the value of the placebo at the end and the value of active at baseline.

Results

Patient characteristics

Thirty-three out of 50 patients (66%) completed the 1-year treatment. Characteristics of these patients are shown in Table 1. Twenty-five of them (75.7%) were female and eight (24.3%) male, with a mean age of 35.5 years (16–51). Seventeen and 16 patients finally composed the active and placebo groups, respectively. Twenty-seven patients had rhinoconjunctivitis and asthma and the rest (six patients) rhinoconjunctivitis alone. Fifteen out of the 17 patients in the active group and 12 out of 16 patients in the placebo group suffered rhinoconjunctivitis and asthma. Twenty-two patients had continuous contact with cats, defined as being in the presence of a cat 5–7 days a week and 11 patients had frequent or sporadic contact (Table 1). During the clinical trial, none of the patients eliminated the cat from their homes or the repeated contact with these pets.

Table 1. Characteristics and cat exposure of the 33 patients that completed the treatment

Group	Symptoms	Gender	Age	Contact with cats
Active	RC	Male	19	One cat at home
Active	RC	Male	42	20 cats at working place (5 days a week)
Active	RCA	Male	26	Three cats at home
Active	RCA	Male	29	Contact 1 or 2 days per week
Active	RCA	Male	41	One cat at home
Active	RCA	Female	16	Five cats at home
Active	RCA	Female	22	Frequent contacts
Active	RCA	Female	23	One cat at home
Active	RCA	Female	23	One cat at home
Active	RCA	Male	31	One cat at home
Active	RCA	Male	24	One cat at home
Active	RCA	Female	26	Two cats at home
Active	RCA	Female	28	One cat at home
Active	RCA	Female	30	Frequent contacts
Active	RCA	Female	33	One cat at home
Active	RCA	Female	37	Frequent contacts
Active	RCA	Female	46	One cat at home
Placebo	RCA	Male	29	Frequent contacts
Placebo	RCA	Female	22	Two cats at home
Placebo	RCA	Female	29	One cat at home
Placebo	RCA	Female	25	One cat at working place (5 days a week)
Placebo	RCA	Female	25	Contact 1 day per week
Placebo	RCA	Female	26	Frequent contacts
Placebo	RCA	Female	29	One cat at home
Placebo	RCA	Female	18	Sporadic contact with cats
Placebo	RCA	Female	25	One cat at home
Placebo	RCA	Female	32	Frequent contacts
Placebo	RCA	Female	30	Contact 1 or 2 days per week
Placebo	RCA	Female	24	One cat at home
Placebo	RC	Female	27	One cat at home
Placebo	RC	Female	21	Sporadic contact with cats
Placebo	RC	Female	51	One cat at home
Placebo	RC	Female	32	One cat at home

RC, rhinoconjunctivitis; RCA, rhinoconjunctivitis and asthma.

Assessment of Fel d 1 airborne levels

The mean airborne Fel d 1 level in the cat room was $6.2 \pm 2.21 \text{ ng/m}^3$. It represents the mean $\pm$ SD of 10 samples collected immediately before and after the days in which the challenges were conducted. There were no statistical significant differences between before and after the treatment (before treatment $5.98 \pm 1.31 \text{ mcg/m}^3$, after treatment $6.52 \pm 3.39 \text{ mcg/m}^3$; ns).

Natural challenge test

Symptoms were evaluated at different intervals during the NCT at the beginning and at the end of the study. At baseline, there were several dropouts after 30 and 60 min of exposure, when one and three patients in the active group, respectively, abandoned the challenge. One further patient on placebo abandoned the challenge after 30 min. At the end of the study, one patient in the active group abandoned the challenge after 60 min and another patient in the placebo group after 15 min. All these abandons were because of exacerbation of symptoms.

Evolution of combined symptom scores (mean and confidence interval [CI]) for active and placebo groups at baseline and at the end of the study are shown in Table 2. At the beginning of the study, there were no significant differences in symptom scores between the active and placebo groups during the challenge test both for total, conjunctival, nasal, bronchial and total scores. After 1 year of treatment, the actively treated group showed a marked reduction in symptom scores during the cat exposure with no statistical significant changes in the placebo group.

When comparing the intragroup symptom scores between baseline and the end of the study, the differences were significant for the active group for all four outcome measures (total, nasal, bronchial and ocular symptoms) (Wilcoxon test, $P < 0.05$), but not for the placebo. When comparing the results obtained at the end between both groups, the power was 0.7821. When the comparison was between the results obtained at baseline and at the end in the group treated with the active preparation, the power was 0.9967. Table 2 shows the statistical analysis of the individual results comparing groups, the results of the Hodges–Lehmann estimator and the percentage of improvement of active vs placebo group.

During the NCT, the PEF was also measured. When comparing the intragroup PEF results between baseline and at the end of the study, the differences were only significant for the active group (Wilcoxon test, $P < 0.05$). Figure 2 shows the evolution of PEF for both groups at baseline and at the end of the study during the NCT. The differences between the placebo and active group at the end of the study were also significant ($P < 0.05$).

Skin test results

At baseline, the median value to produce a 10 HEP reaction in the active group was 2.61 mg (IQ range 1.35–4.54) vs 1.99 (IQ range 1.54–7.40) in the placebo group ($P = 0.943$). At the end the median value was 4.45 mg (IQ range 2.91–7.40) in the active group vs 2.50 mg (IQ range 1.46–9.80) in the placebo group. The differences for the median between baseline and the end was 1.09 (IQ range 0.71–4.25) in the active group vs 0.17 mg (IQ range –0.53 to 2.15) in the placebo group. The difference between baseline and end was statistically significant ($P = 0.042$).

The Wilcoxon signed rank test was used to compare intragroup 10 HEP values at baseline and at the end of the study: the differences were highly significant in the active group ($P = 0.0005$). In the placebo group these differences were not significant ($P = 0.642$). At the end of the study, the active group needed 1.7 times more native allergen extract to achieve a 10 HEP reaction.

Safety and adherence

No local or systemic reactions were reported. None of the 17 withdrawals was caused by an adverse reaction.

Table 2. Evolution of symptom scores (total, nasal, bronchial and ocular) for active and placebo groups

AUC symptom score	Active mean (95% lower and upper CI)	Placebo mean (95% lower and upper CI)	Mann-Whitney (<i>P</i> -value)	Hodges-Lehmann estimator (95% lower and upper CL)	% of improvement of active vs placebo at the end
Total					
Baseline	578.53 (417.21, 739.84)	564.94 (411.82, 720.05)	0.901	10 (–200, 215)	59.01
End	217.06 (112.42, 321.70)	529.53 (341.51, 717.55)	< 0.001	–264 (–363, –168)	
Wilcoxon (<i>P</i> -value)	< 0.001	0.535			
% of improvement	62.48				
Nasal					
Baseline	317.06 (233.38, 400.74)	312.50 (239.26, 385.74)	0.709	9 (–127, 107)	52.32
End	151.62 (89.83, 213.41)	317.97 (223.97, 412.93)	0.002	–159 (–250, –72)	
Wilcoxon (<i>P</i> -value)	0.002	0.959			
% of improvement	52.18				
Bronchial					
Baseline	174.41 (118.10, 237.03)	160.00 (81.60, 238.40)	0.631	18 (–67, 122)	68.11
End	45.74 (10.80, 80.67)	143.44 (61.98, 224.90)	0.118	–45 (–180, 0)	
Wilcoxon (<i>P</i> -value)	0.003	0.263			
% of improvement	73.77				
Ocular					
Baseline	91.91 (45.96, 137.87)	93.44 (48.95, 137.93)	0.845	0 (–67, 62)	71.07
End	19.71 (0.92, 34.89)	68.13 (17.23, 119.02)	0.118	–5 (–82, 0)	
Wilcoxon (<i>P</i> -value)	< 0.001	0.327			
% of improvement	78.56				

AUC, area under curve; CI, confidence interval; CL, confidential limit.

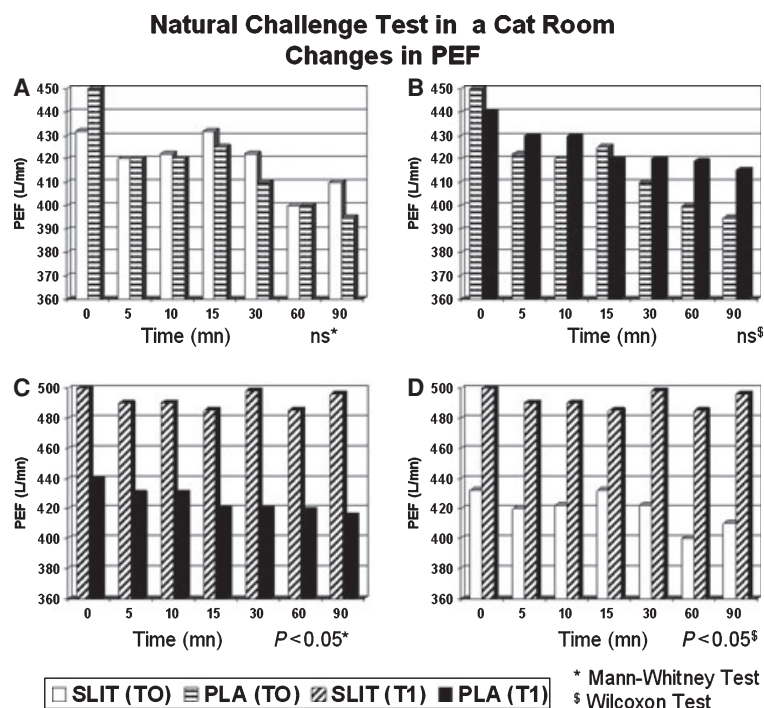


Figure 2. Changes in peak expiratory flow (PEF) during natural challenge test (NCT). SLIT: sublingual immunotherapy group; Placebo: placebo group; T0: before treatment; T1: after 1 year of treatment. (A) Results of NCT for immunotherapy (IT) and placebo groups before treatment. (B) Results of NCT for placebo group before and after placebo treatment. (C) Results of NCT for IT and placebo groups after treatment. (D) Results of NCT for active group before and after immunotherapy treatment.

Seventeen people abandoned the study. The reasons for withdrawal were: four due to a change of residence, two due to pregnancy, one due to change of work, one due to

depression, two for unknown reasons (the investigators tried to contact the patient several times without success), one for renal illness that required several hospital

admissions and six due to a voluntary decision, without any further explanation.

Discussion

The results of this double blind and placebo controlled study provide evidence that cat SLIT is able to improve cat allergy based on NCT. Simulated domestic exposures are able to emulate natural exposure to the allergen and offer a more realistic evaluation of IT efficacy, although they are less easy to perform than specific bronchial challenges with cat allergen extract. There are three methodological steps to be considered on evaluating NCT: (i) the cat room itself; (ii) the method used to measure airborne cat allergen levels; and (iii) the method used to evaluate the patient's response. The volume of cat room and the number of cats along with ventilation, cleaning and disturbances are determinant factors in airborne allergen levels. We used a 21 m³ room with one cat obtaining a median airborne Fel d 1 level of 6.2 ng/m³. We consider an important contribution of this trial the fact that we were able to establish that a concentration of 6 ng/m³ was able to discriminate differences between patients that received placebo or active treatment. This airborne level of Fel d 1 can be considered as a future reference in the evaluation of natural challenge tests to cat. The total duration of natural cat challenge test lasted approximately 6 h, including transportation of the patients. We believed that one of the reasons why some patients could abandon the study was the impossibility to leave work for this long period of time.

Natural exposure challenge to cat (NCT) in a cat room showed that SLIT-treated patients, in contrast with the placebo group, experienced a significant improvement both in subjective outcome parameters, such as symptom score, and in objective outcome parameters, such as PEF. The consistency between both results (subjective and objective) reinforces the conclusion of this trial. Nelson et al. (21) evaluated at the first time efficacy of cat SLIT concluding that SLIT was no more effective than placebo. The design was novel and interesting, including NCT at the first time in the assessment of IT efficacy, although some methodological problems attracted the attention on this report (22). Our results were different and we believe that several methodological differences could contribute to it: (i) patient selection. Nelson et al. excluded patients chronically exposed to cat and patients requiring daily medication. As a result, Nelson et al. (21) evaluated mostly rhinitic patients and only 15% of evaluated patients had asthma. Our patients mostly suffered rhinitis and asthma (75% asthmatic patients); (ii) assessment of cat allergen level. Nelson et al., had problems to assess cat allergen levels in the cat room, as

several determinations were below the detection limit of the assay. We improved the method quantifying Fel d 1 by using anti-Fel d 1 monoclonal antibodies, which improved the sensitivity of the detection method, as well as reproducibility (35). Furthermore, cat airborne allergen levels were reproducible before and after the study for patients in the active and placebo group without finding statistical differences. These differences were significant in the Nelson's trial and (iii) we measured PEF in asthmatic patients allergic to cats, and it was possible to find differences between IT and placebo groups, which was not possible in the Nelson et al. (21) study, as only 15% of evaluated patients had asthma.

Safety was assessed during the study although it was not the aim of the study. Results of this report provided that there were no serious problems with cat SLIT. However, because of the study was not designed to evaluate safety we should consider these results as preliminary because the study is underpowered to detect rare events.

One major criticism of immunotherapy studies is the interference of environmental control measures with the final outcome of the study. We believe that environmental control may be effective in controlling allergic symptoms; therefore, we decided to conduct the study without stressing the use of environmental control measures and allowed exposure to cats at home. Sublingual cat immunotherapy was able to improve cat allergy (confirmed during the NCT). Although the safety of sublingual immunotherapy was not fully assessed during this trial, SIT with a standardized cat dander extract seems to be safe, as none of the patients referred any local or systemic reactions at the administered doses. This conclusion can only be drawn with the doses and schedule used in this study and do not preclude higher doses to produce side effects.

Adherence is a critical factor for the successful outcome of the treatment. It has been reported that, in the case of SLIT, adherence has always been regarded as a weak point, because the treatment is self administered (36). Although results of this report are in agreement with the previous study, at the first glance, we should remember that most of the patients abandoned the study because of causes nonlinked to IT treatment. In summary, results of this double blind and placebo controlled study provide evidence that cat SLIT is able to improve cat allergy based on NCT.

Disclosure of potential conflict of interest

The study has been sponsored by Laboratorios LETI, S.L., Tres Cantos, Madrid, Spain. M. Casanovas and E. Fernández-Caldas are working in R&D of Laboratorios LETI, S.L.

References

- Enberg RN, Shamie SM, McCullough J, Ownby DR. Ubiquitous presence of cat allergen in cat-free buildings: probable dispersal from human clothing. *Ann Allergy* 1993;**70**:471–474.
- D'Amato G, Liccardi G, Russo M, Barber D, D'Amato M, Carreira J. Clothing is a carrier of cat allergens. *J Allergy Clin Immunol* 1997;**99**: 577–578.
- Bollinger ME, Eggleston PA, Flanagan E, Wood RA. Cat antigen in homes with and without cats may induce allergic symptoms. *J Allergy Clin Immunol* 1996;**97**:907–914.
- Liccardi G, Barber D, Russo M, D'Amato M, D'Amato G. Human hair: an unexpected source of cat allergen exposure. *Int Arch Allergy Immunol* 2005;**137**:141–144.
- Munir AKM, Einarsson R, Shou C, Dreborg S. Allergens in school dust. I. The amount of the major cat (Fel d 1) and dog (Can f 1) allergens in dust from Swedish schools is high enough to probably cause perennial symptoms in most children with asthma who are sensitized to cat and dog. *J Allergy Clin Immunol* 1993;**91**:1067–1074.
- Wood RA, Chapman MD, Adkinson NF Jr, Eggleston PA. The effect of cat removal on allergen content in household-dust samples. *J Allergy Clin Immunol* 1989;**83**:730–734.
- Croner S, Kjellmen NIM. Natural history of bronchial asthma in childhood: a prospective study from birth to 14 years of age. *Allergy* 1992;**47**:150–157.
- Ohman JL Jr, Lowell FC. IgE antibody to cat allergens in an allergic population. *J Allergy Clin Immunol* 1977;**60**: 317–323.
- Luczynska CM, Li Y, Chapman MD, Platts-Mills TA. Airborne concentrations and particle size distribution of allergen derived from domestic cats (*Felis domesticus*). Measurements using cascade impactor, liquid impinger, and a two-site monoclonal antibody assay for Fel d 1. *Am Rev Respir Dis* 1990;**141**: 361–367.
- Custovic A, Simpson A, Pahdi H, Green RM, Chapman MD, Woodcock A. Distribution, aerodynamic characteristics, and removal of the major cat allergen Fel d 1 in British homes. *Thorax* 1998;**53**:33–38.
- Custovic A, Simpson B, Simpson A, Hallam C, Craven M, Woodcock A. Relationship between mite, cat, and dog allergens in reservoir dust and ambient air. *Allergy* 1999;**54**:612–616.
- Swanson MC, Agarwal MK, Reed CE. An immunochemical approach to indoor aeroallergen quantitation with a new volumetric air sampler: studies with mite, roach, cat, mouse, and guinea pig antigens. *J Allergy Clin Immunol* 1985;**76**:724–729.
- Wood RA, Laheri AN, Eggleston PA. The aerodynamic characteristics of cat allergen. *Clin Exp Allergy* 1993;**23**: 733–739.
- Van Metre TE Jr, Marsh DG, Adkinson NF Jr, Fish JE, Kagey-Sobotka A, Norman PS et al. Dose of cat (*Felis domesticus*) allergen 1 (Fel d 1) that induces asthma. *J Allergy Clin Immunol* 1986;**78**:62–75.
- Sicherer SH, Wood RA, Eggleston PA. Determinants of airway responses to cat allergen: comparison of environmental challenge to quantitative nasal and bronchial allergen challenge. *J Allergy Clin Immunol* 1997;**99**:798–805.
- Taylor WW, Ohman JL Jr, Lowell FC. IT in cat-induced asthma. Double-blind trial with evaluation of bronchial responses to cat allergen and histamine. *J Allergy Clin Immunol* 1978;**61**: 283–287.
- Ohman JL Jr, Findlay SR, Leitermann KM. IT in cat induced asthma. Double-blind trial with evaluation of *in vivo* and *in vitro* responses. *J Allergy Clin Immunol* 1984;**74**:230–239.
- Van Metre TE, Marsh DG, Adkinson NF, Kagey-Sobotka A, Khattignavong A, Norman PS Jr et al. IT for cat asthma. *J Allergy Clin Immunol* 1988;**82**: 1055–1068.
- Sundin B, Lilja G, Graff-Lonnevig V, Hedling G, Heilborn H, Norrlind K et al. Immunotherapy with partially purified and standardized animal dander extracts I. clinical results from a double-blind study on patients with animal dander asthma. *J Allergy Clin Immunol* 1986;**77**:478–487.
- Hedlin G, Graff-Lonnevig V, Hedlin G, Helborn H, Lilja G, Norrlind K. Immunotherapy with cat- and dog-dander extracts. II. *In vivo* and *in vitro* immunologic effects observed in a 1-year double-blind placebo study. *J Allergy Clin Immunol* 1986;**77**:488–496.
- Lowenstein H, Graff-Lonnevig V, Hedlin G, Helborn H, Lilja G et al. Immunotherapy with cat- and dog-dander extracts. III. Allergen-specific immunoglobulin responses in a 1-year double-blind placebo study. *J Allergy Clin Immunol* 1986;**77**:497–505.
- Álvarez-Cuesta E, Cuesta-Herranz J, Puyana-Ruiz J, Cuesta-Herranz C, Balnco-Quirós A. Monoclonal antibody-standardized cat extract IT: risk-benefit effects from a double-blind placebo study. *J Allergy Clin Immunol* 1994;**93**:556–566.
- Varney VA, Edwards J, Tabbah K, Brewster H, Mavroleon G, Frew AJ. Clinical efficacy of specific IT to cat dander: a double-blind placebo-controlled trial. *Clin Exp Allergy* 1997;**27**: 860–867.
- Wilson DR, Torres Lima M, Durham SR. Sublingual IT for allergic rhinitis. The Cochrane Library, Issue 2. Oxford: Update Software, 2003.
- Nelson HS, Oppenheimer J, Vatsia GA, Buchmeier A. A double-blind, placebo-controlled evaluation of sublingual IT with standardized cat extract. *J Allergy Clin Immunol* 1993;**92**:229–236.
- Bousquet J, Michel FB, Creticos PS. Sublingual immunotherapy for cat allergy. *J Allergy Clin Immunol* 1995; **95**:920–921.
- Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma (ARIA). *Allergy* 2002; **57**:841–855.
- Colloff MJ, Ayres J, Carswell F, Howarth PH, Merret TG, Mitchell EB et al. The control of allergens of dust mites and domestic pets: a position paper. *Clin Exp Allergy* 1992;**22**:1–28.
- Varney VA, Edwards J, Tabbah K, Brewster H, Mavroleon G, Frew AJ. Clinical efficacy of specific immunotherapy to cat dander: a double-blind placebo-controlled trial. *Clin Exp Allergy* 1997;**27**:860–867.
- Taves DR. Minimization: a new method of assigning patients to treatment and control groups. *Clin Pharmacol Ther* 1974;**15**:443–453.
- EAACI. Position paper: Allergen standardization and skin tests. The European Academy of Allergology and Clinical Immunology. *Allergy* 1993; **48**:48–82.
- Nordic Council Medicines. Registration of allergen preparations. Nordic guidelines. Uppsala: NLN Publication No. 23, 2nd edition, 1989.
- Van Metre TE, Marsh DG, Adkinson NF, Fis HE, Kagey-Sobotka A, Norman PS et al. Dose of cat (*Felis domesticus*) allergen I (Fel d I) that induces asthma. *J Allergy Clin Immunol* 1986;**78**:62–75.

34. Immunotherapy Subcommittee of The European Academy of Allergology and Clinical Immunology. Immunotherapy: position paper. *Allergy* 1993;**48** (Suppl. 14):7–30.
35. Chapman MD, Heymann PW, Wilkins SR, Brown MB, Platts-Mills TAE. Monoclonal immunoassays for the major dust mite (*Dermatophagoides*) allergens, Der p I and Der f I, and quantitative analysis of the allergen content of mite and house dust extracts. *J Allergy Clin Immunol* 1987;**80**: 184–194.
36. Bousquet J, Scheinmann P, Guinneeain MT, Perrin-Fayolle M, Sauvaget J, Tonnel AB et al. Sublingual-swallow immunotherapy (SLIT) in patients with asthma due to house-dust mites: a double-blind, placebo-controlled study. *Allergy* 1999;**54**:249–260.

Corrigendum

In (1), the author listing was published as follows:

E. Álvarez-Cuesta, P. Berges-Gimeno, E. G. Mancebo, E. Fernández-Caldas, J. Cuesta-Herranz, M. Casanovas

This has now been requested to read:

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Reference

1. Álvarez-Cuesta E, Berges-Gimeno P, Mancebo EG, Fernández-Caldas E, Cuesta-Herranz J, Casanovas M. Sublingual immunotherapy with a standardized cat dander extract: evaluation of efficacy in a double blind placebo controlled study. *Allergy* 2007;**62**:810–817.