ORIGINAL ARTICLE

Clinical and Immunologic Changes due to Subcutaneous Immunotherapy With Cat and Dog Extracts Using an Ultrarush Up-Dosing Phase: A Real-Life Study

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Abstract

Objective: We aimed to evaluate the efficacy of and immunologic changes caused by subcutaneous immunotherapy (SCIT) in patients with allergy to cat and dog.
Methods: The study population comprised patients with rhinitis and/or asthma and allergy to cat or dog from a previous safety study. All patients had specific IgE to cat and/or dog. The SCIT maintenance dose was administered using an infusion pump over a single 4-hour session, followed by monthly administration over 6 months. Data were gathered on clinical outcomes, pulmonary function, FeNO, rhinitis and asthma symptoms, quality of life (QOL), and scores for the Asthma Control Test and symptom visual analog scale were recorded at baseline and then at 1, 3, and 6 months. Specific IgE and IgG antibody responses to cat and dog allergens were determined.
Results: The study population comprised 61 patients with a mean age of 35.6 (9.7) years, of whom 40 underwent SCIT for at allergy. A significant improvement was observed in rhinitis and asthma symptoms and in QOL, use of medication, visual analog scale score, and Asthma Control Test score at 1 month; these improvements persisted at month 6. The clinical improvement with cat extract was significantly more marked than with dog extract. Nearly half of the patients (49.09%) had an increase of >0.9 in the ESPRINT-15 QOL in allergic rhinitis questionnaire, and 58.18% had an increase of >0.5 in the Asthma Quality of Life Questionnaire score at month 6. Both differences represent the minimal clinical important difference. A significant increase was observed in specific IgG and IgE to different allergens at 3 and/or 6 months.
Conclusions: Ultrarush SCIT with cat and dog extracts has substantial clinical value for many patients.

Key words: Ultrarush subcutaneous immunotherapy. Cat. Dog. Allergy.

Resumen

Objetivo: Nuestro objetivo fue evaluar la eficacia y los cambios inmunológicos causados por la inmunoterapia subcutánea (SCIT) en pacientes con alergia a perro y gato.
Métodos: Se incluyeron pacientes que presentaban rinitis y/o asma con alergia al gato o al perro de un estudio de seguridad previo. Todos tenían IgE específica para gato y/o perro. Usando una bomba de infusión (IP), la dosis de mantenimiento de SCIT se administró durante una sesión de 4 horas, seguida de la administración mensual durante 6 meses. Se recopilaron datos de función pulmonar, FeNO, síntomas de rinitis y asma, calidad de vida (QoL), control del asma (ACT) y escala analógica visual de síntomas (VAS) al inicio y a los 1, 3 y 6 meses. Se determinaron las respuestas específicas de anticuerpos IgE e IgG a diferentes alérgenos de perro y gato.
Resultados: Se incluyeron 61 pacientes con una edad media de 35,6 ± 9,7 años, 40 de los cuales se sometieron a SCIT de gato. Se observó una mejora significativa en los síntomas de rinitis y asma, calidad de vida, el uso de medicamentos, VAS y ACT en el primer mes. Estas mejorías se mantuvieron en el mes 6. La mejoría clínica con el extracto de gato fue significativamente mayor que con el de perro. Se observó un aumento de >0,9 en ESPRINT-15 en el 49,09% de los pacientes, y el 58,18% mostró un aumento de >0,5 en AQLQ en el mes 6, ambas diferencias indican la mínima diferencia importante. Se observó un aumento significativo en IgG e IgE específicas a diferentes alérgenos a los 3 y/o 6 meses.
Conclusiones: La SCIT ultrarápida con extractos de perro y gato induce una mejoría clínica relevante rápida y mantenida en muchos pacientes.

Palabras clave: Inmunoterapia subcutánea ultrarápida. Gato. Perro. Alergia.

Introduction

Previous research [1-9] demonstrated the clinical efficacy of subcutaneous immunotherapy (SCIT) with extracts of cat and dog using a standard administration route and with Fel d 1–derived synthetic peptide immunoregulatory epitopes [10]. Therefore, immunotherapy can be an alternative for the management of patients with cat and dog allergy [11]. However, few studies have analyzed the immune response to cat and dog during SCIT [12-16]. A few years ago, we conducted a real-life observational study on the safety and efficacy of SCIT with cat and dog extracts. In this earlier research, high doses of extracts were administered over 3 days through an infusion pump during the rush up-dosing phase in patients with rhinitis and allergic asthma due to cat or dog. Our work revealed a good safety profile and clinical efficacy for this approach [17-19]. Having demonstrated the safety of an ultrarush up-dosing schedule [20], we set out to perform a real-life study to assess clinical efficacy in terms of symptoms, quality of life, asthma control, and pulmonary function in patients undergoing SCIT with ultrarush up-dosing using the same dog and cat extracts as in our previous studies. We compared our results and assessed the immunologic changes caused by this therapeutic approach.

Methods

We performed a prospective study of patients with rhinitis and/or allergic asthma due to cat or dog. All patients were prescribed SCIT with cat or dog extract (Alutard SQ, Can f 1, 3.21 µg/mL; Fel d 1, 15 µg/mL) and monitored during the first 6 months of treatment. The patients studied here are those included in a previously published study on the safety profile of SCIT for whom serum samples were available [20]. The indications for SCIT were based on the guidelines of the European Academy of Allergy and Clinical Immunology [21]. All patients or their parents or legal guardians provided signed informed consent. The study was approved by the local ethics committee. No control group was included.

The up-dosing phase of SCIT was initiated with the injection of 1.2 mL of the maintenance vial over 4 hours at the first visit, using a portable subcutaneous infusion pump (Medis Infusa T) and an infusion set (Accu-Chek TenderLink), as previously described [20]. Subsequent doses were administered monthly by direct subcutaneous injection (1 mL).

Skin tests with cat and dog extracts (ALK) were performed at 3 concentrations (1/1, 1/10, and 1/100); these tests were conducted at diagnosis, at baseline (day 0), and at 24 hours (day 1), and then at months 1, 3, and 6 of SCIT. Wheal contours were painted and transferred to the case report form. The contours were scanned, and the wheal areas were measured. Changes in wheal area (geometric mean) and the skin tolerance index (STI, indicating the difference in allergen concentration required to elicit the same skin response at different times) were analyzed at different timepoints using baseline values as a reference (day 0).

IgE responses to the dog allergens Can f 1, 2, 3, 4, 5, and 6 and cat allergens Fel d 1 and 7 were analyzed using ELISA as previously described [20]. rFel d 1 and rFel d 7 were produced as described [22,23]. Total IgG and IgG1, 2, 3, and 4 allergen-specific reactivity were measured using the IgE ELISA protocol, after diluting serum 50 times for total IgG and 10 times for IgG subclasses. Secondary horseradish peroxide–conjugated goat anti-human IgG (Thermo Fisher) specific for total IgG and the respective subclasses was used. Immunological assessments were performed at baseline and subsequently at months 3 and 6.

At baseline and then at months 1, 3, and 6 of SCIT, all respiratory tests were performed and questionnaires administered, as in our previous study [2]. Briefly, values for spirometry and bronchodilation testing and fractional exhaled nitric oxide (FeNO) concentration were obtained. In addition, a series questionnaires validated for the Spanish population were administered, as follows: rhinitis quality of life (ESPRINT-15, health-related quality of life in allergic rhinitis), Asthma Quality of Life Questionnaire (AQLQ), Asthma Control Test (ACT), and a visual analog scale (VAS, 10-cm, including nasal, ocular, and bronchial symptoms). Scores for nasal symptoms (itching, congestion, rhinorrhea, sneezing), ocular symptoms (tearing, itching, gritty eye), and pulmonary symptoms (cough, wheezing, dyspnea, exercise-induced asthma) (0, no symptoms; 1, mild; 2, moderate; 3, severe) and a medication score were applied. The response to SCIT was measured considering the minimum clinically important differences (MCID) for questionnaire responses [2].

Associations between immunological parameters and safety and efficacy measures were analyzed in addition to the difference in clinical efficacy between SCIT with cat and dog extracts. Safety monitoring has been described previously [20].

Statistical Analysis

The statistical analysis was based on the Fisher exact test, Wilcoxon test, Friedman test, Kruskal-Wallis test, and a mixed-effects model. $P<.05$ was considered significant.

Results

We included 61 patients (36 women and 25 men), of whom 40 were allergic to cat and 21 to dog; their mean (SD) age was 35.6 (9.7) years. Patients were sensitized to pollens (62.3%), mites (23%), molds (11.5%), cat (93.4%), and dog (78.7%). Allergic rhinitis was present in 90.2% of patients (n=55), allergic conjunctivitis in 62.3% (n=38), and allergic asthma in 82% (n=50). Most patients had persistent symptoms, the 2 most prevalent being moderate/severe persistent rhinitis (43.6%) and mild persistent asthma (46%). Eighty-two percent of patients (n=50) had either a dog or cat at home (direct daily contact was maintained throughout the study), 14.8% had occasional direct contact with these animals (n=9), and 3.2% had indirect contact (n=2).

Fifty-four patients concluded the study (36 cat-allergic and 18 dog-allergic patients). Before the third month of SCIT, 3 cat-allergic patients discontinued SCIT (due to pregnancy, work-related reasons, and systemic reactions to SCIT). Before the sixth month, another cat-allergic patient withdrew from SCIT owing to poor tolerance of treatment, while 3 dog-

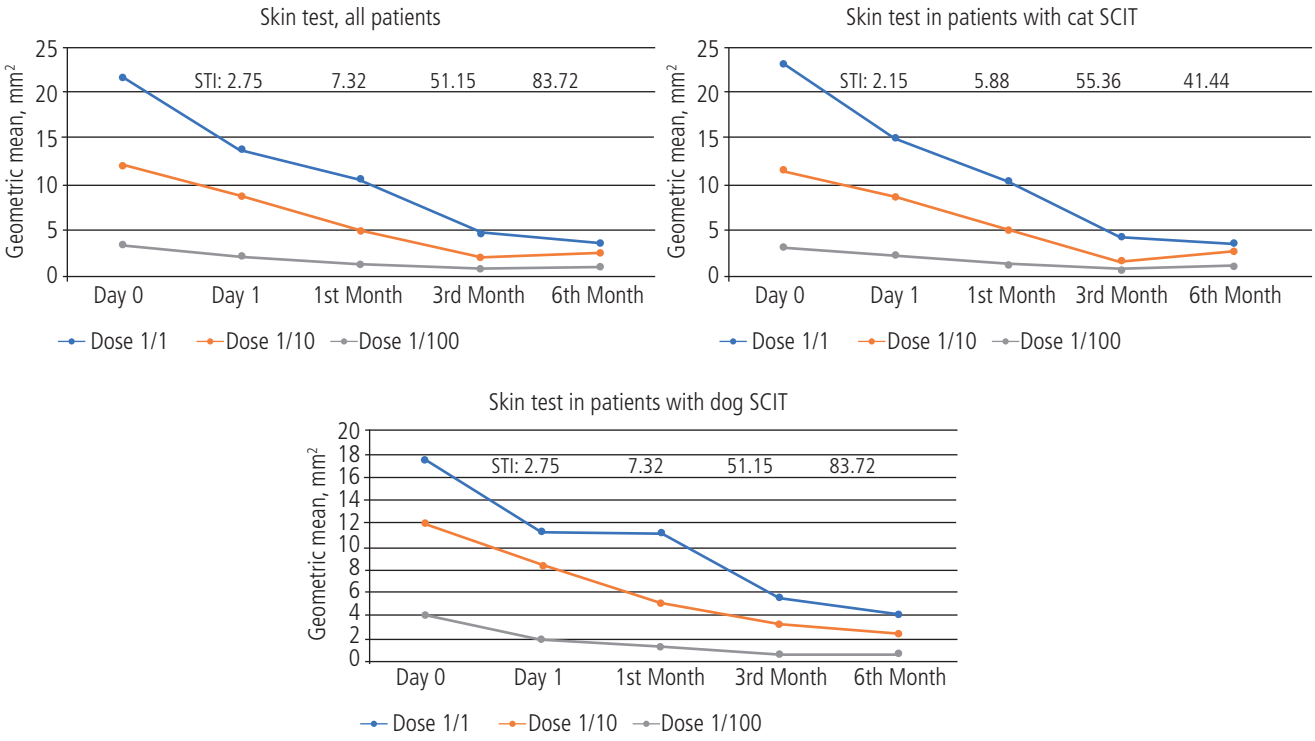

Figure 1. Change in the geometric mean (mm^2) of the skin test results with cat or dog extract at different doses and in the skin tolerance index (STI) at day 1 and then at months 1, 3, and 6 compared to day 0. SCIT indicates subcutaneous immunotherapy.

allergic patients suspended therapy due to travel abroad, discontinuation of contact with the dog at home, and loss to follow-up (Figure 1 supplement).

A skin test revealed an increased STI at all visits after the start of SCIT compared with day 0 (Table 1 supplement and Figure 1). Of note, the STI decreased the day following administration of the ultrarush protocol.

Positive IgE was detected for Fel d 1 in 92% (n=37), Fel d 2 in 10% (n=4), Fel d 4 in 55% (n=22), and Fel d 7 in 42% (n=17); 52.4% of dog-allergic patients had positive results to Can f 1 (n=11), 33.3% to Can f 2 (7), 19% to Can f 3 (n=4), 57.2% to Can f 5 (n=12), and 47% to Can f 6 (n=10) (Table 2 supplement). In the group of dog-allergic patients, 25% were monosensitized to Can f 5.

Values for IgG antibodies (mean) and IgE are shown in Table 3 supplement and Figures 2 and 3. In some cases, a significant increase was observed in the third and sixth months, although in others, the only change was recorded in the third month.

Spirometry values and the results of a bronchodilation test did not show significant changes between assessments; the only significant decrease was observed in FeNO values (P=.015). Mean FeNO decreased from 66.3 to 49.4 ppb (P=.027) in the first month of SCIT and to 48.8 ppb in the third month (P=.016). No significant difference was observed between the third and the sixth month (Figure 4).

The quality-of-life questionnaires in rhinitis (ESPRINT-15) and asthma (AQLQ) showed highly significant changes in all dimensions (ESPRINT-15: symptoms, daily activities, sleep, psychological impact; AQLQ: activity limitation, symptoms, emotional function, and environmental stimuli), as well as in the scales overall. A significant improvement in patient quality of life was seen in the first, third, and sixth months (P<.001 in both questionnaires). No significant differences were observed between the assessments made in the third and sixth months (P>.05) in either questionnaire. Improvements were recorded in all dimensions of ESPRINT-15 and AQLQ until the third month of SCIT, with no further improvement in the sixth month (Figure 4). Nearly half of the patients (49.09%) had an increase of >0.9 (MCID) in ESPRINT-15, and 58.18% had an increase of >0.5 (MCID) in AQLQ at month 6.

Differences in the ACT and VAS scores between baseline and months 1, 3, and 6 of SCIT were statistically signficant (P<.001 in all cases), although no significant difference was observed between the first and third months and third and sixth months. The highest percentage of patients with controlled symptoms was observed in the third month (from 65% to 87.7% of patients with controlled asthma). We observed that 49.09% of patients had an ACT score ≥3 at month 6. The VAS decreased compared with baseline, thus indicating a positive effect of SCIT (Figure 4).

The symptom score improved significantly in the third month after SCIT, for rhinorrhea (P=.000), sneezing (P=.001), cough (P=.003), and dyspnea (P=.009); nasal congestion improved in the first month (P=.02, intensity decreased by 35.8%). Regarding ocular symptoms, there were no significant differences, as was the case for nasal itching, although in the third month, the intensity of symptoms decreased by 33.3%. No

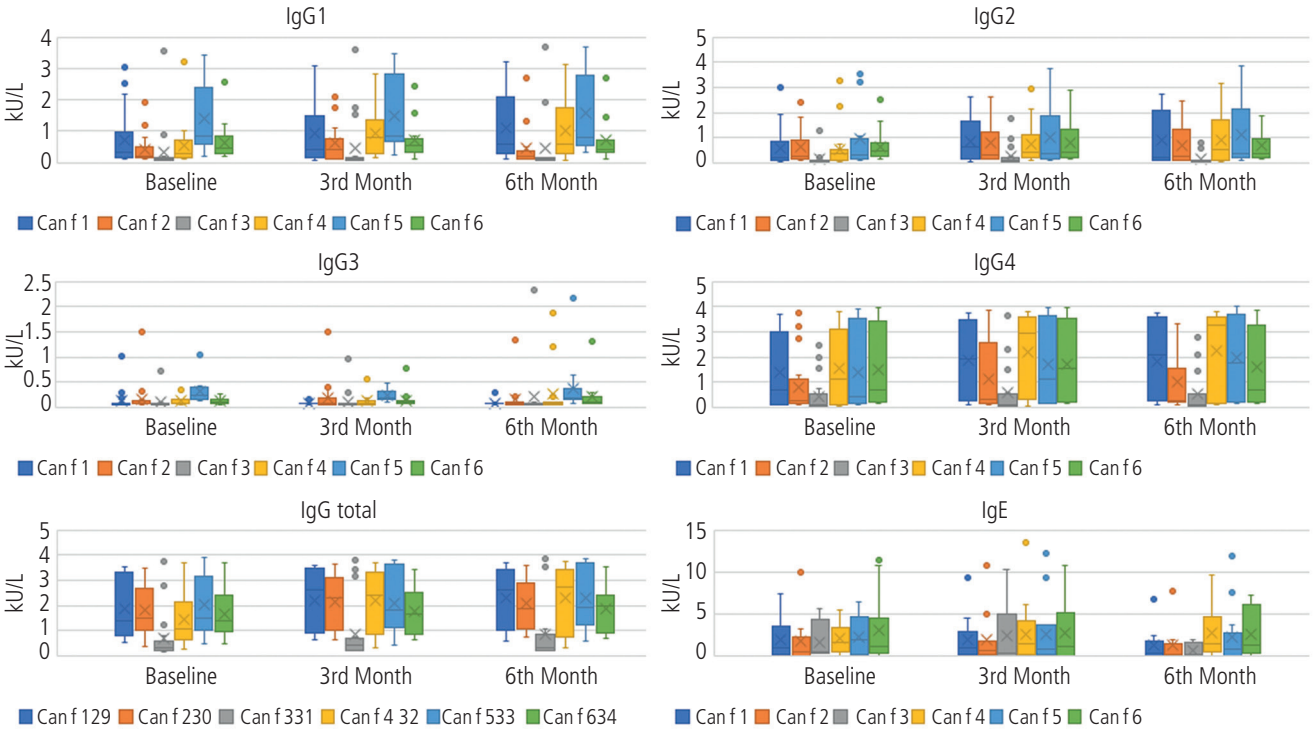

Figure 2. Quantification of immunoglobulin G1, G2, G3, G4, total G, and E to recombinant dog allergens (Can f 1, Can f 2, Can f 3, Can f 4, Can f 5, Can f 6) at baseline and at months 3 and 6 of SCIT. The dots represent patients out of range on mean (SD).

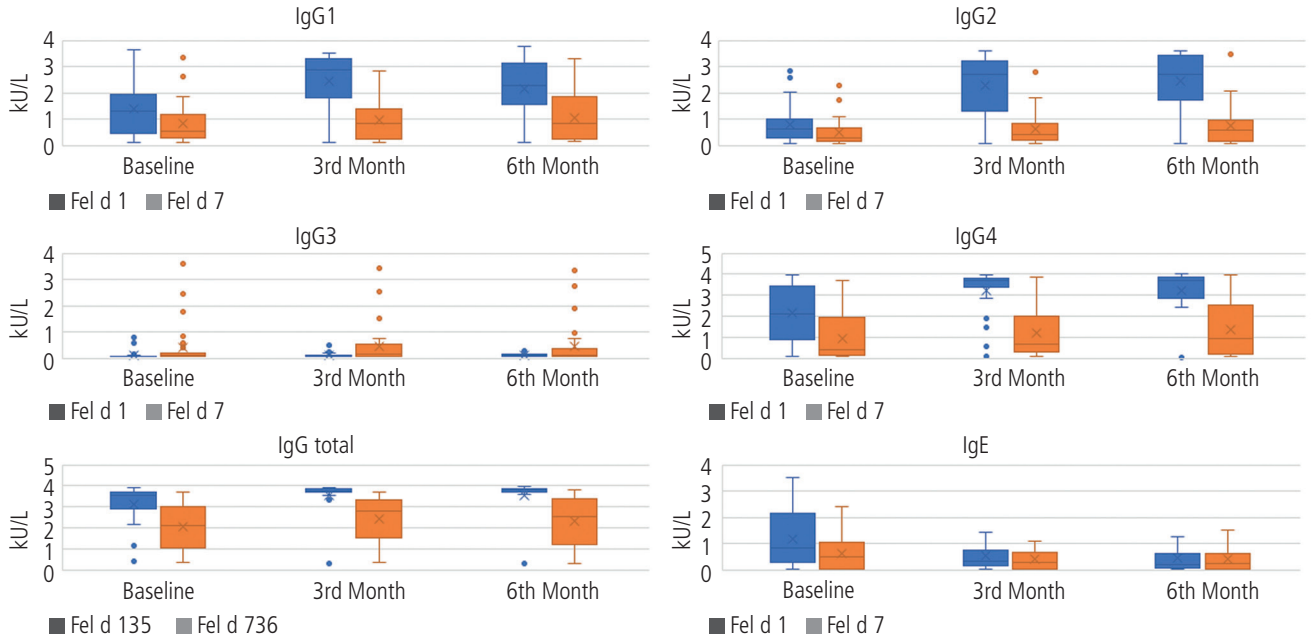

Figure 3. Quantification of immunoglobulin G1, G2, G3, G4, total G, and E to recombinant cat allergens (Fel d 1, Fel d 7) at baseline and at months 3 and 6 of SCIT. The dots represent patients out of range on mean (SD).

significant differences were observed regarding the symptom score between the third and sixth months (Figure 5).

A statistically significant decrease in medications was observed, with use of antihistamines (P=.034) decreasing at month 1. Decreases were observed at the third month of SCIT for use of inhaled ß2-agonists (P=.008), nasal corticosteroids (P=.003), and inhaled corticosteroids (P=.008). No differences were observed between the third and sixth months (Figure 5).

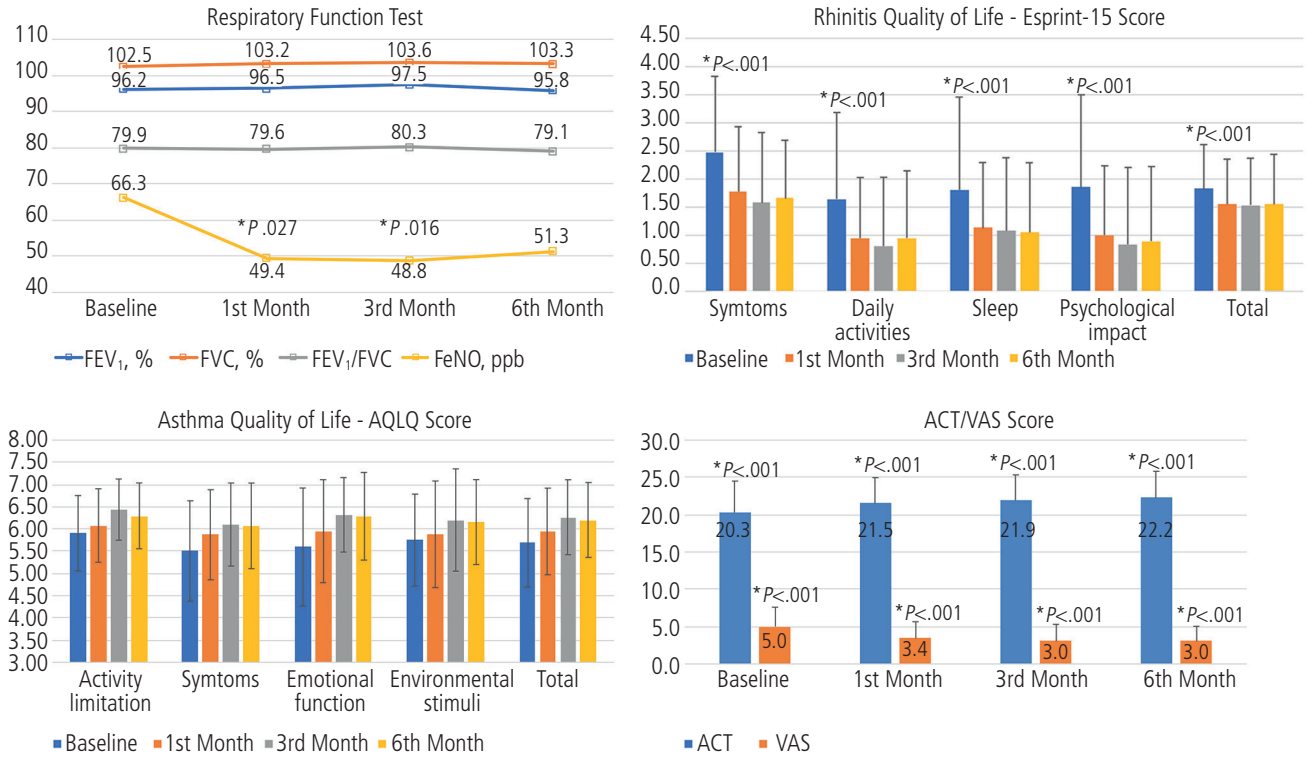

Figure 4. Results of respiratory function testing (spirometry: FEV_1, FVC, FEV_1/FVC), FeNO, ESPRINT-15, AQLQ, ACT, VAS, and symptoms and medication score at baseline and subsequently at months 1, 3, and 6. ACT indicates Asthma Control Test; VAS, visual analog scale.

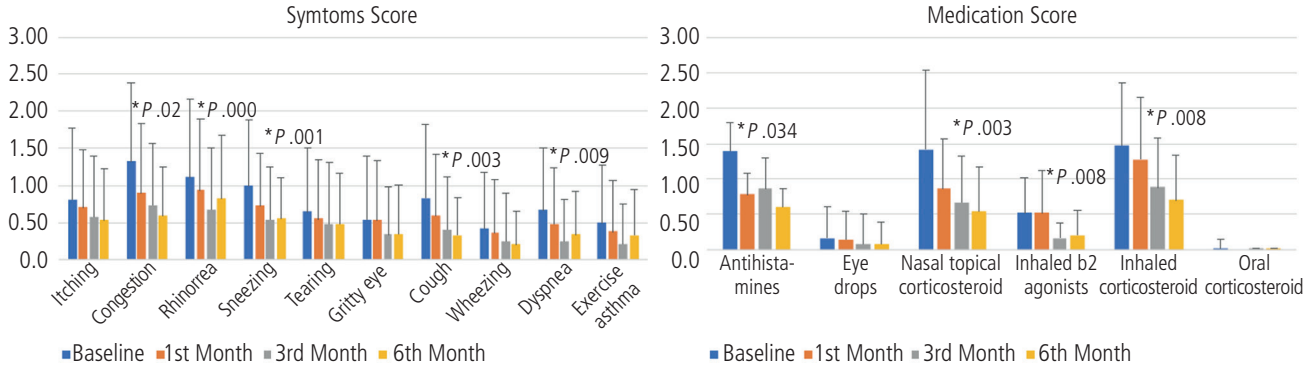

Figure 5. Results of symptoms and medication scores at baseline and at months 1, 3, and 6.

The response to SCIT, according to the scale used in our previous study, was very good in the third and sixth months. When analyzing the response to SCIT separately, we found that the patients who received cat extract had a very good response in the third month, while with the dog extract this was true only in the sixth month. Significant differences in favor of cat extract were observed in the AQLQ (*P*=.009) and ACT (*P*=.023) in the third month, and for the symptom score (*P*=.039) in first month of SCIT.

Cat-allergic patients not sensitized to Fel d 2 had a better quality of life regarding asthma (AQLQ), as measured by limitation of activity (*P*=.044), symptoms (*P*=.034), and total score (*P*=.044) on the AQLQ. They also had better asthma control (ACT) (*P*=.037), a greater decrease in some symptoms, such as runny nose (*P*=.035), tearing (*P*=.043), gritty eye (*P*=.032), and exercise-induced asthma (*P*=.035), as well as a decrease in the use of inhaled ß2-agonists (*P*=.03). For their part, patients who were not sensitized to Fel d 4 presented a more marked decrease in symptoms, such as nasal itching (*P*=.017) and gritty eye (*P*=.002). Dog-allergic patients not sensitized to Can f 2 experienced exercise-induced asthma less frequently (*P*=.029) and less frequently used nasal

corticosteroids (*P*=.016). No significant associations with the IgE molecular profile were observed for other clinical efficacy data, safety profile (previous study), or response to SCIT. An increase in IgG4 was not associated with clinical improvement. Adverse reactions recorded during the study were described in detail in our previous publication [18].

Discussion

A significant decrease in skin test reactivity was observed as a result of SCIT with both cat and dog extract, as described in other studies in which these data were assessed. Skin reactivity generally decreases 12 months after SCIT [4,6-9,13,15,16]. However, in 2 studies in which cat and dog SCIT was administered at different concentrations of the major allergen (0.6, 3, and 15 µg of Fel d 1 and Can f 1), a decrease in skin reactivity was observed following 5 weeks of SCIT at doses of 3 µg and 15 µg of Fel d 1 and Can f 1 [13,16]. In our study, a noticeable decrease in the wheal area was observed within the first 24 hours of the first dose (15 µg Fel d 1/mL for the cat extract and 3.21 µg Can f 1/mL for the dog extract), with a more pronounced decrease seen on subsequent visits, possibly owing to the use of an ultrarush schedule.

As in our 2 previous studies [18,26], we observed similar sensitization profiles for cat and dog allergens; Fel d 1 was the major allergen in allergy to cat, and Can f 1 and Can f 5 were the major allergens in allergy to dog. The prevalence of sensitization to Can f 5 exceeded that of Can f 1, and we observed high monosensitization to Can f 5 in dog allergy, affecting up to 25% of patients. For the first time in Spain, we found a high percentage of sensitization to Can f 6 (47%), and 42% were sensitized to Fel d 7. Nevertheless, these figures are similar to those reported in Swedish patients allergic to dog (35%) and cat (46%) [24,25]. Both lipocalins cross-react with other lipocalins: Fel d 7 with Can f 1 and Can f 6 with Fel d 4 and horse allergen Equ c 1 [25,27].

Variations were observed over time in levels of specific immunoglobulins to cat and dog allergens (IgG, IgG subtypes, IgE). We found a significant increase in the third and/or sixth month of SCIT. Previous studies have also demonstrated a significant increase in IgG and IgG4 to cat [4,8,13-16] and dog extract [9,13,14] in the fifth month or at 1 year of SCIT [8,16]. In the case of the dog SCIT study, a significant immunologic response was observed without clinical improvement, despite the use of high doses of Can f 1 (15 µg/mL) [16]. In contrast, cat SCIT resulted in a significant clinical and immunologic improvement at similarly high doses to the ones used in this study (15 µg Fel d 1) [8].

Regarding specific IgE, most studies do not report significant variations at 1 year of SCIT, except for a study of SCIT for cat allergy, in which a significant increase was found at years 1 and 2 of therapy [13,14]. In our case, Fel d 1 was the only allergen with a significant increase in total IgG, IgG1, IgG2, IgG3, IgG4, and IgE at 3 and 6 months of SCIT. Significant increases, especially in specific IgG4 and total IgG, were also detected for all other allergens. The rapid response of specific immunoglobulins is likely due to the ultrarush protocol used in this study in comparison with the previous ones. The more marked immune response to Fel d 1 can be explained by the high content of this allergen in the extract compared with other allergens.

Pulmonary function remained unchanged throughout therapy, as in the previous study [18]. However, a significant decrease in the FeNO value was observed in the first and third months of SCIT, although no further changes were observed between the third and sixth months of SCIT.

The clinical improvement was significant in the first month of SCIT and continued being significant in the third and sixth months, with no significant changes observed between the third and the sixth month. This improvement included quality of life in rhinitis and asthma (ESPRINT-15 and AQLQ), ACT, and VAS. Nasal and bronchial symptom scores and use of medication decreased significantly at month 3 of SCIT; an exception to this was seen in nasal congestion and the use of antihistamines, which improved at 1 month of SCIT but did not reveal significant changes between the third and sixth months of SCIT, as reported elsewhere [18]. No significant improvement in ocular symptoms was observed, consistent with our previous results using same extracts [18], which showed an overall clinical improvement at month 6 of SCIT. This improvement was maintained at 12 months, albeit without major changes [18]. Of note, the clinical efficacy and immunologic improvement both here and in our previous study [18] were observed despite direct daily contact with pets in 80% of patients. Interestingly, cat-allergic patients not sensitized to Fel d 2 experienced a more marked improvement in symptoms, AQLQ, and ACT, possibly because of a lower content of these allergens in the extract used.

Cat-allergic patients had a better response to SCIT than dog-allergic patients, as also seen in our previous study [18] and elsewhere [3,5,13]. This finding may be due to the higher concentration of Fel d 1 relative to Can f 1 or other dog allergens not contained in the extracts used. In our study, the Can f 1 concentration was 3.21 µg/mL when the recommended dose was 15 µg/mL [16].

In our previous study on efficacy [18], we found no association between efficacy and a specific pattern of sensitization to various allergens. In this study, however, we found that sensitization to Fel d 2 was associated with worse results in asthma quality of life, asthma control, nasal and ocular symptoms, and exercise-induced asthma, as well as in more frequent use of rescue medication for asthma. Other allergens such as Fel d 4 were associated with greater intensity of nasal and ocular symptoms, while Can f 2 was associated with exercise-induced asthma.

Adverse reactions recorded during the study were described in detail in our previous publication [20]. In brief, the sample was divided into patients who received pretreatment with 10 mg of cetirizine and those who did not. The frequency of adverse reactions with premedication decreased from 21.6% to 6.3% (OR, 4.13; 95%CI, 0.89-19.19; *P*=.06), systemic reactions from 17.5% to 6.3% (OR, 3.19; 95%CI, 0.67-15.08; *P*=.14), and local reactions from 5.4% to 0 (OR, 4.75; 95%CI, 0.24-91.10; *P*=.30). Only 2 cat-allergic patients dropped out of the study owing to the adverse effects of SCIT, although the reactions were not severe.

The limitations of our study include the lack of a control group to rule out the placebo effect of allergen immunotherapy.

Rigorous real-life studies are also needed to complete the evidence of placebo-controlled studies [28]. The study is also limited by the small number of patients included, especially in the case of dog allergy.

Conclusions

In this real-life study using an ultrarush schedule, we demonstrate the clinical efficacy of and immunologic changes brought about by SCIT with cat and dog extracts after 1 month of treatment. More remarkable results were obtained in cat-allergic patients than in dog-allergic patients, likely due to the higher concentration of the major allergen (Fel d 1) in the allergenic extract used in this SCIT formulation.

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Conflicts of Interest

JS reports having served as a consultant to Thermo Fisher, MSD, Novartis, Gennetech, Sanofi, Leti, Roche, ALK, FAES FARMA, Mundipharma, and GSK. He has also received lecture fees from Novartis, GSK, Stallergenes, LETI, and FAES FARMA and grant support for research from Thermo Fisher, ALK, and Sanofi.

The remaining authors declare that they have no conflicts of interest.

References

1. Taylor WW, Ohman JL Jr, Lowell FC. Immunotherapy in cat-induced asthma. Double-blind trial with evaluation of bronchial responses to cat allergen and histamine. J Allergy Clin Immunol. 1978;61:283-7.
2. Ohman JL Jr, Findlay SR, Leitermann KM. Immunotherapy in cat-induced asthma. Double-blind trial with evaluation of in vivo and in vitro responses. J Allergy Clin Immunol. 1984;74:230-9.
3. Sundin B, Lilja G, Graff-Lonnevig V, Hedlin 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;77:478-87.
4. Van Metre TE, Marsh DG, Adkinson NF, Kagey-Sobotka A, Khattignavong A, Norman PS Jr, et al. Immunotherapy for cat asthma. J Allergy Clin Immunol. 1988;82:1055-68.
5. Haugaard L, Dahl R. Immunotherapy in patients allergic to cat and dog dander. I. Clinical results. Allergy. 1992;47:249-54.
6. Alvarez-Cuesta E, Cuesta-Herranz J, Puyana-Ruiz J, Cuesta-Herranz C, Blanco-Quirós A. Monoclonal antibody-standardized cat extract immunotherapy: risk-benefit effects from a double-blind placebo study. J Allergy Clin Immunol. 1994;93:556-66.
7. 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;27:860-7.
8. Ewbank PA, Murray J, Sanders K, Curran-Everett D, Dreskin S, Nelson HS. A double-blind, placebo-controlled immunotherapy dose-response study with standardized cat extract. J Allergy Clin Immunol. 2003;111:155-61.
9. Valovirta E, Koivikko A, Vanto T, Viander M, Ingeman L. Immunotherapy in allergy to dog: a double-blind clinical study. Ann Allergy. 1984;53:85-8.
10. Couroux P, Patel D, Armstrong K, Larché M, Hafner RP. Fel d 1-derived synthetic peptide immuno-regulatory epitopes show a long-term treatment effect in cat allergic subjects. Clin Exp Allergy. 2015 May;45(5):974-81.
11. Dávila I, Domínguez-Ortega J, Navarro-Pulido A, Alonso A, Antolín-Amerigo D, González-Mancebo E, et al. Consensus document on dog and cat allergy. Allergy. 2018;73:1206-22
12. Ohman JL Jr, Marsh DG, Goldman M. Antibody responses following immunotherapy with cat pelt extract. J Allergy Clin Immunol. 1982;69:320-6.
13. Hedlin G, Graff-Lonnevig V, Heilborn H, Lilja G, Norrlind K, Pegelow KO, et al. 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;77:488-96.
14. Lilja G, Sundin B, Graff-Lonnevig V, Hedlin G, Heilborn H, Norrlind K, et al. Immunotherapy with cat- and dog-dander extracts. IV. Effects of 2 years of treatment. J Allergy Clin Immunol. 1989;83:37-44.
15. Nanda A, O'connor M, Anand M, Dreskin SC, Zhang L, Hines B, et al. Dose dependence and time course of the immunologic response to administration of standardized cat allergen extract. J Allergy Clin Immunol. 2004;114:1339-44.
16. Lent AM, Harbeck R, Strand M, Sills M, Schmidt K, Efaw B, et al. Immunologic response to administration of standardized dog allergen extract at differing doses. J Allergy Clin Immunol. 2006;118:1249-56.
17. Uriarte Obando SA, Sastre Domínguez J. Safety of rush subcutaneous immunotherapy administered in real life using an infusion pump. Ann Allergy Asthma Immunol. 2015;115:527-9.
18. Uriarte SA, Sastre J. Subcutaneous immunotherapy with high-dose cat and dog extracts: a real-life study. J Inves Allergol Clin Immunol. 2020;30(3):169-74.
19. Sastre J, Vallejo L, Fernandez-Nieto M, Hernandez E, Rico, P. Rush Allergen Subcutaneous Immunotherapy Administered with Infusion Pump. Ann Allergy Asthma Immunol. 2011;107:459-60.
20. Uriarte SA, Sastre J. Safety of an ultrarush (4 hours), subcutaneous immunotherapy with cat and dog extracts using an infusion pump. J Inves Allergol Clin Immunol. 2018;28:430-2.
21. Zuberbier T, Bachert C, Bousquet PJ, Passalacqua G, Canonica GW, Merk H, et al. GA2LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma. Allergy. 2010;65:1525-30.

22. Wintersand A, Asplund K, Binnmyr J, Holmgren E, Nilsson OB, Gafvelin G, et al. Allergens in dog extracts: Implication for diagnosis and treatment. Allergy 2019;74:1472-9
23. Grönlund H, Bergman T, Sandström K, Alvelius G, Reininger R, Verdino P, et al. Formation of disulfide bonds and homodimers of the major cat allergen Fel d 1 equivalent to the natural allergen by expression in Escherichia coli. J Biol Chem. 2003 Oct 10;278(41):40144-51
24. Apostolovic D, Sánchez-Vidaurre S, Waden K, Curin M, Grundström J, Gafvelin G, et al. The cat lipocalin Fel d 7 and its cross-reactivity with the dog lipocalin Can f 1. Allergy. 2016;71:1490-5
25. Käck U, Asarnoj A, Binnmyr J, Grönlund H, Wallén C, Lilja G, et al. Basophil activation testing, IgG, and IgG4 in the diagnosis of dog allergy in children with and without a dog at home. Allergy. 2020;75:1269-72
26. Uriarte SA, Sastre J. Clinical relevance of molecular diagnosis in pet allergy. Allergy. 2016;71:1066-8.
27. Nilsson OB, Binnmyr J, Zoltowska A, Saarne T, van Hage M, Gronlund H. Characterization of the dog lipocalin allergen Can f 6: the role in cross-reactivity with cat and horse. Allergy. 2012;6:751-7.
28. Roche N, Anzueto A, Bosnic Anticevich S, Kaplan A, Miravitlles M, Ryan D, et al. Connected real-life research, a pillar of P4 medicine. Eur Respir J. 2020 Jan 16;55(1) pii: 190228

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