Subcutaneous immunotherapy with high-dose cat and dog extracts: a real-life study

Running Title: Inmmunotherapy with cat and dog extracts

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Abstract

Background: There are scarce efficacy data on immunotherapy administered to patients with cat or dog allergy.

Objetive: We aimed to evaluate the safety and efficacy of subcutaneous immunotherapy (SCIT) in patients with allergy to these two animals.

Methods: Consecutive patients with rhinitis and/or asthma related to sensitization to cat or dog were included in a pragmatic, real-life, prospective observational study. All patients had specific IgE to cat and/or dog. Using an infusion pump (IP), SCIT was administered over 3 sessions as part of a rush protocol, followed by monthly administration over 12 months. Data were gathered on adverse events and clinical outcomes, pulmonary function, FeNO, rhinitis and asthma symptoms, quality of life (QoL), asthma control test (ACT), and visual analog scale (VAS) at baseline, 6, and 12 months.

Results: Sixty-six patients were included: 38 females, 46 allergic to cat and 20 to dog, with ages ranging from 9 to 59 years. During the up-dosing phase, in which IP was used, 8.1% of doses elicited a systemic reaction (SR) and 5.4% caused a local reaction (LR), while 9.3% of doses administered during the maintenance phase (i.e. without IP) developed a SR, and no LRs were recorded. A significant improvement in FEV1, rhinitis and asthma symptoms and results of QoL questionnaires, use of medication, VAS, and ACT was observed at 6 months and continued at month 12. Clinical improvement with cat extract was significantly higher than with dog.

Conclusions: High-dose SCIT has substantial clinical value in many cat and dog allergic patients.

Key words: Cat, Dog, Allergy, Rhinitis, Asthma, Allergen immunotherapy

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Resumen

Antecedentes: Hay pocos estudios sobre la eficacia de la inmunoterapia administrada a pacientes con alergia a perro o gato.

Objetivo: Evaluar la seguridad y la eficacia de la inmunoterapia subcutánea (SCIT) en pacientes con alergia a estos dos animales.

Métodos: Se incluyeron pacientes consecutivos con rinitis y / o asma relacionados con la sensibilización al gato o al perro en un estudio observacional prospectivo, pragmático, en vida real. Todos los pacientes tenían IgE específica para gato y / o perro. La SCIT se administró utilizando una bomba de infusión (IP), en 3 sesiones como parte de un protocolo rápido, seguido de la administración mensual durante 12 meses. Se recopilaron datos sobre efectos adversos y resultados clínicos, función pulmonar, FeNO, síntomas de rinitis y asma, calidad de vida (QoL), prueba de control del asma (ACT) y escala analógica visual (VAS) al inicio, a los 6 y 12 meses.

Resultados: Se incluyeron 76 pacientes: 38 mujeres, 46 alérgicos a gato y 20 a perro, con edades comprendidas entre los 9 y los 59 años. Durante la fase de administración ascendente, se utilizando una IP, el 8,1% de las dosis provocó una reacción sistémica (SR) y el 5,4% causó una reacción local (LR), mientras que el 9,3% de las dosis administradas durante la fase de mantenimiento (es decir, sin IP) desarrolló una SR, y no se registraron LRs. Se observó una mejoría significativa en el FEV1, en los síntomas de rinitis, de asma y en los cuestionarios de la calidad de vida, uso de medicación, VAS y ACT a los 6 meses y continuó a los 12 meses. La mejoría clínica con el extracto de gato fue significativamente mayor que con el perro.

Conclusiones: Las dosis altas de SCIT tienen un valor clínico sustancial en muchos pacientes alérgicos a perros y gatos.

Palabras clave: Gato, Perro, Alergia, Rinitis, Asma, Inmunoterapia con alérgenos

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INTRODUCTION

Data on the efficacy of allergen immunotherapy in patients with cat [1-9] or dog allergy [3,5,10] remain scarce, especially in the case of dog allergy. High dose of standardized extracts have proven effective in treating patients who are allergic to cat. Previous double-blind studies with subcutaneous immunotherapy (SCIT] using standardized cat-allergen extracts have demonstrated that maintenance doses containing 13.2 μg of Fel d 1 [6], 13.8 μg Fel d 1 [4], or 15 μg Fel d 1 [7,8] reduced symptoms related to cat exposure and brought immunologic changes, [2,4,8,11-13]. The efficacy of SCIT with standardized dog-allergen extract has shown less efficacy than SCIT with standardized cat-allergen extract [3,5,10], despite showing immunologic changes [12,14].

The purpose of the present study was to explore the use of high-dose SCIT in patients with allergic rhinitis and asthma due to cat and dog in real-life clinical practice.

MATERIAL AND METHODS

Patients

We conducted a prospective observational study, selecting consecutive patients with rhinitis and/or asthma due to sensitization to cat or dog and for whom treatment with immunotherapy was indicated [15]. All candidates for inclusion expressed a willingness to initiate SCIT after receiving information on the possible benefits of this therapy approach. For a patient to be included, a strong relation between clinical symptoms and exposure to cat or dog was required, and an additional requisite was positive specific IgE to cat or dog extract as evidenced by skin prick test (ALK, Denmark) and/or in serum, specific IgE to whole cat or dog extracts or to Fel d 1, Fel d 2, Fel d 4, Can f 1, Can f 2, Can f 3, or Can f 5 (ImmunoCAP or ISAC, ThermoFisher, Sweden). Patients or their guardians signed an informed consent document. The study was approved by the local ethical committee (FJD-ALG-15/01).

Immunotherapy

Cat or dog extracts (Alutard SQ, Alk-abelló, Spain) were used. Concentration of major allergens were as follows: Fel d 1: 15 μg/ml, Can f 1: 3.21 μg/ml, Can f 5: 0.72 μg/ml [16].

Immunotherapy up-dosing consisted of 3 progressively increasing doses from the maintenance vials (100 000 SQ/ml), i.e. 10 000, 50 000, and 100 000 SQ administered at weekly intervals. Each dose delivered during this phase was administered by an infusion pump (IP) (Infusa T1, Medis, Italy) and up-dosing infusions lasted 30 minutes, as previously described [17,18]. Patients were observed for 30 minutes after the infusion was complete. Subcutaneous injections were applied for monthly maintenance doses.

Adverse reactions (ARs) (local, systemic, immediate, or delayed) were recorded according to the EAACI guidelines [15]. Delayed ARs were monitored by telephone interview after 48 hours of SCIT; for this purpose, patients received instruction on how to monitor ARs if necessary. Patients were not routinely premedicated.

Clinical outcomes

We performed spirometry and bronchodilation testing and measured fractional exhaled nitric oxide (FeNO) concentration. In addition, the following questionnaires validated for the Spanish population were administered: rhinitis quality of life ESPRINT-15 (health-related quality of life in allergic rhinitis), AQLQ (asthma quality of life questionnaire), ACT (asthma control test), and VAS (10-cm visual analogue scale, including nasal, ocular, and bronchial symptoms). Scores for nasal (itching, congestion, rhinorrhea, sneezing), ocular (tearing, itching, gritty feeling), and pulmonary (cough, wheezing, dyspnea, exercise asthma) symptoms (0: no symptoms, 1: mild, 2: moderate, 3: severe) and use of medication were applied. Medication use was scored as follows: antihistamines: 6 points, short acting beta-2 agonists: 2 points, inhaled corticosteroid: 2

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points, nasal topical corticosteroids: 2 points, and oral steroids:4 points. All assessments were performed at baseline and at 6 and 12 months.

To measure response to SCIT the minimum clinically important differences were considered: in the questionnaire ESPRINT-15 (> 0.9) (19], in AQLQ (> 0.5 per dimensional item, an average dimensional item change score of 1.0 was considered as moderate important change, and a change score of at least 1.5 per item was deemed a large important change in an AQLQ dimension) [20], in ACT >3) [21], in symptom score (> 2] between visits.

Associations between the IgE molecular profile and safety outcomes and with the clinical efficacy of cat or dog extract were analyzed as well as the difference in SCIT clinical efficacy between cat and dog extract.

Statistical analysis

Fisher exact test, Wilcoxon test, Friedman test, Kruskal-Wallis test, and a mixed-effects model were used for statistical analysis. P <0.05 was considered as significant.

RESULTS

Patients

Sixty-six patients were included (38 females and 28 males, of whom 46 were allergic to cat and 20 to dog), with ages ranging from 9 to 59 years (mean 34.23±12.1). A 36.3% were sensitized to pollen, 4.1% to profillin, 6% to mites and 6% to other allergens. Allergic rhinitis was present in 98.5% of patients (65) and 97% presented allergic asthma [64]. Most patients had persistent and moderate symptoms (Rhinitis: intermittent 13.8%, mild persistent 21.6%, moderate/severe persistent 64.6%; Asthma: intermittent 23%, mild persistent 36%, moderate/severe persistent 41%). More than 92% of patients (61) had either a dog or cat at home (daily direct

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contact), while 4.6% had indirect contact with these animals (3) and 2 were veterinarians.

Four patients dropped out of the study at the end of the up-dosing phase to continue their treatment in another center; another 4 patients abandoned the study between the 3rd and 6th month (3 due to poor SCIT tolerance, 1 for personal reasons), and 7 patients between the 6th and 12th month (all for personal reasons such as lack of time, distance from the hospital, travel abroad, and discontinuation of contact with pets). Fifty-one patients concluded the study (34 cat- and 17 dog-allergic patients).

Adverse events

During the up-dosing phase, 18 doses (8.1%) of SCIT (all with cat extract) triggered a systemic reaction (SR) and 12 doses (5.4%) produced a local reaction (LR); by comparison, 9.3% of doses (3) administered during the maintenance phase caused a SR, and no LRs were recorded. No SRs were triggered by doses of SCIT with dog extract in either the up-dosing phase or in the maintenance phase (i.e. with or without IP), and 2.1% of doses (2) delivered using an IP caused a LR, none of which occurred in the maintenance phase. ARs to SCIT tended to occur in patients with more severe asthma and worse control, though this difference did not reach statistical significance.

The most frequent symptoms of SRs with SCIT based on cat extract were rhinitis (71.4%) and asthma (71.4%), followed by conjunctivitis (43%) and urticaria (24%). The majority of SRs were immediate (90%) and grade I (62%), and the rest were grade 2 (8 SRs). All SRs were controlled and resolved, treated with antihistamines (100%), inhaled β-2 agonists (71%), systemic corticoids (47%), and epinephrine (42.8%). No cases of anaphylactic shock or hypotension were reported. The onset, grade, and treatment of SRs were similar both in the up-dosing and maintenance phase. All LRs had a late onset and mild intensity and none required treatment. In total, 3 patients were removed from the study due to adverse events (all with cat extract).

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Specific IgE

All patients had a positive IgE (> 0.35 kU/L) and prick test to cat or dog extracts. Eighty-three percent of cat-allergic patients had positive results to Fel d 1, 26% to Fel d 2, and 50% to Fel d 4. Among dog-allergic patients, 79% had positive results to Can f 1, 47% to Can f 2, 26% to Can f 3, and 63% to Can f 5. 21.1% of dog-allergic patients were monosensitized to Can f 5, while monosensitization to lipocalins or serum albumins was not observed. All dog-allergic patients recognized at least one commercially available allergen, while 12% of cat-allergic patients did not recognize any.

Other outcomes

Results of pulmonary function test, FENO values, symptom scores, and ACT, VAS, and medication scores are expressed in Figure 1.

Baseline spirometry was normal in most patients with asthma, and the bronchodilation test did not obtain significant differences across visits. FEV1 increased significantly at 6 months ($p=0.023$), but only by 50 ml which is not clinically relevant. Other spirometric values remained stable during the study.

At the beginning of the study, FeNO was elevated (> 50 ppb) in 77% of patients (47), and FeNO remained elevated at 6 months in 49% of patients (27) and in 54.6% at month 12 [30]. Mean FeNO values decreased by around 10% percent at the end of the study (Figure 1).

The mean increase in ACT was 3.87 and 4.21 at months 6 and 12, respectively ($p<0.0001$ both from baseline), both of which were greater than the minimally importance difference (Figure 1).

The greatest decrease in medication use was seen with antihistamines and short acting β-2 agonists. Doses of inhaled corticosteroids were approximately halved. No patient required systemic steroids throughout the study (Figure 1).

Results of quality of life questionnaires for rhinitis and asthma are expressed in Figure 2. The ESPRINT-15 questionnaire showed that 87.3% of the patients improved at

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month 6, and 80% maintained this improvement at 12 months. The decrease in total score and all dimensions was greater than the minimally important difference (0.9).

At months 6 and 12, all dimensions of AQLQ (activity limitation, symptoms, emotional function and environmental stimuli, and total) increased by more than 0.5 points, the minimally important difference; in many patients, this increase was more than 1, which is considered a moderately important change. The AQLQ showed an overall improvement in 87% of patients in the first 6 months, with 83% maintaining improvement at 12 months. Response to SCIT with cat or dog extract was good or very good in 66.7% of patients. Subjective improvement by patients was observed with the third maintenance dose (month 2 of treatment).

The molecular profile (number of allergens to which the patients were sensitized or the quantitative value of specific IgE to allergens) was not related to the response to SCIT with cat or dog extracts (p=0.864) or with safety profile (p=0.109), FeNO values (p=0.592), direct contact with cat or dog (p=0.39), age (p=0.218), or gender (p=0.697).

At baseline visit, patients with dog allergy experienced a more deleterious impact on their quality of life in terms of to asthma symptoms and emotional parameters (p=0.041, p=0.009, respectively), required greater use of medication in general, especially inhaled corticosteroids (p=0.005) and antihistamines (p=0.006), had higher FeNO values (p=0.001) and higher perceived symptom intensity (VAS). At the 12-month visit, the perceived intensity of their symptoms was maintained (p=0.008), they had an increased need for medication (p=0.02), as well as a worse rhinitis-related quality of life in relation to their daily activities (p=0.042), and lower FEV1/FVC ratio (p=0.049) in comparison with patients with cat allergy. ACT scores at 6 and 12 months of treatment revealed a tendency toward better disease course among patients receiving cat-extract SCIT compared to SCIT with dog extract, though without reaching statistical significance.

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Discussion

Pragmatic trials provide information that may be considered complementary to data from randomized clinical trials [22]. This study, which was carried out in a real-life setting, confirms the efficacy of SCIT using extracts with high doses of allergens of cat and dog. To administer immunotherapy, we used a rush up-dosing phase with an IP, as we described previously, followed by a monthly maintenance dose over a 12-month period. In general, the rush up-dosing and maintenance phase showed a good safety profile, as found in previous studies using IP [17, 18], conventional [23] or other rush schedules [24], and the safety profile of the up-dosing and maintenance phases was even better than some cluster schedules described in the literature. [5]

The SRs to the SCIT were only observed with cat extract; no such reactions were observed with dog extract, and similar result has been found in other studies [5,10]. This extract-specific difference could be due to the high concentration of Fel d 1 (15 μg), the major cat allergen, in comparison to the major dog allergens, Can f 1 (3.21 μg) and Can f 5 (0.72 μg) [16]. Most SRs produced were grade I or II and resolved with appropriate treatment, though 3 patients abandoned the study during the maintenance phase due to side effects.

In this study and others published by our group [16, 25], a high percentage of monosensitized patients to Can f 5 was observed. Can f 1and Can f 5 were the most frequently recognized allergens in dog-allergic patients, followed by Can f 2. In the case of cat-allergic patients, Fel d 1 sensitization was the most frequent, followed by Fel d 4 and Fel d 2. Of note, 12% of cat-allergic patients had a positive IgE to whole cat extract, but they did not recognize the three cat allergens tested. This emphasizes the need to have more allergens available in clinical practice and to control the presence of whole allergens in diagnostic and treatment extracts. The pattern of allergen recognition was not associated with the appearance of adverse events or with treatment efficacy.

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SCIT with cat or dog extract showed clear clinical efficacy at 6 months, and this efficacy was maintained at 12 months of treatment. FEV1, rhinitis and asthma quality of life questionnaires , asthma control test, VAS, score of symptoms and use of medication significantly improved throughout the study even in cases where the patient maintained direct contact with the pet or pets at home, though increase in FEV1 is not clinically relevant, improvement in rhinitis and asthma quality of life questionnaires and asthma control test exceeded its minimal importance difference. In the past, Taylor et al. [1], performed a double-blind placebo-controlled study with 10 cat-sensitized patients, showing that the group that received SCIT with cat had a decrease in cutaneous and bronchial sensitivity to cat extract and similar results were found in other studies [2,3,4]. A less substantial improvement in ocular symptoms was found in our study in comparison with airway symptoms, thus contrasting with studies by Alvarez-Cuesta et al [6] and Varney et al [7] (both with cat extract) and Valovirta et al [10] (with dog extract), who observed decreased conjunctival sensitivity throughout treatment.

Clinical efficacy differed based on the type of extract (cat or dog extract). Clinical improvement with cat extract was significantly higher in terms of symptoms, use of medication, and lower FEV1/FVC ratio than patients allergic to dog. Previous studies reported that SCIT with dog extract was less effective than SCIT with cat extract [3,5,12,19, 26], likely due to the higher concentration of Fel d 1 in comparison with the Can f 1 or Can f 5 concentration in extracts [16], andeven using concentrations recommended in US that is 15 μg/ml of Can f 1 per dose [26]. Specific IgG or IgG4 to cat and dog allergens was not measured in this study, but significant immunologic response with the increase of IgG and/or IgG4 to cat [4,8,12,13,19] or dog [10,12,14] was observed in previous studies using similar extracts of dog and cat (Alutard SQ). The good clinical and immunologic response to SCIT is clearly associated with high doses of major allergens contained in extracts, mainly in the case of cat extracts [3-8,13, 18, 19]. Limitations of this study include a modest number of patients and the lack

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of a placebo-control group. Nevertheless, this study was designed as a pragmatic trial. This trial did not included nasal or bronchial challenge or changes in skin reactivity that could have confirmed the results of this study.

Conclusions

This real-life study reinforces the clinical efficacy of SCIT with high-dose extracts in many cat- and dog-allergic patients. The safety and efficacy profile of this SCIT with cat or dog extract was not related to the IgE molecular profile.

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Author contributions: SAU and JS contributed in design, carry out and writing of this study.

Conflict of interest

JS reports having served as a consultant to Thermofisher, MSD, Novartis, Gennetech, Sanofi, Leti, Roche, ALK, FAES FARMA, Mundipharma, and GSK; having been paid lecture fees by Novartis, GSK, Stallergenes, LETI, and FAES FARMA; as well as having received grant support for research from Thermofisher, ALK and Sanofi.

SU and MJR declare no conflicts of interest.

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Legends to figures

Figure 1. Results of pulmonary function test, FeNO values, symptom scores, Asthma Control Test (ACT), visual analog scale (VAS), and medication scores.

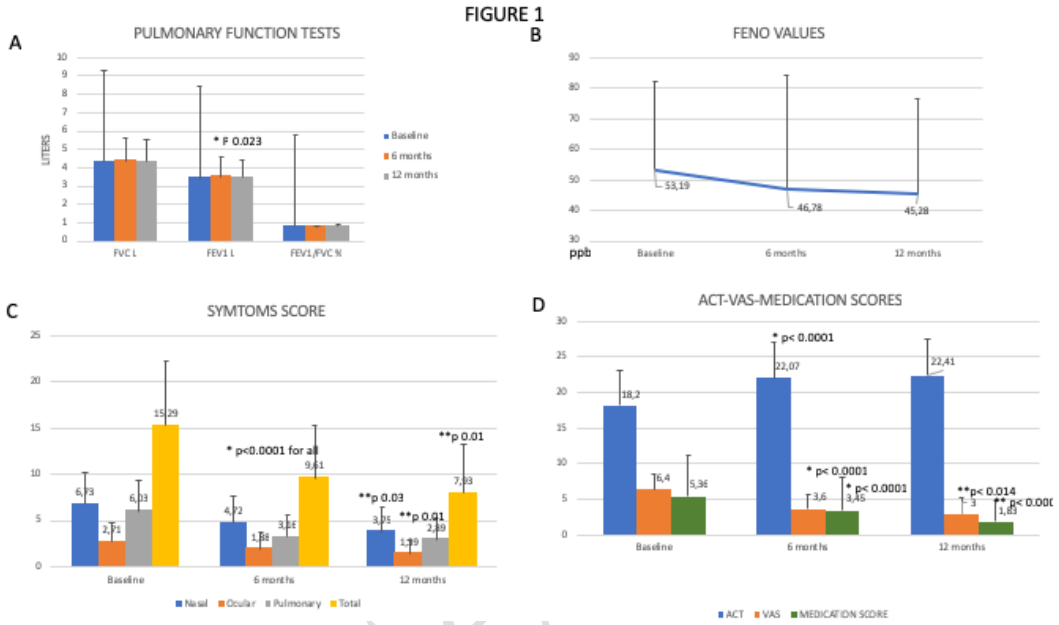

Figure 2. Results of quality of life questionnaires for rhinitis (ESPRINT-15) and asthma (AQLQ)