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Subcutaneous immunotherapy with aeroallergens: safety profile assessment

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Key words

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Summary

Introduction*. Severe systemic reactions (SR) to allergen subcutaneous immunotherapy (SCIT) are rare but local reactions (LR) are common. We aimed to characterize the type of reactions and safety profile.* ***Methods****. Retrospective analysis of medical record from patients under SCIT between 2013-2016.* ***Results.*** *Total of 7372 SCIT injections in 323 patients: 52% female; mean age 30 years (SD 13); mean treatment time 19 months (SD 13). There were 57 patients (17.6% of population, 70% female) with at least one adverse reaction, for 93 reactions described (1.3% injections). There were 79 LR (1.1% injections) in 46 (14.2%) patients: 36 in build-up, 43 in maintenance. There were 14 SR (0.19% injections) in 12 (3.7%) patients: 12 in build-up, 2 in maintenance. All SR were grade 1. The majority of reactions were caused by mite SCIT (69.9%).* ***Conclusions.*** *SCIT is safe and well tolerated, with no report of SR grade > 1.*

Impact statement

Local and systemic reactions after subcutaneous immunotherapy with aeroallergens were analyzed. It was shown that this treatment was well tolerated and had a good safety profile, with no report of severe systemic reactions.

Introduction

Respiratory allergy (allergic rhinitis and asthma) is caused by airborne allergens (dust mite, pollen, fungi, cat and dog epithelium) that when inhaled can trigger airway inflammation in susceptible individuals. Management of respiratory allergy includes allergen avoidance and pharmacotherapy (1). There are some patients who remain symptomatic besides being under treatment. In these cases, allergen immunotherapy (AIT) should be considered (2). Strong evidence suggests that subcutaneous immunotherapy (SCIT) improves symptoms, medication use, and quality of life in these patients (3). AIT is the only treatment that modify the natural history of allergic disease by reducing symptoms upon exposure to aeroallergens (4). During immunotherapy, there is an initial increase of specific IgE (sIgE) levels followed by a progressive decrease. It is also verified an increase in $CD4^+CD25^+$ regulatory T lymphocytes, secreting IL-10 and TGF-ß, which are associated with immunologic tolerance. During treatment, IgG antibodies subtypes, IgG_4 and IgG_1, increase about 10 to 100 times. These subtypes are non-inflammatory with inhibitory activity: they can prevent allergic reaction by conjugating with the allergen, before its binding with IgE, avoiding mastocyte and basophil activation with release of inflammatory mediators. Progressively, immunotherapy acts on T cells to modify peripheral and mucosal Th2 (responsible for allergic reaction) reactions to allergen promoting a Th1 cytokine profile (5, 6). The two major modalities for AIT are subcutaneous and sublingual. SCIT, was introduced more than 100 years ago (7). Immune tolerance is obtained through the administration of increasing amounts

of the same allergen responsible for the allergic symptoms in sensitized individuals.

Adverse reactions may occur, ranging from mild symptoms at the site of injection to anaphylactic reactions (8). They can be classified as either local or systemic reactions and the majority of systemic reactions (SR) occur within 30 minutes of injection, according to European Academy of Allergy and Clinical Immunology (EAACI) guidelines (9, 10). Local reactions (LR) are fairly common, affecting 26% to 82% of the patients and 0.7% to 4% of injections (11-13). They can occur as redness, itching or swelling at the site of injection. They are considered to be large when erythema or swelling diameter is greater than the size of patients' palm (average adult, 8-10 cm) (14). SR are characterized by the occurrence of systemic symptoms, with different severity grades, from mild (Grade 1) to severe systemic reactions, potentially fatal (Grade 5), according to World Allergy Organization (WAO) Subcutaneous Immunotherapy Systemic Reaction Grading System (15). They are less common, affecting 2% to 5% of the patients and 0.1% to 0.2% of injections (15, 16).

The frequency of SR induced by SCIT varies widely according to the allergen extract used, the administration buildup protocol (conventional, cluster or rush), the maintenance dose administered and the severity and type of disease (17-19). The first fatal reaction was described by Lamson RW in 1924 (20). History of uncontrolled or severe asthma is the most important contributing factor for the occurrence of fatal reactions. Other recognized risk factors include dosing errors, a delay in the/no administration of epinephrine during anaphylaxis or concomitant treatment with ß-blockers, a prior history of injection-related SR and administration of SCIT during peak pollen season or an inadequate surveillance period after injection (3, 4, 8, 16, 21). The risk of SR was found to be lower in dust-mite sensitized patients compared with pollen-allergic patients (22). The objectives of this retrospective database review were to characterize the type of reactions after SCIT administration: LR or SR, late or immediate reactions and analyze the safety profile of SCIT in patients.

Methods

Population and study design

Retrospective review of the medical records from patients submitted to SCIT from January 2013 to December 2016, in our Immunotherapy Center (Immunoallergology Outpatient Clinic of Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte). Demographic data (age and gender), diagnosis of allergic diseases (rhinitis, asthma, atopic dermatitis, conjunctivitis or food allergy), aeroallergen sensitization, SCIT composition, date of initiation, duration and SCIT administration schedule were registered. The occurrence of local and systemic reactions was verified by analyzing clinical and nursing records of each patient. There were excluded patients receiving injections at another facility or missing information in patient's medical records concerning SCIT administration. A written informed consent was obtained from all patients and/or their legal representatives before initiating SCIT. The diagnosis, severity and treatment of allergic rhinitis and asthma were established according to the current guidelines − Allergic Rhinitis and its Impact on Asthma (ARIA) (23) and Global Initiative for Asthma (24) −, respectively.

Skin tests and specific IgE

Roxall's® (Hamburg, Deutschland) allergen extracts were used for skin prick tests and serum specific IgE (sIgE) tests were from ImmunoCAP system® (Thermo Fisher Scientific, Uppsala, Sweden). Regarding skin prick tests, all patients were tested with the following allergens: house dust mites, storage mites, pollens (grass, parietaria, olive tree and artemisia), cat and dog epithelium. All patients had positive skin prick tests and/or sIgE tests ≥ 0.70 kU/L, to at least one aeroallergen.

Subcutaneous immunotherapy

SCIT was initiated in patients with allergic symptoms despite being under medical treatment and allergen avoidance. It was chosen considering the results of skin prick tests and/or sIgE tests and by correlating them with patients' symptoms, according to EAACI Guidelines on Allergen Immunotherapy (10) and GA²LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma (25). The route of therapy (subcutaneous) was prescribed taking into consideration the patient's preference, allergic symptoms and personal concerns. All used extracts were polymerized, chemically and physically modified (allergoids), conditioning less allergenicity and increasing efficiency and safety.

Build-up phase was administered as conventional or rush protocols and the maintenance dose was administered at four-to-six-week intervals over a period of three to five years. All injections were given by trained nurses with supervision of the immunoallergologist in the Immunotherapy Center, equipped with material for the treatment of systemic reactions. All patients were monitored for 30 minutes after the SCIT administration.

Safety was studied by analyzing the occurrence of LR and SR, immediate and late reactions (according to the EAACI Immunotherapy Position Paper (26)) and correlating it with the SCIT composition, in order to determine safety profile. Local reactions were classified by measuring the largest reaction diameter. There is no consensus in relation to large local reactions diameter, so we considered local reactions to be large if redness or swelling had > 10 cm of diameter (10). Systemic reactions were classified in grades 1 to 5 (WAO Subcutaneous Systemic Reaction Grading System (15)). Immediate reactions were those which occurred in the first 30 minutes after injection.

Data were anonymized, and their confidentiality guaranteed, and this study protocol was approved by the Ethical Board of Centro Hospitalar Universitário de Lisboa Norte.

Statistical analysis

It was analyzed and compared the groups of patients with and without adverse reactions after SCIT (age, gender, clinical diagnosis, involved SCIT extract) and which factors were associated with its occurrence. Continuous variables were presented as means and standard deviations, or medians and interquartile ranges for variables with skewed distributions, and categorical variables as frequencies and percentages. Normal distribution was confirmed using Shapiro-Wilk test or skewness and kurtosis. For bivariate analysis, t-independent test and Mann-Whitney test were used to compare parametric and non-parametric independent samples, respectively. Categorical variables were compared using Fisher's exact test or the Chi-square test, as appropriate. P-values < 0.05 were considered statistically significant. Analyses were performed using version 27 of SPSS software for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

From a total of 631 patients under SCIT during the study period, 323 patients were included and 308 excluded due to data unavailability. According to the demographic data (**table I**), there was a predominance of female gender (n = 167; 52%), the mean age of the patients was 30 years (SD 13; range 7-73). The age group between 18 and 30 years was the most prevalent with 45% (n = 145), followed by the one between 31 and 50 years with 31.5% (n = 102), between 7 and 17 with 16.4% (n = 53) and the group over 50 years was the least prevalent (n = 23; 7.1%).

The average treatment time was 19.2 months (SD 13) and induction protocol was rush in 78.6% of the patients. Regarding the SCIT composition, there was a predominance of dust mite allergen (n = 220; 68.3%). More information about SCIT composition and patients' diagnosis is detailed in **table I**.

All patients had allergic respiratory disease, with rhinitis being the most frequent diagnosis (n = 313; 97%), followed by asthma (n = 145; 45%), about 40% of patients had concomitant asthma and rhinitis. There were also patients with conjunctivitis (n = 92; 28.5%), atopic dermatitis (n = 52; 16%) and less frequently food allergy (n = 30; 9%).

In the 323 patients included, 7372 SCIT injections (mean 22 injections/patient) were administered.

There were 57 patients (17.6% of the population) with, at least, one adverse reaction: 40 (70%) were female (comparing both genders, the number of adverse reactions was significantly higher in female (P-value = 0.002)), mean age 30.8 years (SD 11.4). The majority (n = 55; 96.5%) had rhinitis, 26 (45.6%) asthma, 16 (28.1%) conjunctivitis, 8 (14%) atopic dermatitis and 3 (5.3%) had food allergy. The age group 18-30 years was more affected, with 33 patients (57.9%) reporting a reaction.

Regarding SCIT composition of the 57 patients with adverse reactions, 65.0% were under mite allergen SCIT (the number of reactions was significantly higher with *Dermatophagoides pteronyssinus* and/or *farinae* (P-value 0.04) and with *Dermatophagoides* plus another mite (P-value 0.002)), followed by pollen (28.0%) and by mite and pollen (7.0%) SCIT. By analysing SCIT composition per reaction, the result is similar: mites were responsible for the majority (65 reactions; 69.9%), followed by pollen (26 reactions; 28.0%) and by mite and pollen (2 reactions; 2.1%). We also observed that from the patients under mite SCIT, 16.8% had an adverse reaction and from the patients under pollen SCIT and 18.0% had an adverse reaction. In a total of 93 adverse reactions described (1.3% of the SCIT injections), 48 (51.6%) were on the build-up and 45 (48.4%) on the maintenance phase (**table II**).

Local reactions

Regarding local reactions (LR), 46 patients (14.2%) had at least one LR, 32 (69.6%) female, mean age 32.3 years (SD 11.8, range 15-57), of a total of 79 (1.1% of the total injections) reactions described: 36 in the build-up phase (17 were immediate, all presented with local edema between 8 and 10 cm; 19 were late, only 5 with local edema > 10 cm) and 43 in the maintenance phase (18 immediate and 25 late reactions).

Only five of the build-up LR, were during a conventional protocol, while the others were during rush protocol.

From the 79 LR, two patients had six, three patients had five LR and the remaining had just one LR. The two patients who had six LR, both were female, under mite allergen SCIT; one of them quit SCIT because of frequent and severe local adverse reactions. The patients that had five LR each, all were female, two were under mite allergen SCIT and the other was under pollen SCIT. None of them quit SCIT during the studied period. No systemic reaction observed in these five patients (**table III**).

Systemic reactions

Regarding systemic reactions (SR), there were 14 (0.19% of the injections) in 12 (3.7%) patients: 66.7% female, mean age 25.9 years (SD 6.0, range 19-41). All were grade 1 (generalized pruritus). The majority (78.6%) were immediate, during build-up (85.7%) and more than a half (8; 57%) occurred in asthmatic patients: five were under mite SCIT, two pollen SCIT and one mite and pollen SCIT (**table IV**).

No fatal reactions were registered. All SR during build-up phase were in rush protocols. Oral antihistamines were given to each patient with SR; no patient received epinephrine and/or systemic corticosteroids.

Discussion

In our population, LR were very common (frequency of adverse drug reaction ≥ 10% (27)), once they occurred in 14.2% of the patients and 1.1% of the administered injections. Although the percentage of patients with LR is below of the values reported in other important

Table I - *Demographic and clinical data from patients under subcutaneous immunotherapy, total population and patients with adverse reactions.*

Variables	Patients			P-value
	Total (n = 323; 100%)	**Without Adverse Reactions (n = 266; 82.4%)**	**With Adverse Reactions (n = 57; 17.6%)**	
Age [mean (SD)] years	30 (SD 13.0)	29 (SD 13)	31 (SD 11.4)	0.227
Age groups				
[7 – 17] n (%)	53 (16.4)	50 (18.8)	3 (5.3)	
[18 – 30] n (%)	145 (45)	112 (42.1)	33 (57.9)	
[31 – 50] n (%)	102 (31.5)	87 (32.7)	15 (26.3)	
[51-65] n (%)	23 (7.1)	17 (6.4)	6 (10.5)	
Gender				0.002
Female n (%)	167 (52)	127 (48)	40 (70)	
Male n (%)	156 (48)	139 (52)	17 (30)	
Clinical diagnosis				
Rhinitis n (%)	313 (97)	258 (97)	55 (96.5)	0.692
Asthma n (%)	145 (45)	119 (44.7)	26 (45.6)	0.530
Rhinitis and Asthma n (%)	129 (40)	103 (38.7)	26 (45.6)	0.769
Conjunctivitis n (%)	92 (28.5)	76 (29)	16 (28.1)	0.540
Rhinitis and Conjunctivitis (%)	91 (28.2)	75 (28.2)	16 (28.1)	0.563
Atopic dermatitis n (%)	52 (16)	44 (16.5)	8 (14)	0.697
Food allergy n (%)	30 (9)	27 (10)	3 (5.3)	0.227
Allergen Immunotherapy extract				
Dermatophagoides (*pteronyssinus* and/or *farinae*) n (%)	172 (53.4)	149 (56)	23 (40.4)	0.04
Dermatophagoides + another mite n (%)	41 (12.7)	27 (10.2)	14 (24.6)	0.002
Storage mites n (%)	7 (2.2)	7 (2.6)	0	0.611
Dermatophagoides + pollen n (%)	13 (4)	9 (3.4)	4 (7.0)	0.590
Grass n (%)	66 (20.4)	54 (20.3)	12 (21.0)	0.488
Parietaria n (%)	10 (3.1)	9 (3.4)	1 (1.7)	0.448
Grass + olive tree n (%)	5 (1.5)	2 (0.8)	3 (5.3)	0.083
Grass + parietaria n (%)	4 (1.2)	4 (1.6)	0	0.458
Grass + artemisia n (%)	2 (0.6)	2 (0.8)	0	0.322
Olive tree n (%)	2 (0.6)	2 (0.8)	0	0.322
Cat epithelium n (%)	1 (0.3)	1 (0.4)	0	0.824

SD: standard deviation.

Table II - *Number of adverse reactions during Subcutaneous Immunotherapy (SCIT).*

Reactions	Build-up			Maintenance			
	Immediate	**Non-Immediate**	**Total**	**Immediate**	**Non-Immediate**	**Total**	
Local (n)	17	19	36	18	25	43	**79**
Systemic (n)	9	3	12	2	0	2	**14**
Total (n)	26	22	**48**	20	25	**45**	**93**

papers (26 to 82% of the patients (11-13)), our percentage of LR per injection, is in line with literature (0.7 to 4% of injections (11-13)). In relation to SR, our data relative to percentage of patients and injections (3.7% and 0.19%, respectively) is in accordance with literature (2 to 5% and 0.1 to 0.2% (15, 16), respectively).

Although some patients with a greater frequency of large LR might be at increased risk of SR (14, 28, 29), published studies suggest that individual LR are not predictive of future SR. In fact, our five patients with more LR did not have subsequent SR. They were instructed to maintain their medication with antihis-

Table III - *Patients with recurrent Local Reactions (LR).*

Patient	Gender	Age	SCIT Allergen	N. reactions	Quit SCIT	Adverse reactions	
						Build up	Maintenance
1	F	29	Mite	6	No	1 non-immediate LR > 10 cm	6 non-immediate LR
2	F	26	Mite	6	Yes	1 immediate LR 8-10 cm	5 non-immediate LR
3	F	51	Mite	5	No	1 non-immediate LR > 10 cm	4 non-immediate LR
4	F	41	Mite	5	No	1 immediate LR 8-10 cm	4 immediate LR
5	F	54	Pollen	5	No	1 immediate LR 8-10 cm	2 immediate LR 3 non-immediate LR

M: male; F: female; LR: local reactions; SCIT: subcutaneous immunotherapy.

Table IV - *Patients with Systemic Reactions.*

Patient	Gender	Age	Allergic disease	SCIT Allergen	Buildup	Maintenance
1	M	31	R, A	Pollen	Grade 1	Grade 1
2	M	30	R, A	Mite	Grade 1	-
3	F	29	R, A, FA	Pollen	Grade 1	Grade 1
4	M	19	R, A	Mite + Pollen	Grade 1	-
5	F	24	R, A, AD	Mite	Grade 1	-
6	F	22	R	Mite	Grade 1	-
7	F	28	R, A, AD	Mite	Grade 1	-
8	M	23	R	Mite	Grade 1	-
9	F	20	R	Mite	Grade 1	-
10	F	41	R, A	Mite	Grade 1	-
11	F	20	R, A	Mite	Grade 1	-
12	F	24	R	Pollen	Grade 1	-

M: male; F: female; R: rhinitis; A: asthma; FA: food allergy; AD: atopic dermatitis; SCIT: subcutaneous immunotherapy.

tamines, in order to minimize the occurrence of adverse reactions after SCIT. Only one of them had to quit SCIT because of frequent LR, as it was impossible to reach the maintenance dose.

As many studies suggest (28, 30, 31), SR are most frequently reported within the first 30 minutes after the administration (immediate reactions) and during the build-up phase, mainly in rush protocols. In our population, 85.7% of the SR were at build-up phase (all during rush protocols) and 78.6% were immediate. From this perspective and as it is recommended, SCIT was administered in the outpatient visit and all patients stay in surveillance for at least 30 minutes, so that severe reactions were promptly assisted.

Many studies do not report differences between male and female nor between adults and children in the occurrence of adverse reactions (32-34). We verified that female had much more reactions (n = 40; 70%) than male. Even in systemic reactions, the majority of the patients were female (n = 8; 67%). We have found three studies reporting a higher SR rate in female (35-37). Regarding age, we also did not find important differences between adults and children. We reported more reactions (n = 33) in the age group between 18 and 30 years, but it also had more patients in comparison with the other age groups.

Generally, reactions are more frequently induced by pollen extracts than by mites (19, 22). Regarding our population, the majority (68.3%) of the patients were only under mite SCIT. That could explain why most of the adverse reactions occurred with mite extract. By analysing the group of patients only under pollen SCIT or only under mite SCIT, it was verified that a higher percentage of patients under pollen SCIT had an adverse reaction: 18.0% *versus* 16.8% in the mite group. SCIT has revealed to be a safe treatment, based on the low frequency and severity of SR (4). However, there is still a small risk of fatal allergic reactions associated with subcutaneous administration of aeroallergens, occurring in one event in 2.5 million of injections (4, 8).

Table V *- Fatal reactions in Subcutaneous Immunotherapy studies.*

	Observation interval	(N)	Number of fatal reactions
Surveillance studies in the US		**Questionnaires**	
Lockey *et al.* (39)	1945-1984	60	24
Reid *et al.* (38)	1985-1989	NS	17
Bernstein *et al.* (3)	1990-2001	646	41
Bernstein *et al.* (40)	2001-2007	806	6
Epstein *et al.* (31)	2008-2011	806	0
Epstein *et al.* (41)	2011-2012	806	1
Other studies		**Population**	
Moreno *et al.* (21)	1996-1997	419	0
Schiappoli *et al.* (33)	2003-2006	1738	0
Cardona *et al.* (42)	2007-2011	575	0
Arêde *et al.* (43)	2007-2012	100	0

NS: not specified.

Since Lockey *et al.* (38) published the first retrospective survey on fatalities from SCIT and skin testing in the United States (US), other surveillance studies in SCIT safety were made in US and Europe (**table V**). By analysing **table V**, it is evident that the number of fatal reactions has significantly decreased passing the years. The first study reported 24 fatal reactions, while the most recent studies have no fatalities described. No fatalities were verified in our population. To minimize the occurrence of serious adverse systemic reactions, all of the studied patients were evaluated before starting SCIT, all of them had well-controlled, mild-to-moderate asthma. Initiation of pollen extract SCIT was administrated out of pollen season: from September to February. As it is a retrospective study from only one centre and there was an exclusion of almost half of the total population due to lack of clinical information about SCIT administration, the results may be limited. This study also does not specify the timing of reactions (how long were patients under SCIT) on maintenance phase.

Conclusions

SCIT has revealed to be safe and well tolerated in the majority of the patients. Only 17.6% of the studied patients and 1.3% of the SCIT administrations registered an adverse reaction.

The majority were LR – affecting 14.2% of our population – a value below of the reported in other studies, and 1.1% of the administered injections, as it is described in literature. SR were common (frequency of adverse drug reactions ≥ 1% and < 10% (27)), once they occurred in 3.7% of the patients and 0.19% of injections, which is in line with other studies (15, 16). We didn't report SR of grade > 1. No fatalities were found. So, SR were infrequent and not severe, occurring mainly during build-up phase. Adverse reactions were mostly caused by mite SCIT, the more frequent used composition in our population and SCIT with *Dermatophagoides pteronyssinus* and/or *farinae* and *Dermatophagoides* plus another mite may be associated with the occurrence of adverse reactions. More than a half of all reactions were non-immediate and occurred at build-up phase. Female had more adverse reactions. Patients who had a higher number of LR didn't have more SR.

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Conflict of interests

The authors declare that they have no conflict of interests.

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