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Self-reported adverse reactions to subcutaneous airborne allergen immunotherapy: a real-life, single center study

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Key words

Adverse reactions; subcutaneous allergen immunotherapy; multiple allergen immunotherapy; extracts dilutional effect.

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Summary

Background. *To estimate the prevalence of self-reported adverse reactions (AdR) to subcutaneous airborne allergen immunotherapy (SCIT) and to describe factors associated with its occurrence.* ***Methods.*** *Real-life, observational, descriptive study of all patients treated with SCIT at a Portuguese allergy unit between 03/2017 and 06/2019, and who answered ≥ 1 time to a pre-SCIT evaluation questionnaire assessing the occurrence of local and/or systemic AdR in the previous administration.* ***Results.*** *939 questionnaires from 231 patients (42% female, 35% with asthma) were included. Most (60%) SCIT preparations had multiple allergens with concentration adjusted to prevent dilution (MA-NoDil), 26% were single allergen with standard concentration (SA-SC), 10% single allergen with higher than standard concentration (SA-HC), and 4% mixtures without concentration adjustment (MA-Dil). SCIT-related AdR were self-reported in 313 (33%) administrations, 97% at the injection site and 11% grade 1 systemic symptoms. In a multivariable model, being a female and having asthma were associated with higher risk of AdR. MA-NoDil SCIT presented a lower risk of AdR compared to SA-SC SCIT.* ***Conclusions.*** *SCIT-related AdR were self-reported in 1/3 of the administrations, most at the injection site. The risk of AdR was higher in females and in patients with asthma. The lower risk of adverse reactions observed in SCIT preparations with multiple allergens with no dilutional effect should be further explored in future, targeted studies.*

Impact statement

Self-reported SCIT-related adverse reactions are common, occurring in 1/3 of the administrations, but almost all at the injection site and most easily tolerable. Females and patients with asthma had a higher odds ratio for self-reported SCIT adverse reactions.

Introduction

Allergen immunotherapy (AIT) is the only disease-modifying treatment for allergic diseases (1). It is usually administered by sublingual (SLIT) or subcutaneous (SCIT) route and both have demonstrated efficacy in reducing both allergic symptoms upon exposure to aeroallergens and the need for rescue medications (1). To achieve long-term benefits, AIT should be continued for a minimum of 3 years (2, 3).

Allergen immunotherapy safety, especially with SCIT, has been a significant concern. In fact, adverse reactions (AdR) associated with SCIT administration are common with some studies reporting that over 85% of patients receiving SCIT experience local, injection site reactions (LR) (1). Conversely, systemic reactions (SR) with SCIT are unusual but potentially severe, including the risk of anaphylaxis (1, 4). Therefore allergen immunotherapy should be administered by or under the close supervision of a trained physician who can recognize early symptoms and signs of anaphylaxis and administer emergency treatment (4). Moreover, all patients should be kept under surveillance at the healthcare facility for at least 30 minutes following injections (4). The rate of SCIT-associated SR of varying severity is relatively low, at around 0.1-0.2% (1). In Portugal, published data shows that SCIT-associated SR are also infrequent, occurring in about 0.1% of all SCIT administrations (5). There are several commonly described risk factors for SCIT-associated SR, including poorly-controlled asthma, infections, physical exercise, administration during pollen season, prior history of SCIT-associated SR, some concomitant medications (such as beta-adrenergic blockers or ACE inhibitors), frequency of administration, dosing error and incorrect administration technique (4, 6-9). Although SR can be severe and even lead to death (1), LR are much more common and can have impact on patient compliance and SCIT schedule or dose (10, 11). Nevertheless, risk factors for SCIT-associated LR or AdR as a whole (including both local and systemic AdR) were seldom evaluated.

In the last couple of years, new SCIT formulations have been released by different manufacturers. These include the possibility to prescribe mixtures of non-homologous allergens without significant loss of efficacy and the use of SCIT preparations with higher than standard allergen concentration. Although the current European guidelines on AIT do not recommend prescribing SCIT with mixtures of non-homologous allergens (2), 60 to 80% of the patients consulting allergists are polysensitized (12). When treating a polyallergic patient with AIT, some allergists use a single-allergen formulation (selecting the most clinically relevant allergen), whereas others prefer to prescribe either a mixture of two or more allergen extracts (preferably adjusting for dilutional effect) or two or more separate allergens (12). The possibility to use mixtures of non-homologous allergens within the same SCIT preparation seems very interesting to treat polyallergic patients. Still, there are unclarified concerns regarding the stability of the preparation (12) and a possible increase in the risk of AdR.

Dose-finding clinical trials suggested that SCIT efficacy increases with higher allergen concentrations, but this may be hampered by an increased risk of adverse reactions (13). Nevertheless, most allergen preparations commercialized in Portugal have no published studies regarding the optimal concentration (efficacy combined with tolerability) nor the associated risk of AdR.

This study aimed to estimate the prevalence of self-reported local and/systemic AdR to SCIT with airborne allergens and to describe factors associated with the occurrence of self-reported AdR, focusing on a possible increased risk in relation to the use of allergen mixtures and higher allergen concentrations.

Materials and methods

Study design

This was an observational, descriptive study that analyzed real-world data collected anterogradely during administrations of SCIT with airborne allergens in a private allergy unit from Northern Portugal, between March 2017 and June 2019. During this period, 497 individuals had SCIT administered at the site.

Participants

This study included data from all individuals who answered at least once to the self-administered questionnaire that is applied prior to SCIT administration as part of the usual clinical care provided at the allergy unit. Patients without any information on SCIT AdR in the filled the questionnaires were excluded. No additional exclusion criteria (*e.g.*, regarding the time since the beginning of SCIT or SCIT composition) were applied. All data were collected during routine care and the analysis was performed using an anonymized dataset with no personal identifier. Therefore, Ethics Committee approval was not required.

Data collection

Data on SCIT AdR were collected using a self-administered paper questionnaire that was implemented in 2017 to have a structured assessment of the conditions for a safe SCIT administration. The questionnaire was delivered to the patient after arriving to the allergy unit and filled while waiting for SCIT administration under the supervision of a healthcare professional that clarified any doubt about the interpretation of the questions, but avoided direct influence on answer selection; this support was only provided when requested by the patient. Children under thirteen years old answered the questionnaires together with their parents; older children were asked to answer the questionnaire by themselves but could ask for parent support when they felt it was needed.

Additional data on allergic disease diagnosis, date of first SCIT administration and physician perception on the relation between SCIT administration and self-reported systemic reactions were collected from the electronic medical records and, when necessary, from specific SCIT administration paper records. No information regarding local AdR was collected from the electronic medical records.

Data on SCIT characterization, including type of extract (*e.g.*, polymerized, depot or aqueous), allergen composition and concentration (with or without dilutional effect) were collected from the SCIT packaging and manufacturer's information.

All the patient data were collected as part of the usual clinical care and they were anonymized before analysis.

Questionnaire description

The questionnaire is provided as **figure 1**.

The collected data on adverse reactions reported to the last SCIT administration and included a symptom checklist considering both local and systemic symptoms. The checklist for local reactions included the presence of swelling and its approximate size (< 5 cm, 5 to 8 cm, and > 8 cm), redness, itching and subcutaneous nodule. The checklist for systemic symptoms ("apart from injection site") was stratified according to the systems that are commonly used for severity classification (14): skin, respiratory, gastrointestinal and cardiovascular systems. Within each body system, the most frequent or particularly relevant symptoms were specifically included. A few additional symptoms that do not directly fit into any of the referred systems but are frequently described in the literature (14) (*e.g.*, metallic taste, headache, itchy and watery red eyes) were also included. Patients could also report other symptoms as free text.

When an AdR was reported, the patient was asked to provide additional details regarding the timing of onset (< 30 minutes, 30 to 60 minutes and > 60 minutes), associated discomfort and impact (not troublesome; mild discomfort − easily tolerable; moderate discomfort − tolerable; and severe discomfort − interfering with daily activities/sleep), need for medical observation and treatment. Additional data regarding recent/current acute illness, and current allergic disease control, including CARAT (Control of Allergic Rhinitis and Asthma Test) and a visual analogue scale assessing eye symptoms, were also collected, but are not used in this analysis.

Classifications and definitions

The classification of swelling dimensions considered in the questionnaire checklist (< 5 cm, 5 to 8 cm, and > 8 cm) was based on the cut-offs that are commonly used to decide on SCIT dose increase (when applicable), keep as is or decrease (15).

The severity of systemic reactions to SCIT was computed using the self-reported systemic symptoms and classified according to the classification proposed by the World Allergy Organization (WAO) (14), including 5 different grades. SCIT allergen composition was classified according to the number of non-homologous allergens into single *vs* multiple allergen (MA) SCIT. Homologous allergens were considered when a high cross-reactivity is reported in the literature, such as between *D. pteronyssinus* and *D. farinae*, and they were considered as a single allergen. Single allergen (SA) SCIT was further classified according to allergen concentration into standard (SC) or higher than standard concentration (HC; *e.g.*, preparations described as "strong" by SCIT manufacturers). MA SCIT was classified according to the presence of dilutional effect, according to the manufacturer's information regarding that specific SCIT preparation: if the manufacturer reported that the dilutional effect of allergen mixture was compensated, the preparation was considered as without dilutional effect (NoDil); if no concentration adjustment was explicitly indicated, the preparation was considered as having dilution effect (Dil). Moreover, to classify the mixtures according to the presence of allergens of different groups, single allergens were grouped into six major classes: mites (*D. pteronyssinus/D. farinae* and *L. destructor*); epithelia (cat and dog); grass, tree (*Olea europea*, *Betula alba* and *Platanus acerifolia*) and weed (*Parietaria judaica*, *Artemisia vulgaris* and *Plantago lanceolata*) pollens; and molds (*Alternaria alternata*).

Statistical analysis

Categorical data were described with absolute and relative frequencies. Continuous variables with normal distribution (*e.g.*, age) were described with mean and standard deviation (SD); those with non-parametric distribution (*e.g.*, time since the beginning of SCIT) were presented as median and percentile 25-percentile 75. Normality was checked using Shapiro-Wilk test and by visual analysis of the variable distribution. A sub analysis including patients that filled at least six questionnaires during the study period was also performed.

Generalized estimating equations were used to develop a repeated measures multivariable logistic regression model to explain the factors associated with the occurrence of AdR. A common anonymized identifier and SCIT composition were used to identify repeated measures (with patient/SCIT composition pairs being the unit of analysis within the model). A univariate analysis was performed with all available variables possibly associated with the occurrence of AdR. Variables with a P-value < 0.250 in the univariate analysis were selected for inclusion in the multivariable regression model. This initial multivariable model was further improved using a stepwise strategy, with additional variables being excluded based on the individual P-value after adjustment and the model's QICC (corrected Quasi Likelihood under Independence Model Criterion). QICC was used to assess goodness-of-fit and the model with the lowest QICC was selected. Results were presented as odds ratio (OR) with 95% confidence intervals (CI). All statistical analyses were performed with IBM SPSS® version 25 (IBM Corporation, Armonk, USA). The forest-plot was created

***Figure 1** - Subcutaneous allergen immunotherapy: pre-administration questionnaire.*

In the last administration of subcutaneous allergen immunotherapy:

A - Did you have any side effects/adverse reactions? ……..**Yes** ☐ **No** ☐

If Yes: a) What were the symptoms (check all the symptoms that occurred)? (If **No** go to **Question B**)

At the injection site	
Swelling - diameter:	
< 5 cm	☐
5-8 cm	☐
> 8 cm	☐
Itching	☐
Redness	☐
Subcutaneous nodule	☐

Systemic symptoms (away from the injection site)					
Skin		Respiratory		Gastrointestinal	
Generalized itching	☐	Rhinitis (runny nose, sneezing, itchy nose, stuffy nose)	☐	Vomit	☐
Urticaria	☐			Diarrhea	☐
Swelling/edema (external)	☐	Itchy throat	☐	Stomachache	☐
		Cough from throat	☐		☐
Other symptoms		Asthma attack **solved** with SOS medication	☐	Cardiovascular	
Metallic taste	☐			Drop in blood pressure	☐
Headache	☐	Asthma attack **not solved** with SOS medication	☐	Loss of consciousness/ fainting	☐
Red, itchy and watery eyes	☐	Swelling of the tongue or tightness in the throat	☐	Other:_____	
Nausea	☐				

b) How long after the injection did the symptoms started?

Less than 30 minutes ☐ **Between 30 and 60 minutes** ☐ **More than 60 minutes** ☐

c) Were the symptoms bothersome? (tick with **x** the answer that best characterizes your symptoms)

☐ - - - - - ☐ - - - - - ☐ - - - - - ☐

0 - no discomfort | 1 - mild discomfort, easily tolerable | 2 - moderate discomfort, tolerable | 3 - severe discomfort that interferes with daily activities/sleep

d) Did you need medical observation? ……. **Yes**☐ **No** ☐

d.1) if YES, where/ by whom were you observed?

Allergist ☐ **Emergency Room** ☐ **Primary care center** ☐

e) Did you need treatment? **…….** **Yes** ☐ **No** ☐

e.1) If Yes, which one?_____ (report all the treatments you remember)

If NO go to Question B

Since the last administration of subcutaneous allergen immunotherapy:

B - Did you start or increase any medication? ……..……. **Yes** ☐ **No** ☐

(If **NO** go to **Question C**)

IF YES: c.1) Specify the reason: **Asthma** worsening ☐ **Rhinitis** worsening ☐ **Skin** problems ☐

Infection ☐ **Other** ☐ _____ Please specify

c.2) Which medication did you start/increase?

Name/drug description*		Dose	When
	Started ☐ Increased ☐		
	Started ☐ Increased ☐		
	Started ☐ Increased ☐		
	Started ☐ Increased ☐		

* If you don't remember the name of your medication you can make a short description, for example: "nasal spray with green cap", "purple disk", "oral corticosteroid", antibiotic…

C - Did you miss work/school because of your allergies (asthma, rhinitis, atopic dermatitis)?

I'm not working/studying ☐ **I didn't miss** ☐ **Missed** ☐ **_____Days**

D - Did you go to the Emergency Room or needed an unscheduled medical appointment due to worsening of your allergies? (asthma, rhinitis, dermatitis) **…….** **Yes** ☐ **No** ☐

If NO go to Question C

Over the past 3 days:

E - Have you had fever and/or symptoms of infection?……. **Yes** ☐ **No** ☐

F - Did your allergic diseases get worse? (asthma, rhinitis, dermatitis)? …….. **Yes** ☐ **No** ☐

The questionnaire also assesses symptom control with CARAT and a visual analogue scale evaluating eye symptoms (not shown).

with MS Excel® version 2006 (Microsoft Corporation, Redmond, USA). P-values < 0.05 were defined as statistically significant.

Results

Description of the study participants and administered SCIT

During the study period, 991 questionnaires were filled (250 patients) and 52 were excluded. Overall, 939 questionnaires, from 231 patients, were included (**figure 2**); 55 (23%) patients filled ≥ 6 questionnaires. Nine patients changed SCIT composition during the study period, with a total of 240 patients / SCIT composition pairs available for analysis (**figure 2**). Most study patients were male and had ≥ 18 years old at the time of the last registered SCIT administration. All had allergic rhinitis and one third had asthma (**table I**). At the time of the questionnaire, the median (P25-P75) time since the beginning of SCIT was 17 (7-30) months; in 37% (n = 343) of the administrations SCIT was ongoing for three or more years. Mites and grass pollens were the most commonly used extracts in the administered SCIT. Almost two thirds were preparations with MA extracts and only 31% of them had allergens from a single group. Most mixtures had concentrations adjusted to prevent dilutional effect (**table I**). All but one (an *Alternaria alternata* extract) were polymerized.

Self-reported AdR: prevalence and characterization

Self-reported SCIT-related AdR were registered in 313 (33%) administrations, corresponding to 111 (48%) patients with at least one AdR. Most (97%) were local AdR and presented with injection site swelling and/or itching. There were 11% (n = 34, corresponding to 4% of all SCIT administrations) with self-reported systemic symptoms (all grade 1; **table II**). Nevertheless, none of these self-reported systemic reactions was recorded by the administering physician as being related to SCIT and there were no SCIT interruptions or schedule/dose changes in relation with these self-reported systemic symptoms.

Thirty-five percent of the AdR started less than 30 minutes after SCIT administration (within the watching period), 30% between 30 and 60 minutes and 35% after 60 minutes. Only four AdR required medical observation, all presenting with local symptoms and one with associated headache; three of them were treated with topical corticosteroid and/or systemic antihistamine (the one with headache had no need for treatment). Three quarters (n = 232) of the self-reported AdR had some associated discomfort, but most (77%) were considered mild and easily tolerable. Only 3 patients (1.2% of those who classified AdR severity) reported severe discomfort that interfered with sleep or daily activities.

Considering patients that filled ≥ 6 questionnaires during the study period, 38 (69%) reported at least one AdR. Twenty of them (53%) reported AdR in less than 50% of the administrations and five (13%) reported SCIT-related AdR in all administrations.

Table I *- Patient (n = 231) and SCIT (n = 240) characteristics.*

	n	%
Sex, female	98	42
Age group, < 18 years old	100	43
Age, mean (SD)	23.6	13.8
Clinical diagnosis		
Allergic rhinitis	231	100
Asthma	80	35
Allergen extracts in administered SCIT		
Mites	182	76
Epithelia	21	9
Grass pollens	124	52
Tree pollens	14	6
Weed pollens	23	10
Molds	2	0.8
Number of non-homologous allergens in SCIT		
One allergen	86	36
Multiple allergens	153	64
Two allergens	111	46
Three allergens	41	17
Four allergens	1	0.4
Number of allergen groups		
One allergen group	49	31
Two allergen groups	93	58
Three allergen groups	17	11
Type of SCIT		
Single allergen, standard concentration	63	26
Single allergen, higher concentration	23	10
Multiple allergens, with dilutional effect	10	4
Multiple allergens, without dilutional effect	143	60

Data is presented as n (%), except when otherwise indicated; SD: standard deviation.

Self-reported AdR: factors associated with reporting

In the univariate analysis, the self-report of AdR to SCIT was significantly associated with female gender, asthma diagnosis, the number of allergens groups included in the SCIT preparation and the type of SCIT (**table III**). Age group, time since the beginning of SCIT and the specific allergen groups included in treatment were not significantly associated with self-reported AdR to SCIT. In the adjusted model, being a female and having asthma were associated with increased risk of reporting adverse reactions to SCIT (OR 1.71 (1.19-2.46) and OR 1.89 (1.30-2.75), respec-

Figure 2 *- Study flowchart.*

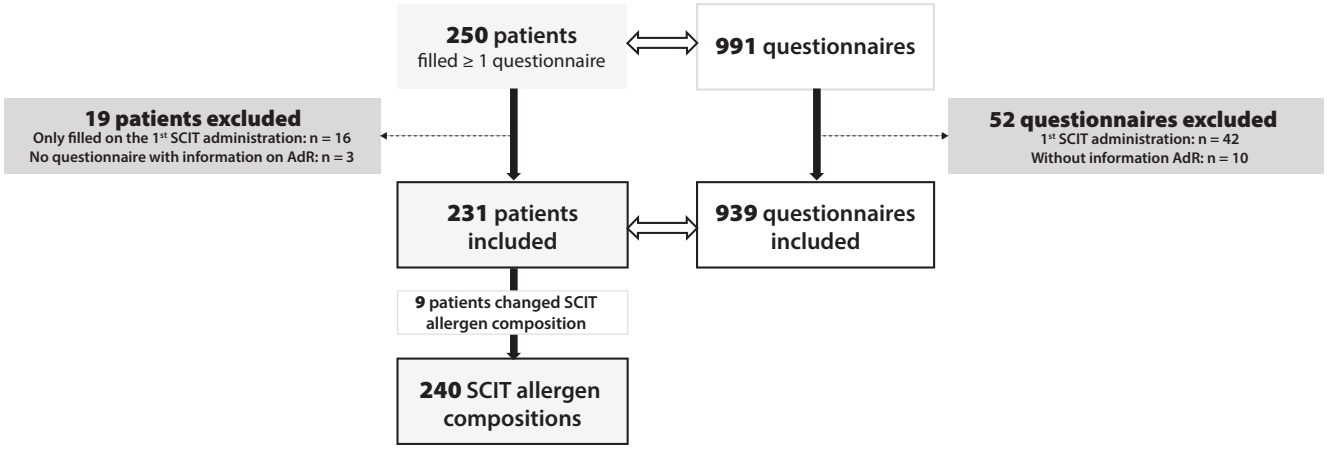

Table II *- Self-reported SCIT adverse reactions, considering all questionnaires (n = 939).*

	n	%
Self-reported adverse reaction	313	33
Local adverse reactions	304	32
Edema (any size)	256	27
< 5 cm	180	19
5-8 cm	58	6
> 8 cm	18	2
Itching	211	22
Erythema	161	17
Subcutaneous nodule	136	14
Systemic adverse reactions	34	4
Generalized itching or urticaria	14	1
Angioedema	7	0.7
Rhinitis	15	2
Conjunctivitis	9	1
Throat itching	1	0.1
Other respiratory symptoms*	0	0
Stomach pain	1	0.1
Vomiting or diarrhea	0	0
Cardiovascular symptoms¥	0	0
Other symptoms†	2	0.2

Percentages for local and systemic adverse reactions were computed based on the total number of administrations; SD: standard deviation; *including cough and asthma exacerbation; ¥including hypotension and syncope; †including metallic taste (n = 0) and headache (n = 2).

tively; **table III** and **figure 3**). The type of SCIT was also significantly associated with AdR, with those under SCIT with MA-NoDil presenting a lower risk of AdR (OR 0.52 (0.35-0.78)). SCIT with SA-HC was not a significant risk factor for self-reported SCIT-related AdR (**table III** and **figure 3**). The number of allergen groups included in the SCIT preparation was not included in the final adjusted model.

Discussion

In this study, patients treated with SCIT with airborne allergens reported adverse reactions in 33% of the administrations. Most adverse reactions were local and with only mild discomfort, easily tolerable. Although systemic symptoms were self-reported in 4% of the administrations, none was considered as SCIT-associated by the administering physician. In the adjusted logistic regression model, the risk of self-reported SCIT-associated AdR was higher in female and patients with asthma. The use of SCIT preparations with MA-NoDil was associated with a lower risk of AdR.

This study assessed the patient's perspective regarding SCIT-associated AdR, using real-life data. To our knowledge, this is one of the few published studies assessing SCIT related AdR based on self-reported patient information; most of the other studies report only physician information, which might be more objective and correspond to a more robust evaluation of the underlying causality relationship, but lack the patient's perspective. Our findings are in agreement with those from previous studies based on self-reported SCIT-related adverse reactions, with a high proportion of local adverse reactions, some reports of systemic symptoms (with higher frequency than when based on physician assessment) and low discomfort. One study in the USA, by Coop *et al.* (16), found a high proportion of patients (reaching 71%) that reported at least one local reaction during SCIT; nevertheless, 82% of

Figure 3 *- Forest plot representing the final adjusted model for risk of self-reported SCIT-related adverse reactions.*

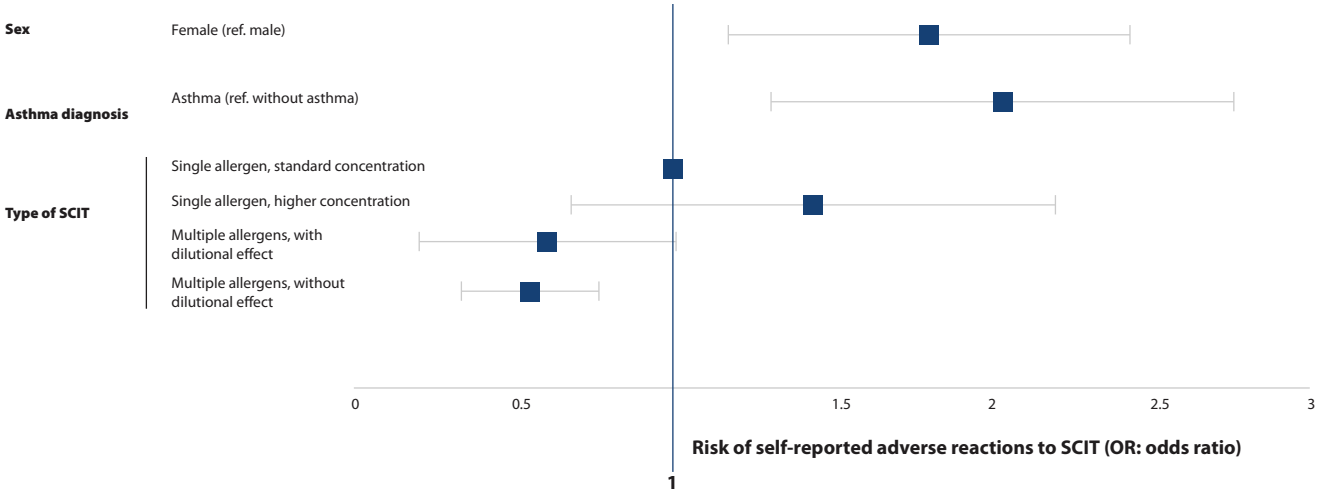

Table III *- Unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CI) for the risk of self-reported SCIT related adverse reactions.*

	Unadjusted			Adjusted		
	OR	**95%CI**	**P-value**	**OR**	**95%CI**	**P-value**
Female (ref. male)	1.84	1.28-2.66	**0.001**	1.71	1.19-2.46	**0.004**
< 18 years old (ref. ≥ 18 years)	0.76	0.54-1.08	0.125		Exc.	
Asthma diagnosis (ref. no asthma diagnosis)	1.75	1.22-2.51	**0.002**	1.89	1.30-2.75	**0.001**
Time since the beginning of SCIT			0.780		NI	
1 year	1.03	0.72-1.47	0.864			
2 years	0.94	0.68-1.30	0.708			
≥ 3 years	Ref.					
SCIT with mites (ref. without mites)	0.80	0.53-1.20	0.273		NI	
SCIT with epithelia (ref. without epithelia)	0.89	0.55-1.46	0.654		NI	
SCIT with grass pollens (ref. without grass pollens)	0.90	0.63-1.28	0.543		NI	
SCIT with tree pollens (ref. without tree pollens)	0.81	0.35-1.85	0.612		NI	
SCIT with weed pollens (ref. without weed pollens)	0.57	0.24-1.35	0.204		Exc.	
Number of allergen groups in SCIT			**0.028**		Exc.	
One allergen group	Ref.					
Two allergen groups	0.61	0.42-0.89	**0.010**			
Three allergen groups	0.65	0.32-1.33	0.239			
Type of SCIT			**0.002**			**0.001**
Single allergen, standard concentration (SA-SC)	Ref.			Ref.		
Single allergen, higher concentration (SA-HC)	1.08	0.60-1.96	0.804	1.25	0.70-2.24	0.460
Multiple allergens, with dilutional effect (MA-Dil)	0.53	0.17-1.62	0.265	0.45	0.19-1.06	0.066
Multiple allergens, without dilutional effect (MA-NoDil)	0.51	0.34-0.77	**0.001**	0.52	0.35-0.78	**0.002**

Molds were not included due to the low number of patients with this SCIT composition, which precluded an adequate risk estimation. Ref.: reference category; NI: not included in the adjusted model due to P-value > 0.25 in the univariate analysis; Exc.: excluded from the final model.

them considered that they were not bothersome at all or were only slightly troublesome. Ninety-six per cent stated they would not stop immunotherapy because of these local reactions (16). Another study, held in Portugal, by Santos *et al.* (17), found that almost 50% of the patients self-reported at least one adverse reaction during SCIT treatment (with at least one year long), most at the injection site. However, there were several patients (13% of the whole study population) reporting asthenia, fatigue, rhinitis and headache, among other systemic symptoms; the authors state that none of the reactions was severe, and most were ill-defined. Nevertheless, it should be highlighted that these self-reported systemic symptoms were noted at a higher frequency than those usually described in the literature, where the usual rate is around 0.1-0.2% per administration (corresponding to 0.6-4.7% of patients) (1, 6, 18). In fact, our results are difficult to compare directly with other studies where the frequency of SCIT-related adverse reactions was assessed and registered by a healthcare professional (6, 18). The patient perspective gives value to additional aspects that are not easily evaluated by the healthcare professional, such as symptomatic, intellectual, psychosocial, spiritual and goal-oriented dimensions of the disease and its treatment (19), and is recognized as being of significant importance in several clinical areas, including pulmonary hypertension (19) and allergic diseases (20, 21). A previous study, by Baiardini *et al.* (21), found that patient's and physician's satisfaction and perceptions related to allergen immunotherapy had a good correlation/agreement. Still, the agreement in the report of adverse reactions was not assessed. In our study, the relatively high frequency of self-reported systemic symptoms that were not recorded by the administering physician as related to SCIT, might be related with these differences in patient's and physician's perspectives, but also with reporting errors. Most questionnaires were completed by the patients themselves. Although there was supervision by a healthcare professional, we cannot exclude that some patients misinterpreted the question on SCIT-related adverse reactions and reported all symptoms that occurred after the last SCIT administration (*e.g.*, rhinitis worsening) even if they were not genuinely perceived as SCIT-related. Our findings regarding risk factors for adverse reactions are also very relevant and can support a more personalized healthcare delivery to patients having their allergic disease treated with SCIT. Although the risk factors for systemic reactions are commonly described (6-9), few studies reported on the risk factors for adverse reactions as a whole (including both local and systemic reactions). We acknowledge that systemic reactions, although rare and usually of moderate severity, especially with polymerized SCIT extracts (6, 22, 23) − that are frequently used in Portugal − are a major understandable concern due to the impact on patient safety and treatment continuation or schedule. Nevertheless, local reactions to SCIT are reported to occur in up to 85% of the patients (1) and, even though they don't seem to be predictive of a higher risk of systemic reactions (1, 16, 24), they could be a major reason for noncompliance with allergen immunotherapy (10, 11). Although several studies failed to support lower SCIT compliance with the occurrence of local reactions (16, 25, 26), most allergists adjust SCIT dose due to local reactions based on the concerns that they cause discomfort that may lead to patient noncompliance and that they may be predictive of future local reactions (27). In this study, most AdR were classified as mildly discomfortable and easy to tolerate but they were frequently recurrent (18 out of 55 patients reported AdR in 50% or more questionnaires and 5 patients reported SCIT-related AdR in all administrations). We could not assess if any dose adjustment or treatment interruption were performed based on these self-reported local AdR.

We found that female sex and having asthma were significantly associated with self-reported SCIT-related AdR. Still, there was no significant increase in the risk of AdR with neither higher than standard SCIT concentration nor multiple allergens (compared to SCIT with a single allergen at standard concentration). We found no significant association between SCIT-related AdR and any specific allergen extract. A previous study, based on physician assessment of pediatric patients, found that AdR were more common in patients undergoing SCIT with multiple allergens and house dust mite (18), which disagrees with our findings. This might be related to the different setting, data collection methods and age group. It is interesting to highlight that, in our study, having SCIT with MA-NoDil seemed to protect against AdR, which is not easy to explain. We cannot exclude that this finding might be related to a sample bias favouring a low reporting of adverse reactions to these SCIT preparations. However, although unpredicted, it may represent a real effect and should be futher assessed in future, targeted studies. These unexpected findings are not new in SCIT. In fact, a few year ago, contrary to the hypothesized, rush SCIT build-up schedules proved at least as safe as traditional, slower build-up schemes (28, 29). In regard of SCIT preparations with MA, one might also argue that mixing non-homologous extracts might lead to inactivation of some relevant components, leading to lower potency. This was a traditional concern regarding natural extracts and the basis for the recommendation against mixing extracts from unrelated allergen groups even in polyallergic patients (2, 12). Nevertheless, in the last couple of years, several immunotherapy manufacturers have been releasing new SCIT polymerized formulations that allow mixing non-homologous allergens keeping the concentration from the SA SCIT. Most manufacturers have internal data supporting high stability and efficacy maintained until the expiry date; however, most stability data regarding these mixtures were not published in peer-reviewed journals.

Another interesting finding in our data is the absence of a significantly increased risk of AdR with SA-HC SCIT concentration. In fact, a previous phase two clinical trial testing a SCIT mite preparation has shown that clinical efficacy incresed at higher SCIT doses; however, it reached a plateau at a concentration of

50,000 AUeq/mL, with the highest concentration being as effective but presenting higher frequency of adverse events (13). The reported adverse events were not severe, but the 50,000 AUeq/mL concentration was chosen for further development (13). However, this kind of data were not available for most SCIT preparations commercially available in Portugal, including for those with SA-HC. Although our data is limited by the low number of these SCIT preparations (corresponding to only 10% of the total), real-world data, collected during routine care, can give valuable insights on the risk of local and systemic AdR in relation to SA-HC preparations. Nevertheless, having published data on the stability of non-homologous SCIT mixtures and performing well-designed clinical trials or large observational studies assessing clinical efficacy and safety of SCIT mixtures and of preparations with higher allergen concentrations is, currently, an unmet need in allergen immunotherapy-related knowledge.

As previously stated, a strength of this study is being one of the few published studies assessing SCIT related AdR based on self-reported patient information and one of the few exploring risk factors for adverse reactions as a whole. However, this study has several limitations. First, this was a questionnaire-based self-assessment without healthcare professional input which might lead to reporting errors (*e.g.*, due to question misinterpretation) or incorrect evaluation of the causality relation between SCIT and AdR. We tried to minimize these bias by supervising and providing support to questionnaire filling whenever asked by the patient; nevertheless, it was not possible to assure that all patients understood all questions correctly. Secondly, during the study period (March 2017 to June 2019, 28 months), considering the 231 patients that were included, we should have around 6,468 questionnaires. This means that our response rate was 15% which is low and limits the interpretation and generalizability of our results. Although the pre-SCIT administration questionnaire was implemented at our site in 2017, it was usually applied with the support of a specific colleague (MP), that could only consistently collect these data on specific week periods. We are now working on a more accessible and straightforward solution, taking advantage of new technologies, that will allow collecting these same data using a readily accessible smartphone or tablet while the patient waits for SCIT administration. Finally, we had no data regarding some variables of interest, including the level of allergic disease control, medication intake (*e.g.*, antihistamine or systemic corticosteroid) that could prevent or largely minimize AdR, and allergen exposure and practice of physical exercise before or readily after SCIT administration. It should be noted that the information regarding disease control is part of the pre-SCIT administration questionnaire. Nevertheless, as the data on SCIT-related AdR are collected only at the following administration, we need to have sequential questionnaires to be able to match the information on AdR with control assessment. Due to the low response rate this was not possible, and we decided not to include data on allergic disease control in this analysis. Future research should include a larger set of clinical variables, namely allergic disease control.

Adverse reactions to subcutaneous allergen immunotherapy were self-reported in one-third of the included administrations. Most adverse reactions were exclusively at the injection site, and most were only mildly troublesome and easily tolerable. The risk of adverse reactions was higher in female sex and patients with asthma, and lower in patients treated with SCIT preparations with multiple allergens and concentrations adjusted to prevent dilutional effect. Additional, well-designed studies, including clinical trials and larger observational studies using real-world data, are urgently needed.

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None.

Contributions

AMP, MP: data management and analysis. AMP: writing - original draft. MP: writing - original draft support. All authors: data collection, critically review, final version agreement.

Conflict of interests

The authors declare that they have no conflict of interests.

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