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Characteristics of Adverse Reactions and Compliance in Patients who Underwent Allergen-Specific Subcutaneous Immunotherapy; Ten-Year Real-Life Data

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ABSTRACT

Objective: Allergen-specific subcutaneous immunotherapy (SCIT) is known as the best therapeutic method that may alter the natural course of allergic diseases, compared to pharmacological and avoidance options. However, some problems such as adverse reactions (ARs), inconvenience, and high costs of a prolonged course of therapy may prevent patients from completing the therapy. The objective of this study was to evaluate the evidence for the potential barriers against the benefits of SCIT in adult patients.

Materials and Methods: An observational study between 2009 and 2019 was performed at the Allergy Clinic of a tertiary hospital. The data of 166 adult patients who underwent SCIT for allergic rhino-conjunctivitis (ARC), and/or asthma or hymenoptera venom anaphylaxis using conventional schedules with standard allergen extracts were evaluated.

Results: SCIT indications were ARC (63%), ARC and asthma (19.3%), and venom anaphylaxis (17.5%). The standardized allergen extracts used were grass pollen (59%), house dust mite (19.9%), and hymenoptera venom (17.5%). The frequency of SCIT-related ARs was 7.4% per injection, and 42.2% per patient. Local ARs were more frequent than systemic ARs (SAR)s. The majority of the SARs were composed of anaphylaxis and generalized urticaria, which were mostly of moderate severity with no deaths. SARs were more common in women, in patients with high injection numbers, and in patients under SCIT with cat allergen or multiple allergens. Most of the SARs occurred immediately after injection, and in the initial phase, whereas the delayed-type of SARs was common in patients with pollen SCIT. Three patients under cat SCIT discontinued treatment due to SARs of immediate and moderate/severe type. Ratios of SARs of venoms were insignificantly higher than aeroallergens. SARs with house dust mite SCIT were rare. Rates of patients' compliance to SCIT were similar between the allergen extracts, with an average of 70%. The most common causes of non-compliance were non-adherence, leaving the current residence, difficulty in obtaining the allergen extracts, and ARs. The frequencies of local and moderate ARs were higher in compliant patients, whereas systemic and severe ARs were higher in non-compliant ones. In the regression model, it was found that ARs increased and patient compliance decreased as the number of injections increased.

Conclusion: This study in the real-life setting for a decade showed that less than half of the patients that underwent SCIT had developed ARs, which were generally local and of moderate severity. In conclusion, these results indicated that each allergen of SCIT had different characteristics of ARs, and the moderate incidence of ARs was not a problem regarding compliance with SCIT. Therefore, SCIT may be preferred in indications of allergy, and has a tolerable balance of ARs and safety.

Keywords: Allergen specific subcutaneous immunotherapy, safety, adherence, compliance, adverse event

INTRODUCTION

Allergen specific subcutaneous immunotherapy (SCIT) is a disease-modifying therapy in immunoglobulin (IgE)-mediated allergic diseases and has been used in clinical practice for decades (1). Allergen extracts are administered in gradually increasing doses, followed by a maintenance dose at regular intervals for at least 3 years (2). Potential benefits of SCIT are considered as the reduction in allergic symptoms of rhino-conjunctivitis (ARC), asthma and hymenoptera venom hypersensitivity, and prevention of

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asthma development or progression, which all result in a beneficial effect on the disease-specific quality of life (2, 3). However, there are some potential barriers against the benefits of SCIT such as tolerability problems due to adverse reactions (AR)s and the prolonged course. The safety profile of SCIT has been documented in several clinical studies, as well as in real life practice. However, it is not known how much importance these problems have on the success of treatment.

The most common ARs were local reactions related to the injection site, followed by systemic ARs (SARs) with a lower frequency (1-4). In a prospective study of respiratory SCIT in France, Germany and Spain, 2.1% of 4316 patients presented at least one SAR, and urticaria was the most frequent symptom followed by rhinitis and bronchospasm (5). Most of the SARs occurred during the initial phase, and were mild in severity. Even though none of the severe SARs were classified as serious, SCIT was withdrawn in 19.3% of patients after having SARs including all severe ones. Furthermore, in patients who continued to receive SCIT, the immunotherapy schedule was changed as reduction in the final dose or restarting the initial phase in more than half of them (5). Regarding the type of allergen extracts, patients treated with grass pollen were reported to experience SARs more frequently compared to those with venom or mite SCIT (6). In a meta-analysis of mite-sensitized asthma subjects treated with SCIT, 3 of these studies did not have severe or systemic AR, while 9.1% and 17.2% of the subjects in 2 studies had systemic and local reactions (7). In large multicenter studies, the frequency of SARs of venom immunotherapy ranged from 8% to 20%, and were usually of mild severity and responsive to anti-allergic pharmacotherapy (8).

Compliance is the degree of adherence of the patients to the recommended treatment plan (dose, frequency/dose schedule, and duration), and according to the World Health Organization (WHO), 50% of patients with chronic diseases are non-compliant (9). Compliance to treatment is important, because non-compliance leads to reduced efficacy, increased symptoms and treatment costs, and reduced quality of life (1). The obstacles to compliance with SCIT are that it requires at least 3 years of regular and continuous hospital visits to administer the allergen shots. Moreover, it does not provide immediate symptom relief for at least 1 year. The occurrence of ARs can cause discomfort and discontinuation of SCIT. In many studies, SCIT compliance was found to be higher than for sublingual immunotherapy, which was generally claimed to be safer (10). In a 30-year retrospective study among patients who completed a 3-year treatment of SCIT, the discontinuation rate due to ARs was only 1.8% (11). Although the recommended treatment period for venom immunotherapy was prolonged to 5 years, the compliance was found to be as high as 84% (12). Contrary to these results, SCIT compliance rates were found to be 23-40% in studies conducted in the Netherlands and Germany (13, 14).

Nowadays, pharmaceutical companies producing allergen extracts direct physicians to prescribe sublingual allergen immunotherapy, since the subcutaneous route has potential risks such as severe SARs and variable compliance rates. Furthermore, the number of studies about SCIT has decreased significantly in the last 10 years. Although sublingual immunotherapy is reported to be a safe and effective alternative, its cost and low compliance rates are the biggest obstacles to its routine use, especially in countries with low income or in economic difficulty. Therefore, physicians should be reminded of the advantages and disadvantages of SCIT. The rationale of this study was that the subcutaneous route of allergen immunotherapy was not recommended because of its potential risks when compared to benefits. The objective of this study was to investigate the balance between the potential benefits and risks of SCIT in adult patients by using conventional schedules with standardized commercial products and various aeroallergens in a real-life clinical practice.

MATERIAL and METHODS

Study Design

This was a prospective and observational study that was conducted from February 2009 to November 2019 at a single tertiary healthcare setting, the Immunology and Allergy Clinic at a University Hospital. Informed consent for SCIT was collected from all patients, and the study was approved by the local Ethics Committee (approval number: 2021.02.04).

Information including the patient's diagnosis, laboratory test results, and SCIT protocol (allergen type, manufacturer company, injection date and schedule, dose, extract concentration) were recorded at every visit from the first dose of SCIT to the last one.

Patient Recruitment

Patient inclusion criteria were: Adults with IgE mediated ARC, asthma or hymenoptera venom anaphylaxis, using the subcutaneous route for allergen immunotherapy, and perennial conventional schedules. Patients under allergen immunotherapy with the sublingual route, schedules with pre-seasonal, rush or clustered protocols, those with allergies to food or mould, and incomplete data were excluded.

Diagnosis of Allergic Diseases, and Indication of SCIT

At the first visit, patients were asked about sociodemographic characteristics, asthma history, and comorbidities. ARC was diagnosed if the patients had a history of at least two of these symptoms: nasal itching, sneezing, rhinorrhea, and/or obstruction, and eye symptoms for more than 4 days a week and for more than 4 weeks a year (2). Asthma diagnosis and severity/control level of asthma were assessed as described in GINA (1). Pulmonary function tests (PFTs) (Sensor Medics-2130 Corp.) were performed at the first visit for all patients, and in the SCIT injection visits for asthma patients or patients who developed dyspnea.

During the first visit, skin prick tests (SPTs) with a battery of common inhalant allergens (ALK, Madrid-Spain), and serum analysis for specific IgE (UniCAP 100-Pharmacia, Uppsala, Sweden) were performed. Atopy was accepted if positivity in SPTs or serum specific IgE was clinically relevant.

Inclusion criteria for immunotherapy were based on the SCIT position paper on patients with ARC and/or asthma (2,8). Immunotherapy was recommended if there was a history of an immediate systemic reaction after a hymenoptera sting, and the demonstration of IgE-mediated serum antibodies to the respective venom.

SCIT Administration

SCIT injections were administered by trained nurses in a room with resuscitation facilities. Patients received no pre-treatment before immunotherapy. Allergen extracts were used from standardized commercial products available in the country such as ALK-Abello (Spain), Allergopharma (Germany), and Stallergenes (France). SCIT conventional programs were planned according to the manufacturer's guide. In the initial phase, injections were administered weekly until the final dose was reached, and in the maintenance phase injections were administered at intervals of 4 weeks in the first year, 5 weeks in the second year, and 6 weeks in the rest years. The dose was reduced and then re-increased according to the manufacturer's recommendations in case of large local and systemic reactions.

Adverse Reactions (ARs)

Patients were questioned for ARs at each injection visit. Any symptoms or signs believed to be potentially related to SCIT injections by an allergy specialist were considered ARs. Redness, itching, or swelling at the injection site were considered local reactions, while cutaneous symptoms (urticaria or angioedema), rhino-conjunctivitis, dyspnea, and cardiovascular symptoms were defined as SARs. A reaction that developed within the first 30 minutes after the injection was considered as an immediate reaction and the remainder as a delayed AR. The severity of SARs was classified according to the assessments of the World Allergy Organization (WAO), and modified as follows: grade 1-2 were "mild" (cutaneous, upper and lower respiratory tract, conjunctival, gastrointestinal symptoms), grade 3 was "moderate" (grade 1-2 plus attack of dyspnea unresponsive to inhaled bronchodilator or laryngeal/uvula/tongue edema), and grade 4 was "severe" (respiratory failure or hypotension) (4).

Compliance

Patients who completed the immunotherapy period, which was a minimum of 3 years for aeroallergens and 5 years for venom treatment were considered "compliant", whereas those who discontinued treatment for more than 2 months were labeled as "non-compliant" (9). Reasons for non-compliance were investigated. Patients who did not follow medical advice, such as through self-care, drug use, or inhaler use were considered "non-adherent".

Statistical Analysis

Data were analyzed with SPSS version 20.0 (IBM, USA). Descriptive analysis was calculated as mean (standard deviation) for continuous variables or frequencies and n (%) for categorical variables. The relationship between two groups was analyzed with the chi-square test for categorical data or Student's t-test for continued data. The odds ratio (OR; 95% confidence interval -CI-) was calculated for compliance to allergen immunotherapy in univariate and multivariate analysis with the following variables: sex, age, type of disease, and type of allergen sensitivity.

P values below 0.05 were accepted as statistically significant. The Raosoft programme was used to calculate the study population. The target population size was 300, and the recommended sample size was 169 with a 5% margin of error and 95% confidence level.

RESULTS

There were one hundred and sixty-six patients (48.2% female, mean age: 36 ± 10.45 yrs., range: 15-61 yrs.) who underwent SCIT (Table I). SCIT indications were ARC (63%), ARC and asthma (19.3%), and venom anaphylaxis (17.5%). The allergens used in SCIT were: Pollens (59%), house dust mites (19.9%), hymenoptera venom (17.5%), and cat (1.8%). SCIT with two different allergen types as house dust mites and grass pollens was used simultaneously in 1.8% of the patients. A total of 6424 injections were administered to the patients during the 10 years.

Two-thirds (57.8%) of 166 patients had none while 42.2% had some ARs. Groups with and without ARs were similar in terms of mean age and frequency of immunotherapy indications. More than 2/3 of the patients had undergone SCIT with aeroallergens. The frequency of patients who had venom immunotherapy was higher in patients with ARs than without (p=0.05). Female gender was more common and the mean number of injections was higher in the group with ARs than without ARs (p = 0.04, p < 0.001).

Among 166 patients, 42.2% had at least one AR, and these were local (68.6%) or systemic (31.4%) (Table II). Of the 6424 injections overall, 475 (7.4%) were reported to result in ARs, of which 6.2% were SARs and the ratio per injection was 4.5/1000. In a total of 22 patients, anaphylaxis (n=16) and generalized urticaria (n=7) were the most common SARs, followed by dyspnea (n=4), ARC (n=1), and both (n=1). ARs were mostly of the immediate type, and developed during the build-up phase, and most of them recovered within 24 hours. No fatalities were reported.

SARs were common in SCIT with cat allergen, multiple allergens (house dust mites and grass pollens), grass pollens, venoms, and house dust mites (Table III). Multiple SARs were observed in 3 patients as 2 patients with cat and one with pollen SCIT. The severity of ARs was generally of moderate severity with pollens, venom, and mix. The only SAR that developed after SCIT with house dust mites was severe, and there were very frequent and serious ARs during SCIT with cat allergen.

The rate of non-compliance and drop-out was 30%, while 38% of the patients had ongoing therapy, and 32% of them had continued SCIT for at least 3 years. The overall compliance rate was 70%. The common causes of non-compliance to SCIT were non-adherence (68%), change in location (22%), difficulty of obtaining SCIT extract (6%), and severe SARs (4%) (Figure 1).

Compliant and non-compliant patient groups were similar in terms of mean age, gender, treatment phase, allergen type, and SCIT indications (Table IV). ARs were observed in only 36% of patients who discontinued SCIT. While the frequency of local and moderate ARs was higher in the compliant group, systemic and severe ARs were higher in the non-compliant group. In addition, the number of injections was higher in the compliant group than the non-compliant group (p < 0.001).

Table I: Characteristics of the study population.

Characteristics n (%)	All (n=166)	Patients with ARs (n=70)	Patients without ARs (n=96)	P
Age (years)*	36 ± 10.45	35.39 ± 10.70	36.45 ± 10.30	0.52
Female gender	80 (48.2)	40 (57.1)	40 (41.7)	0.04
Indications for SCIT;				0.11
ARC	105 (63.3)	38 (54.3)	16 (16.7)	
ARC and asthma	32 (19.3)	16 (22.9)	16 (16.7)	
Anaphylaxis	29 (17.5)	16 (22.9)	13 (13.5)	
SCIT with aeroallergens / venom	137 (82.5) / 29 (17.5)	54 (77.1) / 16 (22.9)	83 (86.5) / 13 (13.5)	0.05
Number of injections*	-	44.37 ± 17.78	34.56 ± 13.90	< 0.001

***:** Mean ± Standard deviation, **AR:** Adverse reactions, **ARC:** Allergic rhino-conjunctivitis, **SCIT:** Subcutaneous allergen specific immunotherapy.

Logistic regression analyzes were performed with a model including age, gender and number of injections (Table V). The number of injections was associated with ARs (Adjusted OR: 1.04, $p < 0.01$) and compliance (Adjusted OR: 0.94, $p < 0.01$).

DISCUSSION

In this observational study, we revealed that SCIT had resulted in mostly tolerable ARs, with a systemic reaction rate of 4.5/1000 injections, and no death within 10 years. There was an almost 50% possibility of developing ARs during SCIT. Rates of SARs due to SCIT were higher with venoms than aeroallergens. SARs with mites were rare, and the delayed-type of SARs were seen only in patients under SCIT with grass pollens. ARs due to SCIT with cat allergen developed mostly immediately in moderate to severe severity and resulted in withdrawal in all patients. These results showed the importance of the settings of SCIT application, including trained personnel, necessary emergency equipment, and medicines when needed.

Table II: Characteristics of allergic reactions due to SCIT.

n (%)	Injection numbers with ARs	Patients with ARs
Number of AR / total SCIT	475 / 6424 (7.4)	70 / 166 (42.2)
Local ARs	446 (93.8)	48 (68.6)
Systemic ARs	29 (6.2)	22 (31.4)
Symptoms of systemic ARs;		
Anaphylaxis	16 (55.2)	12 (54.5)
Generalized urticaria	7 (24.1)	6 (27.3)
Dyspnea	4 (13.8)	2 (9.1)
Rhino-conjunctivitis	1 (3.4)	1 (4.5)
Rhino-conjunctivitis and dyspnea	1 (3.4)	1 (4.5)
Onset of ARs;		
Immediate	23 (79.4)	17 (77.2)
Delayed	6 (10.6)	5 (22.8)
Immunotherapy phase;		
Initial phase	22 (75.8)	19 (86.4)
Maintenance phase	7 (24.2)	3 (13.6)

AR: Adverse reactions, **SCIT:** Subcutaneous immunotherapy.

Table III: Characteristics of systemic ARs after SCIT.

n (%)	Injection	Pollens (n=98)	Venom (n=29)	Cat (n=3)	HDMs (n=33)	HDMs + grass pollens (n=3)
Patients with ARs / total patients	-	13 / 98 (13.3)	4 / 29 (13.8)	3 / 3 (100)	1 / 33 (3)	1 / 3 (33.3)
Total injections with SARs	29	14 / 29 (48.3)	4 / 29 (13.8)	9 / 29 (31)	1 / 29 (3.45)	1 / 29 (3.45)
Severity of ARs;						
Mild	4 (13.8)	3 (21.4)	-	1 (11.1)	-	-
Moderate	17 (58.6)	9 (64.3)	3 (75)	4 (44.4)	-	1 (100)
Severe	8 (27.6)	2 (14.3)	1 (25)	4 (44.4)	1 (100)	
Onset of reaction;						
Immediate	23 (79.3)	8 (57.1)	4 (100)	9 (100)	1 (100)	1 (100)
Delayed	6 (20.7)	6 (42.9)	-	-	-	-

AR: Adverse reactions, **HDMs:** House dust mites, **SARs:** Systemic adverse reactions, **SCIT:** Subcutaneous allergen specific immunotherapy.

Improving the safety of treatment in terms of preventing potentially serious ARs will increase the compliance with SCIT to complete the recommended therapy duration to gain maximum benefit.

In this study, the frequency of ARs due to SCIT was 7.4% per injection and 42.2% per patient, and local reactions were more frequent than systemic ones. In a retrospective study with 30 years of experience, a total of 1087 ARs (1.2% of all

Table IV: Comparison of the study groups classified as compliant and non-compliant.

n (%)	Compliant group (n=116)	Non-compliant group (n=50)	P
Age*	36.44 ± 10.48	34.98 ± 10.42	0.41
Female	55 (47.4)	25 (50)	0.76
ARs;	52 (44.8)	18 (36)	0.15
Local ARs	39 (75)	9 (50)	
SARs	13 (25)	9 (50)	
Severity of SARs;			0.49
Mild	2 (15.4)	2 (22.2)	
Moderate	9 (69.2)	4 (44.4)	
Severe	2 (15.4)	3 (33.3)	
Immunotherapy phase of SARs;			0.77
Initial	11 (84.6)	8 (88.9)	
Maintenance	2 (15.4)	1 (11.1)	
SCIT with aeroallergens / venom	95 (81.9) / 21 (18.1)	42 (84) / 8 (16)	0.05
Indications of SCIT;			0.59
ARC	75 (64.7)	30 (60)	
ARC and asthma	20 (17.2)	12 (24)	
Anaphylaxis	21 (18.1)	8 (16)	
Number of injections*	42.60 ± 15.83	29.64 ± 13.83	< 0.001

*: Mean ± standard deviation, **AR:** Adverse reactions, **ARC:** Allergic rhino-conjunctivitis, **SARs:** Systemic allergic reactions, **SCIT:** Subcutaneous allergen specific immunotherapy.

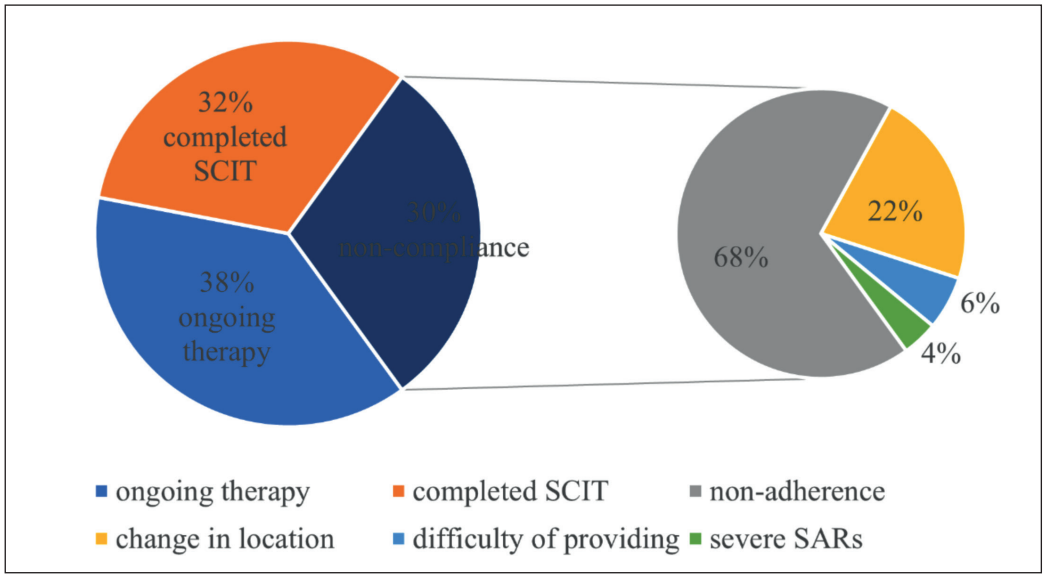

Figure 1. The common causes of non-compliance with SCIT were non-adherence (68%), change in location (22%), difficulty of obtaining SCIT extract (6%), and severe systemic adverse reactions (SAR)s (4%).

Table V: Logistic regression model to predict risk of ARs and compliance.

Variable	Est β	Std. Err.	Adj. OR (95%Cl)	P
For ARs				
Number of injections	0.42	0.12	1.04 (1.01, 1.06)	< 0.001
Female gender	0.59	0.33	1.80 (0.93, 3.49)	0.07
Age	-0.01	0.01	0.98 (0.95, 1.02)	0.45
Non-compliance	0.11	0.39	1.11 (0.51, 2.43)	0.77
For compliance				
Number of injections	-0.06	0.01	0.94 (0.91, 0.96)	< 0.001
Female gender	0.16	0.37	1.18 (0.57, 2.45)	0.64
Age	-0.008	0.01	0.99 (0.95, 1.02)	0.64
ARs	0.05	0.39	1.06 (0.49, 2.29)	0.88

Adj: Adjusted, **ARs:** Adverse reactions, **Est:** Estimated, **OR:** Odds ratio, **Std:** Standard.

injections;) were reported in 23.3% of patients with a rate of 4.9% as systemic, and 76.8% as local reactions (11). In a multicenter study, the frequency of SARs was 2.4% in 4363 patients undergoing SCIT and sublingual immunotherapy (5). Our AR rates appeared to be slightly higher than in the literature, which might be due to the fact that we included only the subcutaneous route, and discarded the sublingual route which was reported to be safer. On the other hand, SCIT with a conventional schedule was the only protocol included in this study, as it was known to be a safer modality compared to the rush and clustered regimens (15). We also included not only patients with ARC, but also those with asthma who have been previously reported to be associated with increased ARs under SCIT (15, 16). In contrast, asthma was not found to be a risk factor in the regression analysis alongside anaphylaxis or rhinitis in this study, while all three patients who underwent SCIT with cat allergen allergen had asthma and developed frequent and severe SARs. Similarly, in the Cochrane analysis of randomized controlled trials, although the risk for ARs was 1 in 16 patients for local reactions, and 1 in 9 patients for SARs, the final decision for SCIT was that it was an useful treatment for allergic asthmatics by improving bronchial hyperactivity, and reducing symptoms and medication use (17). Recently, SCIT with house dust mites was recommended in asthma and immunotherapy guidelines for adults and children as an add-on to regular asthma therapy to decrease symptoms and medication needs (18). However, as we have practiced in our clinic for years, SCIT should be started only in patients with mild, controlled, and stable asthma.

We found that ARs were more common in women, but female gender was not a risk factor when evaluated together with other factors in the regression model. Conversely, in a study conducted in Italy, a significant relationship was found between female gender and ARs (11). Further studies are needed as hormonal status may be a risk factor for systemic reactions.

We found that anaphylaxis and generalized urticaria were the most common SARs after SCIT, followed by dyspnea and rhino-conjunctivitis. Because, immunotherapy with aeroallergens usually causes skin and respiratory side effects, finding a high frequency of anaphylaxis as an AR in this study may be explained by the inclusion of SCIT with cat allergen and venom, as well as aeroallergens. For example, in a study with patients with mite SCITs and airway diseases, ARs consisted primarily of respiratory (88.4%) and cutaneous symptoms (31.5%) (16). On the other hand, anaphylaxis with potentially life-threatening severity as SARs was mostly seen in patients under venom immunotherapy (19-22). Consequently, we think that the probability of developing respiratory distress was higher during immunotherapy with aeroallergens, and the risk of anaphylaxis was higher in SCIT with venom.

The severity of the reactions was assessed by the WAO grading, since it had a better correlation with other classifications, as well as being simpler to apply (4, 23). In this study, the finding that ARs were mostly seen in the initial phase of SCIT was concordant with previous studies, and the severity of the reactions was generally moderate. While Dursun et al. reported that SARs in the initial phase were more severe, another study reported that

fatal reactions often developed during the maintenance phase (15, 20). We found that ARs developed mostly in the immediate type with aeroallergens and venoms, and delayed reactions were only seen in SCIT with grass pollens. Similarly, Gastaminza et al. reported that almost two-thirds of SARs were the immediate type, and most of them were due to grass pollen extracts (21). Even though the rates of immediate type AR were similar to the general type as 42.6% and 63% in other studies, polysensitized patients were found to have a higher frequency of delayed ARs (15, 22). These findings confirm the need for patient observation for at least 30 minutes after immunotherapy injection, and physicians should pay attention to late-onset reactions in patients under SCIT with pollens or multiple allergens.

All SARs observed in patients under SCIT with cat allergen were of the immediate and moderate/severe type, resulting in all patients to withdraw from immunotherapy. Thus, failure to complete the treatment period precluded the expected benefit. These results were also in line with the literature in which SCIT with cat allergen was generally ineffective or had unacceptable ARs (23,24). We found that the ARs during SCIT with mites were rare, and the only systemic reaction with mites was the severe type. Similarly, another study showed that a lower frequency of systemic reactions occurred with mite extracts than with pollens and venoms (21). In contrast, Moreno et al. found higher rates of SRs in patients who received mite SCIT (25). In fact, it is difficult to compare the frequency of ARs between SCIT studies, because they used different brands of allergen extracts, and the different amount of allergens in their content can affect the frequency of side effects. SCIT with venom was found to have similar AR rates as pollen, and almost 13% in both. In previous studies, no difference was found between the rates of AR in the venom and inhalant therapy groups. Moreover, it was suggested that patients with pollen allergy experience AR more frequently during the pollen season than those with venom allergy, and thus it was recommended to reduce the maintenance dose during the pollen season (15, 20). In large multicenter studies, the frequency of systemic ARs with VIT was 8-20%, and the main risk factor for AR was treatment using honeybee venom (8).

Compliance to SCIT is actually challenging, since it requires recurrent visits. Furthermore, slow improvement in symptoms starts at least 1 year after the beginning of SCIT, which may cause impatient subjects feeling that they are not benefiting from immunotherapy. The overall non-compliance rate (30%) was shorter than some studies that found it as 56% and 41% (14, 26). On the other hand, our compliance rate (70%) was similar to others as 68.97% in a prospective study, and 62% in a retrospective study for SCIT, and it was higher than with sublingual immunotherapy as 31% (27, 28). The relatively high compliance rates of SCIT in this study might be due the scheduled appointments, and that they were reminded by phone calls in case of not attending appointments. Supporting this, SCIT guidelines recommend patients to use reminders and communicate with physicians and educate patients to increase adherence (2). The most common causes of non-compliance with SCIT were non-adherence, leaving the current residence, difficulty of obtaining the SCIT extract, and ARs. Although health insurance covered SCIT costs, problems sometimes occurred with reimbursement of the high costs of allergen extracts. Age was not found to be associated with compliance to SCIT, in contrast to a previous study that reported younger and older age groups to be more compatible (29). Furthermore, pregnancy, and poor or no improvement in symptoms were some of the other reasons of non-compliance with SCIT that were not found in this study (27).

In this study, the higher number of injections in the compliant group than the non-compliant group pointed out that compliant patients were able to complete the target duration of SCIT treatment. In the logistic regression model, it was found that the patient's compliance decreased as the number of injections increased. Similarly, in a previous study, it was found that compliance was higher in the short and medium term than in in the long term (30). In addition, they observed that reducing the number of injections in the build-up phase of SCIT increased compliance (30). We also found that the frequency of local and moderate ARs was higher in the compliant group, while severe SARs were more common in the non-compliant group. In conclusion, mild and local ARs had less effect on non-compliance, whereas severe ARs caused interruptions and withdrawals from SCIT, hindering its effectiveness.

The limitations of this study were the small number of patients under SCIT with cat allergen and mixed allergens, which was insufficient to make a meaningful comparison. Nevertheless, the experiences with these allergens were valuable in showing long-term results.

In recent years, companies recommend the sublingual route with its safety advantage against SCIT. However, there are related reports about low compliance, a low safety profile in children, as well as high cost. This decade-long study in a real-life setting showed that less than half of the patients who underwent SCIT had developed ARs, which were generally local and of moderate severity. SCIT with cat allergen or multiple allergens caused the most SARs, mostly of the immediate type and in the initial phase, whereas delayed type ARs occurred only in SCIT with grass pollens. SARs with cat SCIT resulted in all patients discontinuing treatment. The rates of SARs were higher with venoms than aeroallergens, whereas SARs with mites were rare. In conclusion, this study showed that each allergen of SCIT had different characteristics of ARs. The moderate incidence of ARs was not a problem regarding compliance with SCIT. Therefore, SCIT may be preferred in indications of allergy, as it has a tolerable balance of ARs and safety.

Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki, and the study protocol was approved by the institute's committee on human research (Kirikkale University Ethics Committee; approval number 2021.02.04).

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Ayşe Baççıoğlu and **Merve Poyraz** contributed to the design of this work. **Ayşe Baççıoğlu, Ayşe Füsun Kalpaklıoğlu, Merve Poyraz, Sümeyra Alan Yalım, Betül Dumanoğlu, and Gülistan Alpağat** drafted and revised this work.

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None.

Conflict of interest

None.

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