

Subcutaneous Allergen-Specific Immunotherapy Is Safe in Pediatric Patients with Allergic Rhinitis

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Keywords

Adverse reaction · Allergic rhinitis · Asthma · Safety · Subcutaneous allergen immunotherapy

Abstract

Introduction: Subcutaneous allergen-specific immunotherapy (SCIT) is one of the main cornerstones in the treatment of allergic rhinitis in pediatric patients. It has demonstrated symptoms and quality of life improvement, but it is not exempt from adverse reactions (ADVs). Nevertheless, there are a few reports that have evaluated their safety. Our objective was to evaluate the ADVr to SCIT in pediatric patients. **Methods:** We reviewed 786 clinical records with SCIT from 2005 to 2018, comparing the clinical characteristics of patients with ADVs with SCIT versus a group of a similar number of patients who completed SCIT (control group, CG). The analysis of ADVs was according to the World Allergy Organization (WAO) 2010 grading system by frequency analysis, survival curve, and log rank. **Results:** Of 786 patients, 106 (13.4%) presented ADVs, and the patients with ADVr had sensitivity and immunotherapy with at least 2 allergens versus CG $p < 0.001$, containing a combination of standardized and nonstandardized allergens ($p = 0.003$). The ADVs were in the buildup

phase ($p < 0.001$). The survival curve showed that 50% had some reaction at 12 weeks of SCIT. The most frequent ADVr was grade 1 in 73/106 patients (68.8%) and grade 2 in 33/106 (31.1%). The log-rank analysis between the grades of the WAO grading system showed a statistically significant difference ($p = 0.02$). **Conclusions:** The SCIT is safe in pediatric patients. The ADVs are infrequent, grade 1 being the most reported; however, at >12 weeks, the risk of ADVs that involve 2 organs systems increases.

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Introduction

Allergen immunotherapy (AIT) is considered the only therapy that modifies the natural course of allergic rhinitis (AR) [1, 2], and it has been shown to reduce the frequency of the development of asthma in patients with AR [3, 4]. Moreover, several clinical trials have shown a possible reduction in the risk of acquiring sensitization to

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Edited by: D.Y. Wang, Singapore.

new allergens [5] and a decrease in the number of visits to the emergency room due to asthma exacerbations [6]; similarly, AIT contributes to symptomatic control [7] and to an overall improvement in the quality of life in AR patients [8]. In economic terms, one study showed that patients with AIT save approximately 80% more than those who only take pharmacological therapy in the long run [9].

Nevertheless, AIT, as with other therapeutic measures, can cause adverse reactions (ADVRs), although there are few reports of such events [10]. The objective of the present study was to evaluate the safety of subcutaneous allergen-specific immunotherapy (SCIT) administered to pediatric patients with AR in the last 13 years in the Department of Allergy and Immunogenicity at the National Institute of Respiratory Diseases in Mexico City.

Methods

Study Design

Data were collected from the medical records of pediatric patients who received SCIT between 2005 and 2018. We included records of patients diagnosed with AR according to the ARIA (*Allergic Rhinitis and its Impact on Asthma*) guideline criteria [11], who showed positivity to at least one allergen in a skin prick test (SPT) and for whom at least one ADVR to SCIT was documented, local or systemic, based on the World Allergy Organization (WAO) 2010 grading system proposal. All patients with ADVR were contacted by telephone to verify the information.

The severity of the AR and asthma, according to the ARIA and GINA 2008 (Global Initiative for Asthma) guidelines [12], was documented from their medical records, as well as pulmonary function tests (Mater Screen, Jaeger-Germany), eosinophil counts (Beckman Coulter LH750, Brea, CA, USA), and quantification of total serum immunoglobulin E (IgE) (Architect i2000, Roche, Mannheim, Germany) within a time span of no more than 3 months before the ADVR.

Additionally, we compared the basal clinical characteristics between the patients with ADVRs versus a control group (CG), selected randomly and matched by age and gender, defined as the patients who completed SCIT presenting at most a small local reaction (<2.5 cm major diameter), but without ever presenting systemic ADVRs to SCIT administration. We excluded from the analysis patients who had poor adherence to treatment (assessed by not attending to their appointments) or who discontinued the follow-up for causes not related to SCIT (i.e., change of city). This protocol was approved by the Institutional Ethics Committee with the number C41-13.

Allergen Sensitivity

SPTs were performed with 52 allergens (ALK-Abelló, Port Washington, NY, USA) distributed as follows: 16 tree pollens, 11 grass pollens, 7 weed pollens, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cockroach, and 5 epithelia. A 0.9% saline solution was used as a negative control, and histamine hydro-

chloride (1:100) was used as a positive control [13]. The SPT device used was a disposable Duotip polypropylene lancet; a positive result was defined as a wheal with a diameter 3 mm more than that of the negative control.

Subcutaneous Allergen-Specific Immunotherapy

SCIT Justification

All subjects who had the presence of symptoms of AR with or without asthma and evidence of allergic sensitization by the SPT were considered as candidates to SCIT: main considerations included the following: (1) inadequate symptom control, despite pharmacotherapy and avoidance measures; (2) a desire to reduce the morbidity from AR or/and asthma; (3) reduce the risk of anaphylaxis from a future insect sting; and (4) unable to avoid the allergen [14]. Additionally, all the patients should have medical treatment with nasal and/or inhaled corticosteroids plus good clinical control of asthma with an adequate lung function test.

SCIT Composition

SCIT was performed by allergists, according to Mexican guidelines. AIT was individualized and prepared from the dilution of one or more with ALK-Abelló allergens (Pharm, Port Washington, NY, USA) with glycerin at 50% (online suppl. Tables 1, 2; see www.karger.com/doi/10.1159/000513158 for all online suppl. material), considering the medical history, results of SPTs, and exposure to the allergen(s) of each patient. The allergens were chosen by consensus of the allergist in clinical cases sessions, where the following principles were considered necessary, particularly when mixing allergen extracts:

1. Cross-reactivity of allergens: To prevent overdose, the number of allergens was limited in the vial. When pollens are substantially cross-reactive, the selection of a single pollen within the reactive genus or subfamily might suffice. For example, if the patient is sensitive to more than one allergen from the Oleaceae family (*Fraxinus*, *Ligustrum*, and *Olea*), only one allergen was included: because *Fraxinus* is highly prevalent in Mexico City, this allergen was used for desensitization.
2. Optimization of the dose of each constituent: The maintenance vial contained the highest concentration of AIT and provided of a projected effective dose (PED) necessary to induce the efficacy of the treatment without ADVRs. However, in the assumption that PED would have not been reached because the AIT was made up of different allergens (e.g., cat and mites), we chose to prepare 2 vials that contained these allergens separately, and they were applied in different sites within 30-min time span.
3. Enzymatic degradation of allergens: Allergen extracts with high proteolytic enzyme activities (cockroach and molds) were separated from others (pollens, dust, or epithelia), which is necessary in some cases to prepare 2 or more vials to provide AIT with optimal doses of each component. This procedure avoided allergen combinations that might induce degradation of some or all allergens included in AIT.

SCIT Schedule

Before the application of immunotherapy, all patients were informed about the benefits of SCIT as well as the possible adverse effects and complications; in addition, all patients received standard 10 mg of loratadine 1 h before each application; likewise, all the patients should have good clinical control of asthma and nor-

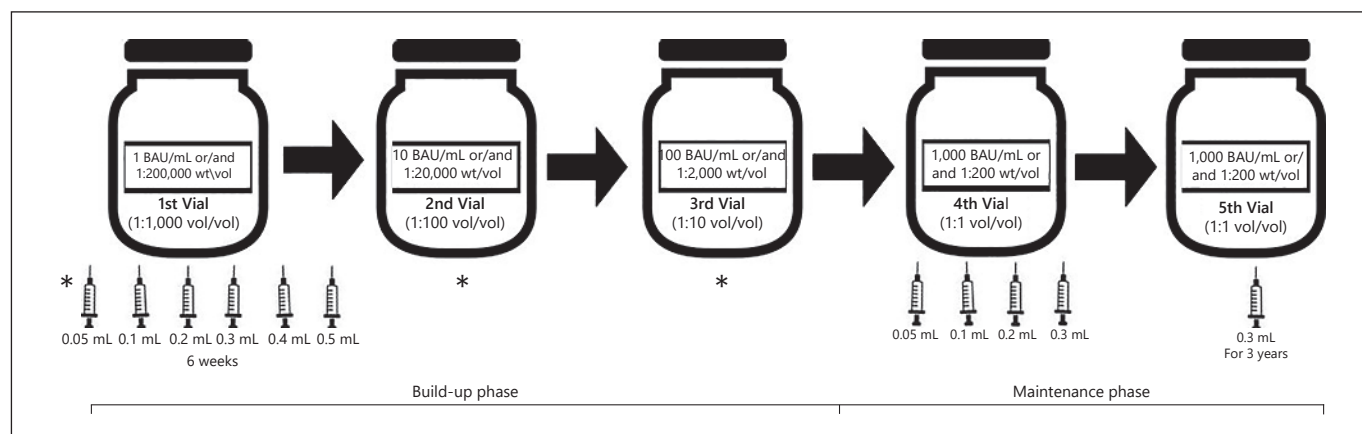


Fig. 1. Schedule of SCIT. Buildup phase: 3 vials, doses from 0.05 to 0.5 mL, for 6 weeks each vial. Maintenance phase: doses from 0.05 to 0.3 mL weekly, then 0.3 mL every second week, for 3 years. SCIT, subcutaneous allergen-specific immunotherapy

Symptom(s)/sign(s) of 1 organ system present: Cutaneous Generalized pruritus, urticaria, flushing, or sensation of heat or warmth Or Angioedema (not laryngeal, tongue or uvular). Upper respiratory Rhinitis (eg. sneezing, rhinorrhea, nasal pruritus, and/or nasal congestion) Or Throat-clearing (itchy throat) Or Cough not related to bronchospasm Or Conjunctival Erythema, pruritus, or tearing Or Other Nausea or Metallic taste or headache	Symptom(s)/sign(s) of more than 1 organ system present Or Lower respiratory Asthma: cough, wheezing, shortness of breath (PEF <40% or FEV₁ drop, responding to an inhaled bronchodilator) Or Gastrointestinal Abdominal cramps, vomiting or diarrhea. Or Other Uterine cramps	Lower respiratory Asthma (eg. 40% PEF or FEV₁ drop, NOT responding to an inhaled bronchodilator) Or Upper respiratory Laryngeal, uvular, or tongue edema with or without stridor.	Lower or upper respiratory Respiratory failure with or without loss of consciousness Or Cardiovascular Hypotension with or without loss of consciousness	Death
Grade 1	Grade 2	Grade 3	Grade 4	Grade 5

Fig. 2. WAO 2010 ADvR grading system. WAO, World Allergy Organization; ADvR, adverse reaction; FEV₁, forced expiratory volume in 1 s.

Table 1. Comparison between ADVr to subcutaneous AIT versus CG

Variable	ADVrs to SCIT <i>n</i> = 106	Complete SCIT <i>n</i> = 106	<i>p</i> value	OR	95% CI
Male, <i>n</i> (%)	59 (55.7)	70 (66)	0.12	–	–
Age, years, <i>n</i> (%)	10 (7–13)	10 (7–13)	0.53	–	–
Children, <i>n</i> (%)	72 (67.9)	73 (66.03)	0.88	–	–
Adolescent, <i>n</i> (%)	34 (32.1)	33 (37.1)			
BMI, kg/m ²	19.65 (16.42–22.85)	19 (16–23)	0.45	–	–
BMI z-score	0.80	0.73	0.21		
Eosinophils, cell/mm ³	400 (150–600)	500 (232.5–800)	0.05	–	–
IgE, UI/L	511 (247–1,160)	429 (179–962)	0.11	–	–
Severe persistent AR, <i>n</i> (%)	50 (47)	65 (61)	0.05		
FEV ₁ /FVC, %	87 (79–88)	92 (80–92)	0.04	–	–
FEV ₁ , %	92.5 (82.25–101)	92 (84.25–102)	0.19	–	–
Number of positive SPT	4 (2–7)	2 (1–5)	0.002	–	–
Polysensitivity SPT, <i>n</i> (%)	83 (78.3)	42 (39.6)	<0.001*	5.49	3–10.05
Number of AIT allergens	2 (1–2)	1 (1–2)	0.09	–	–
Polytherapy, <i>n</i> (%)	50 (47.2)	26 (24.52)	<0.001*	2.74	1.53–4.92
Monotherapy, <i>n</i> (%)	56 (52.80)	80 (75.48)			
Std allergens, <i>n</i> (%)	50 (47.1)	64 (60.3)	0.053		–
NStd, <i>n</i> (%)	23 (21.7)	27 (25.4)	0.51		–
Std plus NStd, <i>n</i> (%)	33 (31.1)	15 (14.1)	0.003 [‡]	2.74	1.38–5.43

AIT, allergen immunotherapy; 95% CI, confidence interval at 95%; FEV₁, forced expiratory volume in 1 s; FVC, forced volume capacity; IgE, immunoglobulin E; OR, odds ratio; SCIT, subcutaneous allergen-specific immunotherapy; SPT, skin prick test; CG, control group; AR, allergic rhinitis; Std, standardized; NStd, nonstandardized; ADVr, adverse reaction. * $\beta \geq 92\%$. [‡] $\beta = 80\%$.

mal lung function test. Written informed consent was obtained from each patient. SCIT was applied following the schedule, actually proposed by the Mexican allergen-specific immunotherapy guidelines [7], which are given as follows:

Buildup phase: Patients started with the vial containing the lowest concentration (1 BAU/mL [Bioequivalent Allergy Unit/milliliter]) and/or 1:200,000 wt/vol (weight/volume), receiving doses from 0.05 to 0.5 mL (0.05, 0.1, 0.2, 0.3, 0.4, and 0.5 mL) weekly, within a period of 6 weeks. Then, patients receive the same schedule from second and third vials, with 10-time incremental concentrations.

Maintenance phase: After finishing the last vial of the buildup phase, patients start with the maintenance concentration vial, from which they shall finally receive the projected effective dose. This vial is also known as 1:1 vol/vol (1,000 BAU/mL and/or 1:200 wt/vol), with doses from 0.05 to 0.30 mL weekly (0.05, 0.1, 0.2, and 0.3 mL) and then 0.30 mL every second week, in order to obtain a monthly maintenance dose of 600 BAU of standardized (Std) allergens and/or 0.6 mL monthly of a 1: 200 wt/v concentration for nonstandardized (NStd) allergens. AIT is planned to be extended for at least 3 years (Fig. 1).

ADVrs: Definition and Classification

ADVrs were defined as the symptoms that children developed within the first 30 min of the administration of SCIT. We included both local and systemic adverse drug reactions. The systemic ADVrs to SCIT were graded according to the WAO 2010 Grading System, which proposes 5 degrees of severity [15] (Fig. 2).

Statistical Analysis

The ADVr frequency analysis was performed with EpiInfo v7.0 (Atlanta, GA, USA) and EpiData (OPS, OMS) using a χ^2 test. Quantitative variables were analyzed with the Mann-Whitney U test, survival curve, and log rank for time to the first ADVr using SPSS v.21 (IBM, Endicott, NY, USA); for logistic regression, we used STATA v.14 (Stata Corp LLC, College Station, TX, USA), and all comparisons were considered statistically significant at *p* value <0.05.

Results

Clinic Characteristics

One hundred six (13.4%) of the 786 allergic children treated with SCIT developed ADVrs. The same number of children who completed 3 years of SCIT without ADVrs was selected as a CG.

Male sex predominated in both groups, mainly conformed by subjects <18 years (~67%), and the median age was 10 years; both groups had equal BMI (19 kg/m² and z-score ~ 0.8). Likewise, blood eosinophil counts and levels of total IgE at the start of SCIT did not show significant differences between the ADVr group and CG (Table 1).

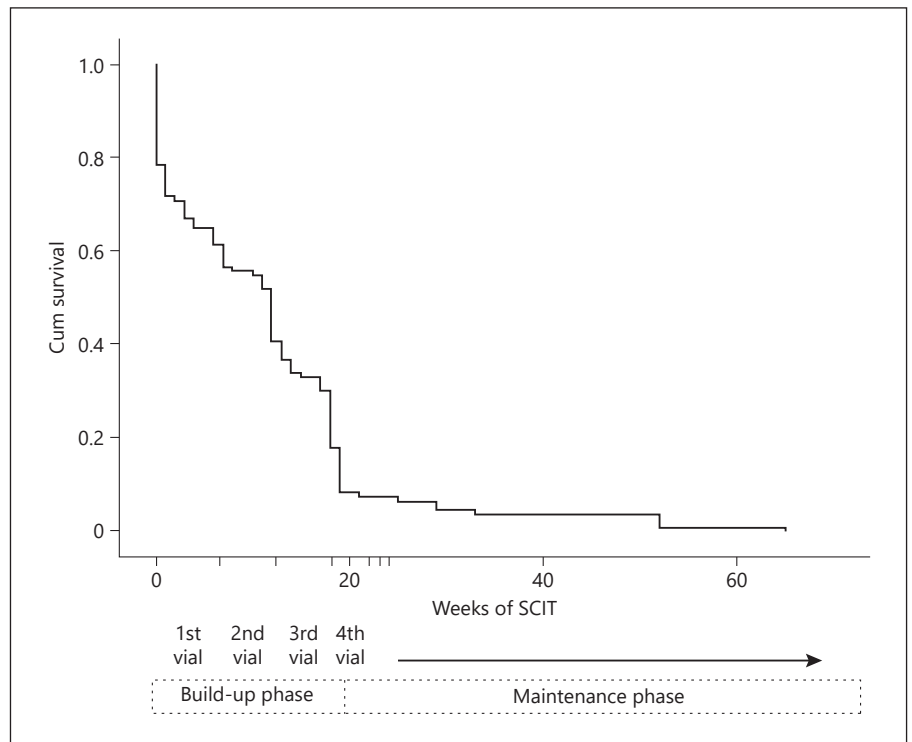


Fig. 3. Survival curve of ADVrs to SCIT. The 50% of the ADVr group presents the symptoms at 12 weeks of SCIT. SCIT, subcutaneous allergen-specific immunotherapy; AVDr, adverse reaction.

At the time of the ADVr to SCIT, 50 patients (47.16%) had persistent moderate to severe rhinitis, according to the ARIA classification, despite pharmacological treatment with intranasal corticosteroids in comparison with 65 (61%) subjects in the CG who presented the same severity. Patients with asthma accounted for 74.5% of patients controlled with step 3 treatment according to the GINA guidelines, with an average intake of 2 maintenance asthma drugs. The lung function test showed a lower forced expiratory volume in 1 s-to-forced volume capacity ratio in the patients with ADVrs than in the CG (87 vs. 92%, $p < 0.05$), although both groups had similar forced expiratory volume in 1 s values, with median of 92% predicted, at the beginning of SCIT.

Polysensitivity (*sensitivity to at least 2 allergens*) in the SPT was higher in the ADVr group than in the CG (78 vs. 39%, $p < 0.001$; OR = 5.4), and the median number of allergens in the ADVr group was 4 (2–7), as opposed to 2 (1–5) ($p = 0.002$) in the CG that completed SCIT. The most frequent allergen sensitivity was almost identical for both groups; the main indoor/outdoor allergens that prevailed in our population were *Dermatophagoides pteronyssinus* and *Fraxinus excelsior* in 70 and 18% of the subjects.

Subcutaneous Immunotherapy

The proportion of immunotherapy prepared with at least 2 allergens (polytherapy) was higher in ADVr than CG (47.2 vs. 24.5%, $p < 0.001$; OR = 2.74); Std allergen extracts were the most frequently used in comparison with Std (47.1 vs. 21.7%) in the ADVr group and 60.36 versus 25.4% ($p < 0.05$) in the CG. A combination of Std and NStd allergens was more used in the ADVr group versus CG (31 vs. 14%, $p = 0.003$; OR = 2.74). The allergens most frequently administered in patients with ADVr were *Dermatophagoides pteronyssinus* in 67 (63.21%) patients, followed by *Fraxinus excelsior* in 20 (18.87%) (Table 1).

Adverse Reactions

The majority of the ADVrs occurred during the build-up phase 83/106 (78.30%) ($p < 0.001$). Grade 1 was the most frequently reported reaction in 73/106 (68.8%) patients; specifying by symptoms, 54/106 (50.9%) had a wheal > 2.5 mm at the application site (we call it “*large local reaction*”); 10/106 (9.43%) presented urticaria, and 9/106 (8.49%) exacerbated rhinitis symptoms. Grade 2 was identified in 33/106 patients (31.1%); lower respiratory symptoms characterized by wheezing and sudden cough (we established the term “*bronchospasm*”) were documented in 14/106 (13.2%) patients. We did not de-

Fig. 4. Frequencies of ADVrs to SCIT. Frequencies of ADVrs and their distribution before and after 12 weeks. SCIT, subcutaneous allergen-specific immunotherapy, ns, nonstatistical significance; AVDr, adverse reaction.

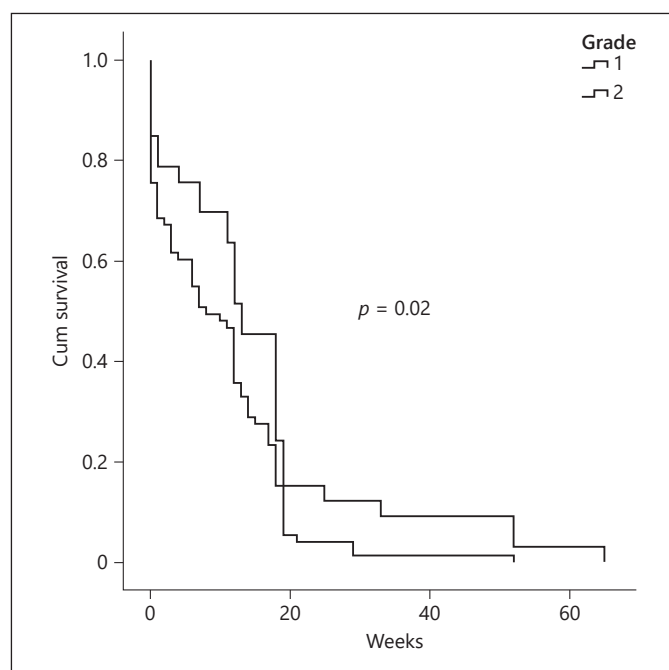
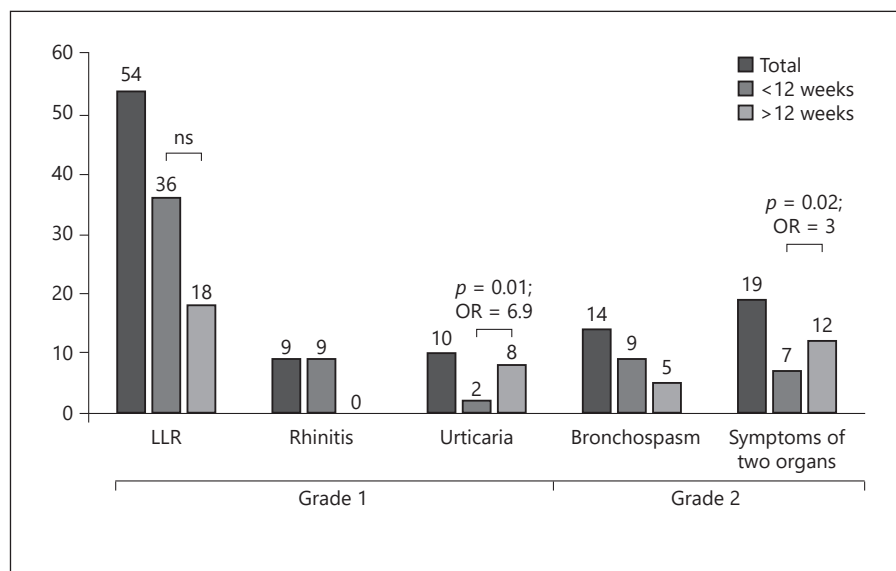


Fig. 5. Log rank between grades of ADVrs log-rank analysis between grade 1 and grade 2. AVDr, adverse reaction.

tect ADVrs that could be classified as grade 3 or 4, and there were no reported fatalities (grade 5).

We established a cutoff point for analyzing the reactions based on the survival curve, which showed that 63/106 (59.4%) patients of all reactions presented before

12 weeks, which corresponds to the final dose of 0.5 mL of the second vial (Fig. 3). At that time, 47/63 (74.6%) corresponding to grade 1, specifically, 36/63 (57.1%) patients had large local reaction, 9/63 (14.2%) had increased rhinitis symptoms, 2/63 (3.1%) had urticaria, 16/63 (25.3%) patients with ADVrs were classified as grade 2, 9/63 (14.2%) had bronchospasm, and 7/63 (11.1%) development symptoms in 2 organ systems.

In contrast, after 12 weeks, 43/106 (40.5%) had at least one ADVr during the last vial of the buildup phase. Grade 1 remained the most frequent ADVr in 26/43 (60.4%), the large local reaction being the most frequent in 18/43 (41.8%) and urticaria was detected in 8/43 (18.6%). Grade 2 was identified in 17/43 (39.5%): bronchospasm in 5/43 (11.6%), and symptoms of 2 organ systems in 12/43 (27.9%) (Fig. 4).

In the same context, the risk of suffering symptoms of 2 organ systems before 12 weeks was lower than that after 12 weeks ($p = 0.02$, odds ratio = 3.0; confidence interval at 95% 1.1–8.6); in this way, the urticarial reaction had $p = 0.01$ (odds ratio = 6.9; confidence interval at 95% 1.4–34.6); no other grade or symptom presented a statistically significant difference ($p > 0.05$) (Fig. 4).

However, depending on the grade of the reaction, the survival curves differed. For example, 50% of the patients who had ADVr classified as grade 1 presented them during the first 8 weeks, and 13 weeks for grade 2. The log-rank analysis between the grades of the WAO grading system showed a statistically significant difference ($p = 0.02$) (Fig. 5). All reactions were treated specifically, that

is, in the case of symptoms of 2 organ systems, all were solved with one dose (0.5 mg equivalent to 0.5 mL) of adrenaline, and for bronchospasm, we prescribed 800 µg of salbutamol during the next hour, and for urticarial reactions, including large local reaction, we prescribed a standard dosage of a second-generation antihistamine. All ADVrs reversed, and no fatal outcomes were reported in the medical records as an ADVr to SCIT; after these therapeutic measures, the patients were kept under observation for 2 h and were scheduled the next day to assess their health condition; likewise, we reported that no patient had ADVrs to any drug used for treat ADVrs to SCIT.

We made a logistic regression including these variables in association with the ADVr presentation. The analysis showed that the model had no significant predictive effect in the multivariate analysis (polysensitivity and administering Std and NStd allergens). Log-rank analysis of the types of allergens administered (Std or NStd) and the number of allergens administered was not able to show significance. Similarly, we analyzed the association of the month of the ADVr to AIT according to the Mexican pollen calendar of principal pollen sensitization in our patients and did not find any association.

Discussion/Conclusion

There are a few reports about SCIT safety in the pediatric population. In the present study, we found that 13.4% of the patients presented local or systemic ADVrs; the ADVr group more often had polysensitization, and AIT was mostly prepared with a mix of Std and NStd allergens in this group. Also, symptoms of 2 organ systems were more frequent after 12 weeks, during the buildup phase.

Nacaroglu et al. [10], Al Samarai et al. [16], and Asero [17] reported that the frequency of ADVrs to AIT is approximately 12%; these data are comparable to those in our study. Consistent with Serrano et al. [18] and Adamic et al. [19], large local reactions were the most frequent ADVrs reported [20] and are associated with systemic reactions [21]. The ADVrs presented mostly during the buildup phase, in accordance with other studies [10, 16]. As an extension of this observation, we demonstrate that there is a 3-fold increased risk of suffering symptoms of 2 organ systems, after 12 weeks. Thus, we could show that the most critical moment was the last part of the buildup phase. To our knowledge, this has not been shown before. Some authors even re-

ported that systemic reactions are most frequent in the maintenance phase [10, 22].

In the comparative analysis, patients with at least 2 allergen sensitivities in the SPT showed 5 times more risk of ADVrs; similarly, patients with polytherapy had a 2-fold increased risk. This increase may be related to the pattern of sensitization in the SPT being predominantly polysensitive, a blend of Std allergens (*Dermatophagoides pteronyssinus*) plus other allergens, that is, *Fraxinus excelsior*, which determined the combination of the allergens included in the immunotherapy. These characteristics of risk factors have been described in other reports. Barth showed that the application of 2 allergen extracts caused an increase in local reactions during the buildup phase as stimulating simultaneously with 2 allergens can be expected to augment the chance of ADVrs [23]. This type of evidence indicates that buildup protocols with multi-allergen SCIT might lead to an increased risk of systemic reactions compared to single-allergen SCIT [24]. Asthma is a disease associated with ADVrs in some reports [20, 25, 26]; although asthma was present in 74% of the population with an ADVr, it did not represent a risk factor for the development of ADVrs in our population.

In the present study, we did not find any clinical laboratory or demographic variables that could serve as a predictive biomarker for the development of ADVrs. In the patients who had completed SCIT, the severity of AR decreased considerably (data not shown). Like Nacaroglu [10], we found an increase at baseline in the levels of serum IgE and peripheral blood eosinophils; however, when performing subsequent statistical analyses, these variables were not found to be risk factors for the development of ADVrs. Furthermore, we did not find associations of any ADVr with the peak of the ash tree pollen season in our geographic zone, which might support the findings of Asero [17], despite guideline recommendations about SCIT. However, the lack of association could also be related to the size of the population that received ash tree pollens as allergens in the vial. The population was too small to perform a statistical comparison. As for the other pollens, there is no clear pollen season in Mexico City as a low-to-moderate level of pollination lasts from October till May.

It is probable that existing conditions inherent in the patients who were not evaluated before the beginning of AIT could have influenced the development of ADVrs, for example, patients with extreme sensitivity to minor allergens, such as Der p 10 (tropomyosin), which is related to the protein that causes anaphylaxis in patients

allergic to shrimp (Pen a 1) [27]. This is a limitation of screening by the SPT with whole allergens.

In this study, we evaluated the safety of the subcutaneous schedule proposed by the Mexican guidelines of immunotherapy using exclusively stock vials with allergens in a glycerin 50% solution, finally resulting in a glycerin 10% solution in the patient vials. We did not evaluate other types of schedules (e.g., rush), administration methods (e.g., sublingual), or other types of diluents (e.g., depot). Bousquet reported that the rush schedule increases ADVrs [26]; however, the application of AIT sublingually reduces the presence of severe reactions [28, 29]. In the latter case, the use of aqueous allergens is safer than depot allergens (aluminum and calcium phosphate) [30], and even the use of low-concentration glycerin is not associated with local reaction rates [31].

Regarding the classification of ADVrs, there is no universally accepted grading system for anaphylaxis because of the complications in classifying the different symptoms that can appear [32]. We decided to use the WAO 2010 grading system because it stipulates that the reaction severity should be determined once the event is over, so that the physician would be able to consider all factors related to the ADVr in the specific context of severe ADVrs [15]. Vidal et al. [33] recently confirmed that this classification has a good correlation with the onset of the reaction and the number of organ systems involved, in comparison with others grading systems (EAACI 2006 and AAAAI/ACAAI); even the WAO 2010 grading system is more accepted than its update published in 2017.

A common problem in the ADVr is the overlap in symptoms in severe reactions [15]; that is why classifying after the event is best. For example, a patient might start with a cutaneous manifestation and subsequently develop wheezing. Once 2 organ systems are involved, this kind of clinical course should be classified as systemic reactions and needs to be treated as anaphylaxis [34]. The early identification of symptoms that require the use of adrenaline is one of the main objectives of WAO 2010 grading [33]; its adequate use based on the guidelines and practice parameters is necessary to reverse them quickly [34].

Our study has some limitations; it is a retrospective study, so we selected cases from medical records. We found some patients who did not continue the therapy for unknown reasons, so we cannot assume they did not present any ADVrs to the SCIT. Considering this proportion of the population, this study could have underestimated the data. Additionally, this study was performed

only in a third-level medical institute. To generalize the recommendations, a multicenter study would have been ideal.

Likewise, it is important to adhere to recommendations suggested in international AIT guidelines, such as restricting the application of SCIT in patients with controlled allergic asthma, the evaluation of lung function before the administration of AIT, and observation of patients for at least 30 min after the injection [35, 36]. Additionally, we would like to propose the programming of patient discussion sessions in order to choose personalized AIT. SCIT administration should always carefully be supervised, but we recommend special attention during the last vial of the buildup phase (in our schedule after 12 weeks), as well as in patients receiving multi-allergen SCIT and/or SCIT with NStd allergens to recognize systemic ADVrs as soon as possible and prevent complications by prompt treatment.

Acknowledgements

We acknowledge the resident medical group of the Department of Immunogenetic and Allergy of INER, for their technical assistance.

Statement of Ethics

This study complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and was approved by the Institutional Ethics Committee with number C41-13.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There is no funding to declare.

Author Contributions

G.F.P.R., D.L.L., and L.M.T. designed the study; G.F.P.R. and K.E.X.R. collected data; and G.P.R., K.E.X.R., D.L.L., F.R.J., and L.M.T. interpreted the data and critically reviewed the manuscript. All authors read and approved the final manuscript.

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Supplementary table 1 Standardized allergens used in Subcutaneous allergen immunotherapy

Standardized Allergen	ALK-abello original concentration (BAU or AU/ml)	Build up (BAU/ml)			Maintenance	Monthly Projected Effective Dose
		1st vial	2nd vial	3rd vial	4th vial	
<i>Agrostis alba</i> BAU/ml	10,000/1	1/1	10/1	100/1	1000/1	600
<i>Anthoxanthum odoratum</i> BAU/ml	10,000/1	1/1	10/1	100/1	1000/1	600
<i>Cynodon dactylon</i> BAU/ml	10,000/1	1/1	10/1	100/1	1000/1	600
<i>Dactylis glomerata</i> BAU/ml	10,000/1	1/1	10/1	100/1	1000/1	600
<i>Dermatophagoides farinae</i> AU/ml	10,000/1	1/1	10/1	100/1	1000/1	600
<i>Dermatophagoides pteronyssinus</i> AU/ml	10,000/1	1/1	10/1	100/1	1000/1	600
<i>Felis domesticus</i> BAU/ml	10,000/1	1/1	10/1	100/1	1000/1	1000
<i>Festuca pratensis</i> BAU/ml	10,000/1	1/1	10/1	100/1	1000/1	1000
<i>Lolium perenne</i> BAU/ml	10,000/1	1/1	10/1	100/1	1000/1	1000
<i>Phleum pratense</i> BAU/ml	10,000/1	1/1	10/1	100/1	1000/1	1000
<i>Poa pratensis</i> BAU/ml	10,000/1	1/1	10/1	100/1	1000/1	1000

BAU-Bioequivalent Allergy Units per ml, AU- Allergy Units per ml

Supplementary table 2. Non-Standardized allergens used in Subcutaneous allergen immunotherapy

Non-standardized Allergen Wt/vol	ALK-abello original concentration wt/vol	Build up			Maintenance	Monthly Projected Effective Dose
		1st vial	2nd vial	3rd vial	4th vial	
<i>Acacia sp</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Acer negundo</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Alnus verrucosa</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Amaranthus palmeri</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Amaranthus retroflexus</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Ambrosia trifida</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Artemisa tridentata</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Artemisa vulgaris</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Atriplex wrightii</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Avena fatua</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Betula verrucosa</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Blattella germanica</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Canis lupus familiaris</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Carya ovate</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Casuarina sp</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Cupressus arizonica</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Eucalyptus sp</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Fraxinus excelsior</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Holcus lanatus</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Juniperus californica</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Juniperus virginiana</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Liquidambar styraciflua</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Medicago sativa</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Olea europaeae</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Plantago lanceolata</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL

<i>Platanus occidentalis</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Populus alba</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Populus deltoides</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Populus tremuloides</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Prosopis sp</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Quercus alba</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Rumex crispus</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Schinus molle</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Taraxacum officinale</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Triticum aestivum</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Ulmus americana</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL
<i>Zea mays</i>	1/20	1/200,000	1/20,000	1/2,000	1/200	0.6mL

Wt/vol-weight/volume