APJAI
Asian Pacific Journal of
Allergy and Immunology

ORIGINAL ARTICLE

Are large local reactions a marker for systemic reactions to subcutaneous immunotherapy in children?

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Abstract

Background: Previous studies involving predominantly adults concluded that the patients developing frequent large local reactions (LLRs) might be at greater risk for systemic reactions (SRs) during subcutaneous allergen immunotherapy (SCIT).

Objective: To determine the rate of side effects to SCIT and evaluate frequency of LLR among pediatric patients with SRs.

Methods: The retrospective study included pediatric patients receiving SCIT. Data on the demographic features, season at onset of SCIT, the indication for treatment, additional allergic diseases, laboratory results, the allergens applied, side effects after injection, grade of SRs, and the total number of injections for each patient were collected retrospectively from the medical records and injection charts.

Results: A total of 19,562 injections were administered to 261 patients with conventional SCIT. The incidence LLRs was 0.2% per injection; 1.15% of all patients (n = 3) experienced LLRs on at least two consecutive visits. Systemic side effects were seen in 1% of all SCIT injections. No grade 3 or grade 4 SRs were observed. Logistic regression analysis showed that having an LLR was 3.32 times (95% CI, 1.313–8. 440; P = 0.011) and initiation of SCIT in summer and spring was 4.309 and 3.056 times than autumn (95% CI, 1.527–12.157, P = 0.006; 95% CI, 1.358–6.849, P = 0.007), respectively, increased risk for an SR.

Conclusion: Having LLRs might predict the risk of SRs at any time during immunotherapy in also pediatric patients. Knowing the risk factors is important for developing a personalized protocol in these patients.

Key words: subcutaneous immunotherapy, large local reaction, systemic reaction, pediatric, children

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Introduction

Subcutaneous allergen immunotherapy (SCIT) is an effective treatment that can modify the natural course of the disease for patients with allergic rhinitis, allergic asthma and hymenoptera venom allergy.[1,2] Although SCIT is generally well tolerated, local and systemic reactions (SRs) ranging from mild to life-threatening anaphylaxis may occur.[3] The rate of SRs with a conventional schedule is reported to be 0.1% to 0.2% per injection.[4,5] Uncontrolled asthma is well known to predict severe SRs, but some studies have reported mixed results for factors including the type of allergen, the high degree of sensitivity, number of injections, the phase of immunotherapy, the type of disease and seasonal exposure.[1,6,7] There have been studies evaluating the relationship of large local reactions (LLRs) with subsequent systemic reactions in patients who receive SCIT. Contrary to a previous study by Ramirez et al that reported no systemic reactions with dose adjustments after a large local reaction were observed , recent studies have concluded that LLRs do not increase the likelihood of subsequent SRs and routinely dose adjustment is not required.[2,8,9] Routine dose adjustments when a LLR occurs from immunotherapy may be time consuming because of additional visits and may be reason of the non-completed immunotherapy.

Fear of adverse reactions for both the patient and the doctor is considered to be a reason of non-adherence to SCIT. Early identification and appropriate management of preventable risk factors can reduce SCIT-related SRs that limits its use and encourage more effective use of this treatment.

We performed a retrospective study of patients receiving SCIT following a conventional schedule in our allergy clinic to determine the rate of systemic reactions associated with SCIT. We also investigated possible risk factors associated with SRs such as frequency of LLRs.

Methods

Patient Population

This retrospective cross-sectional study was conducted at the Department of Pediatric Allergy and Immunology at Kocaeli University, Turkey. All children aged 5 to 18 years who underwent immunotherapy in our clinic between January 2011 and December 2019 were included in the study. Patients who did not complete at least 2-year follow-up were excluded. The local ethics committee at Kocaeli University approved the study (2020/158)

Data on the demographic features, season and the age at onset of SCIT, the indication for treatment, allergen sensitivity at skin prick test (SPT), additional allergic diseases (such as atopic eczema, food allergy, urticaria, drug allergy) family history, test results (blood eosinophil count, total IgE) the allergens utilized in the immunotherapy, local and systemic side effects after injection, symptoms and signs of SR, grade of SR, season and phase of SCIT at time of reactions, and the number of injection visits for each patient were collected from the medical records and injection charts.

Subcutaneous İmmunotherapy

SCIT was performed using a conventional scheme with the appropriate allergen extract on the basis of the patient's SPT results and symptoms. Standardized aluminium hydroxide adsorbed depot allergen extracts (Alutard, ALK, Denmark) were used. The initial standard dose for immunotherapy was 0.1 ml of 100 SQ/ml. Dosages were increased weekly to reach a monthly usual maximum maintenance dose of 0.8 ml of 100,000 SQ/ml. Doses were administered weekly for 4 months and subsequently biweekly for 1 months in the build-up phase and monthly for at least 3 years in the maintenance phase. Patients were examined by a physician before receiving immunotherapy injections for current asthma symptoms and delayed local or systemic side effects had developed after their previous treatment. The injections were applied by the same experienced nurses in our clinic throughout the study period. The patients were observed for at least 1 hour after each injection for possible adverse effects. Large local reaction was defined as swelling and/or erythema larger than 5 cm at the injection site. Systemic or local reactions that occurred > 30 minutes after injections were considered as delayed reactions.[1,2] The rate of systemic reaction was defined as the number of reactions per injections (the total number of reactions/ the total number of injection). Experienced local reactions in a row on at least two visits during the SCIT was defined as a consecutive local reaction. We used the 5-level grading systems of the World Allergy Organization in the assessment of systemic side effects seen post SCIT: grade 1, symptoms involving one organ system (cutaneous, upper respiratory tract, conjunctival, gastrointestinal, other symptoms, such as nausea, headache); grade 2, symptoms involving more than one organ system or gastrointestinal symptoms or asthma symptoms/signs that respond well to inhaled bronchodilators; grade 3, asthma symptoms/signs that do not respond to inhaled bronchodilators or upper respiratory tract (laryngeal, uvula, tongue) oedema with or without stridor; and grade 4, respiratory failure or hypotension, with or without loss of consciousness.[10] SRs were treated with antihistamines, epinephrine, and/or albuterol based on reaction severity and systems involved. Doses were changed according to the recommendations of the manufacturer in the presence of systemic and large local reactions with the previous dose. Patients were not routinely given premedication before injections.

Statistical Analysis

SPSS v21.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Normality was evaluated using the Kolmogorov-Smirnov test and descriptive statistics. Continuous variables are presented as the median (interquartile range). Categorical variables are presented as frequency and percentage. The chi-squared test or the Fisher exact test was used to analyse categorical variables. The Mann-Whitney U test was used to analyse continuous variables. Multivariate logistic regression with backward elimination was performed to assess potential predictors of an SR. Results are presented as odds ratios and 95% confidence intervals (95% CIs). Statistical significance was considered as $P < 0.05$.

Results

A total of 19,562 injections were administered to 261 patients (101 females and 160 males) for conventional SCIT. The indication for immunotherapy was allergic rhinitis and/or allergic conjunctivitis (16%), asthma (32%), asthma plus allergic rhinitis (52%). The patients receiving venom immunotherapy are excluded from study. The average duration of immunotherapy was 42.05 months (minimum, 24 months; maximum, 64 months); 56.3% of the patients (147 of 261) received a single allergen. SCIT was performed for house dust mites in 225 patients (86.2%), grass pollens in 123 patients (47.1%), alternaria in 10 patients (3.8%) and olive pollens in 5 patients (1.9 %).

Six patients could not be complete at least 2-year follow-up course due to reasons not related to side effect of SCIT (low efficacy (n = 1), having autoimmune disease during treatment (n = 1), moving the another city (n = 2), socioeconomic conditions(n = 2)).

Incidence of Side Effects

<u>Local Reactions</u>

A total of 132 local reactions were seen in 19.2% of patients for a rate of 0.67% per injection. Of these local reactions, 70.5% were small local reaction [SLR] that defined as smaller than 5 cm. The large local reaction rate was 0.2%

per injection (8.4% of patients) and 51.2% of these reactions were delayed. A total of 4.6% of patients (n = 12) experienced SLRs on at least two consecutive visits. The rate of large local reactions (LLRs) and SRs in patients with consecutive SLRs was 2.06% and 1.31% per injection. A total of 1.15% of patients (n = 3) experienced LLRs on at least two consecutive visits. No SRs were observed in patients with consecutive LLRs.

Systemic Reactions

Systemic side effects were seen in 1% of all SCIT injections and in 24% of patients. Eighty-one percent of systemic reactions occurred in the maintenance phase of the immunotherapy and 32.5% in the winter; 10.7% of all patients (n = 28) experienced SRs on at least two visit.

Grade 1 SRs occurred in 39% (25 of 64) of the patients who had SRs. Of the patients who had grade 1 reactions, 72% had only one reaction, 24% had two and only one patient had nine reactions. Grade 2 reactions were observed in 76.5% (49 of 64), 34% had only one grade 2 reaction, 18% had two SRs, 16% had three SRs and 32% had 4 to 20 reactions. No grade 3 or grade 4 SRs were observed.

Grade 1 reactions were treated with antihistamines (combined with systemic corticosteroids in % 10 of treatment). Intramuscular epinephrine were used 63.2% of Grade 2 SRs (combined with antihistamines and/or short-acting beta-2 agonists), constituting 50.7% of all SRs. Short-acting beta-2 agonists were given in 36.8% of Grade 2 reactions.

Risk Factors for Systemic Reactions

There were no significant differences for the prevalence of SRs in terms of gender, the mean age at initiation of SCIT, time interval between diagnosis of the initial allergic disease and start of SCIT, initial diagnosis, additional allergic diseases, the presence of atopy in the family, the degree of skin test reactions (for patients receiving HDM and grass pollens SCIT), number of sensitizations in the skin test, allergen extracts administered, SCIT with multiple or single allergen, peripheral eosinophilia and serum total IgE measures (**Table 1**). Both small and large consecutive local reactions had no effect on the occurrence of SRs on the next injection. SRs developed in 54.5% (12 of 22) of patients who had a large local reaction and 21.8% (52 of 239) of those without an LLR (P = 0.001).

Table 1. Characteristics of the patients with and without systemic reactions

	All patients (n = 261)	Systemic reaction (n = 64)	No systemic reaction (n =197)	*P*
Age at start of immunotherapy (years), median (IQR)	9.80 (5.30)	9.60 (3.93)	10.05 (5.60)	0.678
The time interval between diagnosis and the SCIT initiation, median (IQR)	2.50 (3.90)	2.80 (3.88)	2.30 (3.95)	0.216
Sex (male), n (%)	160 (61.30)	34 (53.12)	126 (64)	0.162
Diagnosis (%)				0.090
Asthma	83 (32)	30 (46.87)	106 (53.80)	
Allergic rhinitis	42 (16)	7 (10.93)	35 (17.76)	
Asthma and allergic rhinitis	136 (52)	27 (42.20)	56 (28.42)	
Other allergic disease (food and drug allergy, AD), n (%)	43 (16.50)	6 (9.37)	37 (18.80)	0.137
Allergen extracts, n (%)				0.218
House dust mites (HDM)	123 (47.12)	37 (57.81)	86 (43.60)	
Pollens	26 (10)	5 (7.81)	21 (10.65)	
HDM plus pollens	102 (39.08)	21 (32.80)	81 (41.11)	
Mould	10 (3.83)	1 (1.56)	9 (4.56)	
Season at the start of SCIT, n (%)				0.002
Spring	59 (22.60)	21 (32.81)	38 (19.30)	
Summer	22 (8.42)	9 (14.06)	13 (6.60)	
Autumn	105 (40.21)	14 (21.90)	91 (46.10)	
Winter	75 (28.82)	20 (31.25)	55 (27.91)	
Family history of allergic diseases, n (%)	97 (37.16)	18 (28.12)	79 (40.10)	0.134
SLR, n (%)	40 (15.32)	14 (21.87)	26 (13.20)	0.090
Consecutive SLR, n (%)	12 (4.63)	4 (6.25)	8 (4.06)	0.468

Table 1. (Continued)

	All patients (n = 261)	Systemic reaction (n = 64)	No systemic reaction (n =197)	*P*
LLR, n (%)	22 (8.42)	12 (18.75)	10 (5.07)	0.002
Consecutive LLR, n (%)	3 (1.15)	0 (0)	3 (1.52)	0.750
Total IgE (IU/mL), median (IQR)	410 (694)	378 (704)	437 (681)	0.793
Serum eosinophilia/mm^3, median (IQR)	289 (362)	280 (444)	289 (357)	0.676
The number of positive skin test results, median (IQR)	2 (1)	1 (1)	2 (1)	0.556
The diameter of skin test reactions, mean (SD), mm				
Dermatophagoides pteronyssinus (Dp)	8.50 (3.73)	9.21 (3.87)	8.20 (3.65)	0.168
Dermatophagoides farina (Df)	8.73 (3.70)	9.56 (3.65)	8.38 (3.69)	0.107
Grass pollens	10.53 (5.21)	10.60 (3.50)	10.52 (5.61)	0.977

Abbreviations: HDM, house dust mite; LLR, large local reaction; SCIT, subcutaneous allergen immunotherapy; SLR, small local reaction.

Table 2. Risk factors for systemic reactions

Risk factor	Odds ratio	95% Confidence Interval		*P* value
Sex	1.716	0.940	3.132	0.079
Large local reaction	3.329	1.313	8.440	0.011
Season at start of SCIT				0.014
Summer	4.309	1.527	12.157	0.006
Spring	3.056	1.358	6.849	0.007
Winter	2.113	0.971	4.594	0.060

P values < 0.05 are significant. Diagnosis, family history of allergic diseases, and small local reaction were excluded in backward elimination.

Table 3. The incidence of reactions according to the onset time and phase of immunotherapy

	All, n (%)	Build-up phase, n (%)	Maintenance phase, n (%)
Small local reactions			
Immediate	89 (95.69)	17 (18.27)	72 (77.41)
Delayed	4 (4.30)	1 (1.07)	3 (3.22)
Large local reactions			
Immediate (< 30 minute)	19 (48.71)	1 (2.56)	18 (46.15)
Delayed (> 30 minute)	20 (51.28)	16 (41)	4 (10.25)
Systemic reactions			
Immediate	161 (79.31)	27 (13.30)	134 (66)
Delayed	42 (20.70)	11 (5.41)	31 (15.27)

Logistic regression analysis showed that having an LLR was 3.58 times (95% CI, 1.402–9.133; $P = 0.008$) and initiation of SCIT in summer and spring was 4.579 and 2.856 times than autumn (95% CI, 1.692–12.363, $P = 0.003$; 95% CI, 1.269–6.429, $P = 0.011$), respectively, increased risk for an SR (**Table 2**).

Of the local side effects, 81.5% were immediate and 79.3% of systemic side effects were immediate reactions. The incidence of local and SRs according to the onset time after injection and the phase of immunotherapy are presented in **Table 3**.

Discussion

In our study, we evaluated several parameters as predictors of SRs and the incidence of local and systemic side effects due to SCIT in children. In multivariate logistic regression analysis, only having LLRs and the initial season of SCIT were identified as significant risk factors for SCIT-related SRs in our study. In the present study, we found that the possibility of SRs at any time during immunotherapy was 3.5 times higher in patients experiencing an LLR. Previous studies suggested that LLRs are insensitive predictors of subsequent SRs and reducing the dose at the next injection after an LLR is unnecessary.[9,11-14] In a retrospective study, Roy et al.[15] concluded that there is a statistical difference in the frequency of LLRs between patients who experienced an SR and those who did not, and the authors suggested that LLRs were not predictive of subsequent SRs but the patients developing frequent LLRs might be at greater risk for SRs during SCIT. Since this finding that reported in patients with routine dose adjustment after LLRs, in other studies that followed a no-dose adjustment policy have supported with similar findings.[16,17] There are wide variations between studies in the definition of LLRs and dose adjustment protocols. As a conclusion of these evaluations, we think that prospective multicentre studies investigating the effect of LLRs on SRs are necessary.

The rate of local reactions in our patients was lower than those reported in the literature; similarly wide local reactions were observed in 8.5% of patients and 0.23% of all injections. In our center, before leaving the clinic, the injection sites of all patients are examined by an experienced nurse, even if the patient has no complaint. We believe that local reaction rates are not underestimated even though they were documented retrospectively. This lower local reaction rate may be explained by the use of a cold compress in our clinic when patients feel subjective symptoms such as fullness, tingling sensation and pain. Coop et al.[18] evaluated SCIT-related local reactions, and they concluded that most local reactions are not bothersome to patients and are an uncommon reason for discontinuation. Previous studies showed that local reactions did not predict a repeat local reaction at the subsequent injection, and dose adjustment for local reactions may delay therapy and require additional visits.[9,16] In our clinic, we do not routinely adjust the dose for local reactions, and we did not observe discontinuation of immunotherapy due to these reactions.

In our study, the frequency of systemic reactions was 1% per injections. Previous studies have reported approximately 0.2% SRs per injection.[19,20] The incidence of SRs in our study was higher than those reported in these studies but similar to the values reported for other adult studies and a study performed in children by Tophof et al.[9,11,21] The higher SR rates may be related to our strict follow-up policy after each injection. In our centre, we observed patients for at least 1 hour after injection, and if they have a complaint after leaving the clinic, we instruct them return to the injection room or call us. Previous studies demonstrated that approximately half of the SRs to allergen immunotherapy were delayed and not severe.[2,20] Another explanation for this finding may be an underestimated rate relative to failure to report minor delayed reactions in patients who wait the recommended 30 minutes because families ignore this if they use self-treatment or were treated in an another centre for symptoms occurred out of the office. In addition, there are variations in study designs. For example, Mustafa et al.[13] concluded that it is possible to miss reactions when only antihistamines are used for treatment because patients using epinephrine were included in the study as systemic reactors. In the light of these findings, we emphasize that physicians should question and document appropriately the presence of delayed reactions; a longer observation time should be applied especially for patients with a greater risk for an SR. Developing a standardized form for recording reactions at the start of immunotherapy for each patient could help with the documentation of SRs.

Studies have reported that patients with asthma develop higher SCIT-related systemic side effects.[1,22,23] In our study, there was no correlation between SCIT-related side effects and the presence of asthma. In our centre, in addition to routine evaluation for the presence of current asthma symptoms before injection on the SCIT administration day, follow-up visits every 3 months are arranged for each patients receiving SCIT and asthma control is evaluated. We think that this finding is related to the good asthma control among our patients as a result of this practice, reported to be important for safe administration of immunotherapy.[5,24-26]

The possibility of SRs with start of SCIT in summer was 4.5 times higher and approximately 2.8 times higher in spring than autumn in our study. We have not found any similar findings about this issue in the literature. Patients who started immunotherapy in the spring and summer will be on maintenance therapy in autumn and winter. Although we do not have enough knowledge to explain this finding, we think that the higher allergen content in the maintenance phase, in addition to the frequency of environmental triggers, such as viral infection allergens, could induce SRs in autumn and winter.

In conclusion; having LLRs might be a important factor that increasing the possibility of SRs at any time during immunotherapy. Knowing the risk factors may be an opportunity to develop a personalized treatment for SCIT. Previous studies have shown that dose adjustments after LLR do not affect SRs on the next injections.Further studies focusing on whether starting at a lower dose, slower dose increases during build-up, pre-medication, repeating a dose may affect the rate of reactions in these population at risk for systemic reactions are needed.

Conflicts of interest

None

Funding Source

None

Author contributions

- I.E.S. and M.A. designed this study and analyzed all of the data,
- I.E.S wrote the first drafts of this paper.
- Both of the authors reviewed this manuscript.

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