

Systemic and large local reactions during subcutaneous grass pollen immunotherapy in children

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Abstract

Background: Subcutaneous immunotherapy (SCIT) is the allergen-specific curative treatment of allergic rhinitis. Adverse effects, most of which are local, can be observed during the immunotherapy. These adverse effects have been reported more frequently during the pollen season. The purpose of this study was to estimate the rate of local, large local, and systemic reactions during the treatment, to determine the relationship between adverse reactions and the season in which these reactions occur, as well as the risk factors for adverse reactions during the grass pollen-specific SCIT treatment in children.

Methods: We retrospectively collected and analyzed the data of 261 children who administered grass pollen SCIT between 2008 and 2018.

Results: A total of 261 children (177, 67.8% male), who received grass pollen SCIT, with a mean ($\pm$ SD) age of 12.0 ± 3.0 years at the initiation of SCIT were enrolled to the study. The number of the patients who experienced local and large local reactions was 109 and 30, respectively. In addition, the number of the patients with systemic reactions was 35. After the 12 284 injections, local reactions occurred in 357 (2.9%), and this was followed by systemic reaction as 55 (0.4%) and large local reactions as 40 (0.3%). Frequency of local ($P < .001$) and systemic reactions ($P = .003$) was higher during grass pollen season than out of the grass pollen season. In multivariate analysis, initiation of SCIT during the grass pollen season [OR:7.351, 95%CI:1.532-35.279, $P = .013$] and experiencing local reactions [OR:4.214, 95%CI:2.159-8.224, $P < .001$] were independent predictors for the development of large local and systemic reactions.

Conclusion: SCIT, in which only mild-to-moderate systemic reactions occurred, is safe for the treatment of allergic rhinitis in children. Our study revealed that previous local reactions and initiation of immunotherapy during the grass pollen season were the predictors for large local and systemic reactions during SCIT in children.

KEYWORDS

adverse reactions, allergic rhinitis, children, pollen, subcutaneous immunotherapy

1 | INTRODUCTION

Allergic rhinitis (AR) affects 8.5% of children at the ages of 6 to 7, whereas the ratio strikingly rises up to 44.0% at the age of 13.¹ Thus far, the only curative therapy of AR is allergen-specific immunotherapy.² In allergen-specific immunotherapy, allergen extracts are given to the patients by gradually increasing doses, and therefore, immune tolerance against the culprit allergen is provided.³ Allergen-specific immunotherapies are subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) that are the standard and effective curative treatment modality of AR used in clinical practice.

Although SCIT is generally well tolerated and effective in improving AR symptoms,² adverse reactions including local, large local, and systemic reactions may occur during therapy. Of adverse reactions, 64.0% are seen during the grass pollen season⁴; fatal and near-fatal reactions have been reported more frequent during the grass pollen season compared to out of the grass pollen season.⁵ Only a few studies suggest the initiation of grass pollen SCIT during the grass pollen season due to the absence of correlation between systemic reactions and the grass pollen season.⁶ There are few conflicting data regarding the relationship between adverse reactions and grass pollen season during SCIT in children.

Our study aimed to estimate the rate of local, large local, and systemic reactions during the treatment and to determine whether the adverse reactions occurred during the grass pollen SCIT are affected by the season of administration of immunotherapy. Furthermore, the risk factors for adverse reactions seen in seasons during the grass pollen-specific SCIT in children were revealed.

2 | METHODS

2.1 | Patient population

2.1.1 | Demographic and clinical data

Patients aged 5-18 years who received grass pollen SCIT with the diagnosis of AR with or without allergic conjunctivitis in our outpatient clinic between 2008 and 2018 were reviewed retrospectively. AR was diagnosed in all patients according to international guideline.⁷

All demographic data of the patients, presence of asthma, adverse effects during SCIT, seasons when side effects occurred, the number of the injections applied to each child, skin prick test (SPT), and specific immunoglobulin E (sIgE) results for pollens that SCIT was administered for, sensitization to other aeroallergens including weed, tree, dermatophagoides pteronyssinus (DP), dermatophagoides farina (DF), animal fur, molds (alternaria and cladosporium), total IgE, and eosinophil numbers were recorded from medical files of the children. Patients who sensitized to two or more aeroallergens were accepted as polysensitized.⁸ Polysensitization was determined by SPT/sIgE values. Patients/their parents were asked to describe the family histories of aeroallergen atopy, AR, and asthma.

Key Message

The current study is on adverse effects during pollen specific SCIT. The data regarding adverse effects during SCIT in children is scarce. In our study, we showed that previous local reactions and initiation of immunotherapy in pollen season were the predictors for large local and systemic reactions during SCIT in children.

2.2 | Skin prick testing

Skin prick tests (SPT) with aeroallergens (grass, weed, tree pollens, DP, DF, animal fur, molds) were performed to the patients with positive (histamine) and negative (saline) controls. The test was applied to the volar part of the arm. Positive SPT was accepted as a wheal diameter of 3 mm or larger. The mean SPT result was calculated by taking the average of two perpendicular diameters of the wheal after 15 minutes following the application of allergens to the skin.

2.3 | Serum-specific immunoglobulin E

Total and specific IgE (sIgE) levels were measured via the Pharmacia CAP System (Immunocap-CAP; Pharmacia & Upjohn, Uppsala, Sweden); sIgE levels ≥ 0.35 kU/L were accepted as positive for the allergens.

2.4 | Allergen immunotherapy

Since the children in our country were mainly exposed and sensitized to grass pollen⁹ due to the flora covering our region, all patients had received reduced during for grass pollen. Patients underwent SCIT with Allergovit 006 Grass® (Allergopharma) which has two strengths (A: 1000 TU/mL and B: 10 000 TU/mL) in therapeutic units per mL (TU/mL).¹⁰ Gradually increasing doses were administered at one-week intervals to the patients in whom previous doses were well tolerated. Initial volumes were 0.1, 0.2, 0.4, and 0.8 mL from strength A and followed by 0.15, 0.3, and 0.6 mL from strength B during consecutive 6 weeks in buildup period.¹⁰ After reaching maximum volume, 0.6 mL from bottle B was applied as maintenance therapy at every 4 weeks for up to 3-4 years. All patients were observed for 30 minutes following subcutaneous injections for immediate (reactions observed within 30 minutes) adverse reactions and informed on potential delayed reactions (occurring after 30 minutes).¹¹ The maintenance doses were reduced by 10.0% with each new bottle and adjusted after a systemic reaction. All injections were administered to the lateral part of the upper arm.

2.5 | Adverse reactions

All reactions during injections were recorded on the patients' immunotherapy cards. Based on the diameter of induration, reactions were classified as local, large local, and systemic reactions, if smaller than 10 cm, greater than 10 cm, and widespread skin lesions such as generalized urticaria, angioedema, or other system involvements, respectively, according to well-established scoring systems.¹² Patients with no reaction and local reactions, as well as the patients with large local and systemic reactions, were combined to create two groups. Adverse reactions were analyzed according to occurrence "in grass pollen season" (April, May, June) or "out of grass pollen season" (other than these three months) and in "buildup" or in "maintenance" periods. Grass pollen season is accepted between April 1 and July 1 based upon previously published pollen calendar of Ankara.¹³

2.6 | Statistical analyses

Statistical analyses were performed using SPSS version 22.0 statistical software package (IBM SPSS Statistics). Values for continuous variables were given as either mean $\pm$ standard deviation (SD) or as median [inter-quartile range(IQR)], based on the normality of distribution. The chi-square and Mann-Whitney U tests were used to compare nonparametric values. To determine the significance of variables among adverse reactions groups (no reaction, local, large local, and systemic reactions), *p* for trend was calculated using the Jonckheere-Terpstra test. Variables were selected if the *p* value was less than 0.20 in the univariate analysis and included in multivariate analysis. Odds ratios (ORs) with relevant 95% confidence intervals (CIs) were calculated to evaluate potential associations. Values of *P* < .05 were accepted as significant.

3 | RESULTS

A total of 261 patients (177, 67.8% male) who were given grass pollen SCIT with a mean ($\pm$ SD) age of 12.0 $\pm$ 3.0 years at the initiation of SCIT were included. The characteristics of the participants are summarized in Table 1.

Overall, nine children (3.4%) were initiated SCIT in grass pollen season, and the rest of the population was started during out of the grass pollen season. Of the patients, 78.2% (*n* = 204) received SCIT for a duration of 3-4 years, 10.0% (*n* = 26) for 2-3 years, 5.7% (*n* = 15) for 1-2 years, and 1.5% (*n* = 4) less than 1 year. Of 261 patients, 134 patients (51.3%) had no adverse reactions. The combination of local, large local, and systemic reactions was observed in some of 127 patients (48.6%), who developed adverse reactions during grass pollen SCIT. One hundred and nine patients (41.8%) had local (95 during the grass pollen season, 45 out of the grass pollen season), 30 (11.5%) had large local (10 during the grass pollen season, 20 out of the grass pollen season), and 35 (13.4%) experienced systemic reactions (16 during the grass pollen season, 25 out of the grass pollen season).

TABLE 1 Characteristics of the study population (*n* = 261)

Age at the first dose of grass pollen SCIT (years) ^a	12.0 ($\pm$ 3.0)
Gender (male) <i>n</i> (%)	177 (67.8%)
Total IgE (kU/L) ^b	261.0 (117.5-620.0)
Eosinophil number (/mm ³) ^b	200 (100-400)
Eosinophil (%) ^b	3.2 (2.0-5.3)
Specific IgE for grass pollen which was SCIT given (kU/L) ^b	52.7 (24.9-103.0)
SPT for grass pollen which was SCIT given (mm) ^b	12.5 (9.0-16.0)
Polysensitization (SPT > 3 mm) (<i>n</i> /%)	66 (25.3%)
Tree pollen (<i>n</i> /%)	40 (15.3%)
Weed pollen (<i>n</i> /%)	52 (19.9%)
Animal fur (<i>n</i> /%)	38 (14.6%)
Cat (<i>n</i>)	32 (12.3%)
Dog (<i>n</i>)	7 (2.7%)
Horse (<i>n</i>)	4 (1.5%)
DP/DF (<i>n</i> /%)	15 (5.7%)
Mold (<i>n</i> /%)	10 (3.8%)
Family history of atopy (<i>n</i> /%)	67 (25.7%)
Asthma (<i>n</i> /%)	132 (50.6%)
Patients with local reaction (<i>n</i> /%)	109 (41.8%)
Patients with large local reaction (<i>n</i> /%)	30 (11.5%)
Patients with systemic reaction (<i>n</i> /%)	35 (13.4%)
Grade 1	21 (8.0%)
Grade 2	9 (3.4%)
Grade 3	5 (1.9%)

Abbreviations: DF, dermatophagoides farinae; DP, dermatophagoides pteronyssinus; SCIT, subcutaneous immunotherapy.

^aMean ($\pm$ standard deviation).

^bMedian (inter-quartile range—IQR).

Of the systemic reactions, 21 (8.0%) were grade 1, nine (3.4%) were grade 2, and five (1.9%) were grade 3.¹² These five with anaphylaxis (grade 3 reaction) were treated with adrenalin during systemic reaction (5/35, 14.2%). The incident rate of adrenalin given to the children (adrenalin injection/total injection dose of patient in risk; 5/12284) was 0.04%.

Approximately half of the study population had asthma (*n* = 132, 50.6%). Most of the patients with asthma had polysensitization to other aeroallergens, and these patients were polysensitized also to perennial aeroallergens among all the allergens. None of the patients with asthma had moderate or severe disease. Twelve patients (4.6%) gave up the immunotherapy, for any reasons apart from SCIT-related adverse reactions; 114 patients (43.7%) completed the treatment; and 135 patients (51.7%) continued to receive SCIT during the course of the study.

A total of 12,284 injections were applied to all patients; 23.0% (*n* = 2831) of which were in grass pollen season (Table 2). Majority of these adverse reactions were resulted in local (*n* = 357, 2.9% of all

injections) followed by systemic ($n = 55$, 0.4%) and large local reactions ($n = 40$, 0.3%), respectively. When we consider the number of each reaction type per treatment year/per patient at risk, the incidence rates for local, large local, and systemic reactions were 13.5%, 3.7%, and 4.3%, respectively. Of the injections administered during the grass pollen season ($n = 2831$, 23.0%), 3.5% ($n = 99$) resulted in local, 0.4% ($n = 10$) resulted in large local, and 0.7% ($n = 22$) occurred as systemic reactions (Table 2). Frequency of local and systemic reactions was significantly higher in grass pollen season than during out of the grass pollen season ($P < .001$ for local, $P = .003$ for systemic reactions) (Table 2). In addition, large local reactions were more common during the grass pollen season ($P = .769$). Although local reactions were significantly observed in the buildup period ($P < .001$), large local ($P = .622$) and systemic reactions ($P = .487$) were more likely to occur in maintenance period with no statistical significance. Total IgE levels, SPT and sIgE values applied for grass pollen allergens that the patient underwent SCIT for, age at the first dose of SCIT were not different among the adverse reactions except for eosinophil percentage (P for tend = .023) (Figure 1).

Patients with large local and/or systemic reactions ($n = 59$, 22.6%) had elevated percentage of eosinophils ($P = .034$), increased frequency of local reactions ($P < .0001$), and were initiated to the immunotherapy significantly in grass pollen season compared to the patients with local reactions or without adverse reactions ($P = .016$) (Table 3).

Sixty-six (25.3%) patients had polysensitization with other aeroallergens which was determined by SPT (Figure 2). Patients with polysensitization had older age of initiation of SCIT ($P < .001$), increased SPT values (for grass pollen allergens that SCIT administered for) ($P < .001$), elevated total IgE ($P < .001$), eosinophil count ($P < .001$), and eosinophil percentage ($P < .001$) compared to the monosensitized patients. Furthermore, polysensitized patients had increased frequency of asthma ($P < .001$) and large local reactions ($P < .001$), but not local ($P = .581$) or systemic reactions ($P = .926$) compared to monosensitized participants.

Initiation of SCIT during the grass pollen season, percentage of eosinophils, and local reactions appeared to correlate with large local and systemic reactions in univariate analysis. Multivariate analysis revealed initiation of SCIT during the grass pollen season [OR: 7.351, 95%CI: 1.532-35.279, $P = .013$] and experiencing local reactions [OR: 4.214, 95%CI: 2.159-8.224, $P < .001$] as

independent predictors for the development of large local and systemic reactions (Table 4).

We further performed multiple logistic regression analysis for the risk factors for the development of large local and systemic reactions both during the grass pollen season (Supplementary Table S1) and out of the grass pollen season (Supplementary Table S2). Analysis revealed that initiation of SCIT in grass pollen season [OR: 32.854, 95%CI: 1.489-724.659, $P = .027$] was the independent risk factor; however, older age of SCIT initiation [OR: 0.769, 95%CI: 0.603-0.980, $P = .033$] was the preventive factor for large local and systemic reactions during the grass pollen season (Supplementary Table S1). Additionally, local reactions [OR: 2.802, 95%CI: 1.407-5.581, $P = .003$] were the only risk factor for experiencing large local and systemic reactions in immunotherapy during out of the grass pollen season (Supplementary Table S2).

4 | DISCUSSION

Results of the current study suggested that initiation of SCIT in grass pollen season and local reactions are independent predictors for large local and severe reactions during the grass pollen immunotherapy in children. Moreover, initiation of SCIT during the grass pollen season was an independent risk factor, whereas older age of the initiation of SCIT was a preventive factor for large local and systemic reactions during the grass pollen season. Local reactions were the only risk factor for large local and systemic reactions during out of the grass pollen season. Majority of the adverse reactions were local and frequently seen during the grass pollen season and the buildup period. Nevertheless, systemic and large local reactions were frequently observed during the grass pollen season and the maintenance period.

In the current study, initiation of SCIT during the grass pollen season was a predictor for large local and severe systemic reactions during the immunotherapy in children. Similarly, administration of allergen immunotherapy during the grass pollen season has been reported as a risk factor for systemic reactions.¹⁴ According to guidelines,^{15,16} SCIT should not be started during the grass pollen season due to increased risk of adverse effects in this season. We observed increased frequency of all types of adverse reactions, especially local and systemic reactions, during the grass pollen season as indicated

TABLE 2 Type of the reactions during grass pollen subcutaneous immunotherapy

Total number of injections ($n = 12,284$)	In grass pollen season ($n = 2831$)	Out of grass pollen season ($n = 9453$)	<i>P</i> value	Buildup period ($n = 3183$)	Maintenance period ($n = 9101$)	<i>P</i> value
Total number of injections resulting in LR ($n = 357$)	99/3.5%	258/2.7%	<.001	175/5.6%	190/2.0%	<.001
Total number of injections resulting in LLR ($n = 40$)	10/0.4%	30/0.3%	.769	9/0.3%	31/0.4%	.622
Total number of injections resulting in SR ($n = 51$)	22/0.7%	33/0.3%	.003	12/0.4%	43/0.5%	.487

Abbreviations: LLR, large local reaction; LR, local reaction; SR, systemic reaction.

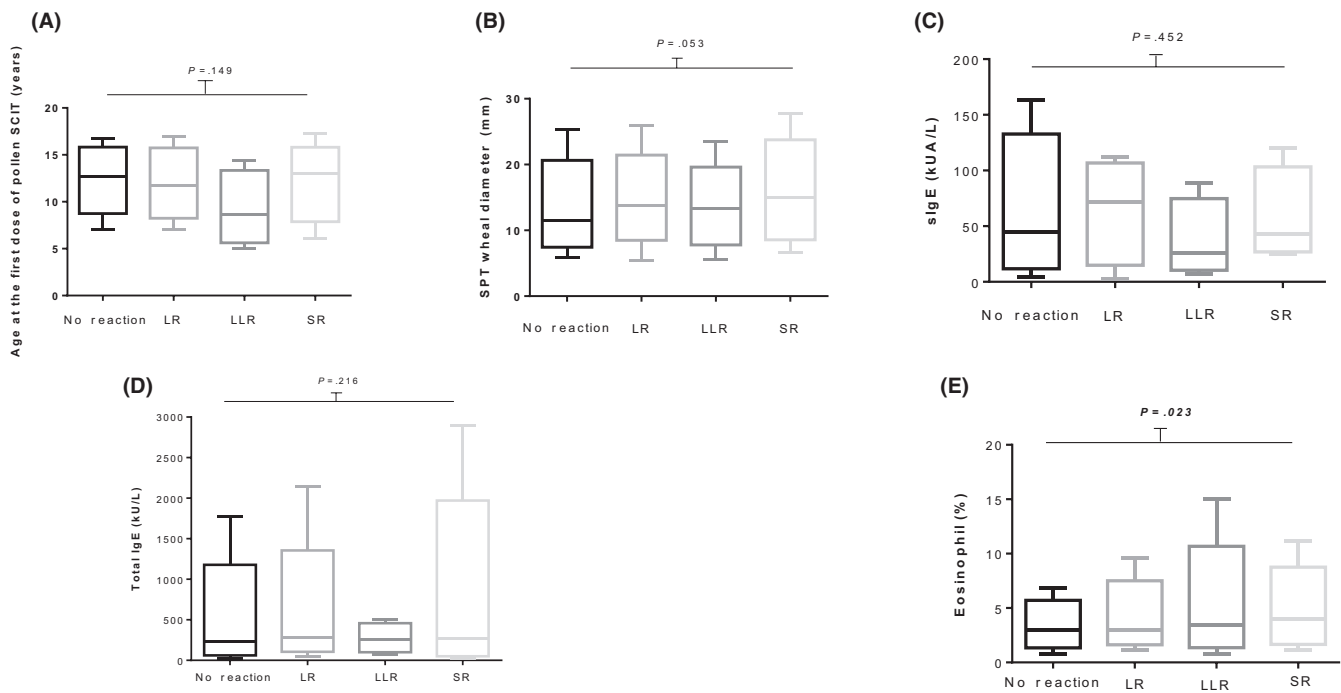


FIGURE 1 Differences in patients with LR, LLR, and SR and without any reactions in regard with A, age at the first dose of grass pollen SCIT (years), B, SPT wheal diameters (mm) for grass pollen at the beginning of SCIT, C, sIgE (kUA/L) for grass pollen at the beginning of SCIT, D, total IgE (kU/L) at the beginning of grass pollen SCIT, E, eosinophil in percent at the beginning of grass pollen SCIT

TABLE 3 Differences in the patients with vs. without large local and/or systemic reactions

	Patients with LLR and/or SR (n = 59)	Patients without LLR and/or SR (n = 202)	P value
Age at the first dose of grass pollen SCIT (years) ^a	12.3 (8.8-14.3)	12.2 (10.1-14.6)	.340
Gender (male)	44 (74.6%)	133 (65.8%)	.207
Polysensitization with other pollens (n/%)	17 (28.8%)	49 (24.3%)	.498
SPT wheal size (mm) ^a	13.5 (10.0-17.7)	12.5 (9.5-16.0)	.296
sIgE value (kUA/L) ^a	44.7 (24.7-98.7)	68.7 (25.3-106.0)	.544
Eosinophil (%) ^a	3.7 (2.2-6.3)	3.0 (2.0-4.8)	.034
Total IgE (kU/L) ^a	254.5 (110.7-558.0)	286.0 (140.5-656.0)	.506
Initiation of SCIT in grass pollen season (n/%)	5 (8.5%)	4 (2.0%)	.016
Presence of LR (n/%)	41 (69.5%)	68 (33.7%)	<.001
Presence of asthma (n/%)	14 (23.7%)	53 (26.2%)	.219
Family history of allergy (n/%)	34 (57.6%)	98 (48.5%)	.733

Abbreviations: LLR, large local reaction; LR, local reaction; SCIT, subcutaneous immunotherapy; SR, systemic reaction.

^aMedian (inter-quartile range—IQR).

previously.¹⁴ Environmental exposure to high burden of grass pollen allergens during the grass pollen season may lead to increased risk of systemic reactions. Therefore, it is recommended that allergen extract dose should not be increased and it should be even reduced during the grass pollen season.¹⁷ In our study, we did not reduce the dose of allergen extract in most of the patients during the grass pollen season, and this may facilitate to observe adverse reactions

more frequently during the grass pollen season as mentioned in a previous report.¹¹

In the current study, local reactions were more frequent during the buildup period, whereas large local and systemic reactions were common during the maintenance period. Besides, these results were compatible with the outcomes of a study consisting of children.¹⁸ Increased frequency of systemic reactions in maintenance period

has been attributed to the cumulative doses during this phase of immunotherapy.¹⁸

Our results showed that local reaction is another independent predictor for large local and severe reactions. Most of the studies reported that local reactions do not predict systemic adverse effects.^{19,20} For this reason, dose adjustment after a local reaction is not recommended. However, as it is understood from our study, there are few contradicting results supporting local reaction as predictor for systemic reaction.^{21,22} Based on these studies and our results, dose adjustment may be necessary in patients who experienced local reactions. Due to all these contradictory data, further studies should be done to evaluate the effect of local reaction for the development of systemic reaction on children.

According to the current study, older age of the initiation of SCIT was protective from large local and systemic reactions during the grass pollen season. Our results are coherent with a previous study²³ reporting that young children are prone to systemic reactions. The reason for increased risk of systemic reaction at young ages has been attributed to administration of the same amount of the allergen

extracts on children from all ages.²³ Therefore, starting with a lower dose of allergen immunotherapy and aiming a lower final dose for younger children have been recommended.²³

Since we did not start grass pollen SCIT in children with severe uncontrolled asthma, we did not find the asthma as a risk factor for systemic reactions in SCIT in contrast to previous studies.¹⁷ Other than asthma, polysensitization and increased allergen sensitivity during systemic reactions have been also shown as risk factors for SCIT.^{24,25} However, we did not identify any relationship between adverse reaction types and neither SPT nor sIgE results. As we could not find SPT and sIgE results for all of the patients, we may say that there is no association between these two parameters and adverse reactions.

In general, as we observed in our study (2.9%) that majority of the resulting adverse reactions following the injections administered to the patients were local.²⁶ In literature, local reactions were reported as 0.38%¹⁸ of the injections on children and as 7.3% on adults.²⁷ On the other hand, 0.32% of the injections resulted in systemic reactions on children during SCIT,²³ and this ratio is 0.80% on adults.²⁷ Similarly, systemic reactions developed in 0.4% of all injections in the current study.

When looking at the ratio of the patients who experienced adverse effects, the ratio of the participants who experienced the local reactions was 26.0%-86.0%,²⁸ and the ratio of the participants who had systemic reactions was 5.0%-7.0%.²⁹ In a study consisting of children,³⁰ the ratio of local reactions was 75.2% and that of systemic reactions was 9.3%. In another study,¹⁸ local, large local, and systemic reactions have been reported in children as 11.9%, 5.0%, and 4.7%, respectively. Our results are higher than literature data especially for large local (11.5%) and systemic reactions (13.4%). Adjuvants, especially in depot forms, used in immunotherapy vaccines also cause adverse effects during SCIT.²¹ Aluminum hydroxide containing extracts, which also we used in our study population, has been shown to cause large local and

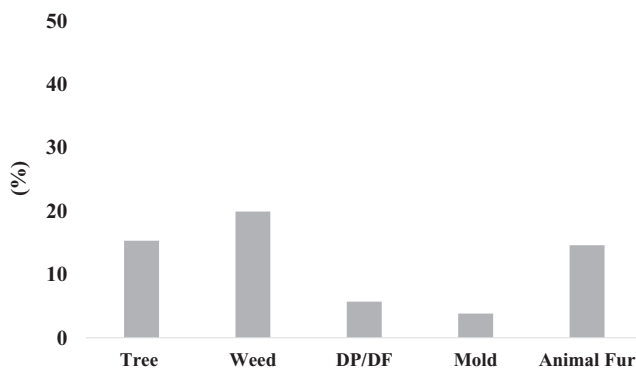


FIGURE 2 Concomitant aeroallergen sensitization of the study population

TABLE 4 Predictive factors for large local and/or systemic reactions during grass pollen subcutaneous immunotherapy

	Univariate			Multivariate		
	OR	% 95 CI	P value	OR	% 95 CI	P value
Age at the first dose of grass pollen SCIT (years)	0.939	0.847-1.040	.227			
Polysensitization with other pollens	1.252	0.653-2.402	.498			
Gender (male)	1.522	0.791-2.927	.208			
SPT wheal size (mm)	1.032	0.972-1.095	.309			
sIgE value (kUA/L)	0.995	0.983-1.008	.442			
Eosinophil (%)	1.146	1.029-1.276	.013	1.121	0.999-1.257	.052
Total IgE (kU/L)	1.000	1.000-1.001	.638			
Initiation of SCIT in grass pollen season	4.583	1.190-17.658	.027	7.351	1.532-35.279	.013
Presence of LR during grass pollen-specific SCIT	4.489	2.399-8.397	<.001	4.214	2.159-8.224	<.001
Presence of asthma	1.443	0.804-2.592	.219			
Family history of allergy	1.158	0.499-2.689	.733			

Abbreviations: LR, local reaction; SCIT, subcutaneous immunotherapy.

systemic reactions.²¹ Aluminum hydroxide containing extracts could represent a potential explanation of the higher number of our patients, who experienced large local and systemic reactions during the immunotherapy, but also other factors could play a role in this phenomenon.

The current study has some limitations. First, it is a retrospectively designed, and there are some missing data related with medical history and laboratory parameters. Second, as this is a single-center study, it is difficult to make generalization based on our data. Despite these limitations, long-term clinical follow-up and a large study population including only children are the most important strengths of the current study. Since we included the children who received SCIT only for grass pollen, not for the other aeroallergens, our study population was homogeneous and therefore we had an objective evaluation.

In conclusion, our study demonstrated that local reaction was the most frequent adverse effect occurred in grass pollen-specific SCIT. It is safe for the treatment of AR in children, in which only mild-to-moderate systemic reactions were observed during the immunotherapy. Our study revealed that local reactions and initiation of the immunotherapy during the grass pollen season were predictors for the large local and systemic reaction during the immunotherapy. There is need of more studies to be able to assess the effect of dose adjustment after local reactions and during the grass pollen season for the prevention of large local and systemic reactions on children.

CONFLICT OF INTEREST

All authors declared that there are no conflict of interest and no funding. All authors approved the final version of the manuscript. The study protocol has been approved by the local ethical committee, and all parents/guardians provided written informed consent.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Supplementary Tables

Supplementary Table 1. Predictive factors for large local and/or systemic reactions during grass pollen specific immunotherapy in grass pollen season

	Univariate			Multivariate		
	OR	% 95 CI	p	OR	% 95 CI	p
Age at the first dose of grass pollen specific SCIT (years)	0.891	0.769-1.031	0.121	0.769	0.603-0.980	0.033*
Gender (male)	1.563	0.600-4.071	0.360			
Polysensitization with other pollens	0.693	0.249-1.926	0.482			
SPT wheal size (mm)	1.011	0.924-1.105	0.816			
sIgE value (kUA/L)	1.009	0.992-1.026	0.325			
Eosinophil (%)	1.104	0.964-1.264	0.153			
Total IgE (KU/L)	1.000	1.000-1.001	0.376			
Initiation of SCIT in grass pollen season	14.500	3.605-58.324	<0.001	32.854	1.489-724.659	0.027*
Presence of LR in grass pollen season	2.026	0.792-5.185	0.141			
Presence of asthma	1.065	0.467-2.431	0.881			
Family history of allergy	0.363	0.092-1.433	0.148			

LR; Local Reaction, SCIT; Subcutaneous immunotherapy

Supplementary Table 2. Predictive factors for large local and/or systemic reactions during grass pollen specific immunotherapy out of grass pollen season

	Univariate			Multivariate		
	OR	% 95 CI	p	OR	% 95 CI	p
Age at the first dose of grass pollen specific SCIT (years)	0.988	0.882-1.108	0.839			
Gender (male)	0.980	0.487-1.970	0.954			
Polysensitization with other pollens	1.548	0.758-3.160	0.230			
SPT wheal size (mm)	1.038	0.972-1.108	0.262			
sIgE value (kUA/L)	0.991	0.976-1.006	0.237			
Eosinophil (%)	1.114	0.993-1.249	0.066			
Total IgE (kU/L)	1.000	0.999-1.000	0.807			
Initiation of SCIT out of the grass pollen season	0.680	0.136-3.391	0.638			
Presence of LR out of grass pollen season	2.937	1.504-5.734	0.002	2.802	1.407-5.581	0.003*
Presence of asthma	1.441	0.744-2.792	0.279			
Family history of allergy	1.691	0.644-4.440	0.286			

LR; Local Reaction, SCIT; Subcutaneous immunotherapy