

Risk stratification of systemic reactions to subcutaneous immunotherapy: A retrospective study

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ABSTRACT

Background: Subcutaneous allergen immunotherapy (SCIT) is a very effective treatment modality; however, it can be associated with both local and systemic reactions (SR). Identifying patient factors that predict SR remains paramount.

Objective: Our aim was to identify the rate of SRs to SCIT as well as identify patient risk factors associated with the development of SRs.

Methods: We conducted an institutional review board approved 10-year retrospective chart review of 459 patients who received SCIT in our clinic. The patients were placed into cohorts according to age, which included pediatric (5–18 years), adult (19–64 years), and senior (>65 years) patients.

Results: An SR ($N = 177$) was identified in 24.8% of the patients ($n = 114$). The incidence of SR per injection was 0.2% (177 SRs of 74,183 total injections). SRs were identified as class 1 ($n = 152$), class 2 ($n = 21$), class 3 ($n = 2$), and class 4 ($n = 2$) according to the 2010 World Allergy Organization's SR grading system. There were no observed differences in the number of SRs with respect to age group. Female patients were more likely to have an SR ($p = 0.02$) overall as well as more than one reaction ($p = 0.002$). Other risk factors included the following: a patient-reported history of food allergy ($p = 0.05$), drug allergy ($p = 0.005$), or positive skin test result to cat and/or dog ($p = 0.01$). In addition, patients who were receiving SCIT to cat and/or dog ($p = 0.004$) or to dust mite ($p = 0.03$) were more likely to have an SR.

Conclusion: In our patient population, the majority of SRs to SCIT occurred in female patients, patients with a history of drug or food allergies, and those who were receiving pet or dust-mite SCIT.

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Subcutaneous allergy immunotherapy (SCIT) is efficacious in patients with allergic rhinitis, asthma, and venom allergy. Candidates for immunotherapy (IT) include patients whose symptoms are not well controlled with medication, patients who cannot tolerate the adverse effects of medication, or those who wish to reduce prolonged use of such medications.¹ However, despite the apparent clinical benefits, SCIT can be associated with local reactions as well as with life-threatening systemic reactions (SR). The prevalence of SRs with SCIT ranges from <1% of patients who receive conventional IT to ~34% of patients who receive rush IT (with premedication).¹ The percentage of SRs per injection with conventional schedules is ~0.2%.¹ Since 2008, there have been seven reported fatalities from SCIT injections.^{2,3}

Although there have been several studies to determine the safety and efficacy of SCIT in adults, there have not been nearly enough studies in pediatric and elderly populations. A study done by Eidelman and Darzentas⁴ in 50 adults (ages < 60 years) and 26 elderly patients (ages > 60 years) demonstrated that SCIT was effective in the elderly, with good results in symptom improvement, similar to adults. Both patient groups had similar reductions in mean symptom scores and mean medication scores.⁴ There was no significant difference in local or SR rates in either age group.⁴ A study by Asero⁵ found that SCIT is equally effective in both geriatric and pediatric patients. This is clinically vital because *de novo* sensitization in elderly patients has been noted.⁵ With few published studies available, health-care providers may be wary of administering SCIT to pediatric and elderly populations, although there is currently no upper or lower age limit for the initiation for SCIT.¹ Our aim was to identify the rate of SRs to SCIT in our patient population and to identify patient risk factors associated with the development of SRs.

METHODS

An institutional review board-approved (NYU Winthrop Hospital; reference 16415) 10-year retrospective chart review was conducted on 459 patients who received SCIT in our allergy/immunology clinic. For this

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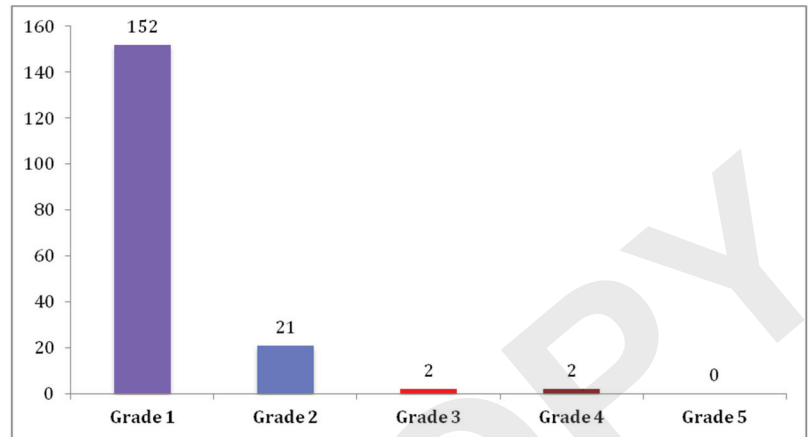


Figure 1. Systemic reactions by grade.

review, the patients were placed into cohorts according to age and included the following: pediatric (ages 5–18 years), adult (ages 19–64 years), and senior (ages ≥ 65 years) patients. The inclusion criterion for the study was all patients who received SCIT to aeroallergens *via* a conventional schedule. The patients who received rush IT or venom IT were excluded from analysis. Data gathered for statistical analysis included patient demographics (age, gender), allergic history (self-reported history of asthma, allergic rhinitis, atopic dermatitis, food or drug allergy), skin-prick test or specific immunoglobulin E results to aeroallergens, treatment allergens administered *via* SCIT and the rate and/or severity, and treatments of all SRs.

SRs were classified according to the 2010 World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System⁶ (Fig. 1), which was the criteria available at the start of data collection. Grade 1 SRs involve signs and/or symptoms of one organ system (cutaneous, upper respiratory, or conjunctival). Grade 2 SRs involve signs and/or symptoms of more than one organ system or involvement of the lower respiratory tract or the gastrointestinal system. Grade 3 SRs involve lower respiratory symptoms that do not respond to inhaled bronchodilators or upper respiratory symptoms, *e.g.*, laryngeal edema. Grade 4 SRs involve respiratory failure or cardiovascular collapse (*i.e.*, hypotension with or without loss of consciousness). A grade 5 SR is classified as death.

Statistics

Counts and percentages were computed to summarize the data overall and within specific groups of interest. The χ^2 and Fisher exact tests were used to test for the overall association between two categorical variables. Kruskal-Wallis nonparametric tests were used to test for distributional differences in the number of SRs between the groups, such as those defined by age and gender. All *p* values are two-sided, and *p* < 0.05 were considered statistically significant.

Table 1 Patient demographics

	<i>n</i> (%)
Age group	
Pediatric (range, 5–18 y)	90 (19.6)
Adult (range, 19–64 y)	335 (73)
Senior (range, 65–88 y)	34 (7.4)
Gender	
Males	196 (42.8)
Females	263 (57.2)
Condition	
Asthma	264 (57.5)
Allergic rhinitis	434 (94.5)
Atopic dermatitis	56 (12.2)
Contact dermatitis	21 (4.5)
Drug allergy	111 (24.18)
Food allergy	87 (18.9)

RESULTS

A total of 459 patients were included for data analysis (Table 1). The patients were placed into cohorts according to their age group. Our subjects included 90 pediatric (ages 5–18 years), 335 adult (ages 19–64 years), and 34 senior (ages ≥ 65 years) patients. There were a total of 177 SRs among 114 patients. The SRs were classified according to the 2010 World Allergy Organization grading scale¹: grade 1 (*n* = 152), grade 2 (*n* = 21), grade 3 (*n* = 2), and grade 4 (*n* = 2). There were no grade 5 reactions. The majority of SRs (97% [*n* = 173]) were grade 1 (*n* = 152) or grade 2 (*n* = 21). A total of 74,183 injections were evaluated. The incidence rate for any SR was 0.2% (177 reactions of 74,183 total injections).

There were no observed differences in the number of SRs with respect to age group, *p* = 0.39 (Table 2). Twenty-one percent (*n* = 19) of the pediatric patients had at least one SR versus 26% of adult patients (*n* = 88) and 21% of seniors (*n* = 7). There also were similar rates of more than one reaction among pediatric pa-

Table 2 SRs by age group and gender

SR	Pediatric, <i>n</i> (%)	Adult, <i>n</i> (%)	Senior, <i>n</i> (%)	Male, <i>n</i> (%)	Female, <i>n</i> (%)
None	71 (79)	247 (74)	27 (79)	158 (81)	187 (71)
1	12 (13)	47 (14)	4 (12)	26 (13)	37 (14)
>1	7 (8)	41 (12)	3 (9)	12 (6)	39 (15)

SR = Systemic reaction.

Table 3 Number of systemic reactions by age group

Grade	Pediatric	Adult	Senior
1	22	121	9
2	4	17	0
3	0	2	0
4	0	2	0
5	0	0	0

Table 4 Systemic reaction rate based on allergic history

	Systemic Reaction, <i>n</i> / <i>N</i> (%)		<i>p</i>
	Present	Absent	
Drug allergy	39/111 (35.1)	75/348 (21.6)	0.005
Food allergy	29/87 (33.3)	85/372 (22.9)	0.05
Atopic dermatitis	18/56 (32.1)	96/403 (23.8)	0.19
Asthma	69/264 (26.1)	45/195 (23.1)	0.51
Contact dermatitis	5/21 (23.8)	109/438 (24.9)	>0.999

tients (8%), adult patients (13%) and senior patients (9%) ($p = 0.48$). All the SRs in the pediatric population were grade 1 ($n = 22$) or grade 2 ($n = 4$). Almost all SRs in the adult population were grade 1 ($n = 121$) or grade 2 ($n = 17$), with only a couple of grade 3 ($n = 2$) and grade 4 ($n = 2$) reactions. All the SRs in the senior population were grade 1 ($n = 9$) (Table 3).

With respect to gender, female patients were more likely to have an SR ($p = 0.02$) as well as more than one SR ($p = 0.002$) (Table 2). With respect to allergic history, associated risk factors in patients with an SR included the following: self-reported history of food allergy ($p = 0.05$), drug allergy ($p = 0.005$), or positive skin test result to cat and/or dog ($p = 0.01$) (Tables 4 and 5). In addition, the patients who received SCIT to cat and/or dog ($p = 0.004$) or to dust mite ($p = 0.03$) were more likely to have an SR (Table 6). There was no association between the total number of allergen ex-

Table 5 Systemic reaction rate based on skin test results

	Systemic Reaction, <i>n</i> / <i>N</i> (%)		<i>p</i>
	Positive Skin Test Result	Negative Skin Test Result	
Pets	83/288 (28.8)	31/171 (18.3)	0.01
Dust mite	99/369 (26.8)	15/90 (16.7)	0.06
Tree	91/340 (26.8)	23/119 (19.3)	0.11
Grass	78/302 (25.8)	36/157 (22.9)	0.57
Weed	73/298 (24.5)	41/161 (25.5)	0.82
Mold	26/124 (21)	88/335 (26.3)	0.27

Table 6 Systemic reaction rate based on treatment allergen

	Systemic Reaction, <i>n</i> / <i>N</i> (%)		<i>p</i>
	IT	No IT	
Pets	83/281 (29.5)	31/178 (17.4)	0.004
Dust mite	100/370 (27.0)	14/89 (15.7)	0.03
Tree	90/340 (26.5)	24/119 (20.2)	0.18
Grass	78/302 (25.8)	36/157 (22.9)	0.57
Weed	76/302 (25.2)	38/159 (24.2)	0.91
Mold	26/120 (21.7)	88/339 (26.0)	0.39

IT = Immunotherapy.

tracts that a patient received and having a SR ($p = 0.112$). In addition, we did not find a relationship between the number of unrelated allergen extracts contained in the IT treatment and having an SR, *i.e.*, the median number of allergen extracts among patients who received cat, dog, or dust-mite IT did not statistically differ between the patients who had an SR versus the patients who did not have an SR ($p = 0.751$). There was no significant association with large local reactions (LLR) that predicted SRs with subsequent injections in our population ($p = 0.06$).

Almost all SRs occurred during the buildup phase of SCIT (171 reactions occurred in the patients during the buildup, and six reactions occurred in the patients who were receiving maintenance). Intramuscular epineph-

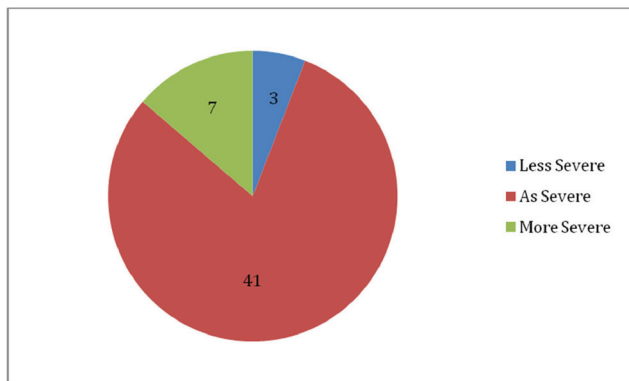


Figure 2. Severity of subsequent systemic reactions (SR).

rine was administered 49 times. All grade 3 and grade 4 reactions were treated with epinephrine. Epinephrine was administered 30 times for grade 1 reactions and 15 times for grade 2 reactions. Other treatment modalities for grades 1 and 2 reactions included oral and/or intramuscular antihistamines, oral corticosteroids, nasal antihistamines, and/or nebulizer treatments. Treatment modalities for each SR were based on the attending physician's discretion.

With regard to subsequent SRs, we did not find an increased odds risk for the occurrence of an SR after the patient had one SR. Among 114 patients who had at least one SR, 44.7% ($n = 51$) had another reaction compared with 55.3% ($n = 63$) of the patients who did not have further reactions ($p = 0.261$). The severity of subsequent reactions is illustrated in Fig. 2. A majority of the patients ($n = 41$) experienced reactions that were as severe as their index reaction, whereas seven patients experienced more-severe reactions, and three patients experienced less-severe reactions.

DISCUSSION

In our study, a total of 74,183 injections were administered to 459 patients and a total of 177 SRs were observed in 114 of these patients. Similar to other published studies, Patients who had SRs were observed in ~0.2% of all injections.^{1,2} Our study was in line with other literature that demonstrated that SCIT is relatively safe, and the number of SRs remained low. In addition, when categorizing the types of SRs, the majority of our reactions were grade 1 and grade 2. There were no fatalities observed in our study.

A retrospective study by Lim *et al.*⁷ compared pediatric and adult SRs when using SCIT. Their study evaluated 120 children and 150 adults; there were a total of 132 SRs among 74 subjects. The incidence of overall SRs was significantly higher in children than in adults ($p < 0.001$), but, when adjusting for gender, phase of SCIT (build-up vs. maintenance), and presence of asthma, was not significant.⁷ A study in 2016 by Bozek *et al.*⁸ examined the safety and efficacy of grass-

specific SCIT in an elderly population and found a safety profile similar to that of younger populations.⁸ In our review, we found that overall SR rates were low and that there was no significant association between age and having a SR (although the number of senior patients was small), which thus reiterates that SCIT can be safe for patients across all age groups. In addition, all SRs in our elderly population were mild (grade 1). Several studies have not shown a significant association between SRs and gender.^{9–11} Interestingly, in our study population, the female patients were more likely to have an SR than their male counterparts (after statistical adjustment for the relative counts of each gender). In addition, the female patients were also more likely to have recurrent SRs.

LLRs are fairly common with aeroallergen SCIT, and a majority of published studies ascertained that LLRs are poor predictors of SRs on subsequent encounters.^{1,12} There, however, are a smaller number of published studies that found that the odds of having LLRs were significantly increased among patients who had systemic allergic reactions.^{13,14} In our study, we did not find an association between SRs and LLRs because both patients with SRs and those without SRs had similar rates of LLRs.

A history of asthma has been reported to be a risk factor in the development of SRs after receiving SCIT.^{15,16} Results of other studies showed that uncontrolled asthma is the greatest risk factor.^{17,18} In our review, a history of asthma was not a significant risk factor for SR. The patients in our study were screened for asthma control *via* a questionnaire before receiving injections, and those with active symptoms were not given their injections.

Animal allergy (cat and/or dog) may be the most common perennial allergen based on skin test results.¹⁹ Also, these allergens can be found in nearly 90% of homes and other indoor areas. They are present in areas without the presence of pets, such as offices and school buildings, and can be transferred by clothing, shoes, and hair.²⁰ In a prospective, longitudinal study conducted by Calderon *et al.*,²¹ the patients sensitized to animal dander or pollen were significantly more likely to experience SRs. Similarly, in our study, we found that patients with positive skin test results to cat and/or dog were more likely to experience SRs.

The type of allergen extract administered has been one of the proposed variables for SR development. Several studies^{22,23} reported more adverse effects with the administration of indoors allergens compared with outdoor allergens. A study done by Alsamarai *et al.*²² found that SCIT with cat, mold, and dust mite were predictive for the development of SRs. Similarly, another study, by Mallerup *et al.*²³ found that SCIT with cat and dust-mite allergen extracts had the highest frequency of SRs. Similarly, in our review, those pa-

tients who received SCIT to cat, dog, and/or dust mite were more likely to experience SRs.

Calderon *et al.*,²¹ noted that the majority of SRs experienced by patients occurred in the buildup phase but were deemed to be mild. Tinkelman *et al.*,¹⁹ however, found that his patients had reactions in both phases (build-up and maintenance). They report that four patients had reactions with the first dose of the weakest concentration but that four different patients also had reactions after receiving their injections for > 2 years (in the maintenance phase).¹⁹ Almost all SRs (96%) occurred during the buildup phase in our study.

The limitations of this study included its retrospective design and relatively small sample size (particularly in the elderly population). In addition, factors that were not investigated in our study but that warrant further investigation include the impact of co-seasonal administration of SCIT, the degree of skin-prick test reactivity or level of allergen-specific immunoglobulin E, the severity of asthma for patients with SRs, and the impact of coexisting medical conditions and concomitant use of medications, *e.g.*, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and β -blockers.

CONCLUSION

Our review reiterated and confirmed that the prevalence of SRs to SCIT was present but remained low. The majority of SRs in our patient population were grades 1 and 2, with only a small number of grade 3 and/or grade 4 reactions, and zero fatal reactions. There were no significant differences in the incidence of SRs with regard to age group (pediatric versus adult versus senior), which thus reiterated that SCIT can be a safe and effective therapy for patients of all age groups. In this study, the majority of SRs to SCIT occurred in female patients, patients with drug or food allergies, and those who received IT to pet or dust mite. Larger, multicenter, prospective studies are warranted to further assess if these patient subsets are at higher risk for SRs and would require more cautious administration of SCIT.

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