

Retrospective evaluation of adverse reactions after subcutaneous allergen-specific immunotherapy in children with house dust mite allergy

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ABSTRACT

OBJECTIVE: Although it is accepted as an effective and safe treatment way, side effects can be observed as a result of subcutaneous immunotherapy (SCIT). In our study, it was aimed to evaluate the local and systemic reactions in children after SCIT and the factors that may be associated with these reactions.

METHODS: Our study included 138 house dust mite allergic patients with asthma and/or allergic rhinitis who underwent SCIT in the Pediatric Allergy and Immunology Outpatient Clinic between November 2013 and April 2022. Sociodemographic, clinical, laboratory features, and development of adverse reactions after SCIT were analyzed from patient files.

RESULTS: The median age of 138 patients was 9.0 years. About 56.5% (n=78) were male, 43.5% (n=60) were female. Of the patients, 55.1% (n=76) had asthma and allergic rhinitis. A total of 7366 SCIT injections were administered to all patients in our clinic. The total number of observed adverse reaction was 118. 50.7% of the patients (n=70) experienced at least one adverse reaction after SCIT. The rate of development of adverse reactions per injection was 1.6% (local: 1.0%, large local: 0.1%, systemic: 0.5%).

CONCLUSION: Although serious systemic reactions and death were not observed in our patients; care should be taken in terms of the development of adverse reactions during SCIT in children.

Keywords: Adverse reaction; allergic rhinitis; asthma; subcutaneous immunotherapy.

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Subcutaneous allergen immunotherapy is the use of repeated doses of a specific allergen for the treatment of IgE-mediated allergic disease [1]. The method takes place in the form of a build-up phase and a maintenance phase. During the build-up phase, the relevant allergen is administered by subcutaneous injections, starting with low doses and increasing the dose at regular intervals until the optimal dose is reached. After the optimal dose, the maintenance phase is started [2–4].

Subcutaneous immunotherapy (SCIT) has been used frequently as a treatment option for allergic diseases for many years. Immunotherapy treatment and avoidance of allergen exposure are etiology-based treatment options in the control of allergic rhinitis and asthma [5].

Safety and effectiveness of SCIT are proven in the treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma, and hypersensitivity to bee venom [6]. Although it is accepted as an effective and safe treatment

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way, adverse reactions can be observed as a result of SCIT. These adverse reactions are examined in two categories as local and systemic. Local adverse reactions can be seen as redness, itching, and swelling at the injection site. A study conducted in our country states the rate of local reactions and large local reactions after SCIT as 17.8% and 10.9%, respectively, in pediatric patients [7]. Systemic reactions can affect many systems such as the skin, respiratory system, gastrointestinal system (GIS), and cardiovascular system. Systemic reactions can be seen as mild allergic rhinitis symptoms and may occur even in the form of fatal reactions such as severe anaphylaxis affecting the cardiac system [8]. Systemic reactions are rare and their prevalence after injection doses varies between 1% and 0.1%. Fatal reactions are also very rare. In the literature, one fatal reaction per 7.2 million SCIT injection doses has been reported [9]. The presence of immune deficiency, chronic infections, autoimmune diseases in remission, and being between 2 and 5 years old are some of the relative contraindications of AIT. Moreover, being under the age of 2, having malign diseases, uncontrolled asthma, or active autoimmune diseases are some of the absolute contraindications of AIT [10–12].

Although SCIT has been shown to be an effective and safe treatment, clinicians should be alert about adverse reactions related to SCIT. In this context, our study aimed to evaluate the frequency of local and systemic reactions in children after SCIT and the related factors that may be associated with these reactions.

MATERIALS AND METHODS

Our study included house dust mite allergic 138 patients with asthma and/or allergic rhinitis who underwent SCIT between November 2013 and April 2022 in the Department of Pediatric Allergy and Immunology. Sociodemographic characteristics of the patients, allergy diagnoses, laboratory parameters (eosinophil, Total IgE), number of SCIT injections, and development of adverse reactions after injections were retrospectively evaluated from patient files. Adverse reactions are classified as local, large local, and systemic. If the swelling and/or redness at the injection site was 2–5 cm in diameter, it was accepted as a local adverse reaction, and if it was >5 cm, it was accepted as a large local adverse reaction. The occurrence of adverse reaction in one or more organ systems is defined as a systemic reaction. Systemic adverse reactions are categorized according to the World Allergy Organization's grading system

Highlight key points

- A total of 7366 SCIT injections were administered to all patients in our clinic. The total number of adverse reactions was 118.
- The rate of development of adverse reactions per injection was found to be 1.6%.
- Care should be taken in terms of the development of adverse reactions during SCIT in children.

[13]: Grade 1: Symptoms are seen in an organ system (skin, upper respiratory tract, conjunctival, etc.); Grade 2: Findings in more than one organ system; Grade 3: Lower respiratory tract (bronchospasm, cough, wheezing, etc.), GIS findings; Grade 4: bronchospasm that does not respond to or worsens with treatment, laryngeal edema with stridor; and Grade 5: Lower or upper respiratory tract failure, cardiovascular system findings such as hypotension, loss of consciousness.

Allergen Specific Immunotherapy

Standardized depot extracts were used during SCIT. One injection per week during the build-up phase was given to the patients receiving house dust mite immunotherapy. The maintenance phase was started approximately 4–8 weeks later and injections were administered once a month during this period. SCIT injections were administered subcutaneously by a doctor and a trained nurse in the outpatient setting. Before the injection, the patients were asked about their current complaints. Injection doses of patients describing asthma-related complaints were delayed for 7 days. During the build-up phase, patients should receive at least 1 h after injection. In the maintenance phase, they were followed in the hospital for at least half an hour for the development of side effects. Appropriate treatment was given to patients who developed systemic and extensive local side effects and the dose of subsequent injection treatments was adjusted accordingly. Antihistaminic premedication was used in patients with recurrent local reactions.

Statistics

Statistical evaluation was performed using IBM SPSS Version 25.0 (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp, Chicago/USA). In the study, median, minimum, and maximum values, numbers (n), and percentages (%) were used for descriptive data. Chi-square test was used for the analysis of the categorical data. The conformity of continuous variables to

TABLE 1. Socio demographic, clinical, and laboratory features of the patients

	Median	Min.	Max.
Age (years)	9.0	5.0	17.0
Gender (%)			
Male		78 (56.5)	
Female		60 (43.5)	
Diagnosis (%)			
Asthma+allergic rhinitis		76 (55.1)	
Allergic Rhinitis		46 (33.3)	
Asthma		16 (11.6)	
Total IgE (IU/mL)	287.50	20.00	4782.00
Eosinophil (absolute) (10 ³ /uL)	380.00	10.00	2530.00
Eosinophil (%)	5.00	0.10	20.50

Min: Minimum; Max: Maximum.

normal distribution was examined by visual (histogram and probability charts) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk tests). Mann–Whitney U test was used for the comparison of more than two groups, which did not fit the normal distribution. Statistical significance level was determined as $p < 0.05$.

Ethics

Ethics committee approval was obtained from the Ethics Committee of studied hospital on September 29, 2022, with decision number 311. The study was carried out in accordance with the Declaration of Helsinki Principles, no personal information was asked to reveal the private lives and/or identities of the participants, and the security of the data was ensured.

RESULTS

In the study, 138 patients who underwent SCIT between November 2013 and April 2022 in the Department of Pediatric Allergy and Immunology were evaluated. The median age of the patients was 9.0 (5.0–17.0) years. 56.5% ($n=78$) of the patients were male and 43.5% ($n=60$) were female. The clinical diagnoses of the patients were asthma and allergic rhinitis (55.1%), allergic rhinitis (33.3%), and asthma 11.6%. When the laboratory values of the patients were examined, the median values of total IgE, eosinophil (absolute), and eosinophil (%) were 287.5 IU/mL (20.0–4782.0), 380.0 10³/uL (10.0–2530.0), and 5.0% (0.1–20.5), respectively (Table 1).

TABLE 2. Features of reactions seen in patients

	(n) %
Number of total injections (n)	7366
Injection number per patients, median (min–max)	54.0 (6.0–110.0)
Occurrence of reaction	
Yes	70 (50.7)
No	68 (49.3)
Number of reactions during therapy period	
1	70 (100.0)
2	35 (50.0)
3	10 (14.3)
4	3 (4.3)
Total	118 (100)
First reaction	
Reaction type	
Local	42 (60.0)
Wide local	4 (5.7)
Systemic	24 (34.3)
Injection in which the reaction occurred, median (min–max)	17.5 (1.0–67.0)
Second reaction	
Reaction type	
Local	23 (65.7)
Wide local	2 (5.7)
Systemic	10 (28.6)
Injection in which the reaction occurred, median (min–max)	24.0 (3.0–71.0)
Third reaction	
Reaction type	
Local	7 (70.0)
Wide local	0 (0)
Systemic	3 (30.0)
Injection in which the reaction occurred, median (min–max)	30.0 (20.0–68.0)
Fourth reaction	
Reaction type	
Local	2 (66.7)
Wide local	1 (33.3)
Systemic	0 (0.0)
Injection in which the reaction occurred, median (min–max)	30.0 (21.0–32.0)

Min: Minimum; Max: Maximum.

A total of 7366 SCIT injections were administered to all patients in our clinic. The total number of adverse reactions was 118. The total number of systemic reactions was 37, local and large local reactions were 74 and 7, respec-

TABLE 3. Grading of systemic reactions

Grading of systemic reactions	Reactions							
	1. reaction		2. reaction		3. reaction		4. reaction	
	n	%	n	%	n	%	n	%
Grade 1	13	54.2	6	60.0	2	66.7	–	–
Grade 2	7	29.2	3	30.0	1	33.3	–	–
Grade 3	4	16.7	1	10.0	–	–	–	–
Grade 4	–	–	–	–	–	–	–	–
Grade 5	–	–	–	–	–	–	–	–

tively. The rate of development of adverse reactions per injection was 1.6% (Local: 1.0%, large local: 0.1%, systemic: 0.5%). At least one reaction was observed after injection in 50.7% of the patients (n=70). Local reactions were seen in 30.4% (n=42) of 138 patients who underwent SCIT, large local in 2.9% (n=4), and systemic reactions in 17.4% (n=24). Two of the 4 patients with large local reactions have developed local reactions in further SCIT application; and in one patient with previous large local reactions, systemic reaction was developed during SCIT.

Adverse reactions were observed in two different injection doses in 35 of 70 patients, three different injection doses in 10, and four different injection doses in three patients. In patients who developed at least one adverse reaction; 60.0% of the first reaction was local, 5.7% was large local, and 34.3% was systemic reaction. Median dose of the first adverse reaction development was 17.5 dose. In patients who developed side effects twice, the second adverse reaction was local in 65.7%, large local reaction in 5.7%, and systemic reaction in 28.6%. The median injection number of second adverse reaction was 24. In patients who developed adverse reactions 3 times, 70.0% of the third adverse reaction was local and 30.0% was systemic reaction. The median injection number of second adverse reaction was 30. Of the three patients who developed adverse reactions 4 times, two had local adverse reactions and one had large local adverse reaction (Table 2).

No Grade 4 and Grade 5 adverse reactions were observed in patients with systemic adverse reactions. Of 24 patients who had at least one systemic reactions, 54.2% had Grade 1, 29.2% had Grade 2, and 16.7% had Grade 3 systemic reactions. Of the 10 patients who developed systemic adverse reactions for the 2nd time, six had Grade 1, three had Grade 2, and one had Grade 3 adverse reac-

tions. Of the three patients who developed systemic adverse reactions for the 3rd time, two had Grade 1 adverse reactions and one had Grade 2 side effects. There were no patients with four systemic adverse reactions (Table 3).

Sociodemographic, clinical, and laboratory parameters of patients who developed and did not develop adverse reactions during SCIT were evaluated. The median age of the patients with adverse reactions was statistically significantly younger than the patients without adverse reactions (10.0 years [6.0–17.0], 9.0 years [4.0–17.0], respectively) (p=0.040). Absolute eosinophil values and eosinophil percentages were significantly higher in patients who developed adverse reactions compared to patients who did not (300.0 10³/uL [10.0–990.0], 510.0 10³/uL [20.0–2530.0]; 3.5% [0.1–16.3], 6.0% [0.2–20.5], respectively) (p=0.017, p=0.005) (Table 4).

DISCUSSION

Evaluation of local and systemic reactions that may develop after subcutaneous allergen immunotherapy is important for the planning the treatment process of patients. In our study, we aimed to evaluate the adverse reactions related to SCIT, 50.7% (n=70) of the children developed adverse reaction. The rate of development of adverse reactions per injection was found to be 1.6%. Similar to our study, in a recent study conducted in our country, adverse reactions were observed in 56.7% of children who underwent SCIT, while adverse reactions were reported at a rate of 2.5% per injection [14].

In our study, the rates of local, large local, and systemic adverse reactions were found to be 1.0%, 0.1%, and 0.5% per injection, respectively. Similarly in the literature, the rates of local, large local, and systemic adverse reactions

TABLE 4. Factors related to occurrence of reaction during SCIT

	Occurrence of reaction		p
	No	Yes	
Gender, n (%)			
Male	36 (52.9)	42 (60.0)	0.403
Female	32 (47.1)	28 (40.0)	
Diagnosis, n (%)			
Asthma+allergic rhinitis	38 (50.0)	38 (50.0)	0.589
Allergic rhinitis	24 (52.2)	22 (47.8)	
Asthma	6 (37.5)	10 (62.5)	
Age (years), median (min–max)	10.0 (6.0–17.0)	9.0 (4.0–17.0)	0.040
Total IgE (IU/mL), median (min–max)	255.0 (20.0–4060.0)	332.0 (25.0–4782.0)	0.054
Eosinophil (absolute) (10 ³ /uL), median (min–max)	300.0 (10.0–990.0)	510.0 (20.0–2530.0)	0.017
Eosinophil (%), median (min–max)	3.5 (0.1–16.3)	6.0 (0.2–20.5)	0.005

Min: Minimum; Max: Maximum.

per injection were 1.9%, 0.4%, and 0.14%, respectively. Similarly, the rate of systemic reaction per injection was reported as 0.2% after SCIT [15].

In our study, local adverse reactions were seen in 30.4% (n=42) of 138 patients, large local reactions in 2.9% (n=4), and systemic reactions in 17.4% (n=24) after SCIT. In a multicenter study conducted between 2012 and 2014, 54.6% of children receiving SCIT treatment had local adverse reactions and 2.2% had systemic adverse reactions in the early time period of SCIT. In the later time period, local and systemic reactions were observed in 56.1% and 7.4% of the patients, respectively [16]. Another study reported the rate of systemic reactions after SCIT as 5.0% [17]. Another study conducted in our country stated that 2.2% of the children had systemic reactions during immunotherapy [18]. According to a systematic review that included studies on pediatric patients; local reactions such as itching, swelling, and urticaria at the injection site were observed in 0–27.0% of patients after SCIT. Systemic reactions (cough, dyspnea, asthma, eczema, etc.) were seen in 6–17% of the patients [19]. In our study, the occurrence of local reactions was similar or less than in the literature; systemic side effects were more common. This may be related to the clinical stage of asthma and allergic rhinitis of the patients. It can be also explained with different approaches in terms of adverse reaction definitions between treatment centers may exist.

In a study, it has been observed that the systemic reactions that develop in children after SCIT were mostly in Grade 1; Grade 4 and Grade 5 systemic reactions were not observed in these patients [20]. Similarly, in our study, 54.2% of the first systemic reactions were Grade 1, 29.2% were Grade 2, and 16.7% were Grade 3. No Grade 4 and Grade 5 systemic reactions were observed in our study.

Absolute eosinophil values and eosinophil percentages were significantly higher in patients with adverse reactions compared to patients without adverse reactions. The age of the patients who did not develop adverse reactions was significantly younger. In the literature, similar to our study, the eosinophil values of patients who developed adverse reactions after SCIT were significantly higher [21].

During the SCIT treatment, the patients developed a maximum of 4 adverse reactions (in three patients). Adverse reactions were more common at higher doses. In patients who develop adverse reaction once, care should be taken in terms of reactions in the continuation of SCIT application. Especially in children with severe reactions, it should be decided whether to continue with SCIT by considering the harm-benefit balance. Dose adjustment should be made in these patients when continued with SCIT [22].

Our study has a larger sample than many similar studies in the literature. The high number of patients is the strength of our study. The clinical data of the patients before SCIT is not evaluated; this is the limitation of our study.

Conclusion

In our study, the development of adverse reactions after SCIT application in children with asthma and allergic rhinitis was evaluated. A total of 7366 doses of SCIT injections were administered. The rate of development of adverse reactions per injection was found to be 1.6%. In patients who developed at least one adverse reaction, the first adverse reaction was observed as 60.0% local, 5.7% wide local, and 34.3% systemic reaction. Although serious systemic side effects and death were not observed in our patients; care should be taken in terms of the development of adverse reactions during SCIT in children.

Ethics Committee Approval: The Umraniye Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 29.09.2022, number: 311).

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REFERENCES

- Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. *Allergy Clin Immunol* 1998;102:558–62. [CrossRef]
- Tsabouri S, Mavroudi A, Feketea G, Guibas GV. Subcutaneous and sublingual immunotherapy in allergic asthma in children. *Front Pediatr* 2017;5:82. Erratum in: *Front Pediatr* 2017;5:187. [CrossRef]
- Gunawardana NC, Durham SR. New approaches to allergen immunotherapy. *Ann Allergy Asthma Immunol* 2018;121:293–305. [CrossRef]
- Webber CM, Calabria CW. Assessing the safety of subcutaneous immunotherapy dose adjustments. *Ann Allergy Asthma Immunol* 2010;105:369–75. [CrossRef]
- Kartal O, Gulec M, Caliskaner Z, Musabak U, Sener O. Safety of subcutaneous immunotherapy with inhalant allergen extracts: a single-center 30-year experience from Turkey. *Immunopharmacol Immunotoxicol* 2015;37:280–6. [CrossRef]
- Kim H, Moote W, Waserman S. *Immunotherapy Manual*. Canadian Society of Allergy & Clinical Immunology; 2016.
- Sasihuseyinoglu AS, Doğruel D, Altıntaş D. Frequency of adverse reactions after subcutaneous allergen immunotherapy in children. *ENT Updates* 2020;10:396–401. [CrossRef]
- Bahceci Erdem S, Nacaroglu HT, Karaman S, Unsal Karkiner CS, Gunay I, Dogan D, et al. Risk of systemic allergic reactions to allergen immunotherapy in a pediatric allergy clinic in Turkey. *Int J Pediatr Otorhinolaryngol* 2016;84:55–60. [CrossRef]
- Epstein TG, Murphy-Berendts K, Liss GM, Bernstein DI. Risk factors for fatal and nonfatal reactions to immunotherapy (2008-2018): post-injection monitoring and severe asthma. *Ann Allergy Asthma Immunol* 2021;127:64–9. [CrossRef]
- Pitsios C, Demoly P, Bilò M, Gerth van Wijk R, Pfaar O, Sturm G, et al. Clinical contraindications to allergen immunotherapy: an EAACI position paper. *Allergy* 2015;70:897–909. [CrossRef]
- Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Allergen immunotherapy: a practice parameter second update. *J Allergy Clin Immunol* 2009;123:1421. Erratum in: *J Allergy Clin Immunol* 2008;122:842.
- Sin BA, Şahiner ÜM, Akkoç T, Bahçeciler Önder NN, Bingöl G, Büyükoztürk S, et al. Allergen Immunotherapy: National Guideline 2016. *Asthma Allergy Immunol* 2016;14 Suppl.
- Cox LS, Sanchez-Borges M, Lockey RF. World Allergy Organization systemic allergic reaction grading system: is a modification needed? *J Allergy Clin Immunol Pract* 2017;5:58–62. [CrossRef]
- Duman Senol H, Topyildiz E, Ekici B, Gulen F, Demir E. Effectiveness and adverse reactions to subcutaneous immunotherapy in children with allergic rhinitis/asthma. *Int J Pediatr Otorhinolaryngol* 2022;162:111292. [CrossRef]
- Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: the World Allergy Organization subcutaneous immunotherapy systemic reaction grading system. *J Allergy Clin Immunol* 2010;125:569–74. [CrossRef]
- Tophof MA, Hermanns A, Adelt T, Eberle P, Gronke C, Friedrichs F, et al. Side effects during subcutaneous immunotherapy in children with allergic diseases. *Pediatr Allergy Immunol* 2018;29:267–74. [CrossRef]
- Schiappoli M, Ridolo E, Senna G, Alesina R, Antonicelli L, Asero R, et al. A prospective Italian survey on the safety of subcutaneous immunotherapy for respiratory allergy. *Clin Exp Allergy* 2009;39:1569–74.
- Karali Z, Çekiç Ş, Şadırvan YH, Canitez Y, Sapan N. The evaluation of local and systemic reactions to subcutaneous house dust mite allergen immunotherapy. *Trends in Pediatrics* 2022;3:43–6. [CrossRef]
- Rice JL, Diette GB, Suarez-Cuervo C, Brigham EP, Lin SY, Ramathan M, et al. Allergen-specific immunotherapy in the treatment of pediatric asthma: a systematic review. *Pediatrics* 2018;141:e20173833.
- Liu W, Zeng Q, He C, Chen R, Tang Y, Yan S, et al. Compliance, efficacy, and safety of subcutaneous and sublingual immunotherapy in children with allergic rhinitis. *Pediatr Allergy Immunol* 2021;32:86–91.
- Aytekin G, Yıldız E, Colkesen F, Arslan S, Caliskaner AZ. Local and systemic reactions due to subcutaneous allergen immunotherapy: our single-center 5-year experience. *KSU Med J* 2022;17:1–8. [CrossRef]
- Roberts G, Pfaar O, Akdis C, Ansotegui I, Durham S, Gerth van Wijk R, et al. EAACI guidelines on allergen immunotherapy: allergic rhinoconjunctivitis. *Allergy* 2018;73:765–98. [CrossRef]