Araştırma Makalesi (Research Article)

Local and Systemic Reactions due to Subcutaneous Allergen Immunotherapy: Our Single-Center 5-Year Experience

Subkutan Allergen İmmunoterapiye Bağlı Lokal ve Sistemik Reaksiyonlar: 5 yıllık Tek Merkez Deneyimimiz

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Özet

Amaç: Subkutan alerjen immünoterapisi (SKIT) alerjik rinit/konjonktivit, astım ve venom duyarlılığının tedavisi için hastalık modifiye edici tek terapötik seçenektir. SKIT, deneyimli merkezlerde ve deneyimli hekimlerince uygulandığında oldukça güvenli bir tedavi yöntemi olsa da, enjeksiyonlar sırasında veya sonrasında bazı olumsuz yan etkilere ve lokal veya sistemik reaksiyonlara neden olabilir. Biz bu çalışmada, son 5 yılda, immünoterapi uygulanan yetişkin hastalarımızda gelişen lokal ve sistemik yan etkileri tanımlamayı ve bu yan etkilere neden olan faktörleri ortaya koymayı amaçladık.

Gereç ve Yöntemler: 5 yıllık sürede, 119 hastaya (58 kadın, 61 erkek) uygulanan toplam 4413 enjeksiyon analiz edildi.

Bulgular: Yaş ortalaması 33.7±12.0 yıl olan toplam 119 hasta çalışmaya dahil edildi (Kadın:58, %48; Erkek:61, %51.3). 119 hastalık çalışma popülasyonunun, 6'sında (%5.0) lokal reaksiyonlar, 21'inde (%17.7) geniş lokal reaksiyon ve 9'unda (%7.6) sistemik reaksiyon gelişti. Tüm enjeksiyonların %0.14'ü lokal reaksiyon, %0.48'i geniş lokal reaksiyon ve % 0.20'si sistemik reaksiyonla ilişkiliydi. Sistemik reaksiyon gelişen dört hastada (%44.4) epinefrin uygulaması gerekti. Yan etki gelişen veya gelişmeyen hastalar arasında IgE düzeyleri ve eozinofil sayıları açısından anlamlı fark vardı (p=0.001 ve p=0.002). Doz artış döneminde ve idame aşamasında gelişen advers reaksiyon oranları arasında anlamlı bir fark vardı (p=0.025).

Sonuç: Klinisyenlerin, SKIT ile ilişkili lokal, geniş lokal ve sistemik reaksiyonlarla ilgili farkındalığı arttırılmalı ve klinisyenler özellikle doz artışı döneminde adverse olaylar açısından daha dikkatli olmalıdır.

Anahtar kelimeler: Advers reaksiyon, Allerjen immünoterapi, Anafilaksi, Venom

Abstract

Objective: Subcutaneous allergen immunotherapy (SCIT) currently represents the only disease-modifying therapeutic option for the treatment of allergic rhinitis/conjunctivitis, asthma, and venom sensitization. Although SCIT represents a fairly safe therapeutic option in the hands of experienced physicians and canters, it may also be associated with certain adverse effects. In this study, we describe the local and systemic adverse effects in our adult patients undergoing immunotherapy over a 5-year period in an effort to define the causative factors.

Material and Methods: A total of 4413 injections administered to 119 patients (58 female, 61 male) were analysed.

Results: A total of 119 patients with a mean age of 33.7±12 years were included (Female: 58, 48%; Male: 61, 51.3%). In the total population of 119 patients, 6 (5%) developed local reactions, 21 (17.7%) developed large local reactions, and 9 (7.6%) had systemic reactions. Of all injections administered throughout the study period, 0.14% were associated with local reactions, 0.48% with large local reactions, and 0.20% with systemic reactions. Four patients with systemic reactions (44.4%) required epinephrine injection. Patients who did or did not develop adverse effects were significantly different with regard to IgE levels and eosinophil counts (p=0.001 and p=0.002). There was a significant difference between the rates of total adverse reactions developing during the build-up or maintenance phase (p=0.025).

Conclusion: Clinicians' awareness regarding the local, large local, and systemic reactions associated with SCIT should be improved, and clinicians should be more careful during the immunotherapy, especially in the build-up phase, for adverse events.

Keywords: Adverse reactions, Allergen immunotherapy, Anaphylaxis, Venom

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INTRODUCTION

Subcutaneous allergen immunotherapy (SCIT) currently represents the only disease modifying therapeutic option for the treatment of allergic rhinitis/conjunctivitis, asthma, and venom sensitization. In SCIT, initially very low-doses of specific antigens are administered via subcutaneous route and the doses are gradually increased at pre-determined time intervals. During this process many cells, organs, and systems are both affected by and contribute to the development of immune-tolerance (1). Although SCIT represents a fairly safe therapeutic option in the hands of experienced physicians and centers, it may also be associated with certain adverse effects and local or systemic reactions during or after injections (2). Local reactions include swelling, redness, and itchiness at the site of injection and may be alleviated by certain measures such as antihistamines, montelukast, ice application, or administration of two divided doses (3-5). On the other hand, systemic reactions are characterized by the involvement of organs or systems distant from the site of injection. Life-threatening systemic reactions frequently occur in the first 30 minutes following the injection, due to various causes (6,7). In this study, we describe the local and systemic adverse effects in our adult patients undergoing immunotherapy over a 5-year period in an effort to define the causative factors.

MATERIALS AND METHODS

Subjects

Patients with asthma, allergic rhinitis/conjunctivitis, or both or subjects with venom allergy undergoing SCIT in our unit between 2014 and 2019 were included in this retrospective cross-sectional study. During this period, a total of 4413 injections administered to 119 patients (58 female, 61 male) were analysed. Demographic data, additional allergic conditions, medication history, type of allergen responsible for the sensitization, content of the immunotherapy, type of reactions, and information regarding the timing of the reaction were collected from patient files or from face-to-face interviews with patients. Diagnosis of asthma, allergic rhinitis/conjunctivitis, or venom allergy were based on international guideline definitions (8,9). Allergen sensitivity was determined using skin prick testing, or by the measurement of specific serum IgE levels. Quantitative determination of serum immunoglobulins IgE was made by means of particle-enhanced immunonephelometry using the Siemens BN II/ BN ProSpec system (Erlangen, Germany). Whole blood count was measured with Sheath reagent using Abbott Cell Dyn 3700 series (Minnesota, USA).

Patients' allergen sensitization was determined by the test panel which contains at least D. pteronyssinus, cat and dog epitelium or hair, A. alternata, Cockroach, D. farinae, grass mix pollens (*F. pratensis, L. perenne, D. plomerata)* weed mix pollens (*Artemisia vulgaris, Chenopodium, Pariteria*) and tree mix pollens (Betula alba, Alnus, Corylus) for patients with symptoms of allergic rhinitis and asthma. These allergens have been shown to be suitable and sufficient as test panels in the adult age group (10). Venom sensitivity was evaluated by measuring allergen-specific IgE in patients with appropriate clinical history. sIgE levels ≥0.35 kUA/L were accepted as positive.

Standardized depot extracts used in the study included ALK-Abello (Madrid, Spain), and Allergopharma (Reinbek, Germany) for SCIT. Dose and frequency of injections of immunotherapy were arranged in line with the recommendations of manufacturers and in accordance with international guidelines (11-13). Patients with susceptibility to more than one allergen family were considered to be polysensitized.

No dose reduction was made in the patients during the pollen season. As a standard, patients were not given antihistamines prior to immunotherapy. During the immunotherapy build-up phase subcutaneous injections were administered weekly for the first 24 weeks, bi-weekly for the next 12 weeks, and then every 4 weeks. Patients were kept under observation for 30 minutes after each injection for local and systemic reactions. Immunotherapy was administered by physicians with experience in this field. Immunotherapy was delayed until resolution of symptoms and normalization of FEV1 (The forced expiratory volume in one second) in patients with uncontrolled asthma symptoms or in those with a FEV1 less than 70% of the expected. Spirometric measurements were obtained using a common protocol with nSpire ZAN 100 spirometer (Health Inc., Oberthulba Germany). Three maneuvers were performed although additional tests may be needed if one or more of the curves are unacceptable. FEV1, ratio of FEV1/FVC (forced vital capacity), peak expiratory flow (PEF) and mean expiratory flow 25%-75% of predicted values for similar age, sex, race and height were recorded.

Dose adjustments were performed for each of the newly prepared extracts and newly opened immunotherapy vials. Appropriate treatment was given in the case of systemic or large local reactions.

Patients were provided information on the reactions that may develop outside the clinic and were asked to record such effects. Also, patients' current symptoms and symptoms that occurred after the previous injection were inquired prior to the application of a new dose. Treatments administered for large local or systemic reactions were based on the established therapeutic guidelines (8,9).

All patients received the conventional immunotherapy, with no patients receiving rush or cluster immunotherapy. No dosage or administration errors were noted among patients who developed adverse effects.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/

or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article

The study protocol was approved by the Ethics Committee of the Necmettin Erbakan University (Number:14567952-928, decision: 2019/1904). Informed consent form was taken from all the patients participating in the study.

Classification of Side Effects

Swelling/redness at the site of injection with a diameter of 2-5 cm or >5 cm was considered local and large local reaction, respectively. A reaction was considered systemic if one or more systems were involved. The type of allergic reactions, antigen content of the injection, time elapsed until the reaction, and the treatment were recorded.

Statistical Analysis

Statistical analysis was performed with IBM SPSS Statistics Version 22 software package (New York, United States). Normally distributed parameters were presented as mean ± standard deviation and data that is not normally distributed were expressed as median (interquartile range: minimum–maximum). Descriptive data were presented as frequencies and percentages and compared using Chi-square test. Comparisons between baseline characteristics were performed by independent Student t, Mann-Whitney rank-sum, Fisher exact or Chi-square tests where appropriate.

RESULTS

A total of 119 patients with a mean age of 33.7±12 years were included (Female:58, 48%; Male:61, 51.3%). The median IgE was 219 IU/L (min:2.3-max:747), mean eosinophil count was 170 (0-1000)/mm3. Of the 119 patients, 77 (64.7%) received aeroallergen immunotherapy, and 42 (35.3%) received venom immunotherapy. There were 52 patients (53.7%) with allergic rhino conjunctivitis, 16 patients (13.4%) with asthma, and 12 patients (10.1%) with combined asthma and allergic rhino conjunctivitis, while 39 patients (32.8%) had no asthma and/or allergic rhino conjunctivitis (All of these 39 patients were those who received venom immunotherapy. Three of the 42 patients who were treated with venom immunotherapy had asthma). Based on the prick test results 77 patients (60.5%) were sensitized to a single allergen (monosensitized), and 42 (39.5%) were polysensitized (Three patients who received venom immunotherapy were polysensitized with both apis mellifera and vespula spp. Thirty-nine patients who received aeroallergy immunotherapy were polysensitized with other aeroallergens). Among patients receiving aeroallergen immunotherapy based on the result of the prick test, 19 (24.8%) were allergic to house mite, 5 (6.5%) to animal dander, 17 (22.1%) to tree-mix allergy (betula, alnus, corylus), 55 (71.4%) to grass pollens, and 28 (36.4%) to weed pollen (artemissia, chenopodium, parieteria).

Of the 42 patients receiving venom immunotherapy 24 (57.1%) were allergic to vespula spp., and 21 (50%) to apis mellifera (Three patients (7.1%) who received venom immunotherapy were polysensitized with both apis mellifera and vespula spp.). In the total population of 119 patients, 6 (5%) developed local reactions, 21 (17.7%) developed large local reaction, and 9 (7.6%) had systemic reaction. Of all injections administered throughout the study period, 0.14% were associated with local reactions, 0.48% with large local reactions, and 0.20% with systemic reactions. Four patients with systemic reactions (44.4%) required epinephrine injection **(Table 1).**

During the mean follow-up duration of 22.2±17.3 months, a total of 4413 subcutaneous injections were performed in 119 patients, of whom 36 (30.25%) developed adverse effects. Patients who did or did not develop adverse effects were comparable in terms of age, gender, number of injections, concomitant disorders (asthma, allergic rhino conjunctivitis, or their combination), presence of mono- or poly-sensitization in prick test, and the number of allergens in the immunotherapies administered. However, the two groups were significantly different with regard to IgE levels and eosinophil counts (p=0.001 and p=0.002, respectively) **(Table 2).**

Patients with local adverse effects, large local adverse effects, and systemic reactions have no significant differences in terms of age, gender, number of injections, concomitant disorders, eosinophil and serum IgE levels **(Table 3)**.

Adverse effects observed in the study occurred during the build-up phase in 77.8% of the cases, and maintenance phase in 22.2%. There was a significant difference between the rates of total adverse reactions developing during the build-up or maintenance phase (p=0.025). Of all local reactions, large local reactions, and systemic reactions 100%, 61.9%, and 100% developed during the build-up phase, respectively. An allergic reaction occurred in 11.1% of the patients with concomitant asthma, in 47.2% of the patients with allergic rhino conjunctivitis, and in 5.6% of those with both asthma and allergic rhino conjunctivitis. Patients with local reactions, large local reactions, or systemic reactions did not differ significantly in terms of the concomitant disorders (p=0.886, p=0.805, p=0.374) **(Table 3)**.

Also, patients with one or multiple antigen sensitivity were not significantly different with respect to the frequency of adverse events (p=0.338). Patients who did or did not develop immunotherapy-related adverse effects did not differ significantly in terms of the presence of sensitivity toward one or more antigens, use of single or multiple antigens for immunotherapy, and the type of allergens contained within the immunotherapy. Again, patients with or without local reactions were not significantly different when analysed with regard to the presence of sensitization toward one or more antigens, use of single or multiple antigens for immunotherapy, and allergen types.

Table 1. Demographic, clinic, and laboratory parameters of study participants		
Parameters		**Findings**
Female, n (%)		58 (48.7)
Distrubition of diagnosis	Asthma AR/ rhino conjunctivitis Asthma+ [1]AR/ rhino conjunctivitis	16 (13.4) 52 (43.7) 12 (10.1)
Eosinophil count, mm³, mean (minimum-maximum)		170 (0-1000)
[2] IgE, IU/L, mean (minimum-maximum)		214 (2.3-747)
Sensitization	Monoallergen Multiple allergen	77 (64.7) 42 (35.3)
Sensitization	Aeroallergens Grass pollens House dust mites Weed pollens Tree mix pollens Animal dander Venom Apis mellifera Vespula spp.	 55 (46.2) 19 (16.0) 13 (13.1) 17 (14.3) 5 (4.2) 24 (57.1) 21 (50)
Aeroallergen allergy • Only grass mix pollens allergy • Only house dust mites allergy • Grass mix pollens + weed mix pollens allergy • Tree mix + grass mix + weed mix pollens allergy • Tree mix pollens + grass mix pollens allergy • Weed mix pollens + grass mix pollens allergy • Grass mix polens + house dust mites alllergy • Only weed mix pollens allergy • Grass mix pollens + weed mix pollens + animal dander • Tree mix pollens + weed mix pollens allergy • Grass mix pollens + animal dander allergy • Tree mix + house dust mites allergy • House dust mites + Cockroach allergy • Only tree mix pollens allergy • Grass mix + animal dander allergy Venom Allergy • Only Apis mellifera allergy • Only Vespula spp allergy • Apis mellifera + Vespula spp allergy		77 21 (27.3) 13 (16.9) 9 (11.7) 7 (9.1) 6 (7.8) 4 (5.2) 4 (5.2) 3 (3.9) 2 (2.6) 2 (2.6) 2 (2.6) 1 (1.3) 1 (1.3) 1 (1.3) 1 (1.3) 42 21 (50) 18 (42.9) 3 (7.1)
[3] SCIT allergens	Monoallergen Multiple allergen	100 (84.0) 19 (16.0)
Adverse reactions	Local reaction, % Wide local reaction, % Systemic reaction, %	6/119 (5.0) 21/119 (17.7) 9/119 (7.6)
Frequency of adverse reactions	Local reactions, % Wide local reactions, % Systemic reactions, %	6/4413 (0.14) 21/4413 (0.48) 9/4413 (0.20)

[1]AR: Allergic rhinitis, [2]IgE: Immunoglobuline E, [3]SCIT: Subcutaneous Immunotherapy.

Table 2. Comparison of demographic, laboratory, and clinic characteristics between patients who did or did not develop adverse reactions

	Patients without Adverse Reactions (n: 83)	Patients with Adverse Reactions (n: 36)	p value
Gender, female n (%)	40 (48.2)	18 (50.0)	0.856
Age, years	33 (17-65)	32 (21-51)	0.547
[1] IgE, IU/L	208 (22.1-445)	214 (2.3-747)	0.001
Eosinophil count, mm^3	134 (0-310)	170 (0-1000)	0.002
Number of injections	31 (1-106)	39 (4-165)	0.067
Concomitant disorders Asthma, n (%) [2]AR Asthma+AR	 12 (14.5) 35 (42.2) 10 (12.1)	 4 (0.11) 17 (47.2) 2 (5.6)	 0.623 0.610 0.280
Sensitization, n (%) Monoallergen Polyallergen	 56 (67.5) 27 (32.5)	 21 (58.3) 15 (41.7)	 0.338
Content of [3]SCIT, n (%) Single allergen Multiple allergen	 79 (95.2) 4 (4.8)	 32 (88.9) 4 (11.1)	 0.208
Venom immunotherapy, n (%)	29 (34.9)	13 (36.1)	0.902
Weed pollen immunotherapy, n (%)	9 (10.8)	4 (11.1)	0.966
Tree pollen İmmunotherapy, n (%)	3 (3.6)	2 (5.6)	0.628
Dust mite immunotherapy, n (%)	15 (18.1)	4 (11.1)	0.341
Grass pollen immunotherapy, n (%)	39 (47.0)	19 (52.8)	0.562

[1] IgE: Immunoglobuline E, [2]AR: Allergic rhinitis, [3]SCIT: Subcutaneous Immunotherapy.

Table 3. Demographic, laboratory, and clinical characteristics of patients with local, large local, and systemic reaction

	Local reaction (n: 6)	Large local reaction (n: 21)	Systemic reaction (n: 9)	p value
Gender, female, n (%)	3 (50.0)	12 (57.1)	3 (33.3)	0.490
Age, years	32 (22-38)	32 (23-51)	30 (21-43)	0.723
[1]IgE, IU/L	209.5 (0-1000)	208 (208-239)	208 (208-208)	0.631
Eosinophil count, cell/mm^3	100 (2.3-747)	134 (100-162)	134 (80-245)	0.471
Number of injections	36 (4-60)	38 (8-81)	54 (7-165)	0.264
Concomitant disorders, n (%) Asthma, n (%) [2]AR, n (%) Asthma + AR, n (%)	 1 (16.7) 2 (33.3) 1 (16.7)	 2 (9.5) 10 (47.6) 1 (4.18)	 1 (11.1) 5 (55.6) 0	 0.886 0.805 0.374
Sensitization, n (%) Monoallergen Polyallergen	 3 (50) 3 (50)	 15 (71.4) 6 (28.6)	 3 (33.3) 6 (66.7)	 0.138
Content of [3] SCIT, n (%) Single allergen Multiple allergen	 3 (50) 3 (50)	 19 (90.5) 2 (9.5)	 6 (66.7) 3 (33.3)	 0.071
Venom IT, n (%)	2 (33.3)	8 (38.1)	3 (33.3)	0.958
Weed pollen IT, n (%)	1 (16.7)	2 (9.5)	1 (11.1)	0.886
Tree pollen IT, n (%)	0	0	2 (22.2)	0.420
Dust mite IT, n (%)	1 (16.7)	3 (14.3)	0	0.466
Grass pollen IT, n (%)	4 (66.7)	9 (42.9)	6 (66.7)	0.370
Time of reaction, n (%) Build-up Maintenance	 6 (100) 0	 13 (61.9) 8 (38.1)	 9 (100) 0	 **0.025**

[1] IgE: Immunoglobuline E, [2]AR: Allergic rhinitis, [3]SCIT: Subcutaneous Immunotherapy.

DISCUSSION

Allergen immunotherapy represents a disease-modifying treatment modality for many common allergic conditions. Among allergen immunotherapy approaches, subcutaneous immunotherapy (SCIT) is the most extensively studied method with considerable clinical experience. Although SCIT is generally quite safe and effective, it may also be associated with treatment related adverse effects, such as local or systemic allergic reactions. In our current study, we found that adverse events due to immunotherapy developed more frequently during the build-up phase than the maintenance phase.

Previous studies generally showed a higher occurrence of immunotherapy related systemic reactions during the build-up phase of the treatment (14-17). Conversely, some others found similar rates of systemic reactions in the build-up and maintenance phases (18), or higher frequency of fatal reactions during the maintenance (19). Sánchez-Borges et al. (20) stated that accelerated build up protocols in cluster immunotherapy are risk factors for systemic reactions. In another study, it was reported that local reactions were more frequent in the build-up phase in pediatric patients who underwent grass pollen immunotherapy, and systemic reactions were observed more frequently in the maintenance phase, although not statistically significant (21). In the current study, when large local and systemic reactions are considered separately, no differences could be noted between build-up and maintenance phases, while the total number of adverse events were significantly higher during the build-up phase as compared to the maintenance phase.

In previous studies involving the use of multiple allergens, an elevated occurrence of local and systemic reactions have been reported (22,23). In the study by Nacaroglu et al. (16) comparing patients with mono- or multiple-allergen sensitization, no difference in systemic reactions was observed, although side effects and systemic effects were more frequent in those receiving immunotherapy with multiple allergens as compared to those receiving mono allergens. Barth et al. (22) reported a systemic reaction incidence of 0.2% and 0.5% in patients receiving mono-allergen or multiple-allergen immunotherapy, respectively. In some previous studies focusing on SCIT, the allergen extracts used for immunotherapy were also proposed to have an association with local or systemic adverse effects (24,25). Sani et al. (25) showed a higher rate of systemic reactions in patients treated with dog/cat or dust mite allergens. Similarly, Liss et al. (24) higher doses of dust mite extract were associated with an increased frequency of mild systemic reactions. On the other hand, Dursun et al. (15) found no difference between allergen extracts used for immunotherapy in terms of local or systemic reactions. Also, in our study we found no difference between patients who did or did not receive dust mite immunotherapy with respect to local or systemic reactions. Similar results also were found for venom, weed pollen, and grass pollen immunotherapy.

Local reactions characterized by redness, swelling, and/or wheals. A redness/wheal diameter between 2-5 cm are considered local reactions, while those exceeding 5 cm are termed as large local reactions. In a 2008 study by Calabria et al. (2) the frequency of local reactions associated with aero-allergens was reported to be associated with allergen concentration, allergen content of the injection, as well as the volume of the allergen, while the glycerin used as an excipient had no effect on reaction frequency. In another study by the same investigators, total local reaction, smaller local reaction, and large local reaction incidence were reported to be 16.3%, 15.9%, and 0.4%, respectively. Kartal et al. (26) reported a rate of 0.062% per injection and 5.2% per patient for local reactions. These authors reported that immunotherapy related local reactions were not a risk factor for the future occurrence of local reactions (27). Roy et al. (28) showed that increased frequency of immunotherapy-related large local reactions represented a risk factor for systemic reactions, particularly emphasizing the importance of the close follow-up of large local reactions. In our study, the incidence of total local reactions was 22.7%, with local and large local reactions representing 5% and 17.7% of such events. Also, 0.14% of the injections were associated with local, and 0.48% were associated with large local reactions, similar to previous reports.

Systemic reactions associated with SCIT involve organs distant from the site of injection. Most of the severe systemic reactions occur within the first 30 minutes following an injection, hence the recommendation to observe patients for a minimum duration of 30 minutes after the injection. The risk of systemic reaction may vary according to the type of allergen, potency of the injected allergen, preparation and modification methods for the allergen, and protocol used (29). Based on the data provided by the Subcutaneous Immunotherapy Surveillance Study (2013-2017), systemic reactions occurred in approximately 0.1% of the injections, with 1 death per 9.1 million injections and 8.7 systemic reactions for every 10.000 injections (30). In a study by Epstein et al. (30), analysing nearly 29.8 million injections administered to 344.480 patients, 1.9% of the patients had systemic reactions, and dose modification during the pollen season in subjects with hypersensitivity was found to lower the risk of systemic reactions. Greenberg et al. (31) observed a systemic reaction rate of 7% among 20.588 injections administered to 628 patients. In the study by Sani et al. (25) 24.8% of the patients had immunotherapy-related systemic reactions, with a systemic reaction incidence per injection of 0.2%. In another study from Turkey, the incidence of adverse and systemic reactions per injection were 2.6% and 1.3%, respectively (15). In our study, 7.6% of the patients had systemic reactions, with a systemic reaction frequency of 0.20% per injection, similar to reported figures (7,15,17,29).

Although immunotherapy has been shown to reduce asthma symptoms as well as bronchial hyperreactivity, uncontrolled asthma remains a strong risk factor for immunotherapy-related side effects (32). Asthmatic patients were found have a higher risk of near-fatal reactions (NFR) during immunotherapy when compared to non-asthmatic patients (33). In another study, patients with a forced expiratory vo-

lume in one second of less than 70% predicted had an increased incidence of bronchospasm after immunotherapy (34). In a Turkish study, asthma, even when well controlled, was reported to be a risk factor for systemic reactions (15). On the other hand, in the study by Nacaroglu et al. (16) asthma did not emerge as a risk factor for systemic reactions, and this finding applied even to uncontrolled asthma. Again, Tinkelman et al. (17) reported no increase in the frequency and extent of systemic reactions in asthmatic patients. In our study asthma, allergic rhino conjunctivitis or their co-existence were not associated with an increase in local, large local, or systemic reactions.

Another factor associated with increased risk of SCIT-related side effects relates to the treatment protocols. Accordingly, an increased risk of adverse events was observed in accelerated treatment schemes (29). Since all patients in our study received the conventional immunotherapy scheme, the observed rate of reactions was lower as compared to historical data from accelerated treatment schemes.

In conclusion, SCIT represents an efficacious therapeutic option for the treatment of allergic disorders. Clinicians' awareness regarding the local, large local, and systemic reactions associated with SCIT should be improved, and clinicians should be more careful during the immunotherapy, especially in the build-up phase, for adverse events.

Conflicts of interests: The authors declare that they have no conflicts of interest.

Ethics and Patient Consent: The study protocol was approved by the Ethics Committee of the Necmettin Erbakan University (Number:14567952-928, decision: 2019/1904). Informed consent form was taken from all the patients participating in the study.

Research Contribution Rate Statement Summary: The authors declare that, they have contributed equally to the manuscript.

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