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Frequency of adverse reactions after subcutaneous allergen immunotherapy in children

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Abstract

Objective: Subcutaneous allergen immunotherapy (SCIT) is an effective treatment method for allergic rhinitis, asthma and venom allergy. The aim of this study was to evaluate the frequency of adverse reactions in children undergoing SCIT.

Methods: This retrospective study included patients that underwent SCIT in our clinic for a period of five years due to a diagnosis of Apis mellifera venom allergy or allergic asthma and/or rhinitis. 303 patients were divided into groups based on the form of SCIT administered and the presence of injection-related reactions.

Results: Mean age at the initiation of SCIT was 10 (range, 5-18) years old. SCIT for aeroallergens was administered to 289 (95.4%) patients and SCIT for venom to 14 (4.6%) patients. Local reactions were observed in 54 (17.8%) and systemic reactions developed in 4 (1.3%) patients. The local reactions mostly occurred after SCIT with Apis mellifera venom (100%), followed by house dust mite (20.6%), mold (16.7%) and grass pollen (16.7%).

Conclusion: Although SCIT is a safe treatment method used for allergic diseases, it must be administered only in centers with appropriate emergency equipment due to the risk of side effects.

Keywords: Subcutaneous immunotherapy, child, adverse reaction, allergy.

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Introduction

Subcutaneous allergen immunotherapy (SCIT) is a treatment method based on the induction of clinical and immunological tolerance in clinically sensitized patients by the administration of allergen extract at an incremental dose beginning from a low dose and at doses causing no side effects. SCIT has been shown to be the sole treatment option affecting the natural course of allergic diseases.[1] The common consensus on the utility of SCIT is that SCIT is a useful treatment method with proven effectiveness when used in well-selected patients and with appropriate indications and techniques.[2] Moreover, SCIT could be a viable treatment option for patients that have been detected to have specific IgE via skin test and/or by *in vitro* methods and present with symptoms after exposure to natural allergen, in patients that present with significant side effects of drug therapy and in patients avoiding long-term drug use.[3] Although SCIT is generally a safe therapy, it can cause undesirable side effects, from a simple local reaction to severe anaphylactic shock.[4] The aim of the present study was to evaluate the frequency of adverse reactions in children undergoing SCIT due to aeroallergen and venom sensitivity in our clinic between 2007 and 2016.

Materials and Methods

Study groups

This retrospective study included patients that underwent SCIT with standard allergen extract in our clinic for a period of five years between January 2007 and December 2016 due to a diagnosis of *Apis mellifera* venom allergy or allergic asthma and/or rhinitis. Allergic asthma, allergic rhinitis and *Apis mellifera* venom allergy were diagnosed according to international guidelines.[5,6] Patients were divided into groups based on the form of SCIT administered and the presence of injection-related reactions. Indications and contradictions for immunotherapy were evaluated based on the American Academy of Allergy, Asthma & Immunology (AAAAI) guidelines.[3] Written consent was obtained from each parent since the participants were between 5-18 years old prior to the initiation of immunotherapy. The study protocol was approved by the local institutional ethics committee (02.03.2018/75-44) and was performed in accordance with the Helsinki Declaration.

Allergen immunotherapy

Allergen immunotherapy was administered using standard allergen extracts available in Turkey, including Allergovit (Allergopharma, Reinbeck, Germany), ALK (ALK- Abellò, Madrid, Spain) or SAY (Stallargen, Antony Cedex, France). Table 1 presents the initial and maintenance doses of SCIT. The initial dose consisted of 1-4 injections per week for patients that underwent aeroallergen immunotherapy (n=289; 95.4%) and 1 vaccine per week for patients that underwent *Apis mellifera* venom immunotherapy (n=14; 4.6%). The maintenance dose, which consisted of 100,000 standardized quality unit of vaccine (SQ-U) 1 ml, was commenced at months 4-6 and was administered monthly to all patients. No dose adjustment was required during pollen season and no grass pollen immunotherapy was administered to any patient. Prior to each injection, the patients were queried about their existing complaints and the com-

Table 1. Initial and maintenance doses of SCIT.

	Initial dose	Maintenance dose
SAY (Stallargen) (Antony Cedex, France)	0.01 IR 0.1 ml	10 IR 0.8 ml
ALK (ALK-Abellò) (Madrid, Spain)	100 SQ-U 0.1 ml	100,000 SQ-U 1 ml
Allergopharma (Reinbeck, Germany)	5 TU 0.2 ml	5,000 TU 1 ml

IR: Index of reactivity, ml: milliliter, SQ-U: standardized quality unit, TU: transforming unit

plaints that emerged after the previous injection, and also a physical examination was performed for each patient. Patients with asthma underwent a pulmonary function test prior to injection and for asthma patients that had existing complaints, injection was postponed by one week. All injections were administered subcutaneously by physicians and trained nurses under outpatient conditions.

Classification of reactions

Reactions associated with immunotherapy were classified as local and systemic based on their width and as early- and late-onset based on their time of onset. Local reaction was defined as the presence of swelling and redness at the injection site, and a large local reaction was defined as a local reaction greater than the size of the patient's palm at the injection site.[7] Systemic reactions were classified based on the grading system proposed by the World Allergy Organization (WAO).[8] Systemic reactions occurring within the first 30 min after injection were classified as early-onset and those occurring 30 min after injection were classified as late-onset systemic reactions. All patients were monitored for reactions for a minimum of 30 min after each injection. Patients that showed systemic or large local reactions were treated accordingly and their subsequent injection doses were re-adjusted.

Statistical analysis

Data were analyzed using SPSS for Windows Version 18.0 (SPSS Inc. Co., Chicago, IL, USA). Data were expressed as median, frequencies (%) and percentages (%).

Results

This study included 303 patients that underwent SCIT in our clinic for a period of five years between January 2007 and December 2016 and had complete clinical records. Mean follow-up period (which was calculated as the time from first presentation to our clinic to the initiation of SCIT) was 2.7 (range, 0.5-14) years. Mean age at the initiation of SCIT was 10 (range, 5-18) years old. Figure 1 presents the distribution of the forms of SCIT administered to our patients. SCIT was administered with a single allergen in 232 (76.6%), two allergens in 66 (21.8%) and three allergens in 5 (1.7%) patients. Local reactions were observed in 54 (17.8%) and systemic reactions developed in 4 (1.3%) patients. Local reactions mostly occurred after SCIT with *Apis mellifera* venom (100%), followed by

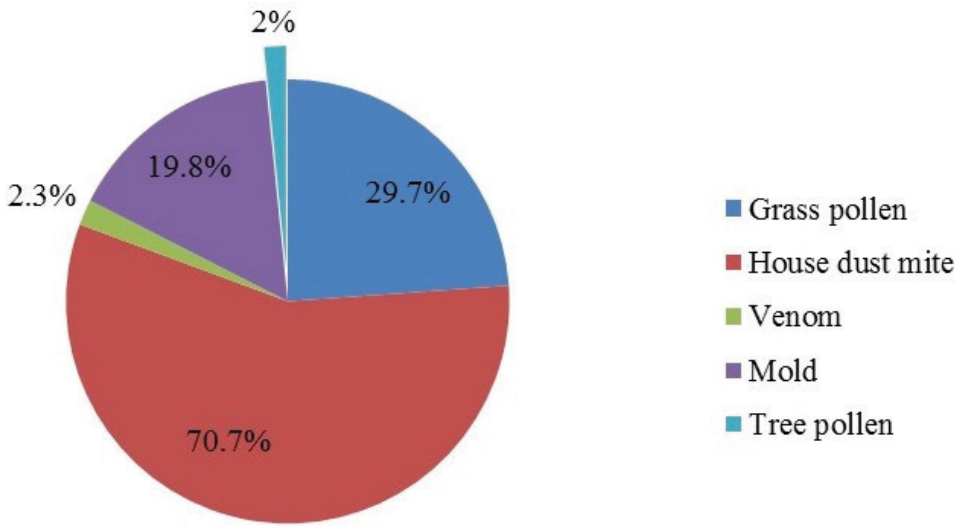

Figure 1. SCIT forms administered in the study.

house dust mite (HDM) (20.6%), mold (16.7%) and grass pollen (16.7%). Fifty-four local reactions were observed, including early-onset local reactions (n=6; 11.1%), late-onset small reactions (n=15; 27.7%) and late-onset large reactions (n=33; 61.1%). Of the local reactions, 20 (44.4%) of them developed during the initial phase. Systemic reactions were generalized pruritis, angioedema, cough and wheezing. Systemic reactions were grade 1 and 2, and none of them required adrenaline. Of the 4 systemic reactions, 1 reaction was observed during the initial phase and the remaining 3 reactions were observed in the maintenance phase. These reactions mostly occurred after SCIT with HDM (1.4%), followed by grass pollen (1.1%). Among these, two (50%) patients had previously developed a local reaction.

Discussion

Allergen-specific immunotherapy essentially aims to overcome allergic inflammation by inducing T-cell tolerance to allergens similar to that of healthy individuals.[9] SCIT has been shown to be an effective treatment for allergic rhinitis and asthma and to prevent anaphylaxis to hymenoptera stings.[10] The literature indicates that SCIT is a low-risk and well-tolerated treatment.[11] In the literature, there is no consensus on lower and upper age limits for the initiation of immunotherapy.[12] In addition, results of a recent study showed that the starting age for SCIT is not a risk factor for adverse effects in multivariate analysis.[13] However, the administration of SCIT may result in local (erythema, swelling and itching at the injection site) and systemic reactions, of which local reactions can be seen in 26-82% and systemic reactions can be seen in 0.7-4% of patients.[14] In our study, the prevalence of large local reactions was 10.89%, which was consistent with the literature. In the literature, there are controversial findings regarding the ability of local reactions to predict local and systemic reactions following injections. La Shell et al. [15] evaluated patients that underwent immunotherapy for fire ants and showed that the development of large local reactions was a risk factor for the development of systemic reactions. In our study, only two (3.7%) patients with local reactions developed subsequent systemic reactions. Contrariwise, another study suggested that local reactions have no utility in predicting local reactions occurring after subsequent injections.[16] A previous Turkish study evaluated the prevalence of large local and systemic reactions in children undergoing SCIT and reported that the administration of injections during the initial or maintenance phase had no significant effect on the prevalence of large local reactions.[7] It is estimated that 1/160,000 anaphylactic reactions occurred for every SCIT visit.[4] SCIT-related systemic reactions in children have been reported to occur in 4% of all patients and in 0.1% of all injections.[17] A previous Turkish study evaluated 108 children that were followed up due to asthma and/or allergic rhinitis with pollen or HDM sensitivity and reported that the prevalence of early-onset systemic reactions after subcutaneous injection was 0.1%.[18] Another study reported this rate as 0.3% in patients that received immunotherapy with pollen and venom.[7] In our study, in line with the literature, the prevalence of systemic reactions was 1.3% and all of those reactions were observed within the first 30 min after injection. On the other hand, late-onset systemic reactions (anaphylaxis) have also been reported after SCIT.[19] Similarly, other studies also reported that late-onset systemic reactions were observed in almost 50% of children undergoing SCIT and noted that those reactions were mostly mild and non-life-threatening.[20,21] For these reasons, patients undergoing immunotherapy should be monitored for the possible risk of injection-related reactions for a minimum of 30 min after injections and should be trained accordingly.[3]

In conclusion, subcutaneous immunotherapy is a safe treatment for allergic patients. However, it should be administered by trained specialists under appropriate safety conditions due to the risk of injection-related reactions.

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Ethics Committee Approval: The study protocol was approved by the local institutional ethics committee (Approval number: 02.03.2018/75-44).

Informed Consent: A written consent was obtained from each parent since the participants were between 5-18 years old.

Author Contributions: Designing the study – DUA, ASS, DD; Collecting the data – ASS; Analysing the data – ASS, DD; Writing the manuscript – ASS; Confirming the accuracy of the data and the analyses – DUA.

Conflict of Interest: The authors have no conflicts of interest to declare.

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