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Risk of systemic allergic reactions to allergen immunotherapy in a pediatric allergy clinic in Turkey

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ABSTRACT

Objectives: Even though allergen immunotherapy is an effective treatment method that has been used on rhinitis, asthma and venom anaphylaxis for over 100 years, systemic reactions (SRs) limit the use of this treatment method. We classified SRs associated with subcutaneous immunotherapy (SCIT) according to the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. Risk factors for the SRs were assessed.

Methods: In this study 67,758 injections to 1350 children with allergic rhinitis and/or asthma were analyzed throughout January 1999–December 2014.

Results: A total of 51 systemic reactions were observed in 39 patients (0.075% per injection, %3 per patient). Mean age of SRs observed patients was 13 ± 2.6 years (range 9.5–16 years) and 64.1% were male, 35.9% were female. 51.3% of SRs were grade 1, 38.5% grade 2, 7.7% grade 3 and 2.6% grade 4. SRs were early onset in 41% of the patients and delayed onset in 59%. 76.9% of SRs were seen during maintenance therapy and 56.4% during peak pollen season. In 28.2% of cases previous local reactions and in 30.8% previous grade 1 reactions were determined. There was no fatal outcome from any of the SRs.

Conclusion: SCIT related SRs are generally of mild severity. Although only 10% of the SRs were grade 3 or 4, there is a still a small risk of severe reactions. 76.9% of SRs were observed during maintenance therapy. Delayed-onset SRs rate in our study is 59%. So both clinicians and parents should be alert about the delayed reactions after SCIT.

1. Introduction

1.1. Background

Subcutaneous allergen immunotherapy (SCIT) is an effective treatment for allergic rhinitis, asthma and venom hypersensitivity and has the potential of producing serious adverse reactions. Adverse reactions are generally classified into 2 categories: local reactions, which can manifest as redness, pruritus, and swelling at the injection site, and systemic reactions (SRs). SRs can range in severity from mild rhinitis to fatal cardiopulmonary arrest. The World Allergy Organization (WAO) developed the Subcutaneous Immunotherapy Systemic Reaction Grading System in an attempt to standardize the severity of immunotherapy triggered reactions [1–4].

The frequency of SCIT related SRs in recent years has been put forth as 0.28–0.1% [5–7]. Grade 1 reaction is the most frequent [6,7]. The risk factors that cause the development of systemic reactions can be listed as uncontrolled asthma, previous reactions to allergen immunotherapy, dosing during peak pollen seasons, concomitant medications, dose of allergen, immunotherapy schedules (cluster and rush), degree of sensitivity, dosing and administration errors, epinephrine administration being delayed or not given, inadequate waiting times after injections, reactions that began after 30 min, administration in medically unsupervised settings [1,2,4,5]. Knowing the frequency and the risk factors of SRs

Abbreviations: SCIT, subcutaneous allergen immunotherapy; AAAAI, American Academy of Allergy Asthma and Immunology; WAO, World Allergy Organization; AIT, allergen immunotherapy.

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will ensure that this effective treatment method is provided in a safer manner.

1.2. Objective

The objective of this study during which we observed our patients who underwent SCIT was to examine the distribution of the systemic reactions observed in accordance with the Grading System of WAO and the risk factors.

2. Materials and methods

2.1. Patients population

All allergen immunotherapy applied patients at the Dr. Behcet Uz Children Hospital in Turkey, Division of Allergy and Clinical Immunology from January 1999 to December 2014 were evaluated in this cross-sectional and retrospective study. During this 15 years time, 67,758 injections applied to 1350 children were analyzed. Information on the demographic data of the patients, their allergic diseases, disease controls, allergens that the patient is sensitized to, allergens used in the allergen immunotherapy, phase of treatment, onset time of the reaction, symptom(s) or sign(s) of SRs, previous local reactions, previous systemic reactions were obtained from the folders of the patients. The study was approved by the Dr Behcet Uz Children's Hospital of Ethics Committee (Approval No:2015/01-03).

2.2. Allergen immunotherapy

Standardized depot extracts, commercially available in Turkey for this study included Allergopharma (Reinbeck, Germany), ALK-Abello (Madrid, Spain) and Stallergens (Antony Cedex, France). The initial dose for immunotherapy was 0.1 ml of 100 SQ/ml (ALK-Abellò, Alutard; aluminum hydroxide adsorbed extract) or 0.1 ml of 0.01 IR/ml (Stallergens, Phostal) for calcium phosphate adsorbed allergen extracts and 0.2 ml of 5 TU/ml for aluminum hydroxide adsorbed extracts (Novo-Helisen Depot, Allergopharma Inc.). Dosages were increased weekly, and the usual maximum dose was 0.8 ml of 100,000 SQ/ml or 10 IR/ml for calcium phosphate-adsorbed allergen extracts, and 1 ml of 5000 TU/ml for aluminum hydroxide-absorbed extracts. In the build-up phase, injections were performed weekly for 24 weeks and subsequently biweekly for 3 months; in the maintenance phase, injections were performed monthly and completed in four years. Patients were observed for 30 min following each injection, and local and systemic reactions developing were recorded.

The immunotherapies were applied subcutaneously by doctors and experienced nurses in the hospital. The subcutaneous injections were given in the lateral and posterior portion of the arm at a 45° angle with a 26-ga (13 mm), insulin or tuberculin syringe at the allergy clinic.

Current symptoms and responses to previous doses of immunotherapy were reviewed prior to administering the next dose. In the presence of systemic and wide local reactions, appropriate treatment was administered and the following dose of immunotherapy was determined by the guide of "Allergen immunotherapy: a practice parameter third update" and recommendations of the manufacturer [8]. All the patients received conventional immunotherapy and none of them received clustered or rush immunotherapy or venom immunotherapy. No premedication was used in any of our patients.

2.3. Classification of adverse reactions

The SRs were rated according to the Grading System of WAO [4]. Grade 1: Symptom(s)/sign(s) of 1 organ system (cutaneous, upper respiratory, conjunctival, other symptoms such as nausea, headache) present; Grade 2: Symptom(s)/sign(s) of more than 1 organ system (lower respiratory (asthma symptoms/signs which respond well to inhaled bronchodilators), gastrointestinal, other) present; Grade 3: Asthma (e.g., 40% PEF or FEV1 drop not responding to an inhaled bronchodilator) or laryngeal, uvula, or tongue edema with or without stridor; Grade 4: Respiratory failure with or without loss of consciousness or hypotension with or without loss of consciousness (Table 1). Early onset defined as beginning ≤30 min, and delayed onset beginning more than 30 min after injections. Edema and/or erythema 2–5 cm in size

Table 1
World Allergy Organization subcutaneous immunotherapy systemic reaction grading system (4).

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptom(s)/sign(s) of 1 organ system present* **Cutaneous** Generalized pruritus, urticaria, flushing, or sensation of heat or warmth_ **or** Angioedema (not laryngeal, tongue or uvular) **or** Upper respiratory Rhinitis – (e.g., sneezing, rhinorrhea, nasal pruritus and/or nasal congestion) **or** Throat-clearing (itchy throat) **or** Cough perceived to originate in the upper airway, not the lung, larynx, or trachea **or** Conjunctival Erythema, pruritus or tearing **Other** Nausea, metallic taste, or headache	**Symptom(s)/sign(s) of more than 1 organ system present** **or** **Lower respiratory** Asthma: cough, wheezing, shortness of breath (e.g., less than 40% PEF or FEV1 drop, responding to an inhaled bronchodilator) **or** **Gastrointestinal** Abdominal cramps, vomiting, or diarrhea **or** **Other** Uterine cramps	**Lower respiratory** Asthma (e.g., 40% PEF or FEV1 drop NOT responding to an inhaled bronchodilator) **or** **Upper respiratory** Laryngeal, uvula, or tongue edema with or without stridor	**Lower or upper** respiratory Respiratory failure with **or** without loss of consciousness **or** **Cardiovascular** Hypotension with or without loss of consciousness	**Death**