Immediate Adverse Reactions to Subcutaneous Allergen Specific Immunotherapy in Respiratory Allergies

Solunum Yolu Allerjilerinde Subkutan Allerjen Spesifik İmmunoterapinin Erken Dönem Yan Etkileri

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ABSTRACT Objective: Allergen immunotherapy has been used in the management of allergic diseases for nearly a hundred years; however, its short term side-effects can effect the decision of starting the therapy. **Material and Methods:** This study is a retrospective evaluation of the immediate local and systemic reactions seen in the cases who were given immunotherapy between March 1997 and September 2008 in the Ege University Faculty of Medicine, Department of Pediatric Allergy and Pulmonology. **Results:** The 541 patients had ages ranging from 6 to 18 years. 64.3% (n= 348) of the patients were having calcium phosphate-adsorbed allergen vaccines, while 35.7% (n= 193) were having aluminium hydroxide adsorbed vaccines. Of the patients, 229 patients had allergic rhinitis (42.3%), 161 had asthma (29.7%), and 151 had both asthma and allergic rhinitis (27.9%). Totally, 28.374 injections were given to the patients. In 4.6% (n=1310) of the injections immediate reactions were detected; 74% (n= 970) of them were observed during the build-up therapy ($p< 0.01$), and 81.6% (n= 1069) of the reactions were detected in the patients who were receiving calcium phosphate-adsorbed vaccines ($p< 0.01$). There was no statistically significant difference in the immediate reaction rates of the subjects when comparing the allergens in the vaccines or the diagnosis of the patients. The frequency of systemic reactions was 0.04% (n= 13); most of these reactions were detected during the build-up therapy and in patients with asthma + allergic rhinitis. With early term interventions, the symptoms of all patients improved in a short time. **Conclusion:** In conclusion, most of the immediate reactions to immunotherapy are local and the systemic ones are controllable through early treatment; so that subcutaneous immunotherapy is a safe treatment modality when it is used for appropriate indications by experienced staff.

Key Words: Allergens; immunotherapy; child; adverse effects

ÖZET Amaç: Allerjen immunoterapi, allerjik hastalıkların tedavisinde yüzyıllardır kullanılmaktadır; ancak bu tedavi modelinin erken dönem yan etkileri, tedaviye başlama kararını etkileyebilmektedir. **Gereç ve Yöntemler:** Bu çalışmada, Ege Üniversitesi Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları AD Solunum-Allerji BD tarafınca Mart 1997-Eylül 2008 tarihleri arası immunoterapi uygulanan hastalarda görülen erken dönem lokal ve sistemik yan etkiler retrospektif olarak değerlendirilmiştir. **Bulgular:** 541 olgunun yaşları 6-18 yıl arasında değişmekteydi. Hastaların %64.3'ü (n= 348) kalsiyum fosfat, %35.7'si (n= 193) alüminyum hidroksit emdirilmiş ürün ile aşılanmaktaydı. Olguların %42.3'ü (n= 229) allerjik rinit, %29.7'si (n= 161) astım, %27.9'u (n= 151) astım + allerjik rinit tanılarıyla izlenmekteydi. Toplam 28.374 enjeksiyonun %4.6'sında (n= 1310) erken dönem reaksiyon olduğu, bunların %74'ünün (n= 970) başlangıç tedavisinde, %81.6'sının (n= 340) ise kalsiyum fosfatlı aşıda görüldüğü saptandı ($p< 0.01$). Aşılarda bulunan allerjenlere veya hastaların tanılarına göre değerlendirildiğinde, erken dönem reaksiyon görülme sıklığı arasında anlamlı bir fark olmadığı gözlendi. On üç enjeksiyonda (%0.04) sistemik reaksiyonun olduğu, özellikle başlangıç tedavisinde ve astım + allerjik rinit tanısıyla izlenmekte olan olgularda bu tip reaksiyonların daha fazla oluştuğu görüldü. Erken dönem müdahale ile bütün olgulardaki semptomlar kısa sürede geriledi. **Sonuç:** İmmunoterapiye bağlı gelişen erken dönem reaksiyonların çoğu lokal düzeyde kalmakta, sistemik olanlar ise erken müdahale ile kontrol altına alınabilmektedir. Bu nedenle, subkutan immunoterapi, deneyimli ekiplerce programlandığında ve doktor kontrolünde doğru endikasyonlarla yapıldığında güvenli bir tedavi seçeneği olarak karşımıza çıkmaktadır.

Anahtar Kelimeler: Allerjenler; immünoterapi; çocuk; istenmeyen etkiler

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Allergen immunotherapy is a therapeutic procedure shown to be effective for allergic patients, but its short and long-term side effects can effect the decision of starting the therapy. Immunotherapy (or desensitization) comprises the gradual administration of increasing amounts of allergen to an individual with allergic disease for inducing immunologic tolerance. Subcutaneous injection immunotherapy (SCIT) is the established and mostly used form of this treatment. Although the evidence supporting the safety and efficacy is modest, immunotherapy can also be administered orally or sublingually.[1] In 1911, injection immunotherapy was introduced for the treatment of seasonal allergic rhinitis, and by 1925 successful treatment of asthma using immunotherapy was reported by several research groups; the initial rationale was to immunize patients against the effects of "pollen toxin".[1,2] Many different explanations for the effects of the treatment have been proposed over the last 70 years, including an increase in IgG "blocking antibodies", the generation of regulatory T-cells, immune deviation from the TH2 to TH1 phenotype, and the production of some form of T-cell tolerance.[3-7]

Administering injections of allergens to an allergic patient always carries the risk of inducing an adverse reaction. Although minor reactions are much more common, systemic reactions are also reported in patients who receive SCIT according to standard schedules.[8,9] In rapid rush protocols, higher rates of systemic reactions are observed. Severe anaphylaxis to immunotherapy is reported rarely; most severe reactions involve classical anaphylaxis with hives, laryngeal edema, bronchospasm, and/or hypotension. Near fatal reactions occur at a rate of approximately five per million injections.[10]

Allergen vaccines are grouped as aqueous non-standardized extracts, aqueous standardized extracts, depot extracts, or modified extracts. Aqueous extracts are effective, especially when standardized, but may expose patients to a higher rate of systemic reactions. Compared to aqueous extracts, depot extracts have lower rates of adverse reactions; the allergen is adsorbed to carriers such as aluminum hydroxide, tyrosine, or calcium phosphate, which allow slow release.[11,12] Primary aim of this study is to determine the frequency of immediate local and systemic reactions to allergen immunotherapy with depot extracts in patients with allergic asthma and allergic rhinitis, secondary aims of the study are a) to compare adverse reaction rates of calcium phosphate and aluminum-hydroxide adsorbed extracts, b) to analyze the effect of the type of disease, the type of allergen, and the phase of treatment on the frequency of immediate adverse reactions.

MATERIAL AND METHODS

Pediatric allergic rhinitis and asthma patients aged from 6 to 18 years with a specific IgE-mediated sensitization to one or more aeroallergens and who were treated with subcutaneous injection immunotherapy (SCIT) between March 1997 and September 2008 in the Ege University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Allergy and Pulmonology were enrolled to the study. Patients were evaluated by medical history, clinical examination, and skin-prick test with common allergens. For the diagnosis of allergic rhinitis, a symptomatic period of at least 4 weeks during the year, with at least two of the following were required: watery rhinorhea, blocked nose, itchy nose, sneezing or night cough as specified in the ARIA criteria (**a**llergic **r**hinitis and its **i**mpact of **a**sthma) for persistent rhinitis.[5,7,13] For the diagnosis of asthma, a previous diagnosis of asthma with proof of reversibility on pulmonary function tests and response to bronchodilators was acceptable.

Biologically standardized extracts in depot (adsorbed in aluminum hydroxide or calcium phosphate) commercially available in Turkey, were used. Allergen extracts in the conventional schedule were supplied by three different laboratories; ALK-Abellò (Madrid, Spain), Allergopharma (Reinbeck, Germany) and Stallergenes (Antony Cedex, France). Patients were divided into two groups; 1) Group 1: patients receiving calcium phosphate adsorbed allergen extracts (ALK-Abellò and Stallergenes), 2) Group 2: patients receiving

aluminum hydroxide adsorbed extracts (Allergopharma). Written informed consents were obtained from all patients before the initiation of immunotherapy, and the guidelines were followed to monitor patients during allergen extract injection.[13] Antihistamine premedication was not used as a routine to increase safety of allergen-specific subcutaneous injection immunotherapy. The initial dose of immunotherapy was 0.1 ml of 100 SQ/ml(ALK-Abellò) or 0.1 ml of 0.01 IR/ml (Stallergens) for calcium phosphate adsorbed allergen extracts and 0.2 ml of 5 TU/ml for aluminum hydroxide adsorbed extracts. Dosages were increased weekly, 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 5000TU/ml for aluminum hydroxide adsorbed extracts. Once the patient reached the maintenance dose or the maximum dose tolerated, the injection schedule was changed to every two, and then to every four weeks. Patients were observed in the outpatient clinic for thirty minutes after injection. Immediate local and systemic reactions were recorded.

Immediate adverse reactions were assessed for presence of hyperemia, induration, local itching, pain, generalized pruritus, feeling of asphyxiation, tightness of the chest, burning sensation of throat, dizziness, itchy watering eyes, sneezing, nasal congestion, rhinorrhea, urticaria, angioedema, cough, wheezing, stridor, abdominal pain, hypotension, and tachycardia. The EAACI position paper on immunotherapy grades the reactions as grade 1 (local reactions), grade 2 (mild systemic symptoms), grade 3 (asthma, laryngeal edema responding to treatment) and grade 4 (anaphylactic shock, poor response to treatment).[13]

Groups were analyzed according to the number of local and systemic reactions and the effect of the type of allergic disease (allergic rhinitis and/or asthma), type of allergen sensitivity (dust mite or grass pollen), and phase of immunotherapy (build-up-initial or maintenance).

Statistical analyses were performed using "SPSS (Statistical Package for Social Sciences) 16.0 for Windows" software. The t-test, one-way ANOVA test, and chi-square test were used to evaluate the data and $p < 0.05$ was accepted as statistically significant.

RESULTS

The 541 patients (66.7% male, 33.3% female) had ages ranging from 6 to 18 (11.58 ± 3.21) years. 64.3% (n= 348) of the patients were receiving calcium phosphate-adsorbed allergen vaccines, while 35.7% (n= 193) were receiving aluminum-hydroxide-adsorbed vaccines. Of the patients, 229 (42.3%) had allergic rhinitis, 161 (29.7%) had asthma, and 151 (27.9%) had both asthma and allergic rhinitis (Table 1). Totally, 28,374 injections were administered to the patients; 61.6% (n= 17,479) of these injections were performed in the calcium phosphate group. In 54.3% (n= 295) of the patients and 4.6% (n= 1310) of the injections, immediate adverse reactions were detected; 74% (n= 970) of them were observed during the build-up therapy, and 81.6% (n= 1.069) of the reactions were detected in the patients who were receiving calcium phosphate adsorbed vaccines ($p < 0.01$) (Table 2, 3). There was no statistically significant difference in the immediate adverse reaction rates of the patients when comparing the allergens in the extracts or the diagnosis of the patients. The frequency of systemic reactions was 0.04% (n= 13); most of these reactions were detected during the build-up therapy and in patients with asthma + allergic rhinitis. Four patients had bronchospasm, 3 had urticaria, 3 had dizziness, 1 had burning sensation of throat, and 1 subject had anaphylactic shock (Table 4). With early term interventions, the symptoms of all patients improved in a short time.

DISCUSSION

All along, immunotherapy is the subcutaneous/sublingual administration of an allergen vaccine, beginning with a very dilute concentration and gradually increasing the dose on a weekly or bi-weekly basis (build-up phase), finally reaching a maintenance dose that is continued for 5 years or more. In the literature to date, SCIT is reported as effective to treat allergic rhinitis, allergic asthma, and hymenoptera hypersensitivity.[14-16] Unlike pharmacotherapy, SCIT targets the underlying ca-

TABLE 1: Characteristics of the patients.

		Group 1(CaPO4) (n=348) (n) (%)	Group 2 (Al OH) (n=193) (n) (%)	Total (n) (%)
Gender	Male	235 (67.5%)	126 (65.3%)	361 (66.6%)
	Female	113 (32.4%)	67 (34.7%)	180 (33.3%)
Diagnosis	Asthma	114 (32.7%)	47 (24.3%)	161 (29.7%)
	Allergic rhinitis	154 (44.2%)	75 (38.8%)	229 (42.3%)
	Asthma + Allergic rhinitis	80 (22.9%)	71 (36.8%)	151 (27.9%)
Type of the allergen	Grass pollen	255 (73.2%)	145 (75.1%)	400 (73.9%)
	Dust mite	75 (21.5%)	42 (21.8%)	117 (21.6%)
	Grass pollen + Dust mite	18 (5.1%)	6 (3.1%)	24 (0.4%)

TABLE 2: Distribution of the patients with immediate local reactions (grade 1) according to the types of allergic disease and allergen.

	Build-up therapy		Maintenance therapy	
	Number of injections (n)	Number of local reactions (n) (%)	Number of injections (n)	Number of local reactions (n) (%)
Asthma	4497	286 (6.3%)	4766	104 (2.1%)
Allergic rhinitis	5387	412 (7.6%)	6086	140 (2.3%)
Asthma + Allergic rhinitis	3745	272 (7.2%)	3893	96 (2.4%)
Grass polen	10544	659 (6.2%)	10612	260 (2.4%)
Dust mite	2552	241 (9.4%)	3453	71 (2.0%)
Grass pollen + Dust mite	533	70 (13%)	680	9 (1.3%)
Total	13629	970 (7.1%)	14745	340 (2.3%)

TABLE 3: Distribution of the immediate adverse reactions according to the type of allergen.

		Number of injections (n)	Number of reactions (n)	Local itching (n)	Hyperemia (n)	Hyperemia +Induration+ Local itching (n)	Systemic reaction (n)
Group 1	Grass pollen	12865	757 (5.8%)	43 (0.3%)	19 (0.14%)	690 (5.3%)	5 (0.04%)
	Dust mite	3706	257 (6.9%)	6 (0.16%)	8 (0.22%)	241 (6.5%)	2 (0.05%)
	Grass pollen + Dust mite	908	55 (6.0%)	2 (0.02%)	6 (0.06%)	47 (5.1%)	0 (0.0%)
Group 2	Grass pollen	8291	162 (1.9%)	18 (0.2%)	3 (0.04%)	137 (1.6%)	4 (0.05%)
	Dust mite	2299	55 (2.3%)	20 (0.8%)	0 (0.0%)	33 (1.4%)	2 (0.08%)
	Grass pollen + Dust mite	305	24 (7.8%)	0 (0.0%)	0 (0.0%)	24 (7.8%)	0 (0.0%)
Total	Grass pollen	21156	919 (4.3%)	61 (0.3%)	22 (0.1%)	827 (3.9%)	9 (0.05%)
	Dust mite	6005	312 (5.1%)	26 (0.4%)	8 (0.1%)	274 (4.5%)	4 (0.07%)
	Grass pollen + Dust mite	1213	79 (6.5%)	2 (0.2%)	6 (0.5%)	71 (5.8%)	0 (0.0%)

use of the disease, and because immunotherapy targets individuals with severe disease, administration of these allergen vaccines can cause adverse, allergic reactions and even death.[14] Adverse systemic reactions seen due to allergen immunotherapy are major problems for both patients and clinicians. Despite many preventive measures against such reactions (premedications, etc.), there is no proven predictive factor for the appearance, type and severity of reactions.[15] Researches have evaluated adverse reactions, seeking to determine the frequency, type, severity, and risk factors associa-

TABLE 4: Distribution of immediate systemic adverse reactions according to the type of allergic disease.

		Systemic reactions (n)	Type of systemic reaction
Group 1	Asthma	2	Dizziness, anaphylaxis
	Allergic rhinitis	1	Burning sensation of throat
	Asthma + Allergic rhinitis	4	Bronchospasm (2), urticaria, dizziness
Group 2	Asthma	1	Bronchospasm
	Allergic rhinitis	2	Urticaria, dizziness
	Asthma + Allergic rhinitis	3	Bronchospasm, urticaria (2)
Total	Asthma	3	
	Allergic rhinitis	3	
	Asthma + Allergic rhinitis	7	

ted with subcutaneous immunotherapy.[14-18] This study is one of largest ever conducted in the pediatric patient population which evaluates the adverse reactions of subcutaneous immunotherapy.

Some of the local reactions, like local swelling at the site of an allergen vaccine injection, are common and does not require specific therapy or adjustment in dosing. However, systemic reactions involving organ-specific systems distant from the injection site can be potentially serious, ranging from rhinorrhea to severe asthma and anaphylactic shock. The rate of adverse reactions depends on a variety of factors, including degree of allergic sensitivity, the dose schedule, the allergen vaccine and formulation and the presence of asthma.[14]

A review of thirty-eight subcutaneous immunotherapy studies using inhalant allergens, demonstrated that the reaction rates increase as the immunotherapy schedule is accelerated and when high or optimal dose regimens (associated with efficacy) are used in highly sensitive patients.[14,19] Nelson et al.[20] reported 4% local reactions in a study using pollen extracts for specific immunotherapy. The patients who received grass pollen immunotherapy in our study, which has clearly a big sample size for a pediatric study, had similar rates of local reactions (4.3%). In patients receiving dust mite immunotherapy, local reaction rate was detected as 5.2%. In both groups, most of the reactions were observed during the build-up period, which was statistically significant ($p< 0.01$).

Calcium phosphate and aluminum hydroxide have been used for many years as immunological adjuvants for allergen vaccines. The efficacy and adverse effects of these immunological adjuvants have been compared in many studies, and in most of these studies calcium phosphate adsorbed extracts were claimed to induce less local reactions.[21-27] However, according to our study, immediate adverse reactions were observed statistically significantly higher in the calcium phosphate group ($p< 0.01$).

The most common risk factors for fatal systemic reactions to allergen immunotherapy include: history of asthma, increasing allergen dose, high allergen sensitivity, history of previous systemic reaction, injection during an active allergen season, new (fresh) extracts, β-blocker therapy.[28] The use of increasingly potent and purified extracts and administration schedules aimed at achieving the highest tolerated dose quickly increases the risk of severe, sometimes fatal, adverse reactions.[29] Lockey et al.[30] demonstrated that in most cases the severe adverse reactions were due to avoidable technical errors such as incorrect prescriptions, incorrect doses, mismatched vials, administration to symptomatic patients, lack of appropriate supervision, and lack of critical care equipment. The incidence of fatal systemic reactions has been reported as one in two million injections. The rate of nonfatal adverse reactions varies from 0.05 to 3.2% (average 0.5%).[19,31,32] The frequency of systemic reactions in our study was 0.04%, which was lower than the studies reported in the medical literature to date. Variability of rates of systemic reactions to subcutaneous injection immunotherapy is because of dif-

ferences in allergen vaccines and treatment protocols. Furthermore, injections by general practitioners or inexperienced physicians may alter the incidence of adverse reactions in these studies. In our study, all injections were administered by experienced staff in the clinic under our direct observation.

In a study from a multiple physician office group, data were obtained from 4578 patients receiving subcutaneous immunotherapy over one year; the systemic reaction rate was one per 1600 patient visits, or one per 47 patients, when receiving full concentration maintenance injections. This rate was significantly higher during the build-up phase, one per 32 patients. Twelve cases were severe involving hypotension or respiratory distress. Twenty-eight of the 98 patients with systemic reactions had the onset of their reaction more than 30 minutes after the injection, none involving hypotension.[32] In a report from Europe on nonfatal reactions to SCIT in 4600 patients receiving aluminium hydroxide adsorbed vaccines from various manufacturers, there were 115 systemic reactions (5.2% of patients and 0.06% of injections) from 1981 to 1990 and 26 systemic reactions over the next decade (1.08% of patients and 0.01% of injections). The latter period, 1991-2000, was associated with fewer systemic reactions, particularly those manifested as asthma and urticaria. In neither period were there any fatalities.[8]

Two surveys was conducted by AAAAI (American Academy of Allergy, Asthma and Immunology), one from 1985 to 1989 and the other from 1990 to 2001, and the researches detected 17 fatalities in each of the surveys. More than 75% of the cases were asthmatic patients, half were on build-up therapy, and more than 80% had onset of symptoms within 30 minutes of their injections. An extension of the 1990-2001 survey focused on reports of near fatal reactions, defined as severe respiratory compromise, hypotension, or both requiring emergency epinephrine treatment; maintenance dosing was involved in 58%, reactions during the height of the allergy season in 46%, dosing errors occurred in 25% and there was a history of a previous systemic reaction in 9% of cases.[10,14]

In the past several years, international guidelines have been introduced to improve both the efficacy and safety of allergen immunotherapy.[33-35] Adherence to guidelines carefully and coordination of doctor, staff and patient roles are crucial to minimize adverse reactions, especially associated with SCIT.[13] The safety precautions to lessen the risk of an adverse reaction to immunotherapy are as follows:[14] (1) Proper patient selection, (2) Special attention to asthmatics, highly allergic patients, (3) Awareness of clinical status on treatment days, postpone dose if unstable, (4) Monitor patient for new medication usage, particularly, β-blockers, (5) Careful dosing-right patient, right dose, (6) Consider dose adjustments during allergy season, (7) Compliance with treatment schedules, (8) Make dose adjustments for newly prepared vaccines, (9) Early recognition and treatment of adverse reactions, (10) Consider discontinuing therapy in repeat reactors, (11) Remain vigilant-reactions can occur after years of maintenance therapy and more than 30 min after dosing.

In conclusion, the frequency of immediate adverse reactions to allergen specific subcutaneous immunotherapy is low. Most of the immediate reactions to immunotherapy are local, and the systemic ones are controllable through early treatment. Immunotherapy is a safe treatment modality when it is used for appropriate indications by experienced staff.

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