The Turkish Journal of Pediatrics 2018; 60: 684-690
DOI: 10.24953/turkjped.2018.06.009

Original

Safety of subcutaneous allergen immunotherapy in children: A retrospective review and bird eye to literature

Esra Toprak-Kanık[1], Özge Yılmaz[1], Ezgi Yangın-Ergon[2], Ahmet Türkeli[1], Hasan Yüksel[1]

[1]Division of Pediatric Allergy and Pulmonology, [2]Department of Pediatrics, Celal Bayar University Faculty of Medicine, Manisa, Turkey.· Email: hyukselefe@hotmail.com

Received: 27th November 2017, Revised: 7th January 2018, 25th February 2018, Accepted: 18th March 2018

SUMMARY: Toprak-Kanık E, Yılmaz Ö, Yangın-Ergon E, Türkeli A, Yüksel H. Safety of subcutaneous allergen immunotherapy in children: A retrospective review and bird eye to literature. Turk J Pediatr 2018; 60: 684-690.

Subcutaneous allergen immunotherapy (SCIT) has been shown to improve clinical course in children with asthma and allergic rhinitis (AR). Systemic and local side-effects may be seen during its administration. The purpose of this study was to evaluate risk factors associated with systemic and local side-effects in children receiving SCIT. We performed a retrospective chart review in the children who received allergen subcutaneous immunotherapy for asthma and/or allergen rhinitis. Demographic data, diagnosis, skin prick test results, presence of additional allergic diseases, the seasonal variation of adverse events in the first and third years of SCIT were recorded. A total of 508 eligible patients were included in the study. Mean age of the children was 10.9±3.2 years, and 65.4% were male. Asthma was present in 21.9% of the children, AR in 44.7%, 33.5% of them had both asthma and AR. According to the skin prick test results, sensitivity to more than one allergen was present in 45.1%, while the most common single-allergen sensitivities were to grass pollen and dermatophagoids (32.5% and 14.4%, respectively). Ratio of systemic and local side-effects was 4.7% and 9.3%, respectively. Local side-effects were more common than systemic reaction. SCIT is a safe treatment modality while using the appropriate dose and with the administration of dose-escalation protocol.

Key words: asthma, allergic rhinitis, subcutaneous immunotherapy, side effects.

Specific allergen immunotherapy is considered as an important treatment modality for the allergic patient that has been the unique intervention which can change the natural course of allergic diseases.[1] With this treatment modality, allergens are given with repeated and increasing doses for immune tolerance.[2,3] Subcutaneous allergen immunotherapy (SCIT) provides significant amelioration in symptoms, drug intake related with asthma as well as in pulmonary function; improves life quality and reduces the risk for new allergic sensitizations.[4,5]

The safety profile of SCIT in the pediatric population has been thoroughly evaluated in most of the clinical studies. It has been accepted that SCIT is safe in children with allergic rhinitis (AR) and mild–moderate asthma. SCIT is generally well tolerated in subjects with correct indication when administered with appropriate doses however, local or systemic adverse reactions may occur[5,6]. Rarely some of them may be fatal and near-fatal adverse events.[7] Data about the clinical effectiveness and prevalence of side-effects is limited for pediatric patients. The aim of this study was to determine the safety of SCIT in a large sample of pediatric population with allergic diseases and to define the factors affecting the side-effects.

Material and Methods

Pediatric patients (6-18 years) with allergic rhinoconjunctivitis (AR) and/or asthma who received SCIT for at least 3 years were included in the study. Data were retrieved from patient's medical record between 2001

and 2011 who were followed up at Celal Bayar University School of Medicine, Department of Pediatric Allergy, using a data collection form which included demographic and clinical characteristics.

The age at commencement of SCIT, gender, diagnoses, presence of food allergies and additional allergic diseases such as urticaria and atopic dermatitis, allergen sensitivity at skin prick test (SPT), local and systemic side-effects after injection were recorded from the medical records of the patients.

Skin prick test

Forty allergen extracts (Allergopharma, Germany) containing mite mix (*D. pteronyssinus, D. farinae*), tree mix, grass mix (*Grasses*) and fungi (*Alternaria*) selected by SPT were administered to all children in the study as similar to the data of our country.[8] At assessment of negative and positive controls by diameter, an induration of 3 mm and above with hyperemia was regarded as positive SPT and reaction less than 3 mm as negative.[9]

An SPT panel covering 12 allergen extracts was sufficient to detect most of the sensitized children and adolescents with recurrent respiratory symptoms.

Administration of subcutaneous specific immunotherapy

In our clinic, SCIT is started with appropriate allergen mixes (Allergopharma, Reinbek Germany) on the basis of the patient's SPT results at a weekly dosage of 0.5 TU/dose. It is administered for a total of 4 years, weekly for 8 months, at 15-day intervals for 6 months and monthly for 34 months in the form of one 5,000 TU. Mite mix (*D. pteronyssinus D. farinae*), grass pollen or fungi (*Alternaria*) are administered from different arms and SCIT is performed with a maximum of two allergen groups.

Assessment of immunotherapy-associated side-effects

Indurations >10 mm and hyperemia >15 mm at the injection site was regarded as a local reaction. Criteria set out by the European Academy of Allergology and Clinical Immunology (EAACI) was used in the assessment of systemic side-effects seen post-SCIT. These are defined as stage 1; non-specific reactions, such as headache, lethargy and joint pain, stage 2; mild systemic reactions [mild-rhinitis asthma responding to antihistamines or inhaled beta agonists PEFR (peak expiratory flow rate) >60%], stage 3; non-life threatening systemic reactions (urticaria, angioedema, severe asthma responding to treatment PEFR <60%) and stage 4; life-threatening systemic reactions (widespread itching, urticaria, erythema, bronchospasm, hypotension, anaphylaxis, shock)[6]. Week of SCIT at appearance of local and systemic side-effects, dose and season were recorded.

This retrospective cohort study was approved by the Celal Bayar University Clinical Research Ethical Committee; approval dated 06.06.2012, No. 193.

Statistical analysis

We used SPSS 15.0 software for data analysis. Categorical variables were compared using the Chi-square test, continuous variables were analyzed using the Mann-Whitney U and Kruskall-Wallis tests. Odds ratio (OR) was obtained using logistic regression analysis. A p value <0.05 was accepted to be statistically significant.

Results

Five hundred and fifty patients with a diagnosis of asthma and/or AR were determined from our medical charts. However, 42 patients were excluded because of the incomplete immunotherapy process due to the socioeconomic conditions without any medical reason. Five hundred eight patients receiving immunotherapy with a diagnosis of asthma and/or AR were enrolled, 176 (34.6%) female and 332 (65.4%) male. Demographic Characteristics are shown in Table I.

Adverse Reactions to Immunotherapy

Maintenance dose was achieved during immunotherapy in all patients. During immunotherapy, local reaction was observed in 47 (9.3%) and systemic reaction in 24 (4.7%). Females represented 66.7% of the cases developing systemic reaction and 38.3% of those developing local reaction. The greater

Table I. Demographic Characteristics of Children.

Age, years	10.9±3.2
Gender, N (%)	
Female	176 (34.6)
Male	332 (65.4)
Disease, N (%)	
Asthma	111 (21.9)
Allergic rhinoconjunctivitis (AR)	227 (44.7)
Asthma and AR	170 (33.5)
Urticaria	42 (8.3)
Atopic dermatitis	8 (1.6)
AR severity, n/N (%)	
Mild intermittent	71/397 (14.0)
Moderate intermittent	235/397 (46.3)
Severe intermittent	22/397 (4.3)
Mild persistent	5/397 (1.0)
Moderate persistent	62/397 (12.2)
Severe persistent	2/397 (0.4))
Asthma severity, n/N (%)	
Intermittent	84 (29.9)
Mild persistent	197 (70.1)
Sensitization, N (%)	
Grass polen	165 (32.5)
Tree polen	25 (4.9)
Mite	73 (14.4)
Mold	16 (3.1)
Mixed	229 (45.1)

AR: allergic rhinoconjunctivitis

prevalence of systemic reactions in female gender was statistically significant (p=0.001; OR=4.050). However, there was no significant difference between the children and the adolescents (p=0.74).

Age at onset of asthma in patients with systemic reaction was 7.0±3.5 years, compared to 5.2±3.3 years in those not developing systemic reaction, the difference was statistically significant (p<0.001). There were no differences regarding the systemic and local reactions among patients with asthma, AR and the patient with both disease (p=0.24). Sensitivity to grasses was present in 45.8% (11/24) of cases with systemic reaction, sensitivity to tree pollen in 16.7% (4/24) and mixed sensitivity in 37.5% (9/24). Both local and systemic reactions were more frequent in spring (31.9% and 25.0%, respectively; Table II). Three out of 15 patients with grass and tree pollen sensitivity exhibited systemic reactions in winter. Less systemic reactions were observed in winter, however the difference was not statistically significant. Among the cases who have systemic reactions (n=24), 23 cases had grade 1 symptoms (%95.8), only 1 case had grade 2 symptoms (%4.2), and none of the cases had grade 3 systemic reactions. Systemic reaction developed in 12.8% (6/47) of patients who had local reaction and 3.9% (18/461) of those without (OR=3.36; %95 CI: 1.266-8.95, p=0.001). The risk for systemic reaction was calculated by binary logistic regression. Female gender was 4.050 times (95% CI: 1.697-9.663; p=0.003), and tree and grass sensitivity was 2.789 times (95% CI: 1.245-6.249; p=0.015) increased risk for systemic reaction (Table III).

Number of attacks in the first year of immunotherapy in subjects with systemic reaction was 0.5±0.8, compared to 1.5±1.4 with those without any systemic reaction (p<0.001).

Discussion

Here, in a retrospective survey of 508 cases, we evaluated the safety of SCIT in a pediatric population. Our results suggest that this treatment modality had few side effects.

Subcutaneous allergen immunotherapy entered into contemporary therapeutic use when it was seen to lead to improvement in clinical findings in allergic patients in whom it was indicated.[10]

Immunotherapy has a very low incidence of side-effect when applied by pediatric allergy specialists in appropriate indications and doses in childhood, although very rare fatal reactions have still been reported.[6,11] The most feared complication of SCIT is systemic reactions. Local or generalized urticaria, angioedema, anaphylaxis and even fatal outcomes may arise.[6,12] Various studies have reported systemic reaction in 2.1-17% of patients. Allergen potential and form of application, dose increase plan, maximum dose, disease severity all contribute to these variations.[13,14] In 1993, the EAACI divided systemic reactions into four stages, beginning with lethargy and headache and progressing to rhinitis, asthma and severe anaphylaxis. The majority of reactions seen post-SCIT are local or early stage (stage 1 and 2) reactions.[6,15] According to the American Academy of Allergy Asthma Immunology (AAAI) data, grade 3-4 reactions are rare and, no fatal reaction had been observed between 2007 and 2011. Stage 4 systemic reaction was observed in one study assessing the effectiveness and reliability of SCIT performed

Table II. Risk Factors for Systemic and Local Reactions.

Risk factors	Type of reaction			
	Systemic, n/N (%) (24 patients)	p	Local, n/N (%) (47 patients)	p
Gender				
Female	16/24 (66.7)	0.001	18/47 (38.3)	0.612
Male	8/24 (33.3)		29/47 (61.7)	
Disease				
Asthma	3/24 (12.5)	0.240	7/47 (14.9)	0.360
AR	10/24 (41.7)		25/47 (53.2)	
Asthma and AR	11/24 (45.8)		15/47 (31.9)	
Sensitization				
Grass pollen	11/24 (45.8)	0.010	15/47 (31.9)	0.690
Tree pollen	4/24 (16.7)		4/47 (8.5)	
Mite	0		2/47 (4.3)	
Mold	0		5/47 (10.6)	
Mixed	9/24 (37.5)		21/47 (44.7)	
Season				
Spring	6/24 (25.0)	0.311	15/47 (31.9)	0.880
Summer	8/24 (33.3)		9/47 (19.1)	
Autumn	7/24 (29.2)		15/47 (31.9)	
Winter	3/24 (12.5)		8/47 (17.0)	

**Fisher's exact test (Chi-square test)*

with grass pollen[16]. In another study, stage 2 reactions were determined at a level of 78%, stage 3 at 20% and stage 4 at 1%.[12] In a retrospective study of 1,350 immunotherapy patients; 39 (2.8%) patients had a systemic reaction and only one of them had grade 4 reaction.[17] Our rate of systemic and local side-effects was 4.7% and 9.3%, respectively. In our study, systemic reaction was seen at a level of 4.7% in 24 patients, stage 1 in 23 patients, and 1 patient with stage 2, grade 3-4 reactions were not determined. The relatively low ratio may be because of the protocol that we perform with slow increasing dose and the case selection for immunotherapy including the AR, mild and moderate asthma patients.

Many surveillance studies have attempted to identify risk factors associated with systemic and severe systemic reactions. In particular, uncontrolled asthma has been associated with fatal and near-fatal reactions.[18,19] Amin et al.[20] observed that 46% of the cases who had severe systemic reactions had a diagnosis of moderate or severe asthma.

Although previous studies have reported a higher prevalence of systemic side-effects in asthmatic patients administered SCIT compared to patients with AR, no difference was determined in our study.[6,21,22] In addition, there was no patient with severe uncontrolled asthma in our study.

Another agent with conflicting outcomes on impact on frequency of systemic reaction is the allergen group applied in SCIT. One study in Denmark involving 1,038 patients with a mean age of 35 years determined a higher risk of systemic reaction after SCIT in asthmatic patients with allergy to household dust compared to SCIT with grass pollens.[12] Moreno et al.[23] reported in a multi centric study involving asthmatic and/or AR patients, higher SCIT-related side-effects in asthmatic patients compared to those with AR and in patients with household dust allergy compared to those with grass/tree pollen allergies. Another study involving AR patients reported a higher number and greater severity of side-effects in SCIT with grass pollen compared to SCIT with tree pollen.[24] However, it is also reported that allergen type administered in SCIT does not affect the rate of systemic reaction.[12] According to our results, there were significantly more systemic reactions among the patients with grass allergy than the patients with mite and mold allergy.

Sensitivity of the patient might have increased

Table III. Univariate and Multivariate Analysis: Factors Independently Associated with Systemic Reaction.

Variables	Univariate analysis*			Multivariate analysis[a]			
	Presence of systemic reaction	Absence of systemic reaction	p*	B	S.E.	Wald	p**	OR (95% CI)
Gender, female/male	16/8	160/324	0.001	1.317	0.449	8.612	0.003	4.050 (1.697-9.663)
Presence of asthma	15	268	0.493	0.501	0.446	1.263	0.261	1.343 (0.577-3.129)
Grass and tree pollen sensitivity	15	175	0.009	-0.272	0.844	27.152	0.015	2.789 (1.245-6.249)

* Chi-square test, **binary logistic regression, CI: confidence interval, OR: Odds ratio

during the period when the exposure of patient to the allergen has increased and hence there is an increased risk of systemic reaction.[20] Kannan et al.[18] observed fatal and severe systemic reactions ranging from 29-41% in peak pollen season while Amin et al.[20] reported near-fatal reactions in 9%. In another study, 56.4% of patients with a systemic reaction were found to be in peak pollen season.[17] Ebstein et al.[25] reported that low doses of allergen may decrease the severity of systemic reactions in the peak pollen seasons. The results of our study suggested that systemic reactions due to immunotherapy were increased in the peak pollen season in the patients with pollen sensitivity. In the light of these findings, the authors suggested that decreasing the immunotherapy allergen dose could help to reduce the risk of systemic reaction when the allergen exposure of the patient has increased.

The prevalence of systemic reactions in traditional immunotherapy doses is reported 0.2% while the risk increases up to 30% due to rapidly increased doses of allergen immunotherapy[26]. We ascribe these variable results among different centers to allergen structure, differences in the dose increase protocol, mode of application and whether premedication was administered or not.

In some studies, a significant portion of the systemic and fatal systemic reactions associated with SCIT have been shown to occur during the enhancement phase of immunotherapy.[19]

In a recent study conducted with 135 patients under SCIT, reported that systemic reactions were significantly higher in the dose increasing period.[27] However, there are also studies that find systemic reactions more frequent and severe in the idiopathic phase.[17,20] In addition, slow dose increase in recommendations may also have affected prevalence of side-effects in line with the allergen extract. In our study, the rate of systemic reactions in dose increased period was significantly higher than in maintenance period. Thus we suggest the use of the traditional method of slowly increased dose immunotherapy should be administered with careful follow-up.

A higher prevalence of side-effects has been seen in protocols which use more than one allergen on the same day.[12] No such variation was seen in our study. This variation among

studies may be due to the characteristics of different patient groups. Age and gender were recognized as the risk factors associated with side-effects, and greater systemic reaction has been reported under the age of 5 years. A multi-centric study performed with venom immunotherapy reported that female gender exhibited more side-effects, although negative conclusions about the correlation with age and gender predominate.[13,23,28] In a study involving 23,610 children and adult patients under immunotherapy, side effects have been shown to be more common in female gender and older ages.[29] There was no significant difference regarding the age group in our study, however side-effects were significantly more common in the female gender.

Limitations of this study were coming from retrospective design which cannot compare the results with a control group. Moreover, the data was obtained from patient records that received the allergen extracts of one single company. Despite these shortcomings, in this research, the patients who had completed the third year of SCIT were evaluated. Safety of SCIT was documented for all types of allergen treatment among all age groups with a large pediatric sample size with a similar panel to those reported by previous Turkish studies.[8]

In conclusion, the clinical effectiveness of SCIT in the treatment of asthma and/or AR has been confirmed in childhood. SCIT is a safe treatment method for patient who is sensitive when administered in an appropriate dose with dose-escalation protocol. It should be noted that systemic and local reactions occur very rarely considering the type of allergen sensitization and seasonal properties in an experienced center.

REFERENCES

1. Akdis CA, Akdis M. Mechanisms of allergen-specific immunotherapy. J Allergy Clin Immunol 2011; 127: 18-27.
2. Burks AW, Calderon MA, Casale T, et al. Update on allergy immunotherapy: American Academy of Allergy, Asthma and Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. J Allergy Clin Immunol 2013; 131: 1288-1296.e3.
3. Moote W, Kim H. Allergen-specific immunotherapy. Allergy Asthma Clin Immunol 2011; 7(Suppl 1): S5.
4. Jacobsen L, Wahn U, Bilo MB. Allergen-specific immunotherapy provides immediate, long-term and preventive clinical effects in children and adults: The effects of immunotherapy can be categorised by level of benefit -the centenary of allergen specific subcutaneous immunotherapy. Clin Transl Allergy 2012; 2: 8.
5. Aryan Z, Comapalati E, Canonica GW, Rezaei N. Allergen-specific immunotherapy in asthmatic children: From the basis to clinical applications. Expert Rev Vaccines 2013; 12; 639-659.
6. Malling H, Weeke. Position paper: Immunotherapy (EAACI) The European Academy of Allergology and Clinical Immunology. Allergy 1993; 48(14 Suppl): 7-35.
7. Calderon MA, Gerth van Wijk R, Eichler I, et al.; European Academy of Allergy and Clinical Immunology. Perspectives on allergen-specific immunotherapy in childhood: An EAACI position statement. Pediatr Allergy Immunol 2012; 23: 300-306.
8. Sahiner UM, Civelek E, Yavuz ST, Buyuktiryaki AB, Tuncer A, Sekerel BE. Skin prick testing to aeroallergen extracts: What is the optimal panel in children and adolescents in Turkey? Int Arch Allergy Immunol 2012; 157: 391-398.
9. Heinzerling L, Frew AJ, Bindslev-Jensen C, et al. Standard skin prick testing and sensitization to inhalant allergens across Europe--a survey from the GALEN network. Allergy 2005; 60: 1287-1300.
10. Madsen F. EAACI 'Standards for practical allergen-specific immunotherapy'. Allergy 2007; 6: 332.
11. Ramirez NC, Ledford DK. Immunotherapy for allergic asthma. Med Clin North Am 2002; 86: 1091-1112.
12. Winther L, Arnved HJ, Malling HJ, Nolte H, Mosbech H. Side-effects of allergen-specific immunotherapy. A prospective multi-centre study. Clin Exp Allergy 2006; 36: 254-260.
13. Mosbech H, Müller U. Side-effects of insect venom immunotherapy: Results from an EAACI multicenter study. European Academy of Allergology and Clinical Immunology. Allergy 2000; 55: 1005-1010.
14. Ebstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. Immediate and delayed onset-systemic reactions after subcutaneous immunotherapy injections: ACAAI/ AAAAI surveillance study of subcutaneous immunotherapy: year 2. Ann Allergy Asthma Immunol 2011; 107: 426-431.e1.
15. Dursun AB, Sin BA, Oner F, Misirligil Z. The safety of allergen immunotherapy (IT) in Turkey. J Investig Allergol Clin Immunol 2006; 16: 123-128.
16. Klimek L, Schendzielorz P, Pinol R, Pfaar O. Specific subcutaneous immunotherapy with recombinant grass polen allergens: First randomized dose-ranging safety study. Clin Exp Allergy 2012; 42: 936-945.
17. Bahceci Erdem S, Nacaroglu HT, Karaman S, 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.
18. Kannan JA, Epstein TG. Immunotherapy safety: What have we learned from surveillance surveys? Curr Allergy Asthma Rep 2013; 13: 381-388.
19. Makatsori M, Calderon MA. Anaphylaxis: Still a ghost behind allergen immunotherapy. Curr Opin Allergy Clin Immunol 2014; 14: 316-322.

20. Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. J Allergy Clin Immunol 2006; 117: 169-175.

21. Saltoun CA. Update on efficacy of allergen immunotherapy for allergic rhinitis and asthma. Allergy Asthma Proc 2002; 23: 377-380.

22. Bernstein DI, Epstein T. Systemic reactions to subcutaneous allergen immunotherapy. Immunol Allergy Clin North Am 2011; 31: 241-249.

23. Moreno C, Cuesta-Herranz J, Fernandez-Tavora L, Alvarez-Cuesta E; Immunotherapy Committee, Sociedad Española de Alergología e Inmunología Clínica. Immunotherapy safety: A prospective multi-centric monitoring study of biologically standardized therapeutic vaccines for allergic diseases. Clin Exp Allergy 2004; 34: 527-531.

24. Winther L, Malling HJ, Mosbech H. Allergen-specific immunotherapy in birch- and grass-pollen-allergic rhinitis. II. Side-effects. Allergy 2000; 55: 827-835.

25. Ebstein TG, Liss GM, Murpy-Brendts K, Bernstein DI. AAAAI and ACAAI surveillance study of subcutaneous allergen immunotherapy, year 3: what practices modify the risk of systemic reactions? Ann Allergy Asthma Immunol 2013; 110: 274-278.

26. 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: 569-574.

27. Rottem M, Egbarya A. Subcutaneous immunotherapy in Northern Israel: Efficacy and safety. Isr Med Assoc J 2014; 16: 539-543.

28. Iglesias-Cadarso A, Hernández-Weigand P. Risk factors for systemic reactions to allergen immunotherapy. Curr Opin Allergy Clin Imunol 2011; 11: 579-585.

29. Schaffer FM, Naples AR, Ebeling M, Hulsey TC, Garner LM. The safety of self-administered allergen immunotherapy during the buildup and maintenance phases. Int Forum Allergy Rhinol 2015; 5: 149-156.