

Subcutaneous Allergen Immunotherapy in Children: Real Life Compliance and Effect of COVID-19 Pandemic on Compliance

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Abstract

Background: Allergen immunotherapy (AIT) is an effective treatment for allergic rhinitis, asthma and venom allergy. Compliance is essential for AIT to obtain maximal benefit as it is a long term treatment. **Objective:** We aimed to evaluate the real life compliance of children with subcutaneous immunotherapy (SCIT) and tried to document the factors associated. Additionally how COVID-19 pandemic effected the compliance of the patients and the reasons of drop-outs were also evaluated. **Method:** Patients diagnosed with allergic rhinitis, allergic asthma or venom allergy and treated with SCIT between 2012 September, 2020 July were analyzed. **Results:** The study population comprised of 201 children (66,7% male) with a median (interquartile range) age of 12,8(9,4-15,2) years during the first injection of SCIT. The overall compliance rate before COVID-19 pandemic was 86,1%. Short AIT follow up time and venom allergy were found to be risk factors for drop out. The leading causes of drop outs were moving to another city/country(32,1%), improvement of symptoms(17,8%), ineffectiveness(14,2%) and adverse reactions(14,2%). During COVID-19 pandemic, among 108 patients receiving AIT, 31(28,7%) dropped out the therapy. The most frequent reasons for drop-outs were fear of being infected with COVID-19(35,4%) and thinking that the AIT practise stopped due to COVID-19 pandemic(29%). Male gender and older age were found to be the independent risk factors for drop out. **Conclusion:** The real life compliance in children was higher than in adults. Nearly one third of children dropped out during COVID-19 pandemic. Male gender and older age are associated with AIT drop out during COVID-19 pandemic.

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Keywords: Aeroallergen, Allergen immunotherapy, Children, Compliance, COVID-19,

House dust mite, Venom

Abbreviations

AIT: Allergen immunotherapy

AR: Allergic Rhinitis

COVID-19: The Coronavirus disease 2019

HDM: House dust mite

SCIT: Subcutaneous allergen immunotherapy

SLIT: Sublingual immunotherapy

SPT: Skin prick test

VIT: Venom immunotherapy

Introduction

Allergen immunotherapy is an effective and game-changing treatment method for allergic rhinitis, venom anaphylaxis and allergic asthma which can provide immune tolerance for many years. Subcutaneous allergen immunotherapy (SCIT) is the most commonly used administration route, and requires repeated administration of allergen extracts for 3 to 5 years depending on the type of allergen applied.

Compliance is essential for AIT to obtain maximal benefit as it is a long term treatment. However non-compliance rates may be as high as 50% in both adults and children¹⁻³. The major factors associated to noncompliance are long duration of treatment, frequency of injections, high medical cost, improvement of systemic reactions over time, poor perceived efficacy, allergic reactions during vaccinations and travelling, and differ between centres, health system structure and cultures⁴⁻⁶. Most of the studies about compliance come either from adult studies or from study populations involving both adults and children; the ones involving only pediatric age group are very limited³.

The Coronavirus disease 2019 (COVID-19) pandemic not only affected people with COVID-19 infection but also disrupted the treatment of patients with chronic diseases. In this period, some changes in the pattern of hospital admissions was recognized. A study from northern Italy showed a significant decrease in acute coronary syndrome related hospitalization rates across several cardiovascular centers in northern Italy during the early days of the COVID-19 outbreak⁷. During that period, a significant increase in mortality was reported that was not fully explained by COVID-19 cases alone, and thought to be due to failure to access medical attention. In this period, we also observed a reduction in pediatric outpatient admissions for AIT.

In the present study we aimed to investigate the real life compliance of children with SCIT and tried to document the factors associated with compliance. Additionally we evaluated how the COVID-19 pandemic effected the compliance of our patients and the reasons that caused drop-outs.

Methods

Study population

Two hundred and one children who had allergic rhinitis, allergic asthma or venom allergy and treated with SCIT at Hacettepe University Medical School Hospital, Department of Pediatric Allergy between 2012 September, 2020 July were included in the study. The study protocol was reviewed and approved by our University Institutional Review Board.

AIT was administered to patients with allergic rhinitis and/or allergic asthma who had uncontrolled AR symptoms along with medical treatments and avoidance measures; AIT was given to patients with asthma only if their disease is allergic and mild to moderate in severity; and venom immunotherapy (VIT) was administered to patients who had a history of at least one systemic reaction after *Apis mellifera* and/or *Vespula* stings and positive diagnostic test reactions (skin prick test(SPT) or specific immunoglobulin E (sIgE) for culprit insect venom.

Patients' demographic data, diagnosis of allergic disease, AIT regimen, date of initiation of AIT, compliance and drop-out were noted from their medical records, retrospectively up to the COVID-19 pandemic period, afterwards it was reported prospectively. The treatment adherence of patients in COVID-19 period was defined as the time between the first confirmed case of COVID-19 in Turkey (March 15, 2020) and June 15, 2020.

Diagnosing Allergic rhinitis/allergic asthma and venom allergy

The diagnoses and therapies of AR and asthma and venom allergy were defined according to the allergic rhinitis and its impact on asthma (ARIA)⁸ and Global Initiative for Asthma (GINA)⁹ and European Academy

of Allergy and Clinical Immunology guidelines¹⁰, respectively.

Immunotherapy Application and Compliance Assessment

Patients were applied one of Alutard SQ 100% vespula or Apis mellifera (Alutard SQ, ALK, Hørsholm, Denmark) venom immunotherapy, Allergovit Grass 006 (Allergopharma Joachim Ganzer KG, Hamburg, Germany) allergen immunotherapy or NovoHelisen Depot HDM %50 DP+%50 DF (Allergopharma Joachim Ganzer KG, Hamburg, Germany) allergen immunotherapies. VIT doses were administered in 1-week intervals and were gradually increased to the maintenance dose over 6 months¹¹. Then, maintenance doses were administered every 4 to 6 weeks for up to 5 year¹². AIT doses for grass allergy and house dust mite(HDM) allergy; were administered in 1-week intervals and were gradually increased to the maintenance doses over 6 weeks in grass and 14 weeks in HDM¹³. Then, maintenance doses were administered every 4 to 6 weeks for up to 4 years.

Compliance was defined as receiving the allergen immunotherapy according to the prescribed treatment course for each patient, and evaluated during the first-year, second-year, third year, fourth-year, and fifth-year, or treatment completion. Patients who had [?]2 two week breaks from their defined treatment schedule per year were accepted to be in excellent compliance, 3 to 4 two week breaks were in good compliance, 5 to 6 two week breaks were fair compliance, and 7 or more two week breaks were poor compliance¹⁴. Patients who had three consecutive months delay from their defined treatment schedule were accepted as dropped out¹⁵. The reasons for drop-out was recorded.

Statistics

Statistical analyses were performed using SPSS version 22.0 statistical software package (IBM SPSS Statistics, USA). First normality tests for continuous variables were performed and as all of the continuous variables were distributed non-normally the results were given as median [inter-quartile range(IQR)]. The chi-square and Mann-Whitney U tests were used to compare nonparametric values. For the risk analysis of drop-outs variables were selected if the p value was less than 0.20 in the univariate analysis and included in multivariate analysis. Odds ratios (ORs) with relevant 95% confidence intervals (CIs) were calculated to evaluate potential associations. Values of $P < .05$ were accepted as significant.

Results

The Real Life Results Before COVID-19 Pandemic (2012 September-2020 March)

There were 201 children who received SCIT injections between 2012 September, 2020 March. According to the demographic data there was a predominance of male gender (134, 66.7%). The median AIT start age was 12.8 (9.4-15.2) years and the median treatment duration was 40.7 (20.4-49.9) months. Of the patients, 47.8% had a family history of atopy. The demographic characteristics of the study participants are summarized in Table I.

The number of the patients treated with immunotherapy for allergic rhinitis, asthma and venom allergy were 154 (76,6%), 10 (5%) and 37 (18,4%), respectively. Regarding the immunotherapy composition, pollen immunotherapy was predominant (78.1%), followed by venom (18.4%) and house dust mite (3.5%). Ninety three patients (46,2%) completed the treatment and 108 patients continued to receive AIT during the course of the study. The overall compliance rate was 86.1%. Among the compliant groups, all patients had excellent compliance in first and second year of therapy. After two years of therapy, 93.6% of patients had excellent compliance and 4,6% and 1,5% had good and fair compliance, respectively. (Table III) Twenty eight patients(13.9%) stopped AIT before recommended time. Two patients dropped out in year 1 (0,99%), 10 in year 2 (5,8%), and 16 (10,8%), after 2 years of therapy. Cumulative proportions of patients who continue allergen immunotherapy over time was analyzed using Kaplan-Meier curves. (Figure I)

In the drop-out group AIT follow up time was significantly low ($p < 0.001$) whereas venom allergy and asthma were significantly higher compared to compliant group ($p < 0.001$). (Table I) Among the drop-out patients, moving to another city/country (32,1%) was the most frequent reason for drop-out. The other reasons

included improvement of symptoms(17,8%), ineffectiveness of the therapy (14,2%), adverse reaction (14,2%), long distance to hospital (6,8%), frequency of injections (10,7%) and inability to access immunotherapy agent (3,5%). (Table II)

COVID-19 pandemic period

The COVID-19 pandemic started officially in mid March 2020 in our country. One hundred and eight patients were receiving AIT, when pandemic started. Among these, 31 patients (28,7%) dropped out the therapy and breaks were observed in 15 patients (13,8%). Among the drop-out group, the median treatment duration was 40 (29-49,8) months. The most frequent reason for drop-out was fear of being infected with COVID-19 (35.4%), thinking that the AIT practise stopped due to COVID-19 pandemic (29%). The other reasons included transportation problems due to intercity transportation and and curfew (22.7%), inability to access medication (6.5%) having a COVID-19 infected family number (3.2%) and few doses left to finalize the treatment (3.2%) (Table II).

Drop-out rate was significantly higher in older age($p=0.004$) and male gender($p=0.045$).(Table IV) AIT duration was significantly high in the drop-out group according to the compliant group($p=0.018$).

We further performed univariate and multivariate logistic regression analysis for the risk factors for the development of the drop-out during the COVID-19 pandemic. Male gender [OR:2.972, 95%CI:1.132-7.804, $P = .027$] and higher age [OR:1.209, 95%CI:1.064-1.375, $P = .004$] were found to be the independent risk factors for drop-out during COVID-19 pandemic.(Table V)

Discussion

Results of our study showed that the overall compliance rate among patients receiving AIT was 86,1% and short duration of AIT and receiving venom or asthma immunotherapy were found to be associated with non-compliance. In addition, the most common reasons for drop-out were moving to another city, improvement of symptoms and ineffectiveness. However, nearly one-third of children dropped out during the COVID-19 pandemic, and fear of being infected with COVID-19 was the most common reason.

Compliance rates for SCIT range from 44% to 89%, in the present study compliance found to be better than other studies³. Similar to our results, Pajno et al found that AIT compliance of children on SCIT was 89%⁴. In a population of 311 allergic adult and child patients receiving dust mite SCIT in China, 34,5% of cases were noncompliant and ineffectiveness(28%) was the leading reason for drop-out¹⁵. The cost of AIT in our country is under the umbrella of social security system. This may be a major reason for high compliance rates we achieved. Additionally our staff reminds the patients if a patient does not come to a regular visit (except COVID-19 period).

We concluded that drop-out was significantly higher in patients who receiving immunotherapy for asthma and venom allergy. As the patients who received VIT admitted from another city, most of them dropped out due to the long distance or frequency of injections. However in previous studies, the association of kind of respiratory allergic diseases and adherence were inconsistent. In one study, allergic conjunctivitis were found associated with non-adherence whereas in other study patients with asthma and rhinitis were found more adherent^{16,17}. More et al reported that the kind of respiratory allergic diseases was not correlated with adherence¹⁸.

In the current literature the data about the AIT compliance were mostly attained from studies in adults, and there are few data related to SCIT adherence in children. The studies comparing different age groups with respect to the AIT compliance give us conflicting results^{19,20}. Yang et al found that children had higher adherence than adults¹⁵. Lee et al concluded that patients aged <20 years and 20-40 years were more likely to be nonadherent than those aged >40 years. Rhodes found, nonadherent patients were younger²¹.

In the present study, gender did not influence the adherence rate before pandemic. However during the COVID-19 pandemic period males dropped out more significantly. Musa, Rhodes and Gelincik found no

correlation with gender^{5,20,21}. Rhodes found, males were more nonadherent²¹. However in Yang' and Lower's study males had higher adherence^{2,15}.

Our results suggested that moving to another city (32,9%) was the main cause of drop-outs. Due to the lack of allergologists in some cities, treatment could not be resumed. In addition, all of the patients receiving AIT were at school age, and increased injection frequency, transportation to different city and long distances probably caused school absences and AIT drop-out.

Improvement of symptoms was the second leading reason of drop out (17,9%). Lourenco reported that the frequency of drop-out because of clinical improvement was 23% and mostly during the second and third year of SCIT¹⁹. Yang reported it as 22%¹⁵.

We found treatment ineffectiveness (14,3%) as another important reason of AIT drop-outs. Ineffectiveness was reported in previous studies in 8 to 66% of drop-out results^{1,4,15,19,20}. Adverse reactions were also reported in several studies as a reason for drop-outs in 3,9% to -11% of drop-outs^{19,21}. Systemic reactions were also one of the leading reasons for drop-out (14,3%) in the present study although it was not reported frequently in our center previously^{22,23}(24). In contrast to literature, cost was not a reason for drop-out in the present study as AIT treatment is covered by social security system of our country.

During the COVID-19 pandemic period, in allergy department, patient admissions were stopped except for emergency situations and immunotherapy vaccination. Even so, among the 108 patients receiving AIT, 31 (28,7%) dropped out. Fear of being infected with COVID-19 was the most reason. Although the necessary precautions were taken, the patients chose not to continue to AIT, as the hospital was a COVID-19 pandemic center. Twenty nine percent of patients dropped out thinking that the AIT was cancelled because of the news on the press that the admissions of patients stopped except for emergencies. In COVID-19 pandemic period, intercity transportation was banned and, in most of the cities including Ankara curfews were declared. This situation resulted in 22,7% of patients's drop-out due to transportation problems. Six and a half percent of patients could not get access to allergen extract. One patient was unable to continue AIT, as his father, a health worker, was hospitalized because of COVID-19 pneumonia. One patient's AIT was terminated earlier, who was an out of town patient and in the final months of AIT.

Older age and male gender were correlated with drop-out during the COVID-19 pandemic. Closure of schools and home-quarantine during pandemic was reported to cause anxiety in adolescents²⁴. Older adolescents may have taken the treatment responsibility themselves and tended to refuse outpatient admission. Besides, male sex was reported as a risk factor for COVID-19 severity²⁵. These might be associated with reduced outpatient admissions.

Longer AIT duration, was found to be associated with drop-out during the COVID-19 pandemic period. We may speculate that the effectiveness of the AIT up to this period, might cause noncompliance.

Although our study brings some new data to the field there are some limitation. Firstly, this is a retrospective study up to the COVID-19 pandemic period, and there are some missing data related laboratory parameters. Secondly, in the present study, definition of compliance differs from in many studies and may lead to difficulty in comparing factors associated with AIT compliance. Thirdly, some of the patient's immunotherapy is still ongoing. Therefore the compliance rate may be higher than other studies for this reason. Despite this limitations, the present study had the benefits of a large study population including only children and analyzes the effect of COVID-19 pandemic on AIT for the first time.

Conclusion:

In conclusion our study demonstrated that the SCIT compliance of children is higher than adults. Moving to another city, improvement of symptoms and ineffectiveness are the leading reasons for drop-out. Besides, COVID-19 pandemic significantly reduced the compliance of AIT, nearly one-third of children, especially in older ages and males. However, we conclude that the drop-outs during the COVID-19 pandemic can be prevented by an effective physician and patient/family communication and, by helping with problems and doubts.

CONFLICT OF INTEREST

All authors declared that there are no conflict of interest and no funding. All authors approved the final version of the manuscript. The study protocol has been approved by the local ethical committee, and all parents/guardians provided written informed consent.

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TABLES

Table I. Demographic and clinical characteristics of study population

	Whole group, n=201	Compliant group n=173	Drop-out Group n=28	P
AIT start age*	12,8 (9,4-15,2)	12,9 (9,9-15,3)	11,1 (7,5-14,8)	0,081
Current age*	15,9 (13,1-18,8)	16,0 (13,2-18,8)	15,5 (11,6-18,8)	0,250
Gender M (%)	134 (66,7%)	112 (64,7%)	22(78,6%)	0,150
AIT duration	40,7 (20,4-49,9)	43,5 (24,1-50,4)	23,6 (14,3-35,6)	<0.001
Reasons for AIT	Reasons for AIT			
-Asthma n(%)	10 (5,0%)	4 (2,3%)	6 (21,4%)	
-AR±Asthma n(%)	154 (76,6%)	138 (79,8%)	16 (57,2%)	
-Venom, n(%)	37(18,4%)	31(17,9%)	6 (21,4%)	<0.001
Family history of atopy, n(%)	96 (47,8)	84 (48,5%)	12 (42,8%)	
Type of AIT n(%)	Type of AIT n(%)			
-Grass	157 (78,1)	135 (78,1%)	22 (78,6%)	
-Venom	37 (18,4)	31 (17,9%)	6 (21,4%)	0,523
-House dust mite	7 (3,5)	7 (4,0%)	-	
Total IgE kU/L*	218,5 (110,2-467,7)	202 (100-439)	290 (184-814)	0,024
Esinophil number /mm3*	200 (100-400)	200 (100-300)	300 (100-400)	0,108
Eosinophil %*	3,1 (1,9-5,4)	3,1 (1,9-4,9)	3.5 (2,4-5,9)	0,217

*Median (interquartile range)

Table II. Reasons of drop-outs before COVID-19 pandemics and during COVID-19 pandemics

Before COVID-19 pandemic n(%) Total population:201	Before COVID-19 pandemic n(%) Total population:201	During
Systemic reaction	4 (14,3)	Fear of
Moving to another city	9 (32,1)	Thinki
Long distance	2 (7,1)	Proble
Poor efficacy of AIT	4 (14,3)	Inabili
Improvement of symptoms	5 (17,9)	Having
Frequency of injections	3 (10,7)	Few do
Inability to access medication	1 (3,6)	
Total drop-outs	28 (100)	Total c

Table III. The compliance and drop-out numbers of the whole study population.

Drop-out	Drop-out	Compliance	Compliance	Compliance	Compliance
		Excellent	Good	Fair	Bad
1st year n:201	2 (1%)	199 (99%)	0	0	0
2nd year n:172	10 (5,7%)	162 (94,3)	0	0	0?>?
3rd year n:147	16 (10,8%)	123 (83,8%)	6 (4%)	2 (1,4%)	0

Table IV. Demographic and clinical characteristics of the drop-out patients during COVID-19 pandemic

	COVID-19 drop-out group n=31	COVID-19 compliant group n=77	P
AIT start age*	14.3 (11,0-16,4)	12.9 (8,8-15,2)	0,094
Current age*	17.5 (13,6-19,2)	14.5 (10,8-17,1)	0,004
Gender M (%)	23/8 (66,7)	41 (53,2)	0,045
AIT duration	40.0 (29,0-49,8)	28.6 (9,8-42,2)	0,018
Reasons for AIT	Reasons for AIT		
-Asthma n(%)	0 (0,0)	3 (3,9)	0,356
-AR±Asthma n(%)	25 (80,6)	60 (77,9)	
-Venom, n(%)	6 (19,4)	14 (18,2)	
Family history of atopy, n(%)	20 (64,6)	46 (59,7)	0,979
Type of AIT n(%)	Type of AIT n(%)		
-Grass	22 (71%)	59 (76,6%)	0.689
-Venom	6 (19,4%)	14 (18,2%)	
-House dust mite	3 (9,6%)	4 (5,2)	
Total IgE*,kU/L	197 (26-512)	196 (70-312)	0.918
Eosinophil number /mm3*	200 (100-400)	200 (100-400)	0.765
Eosinophil %*	2.9 (1.3-6.0)	3.2 (1.9-5.8)	0.823

Table V. Results of univariate and multivariate analysis of factors associated with AIT compliance during the COVID-19 pandemic.

	Univariate	Univariate	Univariate	Multivariate	Multivariate	Multivariate
	OR	95%CI	P	OR	95%CI	P
Current age	1,193	1,051-1,354	0,006	1,209	1,064-1,375	0,004
Gender (Male)	2,524	1,005-6,339	0,049	2,972	1,132-7,804	0,027
Duration of AIT	1,040	1,011-1,070	0,007			

Figure Legends:

Figure I:Allergen immunotherapy compliance over time by Kaplan-Meier analysis

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