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Adherence to Subcutaneous Allergen Immunotherapy in Southeast Turkey: A Real-Life Study

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Background: Subcutaneous immunotherapy (SCIT) in allergic rhinitis (AR) and asthma is a very effective treatment, but adherence is still a serious problem. Studies addressing real-life adherence to SCIT are rare in the literature. The aim of this study was to evaluate the adherence to SCIT in AR and asthma.





Material/Methods: The medical records of patients prescribed SCIT for treatment of AR and/or asthma were evaluated. Patients who continued the SCIT treatment as prescribed were defined as adherent, patients who stopped the treatment before the recommended period were defined as nonpersistent, and those who never started the treatment were defined as primary poor adherence. Age, gender, residence, type of SCIT, comorbidities, occupation, income, and adverse reactions were evaluated between these groups.

Results: Ninety-five patients prescribed SCIT for the treatment of AR and/or asthma formed our cohort (female/male: 51/44). The mean (SD) age and duration of SCIT were 32.2 ± 10.0 (range, 17–63) years, 14.4 ± 12.7 (1.0–58.5) months, respectively. Sixty-two (65.3%) patients were adherent, (28.4%) patients were nonpersistent, and 6 (6.3%) patients were primary poor adherent. Nineteen (21.4%) patients had local adverse reactions and one (1.1%) had anaphylaxis. There were no differences between groups for age, gender, residence, type of SCIT, comorbidities, income, or occupation. The most frequent reason of nonpersistence was the cost of treatment.

Conclusions: Our study found that adherence to SCIT is low in a real-life setting in southeast Turkey, similar to most previous adherence studies.

MeSH Keywords: **Asthma • Desensitization, Immunologic • Immunotherapy • Medication Adherence • Patient Compliance • Rhinitis, Allergic, Perennial**

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Background

Allergic respiratory diseases are a major global public health problem. Asthma affects an estimated 300 million individuals [1] and allergic rhinitis (AR) affects 10% to 40% of the population worldwide [2]. It reduces quality of life as well as school and work performance, increasing medical costs [2]. Therefore, appropriate treatment of these diseases is very important.

Oral and/or nasal antihistamines, nasal corticosteroids, and montelukast are used in the treatment of AR. Inhaled corticosteroids, long-acting beta-adrenoreceptor agonist, montelukast, tiotropium, theophylline, omalizumab, and anti-interleukin 5 are used in the treatment of asthma [1–3]. But despite all of these medications, allergen-specific immunotherapy (SIT) is a cornerstone in the management of allergic respiratory diseases and SIT has great effect in reducing symptoms and medication scores, as well as improving quality of life. It induces sustained disease-modifying effects based on changes in specific immunologic markers in the treatment of allergic rhinitis and asthma [4]. Subcutaneous administration is the main route of allergen immunotherapy because of its superior effectiveness [5]. It is recommended that a minimum 3-year duration of SIT therapy is needed to obtain an adequate clinical and immunological response and for long-term efficacy [6].

Non-adherence to plans of medical therapy is reported to range from 30% to 60% in chronic diseases [7]. Adherence is essential in SIT, as it is in all long-term medical treatments. Subcutaneous immunotherapy (SCIT) is administered weekly to monthly in a physician's office or in a hospital, and the patient may not see clear improvements for the first 6 months of treatment [8]. For such reasons, real-life adherence to SCIT may be lower than in other long-term medical treatments. Studies on real-life adherence to SCIT are insufficient in the literature [8,9]. Furthermore, adherence reports from randomized controlled studies may not show true compliance because patients are strictly followed up. Retrospective studies may be able to reflect real-life conditions better than other study designs [10].

The aim of this study was to evaluate adherence to SCIT in patients with allergic asthma and rhinitis who live in southeast Turkey and to determine the factors that affect adherence in real-life conditions.

Material and Methods

Patients and study design

Ninety-five patients who had severe allergic rhinitis and/or asthma and were treated with allergen SCIT in our outpatient clinic were included in the study. All 95 patients had allergic

rhinitis, and 19 of these patients (20%) had concomitant allergic rhinitis and asthma. The diagnoses and therapies of AR and asthma were appropriate according to the allergic rhinitis and its impact on asthma (ARIA) [2] and Global Initiative for Asthma (GINA) guidelines [11]. All patients had classical symptoms of AR, including nasal itching, sneezing, rhinorrhea, or nasal congestion. Some of them also had itching of the palate, post-nasal drip, and cough. Skin prick tests were performed to all patients to evaluate their atopic status and allergic sensitizations. All patients had positive prick tests and there was a correlation between their symptoms and results of the skin prick tests. Oral H1-antihistamine and intranasal corticosteroid treatments were prescribed to all patients for at least 3 months. SCIT was administered to patients who had uncontrolled symptoms with medical treatments. According to the treatment strategy of the Turkish Ministry of Health, SCIT therapy can be given to patients whose symptoms cannot be controlled with medical treatments for at least 3 months. Patients who had wheezing, cough, shortness of breath, or chest tightness were also evaluated by chest physicians, and spirometric tests were performed for these patients. After evaluation, 19 patients were diagnosed with asthma. Oral H1-antihistamine and intranasal corticosteroid were prescribed for AR and inhaled corticosteroids and montelukast were prescribed to patients who had asthma. After appropriate treatment, their asthma was well controlled and spirometry tests were normal. When symptoms of asthma were well controlled, allergen immunotherapies were started.

Single and/or premixed allergen extracts and conventional immunotherapy schedules were used, consisting of one injection every week to reach the maintenance dose. Maintenance therapy was administered every 4 weeks. The high-dose hypoallergenic pollen preparations (Allergovit; Allergopharma GmbH & Co. KG, Hamburg, Germany) for pollen allergies and mite extract preparations (Novo-Helisen® Depot; Allergopharma GmbH & Co. KG, Hamburg, Germany) were used for SCIT. All patients were observed for adverse effects at least 30 min after the injections and they were also told that there was a possibility of delayed reactions. All patients were evaluated before and after every application of SCIT for efficacy and adverse reactions, and these were noted.

Patients' age, gender, employment status, place of residence, monthly household income, comorbidities, diagnosis of allergic disease, type of allergen extract prescribed, immunotherapy regimen, and date of initiation of immunotherapy were noted from their medical records. The reasons cited by patients who stopped or never started the prescribed treatment were evaluated.

Patients who continued the immunotherapy schedules as prescribed were defined as 'adherent', those who stopped therapy

prematurely were defined as 'nonpersistent', and those who never started the therapy were defined as 'primary poor adherent' [12].

Adverse reactions to SCIT are classified into 2 categories: local reactions and systemic reactions. Local reactions are defined as erythema, pruritus, and swelling at the injection site. Systemic reaction is defined as a range from mild to very severe life-threatening anaphylaxis [13].

We determined whether monthly household income was higher or lower than the threshold of poverty. The threshold of poverty of a family of 4 people in Turkey was used to determine the socioeconomic status of the patients.

Data for this study were taken from patients' files. The study was approved by the Gaziantep University Clinical Trials Ethics Committee.

Statistical analysis

In statistical analysis, categorical variables were given as numbers and percentages, and continuous variables were presented with mean \pm standard deviation (SD) and median (min-max value) for descriptive analyses. Pearson chi-square and continuity correction chi-square tests were used for comparison of categorical variables between groups. Kruskal-Wallis test was used for comparison of data sets which were not normally distributed for the variables. The effect of the economic situation on treatment adherence was evaluated by univariate binary logistic regression analysis. $P < 0.05$ was considered statistically significant.

Results

Demographic and clinical characteristics of the patients included in the study are given in Table 1.

The mean \pm SD age of these patients was 32.2 ± 10.0 years (range, 17–63 years), and most patients were women ($n=51$ [53.7%]).

The mean \pm SD duration of SCIT was 14.4 ± 12.7 months (range, 1.0–58.5 months). Sixty-two (65.3%) patients were adherent to prescribed treatment schedule, 27 (28.4%) patients were nonpersistent, and 6 (6.3%) of them were primary poor adherent.

There was hypertension in one patient (1.1%) and diabetes mellitus in one (1.1%) as comorbidities. Seventy-two (75.8%) of the patients resided in the same city, Gaziantep, and 23 (24.2%) of the patients resided in another city. There were 25

(26.3%) housewives, 24 (25.3%) students, and 1 (1.1%) unemployed person in the study, and 45 (47.3%) of the patients had jobs. Seventy-four (77.9%) of the patients had an income higher than the poverty threshold of a family consisting of 4 people. Forty (42.1%) of the patients were polysensitized, and because of this, double-bottle SCIT was given. Fifty-five (57.9%) of the patients had single SCIT. The numbers of patients who had SCIT for only house dust mites, only grasses, and only grasses and cereals were 25, 19, and 9, respectively. Eleven of the patients had SCIT for dust mites and a pollen as a double bottle. The other patients were prescribed a mixture of pollen allergens.

When the adherent, nonpersistent, and primary poor adherent groups were compared by demographic and clinical features, no differences were found between groups in age, gender, residence, occupation, type and number of allergen immunotherapy, and adverse reactions, but there was a significant difference between groups in monthly household income ($p=0.002$) (Table 2).

The reasons cited by the patients who were nonpersistent to the prescribed treatment schedule were pregnancy (11.1%), inconvenience (14.8%), financial problems (33.3%), adverse effects (11.1%), unimproved symptoms (14.8%), moving to another city (7.4%), and family problems (7.4%). The reasons cited by the patient who was primary poor adherent was lack of belief in the benefit of treatment. The reasons why the 5 patients were primary non-adherent were not evaluated because the patients could not be reached.

Discussion

In our study, 65.3% of the patients were adherent to the prescribed SCIT schedule for respiratory allergies. When we look at the literature, adherence rates of studies on SCIT were very different but the majority of the rates were $<70\%$, as in our study [14–18]. In the studies of Rhodes, More and Hagan, and Pajno et al., adherence rates were reported as 88%, 77%, and 89%, respectively [19–21]. In a recent study from Turkey, Gelincik et al. reported an 87.3% adherence rate [22].

These previous studies found that the high adherence rate might due to a close relationship between allergists and their patients during SCIT, and that the follow-up period in the same center improved the outcome of SCIT [22]. Tinkelman et al. reported that SCIT adherence was significantly higher in patients who received their injections at their allergist's clinic (89.23%) compared to those who received their immunotherapy at an outside physician's office (65.18%) [15]. However, in our outpatient clinic, the same allergist always examined the patients and the same allergy nurse administered the injections

Table 1. Baseline demographic and clinical characteristics of 95 patients.

Characteristic	Finding	
Age (mean \pm SD) (y)	32.2 \pm 10.0	
Female, No. (%)	51	(53.7)
Residence, No. (%)		
In the same city	72	(75.8)
Another	23	(24.2)
Occupation, No. (%)		
Housewives	25	(26.3)
Students	24	(25.3)
Unemployed	1	(1.1)
White-/blue-collar workers	45	(47.3)
Monthly household income, No. (%)		
>Threshold of poverty	74	(77.9)
<Threshold of poverty	21	(22.1)
Type of allergen immunotherapy, No. (%)		
Dust mites	25	(26.3)
Pollens (grass, grass and cereal, tree)	59	(62.1)
Dust mites and pollen	11	(11.6)
Number of allergen immunotherapy, No. (%)		
Single bottle	55	(57.9)
Double bottle	40	(42.1)
Comorbidity, No. (%)		
None	74	(77.9)
Asthma	19	(20.0)
Hypertension	1	(1.1)
Diabetes mellitus	1	(1.1)
Adverse reactions, No. (%)		
None	69	(77.5)
Local	19	(21.4)
Systemic	1	(1.1)
Adherence to SCIT, No. (%)		
Adherent	62	(65.3)
Nonpersistent	27	(28.4)
Primary poor adherent	6	(6.3)

SCIT – subcutaneous immunotherapy.

Table 2. Demographic and clinical characteristics of patients.

	Patients			P value
	Adherent	Nonpersistent	Primary poor adherent	
Age (mean ±SD) (y)	32.6±11.2	31.2±7.9	33.3±7.6	NS
Gender, No. (%)				NS
Male	28 (63.6)	11 (25.0)	5 (11.4)	
Female	34 (66.7)	16 (31.4)	1 (2.0)	
Residence, No. (%)				NS
In the same city	49 (68.1)	20 (27.8)	3 (4.2)	
Another	13 (56.5)	7 (30.4)	3 (13.0)	
Occupation, No. (%)				NS
Housewives	16 (64.0)	8 (32.0)	1 (4.0)	
Students	16 (66.7)	7 (29.2)	1 (4.2)	
White-/blue-collar workers	29 (64.4)	12 (26.7)	4 (8.9)	
Unemployed	1 (100.0)	0 (0.0)	0 (0.0)	
Monthly household income, No. (%)				0,002
> Threshold of poverty	7 (33.3)	12 (57.1)	2 (9.5)	
< Threshold of poverty	55 (74.3)	15 (20.3)	4 (5.4)	
Type of allergen immunotherapy, No. (%)				NS
Dust mites	40 (67.8)	15 (25.4)	4 (6.8)	
Pollens (grass, grass and cereal, tree)	13 (52.0)	11 (44.0)	1 (4.0)	
Dust mites and pollen	9 (81.8)	1 (9.1)	1 (9.1)	
Number of allergen immunotherapy, No. (%)				NS
Single bottle	33 (60.0)	19 (34.5)	3 (5.5)	
Double bottle	29 (72.5)	8 (20.0)	3 (7.5)	
Adverse reactions, No. (%)				NS
None	48 (69.6)	21 (30.4)	–	
Local or systemic	14 (70.0)	6 (30.0)	–	

SD – standard deviation; NS – nonsignificant.

throughout the treatment. Also, our patients can contact the allergist whenever they want and they received their SCIT in our outpatient clinic. Despite all these factors, our adherence rate was lower. More and Hagan found that patients receiving a conventional schedule of SCIT were more compliant than those on a rush schedule, at 80.0% versus 48.4% ($P<0.001$), and they explained that this result was due to the higher frequency of adverse effects [20]. Even though the most frequent immunotherapy initiation schedule was the clustered method in the Gelincik et al. study, their adherence rate was higher [22]. In the present study, most of the patients received a conventional schedule of SCIT, but our adherence rate was 65.3%. When we compared adherent and nonpersistent groups by adverse reactions, there was no difference between groups ($p=0.970$). In our study, we compared the adherent, nonpersistent, and primary poor adherent groups

as demographic features. There were no differences between groups in age, gender, residence, or occupation. In the literature, demographic factors were reported to effect SCIT adherence. Lower et al. [16] found males were more compliant than females, whereas Rhodes [19] showed that men aged 16–25 years were more likely to withdraw from their study. Gelincik et al. found that adherence was more frequent in female patients ($p=0.018$) [22]. However, in some studies gender did not have an influence on adherence [15,20]. Rhodes and More showed that older age was associated with higher adherence [19, 20] but Gelincik et al. reported that the mean age of patients who were adherent and the mean age of those who were not adherent were not significantly different [22]. In this study, we found that having a higher monthly household income than the poverty threshold for a family consisting of 4 people affected adherence ($p=0.002$). The effect of this

status on the interruption of treatment was 6.3-fold. All of the patients in this study had health insurance supported by the government. This health insurance pays 80% of the cost of the SCIT. However, the patients initially have to pay all of the cost of vaccine, and later the health insurance repays 80% of the cost, but the time for this refund is changing and the patients have to wait a long time to get their payment back. We think that this may be the main cause of lower adherence rate in our study. Vaswani et al. reported that inadequate refund for allergen extract and allergy injections by health insurers is the most common reason cited for non-adherence to SCIT [23], and Ruiz et al. also reported that one of the major causes of non-compliance was the cost of treatment [17]. In this study, the geographical distance from the clinic was not determined to be a negative factor affecting the adherence rate. The reasons cited by the patients who were nonpersistent to the prescribed treatment schedule were pregnancy (11.1%), inconvenience, (14.8%), financial problems (33.3%), adverse effects (11.1%), unimproved symptoms (14.8%), moving to another city (7.4%), and family problems (7.4%). Three of the patients interrupted the SCIT because of pregnancy. Although continuation of SCIT is safe during pregnancy [24], they wanted to stop the SCIT. In our study, the main reason for discontinuation of SCIT was financial problems, as in the studies of Ruiz et al. [17] and Pajno et al. [21]. Most of the SCIT adherence studies revealed reasons for interrupted SCIT as inconvenience, systemic reactions, and unimproved symptoms [16,19-21], similar to our findings. Rhodes reported that the 5 most common reasons for early dropout were concurrent medical problems, noncompliance, change of residence, inconvenience, and allergic reactions [19]. In our study, 2 of the patients stopped the treatment because of moving to another city. In our study, all patients had severe AR and 37.9% of patients had dust mite sensitization, unlike a study from Greece that found 59.7% of patients with AR had dust mite sensitization [25]. We think, the reason for these conflicting results is the climate difference between the 2 regions.

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In the group of patients with AR and asthma (n=19), there was only 1 patient who was primary poor adherent and there was no patient who was nonpersistent. Eighteen (94.7%) of the patients were adherent. In another group, who had AR without asthma (n=76), there were 44 (57.9%) patients who were adherent, 27 (35.5%) patients who were nonpersistent, and 5 (6.6%) patients who were primary poor adherent. These groups were compared statistically, but the p value is not applicable because there were no patients who were nonpersistent in the asthmatic group, but 94.7% of the patients with asthma were adherent. It was a high and important percentage. Compared with asthma, AR might not appear to be serious because it is not associated with severe morbidity and mortality. However, the burden and costs of AR are important [2]. The important difference between groups may be due to this fact.

To increase the adherence, smartphone applications may be useful, as shown in the study of Cao et al. [26].

Our study has a few limitations. One is the small size of the cohort, and our study was conducted in a single center as a pilot study. A strength is that it is the first report of adherence data from southeast Turkey in real-life conditions. Additionally, we believe that retrospective analyses are very important because they reflect real-life conditions and patients are clinically heterogeneous.

Conclusions

Our study found that adherence to SCIT is low in a real-life setting in southeast Turkey, similar to most other adherence studies, and the main reason for non-adherence to SCIT was financial problems.

Conflict of interest

None.

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