

Patient compliance in subcutaneous immunotherapy

Hikmet Tekin Nacaroglu, Canan Sule Unsal Karkiner, Ilker Gunay, Semiha Bahceci, Muge Ayanaoglu, Done Dogan, Demet Can

Department of Pediatric Allergy, Dr Behcet Uz Children's Hospital, Izmir, Turkey

Abstract

Introduction: Allergen-specific immunotherapy is a treatment modality aiming at ameliorating symptoms for an individual known to be atopic. In the achievement of the treatment, it is important that immunotherapy is applied with ideal dosage and in regular intervals and the patient compliance is essential.

Aim of the study was to evaluate compliance with immunotherapy protocols of patients who were treated with subcutaneous allergen-specific immunotherapy (SCIT) in our clinic and their reasons for quitting the treatment.

Material and methods: All SCIT patients who had completed immunotherapy as well as those whose program was incomplete in 1993–2007 were evaluated retrospectively. Parameters thought to have an effect on compliance such as age, sex, diagnosis of the patients, onset age of immunotherapy, number of injections, SCIT termination period and the place where immunotherapy was performed were gathered from patient files, and reasons for terminating immunotherapy were examined.

Results: The percentage of patients who completed their program was 73.8%. The first two reasons for quitting the treatment were hardness and troublesomeness of the therapy (42.8%), and the high cost (23.8%). Systemic reaction development followed with a ratio of 20% which was the most frequently seen medical cause of noncompliance. The compliance of the cases who continued their treatment in our clinic was found to be significantly high ($p = 0.001$).

Conclusions: It is considered that patients and parents have to be informed regularly about the progress of the disease and immunotherapy program for the efficacy of SCIT treatment.

Key words: adherence, children, compliance, immunotherapy, subcutaneous.

Address for correspondence:

Hikmet Tekin Nacaroglu, Department of Pediatric Allergy, Dr Behcet Uz Children's Hospital, Izmir, Turkey, phone: 90 232 411 63 19, fax: 90 232 489 23 15, e-mail: tekin212@gmail.com

INTRODUCTION

Allergen-specific immunotherapy is a treatment modality aiming at ameliorating symptoms for an individual known to be atopic, by means of immunomodulation through application of allergic extracts with gradually increasing doses [1]. In the achievement of the treatment, it is important that immunotherapy is applied with ideal dosage and in regular intervals and patient compliance is essential. This treatment is thought to be complex, expensive and most of the time ineffective. All these together with the related adverse events affect the patient compliance [2]. Identification of the factors known to have an effect on compliance will increase the success of immunotherapy.

AIM

This study was aimed to evaluate the compliance with immunotherapy protocols of patients who were treated with subcutaneous allergen-specific immunotherapy (SCIT) in our clinic and their reasons for terminating the treatment.

MATERIAL AND METHODS

This case-control based study was carried out at the Department of Pediatric Allergy and Immunology in Dr Behcet Uz Hospital, Izmir. All patients involved in the immunotherapy program beginning in 1993, which was the foundation year of the clinic,

formed the target population of the study. Therefore, all SCIT patients who had completed as well as those who left their conventional immunotherapy program incomplete in 1993-2007 were evaluated retrospectively. Approval by the local ethic committee was granted.

Age, gender, diagnosis of the patients, onset age of immunotherapy, number of injections, SCIT termination period and the place where immunotherapy was performed as well as the causes for terminating immunotherapy were examined retrospectively from the patient files. The patients who completed the immunotherapy versus the patients who discontinued were compared in terms of parameters indicated. Cases which discontinued the SCIT treatment were separated into two groups.

Regarding the causes for discontinuation of SCIT therapy; financial causes, negligence and unwillingness of the parents considering the therapy being hard and troublesome were classified as the "family-related causes" group, others discontinued because of the development of systemic reactions, anaphylaxis, additional diseases and refractory asthma were classed as "medical causes" group. The two groups were compared in terms of the parameters mentioned above.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences program (SPSS for Windows 15.0 Chicago, USA). Values of continuous variables were given as either mean \pm standard deviation or as median, based on the normality of distribution. Student's independent-*t* test was used in the comparison of normal and homogeneous distribution of the parametric values. Chi-square and Mann Whitney *U* test were used to compare nonparametric values, $p < 0.05$ was considered a significant value.

RESULTS

Four hundred and one patients were determined to have been admitted to the immunotherapy program between 1993 and 2007. Of those, 265 (66.1%) patients were males, and 136 (33.9%) were females. The average age of the patients at admission was 8.8 ± 3.1 years. The average age for starting immunotherapy was 9.7 ± 3.1 years. And the diagnosis distribution for the patients was as follows: 61.3% ($n = 246$) asthma, 17% ($n = 68$) allergic rhinitis, 21.7% ($n = 87$) both asthma & allergic rhinitis. Subcutaneous allergen-specific immunotherapy allergen distribution was found to be house dust – 57.6% ($n = 231$), grass pollen – 46.6% ($n = 187$), and olive pollen – 19.5% ($n = 78$). Examining the injection count

for each session of SCIT patients, it was seen that 30 (7.5%) patients were given a double injection and 371 (92.5%) patients a single injection. All the injections were administered in our clinic to 276 (68.8%) cases, whereas 125 (31.2%) cases received their injections after the maintenance treatment in an external center. Average SCIT treatment duration was determined to be 39.6 ± 17 months.

The number of the patients completing their program was 296 (73.8%). A total of 105 (26.2%) patients discontinued the treatment for a variety of reasons. Examining the treatment periods it was determined that 23 (21.9%) patients discontinued the treatment at the beginning and 82 (78.1%) patients during the maintenance period. Among the reasons for discontinuation, hardness and troublesomeness of the therapy were placed at the top – 42.8% ($n = 45$). The other reasons were financial causes followed it – 23.8% ($n = 25$); systemic reaction development – 20% ($n = 21$), the family finding the treatment unnecessary – 5.7% ($n = 6$), anaphylaxis – 4.8% ($n = 5$), additional disease development – 1.9% ($n = 2$), and the disease not being under control – 1% ($n = 1$).

No statistically significant difference was determined between the patients completing and discontinuing SCIT when examining them with regard to age at admission, gender, diagnosis, immunotherapy starting age, and injection count. The compliance of the cases who continued their treatment in our clinic was found to be significantly high ($p = 0.001$). On the other hand, treatment discontinuation proportion was higher for the cases who received their injections in an external center. Examining the SCIT periods it was seen that a significant proportion of the cases had terminated the treatment during the maintenance period ($p = 0.001$). The characteristics of the patients who completed or discontinued the treatment are shown in Table 1.

When we categorize the treatment discontinuation reasons in groups, we see that 72.4% ($n = 76$) of the patients were classified in the "family-related causes" group whereas 27.6% ($n = 29$) were in the "medical causes" group. The patients who discontinued the treatment because of the family-related causes and the medical causes were examined to determine whether there was a statistical difference between them in terms of application age, diagnosis, sex, SCIT starting age, SCIT discontinuation period, injection count and injection application place. No statistical differences were found between these two groups in terms of sex ($p = 0.220$), age at hospital admission ($p = 0.697$), average SCIT starting age ($p = 0.915$), injection count per session ($p = 0.712$) and SCIT discontinuation period ($p = 0.605$). The average SCIT duration for the patients who discontinued the treatment due to "family-related causes"

Table 1. The characteristics of the patients completing and quitting subcutaneous allergen-specific immunotherapy (SCIT)

		Quit SCIT	Completed SCIT	p
Admission age		9.03 ±3.13	8.77 ±3.12	0.462
Gender	Male	65 (24.5%)	200 (75.5%)	0.491
	Female	40 (29.4%)	96 (70.6%)	
Multiple allergen		57 (28.3%)	144 (71.7%)	
Diagnosis distribution	Asthma	69 (28%)	177 (72%)	0.807
	Asthma/A. rhinitis	19 (21%)	68 (79%)	0.576
	A. rhinitis	17 (25%)	51 (75%)	0.285
Average SCIT starting age		9.88 ±3.26	9.65 ±2.99	0.503
SCIT injection count	1	98 (26.4%)	273 (73.6%)	0.712
	2	7 (23.3%)	23 (76.7%)	
SCIT application place	Clinic	59 (21.4%)	217 (78.6%)	0.001
	External center	46 (36.8%)	79 (63.2%)	
SCIT quit period	Beginning	23 (21.9%)		0.001
	Maintenance	82 (78.1%)		

Table 2. The characteristics of the groups separated according to the reasons breaking the compliance

		Family-related causes (n = 76)	Medical causes (n = 29)	p
Admission age		8.95 ±3.28	9.21 ±2.79	0.697
Sex	Male	48 (65.8%)	17 (53.1%)	0.220
	Female	25 (34.2%)	15 (46.9%)	
Diagnosis distribution	Asthma	55 (75.3%)	14 (43.7%)	0.297
	Asthma/A. rhinitis	63 (86.3%)	25 (78.1%)	0.295
	A. rhinitis	18(24.7%)	18 (56.3%)	0.002
Average SCIT starting age		9.86 ±3.44	9.93 ±2.87	0.915
SCIT injection count	1	70 (95.9%)	28 (87.5%)	0.712
	2	3 (4.1%)	4 (12.5%)	
SCIT application place	Clinic	32 (43.8%)	27 (84.4%)	0.001
	External center	41 (56.2%)	5 (15.6%)	
SCIT quit period	Beginning	17 (23.3%)	6 (18.8%)	0.605
	Maintenance	56 (76.7%)	26 (81.2%)	
Average SCIT quit duration		17.2 ±10.5	23.1 ±13.8	0.020

was 17.2 ±10.5 months, whereas due to medical causes was 23.1 ±13.8 months. Discontinuation due to family-related causes occurring in early periods was seen to be statistically significant ($p = 0.020$). Most of the patients resuming their SCIT program in an external center were found to discontinue the treatment due to family-related causes, whereas the patients resuming their SCIT program in our clinic were mostly found to terminate their treatment because of the medical causes ($p = 0.001$).

When examining the impact of the allergic disease type on treatment discontinuation, no statistically significant difference was found between the

asthma group and the group with the association of asthma and allergic rhinitis ($p = 0.297$, $p = 0.295$). However, the treatment discontinuation rate of the patients with allergic rhinitis diagnosis was observed to be higher because of the medical causes ($p = 0.002$) (Table 2).

DISCUSSION

Allergen-specific immunotherapy is a treatment method aiming at development of immunological tolerance via the administration of the allergen with

controlled increasing doses [3, 4]. This method provides an apparent decrease in the symptoms related to asthma as well as an increase in the quality of life and it reduces the medication need for disease control [5, 6]. Besides blocking the emergence of new sensitizations, SCIT also prevents the development of asthma in patients with allergic rhinitis by having an effect on the natural course of the disease [7]. The application of immunotherapy with proper dosage and in regular intervals is important for the success of SCIT treatment. For this, the compliance of the patients is essential. However, the compliance to this immunotherapy method is limited because of the potential life-threatening systemic side effects and the discomfort caused by repetitive injections in childhood age groups. The other reasons having an impact on compliance are the high cost and difficulty of the treatment, the opinion about the treatment as being ineffective, and family problems [2, 8–10].

In our study, 73.8% of the patients completed the SCIT program. In total 26.2% patients discontinued the treatment for a variety of reasons. Among the reasons for discontinuation, hardness and troublesomeness of the therapy were placed at the top – 42.8%. In this study, no statistically significant difference was determined between the patients completing and discontinuing SCIT when examining them with regard to age at admission, sex, diagnosis, immunotherapy starting age, and injection count. In the early studies about SCIT compliance, compliance to the treatment was reported as roughly 50% both for the adults and the children, by Cohn and Pizzi and Lower *et al.* [11, 12]. It was indicated that the reason for this poor result might be the protocol used which requires one injection weekly in the first year and one injection every two weeks in the second year. Cohn and Pizzi [11] carried out their study on 217 allergic rhinitis and/or asthma patients receiving SCIT treatment. In their study, they stated that 50% of the cases having allergic rhinitis, and 48% of the cases having both asthma and allergic rhinitis had discontinued the treatment. Treatment difficulty was determined to be the most important termination reason representing 55% of the cases. The rate of treatment discontinuation for the same reason for the cases having both asthma and allergic rhinitis was determined to be 22%. Lower *et al.* [12], in their study involving 315 patients aged between 5–18 years having asthma or allergic rhinitis, stated that 44% of the cases had discontinued the treatment and male patients had shown a higher compliance. In the studies carried out in the subsequent years, more reasonable results started to be obtained and the reason for that was thought to be the use of better injection schemes. In a study implemented by Ruiz *et al.* [13] on 247 patients, the compliance ratio

was reported as 38%. In this study, the reasons for noncompliance were stated to be the high cost of the treatment and the patient's feeling of being cured. Also the worsening of the disease was determined to be another reason for quitting the treatment. In 1999, Rhodes [14] carried out a study without waiting until the end of the 3-year long treatment period and determined that 12% of the cases had quit the treatment. The most frequent reasons for quitting the treatment were ongoing medical problems, difficulty of the treatment and side effects of the treatment.

In consistency with the literature, the compliance of the cases taking the treatment in our clinic was found to be significantly high. The compliance ratio of the patients taking the injections outside of our allergy center was found to be lower. Tinkelman *et al.* [15] carried out a study with special patients and in this study they determined the compliance ratio as being 35% for the cases that had their injections in an external center. Continuing the treatment in a different center after the maintenance period appears to be a risk factor for compliance.

In our study, a significant number of the cases were determined to withdraw from the immunotherapy treatment in the maintenance period ($p = 0.001$). The average SCIT duration for the patients who discontinued the treatment due to family-related causes was 17.2 ± 10.5 months, whereas due to medical causes was 23.1 ± 13.8 months. Discontinuation due to family-related causes occurring in early periods was seen to be statistically significant. Most of the patients resuming their SCIT program in an external center were found to discontinue the treatment due to family-related causes, whereas the patients resuming their SCIT program in our clinic were mostly found to terminate their treatment because of medical causes. These results show that SCIT program should be arranged and continued by the allergy specialists in experienced centers. In the study of Pajno *et al.* [16] in hospital and clinics with 2774 patients having one of SCIT/sublingual immunotherapy (SLIT)/LNIT treatments, 10.9% of the cases were found to have compliance problems. When the treatment discontinuation period is examined, no difference in terms of compliance was determined between the starting and the maintenance periods. It was seen that most of the patients receiving treatment in the hospital withdrew in the beginning or in the second year of the treatment, whereas the patients taking the treatment in external centers generally terminated the treatment at the end of the first year.

It is seen that the compliance varies between 44% and 89% when the studies with adults and children about SCIT compliance are analyzed (48% in SCIT in adults by Cohn and Pizzi, 44% in SCIT

in children by Lower *et al.*, 65% in adults SCIT by Tinkleman *et al.*, 62% in adults by Ruiz *et al.*, 88% in adults by Rhodes, 89% in children SCIT by Pajno *et al.*) [11–17]. The main reasons for quitting the treatment were put in order as follows: frequent injection intervals, difficulty of the treatment and insufficient information for the patients concerning the treatment. In the study of Sade *et al.* [18], it was emphasized that the patients taking SCIT treatment were barely informed and had great expectations. While 40% of the patients thought that their allergy conditions would recover completely, 20% of them expected recovery in days or weeks. One quarter of the patients were determined to know the allergen with which the SCIT was applied and one third of the patients had knowledge regarding side effects. In our study, the reason for quitting the SCIT treatment which ranked first was family-related causes. The subsequent reasons were medical causes, which are more difficult to improve. We suppose that informing the parents about the effectiveness and adverse effects related to immunotherapy from the beginning and during the progress should decrease the rate of discontinuation due to family-related causes. As a mutual outcome of all these studies, it is accepted that the SCIT compliance can be increased by the use of optimal allergen extracts, appropriate treatment schemes and the cooperation between the doctors and the family. Moreover, arranging the treatment by considering social factors, education, the economic status of the family, and informing the patients about the progress of the disease and the immunotherapy program may help to improve compliance [2, 18].

CONCLUSIONS

In the studies performed with pediatric age groups, SCIT compliance differs in a wide range from 44% to 89%. In our study SCIT compliance was found to be 73.8%. The most frequently encountered treatment discontinuation reason was determined to be family-related reasons, and not side effects or complications. Family-related reasons do not appear only because of sociocultural deficiencies but also because the patients and their families are not sufficiently informed about the necessity and efficiency of the treatment, in other words due to lack of education. Owing to these motives, to perform the SCIT treatment more effectively, it is considered that information about the progress of the disease and the immunotherapy program should be given not only at the beginning but also repeated in regular intervals. Therefore, we think that immunotherapy should be carried out in experienced centers under

the supervision of allergy specialists to ensure the compliance.

Authors declare no potential conflict of interest.

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