



Real-life adherence to subcutaneous immunotherapy: What has changed in the era of the COVID-19 pandemic

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ABSTRACT

Background: Allergen immunotherapy (AIT) must be continued for 3 years, to achieve a long-term modifying effect. Adherence is a key to ensure effectiveness. The objective of this study was, first of all, to evaluate the adherence with subcutaneous immunotherapy (SCIT) and to identify the main causes of SCIT withdrawal in real-life practice in our clinic. Secondly, we also aimed to investigate to what extent the COVID-19 pandemic altered our SCIT receiving patients' treatment adherence behaviors and the factors that affected their decisions.

Methods: Retrospective analysis of the medical records of patients ages ≥ 18 years, who had started SCIT in January 2014 or later until September 2020 in our department for the diagnosis of allergic rhinitis, allergic asthma or venom allergy, were included in the study. Adherence was determined as the accomplishment of 3 years of SCIT.

Results: A total of 124 patients (72 female [58.1%]; median age, 35 [19-77] years) were included. The adherence rate to SCIT in our tertiary center's real-life setting was 56.25% with a follow-up duration of 3 years before COVID-19 pandemic. Dose modification, defined as reducing patient's planned SCIT dose due to a systemic allergic/large local reaction or missed injection, and its frequency, which is the number of dose adjustments done throughout the SCIT, was found to be the only factor related to nonadherence. But with the pandemic only in 6 months, among 63 patients receiving SCIT, 15 patients (23.81%) dropped out, and the most common reason was fear of being infected with COVID-19 virus during receiving SCIT in hospital (93.33%). The only independent predictor of drop-out during the COVID-19 pandemic was short duration of AIT ($p = 0.012$). When we compare the dropped-out cases before and after the start of pandemic, AIT duration was significantly shorter in pandemic period ($p = 0.005$).

Conclusion: Adherence rate to SCIT in our real-world setting study was 56.25% before the COVID-19 pandemic. Our results indicated that patients requiring dose modification were more prone to be non-adherent. Approximately one quarter of patients dropped-out with the start of pandemic, almost all due to fear of being infected during receiving SCIT in hospital. Since short SCIT follow-up time was found to be the only risk factor for drop-out during the COVID-19

pandemic, we believe that patients who are in the early phases of their treatment should be observed more closely and their concerns should be answered by their doctors.

Keywords: Adherence, Allergen immunotherapy, COVID-19, Real-life evidence, Subcutaneous immunotherapy

INTRODUCTION

Allergen immunotherapy (AIT) has been used to treat allergic diseases such as allergic rhinitis, allergic asthma, and venom allergies for over a century by inducing and maintaining an allergen-specific tolerance.¹ It involves the gradual administration of increasing doses of the causative allergens in different forms, conventionally as subcutaneous (SCIT) or sublingual (SLIT). This is the one and only therapy that modulates T- and B- cell responses, antibody isotypes and functionally limits mast cells, eosinophils, and basophils.² Besides, analyses by the European Academy of Allergy and Clinical Immunology (EAACI) proved the cost-effectiveness of this disease-modifying therapy option.³

Despite the fact that AIT is the only therapy that offers the possibility of long-term cure after its cessation, also the possibility of preventing the new sensitizations and onset of asthma by modifying the underlying disease, patient adherence is very low regardless of the mode of delivery.⁴ A minimum duration of 3-years of AIT, with an optimized dosing scheme, is required to achieve an adequate long-term efficacy.⁵ However, adherence to SCIT in real-world studies is poor. While in clinical trials the reported adherence rate is around 80–90%, with a follow-up duration of 3 years SCIT in adults, there is a wide variation of reported adherence rates in real-life studies ranging from 23 to 88%.^{6,7} This research difference in rates of adherence may be due to the type of treatment regimen used (different allergen vaccine, schedule), patient group studied (different populations, age group, country), or measure of adherence used.⁸ Causes of poor adherence may be due to patient, disease, treatment, or healthcare system related factors.⁹ The reasons for AIT drop-out are varied, and the most common identified reasons for

discontinuing SCIT are summarized as inconvenience, concurrent illness, perceived ineffectiveness, symptom improvement, change in residence or clinic, adverse reaction, systemic reaction, local reaction, and cost or lack of insurance.¹⁰ A Cochrane review of 182 randomized clinical trials about interventions for enhancing medication adherence, concluded that improving adherence for chronic health problems are mostly complex and multifactorial. Furthermore, it appeared to be impossible to predict which interventions will or will not work in a particular setting and over a given timeframe.¹¹ So, there may also be differences in nonadherence reasons depending on the timepoint of treatment. In a recent study, economic problems were identified as the main reason for nonadherence in the first year, while the perception of non-improvement was in subsequent years.¹² In another study, it was found that in the first year of SCIT, inconvenience (40.7%) was the most significant reason for discontinuation, followed by perception of ineffectiveness (20.3%) and improvement of symptoms (15.3%). By the third year of SCIT, although the commonest reason stayed the same as inconvenience (40%) for nonadherence, it was followed by improvement of symptoms (35%) and then by perception of ineffectiveness (20%).¹³ Evidence suggests that adequate education remains as the cornerstone of adherence improvement, since the patients need better knowledge of what to expect and when from their AIT.

The coronavirus disease 2019 (COVID-19) outbreak was declared a pandemic on March 11, 2020, by the World Health Organization (WHO).¹⁴ During this pandemic, many regulatory workgroups advise to continue AIT without interrupting in asymptomatic patient without suspicion of SARS-CoV-2 infection, especially in potentially life-threatening venom allergy.^{15–17} In the COVID-19 era and its aftermath, we may see

worsening adherence to therapy due to known factors that affect adherence and others that are unique to what is happening currently.

The main objective of this study was, first of all, to evaluate the rate of adherence to SCIT and to identify the main causes of SCIT withdrawal in real-life practice in our clinic. Secondly, to investigate to what extent SCIT receiving patients altered their treatment during COVID-19 pandemic and the factors that affected their decisions.

MATERIAL AND METHODS

Study population and design

One hundred twenty-four patients ages ≥ 18 years, who had started SCIT in January 2014 or later until September 2020 in our clinic for the diagnosis of allergic rhinitis, allergic asthma, or venom allergy, were included in the study. The patients' medical records were evaluated anonymously and retrospectively. The study protocol was reviewed and approved by the local Clinical Research Ethics.

Patients' demographic data (age, gender, residency, history of other medical conditions), names of the allergens to which the patients were sensitized (determined by skin prick test and/or allergen-specific allergen positivity), allergic disease diagnosis and duration, SCIT composition and date of initiation, also SCIT administration schedule were registered and evaluated. Furthermore, appearance of adverse events due to SCIT such as local and systemic reactions, dose modifications performed, use of premedication, noncompliance and adherence to SCIT were also assessed. Systemic reactions were graded from 1 to 4 according to World Allergy Organization (WAO) grading system.¹⁸ Reducing the patient's planned SCIT dose due to a systemic allergic reaction, large local reaction (defined as redness and induration >6 cm in diameter at the injection site), or missed injection (when interval between two consecutive administrations exceeds 2 weeks in the build-up phase or 10 weeks in the maintenance phase) was considered as dose modification. For large local reactions, dose modification was done when other interventions, such as premedication with oral antihistamine and/or dividing the dose between two arms were ineffective. The

treatment adherence of patients during COVID-19 pandemic period in Turkey was defined as the time starting on 11 March 2020 with the first confirmed case until end of September 2020, during a six-month period. The reasons for SCIT drop-out after COVID-19 pandemic were also evaluated.

The diagnoses and treatment of AR, asthma and venom allergy were appropriate according to current guidelines; the Allergic Rhinitis and its Impact on Asthma (ARIA), Global Initiative for Asthma (GINA) and European Academy of Allergy and Clinical Immunology (EAACI) guidelines, respectively.¹⁹⁻²¹

A written informed consent was obtained from all patients before initiating SCIT. Clustered or conventional immunotherapy schedules with pre-mixed or single allergen extracts were used. In the clustered schedule, 2 or 3 injections per visit per week were applied to reach the maintenance dose in 6 weeks. The conventional method with purified depot preparations consisted of one injection per visit every week to reach the maintenance dose in 16 weeks. But the conventional method with allergoid immunotherapy extracts was applied with 1 injection every week for a total of 7 weeks to reach the maintenance dose. The maintenance dose was administered at 4-6-week intervals over a period of 3-5 years. During full SCIT course all injections were administered by trained nurses with supervision of a doctor in our allergy clinic, equipped with material for emergency resuscitation. All patients were evaluated before and 30 min after the SCIT administration, also each injection was recorded.

The patients' records were reviewed and any subject who missed at least 2 consecutive planned SCIT doses between subsequent injections was defined as noncompliant. Adherence was determined as the accomplishment of 3 years of SCIT. Patients who had 8 consecutive week delay from the build-up phase or 16 consecutive week delay from the maintenance phase was defined as dropped-out.²² The patient's reason for dropping out of SCIT during the COVID-19 pandemic was determined during a phone contact and recorded with the verbal consent of the patient.

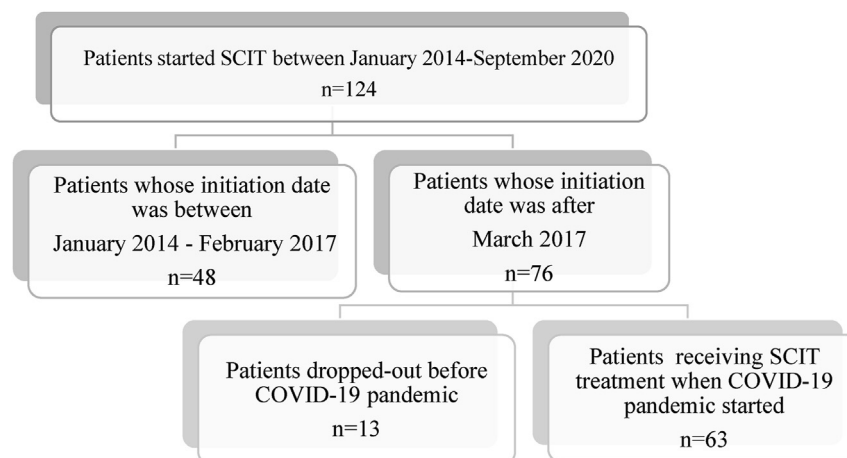


Fig. 1 Study flowchart and design

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 25 (SPSS, Chicago, IL) was used for the statistical analysis of this study. Normality tests for continuous variables revealed that all of the continuous variables were distributed non-normally. Descriptive statistics (frequencies, median and minimum-maximum) were calculated. The univariate analyses to identify variables associated with SCIT adherence were investigated using Chi-square, Fisher exact and Mann-Whitney U tests, where appropriate. For the multivariate analysis, the possible factors identified with univariate analysis were further entered into the binary logistic regression analysis to determine independent predictors of patient outcome. We compared Kaplan-Meier curves for all time-to-event outcome (drop-out) measures with the standard log-rank test. A p -value <0.05 was considered statistically significant.

RESULTS

Clinical data

Medical records of 124 patients under SCIT during the study period were evaluated with respect to the flowchart summarized in Fig. 1. According to the demographic data of this whole group 57 patients (46%) were diagnosed as having AR, 28 patients (22.5%) had concomitant AR and asthma, and 39 patients (31.5%) had venom allergy. A total of 72 patients were women (58.1%) and the median age was 35 (min-max, 19-77 years). The median duration of SCIT

was 23.75 months (min-max, 0-67.75) and total of 34 patients (27.41%) dropped-out of SCIT before 3 years of treatment were completed. The demographic and clinical characteristics of the whole group are shown in Table 1. In the drop-out group, need for a dose modification and number of dose modifications made were statistically higher ($p = 0.002$ and $p = 0.001$, respectively). Other factors like age, gender, place of residency, presence of a comorbid disease, diagnosis, type of allergen extract, SCIT build-up scheme, presence or frequency of local/systemic reactions, or need for premedication evaluated showed no effect on dropping-out of SCIT.

Immunotherapy adherence before COVID-19 pandemic (January 2014-February 2020)

From a total of 124 patients under SCIT during the study period, 48 patients whose initiation date was between January 2014-February 2017 were evaluated for this subgroup in order to achieve the three-year follow-up to calculate the adherence rate. For this subgroup median age was 33.5 years (range 20-64 years), and female/male ratio was 1:1. Among these, 75% were residents of our home city. Twenty-eight patients (58.3%) were diagnosed as having AR, 8 patients (16.7%) had concomitant AR and allergic asthma, and 12 patients (25%) had venom allergy with a median duration of disease 10 years (range 2-40 years). Twenty-two patients (45.83%) were both compliant and adherent, and 6 patients (12.5%) were both noncompliant and nonadherent. Overall, 21 patients (43.75%) were nonadherent. The

	Total (n = 124)	Run-on (n = 90)	Drop-outs (n = 34)	p
Age (years), median (min-max)	35 (19-77)	35.5 (19-77)	34 (21-64)	0.458
Gender (F), n (%)	72 (58.1)	53 (41.1)	19 (55.9)	0.762
Residence, n (%)				0.982
Intown	95 (76.6)	69 (76.7)	26 (76.5)	
Uptown	29 (23.4)	21 (23.3)	8 (23.5)	
Diagnosis of allergic disease, n (%)				0.208
Allergic rhinitis	57 (46)	39 (43.3)	18 (52.9)	
Allergic rhinitis+ Asthma	28 (22.5)	24 (26.7)	4 (11.8)	
Venom allergy	39 (31.5)	27 (30)	12 (35.3)	
Disease duration (years), median (min-max)	10 (1-40)	10 (1-40)	10 (2-24)	0.997
Type of allergen sensitized, n (%)				0.474
Pollen	46 (37.1)	35 (38.9)	11 (32.4)	
HDM	9 (7.3)	5 (5.6)	4 (11.7)	
Cat	3 (2.4)	3 (3.3)	0	
Venom	26 (21)	17 (18.9)	9 (26.5)	
Polysensitized	40 (32.2)	30 (33.3)	10 (29.4)	
Type of allergen extract				0.203
Pollen	61 (49.1)	46 (51.1)	15 (44.2)	
HDM	12 (9.7)	6 (6.7)	6 (17.6)	
Cat	4 (3.2)	4 (4.4)	0	
Venom	39 (31.5)	27 (30)	12 (35.3)	
Inhalant allergen mix	8 (6.5)	7 (7.8)	1 (2.9)	
Presence of comorbid disease, n (%)	31 (25)	26 (28.9)	5 (14.7)	0.104
AIT build-up scheme, n (%)				0.172
Clustered	19 (15.3)	14 (15.6)	5 (14.6)	
Conventional, 7 weeks	66 (53.3)	50 (55.6)	16 (47.1)	
Conventional, 15 weeks	33 (26.6)	24 (26.7)	9 (26.5)	
Clustered → Conventional	6 (4.8)	2 (2.1)	4 (11.8)	
Occurrence of Local adverse reaction, n (%)	65 (50)	44 (48.9)	18 (52.9)	0.687
No. of Local adverse reactions, med (min-max)	0.5 (0-10)	0 (0-9)	1 (0-10)	0.430
Occurrence of Systemic adverse reaction, n (%)	17 (13.7)	9 (10)	8 (23.5)	0.076
No. of Systemic adverse reactions, med (min-max)	0 (0-6)	0 (0-5)	0 (0-6)	0.051
Systemic adverse reaction grade ^a , n (%)				0.154
1	12 (9.7)	6 (6.7)	6 (17.6)	
2	1 (0.8)	1 (1.1)	0	
3	1 (0.8)	0	1 (2.9)	
4	3 (2.4)	2 (2.2)	1 (2.9)	
No. of patients using premedication, n (%)	58 (46.8)	44 (48.9)	14 (41.2)	0.443
Dose modification requirement, n (%)	46 (37.1)	26 (28.9)	20 (58.8)	0.002
No. of dose modifications, med (min-max)	0 (0-8)	0 (0-6)	1 (0-8)	0.001

(continued)

	Total (n = 124)	Run-on (n = 90)	Drop-outs (n = 34)	p
No. of patients experienced noncompliance, n (%)	19 (15.3)	11 (12.2)	8 (23.5)	0.119
No. of events of noncompliance, med (min-max)	0 (0-2)	0 (0-2)	0 (0-2)	0.102
Duration of AIT (months), med (min-max)	23.75 (0-67.75)	31.98 (1.61-67.75)	20.24 (0-35.29)	0.001
No. of patients from every follow-up year, n (%)				0.006
1st year	39 (31.5)	24 (26.7)	15 (44.1)	
2nd year	24 (19.3)	16 (17.8)	8 (23.5)	
3rd year	29 (23.4)	18 (20)	11 (32.4)	
4th year	21 (16.9)	21 (23.3)	-	
5th year	8 (6.5)	8 (8.9)	-	
6th year	3 (2.4)	3 (3.3)	-	

Table 1. (Continued) Clinical characteristics and demographic data of the SCIT patients before COVID-19 pandemic. **Abbreviations:** F, female; HDM, house-dust mite; med, median; No., number. a. According to WAO classification¹²

demographic data and clinical features of the patients depending on their adherence status to SCIT are shown in Table 2. Need for a dose modification and number of dose modifications made were statistically higher in the nonadherent group ($p = 0.028$ and $p = 0.048$, respectively). But other factors like age, gender, place of residency, presence of a comorbid disease, diagnosis, type of allergen extract, SCIT build-up scheme, presence or frequency of local/systemic reactions, or need for premedication did not have an effect on the adherence rate. Five patients (10.42%) in the first year, 6 patients (12.5%) in the second year, and 10 patients (20.83%) in the third year of SCIT abandoned their treatment.

Immunotherapy adherence during COVID-19 pandemic

Sixty-three patients were in the first 3 years of SCIT when the COVID-19 pandemic started. During the first 6 months of the pandemic, 15 patients (23.81%) dropped-out of the therapy, and breaks, unscheduled gaps, in SCIT were observed in 5 patients (7.94%). The most frequent reason for discontinuation (14 patients-93.33%) and all breaks (100%) was fear of being infected with the COVID-19 virus during receiving SCIT in the hospital. The only other reason for termination was frequent systemic reactions for 1 patient. Non-adherence was significantly higher in patients with

lesser local reactions, surprisingly ($p = 0.045$). Duration of AIT was significantly shorter in the drop-out group than in the adherent group ($p = 0.001$) (Table 3).

A binary logistic regression analysis was performed to determine the independent factor associated with SCIT drop-out during the COVID-19 pandemic, with the defined borderline significant factors ($p = 0.012$). As a result, AIT duration was the only factor identified (Table 4).

We further compared the characteristics of drop-outs from SCIT before and during the COVID-19 pandemic period. AIT duration was significantly shorter in the drop-outs during the COVID-19 pandemic period ($p = 0.005$) (Table 5).

Cumulative proportions of patients who continue allergen immunotherapy over time was analyzed using Kaplan-Meier curves (Fig. 2).

DISCUSSION

Our study showed that the adherence rate to SCIT in our tertiary center's real-life setting is 56.25% with a follow-up duration of 3 years before COVID-19 pandemic. Dose modification and its frequency is found to be the only factor related with nonadherence. In accord with this finding, we observed that occurrence of dose modification increases the risk for nonadherence for overall

	Adherent (n = 27)	Nonadherent (n = 21)	p
Age (years), median (min-max)	34 (20-60)	33 (21-64)	0.843
Gender (F), n (%)	11 (40.7)	13 (61.9)	0.146
Residence, n (%)			0.401
Intown	19 (70.4)	17 (81)	
Uptown	8 (29.6)	4 (19)	
Diagnosis of allergic disease, n (%)			0.891
Allergic rhinitis	15 (55.6)	13 (61.9)	
Allergic rhinitis+ Asthma	5 (18.5)	3 (14.3)	
Venom allergy	7 (25.9)	5 (23.8)	
Disease duration (years), median (min-max)	10 (2-40)	10 (3-24)	0.753
Type of allergen sensitized, n (%)			0.340
Pollen	11 (40.7)	8 (38.1)	
HDM	1 (3.7)	4 (19)	
Cat	1 (3.7)	0	
Venom	5 (18.5)	5 (23.8)	
Polysensitized	9 (33.3)	4 (19)	
Type of allergen extract			0.097
Pollen	13 (48.1)	10 (47.6)	
HDM	1 (3.7)	5 (23.8)	
Venom	7 (25.9)	5 (23.8)	
Inhalant allergen mix	6 (22.2)	1 (4.8)	
Presence of comorbid disease, n (%)	6 (22.2)	3 (14.3)	0.712
AIT build-up scheme, n (%)			0.795
Clustered	5 (18.5)	3 (14.3)	
Conventional, 7 weeks	16 (59.3)	11 (52.4)	
Conventional, 15 weeks	5 (18.5)	5 (23.8)	
Clustered → Conventional	1 (3.7)	2 (9.5)	
Occurrence of Local adverse reaction, n (%)	13 (48.1)	11 (52.4)	0.771
No. of Local adverse reactions, med (min-max)	0 (0-9)	1 (0-10)	0.496
Occurrence of Systemic adverse reaction, n (%)	2 (7.4)	4 (19)	0.383
No. of Systemic adverse reactions, med (min-max)	0 (0-5)	0 (0-2)	0.247
Systemic adverse reaction grade ^a , n (%)			0.203
1	1 (3.7)	3 (14.3)	
2	0	0	
3	0	1 (4.8)	
4	1 (3.7)	0	
No. of patients using premedication, n (%)	14 (51.9)	10 (47.6)	0.771
Dose modification requirement, n (%)	7 (25.9)	12 (57.1)	0.028
No. of dose modifications, med (min-max)	0 (0-4)	0 (0-3)	0.048
No. of patients experienced noncompliance, n (%)	5 (18.5)	6 (28.6)	0.498
No. of events of noncompliance, med (min-max)	0 (0-2)	0 (0-2)	0.396

Table 2. Demographic and adherence-related characteristics of the SCIT patients during 3-year follow-up before CoVID-19 pandemic. **Abbreviations:** F, female; HDM, house-dust mite; med, median; No., number. a. According to WAO classification¹²

	Ongoing SCIT (n = 48)	Drop-outs (n = 15)	P
Age (years), median (min-max)	36.5 (19-77)	38 (20-72)	0.846
Gender (F), n (%)	33 (68.8)	9 (60)	0.530
Residence, n (%)			0.945
Intown	38 (79.2)	12 (80)	
Uptown	10 (20.8)	3 (20)	
Diagnosis of allergic disease, n (%)			0.734
Allergic rhinitis	19 (39.6)	5 (33.3)	
Allergic rhinitis+ Asthma	15 (31.3)	4 (26.7)	
Venom allergy	14 (29.2)	6 (40)	
Disease duration (years), median (min-max)	10 (2-31)	15.5 (1-20)	0.199
Type of allergen sensitized, n (%)			0.669
Pollen	20 (41.7)	4 (26.7)	
HDM	3 (6.3)	1 (6.7)	
Cat	2 (4.2)	0	
Venom	9 (18.8)	3 (20)	
Polysensitized	14 (29.2)	7 (46.7)	
Type of allergen extract			0.187
Pollen	27 (56.3)	6 (40)	
HDM	3 (6.3)	2 (13.3)	
Cat	4 (8.3)	0	
Venom	14 (29.2)	6 (40)	
Inhalant allergen mix	0	1 (6.7)	
Presence of comorbid disease, n (%)	17 (35.4)	3 (20)	0.263
AIT build-up scheme, n (%)			0.270
Clustered	6 (12.5)	3 (20)	
Conventional, 7 weeks	27 (56.3)	7 (46.7)	
Conventional, 15 weeks	15 (31.3)	4 (26.7)	
Clustered → Conventional	0	1 (6.7)	
Occurrence of Local adverse reaction, n (%)	27 (43.8)	4 (26.7)	0.045
No. of Local adverse reactions, med (min-max)	1 (0-4)	0 (0-4)	0.079
Occurrence of Systemic adverse reaction, n (%)	4 (8.3)	3 (20)	0.209
No. of Systemic adverse reactions, med (min-max)	0 (0-2)	0 (0-5)	0.183
Systemic adverse reaction grade ^a , n (%)			0.203
1	3 (6.3)	2 (13.3)	
2	1 (2.1)	0	
3	0	0	
4	0	1 (6.7)	
No. of patients using premedication, n (%)	26 (54.2)	4 (26.7)	0.063
Dose modification requirement, n (%)	13 (27.1)	6 (40)	0.341
No. of dose modifications, med (min-max)	0 (0-2)	0 (0-6)	0.308
No. of patients experienced noncompliance, n (%)	5 (10.4)	1 (6.7)	0.666

(continued)

	Ongoing SCIT (n = 48)	Drop-outs (n = 15)	P
No. of events of noncompliance, med (min-max)	0 (0-2)	0 (0-1)	0.657
Duration of AIT (months), med (min-max)	23.32 (7.1-40.9)	14.65 (1.61-23.59)	0.001
No. of patients from every follow-up year, n (%)			0.046
1st year	17 (35.4)	7 (46.7)	
2nd year	12 (25)	8 (53.3)	
3rd year	14 (29.2)	0	

Table 3. (Continued) Clinical characteristics and demographic data of the SCIT patients during CoVID-19 pandemic. **Abbreviations:** F, female; HDM, house-dust mite; med, median; No., number. a. According to WAO classification ¹²

drop-outs (27.42%) of the whole group before COVID-19 pandemic. But with the pandemic only in 6 months 15 patients (23.81%) dropped out, and the most common reason was fear of being infected with COVID-19 virus during receiving SCIT in hospital (93.33%). The only independent predictor of drop-out during COVID-19 pandemic was short duration of AIT ($p = 0.012$). From 15

patients dropped-out; 7 patients (46.7%) were from first year, 8 patients (53.3%) were from second year, and none were from third year of SCIT treatment. When we compare the dropped-out cases before and after the start of pandemic, AIT duration was significantly shorter in pandemic period ($p = 0.005$).

Adherence rates for SCIT from controlled studies are noticeably high, but they are partially biased, as patients are strictly selected, instructed, and observed. In order to retrieve more reliable data, real-life studies are important.⁸ The adherence rate of previous real-life SCIT studies in adults ranges between 23 and 88%, most of them being <70% in line with our work.^{6,23} The adherence rate of 56.25% that our patients observed is also comparable with other chronic diseases such as cardiovascular disease, which is approximately 50%.²⁴ In our large tertiary allergy clinic patients are examined before and 30 min after each injection by the allergist, and the same allergy nurses apply the shots. Also, all of our SCIT patients had government-assisted health

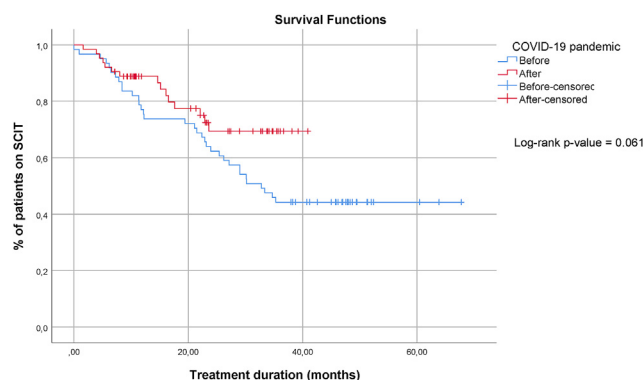


Fig. 2 Kaplan-Meier curves for adherence in SCIT patients by the beginning of the COVID-19 pandemic, with the results of the log-rank comparisons between the curves

	OR	p	95% CI
Disease duration	0.892	0.128	0.770-1.034
Occurrence of Local adverse reaction	2.075	0.660	0.081-53.376
Occurrence of Systemic adverse reaction	0.084	0.093	0.005-1.507
Patients using premedication	2.460	0.590	0.093-65.032
Duration of AIT	1.151	0.012	1.032-1.283

Table 4. Binary logistic regression analysis results to predict independent factors for SCIT nonadherence during COVID-19 pandemic

Drop-outs	Pre-pandemic (n = 21)	Post-pandemic (n = 15)	p
Age (years), median (min-max)	33 (21-64)	38 (20-72)	0.480
Gender (F), n (%)	13 (61.9)	9 (60)	0.908
Residence, n (%)			1.000
Intown	17 (81)	12 (80)	
Uptown	4 (19)	3 (20)	
Diagnosis of allergic disease, n (%)			0.238
Allergic rhinitis	13 (61.9)	5 (33.3)	
Allergic rhinitis+ Asthma	3 (14.3)	4 (26.7)	
Venom allergy	5 (23.8)	6 (40)	
Disease duration (years), median (min-max)	10 (3-24)	15.5 (1-20)	0.683
Type of allergen sensitized, n (%)			0.314
Pollen	8 (38.1)	4 (26.7)	
HDM	4 (19)	1 (6.7)	
Cat	0	0	
Venom	5 (23.8)	3 (20)	
Polysensitized	4 (19)	7 (46.7)	
Type of allergen extract			0.702
Pollen	10 (47.6)	6 (40)	
HDM	5 (23.8)	2 (13.3)	
Venom	5 (23.8)	6 (40)	
Inhalant allergen mix	1 (4.8)	1 (6.7)	
Presence of comorbid disease, n (%)	3 (14.3)	3 (20)	0.677
AIT build-up scheme, n (%)			0.952
Clustered	3 (14.3)	3 (20)	
Conventional, 7 weeks	11 (52.4)	7 (46.7)	
Conventional, 15 weeks	5 (23.8)	4 (26.7)	
Clustered → Conventional	2 (9.5)	1 (6.7)	
Occurrence of Local adverse reaction, n (%)	11 (52.4)	4 (26.7)	0.123
No. of Local adverse reactions, med (min-max)	1 (0-10)	0 (0-4)	0.079
Occurrence of Systemic adverse reaction, n (%)	4 (19)	3 (20)	1.000
No. of Systemic adverse reactions, med (min-max)	0 (0-2)	0 (0-5)	0.871
Systemic adverse reaction grade ^a , n (%)			0.907
1	3 (14.3)	2 (13.3)	
2	0	0	
3	1 (4.8)	0	
4	0	1 (6.7)	
No. of patients using premedication, n (%)	10 (47.6)	4 (26.7)	0.204
Dose modification requirement, n (%)	12 (57.1)	6 (40)	0.310
No. of dose modifications, med (min-max)	0 (0-3)	0 (0-6)	0.180
No. of patients experienced noncompliance, n (%)	6 (28.6)	1 (6.7)	0.200

(continued)

Drop-outs	Pre-pandemic (n = 21)	Post-pandemic (n = 15)	p
No. of events of noncompliance, med (min-max)	0 (0-2)	0 (0-1)	0.094
Duration of AIT (months), med (min-max)	23.91 (0.92-35.29)	14.65 (1.61-23.59)	0.005
No. of patients from every follow-up year, n (%)			0.009
1st year	5 (23.8)	7 (46.7)	
2nd year	6 (28.6)	8 (53.3)	
3rd year	10 (47.6)	0	

Table 5. (Continued) Comparison of clinical characteristics and demographic data of the drop-out SCIT patients before and after CoVID-19 pandemic. **Abbreviations:** F, female; HDM, house-dust mite; med, median; No., number. a. According to WAO classification¹²

insurance. Even though we have a close cooperation with the patients, and the cost is covered by health insurance, our discontinuation rate is higher than Gelincik et al observed, which makes us think that in a multifactorial event like adherence these 2 may not be the main factors as opposed.²⁵ In fact, like us Cox et al in their review concluded that AIT adherence is equally poor regardless of whether or not treatment is administered in a medically supervised setting and comparable to poor adherence with long-term pharmacotherapy.¹⁰ Although our adherence rate is in line with most SCIT studies, and there is no consensus about an acceptable adherence rate, it is obvious that there is a strong need for further adherence improvement in order to gain the full benefit from AIT. At this point it becomes particularly important to identify potentially non-adherent SCIT patients and follow them closely. The reasons for SCIT withdrawal are also variable among the literature; there is a lot of heterogeneity, and the identified factors vary from one study to another. Therefore, to be able to evaluate the changing adherence pattern of our SCIT patients we compared the factors in 2 different time-zones, before and during the COVID-19 pandemic, in the same clinic.

In this study, no statistical differences were found between adherent and non-adherent groups in what concerns age, gender, residence, clinical diagnosis, disease duration, allergenic composition, or build-up scheme of the SCIT before the COVID-19 pandemic. When we reviewed demographic factors associated with nonadherence in the literature, in some studies gender and age did not have an impact on adherence, while in others they have. Lourenco

et al, like us, has not found differences in age or gender.¹² Lemberg et al detected no difference based on sex but nonadherent patients were younger, whereas Gelincik et al reported no difference based on age but nonadherent patients were males, and Rhodes et al found that nonadherence was higher in younger male patients.^{7,25,26} Likewise, according to Donahue et al patients suffering from both asthma and rhinitis were more likely to continue SCIT than patients with only 1 disease.²⁷ But others found no correlation between adherence and diagnosis.^{12,13,25} The use of a shorter build-up phase seemed to improve patients' adherence to SCIT in 1 study, but in our study AIT build-up scheme showed no impact on adherence.²⁸

Overall, in our study clinical factors such as local or systemic reactions, need for premedication, and noncompliance did not have a significant effect on adherence. Similar to our study, in their study Yang et al found no difference between the adherent and nonadherent group in terms of the incidence of adverse reactions.¹³ Also, when we look at patient-reported reasons for SCIT nonadherence, in a review of more than 25 studies it appears that local and systemic reactions are not the main reasons for discontinuation (4% and 1-16% respectively).¹⁰ However, in our study, the only factor found related to nonadherence was need for dose modification and its frequency. The dose modification was done due to previous systemic or large local reactions or long intervals between 2 consecutive administrations. This led patients to return to the appropriate step of the build-up scheme and cause inconvenience, which was defined as one of the main reasons for discontinuation of SCIT.^{8,10,12} Also, this finding of ours was

confirmed with our over-all group drop-outs too. To the best of our knowledge, this is the first time that effect of dose modification has been studied on SCIT adherence.

The COVID-19 pandemic caused rapid changes in our daily clinical practice; patient admissions were markedly decreased. With the start of pandemic in a 6-month period among 63 patients receiving SCIT in our clinic, 15 patients (23.81%) dropped out, and the main reason was “fear of being infected with COVID-19 virus during receiving SCIT in hospital” (93.33%). Only one patient (6.67%) dropped out because of repetitive systemic reactions. In line with our findings in their study of children’s SCIT adherence during COVID-19, Celik et al reported the drop-out rate as 20.51% and cited fear of COVID-19 transmission as the main reason.²⁹ On the other hand, Martinez-Lourido et al from Spain reported a drop-out rate as 6.5% in venom SCIT patients during pandemic.³⁰

In this study, shorter duration of AIT was found to be the only independent risk factor associated with SCIT drop-out during the COVID-19 pandemic period. This was a new risk factor which was not observed before the pandemic, and shows the development of a new behavior in our patients. Concerning the duration of SCIT as a suspension factor among literature, it has been documented that patients compliant with the first year of treatment are less likely to drop-out.^{13,26,31} This was attributed to the frequent injections in the up-dosing phase, and premature perceived ineffectiveness of AIT.¹³ Lourenco et al showed more than half of the nonadherent patients discontinued AIT during the first year of the treatment.¹² Therefore, these results may indicate that under the anxiety factor of COVID-19 viral transmission, first or second year SCIT patients, who are already known as poor adherents, may be more prone to drop-out of the treatment. We believe that if patients in the early phases of their SCIT observed more closely and identified beforehand, therapy route may be discussed and changed to SLIT, which is not covered by government health insurance in our country.

The key elements of an effective AIT adherence intervention plan come from providing sufficient and effective education and information about health, illness, and treatment steps including dose adjustments; incorporation of standardized follow-up visits, and especially now in the era of the COVID-19 pandemic employment of telecommunication technologies with a communication strategy composed of patient-centered care, shared decision making, and motivational interviewing strategies to the patient.^{32,33} Not a one-size-fits-all education, but a tailored one according to patient’s health literacy level should be delivered to achieve the best adherence. The necessity of effective education for improving SCIT adherence was shown in a study which was executed in 5 countries (USA, France, Spain, Germany, and Russia) involving 261 patients. The participants, who were either recent nonadherents or “non-starters” (having decided not to initiate AIT recommended by their physician), completed an internet survey before and after a new communication template on allergy and allergen immunotherapy was presented. The result was critical: 28% of the participants were not aware of the allergen they were receiving during AIT. Twenty-seven percent reported that they had not been told allergy was a chronic condition. Early abandoners held its low effectiveness (39%) and expense (39%) responsible for therapy discontinuation. After new communication template, participants of the survey felt much more enlightened and more likely to start or fulfill AIT.³⁴ As a result, this research clearly reveals that a lack of education in AIT patients hampers treatment success. Also, increasing medical data demonstrate the importance of pre-AIT education, clinic telephone follow-up calls and more frequent clinic visits for improving adherence to AIT.³⁵⁻³⁷ Although there is a close relationship between allergists and their patients in our clinic, since the same allergy team (doctors and nurses) observes the patients at each shot and discusses their therapy route, the rate of adherence was not as high as expected, dose modifications being the major cause. In fact, during routine visits, it is difficult to arrange a structured educational program, and our results prove it. To be effective, doctors might plan to

optimize the time for education during a consultation. Additional investigations are needed from prospective studies, where we can get more detailed information addressing this dimension of adherence.

This study is limited by its retrospective design and single-institution small sample size. More evidence is needed from larger samples in prospective studies. Also, because of the new and ongoing nature of the COVID-19 pandemic, some of the patient's SCIT from the pandemic group is still ongoing. We were only able to give drop-out rate but not adherence rate, for this group. In spite of these limitations, this is the first adult study comparing the effect of the COVID-19 pandemic on SCIT adherence attitudes.

CONCLUSION

As a common consequence of large local reaction, systemic reaction, and long noncompliance, "dose modification" done during SCIT may be good indicator for identifying patients who are likely to be non-adherent. Also, sadly, there is still an ongoing pandemic with new variants and waves. So, during this COVID-19 pandemic we believe that patients who are in the early phases of their SCIT should be observed more closely and their concerns should be answered by their doctors; if needed, treatment route may be changed to SLIT when possible, a home-based treatment. By identifying patients prone to be non-adherent, we may fine tune patient attributes in place and on time to improve adherence to treatment and success of it.

Abbreviations

AIT, Allergen immunotherapy; AR, Allergic Rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; COVID-19, Coronavirus disease 2019; EAACI, European Academy of Allergy and Clinical Immunology; GINA, Global Initiative for Asthma; SCIT, Subcutaneous immunotherapy; SLIT, Sublingual immunotherapy; WHO, World Health Organization

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Contributions of authors

The first and second author designed the study and collected the data, the first author analyzed and interpreted

the data and wrote the manuscript. All the authors critically revised and approved the final version of the manuscript and agree to be accountable for all the aspects of the work.

Consent for publication

All the authors agree on publishing the submitted document.

Availability of data and materials

The de-identified data that support the findings of this study are available upon reasonable request.

Ethics approval

The study protocol was reviewed and approved by the Ankara Kecioren Educational Research Hospital Clinical Research Ethics Committee (2012-KAEK-15/2181).

Declaration of competing interest

The authors report no competing interests.

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