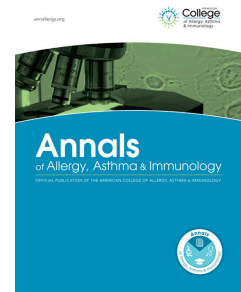


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Full title: Effect of Patient and Parental Anxiety on Adherence to Subcutaneous Allergen Immunotherapy During COVID-19 Pandemic

Running title: Adherence to Subcutaneous Allergen Immunotherapy During the COVID-19 Pandemic

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Ilknur Kulhas Celik: She made substantial contributions to design of study, analysis and interpretation of data; drafted the article and reviewed it critically for important intellectual content; gave final approval of the version to be published

Azize Pinar Metbulut: He has given final approval of the version to be published, made substantial contributions to design of study, drafted the article and agrees to be accountable for all aspects of the study related to its accuracy or integrity.

Ozden Sukran Uneri: She made substantial contributions to analysis of data; reviewed the article critically for important intellectual content; gave final approval of the version to be published and agrees to be accountable for all aspects of the study related to its accuracy

Gulser Senses Dinc: She made substantial contributions to analysis of data; reviewed the article critically for important intellectual content; gave final approval of the version to be published and agrees to be accountable for all aspects of the study related to its accuracy .

Emine Dibek Misirlioglu: She made substantial contributions to analysis of data; reviewed the article critically for important intellectual content; gave final approval of the version to be published and agrees to be accountable for all aspects of the study related to its accuracy

All of authors certify that they have collectively written at least 90 percent of the manuscript.

The global spread of SARS-CoV-2 has resulted in over a million deaths to date, despite many strategies implemented to limit transmission, such as social distancing, wearing face mask and quarantining/isolation^{1,2}. These strategies were also applied in health care facilities, including recommendations for minimizing face-to-face meetings in allergy and immunology clinics and taking necessary precautions to minimize the risk of transmission³.

Discontinuing SCIT is not recommended in patients who do not have COVID-19 or were previously infected. It is also recommended that the interval between doses can be extended to 2 weeks in the build-up phase and up to 6 weeks in the maintenance phase³⁻⁵.

A recent study showed that the anxiety levels of the parents of children hospitalized during the COVID-19 pandemic were higher than those of parents whose children were hospitalized before the pandemic⁶. Patients receiving SCIT and their parents must continue to come to the hospital for SCIT during the pandemic.

We aimed to evaluate effect of patient and parental anxiety on adherence to SCIT during COVID-19 pandemic

Patients who underwent venom and aeroallergen SCIT in our pediatric allergy and immunology clinic in hospital during the COVID-19 pandemic between May 1 and September 1, 2020 and their parents were included in our study. The patients' age, sex, SCIT type, phase, and duration, adherence to SCIT since the start of the pandemic were recorded

The study was approved by the ethics review committee of Ankara City Hospital and by the Turkish Ministry of Health. Written informed consent was obtained from the parents of the patients.

As per recommendations, the interval between doses was extended to 2 weeks in the build-up phase and 6 weeks in the maintenance phase, and the patients were informed. The patients were classified as adherent (patients who continued SCIT according to schedule during the pandemic), nonadherent (patients who continued SCIT during the pandemic but with

between-dose intervals longer than 2 weeks in the build-up phase and 6 weeks in the maintenance phase), or discontinued treatment (patients who did not present for SCIT at all since the pandemic started).

The anxiety levels of our patients were assessed using the State–Trait Anxiety Inventory for Children(STAI–C), which is a tool to evaluate state and trait anxiety in children aged 8 to 18 years⁷⁻⁸. Patients older than 18 and parents were assessed using the STAI⁹. Like the STAI–C, the STAI consists of the state anxiety scale and the trait anxiety scale with higher scores reflecting higher anxiety level.

Statistical analyses were performed using IBM SPSS Statistics version 22.0 statistical software package for Windows (IBM Corp., Armonk, NY, USA). The chi-square test was used to compare nonparametric data; the Mann–Whitney U test was used for comparisons among non-normally distributed continuous variables and independent samples t-test for normally distributed continuous variables. A value of $p < 0.05$ was considered statistically significant.

The study included 78 patients (62.8% male) who started SCIT (8 patients venom, 70 patients aeroallergen) in our clinic in the hospital and attended treatment regularly before the pandemic. The mean age of the patients was 14.87 ± 3.48 (min–max: 8–23.5) years.

After the start of the pandemic, 39 (50%) patients continued SCIT regularly (adherent group), 23 patients continued treatment with extended dose intervals (nonadherent group), and 16 patients discontinued treatment.

Of the 16 patients (68.8% male) who discontinued treatment, 10 patients were in the build-up phase and 6 were in the maintenance phase. When asked the reason for SCIT discontinuation, 16 patients cited fear of COVID-19 transmission. Significantly more patients who discontinued treatment were in the build-up phase compared to patients who continued SCIT ($p = 0.006$) (Table 1).

Twenty-three patients exceeded the recommended between-dose intervals. When asked the reason for SCIT nonadherence, 22 patients cited fear of COVID-19 transmission and 1 patient had to extend the dose interval due to a quarantine because his father had a confirmed COVID-19 infection.

Among the patients who continued treatment, mean state anxiety score was 35.6 ± 8.3 (min–max:20–54) and mean trait anxiety score was 33.7 ± 7.5 (min–max:23–52). Among parents, the mean state and trait anxiety scores were 36.6 ± 9 (min–max:21–54) and 40.9 ± 7.6 (min–max:25–58), respectively. Comparison of patients who continued to adhere to the SCIT dose schedule during the pandemic and those who continued treatment but with nonadherence showed no statistically significant difference in patient state anxiety score or parental state and trait anxiety scores, while trait anxiety score was higher among nonadherent patients compared to adherent patients ($p=0.02$) (Table 1).

It is recommended to continue treatment with extended dose intervals for patients already receiving SCIT⁸. All of our patients started SCIT before the pandemic. Patients in the build-up phase accounted for a significant proportion of patients who discontinued treatment. Patients in the build-up phase had only been receiving treatment for a few months and had to come every 2 weeks until this phase was complete. In contrast, patients in the maintenance phase had been visiting our clinic in the hospital for treatment for years and needed to come every 6 weeks during the pandemic. The higher rate of treatment cessation during the build-up phase may be due to these patients having invested less time in treatment before the pandemic and being required to visit clinic in the hospital more frequently.

Yuan et al. reported that anxiety was more pronounced in the parents of children hospitalized during the pandemic⁶. Our patients were present in the hospital for approximately one hour to receive SCIT. Our evaluation showed that there was no difference in patient or parental state anxiety and parental trait anxiety between the adherent and nonadherent

groups, whereas trait anxiety was higher among nonadherent patients. The patients in our sample were predominantly adolescents. Our findings are consistent with data from studies indicating that in this age group, patients themselves have a greater effect on treatment processes¹⁰.

In conclusion, half of our patients were fully adherent to SCIT during the pandemic. Trait anxiety level of the patients was the only patient or parental anxiety factor associated with poorer SCIT adherence. Therefore, we believe that treatment adherence may be improved if allergists refer patients observed to be particularly anxious for child psychiatric evaluation.

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Table 1: Demographic characteristics and State-Trait Anxiety Inventory scores of patients receiving subcutaneous immunotherapy (SCIT) and their parents

	Continued SCIT, adherent (n=39)	Continued SCIT, nonadherent (n=23)	Discontinued SCIT (n=16)	p value (adherent vs. nonadherent)	p value (continued vs. discontinued)
Patient sex, n (%)					
Female	24 (61.5)	14 (60.8)	11 (68.7)	0.85	0.58
Male	15 (38.5)	9 (39.2)	5 (31.3)		
Patient age (years)					
Mean±SD	14.4±3.6	15.5± 3.38	14.9±3.32	0.25	0.90
Parent age (years)					
Mean±SD	42.5±5.8	43.35±6.65	NA	0.63	-
Phase of SCIT, n (%)					
<i>Build-up phase</i>	16 (41)	0 (0)	10 (62.5)	<0.001	0.006
<i>Maintenance phase</i>	23(59)	23 (100)	6 (37.5)		
Patient state anxiety score					
Mean±SD	33.24±7.08	35.5±8.38	NA	0.33	-
Patient trait anxiety score					
Mean±SD	34.39±7.38	39.5±8.5	NA	0.02	-
Parental state anxiety score					
Mean±SD	36.89±9.86	39.11±8.10	NA	0.40	-
Parental trait anxiety score					
Mean±SD	40.37±7.87	42.84±7.47	NA	0.26	-

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