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Effect of patient and parental anxiety on adherence to subcutaneous allergen immunotherapy during the coronavirus disease 2019 pandemic

The global spread of severe acute respiratory syndrome coronavirus 2 has resulted in more than a million deaths to date despite many strategies implemented to limit transmission, such as social distancing, wearing a face mask, quarantining and 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 transmission.[3]

Discontinuing subcutaneous immunotherapy (SCIT) is not recommended in patients who do not have coronavirus disease 2019 (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 phase.[3-5]

A recent study found 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 pandemic.[6] Patients receiving SCIT and their parents must continue to come to the hospital for SCIT during the pandemic. We aimed to evaluate the effect of patient and parental anxiety on adherence to SCIT during the COVID-19 pandemic.

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

Per the recommendations, the interval between doses was extended to 2 weeks in the build-up phase and 6 weeks in the maintenance phase; 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 (STAI) for children, which is a tool to evaluate the state and trait anxiety in children aged 8 to 18 years.[7-8] Patients older than 18 years and the parents were assessed using the STAI.[9] Similar to the STAI for children, the STAI consists of the state anxiety scale and the trait anxiety scale with higher scores reflecting higher anxiety levels.

Statistical analyses were performed using Statistical Package for the Social Sciences software version 22.0 for Windows (International Business Machines Corporation, Armonk, New York). The χ^2 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 $P < .05$ was considered statistically significant.

The study included 78 patients (62.8% male) who started SCIT (8 patients for venom, 70 patients for aeroallergen) in our hospital clinic and attended treatment regularly before the pandemic. The mean (±SD) age of the patients was 14.87 (±3.48) (minimum-maximum [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 with patients who continued SCIT ($P = .006$) (Table 1).

A total of 23 patients exceeded the recommended between-dose intervals. When asked regarding the reason for SCIT nonadherence, 22 patients cited fear of COVID-19 transmission and 1 patient had to extend the dosing interval owing to quarantine (because his father had a confirmed COVID-19 infection).

Among the patients who continued treatment, the mean state anxiety score was 35.6 (±8.3) (min-max: 20-54) and the mean trait anxiety score was 33.7 (±7.5) (min-max: 23-52). Among the 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. A comparison of patients who continued to adhere to the SCIT dose schedule during the pandemic and those who continued treatment but with nonadherence revealed no statistically significant difference in patient state anxiety score or parental state and trait anxiety scores (P =.33; .04; .26 respectively), whereas trait anxiety score was higher among nonadherent patients compared with adherent patients ($P = .02$) (Table 1).

It is recommended to continue treatment with extended dose intervals for patients already receiving SCIT.[8] All of our

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Table 1
Demographic Characteristics and State-Trait Anxiety Inventory Scores of Patients Receiving Subcutaneous Immunotherapy and Their Parents

Characteristic	Continued SCIT, adherent (n = 39)	Continued SCIT, nonadherent (n = 23)	Discontinued SCIT (n = 16)	*P* value[a] (adherent vs nonadherent)	*P* value[b] (continued vs discontinued)
Patient sex, n (%)					
Female	24 (61.5)	14 (60.8)	11 (68.7)	.85	.58
Male	15 (38.5)	9 (39.2)	5 (31.3)		
Patient age (y)					
Mean ± SD	14.4 ± 3.6	15.5 ± 3.38	14.9 ± 3.32	.25	.90
Parental age (y)					
Mean ± SD	42.5 ± 5.8	43.35 ± 6.65	NA	.63	—
Phase of SCIT, n (%)					
Build-up phase	16 (41)	0 (0)	10 (62.5)	**<.001**	**.006**
Maintenance phase	23(59)	23 (100)	6 (37.5)		
Patient state anxiety score					
Mean ± SD	33.24 ± 7.08	35.5 ± 8.38	NA	.33	—
Patient trait anxiety score					
Mean ± SD	34.39 ± 7.38	39.5 ± 8.5	NA	**.02**	—
Parental state anxiety score					
Mean ± SD	36.89 ± 9.86	39.11 ± 8.10	NA	.40	—
Parental trait anxiety score					
Mean ± SD	40.37 ± 7.87	42.84 ± 7.47	NA	.26	—

Abbreviations: NA, not applicable; SCIT, subcutaneous immunotherapy.
[a]*P* values in the 5th column refer to the comparisons between adherent and nonadherent patients using the chi square and student t-test.
[b]*P* values in the last column refer to the comparisons between continued and discontinued patients using the chi square and student t-test.

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 hospital clinic 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 attributed to the fact that these patients had invested less time in treatment before the pandemic and were being required to visit a hospital clinic more frequently.

Yuan et al[6] reported that anxiety was more pronounced in the parents of children hospitalized during the pandemic. Our patients were present in the hospital for approximately 1 hour to receive SCIT. Our evaluation revealed 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 the data from studies indicating that in this age group, the patients themselves have a greater effect on treatment processes.[10]

In conclusion, half of our patients were fully adherent to SCIT during the pandemic. The 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 the patients who were observed to be particularly anxious for child psychiatric evaluation.

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Inhaled triple therapy and airway hyperresponsiveness in persistent asthma

Adding a long-acting muscarinic antagonist (LAMA) is recommended in the guidelines for a patient with asthma not controlled on inhaled corticosteroid (ICS)/long-acting β-agonist (LABA). The change in forced expiratory volume in 1 second (FEV1) resulting from the addition of LAMA to ICS/LABA may be relatively small or less than the minimal clinically important difference, and as such, improved airway caliber is not the primary mechanism for a reduction in exacerbations with LAMA therapy.[1] Exacerbations are, in part, determined by the effects on airway hyperresponsiveness (AHR) in which a LAMA might be expected to confer additional airway smooth muscle–stabilizing effects when added to ICS/LABA.[2] Aside from effects on airway smooth muscle, there may be neuronal and paracrine actions of LAMAs that may reduce exacerbations.[1] Indirect challenge tests with agents such as mannitol are thought to be more physiological than direct agents such as histamine or methacholine in that they better reflect the underlying inflammation status as opposed to the function of airway smooth muscle alone.[3]

There are 2 randomized crossover trials that have prospectively evaluated the effects of adding-in LAMA as tiotropium to ICS/LABA as triple therapy using indirect bronchial challenge with mannitol in persistent asthma. In 1 study, mannitol AHR was the primary end point measured at trough after dosing for 4 weeks in 14 nonsmoking patients with persistent asthma taking ICS at a beclomethasone dipropionate equivalent dose of 429 μg/day. In comparison with ICS along with LABA (as indacaterol), adding tiotropium as triple vs dual therapy conferred a nonsignificant 0.85 geometric mean fold (gmf) difference (ie, the ratio for triple vs dual therapy) in mannitol sensitivity for the provocative dose (PD) to induce a 15% decrease in FEV1 and a nonsignificant 0.95 gmf difference in mannitol reactivity for the response dose ratio (RDR), expressed as maximum percent fall in FEV1 per milligram of mannitol.[4]

Previously unpublished data from the study of Jabbal et al[5] are presented here from a posthoc analysis among a subgroup of 9 of 16 current smokers with persistent asthma who were responsive to mannitol, a secondary end point (Fig 1). The mean values were as follows: FEV1 of 79%, age 44 years, and beclomethasone dipropionate equivalent dose of 800 μg/day. For effects after 3 weeks measured 1-hour after inhalation, adding tiotropium to beclomethasone dipropionate 800 μg/d with LABA (as olodaterol) as triple vs dual therapy conferred a nonsignificant ($P = .22$) 0.58 gmf difference (ie, the ratio for triple vs dual therapy) in mannitol sensitivity for the PD to induce a 30% increase in resistance at 5 Hz (R5). The absolute geometric mean (95% confidence interval) values for PD to induce a 30% increase in R5 were 138 (60,317) mg vs 238 (123,461) mg for triple and dual therapy, respectively, indicating increased AHR with triple therapy. Hence, a gmf ratio of less than 0.5 or greater than 2.0 would be clinically relevant per se, given that this exceeds a $\pm$ 1 doubling dose difference in protection.

There was a nonsignificant ($P = .19$) 1.91 gmf difference in mannitol reactivity for the RDR, expressed as the maximum percent increase in R5 per milligram of mannitol.[5] Respective absolute values for the geometric mean (95% confidence interval) RDR values expressed as the percent change in R5 per milligram of mannitol with dual vs triple therapy were 0.10 (0.04-0.25) and 0.20 (0.09-0.42). We appreciate the limitations of reduced sample size in a subgroup posthoc analysis, which might result in confounding the type 2 error.

These findings suggest that LAMAs may not attenuate indirect AHR to mannitol when given as add-on therapy to ICS/LABA in either smokers or nonsmokers with persistent asthma. This begs the question as to whether LAMAs might influence direct-acting AHR owing to functional antagonism of the airway smooth muscle induced by histamine or methacholine. In this regard, Britton et al[6] found concordant dose-related improvements in FEV1 with salbutamol and ipratropium, whereas only salbutamol produced attenuation of histamine-induced AHR, suggesting that airway geometry is relatively disconnected from improvements in AHR with muscarinic antagonists.

To date, the results of clinical trials have illustrated marginal effects on asthma exacerbations when comparing single-inhaler triple vs dual therapy, given by means of the same inhaler delivery system. The large multicenter trials TRIMARAN and TRIGGER[7] compared medium- and high-dose formulations of beclomethasone dipropionate/formoterol/glycopyrronium vs beclomethasone dipropionate/formoterol, resulting in 15% and 12% respective reductions in exacerbations as a coprimary end point. The reduction in exacerbations for triple vs dual therapy was only significant in TRIMARAN for the medium doses. Statistically significant improvements in the coprimary end point of FEV1 with triple therapy amounted to 57 mL in TRIMARAN and 73 mL TRIGGER, being less than the minimal clinically important difference of 230 mL. The CAPTAIN trial[8] compared medium- and high-dose formulations of fluticasone furoate/vilanterol/umeclidinium vs fluticasone furoate/vilanterol, conferring 22% and 3% respective differences in exacerbations as a key secondary end point. Statistically significant improvements in the primary end point of FEV1 amounted to 110 mL with medium-dose triple and 92 mL with high dose triple therapy. Greater reductions in exacerbations were seen in association with raised baseline eosinophil counts (>300/μL) and exhaled-breath nitric oxide (>50 parts per billion) with combination treatments containing high vs medium doses of fluticasone furoate. Notably, no patients in these 3 trials were current smokers, which makes it difficult to extrapolate the findings to a wider population in a real-life clinical setting, especially in areas of socioeconomic deprivation. Hence, it seems that marginal reductions in exacerbations conferred by triple vs dual inhaler therapy are not explained by attenuated AHR owing to LAMA. It is debatable whether commensurate small improvements in airway caliber may

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