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Original Article

The effect of the COVID-19 pandemic on long-term treatment compliance and disease control in children with persistent asthma

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ABSTRACT

Background. No long-term data exists on asthma treatment compliances (ATC), exacerbations (AE), and control (AC) during the COVID-19 pandemic in children. This study aimed to evaluate ATC, AE, AC and the related factors among children with persistent asthma (PA) within the first year of the pandemic

Methods. Children aged 6-18 years with PA who were under regular inhaled corticosteroid treatment for at least a year prior to the first COVID-19 case in Türkiye were included. Data on AE and AC were collected from medical files. Factors affecting ATC and AC as well as COVID-19 history were assessed by means of a questionnaire.

Results. The study included 247 cases. COVID-19 was detected in 14.5% of them. In the first year of the pandemic, ATC decreased to 56.7% and the most common reason was the absence of asthma symptoms. There was a significant improvement in AC ($p<0.001$). The number of upper respiratory tract infections (URTI) and AE were significantly decreased during the first year of the pandemic ($p<0.001$). COVID-19 infection, smoking in the household, school attendance, a family member working outside the home, house dust mite sensitization or allergic rhinitis had no significant effect on AC ($p>0.05$). Regression analysis determined that children who did not have any URTI had 2.4 times better AC compared to those who had ($p= 0.02$; %95 CI: 1.1-5.4).

Conclusions. Although ATC decreased significantly in the long-term in the first year of the pandemic, significant improvement was observed in AE and AC compared to the previous year, which was related only to not having URTI.

Key words: asthma, children, compliance, COVID-19, exacerbation, treatment.

The COVID-19 epidemic was declared as a pandemic on March 11, 2020[1]. The COVID-19 infection has produced milder illness in children than in adults.[2-4] During the pandemic, chronic lung disease, diabetes, and cardiovascular diseases were considered comorbidities that represented a risk in terms of COVID-19.[5] However, studies have not as yet pointed to an increased risk for COVID-19 among individuals with asthma.[2,6-8] In fact, improvements in pediatric AC during the pandemic have been reported in cross-sectional studies.[9-11] Almost all of the studies have indicated that the main reason for this was the decline in the incidence of upper respiratory tract infections (URTI) and reduced air pollution.[9,12-14] On the other hand, asthma treatment compliance (ATC) has a significant impact on asthma control (AC).[15-17] Generally, ATC among children was reported between 30-70% prior to the pandemic.[18-20] There is no study that assesses the long-term ATC in children with asthma during the COVID-19 pandemic. During the pandemic there were a

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limited number of studies in which ATC and its effect on AC were investigated.[21] The few studies that explore ATC either compare the period of quarantine with the previous period[21] or provide a one-year extrapolation based on a short interval.[10] Most studies, however, are short-term accounts[22,23] based on doctor's statements[9], or studies that have not queried the patient's history of COVID-19 infection.[10,21,23] In addition, there are a few long-term studies about asthma exacerbations (AE) and AC among children during the pandemic.[24,25] Therefore, we aimed to compare the first year of the pandemic with the previous year in terms of its effects on long-term ATC, AE, and AC among 6-18 year old children with persistent asthma (PA) who exhibited high levels of ATC before the pandemic.

Materials and Methods

Study sample

Children between 6-18 years of age who were being followed up with a confirmed diagnosis of persistent asthma and had been regularly taking inhaled corticosteroids (ICS) for at least one year prior to the first recorded case of the COVID-19 infection in Türkiye in March 2020 were invited to participate in the study. Cases with a diagnosis of asthma that were being followed up for less than one year prior to the pandemic, and those whose compliance was poor were excluded from the study since they were not receiving ICS treatment regularly.

Questionnaire

A questionnaire of 26 items (ATC: 8 questions, COVID-19 history: 11 questions, factors that may affect AC other than COVID-19 infection during pandemic: 7 questions) was administered to families and children consenting to participate at designated appointment times (Supplement). The meetings were held separately, face-to-face, and in keeping with COVID-19 safety precautions.

Definitions

Definitive COVID-19 infection: The child with asthma is symptomatic and has tested positive on the SARS-CoV-2 PCR test.

Possible COVID-19 infection: The child with asthma is symptomatic but the SARS-CoV-2 PCR test has not been administered by the filiation team because at least one person in the same household has a diagnosis of COVID-19 with a PCR test at the same time.

Compliance: The participants who had stopped taking ICS treatment after March 2020 without consulting to the department were defined as *noncompliant,* while those who continued their treatment as advised were defined as *compliant*.

Asthma exacerbations: AE were grouped according to the medical files using a written AE plan at home, need for systemic corticosteroids use, emergency department application or hospitalization.

Asthma control: AC was evaluated categorically as recommended by the GINA 2020 asthma diagnosis and treatment guidelines and defined as well-, partially-controlled and uncontrolled.[26]

In the study, AC and AE were evaluated from the medical records of the participants. The first year of the COVID-19 pandemic (March 2020-March 2021) was compared to the year prior to the pandemic (February 2019-February 2020) in terms of compliance with asthma treatment and AE. Evaluation of AC was made twice–at the last visit in 2019 and at the end of the first year of the pandemic. History of COVID-19 infection, ATC, and the factors that may affect AC during COVID-19 pandemic were evaluated by the questionnaire.

Ethics committee approval

Ethical approval was obtained from Gazi University Ethics Committee (Date: 31.05.2021/ No:498). All participants gave informed consent for the study.

Statistical analysis

The data of the study were analyzed with the SPSS (Statistical Package for Social Sciences) for Windows 22.0 program (SPSS Inc, Chicago, IL) package program. The Kolmogorov-Smirnov Test was used to assess normal distribution. The McNemar and chi-square tests were used in the comparison of categorical variables. In the multivariate analysis, significant parameters in univariate analysis were subjected to logistic regression analysis. The Hosmer-Lemeshow test was used to determine the goodness of fit of the model. A p value of less than 0.05 was accepted as statistically significant.

Results

Screening

There were 486 children with persistent asthma between 6-18 years of age who were on regular ICS treatment and attending their check-up visits regularly for more than a year. The final analysis included 247 participants after exclusion of the cases that did not give consent, those who stopped taking ICS treatment before the pandemic and could not be contacted (Fig. 1). The demographic details of the participants are presented in Table I. Forty-eight percent of the participants were taking a high dose of ICS. Of those taking high doses, 97.5% were between the ages 6-11 years old.

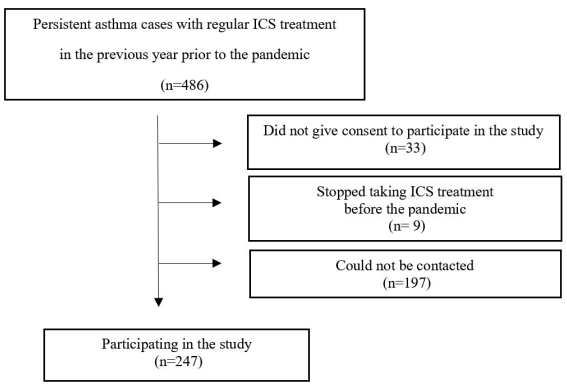

Fig. 1. Study group.

Long term compliance with asthma treatment during the COVID-19 pandemic

In the first year of the pandemic, 107 patients stopped taking ICS treatment (43.3%). Of these individuals, 8 had recurrence of asthma symptoms upon stopping their treatment (7.4%), and 7 of them (87.5%) started taking their medications again but none were hospitalized for asthma.

Table I. Demographics.

	n (%)
Age, year	
6-11	167 (67.6)
≥12	80 (32.4)
Male	156 (63.2)
Current age, months	121 (75-234)
Age at asthma diagnosis, months	66 (8-176)
Aeroallergen sensitivity	107 (43.3)
Pollen	78 (72.8)
Dust mites	56 (52.3)
Animal epithelia	49 (45.7)
Mold	18 (16.8)
Allergic comorbidity	79 (31.9)
Allergic rhinoconjunctivitis	29 (36.7)
Atopic dermatitis	11 (13.9)
Food allergy	3 (3.7)
Asthma controller treatment	247 (100)
ICS	132 (53.4)
ICS- LABA (Fixed dose combination treatment)	95 (38.5)
ICS plus LTRA	11 (4.5)
ICS- LABA (Fixed dose combination treatment) plus LTRA	9 (3.6)
Daily ICS doses, by age	
Age 6-11 years	167 (67.6)
Low	21 (12.5)
Moderate	29 (17.5)
High	117 (70)
Age ≥12 years	80 (32.4)
Low	64 (80.0)
Moderate	13 (16.2)
High	3 (3.8)

Continuous variables are shown as median (min-max). ICS: Inhaled corticosteroid; LABA: Long-acting bronchodilator inhaler; LTRA: Leukotriene receptor antagonists.

The discontinuation of ICS treatment, which began shortly after the onset of the pandemic, persisted throughout the study period. During this first year of the pandemic, the highest and lowest termination rates of ICS treatment were seen in April 2020 (n: 23, 21.4%) and November 2021 (n:2, 1.8%), respectively (Fig. 2). The absence of asthma symptoms was the most commonly cited reason for discontinuing ICS treatment (n: 94, 92.5%).

Asthma control during the COVID-19 pandemic

A comparison of the AC of the participants prior to the COVID-19 pandemic and at their last checkup at the end of the first year of the pandemic is presented in Table II. Asthma control did not change in 59.2%, improved in 35.2% and worsened in 5.6% of the cases, respectively compared to the last control before the pandemic. There was a significant improvement overall in AC compared to the period prior to the pandemic (p<0.001) (Table II).

Factors that may impact AC during the COVID-19 pandemic

COVID-19 infection

Seventy-five cases had a household member with a definite history of COVID-19 infection (30.4%). There were 21 children with definite and 15 with probable COVID-19 infection (8.5% and 6.1%, respectively). Three of them applied to the hospital due to COVID-19 symptoms (fever, myalgia, diarrhea, etc) but not for asthma symptoms. COVID-19 infection did not have any impact on AC (p= 0.52).

Asthma exacerbations

Table II presents a comparison of AE before and during the COVID-19 pandemic. The percentage of cases with AE decreased from 30.8 to 10.5% at the end of the first year of pandemic compared to the previous year (p<0.001). There were significant differences in terms of exacerbations requiring systemic corticosteroid (SCS) use and application to the emergency department (p<0.001 for both) but not for those that required hospitalization (p>0.05).

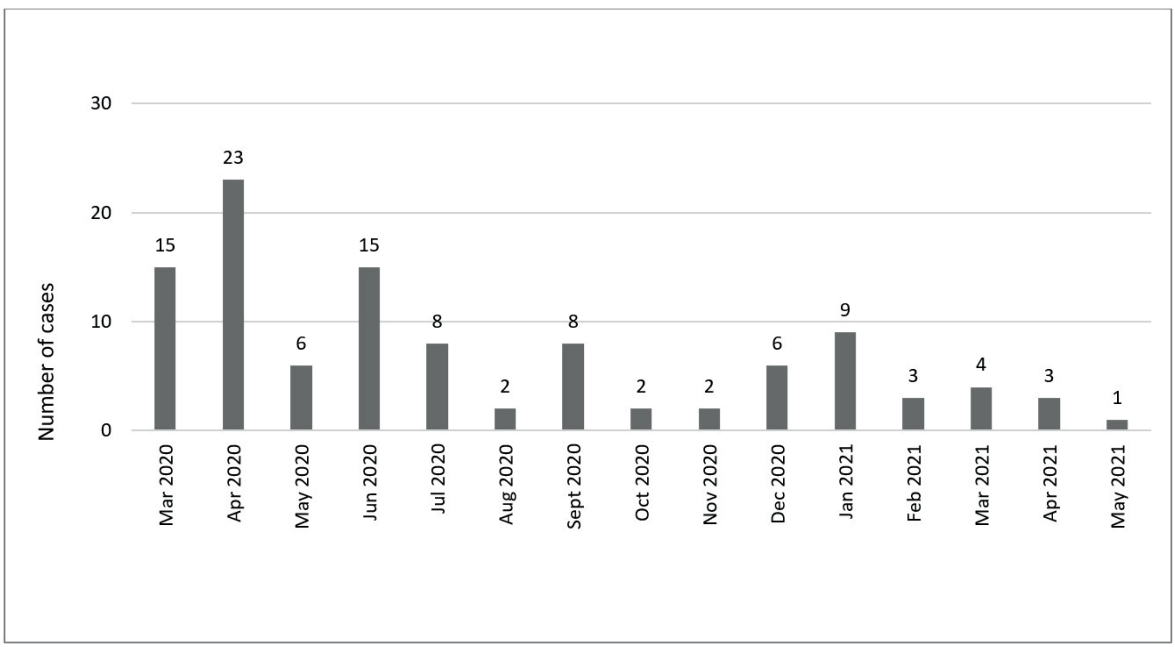

Fig. 2. Distribution of patients that stopped taking ICS treatment by months.

Table II. Comparison of asthma control and exacerbations before and after the first year of COVID-19 pandemic.

	In the year before pandemic n (%)	In the first year of pandemic n (%)	p
Asthma control			
Well-controlled	146 (59.1)	216 (87.4)	<0.001
Partially controlled	85 (34.5)	30 (12.1)	<0.001
Uncontrolled	16 (6.4)	1 (0.5)	<0.001
Asthma exacerbations			
Systemic corticosteroid use	55 (72.3)	7 (26.9)	<0.001
Emergency department admission	53 (69.7)	9 (34.6)	<0.001
Hospitalization	5 (6.5)	2 (7.6)	0.453

Other factors

Only 21.4% of persistent asthmatic children whose AC worsened stopped taking their daily ICS treatment. Distribution of treatment non-compliance was similar between AC groups and it did not affect the overall AC during the pandemic (p= 0.17). In the univariate analysis, it was found that pollen sensitization (p= 0.04) had an effect on AC during the pandemic, whereas house dust mite sensitization (p= 0.07), any aeroallergen sensitization (p= 0.09), and comorbid allergic rhinitis (p= 0.21) did not have a significant impact.

Data about remaining factors that may affect AC are shown in Table III. During the pandemic the number of URTI decreased in 79.7% of the cases and the median number of URTI was found to be significantly lower compared to the year before the pandemic (p<0.001). Smoking in the household, attendance at school and the presence of someone employed outside the home did not impact AC during the COVID-19 pandemic (Table III). There were 172 participants who have a sibling (69.6%) and 105 of them had continued daycare (61%) for the periods permitted by the Ministry of Health during the pandemic. Presence of a sibling who goes to daycare during the pandemic did not affect AC (p= 0.115).

A logistic regression analysis was performed to evaluate the independent effect of URTI, AE requiring SCS use or emergency department admission and pollen sensitization on AC, all of which showed statistically significant impacts in the univariate analyses. Only URTI was found to have a significant impact on AC throughout the pandemic. Children who did not get URTI had 2.4 times better AC compared to children that experienced URTI during the pandemic (p= 0.02; %95 CI:1.1-5.4).

Discussion

Although many studies exist on asthmatic children during the COVID-19 pandemic, none of them have examined the long-term effects of COVID-19 exclusively on children with persistent asthma.[8,13,21,25,26] Therefore,

Table III. Other factors that impact asthma control during the COVID-19 pandemic.

	In the year before pandemic n (%)	In the first year of pandemic n (%)	p
Number of URTI	3 (0-10)	0 (0-5)	<0.001
Smoking in the household	119 (48.1)	124 (50.2)	0.568
School attendence	247 (100)	167 (67.6)	n.a.
Family member working outside home	247 (100)	224 (90.7)	n.a.

Continuous variables have been expressed in medians (min-max). URTI: upper respiratory tract infections.
n.a.: non attributable.

this study examined ATC, AC, and AE in persistent asthmatic children aged 6-18 years old who had previously demonstrated good ATC before the onset of the COVID-19 pandemic for a one year period. At the end of the first year of the pandemic, almost half of the cases (43.3%) had stopped taking their ICS treatment. Despite the significant decline in ATC during the first year of the pandemic, there were significant improvements in AC and a decrease in AE that required the use of SCS and emergency department admissions, compared to the previous year. Infection with COVID-19 did not impact AC or the risk of AE in the study population. Moreover, the number of URTI decreased by almost 80% compared to the previous year. The absence of URTI was identified as the only factor that influenced AC in the study.

Long term compliance with asthma treatment during COVID-19 pandemic

While studies on childhood AC during the pandemic have provided data on AE, many fail to evaluate long-term adherence to asthma treatment.[9,10,21,23,25] In published studies, ATC has generally been evaluated for short periods of time ranging from 3 to 6 months at the beginning of the pandemic.[10,12,14,21,23] It was usually reported to increase or improve in studies evaluating the beginning of pandemic for shorter periods such as 3 months[10,21] although the contrary also exists.[12,14] On the other hand, another study comparing the first 6 months of the pandemic to the same periods two years ago, reported a decrease in the refills of asthma medications.[23] We found that long term ATC over a year during the pandemic is low even in children with persistent asthma. The initial rise in ATC during the pandemic, followed by a subsequent decrease in later stages in other studies, can be attributed to asthma being initially categorized as a high-risk chronic illness in relation to COVID-19. In our study, parents mostly stopped ICS treatment for their children in the initial months of the pandemic. The most common reason for non-compliance was reported as their children having no asthma symptoms. Anxiety related to the pandemic was a distant second reason. We think that the greater decrease in ATC at the beginning of the pandemic may be related to families' concerns about the potential COVID-19 risk associated with their children's inhaler corticosteroid treatment.

Asthma control

In our study, we assessed AC categorically and observed a significant improvement in more than one third of our patients. Specifically, we found that the number of well-controlled asthma had increased, while that of partially controlled and uncontrolled asthma had decreased over the first year of the pandemic compared to the previous year. This finding supports previous short-term studies that have shown improvements in asthma control at the beginning of the pandemic.[10-12,14,22] The improvement during the first wave of the COVID-19 pandemic, was explained by reduced exposure to asthma triggers such as URTI[10,12,14,22], outdoor pollution[14], and increased treatment adherence[10] in these studies. We investigated many factors that may affect AC such as ATC, COVID-19 infection, AE, number of URTI, allergen sensitizations, comorbid allergic rhinitis, smoking in the household, school attendance, sibling that attends a nursery, and family members working outside the home in this study. Despite a decreasing ATC during the first year of the pandemic, worsening of asthma control was observed in only a small proportion of our patients, around 5.6%. However, treatment non-compliance even in children with persistent asthma did not have an impact on AC during the first year of the pandemic. This is certainly an unexpected finding, but it appears that all the precautions taken during the pandemic helped mitigate the impact of treatment noncompliance on AC.

The second factor investigated that may impact AC was COVID-19 infection. Almost 15% of the participants in our study were infected with COVID-19, but none of them experienced any

worsening of AC, nor any significant AE related to COVID-19 or severe COVID-19 infection. Consistent with our study findings, a study evaluating 1205 children with mild asthma for COVID-19 infection revealed that none of the 16 cases that tested positive for COVID-19 exhibited a decline in AC.[22] Although the exact reason is unknown, COVID-19 infection seems not be an important trigger of asthma symptoms as human rhinoviruses. Additionally, guidelines have not shown an increased risk for severe COVID-19 in individuals with well-controlled asthma.[27] Despite all of our patients having persistent asthma, the majority of them were either well- or partially-controlled with very few cases of uncontrolled asthma before the pandemic, which may help to explain our findings.

Another important factor that may impact AC is AE. Both short-term and long-term studies have demonstrated a decrease in asthma-related emergency department visits and hospitalizations in relation to AE.[10,13,21,23,24] It is believed that this reduction was partly due to a decrease in widespread viral triggers of asthma, such as the human rhinovirus. Our study also found a decrease in viral URTI during the COVID-19 pandemic compared to the previous year. This reduction was associated with a decrease in AE that required the use of SCS and admission to the emergency department. However, no significant difference was observed in the number of AEs requiring hospitalization in the first year of the pandemic compared to the year before. We believe this may be due to the already low rates of hospitalization in the pre-pandemic period.

Considering aeroallergen sensitization and related comorbid atopic disease AR, only pollen sensitization but not house dust mite (HDM) sensitization or AR was found to be significantly different in children whose AC was worsened. These findings are consistent with those of a short-term study in which the researches did not show any detrimental effect of HDM allergy in AC.[14] This may be due to increased hygienic measures also implemented in many houses during the pandemic which might have also decreased HDM load. There could be a connection between pollen allergies and the increase in people spending more time outdoors when quarantine restrictions were lifted, as well as the frequent ventilation of homes during quarantine periods.

Presence of a sibling who goes to daycare, school attendance, and family members working outside the home, smoking in the household during the pandemic were other factors investigated considering their impact on AC but they did not influence AC. Last but not least is the number of URTI during the first year of the pandemic which was found to significantly decrease with respect to the pre-pandemic period. The reduction may have been influenced by several factors such as the absence of in-person education, children staying at home, social distancing, increased use of masks, and hand washing. A logistic regression of factors that impacted AC in the univariate analysis revealed that only the number of URTI had an independent effect on AC. Children who did not experience URTI had 2.4 times better AC compared to those who did.

The strengths of our study include the fact that all study participants had persistent asthma and were fully and regularly compliant with ICS treatment prior to the pandemic. To the best of our knowledge, this is the first study in Türkiye to conduct a long-term comparison between the year prior to the pandemic and the first year of the pandemic, with regards to ATC, AE and AC among children with asthma, and the factors influencing these parameters. The weaknesses of the study include the limited number of cases with worsened AC during the first year of the pandemic and reliance on data sources from medical records and self-reported questionnaires.

In conclusion, this study is important because it is the first to investigate the impact of the COVID-19 pandemic on long-term ATC, AC, and AE. Despite a significant decline in treatment compliance, the reduction in asthma

exacerbations, emergency room visits, and use of SCS during the first year of the pandemic compared to the year prior is a positive outcome. Moreover, it is noteworthy that these factors were associated with a decrease in the number of URTI experienced. Asthma control was not affected in children with persistent asthma who were infected with COVID-19.

Ethical approval

Ethical approval was obtained from Gazi University Ethics Committee. (Date: 31.05.2021/ No:498). All procedures performed were in accordance with the ethical standards and with the 1964 Helsinki Declaration and its later amendments. All participants gave informed consent for the study.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: AB, SOO, SPT, GY, HIEK; data collection: SOO, GY; analysis and interpretation of results: SOO, AB; draft manuscript preparation: SOO, AB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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