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PHARMACOTHERAPY



The course of COVID-19 in patients with severe asthma receiving biological treatment

Gülseren Tuncay, MD , Mehmet Erdem Cakmak, MD , Ozge Can Bostan, MD , Saltuk Bugra Kaya, MD, Ebru Damadoglu, MD, Gül Karakaya, MD and Ali Fuat Kalyoncu, MD

Faculty of Medicine, Division of Allergy and Clinical Immunology, Hacettepe University, Ankara, Turkey

ABSTRACT

Objective: In order to decrease the use of systemic corticosteroids and prevent asthma exacerbations, EAACI and GINA made recommendations in favor of severe asthma patients continuing the use of biologicals during the pandemic. However, the course of SARS-CoV-2 infection remains uncertain, especially in patients taking biological therapy for severe asthma. The aim of this study was to demonstrate the clinical course of COVID-19 in severe asthmatic patients receiving biological treatment.

Methods: A total of 75 patients under the care of a tertiary level allergy clinic and receiving omalizumab or mepolizumab, which are the approved biologicals for severe asthma in Turkey, were included in the survey between April 1 and December 31, 2020. A questionnaire was administered via a telephone call by one of the treating physicians.

Results: Of the total patients, 46 (61%) were receiving mepolizumab and 29 (39%) omalizumab. Of the patients, 14 (19%) had COVID-19, 9 (64%) had pneumonia, 4 (29%) were hospitalized. A total of 12 (16%) patients interrupted biological treatments because they did not want to attend hospital for injections during the pandemic. The incidence of COVID-19 was higher in patients who have interrupted biological treatment ($p < 0.001$). In addition, the risk of having COVID-19 was higher in the ones who have interrupted their biological treatment (Relative risk: 2.71; 95% Confidence interval: 1.21–6.06). Asthma control was better in patients attending regular injections ($p = 0.006$).

Conclusion: Severe asthma itself seems to be a risk factor for COVID-19, whether biological treatment has a role in the disease course needs further research.

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Introduction

The SARS-CoV-2 virus emerged in Wuhan, China, in December 2019, and was defined as the agent of coronavirus disease 2019 (COVID-19). With the rapid spread of this highly infectious disease across many countries, a global pandemic was declared by the World Health Organization in March 2020 (1). The clinical course of the disease has caused confusion in healthcare systems, and there is a need for reliable information about course of the disease in severe asthma patients.

Many studies have been published about whether severe asthma was a risk factor, and how asthma treatments have affected the course of COVID-19, and if treatment changes were required (2–6). However, the studies on severe asthma and COVID-19 published during the pandemic are quite limited. Both the

European Academy of Allergy and Clinical Immunology (EAACI) and Global Initiative for Asthma (GINA) made recommendations in favor of the use of biologicals during the pandemic (7,8). First, the EAACI reviewed previous experiences of other viral infections and made recommendations based on the results of meta-analyses (7). During the pandemic there has been increased use of telemedicine facilities, which has brought a different dimension to the medical world (2). To the best of our knowledge, there are only three publications on this subject in Turkey, two of which are case reports of two patients receiving omalizumab for severe asthma (9–11). The course of COVID-19 remains uncertain, especially in patients taking biological therapy. Information on the safety of biologicals during viral infections has been derived from phase 3 studies of biological treatments, and

their impact on the course of COVID-19 needs to be clarified.

The most comprehensive case series reported to date is by Rial et al. in which 35 (6.4%) of 545 patients with severe asthma were diagnosed with COVID-19 while receiving biologicals for severe asthma (12). GINA recommends that during the pandemic asthmatic patients continue the controller medications they have been using, including inhaled corticosteroids and biologicals. GINA also recommends adding a biological agent for selected patients with severe asthma in order to reduce the need for oral corticosteroids, which would have been administered before the pandemic (8). It is still not clear which biologicals are safer, and there are still concerns that severe asthma patients may be at high risk for severe COVID-19. The aim of this study was to demonstrate the clinical course of COVID-19 in severe asthma patients who were receiving biological treatments.

Methods

The study initially included a total of 81 severe asthma patients receiving biological agents between April 1 and December 31, 2020 at a tertiary level allergy clinic. After the exclusion of 6 patients who did not want to participate in the study, a total of 75 patients were evaluated. The study inclusion criteria were the provision of verbal informed consent, age ≥ 18 years, and the use of a biological agent for a diagnosis of severe asthma. The available and currently approved biological treatments for severe asthma in Turkey are omalizumab and mepolizumab; all the patients included in the study were receiving either of these drugs.

The study was conducted in accordance with the ethical standards of the Declaration of Helsinki, revised in 2013, and was approved by Hacettepe University Ethics Committee (GO 21/120). Before registration in the study, all participants provided verbal informed consent through an audio recording during a telephone call. After obtaining verbal consent, the calling physician administered a questionnaire. Patients were asked whether they complied with COVID-19 precautions, whether they had COVID-19, and which symptoms they experienced during infection, how the diagnosis was established, if the patient had been hospitalized or admitted to intensive care unit (ICU), and how long the symptoms lasted. They were also asked if they had stopped or interrupted asthma medications, and/or did not attend for biological injections during the pandemic. The Asthma

Control Test (ACT) was administered to patients with COVID-19 at least one month after COVID-19 treatment. The interruption was defined as not attending the planned injection visit at least 1 week. Patients who interrupted and continued treatment were compared in terms of interruption times, having COVID-19, hospitalization, and asthma control.

The diagnosis of SARS-CoV-2 was based on Polymerase chain reaction (PCR) test positivity or typical computed tomography (CT) findings with compatible clinical findings for COVID-19. The demographic data and laboratory values were obtained from the hospital database and patient files.

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS vn. 22.0 software. Descriptive data were presented as number (n) and percentage (%). Numerical variables showing normal distribution were stated as mean $\pm$ standard deviation (SD) values, and otherwise as median and range values. The Chi-Square or Fisher Exact test were used for categorical variables, and continuous variables were analyzed using the Mann-Whitney U test, or the Kruskal Wallis test. A value of $p < 0.05$ was considered statistically significant.

Results

A questionnaire was administered via a telephone call to a total of 75 patients, comprising 28 males and 47 females with a median age of 46 years (range, 22–78 years). Of the total patients, 41 (55%) were university graduates. The median body mass index (BMI) was 25.5 kg/m² (range, 18.1–42.9); 22 (29%) were obese (BMI ≥ 30 defined as obese). The characteristic features of the patients are summarized in Table 1.

Mepolizumab was the biological used in 46 (61%), and omalizumab in 29 (39%) patients. The median duration of the biological treatment was 12 months (range, 2–96 months). There was no difference between patients using omalizumab and mepolizumab in terms of susceptibility regarding predisposition to SARS-CoV-2 infection ($p = 0.19$).

Of the 14 (19%) patients diagnosed with SARS-CoV-2 infection, 8 (57%) were receiving omalizumab, and 6 (43%) mepolizumab. The characteristics of the SARS-CoV-2 positive patients are summarized in Table 2.

A total of 12 (16%) patients interrupted biological treatments because they did not want to attend clinical

Table 1. Demographics and disease characteristics of the patients ($n=75$).

Characteristics	Values			P value
	COVID-19, 14 (19%)	No COVID-19, 61 (81%)	Total 75 (100%)	
Age, years, median	45.5 (range, 25–61)	46 (range, 22–78)	46 (range, 22–78)	
≥65 years, n (%)	0 (0%)	7 (12%)	7 (9%)	NA
Sex				
Female, n (%)	8 (57%)	39 (64%)	47 (63%)	0.63
BMI				
Obese, n (%)	6 (43%)	16 (26%)	22 (29%)	0.37
Smoking				0.63
Current	0 (0%)	2 (3%)	2 (3%)	
Past	2 (14%)	5 (8%)	7 (9%)	
Comorbidities				
Rhinitis	14 (100%)	51 (84%)	65 (87%)	0.19
Hypertension	1 (7%)	11 (18%)	12 (16%)	1.00
Thyroid disease	2 (14%)	9 (15%)	11 (15%)	0.67
Type 2 Diabetes Mellitus	1 (7%)	5 (8%)	6 (8%)	0.31
Gastroesophageal reflux disease	1 (7%)	4 (7%)	5 (7%)	1.00
Others*	2 (14%)	13 (21%)	15 (20%)	0.58
Biological received				
Omalizumab, n (%)	8 (57%)	21 (34%)	29 (39%)	0.68
Mepolizumab, n (%)	6 (43%)	40 (66%)	46 (61%)	0.11
Duration of the biological treatment, median months	16 (range, 3–60)	11 (range, 2–96)	12 (range, 2–96)	0.05
Interrupted biological treatment, n (%)	8 (57%)	4 (6.6%)	12 (16%)	<0.001
ACT				
≤19 points, n (%)	6 (43%)	18 (30%)	24 (32%)	0.33
Sensitization to inhalant allergens, n (%)	4 (29%)	26 (43%)	30 (40%)	0.33

*Others include atherosclerotic heart disease ($n=2$), arrhythmia ($n=2$), valvular heart disease ($n=1$), idiopathic pulmonary fibrosis ($n=1$), rheumatoid arthritis ($n=1$), ankylosing spondylitis ($n=1$), essential thrombocytosis ($n=1$), liver failure ($n=1$), eosinophilic granulomatous with polyangiitis ($n=1$), familial Mediterranean fever ($n=1$), chronic urticaria ($n=1$), nephrolithiasis ($n=1$), and osteoporosis ($n=1$).

Table 2. Characteristics of the patients who had COVID-19.

Characteristics	Values
Age, years, median	45.5 (range, 25–61)
<65 years, n (%)	14 (100%)
Sex	
Female, n (%)	8 (57%)
BMI	
Obese, n (%)	6 (43%)
The medications for COVID-19	
Favipiravir	12 (86%)
Hydroxychloroquine	6 (43%)
Enoxaparin	4 (29%)
Severity of COVID-19	
Mild symptoms*, n (%)	3 (21%)
Pneumonia, n (%)	9 (64%)
Hospital admission, n (%)	4 (29%)
ICU admission, n (%)	2 (14%)
Death, n (%)	1 (7%)
Duration of symptoms, median days	5 (range, 3–12)
Comorbidities	
Rhinitis	14 (100%)
Hypertension	2 (14%)
Thyroid disease	2 (14%)
Diabetes mellitus	1 (7%)
Chronic Urticaria	1 (7%)
Nephrolithiasis	1 (7%)
Arrhythmia	1 (7%)
Rheumatoid arthritis	1 (7%)
Gastroesophageal reflux disease	1 (7%)
Biological received	
Omalizumab, n (%)	8 (57%)
Mepolizumab, n (%)	6 (43%)
Duration of the biological treatment, median months	16 (range, 3–60)
Interrupted biological treatment, n (%)	8 (57%)
Sensitization to inhalant allergens, n (%)	4 (29%)

*Mild symptoms were described as fever, chills, cough, fatigue, headache, joint pain, weakness, runny nose, and no need for oxygen support.

visits during the pandemic. The median duration of treatment interruption was 1.2 (range, 1–2.5) week in patients without COVID-19, and 2.5 (range, 1–16)

weeks in patients with COVID-19. ($p<0.001$). Eight (67%) patients in the group who interrupted treatment and 6 (10%) patients in the regularly continued group

had COVID-19. In addition, 2 (25%) and 2 (33%) patients were hospitalized in groups who have and have not interrupted treatment, respectively. The incidence of COVID-19 was higher in patients who interrupted treatment ($p < 0.001$). There was a statistically significant difference in the incidence of COVID-19 and hospitalization between those who continued biological therapy and those who interrupted it ($p < 0.001$).

The interruption information of those who have and have not had COVID-19 are detailed in Figure 1. Asthma control was significantly better in 63 (84%) patients who had continued regular injections compared to 12 (16%) patients who had interrupted ($p = 0.006$). Of the 14 (19%) patients diagnosed with SARS-CoV-2 infection, 6 (43%) continued regular injections, and 8 (57%) patients interrupted their biological treatment. The risk of having COVID-19 was detected to be higher in the group that interrupted treatment (Relative risk:2.71; 95% Confidence interval:1.21–6.06). The most common thorax CT finding in patients with COVID-19 pneumonia was peripherally located ground glass density. COVID-19 pneumonia had been diagnosed in 9 (64%) patients and of these, 4 patients were hospitalized, and 2 were followed up in the ICU because of respiratory failure. While favipiravir was recommended to all those who received treatment, two patients refused to take it. Enoxaparin was given as anticoagulant treatment to four inpatients. The characteristics of patients diagnosed with COVID-19 are shown in Table 2.

Interruption or continuation of biological therapy was prior to the diagnosis of COVID-19. The first patient followed up in the ICU was a 46-year-old, non-obese male with a 4-year history of diabetes, and allergic rhinitis. The patient had been receiving mepolizumab for the last four months, and previously omalizumab for eight months; the treatment was

changed to mepolizumab because of lack of response. The patient was hospitalized for a total of one week and followed up in the ICU for two days. The second patient followed up in the ICU was a 54-year-old obese female with a 2-year history of diabetes and Familial Mediterranean fever (FMF). This patient had been receiving omalizumab as a biological treatment for the last five years. Mortality developed due to septic shock and multi-organ failure after 14 days of treatment in the ICU. All four of the hospitalized patients had uncontrolled asthma before SARS-CoV-2 infection.

The asthma medications received by the patients are shown in Table 3. No significant difference was determined between SARS-CoV-2 positive and negative patients in terms of the drugs used ($p = 0.20$). All the patients stated that they had complied with the COVID-19 precautions of mask, social distancing, and hand hygiene.

The biological treatments were paused in 8 (11%) patients with a delay of 1 to 16 weeks because of having COVID-19.

Discussion

In the current study, patients with severe asthma who had been receiving omalizumab or mepolizumab during the pandemic were evaluated and it was observed that poor asthma control, severity of asthma, comorbidities, and the use of biologicals might all have had an effect on the frequency and severity of COVID-19. In the EAACI statement, published in November 2020, the recommendation was to continue the same drug regimens that patients have been using before the pandemic with close follow-up (7). In line with the recommendations, we have not changed our decisions regarding starting or maintaining the

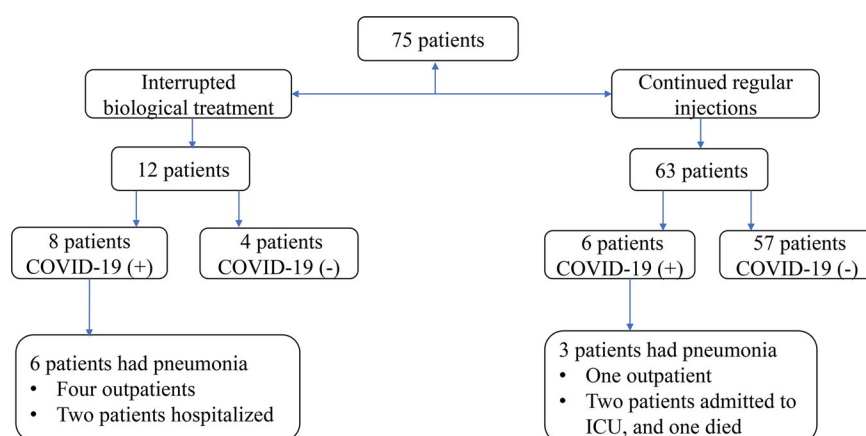


Figure 1. The flow chart of the study population ($n = 75$).

Table 3. Asthma medications and clinical characteristic of patients with and without COVID-19.

	COVID-19, 14 (19%)	No COVID-19, 61 (81%)	Total 75 (100%)	p value
Age, years, median				
≥65 years, n (%)	0 (0%)	7 (12%)	7 (9%)	NA
Sex				
Female, n (%)	8 (57%)	39 (64%)	47 (63%)	0.63
BMI				
Obese, n (%)	6 (43%)	16 (26%)	22 (29%)	0.37
ICS* plus LABA**	13 (93%)	57 (93%)	70 (93%)	0.75
Nasal corticosteroids	11 (79%)	29 (48%)	40 (53%)	0.05
Montelukast	10 (71%)	42 (69%)	52 (69%)	0.74
Oral corticosteroids	1 (7%)	9 (15%)	10 (13%)	0.45
Tiotropium	6 (43%)	14 (23%)	20 (27%)	0.12
Omalizumab	8 (57%)	21 (34%)	29 (39%)	0.68
Mepolizumab	6 (43%)	40 (66%)	46 (61%)	0.11
ACT ¹ ≤19 points, n (%)	6 (43%)	18 (30%)	24 (32%)	0.33
Interrupted biological treatment, n (%)	8 (57%)	4 (6%)	12 (16%)	0.00

*ICS: Inhaled corticosteroids

**LABA: Long-acting beta-2 agonist.

¹ACT: Asthma Control Test. Measured at the time of telephone call.

biological treatments for severe asthma during the pandemic. In addition, EAACI published a report of early experiences of the last ten years on the use of biological treatments in severe asthmatic patients during the SARS-CoV-2 infection in September 2020 (13). The recommendation was for interruption of the biological therapies for severe asthma while receiving treatment for COVID-19 or until recovery, as was applied in our clinic.

Current evidence does not demonstrate a higher risk for severe COVID-19 in asthmatic individuals (14). There are publications from other countries about the course of SARS-CoV-2 infection in patients receiving biologicals with severe asthma (3,4,15,16). In the most comprehensive series in the literature by Rial et al., 545 patients on biological agents for severe asthma were included for evaluation (12). Of the hospital-admitted patients, seven presented with pneumonia and two were severe, of which one was a patient receiving mepolizumab who required admission to ICU and the other, who was receiving omalizumab died because of COVID-19 complications. SARS-CoV-2 seroprevalence in the general population in Spain was reported to be 5.2%, and this rate was similar to that in an asthma cohort (6.4%). Other reports on patients with asthma with COVID-19 have shown similar trends to those reported from Spain (13,17). However, the COVID-19 rate in our study population was 19%, and the rate in the study by Rial et al. was lower than the rate in the general population in Turkey. According to the information from the Ministry of Health in Turkey, the highest incidence was 17.2%, in the situation report between 19 and 25 October in 2020 (18), whereas the hospitalization rate and COVID-19 pneumonia rate in inpatients in the cohort study by Rial et al. were 22.9% and 87%, respectively. The rate of COVID-19

pneumonia in the study by Rial et al. represented inpatients only, as outpatient COVID-19 pneumonia cases were not included. Furthermore, the PCR test for SARS-CoV-2 and thorax CT were administered to all symptomatic or suspicious patients participating in the current study, unlike the cohort study by Rial et al. The hospitalization rate in the current study was 29%, which was higher when compared to this cohort. The rate of COVID-19 pneumonia was 64% which was much higher than the rate reported in the general population in Turkey (5.6%).

Teach et al. and Busse et al. reported a lower incidence of viral infections under treatment with omalizumab, since it may increase the functionality and the production of IFN- α by plasmacytoid dendritic cells. The increase in IFN- α may enhance defence against virus-induced asthma exacerbations (19,20). Moreover, Vultaggio et al. suggested that anti-IL-5 antibody (mepolizumab) leads to an equal or lower risk for viral infections than the placebo groups (7).

Contrary to the literature, there may be several reasons why more severe COVID-19 was detected in patients with severe asthma who used these agents in real life. First, this was a retrospective real-life study, in which most patients had uncontrolled asthma at the time of infection, and many had comorbidities. Second, the infection dynamics of SARS-CoV-2 may be different from those of other viral infections.

Another important topic regarding severe asthma patients receiving biologicals was comorbidities. Advanced age and hypertension have been reported as risk factors for severe COVID-19 (12). However, no difference was determined between the current study patients with and without COVID-19 in respect of comorbidities or advanced age. Chhiba et al. showed that asthma was not a risk factor for hospitalization in COVID-19 after adjusting for age, sex,

and comorbidities, and use of inhaled or oral corticosteroids was not associated with an increased risk of hospitalization (17).

In the current study, the ACT scores were significantly high and asthma control was better among patients who continued biological therapies regularly ($p=0.006$). This can be interpreted as showing the need for very close follow up of severe asthmatic patients and urgent telemedicine applications to check for asthma control and medication use in these patients. During the SARS-CoV-2 pandemic, both because of the restrictions, and the reluctance of patients to attend regular visits, it has not been possible to examine most patients face to face. It is highly likely that in the near future, mild to moderate as well as severe asthma patients will be followed up with telemedicine applications (21).

This study had some limitations, primarily the retrospective design and relatively small number of patients. Another limitation was that patients with severe asthma using GINA step 4–5 treatment without biologicals were not included. This may have restricted the interpretation of pure effect of biologicals on COVID-19 severity, although it was thought that patients not receiving biologicals were different and not comparable in terms of asthma severity.

Compared to other European populations (6.4%), documented COVID-19 infection rate was higher in the current study patients (19%) with severe asthma receiving biological treatments (12,13). The documented pneumonia incidence among hospitalized patients in previous studies were 87% whereas, all hospitalized patients ($n:4$, 100%) in our cohort had pneumonia. Possible explanations for this higher rate may be that first, many patients did not attend clinical visits for injections and interrupted their treatment, which resulted in high uncontrolled asthma rates in this group, and second, the severe asthma subgroup receiving biologicals may be the true risk factor for severity of COVID-19. Finally, asthma control should be optimized during the pandemic and telemedicine facilities that may help in the monitoring of asthma should become widely used. The role of biological treatments in the severity of COVID-19 needs further research.

Author's contributions

A.F.K. conceived of presented idea, G.T, M.E.C, O.C.B, S.B.K contributed to sample preparation. G.T took the lead in writing the manuscript, A.F.K, E.D, and G.K contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript.

Declaration of interest

The authors declare that there is no conflict of interest.

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ORCID

Gülseren Tuncay  <http://orcid.org/0000-0001-6529-9750>
Mehmet Erdem Cakmak  <http://orcid.org/0000-0001-7899-3004>

Ozge Can Bostan  <http://orcid.org/0000-0002-4528-5404>

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