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Cross-sectional study: COVID-19 infection in patients with severe bronchial asthma receiving monoclonal antibody treatments

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Abstract:

BACKGROUND AND AIM: The aim of this study was to expose the course of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in patients with severe bronchial asthma receiving monoclonal antibody (MAb) treatments and in patients not receiving MAb treatment.

METHODS: In this retrospective study, 211 adult patients with severe bronchial asthma (155 females and 56 males), who were being followed up in a tertiary allergy clinic between June 2020 and December 31, 2020, were evaluated.

RESULTS: A total of 211 patients with severe bronchial asthma were included in the study (155 females and 56 males). The mean age was 42 years (18–79 years). Thirty-six patients (17.1%) were on mepolizumab treatment and 58 patients (27.5%) were on omalizumab treatment. Fifty-seven patients (27%) became infected with the SARS-CoV-2 during the study. The rate of SARS-CoV-2-related pneumonia was 7.6%. There was a significant difference between the patients on omalizumab treatment, patients on mepolizumab treatment, and the nonreceivers in terms of the rate of SARS-CoV-2-related pneumonia (p=0.023). No difference was found between the patients with severe bronchial asthma on omalizumab treatment and those on mepolizumab treatment in terms of the rate of pneumonia (p=0.752). No significant difference was found between the patients receiving omalizumab and/or mepolizumab treatments and nonreceivers in terms of SARS-CoV-2-related hospitalization (p=0.191).

CONCLUSIONS: The frequency of SARS-CoV-2 infection and the rate of SARS-CoV-2-related hospitalizations did not increase in patients with severe bronchial asthma on MAb treatment compared with patients who did not receive treatment.

Keywords:

COVID-19, mepolizumab, omalizumab, SARS-CoV-2, severe bronchial asthma

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Introduction

Since the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) disease was first reported in Wuhan, China, in December 2019, it has affected the whole world. It was declared a pandemic by the World Health Organization in March 2020. As the virus is highly contagious, it has spread throughout the world and has led to the death of more than five million people since it was first reported.[1]

Bronchial asthma is the most common chronic airway disease. Several studies have reported that chronic diseases negatively influence the course of the coronavirus disease 2019 (COVID-19). Viral infections are major triggers of bronchial asthma exacerbations; thus, there are some doubts on whether SARS-CoV-2 may promote bronchial asthma exacerbations. Furthermore, like bronchial asthma, SARS-CoV-2 also involves the lower respiratory tract causing morbidity and mortality. Obscurities about the effects of inhaled corticosteroids (ICS) and monoclonal antibody (MAb) treatments used by bronchial asthma patients on the course of SARS-CoV-2-related inflammation are also challenging for clinicians. Moreover, the lack of availability of bronchial asthma treatments due to SARS-CoV-2-related restrictions may also be a challenge for asthma patients. These problems have identified some questions about the effect of SARS-CoV-2/COVID-19 on the course of bronchial asthma, which has formed the basis for many studies.[2,3] However, controversial results for asthmatic patients and the course of the SARS-CoV-2/COVID-19 infection have been reported.[4–8] Although international guidelines[9] recommend continuing asthma treatments (e.g., ICS, long-acting beta-agonists, and monoclonal antibodies) to prevent asthma exacerbations and provide disease control, the number of relevant epidemiological and clinical studies is limited.[10–12]

This study aimed to expose the course of SARS-CoV-2 in patients with severe bronchial asthma and compare the prevalence of SARS-CoV-2/COVID-19 infection, hospitalization, and mortality rates in patients with severe bronchial asthma receiving MAb treatments with those not receiving MAb treatment (nonreceivers).

Materials and Methods

A total of 239 adult patients with severe bronchial asthma, who were being followed up in a tertiary allergy clinic between June 2020 and December 31, 2020, were selected for the study. Twenty-eight patients were excluded from the study due to nonadherence to treatments and missing data in their files, and the remaining 211 patients with severe bronchial asthma were included in the study. The demographic and clinical data, including gender, age, smoking status, body mass index (BMI), and current and past symptoms, were retrieved from the medical files registered on the first visit. The diagnosis of severe bronchial asthma was made according to the diagnostic criteria of the Global Initiative for Asthma.[13]

The diagnosis of SARS-CoV-2 was performed using a positive polymerase chain reaction (PCR) test in patients with a consistent clinical presentation for COVID-19 or by consistent computed tomography findings. Lung imaging and laboratory results of all patients were reviewed retrospectively. SARS-CoV-2 (+) patients with pulmonary infiltrates accompanied by appropriate clinical findings were accepted as "SARS-CoV-2-related pneumonia."

The Abbott Cell Dyn 3700 series (Sheath reagent) was used to measure a whole blood count, and the quantitative determination of serum immunoglobulin (Ig) E was made by means of particle-enhanced immunonephelometry using the Siemens BN II/ BN ProSpec system. Spirometric measurements were obtained using a standard protocol with an nSpire ZAN 100 spirometer. Forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and the ratio of FEV_1/FVC, and age, sex, race, and height were recorded. The study was approved by Karatay University Ethics Committee (Meeting number: 9, Decision number: 2021/033). The study was carried out in accordance with the principles of the Helsinki Declaration.

Statistical analysis

Statistical analysis was performed with the IBM SPSS Statistics Version 22 software package. Normally distributed parameters were presented as mean±standard deviation, and the data that were not normally distributed were expressed as the median (interquartile range: minimum–maximum). Descriptive data were presented as frequencies and percentages and were compared using a Chi-squared test. Comparisons between baseline characteristics were performed using independent Student's t, the Mann-Whitney rank sum, Fisher's exact, and/or Chi-squared tests as appropriate. Comparisons of more than two categorical independent variables were made using the Chi-squared post hoc analysis and the adjusted p-

value Bonferroni method. In the Bonferroni method, there is no significant difference between the columns found by the same letters in pairwise comparisons. The results were considered statistically significant for $p<0.05$. The analyses were performed using Statistical Package for the Social Sciences, version 22 (IBM Corp., Armonk, NY, USA).

Results

A total of 211 patients with severe bronchial asthma were included in the study (155 females and 56 males). The mean age was 42 years (18–79 years). None of the patients had been vaccinated with COVID-19 vaccines. Forty-nine patients (23.2%) were obese (BMI ≥30), and 35 patients (16.6%) were smokers. The mean serum IgE level was 125.50 (7–3370) IU/mL and the eosinophil count was 240 (1.52–2390) cells/mL. Of the patients, 60.7% (n=128) who were being followed up had the diagnosis of allergic bronchial asthma, and 39.3% (n=83) had nonallergic bronchial asthma. Of the total patients, 128 (60.7%) had an allergy to at least one allergen, and the rest were nonallergic. Thirty-six patients (17.1%) were on mepolizumab treatment, and 58 patients (27.5%) were on omalizumab treatment. Fifty-seven patients (27%) became infected with the SARS-CoV-2 during the study. The clinical characteristics of the patients are summarized in Table 1.

The study participants were divided into three groups: patients with severe bronchial asthma on omalizumab treatment, patients with severe bronchial asthma on mepolizumab treatment, and patients with severe bronchial asthma not receiving MAb treatment. No significant difference was found among the three groups in terms of age, gender, presence of obesity, smoking status, accompanying allergic (rhinitis and urticaria) and nonallergic comorbidities (type 2 diabetes mellitus, hypertension, and coronary artery disease), asthma duration, baseline eosinophil count, and frequency of infection with the SARS-CoV-2. However, there was a significant difference between the three groups in terms of sensitivity to allergens and serum IgE levels (p=0.001 and p=0.001, respectively).

When the SARS-CoV-2 positive and negative bronchial asthma patients were compared, there were

Table 1: Demographic, clinical, and laboratory parameters of patients with severe asthma according to MAb treatment

Parameters	Total (n=211)		Patients receiving mepolizumab (n=36)		Patients receiving omalizumab (n=58)		Patients not receiving biologics (n=117)		p
	n	%	n	%	n	%	n	%	
Mean age (min-max) (years)	42 (18–79)		44 (19–67)		51 (19–79)		39 (18–69)		0.459
Gender, female	155	73.5	23	63.9	42	72.4	90	76.9	0.295
BMI, obesity	49	23.2	8	22.2	15	25.9	26	22.2	0.855
Smoking status, current	35	16.6	5	13.9	11	19.0	19	16.2	0.804
Comorbidities									
Rhinitis	122	57.8	17	47.2	38	65.5	67	57.3	0.214
Urticaria	12	5.7	2	5.6	3	5.2	7	6.0	0.976
HT	25	11.8	6	16.7	7	6.9	12	13.9	0.581
Type 2 DM	12		4	11.1	4	6.9	4	3.4	0.196
CAD	10	4.7	3	8.3	5	8.6	2	1.7	0.069
Sensitization to inhalant allergens	128	60.7	12	33.3	58	100	58	49.6	**0.001**
Mean duration of asthma (min-max) (years)	6 (1–30)		9.5 (2–30)		10 (2–30)		5 (1–20)		0.078
Mean serum IgE (min-max) (IU/mL)	125.50 (7–3370)		115 (17–1560)		177 (17.3–3370)		125 (7–1827)		**0.001**
Mean eosinophil count (min-max) (cell/mL)	240 (10–2390)		965 (240–2390)		235 (10–1830)		190 (10–1420)		0.370
SARS-CoV-2*	57	27	7	19.4[a]	16	27.6[a]	34	29.1[a]	0.521

*, a: Post hoc analysis of Chi-squared, the adjusted p-value Bonferroni method. a: Post hoc analysis of Chi-squared, the adjusted p-value Bonferroni method. MAb: Monoclonal antibody, BMI: Body mass index, HT: Hypertension; DM: diabetes mellitus; CAD: Coronary artery disease; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2, Ig: Immunoglobulin

Table 2: Demographic and clinical characteristics of patients with severe asthma according to SARS-CoV-2

Parameters	SARS-CoV-2 (+) (n=57)		SARS-CoV-2 (–) (n=154)		p
	n	%	n	%	
Mean age (min-max) (years)	47 (20–79)		40 (18–72)		**0.037**
Gender, female	46	80.7	109	70.8	0.147
BMI, obese	11	19.3	38	24.7	0.411
Smoking, current	11	19.3	24	15.6	0.520
Comorbidities					
Rhinitis	36	63.2	86	55.8	0.339
Urticaria	5	8.8	7	4.5	0.239
HT	11	19.3	14	9.1	**0.042**
Type 2 DM	7	12.3	5	3.2	**0.012**
CAD	1	1.8	9	5.8	0.214
Sensitization to inhalant allergens	39	68.4	89	57.8	0.160
Duration of asthma (years)	6 (1–30)		6 (1–29)		0.965
Mean serum IgE (min-max) (IU/mL)	125 (12–3370)		125.5 (7–2830)		0.865
Mean eosinophil count (min-max) (cell/mL)	190 (10–1450)		285 (10–2390)		**0.015**
MAb treatment					
Omalizumab	16	28.1	42	27.3	0.908
Mepolizumab	7	12.3	29	18.8	0.261
Mean duration of the biological treatment (min-max) (months)	16 (6–116)		16 (3–110)		0.751

SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2, BMI: Body mass index, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, Ig: Immunoglobulin, MAb: Monoclonal antibody

no significant differences between the groups in terms of gender, presence of obesity, smoking status, accompanying allergic diseases (presence of rhinitis and urticaria), other accompanying nonallergic comorbidities (CAD), accompanying allergic diseases and nonallergic comorbidities (CAD), duration of asthma, serum IgE levels, the MAb treatment they were receiving (omalizumab or mepolizumab), and the duration of the treatment with MAbs. A significant difference was found in terms of age, nonallergic comorbidities (type 2 DM and HT), and eosinophil count (p=0.042, p=0.012, and p=0.015, respectively) (Table 2).

For the 211 patients included in the study, the rate of pneumonia was 7.6% (n=16). A significant difference was found between the patients with severe bronchial asthma receiving MAb treatment and the nonreceivers with regard to the rate of SARS-CoV-2-related pneumonia (p=0.002) (Table 3).

There was a significant difference between the patients receiving MAb treatment and the nonreceivers in terms of the rate of SARS-CoV-2-related pneumonia (p=0.023). The rate of SARS-CoV-2-related pneumonia was not different in patients receiving omalizumab and mepolizumab treatment (p=0.752). However, significant differences were found between the patients receiving omalizumab treatment and nonreceivers and between the patients receiving mepolizumab treatment and nonreceivers in terms of the rate of SARS-CoV-2-related pneumonia (p=0.008 and p=0.014 respectively) (Table 3).

During the study period, a total of 9 patients (6 patients receiving omalizumab treatment and 3 nonreceiver patients) were hospitalized due to COVID-19 infection. Hospitalization rates were not significantly different between the patients receiving MAb treatment and nonreceivers (p=0.191) (Table 3).

During the study period, only one patient required intensive care treatment because of a COVID-19 infection. The patient was a 79-year-old female who had a diagnosis of bronchial asthma for 30 years and was receiving omalizumab treatment of 300 mg every 4 weeks for 30 months. No patient was lost due to a COVID-19 infection.

Discussion

There were three featured findings of the presented study. First, patient age and the frequency of nonallergic comorbidities (type 2 DM and HT) of the SARS-CoV-2 (+) patients were higher compared to the SARS-CoV-2 (–) patients. Se-

Table 3: Comparison of asthma patients with SARS-CoV-2 associated pneumonia in terms of MAb therapy

	Mepolizumab (n=7)		Omalizumab (n=16)		Controls (n=34)		p
	n	%	n	%	n	%	
Pneumonia*							
Yes	4	57.1[a]	8	50[a, b]	5	14.7[b]	0.009
No	3	42.9[a]	8	50[a, b]	29	85.3[b]	

	MAb group (n=23)		Control group (n=34)		p
	n	%	n	%	
Pneumonia					
Yes	12	52.2	5	14.7	0.002
No	11	47.8	29	85.3	

	MAb group (n=23)		Control group (n=34)		p
	n	%	n	%	
Hospitalization					
Yes	6	26.1	3	8.8	0.137
No	17	73.9	31	91.2	

*: Post-hoc analysis of Chi-squared, the adjusted p-value Bonferroni method. [a, b]: Post-hoc analysis of Chi-squared, the adjusted p-value Bonferroni method. SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2, MAb: Monoclonal antibody

cond, the frequency of SARS-CoV-2 infection and SARS-CoV-2-related hospitalizations were similar in all patients included in the study. Finally, and excitingly, the rate of SARS-CoV-2-related pneumonia in patients on MAb treatment was higher when compared with the patients with severe bronchial asthma not receiving MAb treatment.

Studies performed with different patient groups since the onset of the pandemic revealed that comorbidities like type 2 DM, HT, CAD, and advancing age are well-documented risk factors for COVID-19-related hospitalization and intensive care requirement, intubation, and higher mortality.[14–18] Comorbidities also play a significant role in poor disease progression in COVID-19 infection.[2,19] Thus, older patients and the higher frequency of nonallergic comorbidities in the study's SARS-CoV-2 positive participants were consistent with the literature.

In the presented study, the SARS-CoV-2 and SARS-CoV-2-related hospitalization rates were found to be similar in all three groups. Chhiba et al.[20] reported no increased risk of COVID-19-related hospitalizations in bronchial asthma. In similar studies conducted with bronchial asthma patients, it was reported that the prevalence of COVID-19 infection is lesser or not increased. Therefore, patients with bronchial asthma should continue their prescribed treatments-ICS, long-acting beta-agonists, and anticholinergics-without any interruption.[4,21,22] Many studies also support this management for patients receiving MAb treatments. However, some other studies aimed at pathophysiology have contrary results.

It has been demonstrated that omalizumab executes an antiviral effect by downregulating the high-affinity IgE receptors on the surface of plasmacytoid dendritic cells[23] and reduces the expression of TLR7 (Toll-like receptor), which is a receptor that triggers innate immunity.[24] It has also been shown that the omalizumab small peptide segment reduces the synthesis of IL-6, IL-1β, and TNF-α in bronchoalveolar lavage, periostin levels, and lipopolysaccharide-induced acute lung injury.[25]

Furthermore, omalizumab has been found to increase the interferon-induced antiviral effects of influenza-virus-induced peripheral blood mononuclear cells and rhinovirus-induced plasma dendritic cells.[23] Omalizumab treatment

should therefore be considered to have a protective effect against SARS-CoV-2/COVID-19 infection. Opposed to this idea, it has been suggested that type 2 inflammation reduces vulnerability to SARS-CoV-2 and alleviates the course of COVID-19 infection. With this viewpoint, MAb treatments like omalizumab, which blockade the type 2 inflammation at various stages, may negatively affect the course of COVID-19 infection in patients with severe asthma.[12]

Mepolizumab reduces viral influx by inhibiting CD147 and inhibits respiratory epithelial injury by reducing the eosinophil count and eosinophil-induced chemokines and cytokines.[26] In addition, mepolizumab injections have been shown to increase antiviral effectiveness by increasing secretory IgA and the number of natural killer cells in the respiratory epithelium in patients with severe asthma.[27–29] Aside from these studies supporting the idea that mepolizumab may be protective against SARS-CoV-2/COVID-19 infection, there are also contrary studies suggesting that eosinophilia may be protective against COVID-19 infection in patients with severe bronchial asthma because mepolizumab reduces blood and tissue eosinophils via an anti-IL-5 effect, suppressing the eosinophil-induced antiviral immunity, and because eosinopenia has an impact on COVID-19-related mortality.[30–33]

Considering the real-life data, in a study based on the Belgian Severe Asthma Registry, Hanon et al.[34] reported that 4 out of 129 patients on omalizumab treatment for severe asthma were found to have been infected with COVID-19, and none of these patients required hospitalization. In the same paper, 7 (2.3%) out of 305 patients on anti-IL-5 or anti-IL-5R treatments were found to have been infected with COVID-19, and 4 patients were hospitalized. Three (1.2%) out of 242 patients with severe asthma not receiving MAb treatment were found to have been infected with COVID-19, and 1 patient required hospitalization.

Rial et al.,[35] however, reported that 14 (5.32%) out of 263 patients with severe bronchial asthma on omalizumab treatment had been infected with COVID-19 and 1 patient was hospitalized and that 11 (7.14%) out of 154 patients with severe bronchial asthma on mepolizumab treatment had been infected with COVID-19 and 3 of these patients were hospitalized. In another study, the SARS-CoV-2-related hospitalization rate was reported as 0.23% in asthmatics on MAb treatment (0/641 in patients with severe asthma on omalizumab treatment and 2/308 in patients with severe asthma on mepolizumab treatment).[10] These reports suggest that COVID-19-related hospitalization in patients on MAb treatment are low, and the course of COVID-19 infection is relatively mild. In contrast to these studies, Eger et al.[12] reported the frequency of SARS-CoV-2 infection in asthmatic patients receiving MAb treatment as 1.42% and the rate of COVID-19-related hospitalizations in patients with severe asthma on MAb treatment as 1.28%. The study proposed that this rate is 0.28% in the Dutch population, and the course of COVID-19 infection is more severe in patients with severe asthma on MAb treatment, increasing the rate of hospitalization by 14 times and the rate of intubation by 41 times.

In this study, the rate of SARS-CoV-2-related pneumonia in patients with severe asthma on MAb treatment was higher compared with the patients with severe asthma not receiving MAb treatment. Varying rates and results have been reported in relevant studies. Rial et al.[35] reported the rate of SARS-CoV-2-related pneumonia in patients with severe bronchial asthma on MAb treatment as 6.4%, with similar rates of pneumonia between patients with severe asthma on and not on MAb treatment. However, in two different Turkish studies, the frequency of SARS-CoV-2 infection in patients with severe asthma on MAb treatment was determined to be 15.5% and 19%.[11,36] Tuncay et al.[11] reported that 9 (12%) out of 75 patients on MAb treatment developed pneumonia. In the present study, the frequency of SARS-CoV-2 infection was found to be 27%, and the rate of SARS-CoV-2-related pneumonia was 7.6%.

It can be considered that different results are due to the varying durations of the studies.

While the study by Eger et al. involves the first 45-day period of the pandemic, the study by Rial et al. involves a 3-month period. The present study evaluates the frequency of SARS-CoV-2 infection during a 6-month period. It is obvious that an extremely contagious virus such as SARS-CoV-2 will eventually infect more individuals over time and will lead to an increase in seroprevalence of SARS-CoV-2. Moreover, the severity and seroprevalence of SARS-COV-2/COVID-19 infection are not homogenous in different regions within the same timeframe. When SARS-COV-2 is under control in a region, a peak of SARS-CoV-2 infection may be observed in another country, or while the first SARS-CoV-2 wave cannot be controlled in one country, another country is already dealing with the second wave of SARS-CoV-2. Therefore, different results may have been obtained due to the heterogeneity of the

study periods and the regions of interest. In addition, due to the fact that PCR and other rapid diagnostic laboratory tests were not used in many countries, especially at the beginning of the pandemic, the studies conducted in this period may have caused the low incidence of SARS-CoV-2 infection. Although the rate of SARS-CoV-2-related pneumonia is higher in patients on MAb treatment compared with patients not receiving MAb treatment, similar rates of SARS-CoV-2-related hospitalizations in both groups suggest that pneumonia has a milder course in patients on MAb treatment, and therefore it has not increased SARS-CoV-2-related hospitalizations.

This study has some limitations. The number of patients who were on omalizumab or mepolizumab treatment and had SARS-CoV-2-related pneumonia and who were hospitalized or admitted to the intensive care unit is low, particularly due to the relatively small study population. No mortality occurred. In addition, there were insufficient data relating to treatments such as oral or systemic steroids used to treat patients infected with SARS-CoV-2. A small sample size limits the power of statistical data and makes data interpretation challenging.

In conclusion, in this cohort study, the prevalence of SARS-CoV-2 infection and the rate of SARS-CoV-2-related hospitalizations were not found to be increased in patients with severe asthma on MAb treatment compared with patients not receiving MAb treatment. These results were in parallel with current recommendations emphasizing the continuation of MAb treatment while infected with COVID-19.

Conflicts of interest

There are no conflicts of interest.

Ethics Committee Approval

The study was approved by the Karatay University Ethics Committee (No: 2021/033, Date: 16/02/2021).

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Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept – E.A.; Design – E.A.; Supervision – G.A.; Funding – E.A.; Materials – E.A., G.A.; Data collection &/or processing – E.A., G.A.; Analysis and/or interpretation – G.A.; Literature search – E.A.; Writing – E.A., G.A.; Critical review – E.A., G.A.

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