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No increased risk of severe COVID-19 in asthma treated with biologics

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Abstract:

BACKGROUND AND AIM: Biologics can be used safely for patients with severe asthma during the coronavirus pandemic, but there is still a lack of information regarding their effects during SARS-CoV-2 infection. The aim of this study was to evaluate the impact of biologic therapies on the course of SARS-CoV-2 infection and to assess the outcome of COVID-19 for severe asthmatics in pandemic conditions.

METHODS: A total of 100 severe asthma patients treated with biologics (7 treated with dupilumab, 22 with mepolizumab, and 71 with omalizumab) were included. Patients' demographic, clinical, and laboratory findings as well as the course of the COVID-19 disease were evaluated.

RESULTS: Of the total 100 patients, 15% of patients were diagnosed with COVID-19. There were no significant differences between SARS-CoV-2 positive and negative patient groups in terms of demographic features, atopy, comorbidity, duration of asthma, and duration of biological use. The body mass index (BMI) was higher in the SARS-CoV-2 negative group than the positive group (p=0.005). Asthma exacerbation during COVID-19 was observed in 3 patients, and only 2 were hospitalized for 5 days. SARS-CoV-2 positive group exhibited lower eosinophil and lymphocyte levels when infected with COVID-19 than before COVID-19 (p=0.01 and p=0.0009 respectively).

CONCLUSIONS: The rate of COVID-19 infection was higher in patients with severe asthma receiving biologics than in the general population. However, it can be speculated that treatment with biologics may have protection against severe COVID-19 and mortality. Further studies are required to investigate the role of biologic agents, which affect the level and function of eosinophils in viral infections, especially SARS-CoV-2.

Keywords:
Asthma, biologic agents, COVID-19, dupilumab, mepolizumab, omalizumab

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Introduction

Humanity has been struggling with the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) since December 2019.[1] The spectrum of SARS-CoV-2 infection ranges from lack of symptoms or mild symptoms to severe illness and death. While some risk factors that

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contribute to more severe diseases have been reported, it has been shown that individuals, even teenagers and young adults, with no risk factors can also have very severe COVID-19.[2,3] Patients with asthma are known to be highly susceptible to infections with microorganisms that commonly affect the respiratory system, and respiratory viral infections are an important cause of morbidity in asthma.[4] In uncontrolled asthma, the severity and course of virus-induced exacerbation are poor,[5] and given this, it has been assumed that patients with severe asthma are at greater risk of contracting COVID-19. In spite of the fact that among hospitalized COVID-19 patients, asthma, diabetes, and obesity are the most common comorbidities,[6] variable rates of infection and severe clinical outcomes of COVID-19 have been reported among asthma patients.[7–11] Although one study suggests that there is no relationship between severe asthma and COVID-19 transmission rate, severity, mortality, and complications,[12] large observational studies in which patients with severe asthma can be adequately represented are needed.

The role of severe asthma itself in the progression of COVID-19 is still unclear, and there are concerns about the effects of asthma medication on the course or severity of the disease. The biologics such as omalizumab (an anti-immunoglobulin E [IgE] antibody), mepolizumab, and reslizumab (interleukin [IL]-5 blockers), benralizumab (an IL-5 receptor blocker), and dupilumab (an IL-4 receptor-α and a receptor shared by IL-4 and IL-13 blocker) have been used to treat severe asthma. In particular, the effects of biologics used for asthma treatment on COVID-19 may differ and have not yet been clarified. The aim of the current study is to evaluate the safety of biologics for severe asthmatics in pandemic conditions and to determine the impact of biologic therapies on the course of SARS-CoV-2 infection.

Materials and Methods

Study population

This case–control study was performed in three tertiary outpatient clinics. Severe asthma was diagnosed according to recent European Respiratory Society/American Thoracic Society (ERS/ATS) and Global Initiative for Asthma (GINA) guidelines.[13,14] The patient's SARS-CoV-2 infection was confirmed by a positive result on a real-time polymerase chain reaction (RT-PCR) assay of nasal or pharyngeal swabs in accordance with the World Health Organization guidelines.[15] Patients aged 18 years and older were included in the study. Patients who did not give informed consent were excluded from the study. The study population consisted of 100 severe asthma patients who were treated with biologics. They were monitored throughout the 1-year period (March 11, 2020, to March 11, 2021), and their follow-up data were collected. At the end of the 1-year follow-up period, patients without SARS-CoV-2 RT-PCR positivity and/or without any COVID-19-related symptoms were included in the SARS-CoV-2 negative group. The evaluation of clinical and laboratory parameters of SARS-CoV-2 positive patients was performed two times; the first on the third day of illness and the second at fourth week of recovery from illness. This study was conducted in accordance with the World Medical Association Declaration of Helsinki. The Turkish Ministry of Health also approved the study (protocol number/date: 2021-03-19T13_46_2/2021). The study was approved by the institutional ethics committee (protocol numer/date: E2-21-654/2021), and written informed consent was obtained from all the study participants.

Demographic and clinical assessment of study population

The demographic details, laboratory findings, and clinical features, including the presence of additional chronic medical conditions such as diabetes, hypertension, ischemic heart disease, and obesity, were collected from patients' medical records. The level of asthma control was evaluated with the Asthma Control Test (ACT).[16] An ACT score of <16 was defined as very poorly controlled, 16–19 as not well-controlled, and 20–25 as well-controlled asthma. Atopy was defined by the presence of at least one positive skin test result to a common aeroallergen.

Statistical analysis

Statistical analyses were performed using the SPSS 25.0 package program (SPSS Inc., Armonk, NY, USA). GraphPad Prism software (San Diego, CA, USA) was used for graphical analysis. Continuous variables were expressed as mean±standard deviation or median with interquartile range (IQR), and categorical variables are expressed as frequency (%). The Chi-squared test and the Mann-Whitney U test were used to compare categorical and continuous variables, respectively. Wilcoxon matched-pairs signed ranks test was used to compare variables before biologic treatment, during biologic treatment, during COVID-19, and after COVID-19 periods. p-value less than 0.05 was considered statistically significant.

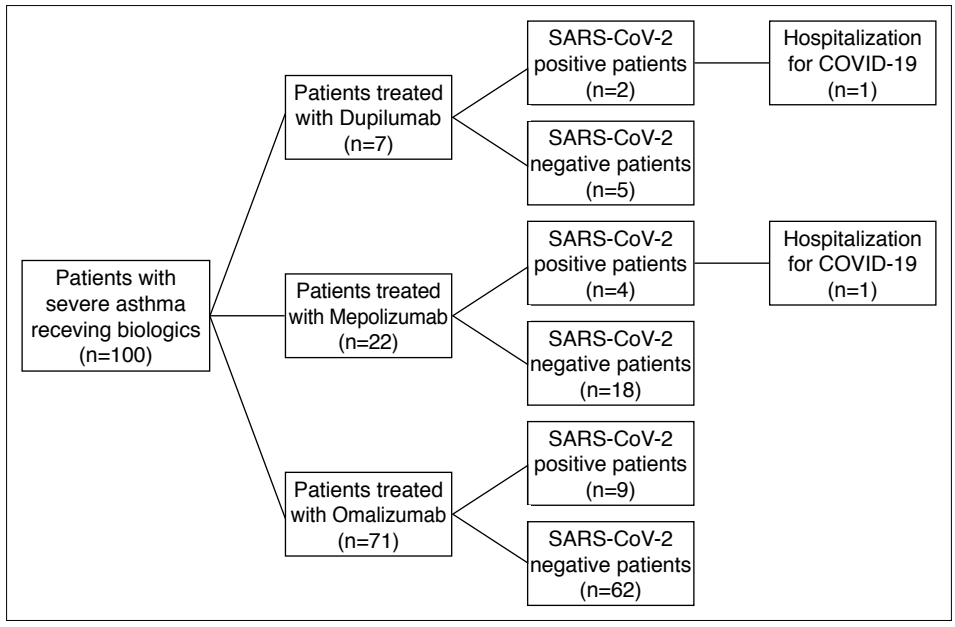

Figure 1: Flow chart of patients with severe asthma receiving biologics

Results

A total of 100 severe asthma patients treated with biologics were evaluated: seven (7%) patients treated with dupilumab, 22 (22%) with mepolizumab, and 71 (71%) with omalizumab. All the patients were also treated with moderate or high-dose inhaled corticosteroids according to the ERS/ATS and GINA guidelines.[13,14] Among the 100 patients, RT-PCR was positive in 15 (15%) patients. Of these patients (P1–P15) who recovered from COVID-19 following SARS-CoV-2 infection, two were treated with dupilumab, four with mepolizumab, and nine with omalizumab. The flow chart of patients with severe asthma receiving biologics is shown in Figure 1. All patients had mild COVID-19, with only two patients (P1 and P15) hospitalized for 5 days. The clinical and demographic characteristics of these patients are detailed in Table 1.

The age range of patients was from 18 to 79 years. The mean age±standard deviation of the SARS-CoV-2 positive patients was 48.13±12.82 years and 73% (n=11) of them were females. The mean age of the SARS-CoV-2 negative patients was 49.51±14.04 years and ~72% (n=61) of them were females. The mean BMI of the patients in the SARS-CoV-2 positive group was 23.2±4.3, while it was 27.6±5.6 in the SARS-CoV-2 negative group, and there was a statistically significant difference between them (p=0.005). A total of 17 patients were obese (BMI ≥30 kg/m^2). Atopy was present in 85 patients, and the house dust mites sensitivity, the most common sensitizing allergen, was detected in 82 of 85 patients. The pollen sensitivity was present in two patients and mold sensitivity was present in one patient. The mean asthma duration was 13.52±7.99 years, and the mean duration of biologic agent use was 7.99±1.48 years. The details of rhinitis, chronic sinusitis with nasal polyposis, bronchiectasis, gastroesophageal reflux disease, additional comorbidities, additional drugs used for comorbidities, and smoking status of patients are shown in Table 2.

The leukocyte, lymphocyte, eosinophil, thrombocyte, and hemoglobin levels of patients before using biological treatment were similar in SARS-CoV-2 positive and negative groups (Table 3). Those parameters of the patients were also similar during biologic therapy, except that the total leukocyte count was higher in the SARS-CoV-2 positive group (p=0.04) (Table 3). The median total IgE levels of SARS-CoV-2 negative patients were higher than the positive group, but a statistically significant difference was not found (Table 3). Six of SARS-CoV-2 positive patients had eosinopenia (<100 cell/mm^3), and the overall eosinophil levels of these patients were lower during COVID-19 (100, IQR: 20–300) compared with the values before biologic use (450, IQR: 350–1000), of the pre-COVID-19 period (300, IQR: 100–420), and of the post-COVID-19 period (200, IQR: 100–350) [Fig. 2a]. Six of SARS-CoV-2 positive patients had lymphopenia, and the overall lym-

Table 1: Demographic and clinical characteristics of patients

Patient no	Age (years)	Sex	BMI (kg/m^2) (years)	Duration of asthma	Type of asthma	Type of biologic therapy	Duration of biologic therapy (years)	COVID-19-related symptoms	ACT during COVID-19	Hospitalization for COVID-19	COVID-19 treatment	Pneumoniae on Thorax CT	Administration of biologics after COVID-19
P1	47	F	28.4	25	Eosinophilic nonallergic	Dupilumab 300 mg/ 14 days*	7	Dyspnea, fever, headache, myalgia	13	Yes	Paracetamol 500 mg (po) 2×1 enoxaparin 4000 IU/0.4 mL (sc) 1×1 ¶favipiravir Budesonide and salbutamol+ ipratropium (nebulized), 2 L/min nasal oxygen	Bilaterally pneumonic consolidations	Scheduled time
P2	40	F	22.7	20	Eosinophilic nonallergic	Dupilumab 300 mg/ 14 days*	7	Myalgia, headache, cold symptoms	22	No	Favipiravir	No	Scheduled time (during favipiravir treatment)
P3	51	F	21	20	Allergic	Omalizumab 450 mg/ 14 days	3	Loss of smell and taste, headache, myalgia	17	No	Acetylsalicylic acid 100 mg (po) Favipiravir	NA	Delayed one week
P4	50	M	20	20	Allergic	Omalizumab 450 mg/ 14 days	2	Myalgia, weakness, fever, cough, dyspnea	14	No	Enoxaparin 4000 IU/0.4 mL (sc) 1×1 Favipiravir Methylprednisolone 40 mg/day Budesonide and salbutamol+ ipratropium (nebulized), 2 L/min nasal oxygen	Bilaterally pneumonic consolidations and ground glass opacities	Delayed one week
P5	66	F	26	14	Allergic	Omalizumab 300 mg/28 days	4	Myalgia, fatigue	21	No	Favipiravir	Bilaterally lower lobe ground glass opacity	Scheduled time
P6	25	F	19	15	Allergic	Omalizumab 300 mg/28 days	1	Myalgia, tachycardia, fatigue	22	No	Favipiravir Paracetamol 500 mg (po) 2×1	NA	Scheduled time
P7	29	M	21	20	Allergic	Omalizumab 450 mg/28 days	6	Myalgia, weakness, back pain, fever	20	No	Favipiravir	Pneumonic consolidation	Scheduled time
P8	55	F	23	8	Allergic	Mepolizumab 100 mg/28 days	1	Weakness, fever, nausea	17	No	Favipiravir	NA	Scheduled time
P9	64	M	19	20	Eosinophilic nonallergic	Mepolizumab 100 mg/28 days	3	Mild weakness	18	No	Enoxaparin 4000 IU/0.4 mL (sc) 1×1 Favipiravir	No	Scheduled time
P10	42	M	20	8	Eosinophilic nonallergic	Mepolizumab 100 mg/28 days	3	Myalgia, weakness	21	No	Enoxaparin 4000 IU/0.4 mL (sc) 1×1 Favipiravir	No	Scheduled time
P11	66	F	28.1	10	Allergic	Omalizumab 300 mg/28 days	4	Weakness	23	No	Favipiravir	Bilaterally pneumonic consolidations and ground glass opacities	Scheduled time
P12	57	F	32	20	Allergic	Omalizumab 300 mg/28 days	3	Myalgia, fever, cough	25	No	Enoxaparin 4000 IU/0.4 mL (sc) 1×1 Favipiravir	Bilaterally pneumonic consolidations and ground glass opacities	Scheduled time

Table 1: Cont.

Patient no	Age (years)	Sex	BMI (kg/m^2) (years)	Duration of asthma	Type of asthma	Type of biologic therapy	Duration of biologic therapy (years)	COVID-19-related symptoms	ACT during COVID-19	Hospitalization for COVID-19	COVID-19 treatment	Pneumoniae on Thorax CT	Administration of biologics after COVID-19
P13	51	F	28.6	5	Allergic	Omalizumab 150 mg/28 days	1.5	Myalgia, fatigue	21	No	Favipiravir	Bilaterally pneumonic consolidations and ground glass opacities	Scheduled time
P14	47	F	19.8	17	Allergic	Omalizumab 150 mg/28 days	1	Myalgia, fatigue	22	No	Favipiravir	NA	Scheduled time
P15	32	F	19.21	10	Eosinophilic nonallergic	Mepolizumab 100 mg/ 28 days	2	Myalgia, weakness, fever, cough, dyspnea	12	Yes	Enoxaparin 4000 IU/0.4 mL (sc) 1x1 Favipiravir Methylprednisolone 40 mg/day Budesonide and salbutamol+ ipratropium (nebulized), 4 L/min nasal oxygen	Pneumonic consolidation and ground glass opacities	Scheduled time

*P1 and P2 have been treated with dupilumab 300 mg per 14 days since May 2014 (as part of DRI12544 in LTS12551 and NPP15080 studies). BMI: Body mass index, ACT: Asthma Control Test, CT: Computed tomography, F: Female, M: Male, NA: Thorax computed tomography was not done, sc: Subcutaneous, Favipiravir 2×1600 mg (po) loading dose on the first day and then 2×600 mg (po) for 4 days

phocyte count was lower during COVID-19 than before COVID-19 (p=0.0009) and after COVID-19 (p=0.001) [Fig. 2b]. Asthma exacerbation at the time of COVID-19 diagnosis was observed in three patients (P1, P4, and P15) whose ACT scores were determined to be <15, and two of them were hospitalized. The other three patients (P3, P8, and P9) exhibited poorly controlled asthma. The mean ACT scores for the SARS-CoV-2 positive and negative patients were similar during the pre-COVID-19 period (22.53±1.55 and 22.38±1.87, respectively). The mean ACT scores of patients who had COVID-19 were found to be lower during COVID-19 (22.53±1.55) than pre-COVID-19 (19.20±3.87) and post-COVID-19 (21.46±2.19) periods [Fig. 2c]. Although three (20%) of the patients had comorbidities that could have increased their risk of contracting COVID-19 and could affect the course of the disease, all of them had mild cases. All patients continued to be treated with high/moderate dose of inhaled corticosteroids/long-acting β2-agonists while infected with COVID-19; only two patients (P4 and P15) required systemic corticosteroid treatment during COVID-19, and all of our patients recovered without any sequelae.

Discussion

There is currently a necessity to complete more comprehensive evaluations to determine the association between severe asthma treated with biologics and the contracting of COVID-19 as well as the risk of severe disease from COVID-19. Our study, which has included the largest sample size in this topic to our knowledge, addressed these questions and found that the use of biologics in severe asthma does not have a negative impact on the progression and outcome of COVID-19. Although COVID-19 was found to be mild in patients with severe asthma using biologics and no deaths were observed, the prevalence and risk of COVID-19 contracting was higher in this group than in the general population (15% vs 3.31%, OR: 5.15, 95% CI: 2.98–8.93, p<0.0001) during the study period.[17]

It has been reported that COVID-19 is often mild in asthmatic patients and that inhalers and biologics can be used safely.[18,19] Similarly, our findings supported these reports. In addition, in a recent study, similar to our study results, the frequency of COVID-19 was found to be high, but the disease severity was mild.[20] On the other hand, another study reported that asthma was the most common comorbid atopic disease in COVID-19 patients, and the rates of hospital and intensive care admis-

Table 2: Clinical characteristics of severe asthmatic patients treated with biologics

Features	Group		p
	SARS-CoV-2 negative (n=85)	SARS-CoV-2 positive (n=15)	
Duration of asthma (years) (mean±SD)	13.17±8.28	15.46±5.97	0.31
Duration of biologic treatment (years) (mean±SD)	2.75±1.36	3.19±2.08	0.29
Atopy (n)	76	9	**0.03**
Allergic rhinitis (n)	20	6	0.18
CRSwNP (n)	11	2	0.96
Bronchiectasis (n)	4	–	0.39
GERD (n)	24	5	0.69
Smoking status (active) (n)	19	–	0.20
Additional comorbidities (n)			
Hypertension	12	3	0.83
Diabetes mellitus	7	2	
Hypothyroidism	3	1	
Coronary artery disease	4	1	
Chronic spontaneous urticaria	5	1	
Rheumatologic diseases	2	1	
Aortic aneurism	–	1	
Additional drugs (n)			
ACE-inh	11	4	0.79
Metformin	7	1	
ARB	5	–	
Levothyroxine	3	1	
Antihistamine	12	5	
Leflunomide	–	1	
Hydroxychloroquine	1	1	
Beta-blocker	4	2	
Nasal corticosteroids	16	4	

Bold values specify statistical significance at the p<0.05 level. GERD: Gastroesophageal reflux disease, CRSwNP: Chronic rhinosinusitis with nasal polyps, ACE-inh: Angiotensin-converting enzyme inhibitors, ARB: Angiotensin receptor blockers, SD: Standart deviation

sion and intubation were higher in asthmatic patients.[21,22] Likewise, in another recent study, the rate of hospital admission was found to be 14 times, the intubation rate 41 times, and the mortality rate 5 times higher in patients receiving biologics compared with the normal population with COVID-19.[23] In our study, we found that the rate of hospital admission is lower in asthmatic patients using biologics than in the normal population, and there was no severe patient who required intensive care or intubation. Similar to our results, in a previous study, out of 865 patients (omalizumab, n=641; mepolizumab, n=308; benralizumab, n=98; and reslizumab, n=26) treated with biologics, only 20 patients had a confirmed diagnosis of COVID-19, of which two were admitted to the hospital.[24] In severe asthma patients treated with biologics, the need for hospitalization for COVID-19 was significantly lower than the general population and those who did not receive biologics (0.23% vs 26%).[24] In line with these findings, treatment with biologics may be associated with a protective effect against severe COVID-19.

The rate of obesity, which is a known risk factor for severe COVID-19, was high in the previous study,[23] but in our SARS-CoV-2 positive group, only four patients were overweight and there was one obese patient. Moreover, in this study, BMI was significantly higher in the SARS-CoV-2 negative group than in the positive group. This suggests that the higher incidence of severe COVID and the poor disease outcomes found in that study may not be associated with severe asthma itself or with treatment with biologics or comorbid obesity,[23] but may have resulted from additional causes. In addition, a previous study reported that underlying allergic or nonallergic asthma and allergic rhinitis were related to higher rates of SARS-CoV-2 infection and severe disease.[22] This aligns with our finding that COVID-19 contracting was higher in patients with severe asthma than in the general population (15% vs 9.55%). However, the disease was not serious, and the clinical outcomes did not differ from the general population in our study.

Table 3: Laboratory parameters of SARS-CoV-2 positive and negative groups

	SARS-CoV-2 negative (n=85)	SARS-CoV-2 positive (n=15)	p
LEU count (cell/mm^3)			
Before biologics	7992.53±2800.46	7914.06±1625.97	0.66
During biologics	7771.73±2314.53	11 977.33±1567.1	**0.04**
LYM count (cell/mm^3)			
Before biologics	2182±1011.6	2089.3±558	0.57
During biologics	2184.9±958.7	2125.3±101.2	0.72
EOS count (cell/mm^3)			
Before biologics	449±483.7	690.6±426.1	**0.01**
During biologics	280.2±283.7	406±366.9	0.13
PLT count (cell/mm^3)			
Before biologics	290996.9±83016.7	295 766.6±68 596.6	0.47
During biologics	282269.8±73617.6	307 866.6±72 927.4	0.14
HGB (g/dL)			
Before biologics	13.38±1.62	12.66±0.43	0.33
During biologics	13.36±1.54	12.70±0.38	0.34
Total IgE (IU/mL) (median±IQR)	211 (57–495)	97 (72–224)	0.34

Bold values specify statistical significance at the p<0.05 level. LEU: Leukocyte, LYM: Lymphocyte, EOS: Eosinophil, PLT: Platelets, HGB: hemoglobin, IQR: Interquartile range

Some evidence suggests that type 2 inflammation can reduce susceptibility to SARS-CoV-2 infection and COVID-19 severity by various mechanisms.[22,25,26] Biologic agents used to treat severe asthma block pathways related to type 2 inflammation,[22,27] which suggests that these biologics may adversely influence the protective effects of type 2 inflammatory environment. Our findings, on the other hand, weaken this hypothesis. Omalizumab was the first and most used biologic agent for the treatment of severe allergic asthma that blocks all IgE-dependent immunological events.[27,28] Unlike other biologics indicated in severe asthma, omalizumab is the only biologic with proven antiviral effects, and the key effector cells in the omalizumab-induced antiviral response are plasmacytoid dendritic cells.[27,28] All of our patients who were treated with omalizumab had mild disease, similar to previous studies,[19,29] and our findings suggest that the use of omalizumab does not have a negative impact on clinical outcomes of COVID-19.

While IL-4 plays an important role in Th2 cell differentiation, eosinophil recruitment, IgE production by class switching of B cells, and lung remodeling, IL-13 also causes airway hyperreactivity and fibroblast proliferation.[30] Dupilumab, a human monoclonal antibody used in the treatment of severe asthma, blocks the common receptor component of IL-4 and IL-13, which are two cytokines of type 2 cell-mediated immunity.[27,30] IL-13, which is targeted by dupilumab, decreases angiotensin-converting enzyme-2 and increases transmembrane serine protease-2 gene expressions, so it has both a positive and negative role in COVID-19 infection.[31] It was reported that neutralizing IL-13 reduces the severity of the disease.[32] In line with the previous reports,[33,34] both of the patients in our study who had been treated with dupilumab for approximately 7 years recovered completely from COVID-19. Given this, blocking IL-4 and IL-13 may not contribute to poor COVID-19 outcomes and may instead protect against severe disease.

In a previous study, type 2 immune response biomarkers such as eotaxin-2, eosinophils, IL-5, IL-13, and IgE were found to be increased in severe COVID-19 patients.[35] Moreover, it has been reported that IL-5 can be predictive of mortality,[35] and higher eosinophil levels (>0.05×10^9 L^{-1}) were associated with survival.[36] In addition, previous studies reported that eosinophil levels decreased in patients with mild to severe disease,[37,38] and the low eosinophil counts may be related to severe disease.[25,39] Consistent with these previous reports, we found reduced eosinophil levels in the peripheral blood of our patients. There is no evidence that eosinopenia induced by anti-eosinophil drugs results in increased susceptibility to viral infections. IL-5 plays a central role in eosinophil biology,[40] and mepolizumab, an anti-IL-5 monoclonal antibody, reduces the number of eosinophils and their migration to the lungs. The four patients in our study who were treated with mepolizumab did not require intensive care admission or ventilation support, but two of them had risk factors associated with severe COVID-19 and death,

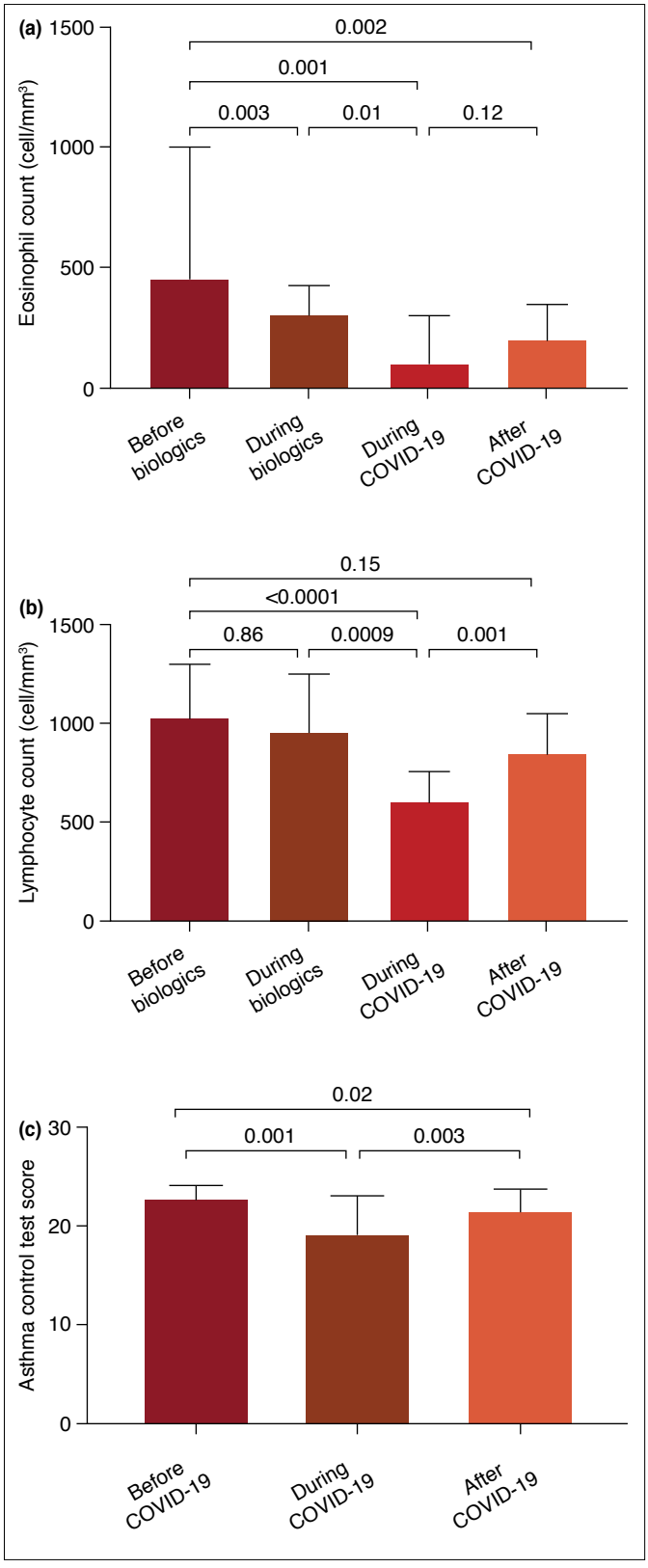

Figure 2: Laboratory and clinical findings of severe asthma patients with confirmed SARS-CoV-2 infection during biologic therapy: (a) eosinophil levels; (b) lymphocyte levels; (c) Asthma Control Test score

regardless of severe asthma or biological use. Similar to previous reports, all patients treated with mepolizumab in our series recovered without any negative respiratory outcomes.[41] In contrast to our study, it was reported that the incidence of COVID-19 was low (only 7 patients, 2.3%) in patients treated with anti-IL-5 or anti-IL-5R in Belgian Severe Asthma Registry data[42] and was 7.1% in patients receiving mepolizumab in a large cohort study.[19] In our study, the higher rate of COVID-19, especially in patients receiving dupilumab and mepolizumab, may be due to the small cohort size. However, it is not yet known exactly how eosinophil levels and anti-IL-5 drugs affect inflammation in asthmatics with SARS-CoV-2.

Eosinophils are among the most important cells in type 2 inflammation and are protective against viral infection.[40,43] However, it has become necessary to thoroughly investigate the role of eosinophils in viral infections, particularly SARS-CoV-2 infection. Despite the use of biologics that affect eosinophil numbers and functions and the fact that eosinophil counts decreased significantly during COVID-19, the disease progression was mild in our patients. With our current knowledge, it is difficult to determine why the disease has not been severe in patients using dupilumab, which prevents eosinophil function and its recruitment into tissue. Moreover, the eosinophil count, which was already decreased due to the biologic, decreased even further in the patients in our study with comorbidities, such as diabetes and advanced age, who used mepolizumab, but the disease remained mild. Given this, there is reason to speculate that eosinophils do not play the same role in all viral infections or that eosinophils struggle with SARS-CoV-2 before they are recruited into the tissue.

The strength of our study is that it is the first study conducted in our country, which has the highest number of patients treated with three different biologic agents. However, the unequal number of patients in each group and the low number of patients especially in the dupilumab and mepolizumab groups are limitations of our study. In addition, comparative studies with larger patient numbers are needed, including patients with different asthma severity who are not using biologic drugs.

Conclusion

In conclusion, the long-term use of the biologic agents dupilumab, mepolizumab, and omalizumab to treat

severe asthma was not found to be a risk factor for developing severe COVID-19. Due to a lack of evidence of harm caused by biologic therapies administered during the COVID-19 pandemic, a continuation of treatment is important in indicated asthmatics. Moreover, from the results of the current and previous studies, it was speculated that biologics protect from severe COVID-19 disease, but not from the transmission of SARS-CoV-2 infection. Further, due to the protective effects of biologics used in type 2 inflammation, especially omalizumab, the possibilities of their use in the treatment of COVID-19 in selected patient groups is a topic worthy of further investigation. The role of biologic agents and eosinophils should be investigated and reevaluated in viral infections, especially in SARS-CoV-2.

Conflicts of interest

There are no conflicts of interest.

Ethics Committee Approval

The study was approved by The Ankara City Hospital No 2 Clinical Research Ethics Committee (No: E2-21-654, Date: 30/06/2021).

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Peer-review

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Authorship Contributions

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