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The Frequency and Severity of COVID-19 in Patients Receiving Biological Agents and Risk Factors: Experience of an Allergy Clinic

Sadan SOYYIGIT[1,2], Sengul BEYAZ[2], Zeynep CELEBI SOZENER[2]

[1] Division of Immunology and Allergic Diseases, Department of Chest Diseases, Ankara Yıldırım Beyazıt University Faculty of Medicine, Ankara, Turkey
[2] Department of Immunology and Allergic Diseases, Ankara City Hospital, Ankara, Turkey

Corresponding Author: Sadan Soyyigit ✉ sadansoyyigit@gmail.com

ABSTRACT

Objective: The effect of biological agents used in severe allergic diseases on the risk of coronavirus disease 2019 (COVID-19) and the course of the disease still remains unclear. The aim of the study was to evaluate retrospectively the frequency and severity of COVID-19 to determine risk factors and to present real-life data in patients using biological agents.

Materials and Methods: Patients who have used omalizumab or mepolizumab for at least six months were questioned retrospectively in terms of a history of COVID-19. Patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) polymerase chain reaction (PCR) or serological IgG positivity, symptoms, lung involvement, the need for supplemental oxygen, hospital and intensive care admission, and mortality were queried.

Results: Of the 71 patients (omalizumab/mepolizumab: 51/20) included in the study, the average age was 37.2±12.9, and the female/male ratio was 46/25. Of the 11 patients (omalizumab/mepolizumab: 6/5) with SARS-CoV-2 positivity, two were hospitalized for pneumonia and needed oxygen. However, intensive care was not required and they survived. There was no significant difference between mepolizumab users who had COVID-19 and those who did not in terms of baseline and post-treatment 6th-month eosinophil values (p= 0.7, p= 0.59, respectively). It was established that eosinopenia developing after treatment did not increase the risk of COVID-19 in patients using mepolizumab [RR (95% Cl) 0.99 (0.97-1.02), p=0.88].

Conclusion: According to our single center data, we found the risk of severe COVID-19 in patients using biological agents to be quite low. Especially, eosinopenia that developed after mepolizumab treatment did not constitute a risk factor for the severity of COVID-19.

Keywords: COVID-19, severe asthma, chronic spontaneous urticaria, omalizumab, mepolizumab

INTRODUCTION

In allergy clinics, a sizable proportion of individuals with severe allergic disease undergo treatment with biological agents (1). During the pandemic period, various guidelines have made recommendations regarding the safety and use of biological agents. The EAACI guidelines and other allergy guidelines have suggested that biological agents targeting type-2 inflammation should be maintained during the treatment of severe asthma, atopic dermatitis, chronic sinusitis with nasal polyp (CRSwNP), and chronic spontaneous urticaria (CSU) during the pandemic period (2).

There is not adequate evidence indicating that the drugs used in patients with severe allergic diseases increase the risk of coronavirus disease 2019 (COVID-19). The uncertainty of potential risks seems to be associated with the complexity of the immune response during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. In severe COVID-19 cases, organ damage develops in association with cytokine storm and consequent exces-

ORCID Sadan Soyyigit / 0000-0003-3270-5884, Sengul Beyaz / 0000-0002-1505-4293, Zeynep Celebi Sozener / 0000-0003-4188-0959

sive release of proinflammatory type 1 and 3 cytokines. It is known that the immune system activates proinflammatory Th1, Th17, and regulatory T cells in order to prevent the increase in lung damage caused by COVID-19. In addition, hypotheses claiming that anti-inflammatory type 2 responses are also increased have been put forward. It has also been reported that eosinophils play an important role in the immune response. It has been proposed that low eosinophil levels are associated with more severe disease while high eosinophil levels indicate a better prognosis, but this issue has not been clarified yet (2).

It has been demonstrated that biological agents employed in the treatment of severe allergic diseases do not increase susceptibility to viral infections and that especially omalizumab exerts antiviral effects via its anti-inflammatory and immunomodulatory effects, hence preventing virus-associated asthma attacks (2).

In addition, it has been suggested that the suppression of type 2 inflammation with biological agents may aggravate COVID-19, and hence it was stated in a guideline that they should not be used in an active infection. However, there is no evidence indicating that the use of omalizumab and mepolizumab increases the risk of COVID-19 (3,4).

In recent studies, the rate of allergic diseases in patients with COVID-19 has been evaluated (5). Therefore, the aim of the present study was to determine the frequency and severity of COVID-19 in patients using biological agents due to severe allergic diseases in our clinic and to establish whether the use of biological agents is a risk factor for COVID-19 disease.

MATERIALS and METHODS

The present study was designed as a retrospective cohort study. The application made to the Ministry of Health, General Directorate of Health Services, Scientific Research Platform with the '2021-12-03T17-02-09 application form' was accepted on 12.4.2021. Ethical approval was obtained from the Ankara City Hospital Ethics Committee (Date: 08.12.2021, No: E2-21-1119) and written informed consent was obtained from all study subjects.

Patients over the age of 18 who received Anti-IgE (omalizumab) and Anti-IL-5 (mepolizumab) treatment and were followed at the Ankara City Hospital Immunology and Allergic Diseases Clinic between March,11, 2020 (the date of the first COVID-19 case was reported in Turkey) and December 31, 2021 were included in the present study. The inclusion criterion was to receive omalizumab or mepolizumab for at least 6 months. Information regarding COVID-19 [Nasopharyngeal swab polymerase chain reaction (PCR) or serology (SARS-CoV-2 IgG), COVID-19 symptoms (chills-fever, dry cough, weakness, myalgia, sore throat, loss of taste and smell, headache, dyspnea, expectoration, nausea-vomiting, diarrhea), lung involvement, hospital admission, oxygen need, and mortality] was retrieved from the patients' medical records, and any missing information was completed by obtaining information from the patients by phone. Diabetes mellitus, cardiovascular disease, and obesity were queried as risk factors for COVID-19. Severe COVID-19 patients were defined according to one of the following criteria: (1) Severe pneumonia [patients with clinical signs of pneumonia (fever and/or cough and/or dyspnea) and resting oxygen saturation <90% and/or tachypnea (respiration rate>30/min)]; (2) critical severity group (patients with acute respiratory distress syndrome (ARDS), sepsis or septic shock). In addition, parameters and laboratory results used in clinical monitoring were obtained in patients using biological agents. In patients who use omalizumab or mepolizumab for severe asthma, baseline asthma control test (ACT), forced expiratory volume 1 second (FEV_1), FEV_1 (predictive%), total immunoglobulin E (tIgE) values, baseline and post-treatment 6th month peripheral eosinophil counts, and the presence of atopy (skin prick test positivity and/or the presence of allergen-specific IgE) were recorded. In patients receiving omalizumab for CSU, the urticaria activity score 7 (UAS7) was evaluated at the baseline and at the 6th month of treatment.

Statistical Analysis

For statistical analysis, the SPSS version 22 software (SPSS, Chicago, III., USA) was used. Assumptions of normality were tested by using visual (histogram and probability graphics) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyses were expressed with mean and standard deviation for normally distributed variables, with median and interquartile ranges for not normally distributed variables, and with frequency for ordinal variables. Comparisons between groups were made with the Mann-Whitney U test. The difference in frequency between the groups was evaluated with the Chi-square test or Fischer's Exact test (when values obtained did not meet Chi-square test assumptions). The relations between the use of a biological agent (omalizumab and mepolizumab), allergic diseases (severe asthma and CSU),

eosinophil and tIgE values, and COVID-19 were evaluated by Logistic Regression analysis. *P* value of <0.05 was considered statistically significant.

RESULTS

Seventy-one patients receiving biological agents in our adult allergy clinic were included in the present study. The mean age of the patients was 37.2±12.9 and the female/male ratio was 46/25. Fifty-one patients received omalizumab and 20 patients mepolizumab. Omalizumab indications were CSU (n=42, 59.2%), severe allergic asthma (n=8, 11.3%), and allergic bronchopulmonary aspergillosis (ABPA) (n=1, 1.4%), while indications for mepolizumab were severe eosinophilic asthma in 16 (22.5% patients), CRSwNP in 3 (4.2%) patients, and EGPA (eosinophilic granulomatosis with polyangiitis) in 1 (1.4%) patient. In patients with CSU treated with omalizumab, the dose regimen was 300 mg subcutaneously every four weeks. The 8 patients with severe allergic asthma treated with omalizumab given subcutaneously were distributed as 600 mg every four weeks in three patients, 450 mg every four weeks in one patient, 300 mg every four weeks in two patients, 150 mg every four weeks in one patient, and 525 mg every two weeks in one patient. The patient with ABPA was also receiving 600 mg omalizumab every two weeks. The dose of mepolizumab administered in patients with severe eosinophilic asthma and/or CRSwNP was 100 mg subcutaneously every four weeks, and 300 mg subcutaneously every four weeks in one EGPA patient. Six (8.5%) patients discontinued treatment at their own request. Treatment was discontinued due to a lack of benefit in 2 (2.8%) patients and resolution of disease in 27 (%38) patients, while treatment was continued in 36 (%50.7) patients.

Demographic and COVID-19 clinical characteristics of the patients on omalizumab and mepolizumab treatment are presented in Table I. The median number of doses of biological agents they received between March 11, 2020 and December 31, 2021 was 9 (6-49) for omalizumab and 14 (6-30) for mepolizumab.

The baseline median tIgE levels was 419 IU/ml (12-2871) in patients using omalizumab. In patients using mepolizumab, the mean eosinophil level was 1390.7±1295 cell/mcL at baseline while it was found to be 84.7±54.5 cell/mcL at the 6th month post-treatment. In asthma patients, the mean FEV_1 (pred%) was 75.4±30.4 in the omalizumab group, while it was 80.1±24.8 in the mepolizumab group. The mean ACT value was 13.5± 5.8 at the baseline and 21.1± 9.3 at the 6th month post-treatment in the omalizumab group while the corresponding figures were 16.8±4.1 and 24.9± 0.2 in the mepolizumab group, respectively. Among CSU patients using omalizumab, the median UAS7 value was found to be 42 (13-42) at the baseline and 0 (0-35) at the 6th month post-treatment.

In 62 (87.3%) patients overall, information on COVID-19 was accessed either from their files or by phone. Forty-two patients underwent COVID-19 vaccination [Synovac®, n=10 (66.7%), Biontech®, n=28 (23.8%), Synovac® and Biontech®, n=4 (9.5%)]. Forty patients underwent a PCR test due to the presence of symptoms/having contact with cases or for screening before investigations and positivity was found in 11 patients. Of these patients, six were in the omalizumab group and five in the mepolizumab group. Nine patients had mild and two had a severe course of COVID-19. The patients with severe COVID-19 were on mepolizumab treatment.

The COVID-19-associated characteristics of patients with severe asthma using biological agents are illustrated in Table II. Of the six patients, five used mepolizumab for severe eosinophilic asthma and one received omalizumab for severe allergic asthma. No significant difference was found between patients who used omalizumab for severe asthma and those who used mepolizumab in terms of frequency of COVID-19 (p=0.36). None of the patients used oral corticosteroids in addition to biological agents. All patients underwent COVID-19 vaccination except for patient number 5. No patient had any risk factor for severe COVID-19 other than patient number 2 (cardiovascular disease). Cough (n=1, 16.6%), loss of taste and smell (n=2, 33.3%), weakness (n=3, 50%), chills-fever (n=2, 33.3%), myalgia (n=2, 33.3%), and dyspnea (n=1, 16.6%) were the presenting symptoms in the patients. In patients number 3 and number 6, pneumonic consolidation was detected with thorax CT and the resting oxygen saturation was <90%. However, neither patient needed intensive care for oxygen support during follow-up, although they were hospitalized for nasal oxygen demand.

Characteristics associated with COVID-19 are demonstrated in patients receiving omalizumab for a CSU indication in Table III. SARS-CoV-2 positivity was detected with PCR in four patients and with serological SARS-CoV-2 IgG in one patient. Only two patients underwent COVID-19 vaccination and they had only mild symptoms of COVID-19. Patient number 5 had positive serology but

displayed no symptom of COVID-19. Symptoms in other patients were cough (n=1, 20%), loss of taste and smell (n=2, 40%), weakness (n=3, 60%), chills-fever (n=3, 60%), myalgia (n=3, 60%), and dyspnea (n=1, 20%). Lung involvement, oxygen need, hospital admission, or death did not occur in any patient.

To evaluate the risk of having COVID-19, eosinophil levels at baseline and at post-treatment 6th month in the mepolizumab group and baseline tIgE levels in the omalizumab group were compared. In the mepolizumab group, although baseline eosinophil levels were found to be lower in those who had COVID-19 than those who do did not have COVID-19, the difference was not statistically significant (p=0.7) (Figure 1A). There was no significant difference in 6th month post-treatment eosinophil values between the group that had COVID-19 and the group without it (p=0.59) (Figure 1B).

Table I: Characteristics of patients receiving omalizumab and mepolizumab

	Omalizumab	Mepolizumab
Patients (n)	51	20
Age, year (mean±SD)	36.8 ±11.6	38.4±15.9
Gender, n (%)		
Female	37 (72.5)	9 (45)
Male	14 (27.5)	11 (55)
Current smoker, n (%)	6 (11.8)	2 (10)
Body mass index (mean±SD)	25.0±5.0	25.6±1.04
Duration of disorder, month, median (min-max)	30 (6-312)	60 (8-276)
Biologic doses, median (min-max)	9 (6-49)	14 (6-30)
Comorbidities, n (%)		
Diabetes mellitus	4 (7.8)	1 (5)
Hypertension	1 (2)	1 (5)
Thyroid disorders	3 (5.9)	0
Ischemic heart disease	1 (2)	1 (5)
Atopic diseases, n (%)		
Asthma	9 (17.6)	17 (85)
Allergic rhinitis	7 (13.7)	2 (10)
Nonsteroidal anti-inflammatory drug allergy	7 (13.7)	4 (20)
Venom allergy	1 (2)	0
Nasal polyp	3 (5.9)	14 (70)
Samter's triad	2 (3.9)	4 (20)
Atopy, n (%)	14 (27.5)	8 (40)
COVID-19 vaccine doses, median (min-max)	2 (1-4)	2 (2-4)
COVID-19 vaccines, n (%)	28 (63.6)	14 (77.8)
Sinovac®	18 (64.3)	10 (71.4)
Biontech®	7 (25)	3 (21.4)
Sinovac® and Biontech®	3 (10.7)	1 (7.1)
PCR test, median (min-max)	2 (1-30)	2 (1-6)
PCR test for COVID-19, n (%) results	26 (59.1)	14 (77.8)
Positive	6 (23)	5 (35.7)
Negative	20 (77)	9 (64.3)
Presence of COVID-19, n		
Mild	6	3
Severe	0	2

COVID-19, Coronavirus disease 2019; PCR, Polymerase Chain Reaction

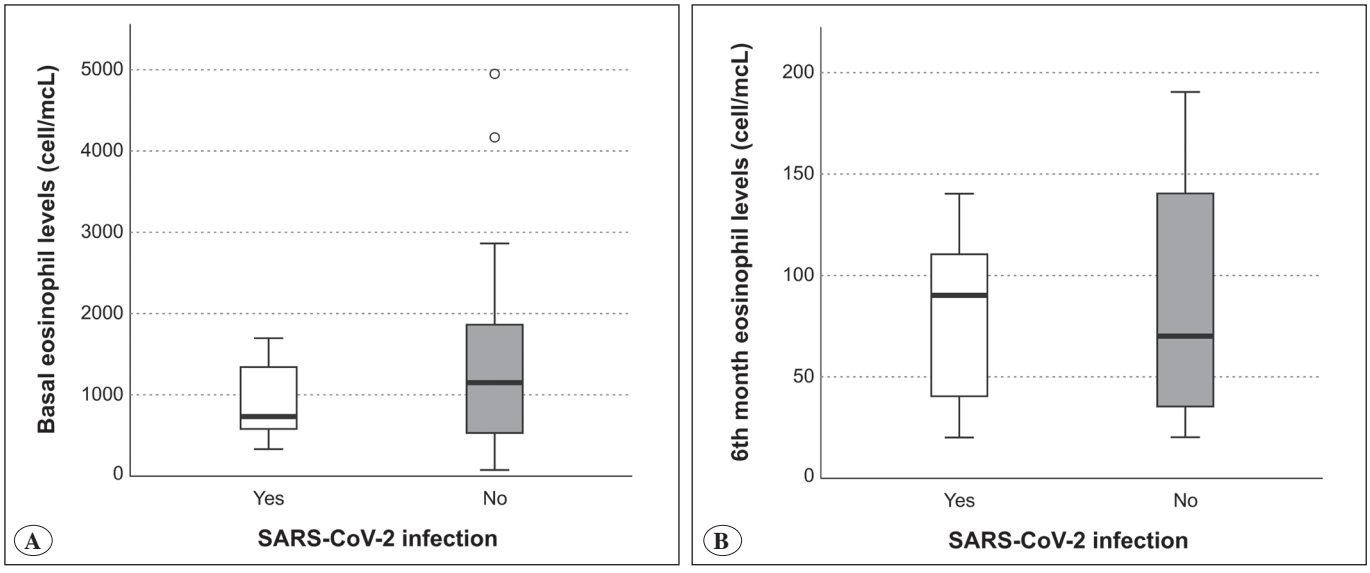

Figure 1. Baseline **(A)** and 6th month **(B)** eosinophil values in severe asthmatic patients receiving mepolizumab with and without COVID-19 (The differences for A and B were not significant, p>0.05).

Table II: Clinical characteristics, treatments and outcomes in patients with severe asthma and COVID-19

Patient	1	2	3	4	5	6
Age	21	60	63	20	26	57
Gender	M	M	M	M	M	M
Asthma phenotype	severe eosinophilic	severe eosinophilic	severe eosinophilic	severe eosinophilic	severe allergic	severe eosinophilic
FEV1 (%pred)	102	55	60	98	88	not known
Biologic	mepolizumab	mepolizumab	mepolizumab	mepolizumab	omalizumab	mepolizumab
OCS (mg/day)	none	none	none	none	none	none
Co-morbidities	samter triad	ischemic heart disease	samter triad	nasal polyp	allergic rhinitis	nasal polyp
COVID-19 vaccines	yes	yes	yes	yes	no	yes
Biologic doses before of COVID-19 infection	17	14	7	6	15	8
SARS-COV2 confirmed test	PCR	PCR	PCR	PCR	PCR	PCR
COVID-19 symptoms	loss of taste and smell	weakness	chills-fever, weakness, myalgia	chills-fever	loss of taste and smell	cough, weakness, dyspnea, myalgia
Presence of pneumonia	no	no	yes	no	no	yes
Hospitalisation for oxygen therapy	no	no	yes	no	no	yes
Admission to ICU for intubation	no	no	no	no	no	no
Duration of hospitalisation days	n/a	n/a	9	n/a	n/a	13
Death	no	no	no	no	no	no

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, **COVID-19:** Coronavirus disease 2019, **FEV1:** Force expiratory volume in the first second, **OCS:** Oral corticosteroid, **ICU:** Intensive care unit, **M:** male, **n/a:** Not applicable

Although baseline tIgE levels were found to be higher in the group with COVID-19 in patients receiving omalizumab, the difference was not significant (p=0.24) (Figure 2).

In the mepolizumab group, the baseline and post-treatment 6th month eosinophil values did not constitute a risk factor for COVID-19 [RR (95% CI) 1.0 (0.99-1.0), p=0.24 and 0.99 (0.97-1.02), p=0.88, respectively]. In the omalizumab group, baseline tIgE values were not found to be a risk factor for COVID-19 [RR (95% CI), 1.0 (0.99-1.0), p=0.99)].

DISCUSSION

There is not much evidence on the risk of severe COVID-19 in patients with allergic diseases, and information on severe allergic phenotypes is especially scarce. Recently, the use of biological agents suppressing type 2 inflammation has rapidly increased in allergic diseases such as severe asthma, atopic dermatitis, CRSwNP, and CSU. The effect of such biological agents targeting type 2 inflammation on the frequency of COVID-19 and the course of the disease remains unknown (2). All over the world, anti-IL-5 monoclonal antibodies (mepolizumab and reslizumab) and IL-5 receptor (IL-5Rα) antagonist (benralizumab), IL-4 receptor (IL-4Rα) antagonist (dupilumab), humanized anti-IgE monoclonal antibody (omalizumab) are biologic agents that are frequently used in severe allergic diseases.

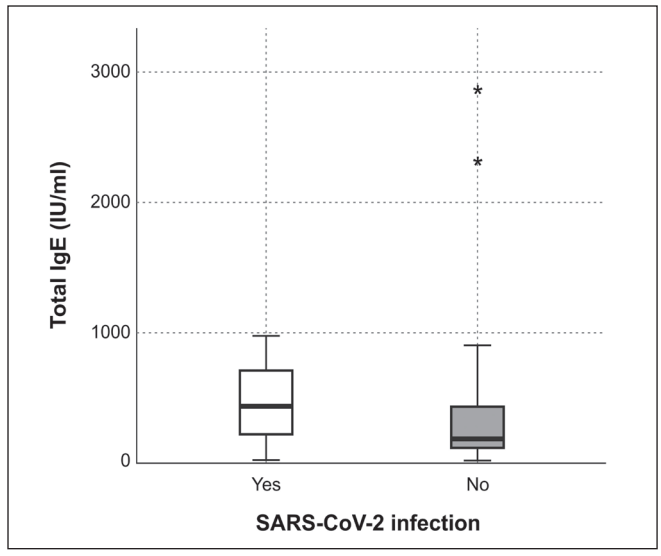

Figure 2. Baseline total IgE values in patients receiving omalizumab with and without COVID-19 (The difference was not significant between groups, p>0.05).

Table III: Clinical characteristics, treatments and outcomes in patients with urticaria and COVID-19

Patient	1	2	3	4	5
Age	40	23	39	56	26
Gender	F	F	F	M	F
OCS (mg/day)	none	none	none	none	none
Co-morbidities	none	hashimoto's thyroiditis	hashimoto's thyroiditis	asthma and allergic rhinitis	none
COVID-19 vaccines	no	no	yes	yes	no
Number of omalizumab doses (Before COVID-19 infection)	23	6	16	6	none
SARS-CoV2 confirmed test	PCR	PCR	PCR	PCR	serology
COVID-19 symptoms	chills-fever myalgia loss of taste and smell	cough loss of taste and smell weakness	chills-fever weakness myalgia	chills-fever weakness myalgia dyspnea	none
Presence of pneumonia	no	no	no	no	no
Hospitalisation for oxygen therapy	no	no	no	no	no
Admission to ICU for intubation	no	no	no	no	no
Duration of hospitalisation days	n/a	n/a	n/a	n/a	n/a
Death	no	no	no	no	no

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, **COVID-19:** Coronavirus disease 2019, **OCS:** Oral corticosteroid, **ICU:** Intensive care unit, **M:** Male; **F:** Female, **n/a:** Not applicable

There are only two licensed biological agents in our country, i.e., omalizumab and mepolizumab. Hence, we wanted to evaluate the frequency and severity of COVID-19 in patients using biological agents for the aforementioned indications in our clinic.

SARS-CoV-2 infection activates many components of the immune system. At the first phase of infection, eosinophils play an important role in the response. However, in later phases, the number of eosinophils starts to decrease. It has been reported that low levels of eosinophils lead to a more severe course of COVID-19, while high levels of eosinophils are associated with a better prognosis (6). Expansion and activation of the eosinophils are stimulated by type 2 cytokines, particularly IL-5. However, it has been proposed that suppression of type 2 inflammation in the early period of COVID-19 with IL-5 inhibitors, notably mepolizumab, may give rise to aggravation of the disease (2,6). There is no clear information in the literature on the potential effect of biological agents on immune response in COVID-19 at present (7). Another speculation is that biological treatments targeting type 2 inflammation may have a protective effect against COVID-19. It has been reported that omalizumab treatment improves type-1 IFN responses to respiratory viruses and enhances the antiviral response by influencing mast cell and basophil production and activation (8). This effect was supported by a pediatric study (9). In addition, anti-Th2 inflammation treatments increase the Th1 response indirectly via an immunomodulatory effect, playing a role in the control of viral infections. In severe COVID-19 patients, a marked Th2 response associated with increases in cytokines such as IL-5, IL-13, eotaxin, IgE, and eosinophils has been reported (7). In these patients, IL-5 and IL-4 inhibitors may indirectly increase the Th1 response. In support of this opinion, COVID-19 occurred in none of the 184 patients receiving omalizumab between February 1, 2020, and April 30, 2021 (10). In our case series, COVID-19 occurred in 15.5% of patients using biological agents, and the disease was observed to have a milder course especially in patients using omalizumab for CSU. Besides, it was determined that baseline tIgE did not increase the risk of COVID-19 in patients using omalizumab for asthma or CSU. In view of these findings, it is possible to conclude that omalizumab exerts no effect on the course of COVID-19 in patients with CSU, although we could not evaluate other immune mechanisms.

COVID-19 in a patient using omalizumab was first reported by Lommatzsch et al (11). The patient was a 52-year-old male with severe asthma, and no respiratory complications developed in the patient whose asthma control did not differ from the pre-pandemic period. According to the data of RAPSODI (Registry of Adult Patients with Severe asthma for Optimal Disease management), it was determined that 1.42% of the severe asthma cases treated with biological agents in the first month of the pandemic period were diagnosed with COVID-19, and seven patients were admitted to hospital. Among these patients, two patients receiving omalizumab required intensive care unit admission but recovered. However, it was emphasized that hospitalized patients had risks of severe COVID-19 such as obesity, diabetes mellitus, and cardiovascular disease (12). In the present study, two patients receiving mepolizumab for severe asthma were hospitalized for COVID-19 pneumonia and required supplemental oxygen but neither intensive care admission nor death occurred. Although two patients were classified as severe COVID-19, due to oxygen saturation of <%90 associated with pneumonia, they recovered without the development of complications.

In a case series reported from Turkey, COVID-19 was detected in nine of 62 cases who used omalizumab, and none had a severe course of disease (13).

Mepolizumab and reslizumab are humanized anti-IL-5 monoclonal antibodies that cause a decrease in eosinophils. Benralizumab exerts the same effect by binding to the IL-5 receptor on the eosinophil surface. Renner et al. first reported mild COVID-19 in a 41-year-old asthma patient receiving anti-IL-5 (benralizumab) treatment. They have subsequently reported COVID-19 in other two patients using benralizumab for asthma, chronic sinusitis, and nasal polyp. Even though the patients were aged 65 or over, no complications or asthma attacks occurred (14). In our series, COVID-19 was not detected in patients using omalizumab or mepolizumab for indications other than severe asthma.

According to data from the Severe Asthma Network in Italy (SANI) cohort at the first wave of the pandemic, 1.3% of the cases with COVID-19 used omalizumab and 2.9% mepolizumab. The authors have argued that patients using omalizumab was influenced to a lower degree by SARS-CoV-2 infection, even if there was no statistical data. In all cohorts, one of the two patients who died used mepolizumab. In addition, in this cohort, the rate of COVID-19 mortality was lower in asthma patients receiving biological agents (7.7%) than that in the general community (14.5%), which led the authors

to state that biological agents did not increase mortality (15). In the study of Eger et al, COVID-19 developed in six patients receiving anti-IL-5 biological agent treatment (mepolizumab, n=3, reslizumab, n=1, benralizumab, n=2), and among these, one patient receiving mepolizumab died after being hospitalized for oxygen supplementation (12). In our series, no death occurred among severe asthma patients receiving mepolizumab, despite pneumonia and hypoxia.

In a study conducted in Belgium, it was established that the use of biological agents in patients with severe allergic eosinophilic asthma does not increase the risk of COVID-19. Five patients were admitted to the hospital and asthma attack, steroid use, intensive care need, or death was not encountered in any of them. Only three patients required oxygen supplementation. No difference was found between patients receiving omalizumab and those receiving IL-5 antagonists with respect to the rate of SARS-CoV-2 (16). In a recent multicenter cohort study, COVID-19 was not found to be more frequent in these patients in comparison to the general population (17). In our cohort, five of the severe asthma patients who used biological agents and had COVID-19 used mepolizumab and one omalizumab. Although the majority of severe asthma patients who had COVID-19 were mepolizumab users, the difference was not statistically significant. Nevertheless, there were few patients in this retrospective study, and it is obvious that larger cohorts are required to reach a conclusion on this issue.

It is known that eosinopenia is a biomarker for severe COVID-19. Anti-IL-5 and anti-IL-5 receptor-blocking monoclonal antibodies may lead to concerns about the risk of severe COVID-19 in this patient group. Although there are case series on omalizumab, benralizumab and dupilumab in asthma patients, there is a paucity of studies on eosinopenia caused by anti-IL-5 monoclonal antibodies (6). In the present study, baseline and post-treatment 6th-month eosinophil values in the mepolizumab group were not found to be associated with COVID-19 risk. In addition, no significant difference was found between mepolizumab users in terms of eosinophil values at baseline and post-treatment 6th month between patients with and without COVID-19. As adequate data collected by clinical and epidemiological studies on the risk of eosinopenia and COVID-19 caused by anti-IL-5 agents is not available, guidelines still recommend use of this biological agents during the pandemic period.

In a small case series, it has been reported that the use of omalizumab had no adverse effect on the severity and course of COVID-19 despite lung involvement in two cases with CSU (18). In clinical studies with larger patient series, it was observed that three of seven patients with CSU who used omalizumab experienced no symptoms during COVID-19 (19). In our case series, five patients with chronic urticaria using omalizumab had COVID-19 disease with mild symptoms. We found that omalizumab did not increase the frequency and severity of COVID-19 in patients with CSU consistent with current data.

In the case series of Muntean et. al., it was established at 13.9% of CSU patients with COVID-19 received omalizumab treatment and all of these cases had moderate-severe COVID-19. No significant difference was found between the omalizumab group and the conventional treatment group with regard to the severity of COVID-19, indicating that there was no evidence of increased severe COVID-19 risk in the omalizumab group (20). In another study, no significant difference was found between patients who used solely oral antihistamines and those who used omalizumab in addition to antihistamines in terms of SARS-CoV-2 RT-PCR positivity (21). Unlike these studies, COVID-19 frequency and severity were evaluated only in CSU patients using omalizumab in the present study. As our data was retrospective, there was no control group.

It has been reported in the literature that CSU symptoms may be aggravated in severe COVID-19. Therefore, biological agents may be warranted. However, in patients with COVID-19 accompanied by inflammatory skin disease, the employment of immune suppressive drugs are debatable (22). In our patients with COVID-19, activation of CSU symptoms did not occur.

Criado et al. observed that omalizumab treatment commenced for urticaria control had no adverse effect on the course of COVID-19 in a 54-year-old female patient with CSU whose urticaria symptoms were aggravated in accompaniment to COVID-19 pneumonia (23). In our case series, there was no case using omalizumab for CSU activation in COVID-19.

To date, the role of type 2 cytokines in the severity and pathogenesis of COVID-19 has still not been completely clarified. The use of biological agents suppressing type 2 inflammation has raised two questions. The first question is whether these agents increase the risk of COVID-19 development and its severity. The second question is about

the severity of COVID-19 symptoms caused by the immunosuppressive effect of biological agents in patients with severe asthma, CRSwNP, and CSU. However, there are not enough studies in the literature addressing these questions (24).

We think that the most important limitation of our study is that it is not a prospective study. Knowing the eosinophil values at the time of diagnosis of COVID-19, especially in patients with severe asthma using mepolizumab, will be very valuable in terms of demonstrating the risk of eosinopenia for COVID-19. Another important limitation is the absence of a severe asthmatic patient group not treated with biologics as a control group.

In conclusion, given the present data, it may be thought that treatment with anti-Th2 biological agents may be safe and reliable in the COVID-19 pandemic period. It may be stated that omalizumab in particular protects against severe COVID-19 infection in patients with CSU and decreases susceptibility to this disease. The majority of severe asthma cases who had COVID-19 are those who use anti-IL-5 agents. Further investigation of immune mechanisms, especially in COVID-19 patients using mepolizumab, will yield more accurate information. Therefore, it is evident that further prospective studies on the side effects and safety of biological agents in the pandemic period are warranted.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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Authorship Contributions

Concept: **Sadan Soyyigit,** Design: **Sadan Soyyigit,** Data collection or processing: **Sadan Soyyigit, Sengul Beyaz, Zeynep Celebi Sözener,** Analysis or Interpretation: **Sadan Soyyigit,** Literature search: **Sadan Soyyigit, Sengul Beyaz, Zeynep Celebi Sözener,** Writing: **Sadan Soyyigit,** Approval: **Sadan Soyyigit.**

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