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SARS-Cov-2 Infection in Severe Asthma Patients Treated With Biologics



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What is already known about this topic? The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to cause significant morbidity and mortality all over the world. Previous studies have provided evidence that COVID-19 in severe asthmatics receiving different types of biological treatments is not associated with greater risk of hospitalization, intensive care unit admission, or death.

What does this article add to our knowledge? Our study confirms that the use of biologics for the treatment of severe asthma is safe during the pandemic, and despite the initial concerns, COVID-19 is not more common in asthmatics treated with biologics compared with general population.

How does this study impact current management guidelines? Administration of biologics is not necessary to be postponed due to SARS-CoV-2 infection.

BACKGROUND: At the beginning of the pandemic, there have been considerable concerns regarding coronavirus disease 2019 (COVID-19) severity and outcomes in patients with severe asthma treated with biologics.

OBJECTIVE: To prospectively observe a cohort of severe asthmatics treated with biologics for the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and disease severity during the COVID-19 pandemic.

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Abbreviations used

COVID-19- Coronavirus disease 2019

ICU- Intensive care unit

IQR- Interquartile range

LAMAs- Long-acting muscarinic antagonists

PCR- Polymerase chain reaction

pDCs- Plasmacytoid dendritic cells

SARS-CoV-2- Severe acute respiratory syndrome coronavirus 2

METHODS: Physicians from centers treating patients with severe asthma all over Greece provided demographic and medical data regarding their patients treated with biologics. Physicians were also asked to follow up patients during the pandemic and to perform a polymerase chain reaction test in case of a suspected SARS-Cov-2 infection.

RESULTS: Among the 591 severe asthmatics (63.5% female) included in the study, 219 (37.1%) were treated with omalizumab, 358 (60.6%) with mepolizumab, and 14 (2.4%) with benralizumab. In total, 26 patients (4.4%) had a confirmed SARS-CoV-2 infection, 9 (34.6%) of whom were admitted to the hospital because of severe COVID-19, and 1 required mechanical ventilation and died 19 days after admission. Of the 26 infected patients, 5 (19.2%) experienced asthma control deterioration, characterized as exacerbation that required treatment with systemic corticosteroids. The scheduled administration of the biological therapy was performed timely in all patients with the exception of 2, in whom it was postponed for 1 week according to their doctors' suggestion.

CONCLUSION: Our study confirms that despite the initial concerns, SARS-CoV-2 infection is not more common in asthmatics treated with biologics compared with the general population, whereas the use of biologic treatments for severe asthma during the COVID-19 pandemic does not seem to be related to adverse outcomes from severe COVID-19. © 2022 American

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Key words: Severe asthma; COVID-19; Biologics; Mepolizumab; Omalizumab; Benralizumab; Exacerbation; SARS-CoV-2

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),¹ continues to cause significant morbidity and mortality all over the world. The natural history of COVID-19 is characterized by 3 main phases, with different symptoms ranging from asymptomatic or mild disease to acute respiratory distress syndrome with multiorgan failure and shock.² The commonest cause of death in patients with severe COVID-19 is associated with lung involvement,³ and this is probably the reason why, in the beginning of the pandemic, respiratory diseases, including asthma, have been considered as potent risk factors for severe disease. Furthermore, because respiratory viral infections have been well recognized as risk factors for asthma exacerbations,^{4,5} it was initially hypothesized that SARS-CoV-2 infection would also act as an exacerbation trigger; however, up-to-date, relevant published reports studying asthmatic patients have provided controversial results on whether asthmatic patients are at increased risk of experiencing more severe disease.⁶⁻¹³ Similarly, although an early study has shown poor outcomes after SARS-CoV-2 infection in patients with severe asthma treated with biologics,⁷ several further case reports¹⁴⁻¹⁹ as well as recent studies in large cohorts^{20,21} have provided evidence that COVID-19 in severe asthmatics receiving different types of biological treatments is not associated with greater risk of hospitalization, intensive care unit (ICU) admission, or death.

In this multicentered study, we aimed to prospectively observe a cohort of severe asthmatics treated with biologics for the risk of SARS-CoV-2 infection, and COVID-19 severity and outcome and to assess any differences in all above with respect to the different biological treatments administered.

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TABLE 1. Demographic and functional characteristics of the study participants according to the use of biological therapy

Variable	All (N = 591)	Omalizumab (N = 219)	Mepolizumab (N = 358)	Benralizumab (N = 14)	P value
Age (y)	57.0 (47.0, 68.8)	55.0 (46.0, 64.0)	60.0 (50.0, 69.0)	43.0 (37.0, 49.7)	<.001
Sex (female), n (%)	386 (65.3)	130 (59.4)	247 (69.0)	9 (64.3)	.062
Smoking status (current smokers), n (%)	128 (21.7)	36 (16.4)	87 (24.3)	5 (35.7)	.131
Pack-years	0.0 (0.0, 11.0)	0.0 (0.0, 10.0)	0.0 (0.0, 13.0)	5.0 (0.0, 15.0)	.312
BMI (kg/m ²)	27.4 (24.6, 32.0)	27.0 (25.0, 32.0)	27.0 (24.6, 32.4)	23.7 (22.0, 30.7)	.241
FEV ₁ * (% pred)	76.0 (64.7, 90.2)	74.0 (64.0, 91.0)	78.0 (64.5, 90.0)	77.0 (64.8, 98.0)	.870
Asthma duration (y)	22.0 (12.0, 34.0)	24.0 (15.0, 37.0)	20.0 (10.0, 31.3)	13.0 (6.0, 26.3)	<.001
Asthma treatment, n (%)					
LABA	360 (60.9)	134 (61.2)	217 (60.6)	9 (64.3)	.914
LAMA	285 (48.2)	81 (37.0)	197 (55.0)	7 (50.0)	<.001
LTRA	214 (36.2)	82 (37.4)	126 (35.2)	6 (42.9)	.571
ICS	591 (100)	219 (100)	358 (100)	14 (100)	1.000
High ICS dose†, n (%)	542 (91.7)	191 (87.2)	337 (94.1)	14 (100)	.007
Use of nasal corticosteroids, n (%)	151 (25.5)	73 (33.3)	77 (21.5)	1 (7.1)	.005
Atopy, n (%)	305 (51.6)	219 (100)	82 (22.9)	4 (28.6)	<.001
Duration of treatment with biologics (mo)	27.0 (13.0, 40.0)	38.0 (13.0, 94.0)	24.0 (15.0, 36.0)	12.0 (9.7, 17.3)	<.001
OCS maintenance therapy	106 (17.9)	40 (18.3)	62 (17.3)	4 (28.6)	.553
OCS dose (mg of prednisolone or equivalent)	5.0 (5.0, 10.0)	5.0 (5.0, 10.0)	5.0 (2.5, 10.0)	3.8 (2.5, 5.0)	.167
SARS-CoV-2 infected, n (%)	26 (4.4)	9 (4.1)	16 (4.5)	1 (7.1)	.861
Hospitalization for COVID-19, n (%)	9 (1.5)	—	9 (2.5)	0 (0.0)	N/A
Duration of hospital stay (d)	13.5 (4.3, 19.8)	—	13.5 (4.3, 19.8)	—	N/A
ICU admission for COVID-19, n (%)	1 (0.2)	—	1 (6.2)	—	N/A
Death from COVID-19, n (%)	1 (0.2)	—	1 (6.2)	—	N/A

Data are presented as n (%) or median (interquartile range) unless otherwise indicated.

Bold indicates statistically significant differences.

BMI, Body mass index; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; ICU, intensive care unit; LABA, long-acting β-agonists; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonists; N/A, not applicable; OCS, oral corticosteroids.

*FEV₁ measure was performed in the last 6 months before inclusion to the database.

†ICS dose was calculated according to the GINA report dosing tables.

METHODS

Study design

On March 2020, once the first COVID-19 cases were reported in Greece, respiratory physicians all over the country, involved in the treatment of severe asthmatic patients, were called to provide data of their patients currently being treated with biologics in their outpatient clinics and offices. Eligible patients should be over 18 years old, have a confirmed diagnosis of severe asthma according to ERS/ATS criteria,²² and should be currently treated with biologics for at least 4 months, according to 2020 GINA guidelines.²³ Exclusion criteria included refusal of the patient to participate in the study, non-adherence to treatment, and drug interruption for any reason (apart from treatment being postponed due to COVID-19 according to the physician's decision). Physicians were also asked to prospectively follow up their patients, to contact them regularly, and to perform molecular tests for SARS-CoV-2 in case a patient presented any suspicious symptoms. Patients were also asked to contact their treating physicians in case they experience any relevant symptoms. All cases found positive for SARS-CoV-2 infection were recorded, and data on asthma deterioration as well as disease severity and outcomes were also prospectively collected. All patients were prospectively followed up to April 2021 when vaccination was initiated for patients with severe asthma.

Data collection

In all patients, demographic characteristics, disease duration, forced expiratory volume in 1 second (measured during the previous 6 months), and treatments for asthma (including inhaled therapies and oral corticosteroid use) were recorded. Furthermore, data on the type of biologic therapy and treatment duration were also recorded. In every case the patient experienced suspicious symptoms of SARS-CoV-2 infection (such as fever, cough, tiredness, loss of taste or smell, sore throat, headache, aches and pains, diarrhea, difficulty in breathing or shortness of breath, chest pain, loss of speech or mobility, and confusion), a polymerase chain reaction (PCR) test was performed, and in cases SARS-CoV-2 infection was documented, the physicians were asked to provide data regarding disease severity, need for hospital and/or ICU admission, occurrence of symptoms suggesting an asthma exacerbation, medication postponement due to SARS-CoV-2, and the outcome of the patient. Asthma exacerbation was defined as deterioration of asthma symptoms (ie, dyspnea, cough, wheezing, and/or chest tightness), which required an increase in the use of bronchodilators together with treatment with antibiotics and/or systemic corticosteroids.²³ For patients who were admitted to the hospital, information regarding the presence of SARS-CoV-2-related pneumonia, duration of hospital stay, need for mechanical ventilation and/or ICU admission,

TABLE II. Comparison of patients experiencing and not experiencing SARS-CoV-2 infection

Variable	Patients with SARS-CoV-2 infection (N = 26)	Patients without SARS-CoV-2 infection (N = 565)	P value
Age (y)	55.5 (46.7, 66.5)	58.8 (47.0, 68.0)	.725
Sex	15 (57.7)	371 (65.7)	.404
Smoking status (current smokers)	8 (30.8)	120 (21.2)	.307
Pack-years	0.0 (0.0, 12.5)	0.0 (0.0, 11.3)	.941
BMI (kg/m ²)	26.0 (24.6, 30.7)	27.5 (24.6, 32.0)	.313
FEV ₁ (% pred)	75.2 (61.9, 87.5)	76.0 (65.0, 90.9)	.506
Asthma duration (y)	23.0 (7.7, 36.3)	22.0 (12.0, 34.0)	.620
Type treatment with biologic			.861
Omalizumab	9 (34.6)	210 (37.2)	
Mepolizumab	16 (61.5)	342 (60.5)	
Benralizumab	1 (3.8)	13 (2.3)	
Duration of treatment with biologics	12.0 (7.0, 25.0)	28.0 (14.0, 31.0)	<.001
High ICS dose*, n (%)	24 (92.3)	518 (91.7)	.910
Use of nasal corticosteroids, n (%)	7 (26.9)	144 (25.5)	.954
Atopy, n (%)	10 (38.5)	295 (52.2)	.078
OCS maintenance therapy	3 (11.5)	103 (18.2)	.385
OCS dose (mg of prednisolone or equivalent)	5.0 (5.0, 5.0)	5.0 (5.0, 10.0)	.650

Data are presented as n (%), or median (interquartile range) unless otherwise indicated.

Bold indicates statistically significant differences.

BMI, Body mass index; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; OCS, oral corticosteroids.

*ICS dose was calculated according to the GINA report dosing tables.

and the patient's outcome was also provided by the treating physician. The study protocol was approved by the local ethics committee of "Attikon" University Hospital, and all patients provided their consent to be included in the database.

Statistical analysis

Categorical variables are presented as n (%), whereas numerical variables are presented as mean ± standard deviation or median (interquartile ranges [IQR]) for normally distributed and skewed data, respectively. Normality of distributions was checked with the Kolmogorov-Smirnov test. Comparisons of variables between groups were performed using the Mann-Whitney *U*-test and the Kruskal-Wallis test, as appropriate. Statistical significance was established at *P* < .05. Data were analyzed using SPSS 17.0 for Windows (SPSS Inc., Chicago, Ill).

RESULTS

A total of 23 asthma clinics from Greece provided data of 591 severe asthmatic patients treated with biologics. The mean age of the patients was 57 ± 14 years; 63.5% of included subjects were female. The mean asthma duration was 24 ± 14 years. Of the patients included in the study, 219 (37.1%) were receiving omalizumab, whereas 358 (60.6%) and 14 (2.4%) were receiving mepolizumab and benralizumab, respectively. The low number for benralizumab-treated patients was attributed to a late release of the drug in Greece according to regulatory authorities. A total of 305 (51.5%) patients were atopic. Patients receiving omalizumab were as expected atopic, whereas among those receiving mepolizumab and benralizumab, atopy was present in 22.9% and 28.6%, respectively. The mean duration of therapy with biologics was 36 ± 13 months. A SARS-CoV-2 infection was documented in 26 (4.4%) patients, 9 (34.6%) of whom required hospitalization for severe COVID-19. Concerning patients'

characteristics, mepolizumab recipients were significantly older, whereas those who were administered omalizumab had a longer asthma duration, received less frequently long-acting muscarinic antagonists (LAMAs), and were on biologic therapy for a significantly longer period of time. Demographic and functional characteristics of the study participants are shown comprehensively in Table I.

Comparison of patients according to SARS-CoV-2 infection, type of biological treatment, and requirement of hospital admission

Patients infected from SARS-CoV-2 were receiving biologic therapy for a shorter period of time (months) compared with those not infected, that is, median (IQR): 12.0 (7.0, 25.0) vs 28.0 (14.0, 41.0), *P* < .001. No other differences were observed between these 2 groups of patients, as shown in Table II.

Among the 26 patients experiencing COVID-19, omalizumab had been administered in 9 (34.6%) patients, whereas 16 (61.5%) had been receiving mepolizumab and 1 (3.9%) patient had been receiving benralizumab. Patients with COVID-19 receiving omalizumab were mainly male and were more often receiving oral corticosteroids, in contrast to patients receiving the other 2 types of biologics.

Nine patients required hospital admission due to COVID-19, with most of them being female, 8 of 9 patients (88.8%). All hospitalized patients had clinical and radiological manifestations of pneumonia. Asthma duration (years) was significantly longer in patients who required hospitalization compared with those who did not (median [IQR]: 35.0 [23.5, 41.0] vs 10.0 [6.5, 25.5], *P* = .009). Finally, hospitalized patients were more frequently receiving LAMAs (77.8% vs 35.5%, for patients requiring and not requiring hospital admission, respectively, *P* = .039). Interestingly, all patients requiring hospital admission were on treatment with mepolizumab, and 1 patient in this

TABLE III. Comparison of patients experiencing SARS-CoV-2 infection according to the type of biologic

Variable	Omalizumab SARS-CoV-2 infected (N = 9)	Mepolizumab SARS-CoV-2 infected (N = 16)	Benralizumab SARS-CoV-2 infected (N = 1)	P value
Age (y)	55.0 (40.0, 65.0)	57.5 (48.5, 70.3)	52.0	.416
Sex (female), n (%)	2 (22.2)	12 (75.0)	1 (100)	.026
Smoking status (current smokers), n (%)	1 (11.1)	7 (43.8)	1 (100)	.188
Pack-years	0.0 (0.0, 3.8)	2.5 (0.0, 21.5)	0.0	.295
BMI (kg/m ²)	26.0 (25.5, 30.7)	25.3 (24.6, 33.9)	20.0	.297
FEV ₁ (% pred)	77.0 (66.4, 99.5)	74.1 (55.0, 82.0)	89.0	.279
Asthma duration (y)	23.0 (10.0, 33.0)	26.5 (7.3, 38.8)	6.0	.439
Duration of treatment with biologics(mo)	11.0 (7.0, 13.0)	15.5 (9.3, 34.0)	6.0	.109
High ICS dose*, n (%)	8 (88.9)	15 (93.8)	1 (100)	.870
Use of nasal corticosteroids, n (%)	2 (22.2)	5 (31.3)	0 (0%)	.692
Atopy, n (%)	9 (100)	1 (6.3)	0 (0%)	<.001
OCS maintenance therapy	1 (11.1)	1 (6.3)	1 (100)	.017
OCS dose (mg of prednisolone or equivalent)	5.0 (5.0, 5.0)	5.0 (5.0, 5.0)	5.0	1.000
Hospitalization for COVID-19, n (%)	0 (0.0)	9 (56.3)	0 (0.0)	N/A
Duration of hospital stay (d)	N/A	13.5 (4.3, 19.8)	N/A	N/A
ICU admission for COVID-19, n (%)	0 (0.0)	1 (6.2%)	0 (0.0)	N/A
Death from COVID-19, n (%)	0 (0.0)	1 (6.2%)	0 (0.0)	N/A

Data are presented as n (%), or median (interquartile range) unless otherwise indicated.

Bold indicates statistically significant differences.

BMI, Body mass index; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; ICU, intensive care unit; N/A, not applicable; OCS, oral corticosteroids.

*ICS dose was calculated according to the GINA report dosing tables.

group was admitted and died in the ICU due to COVID-19 complications.

Finally, there was no difference in atopic status between patients infected and not infected from COVID 19 and those who required hospitalization due to severe COVID-19 compared with those who were not hospitalized. Comparisons of patients infected from SARS-CoV-2 according to the type of biological treatment and requirement of hospital admission are presented in Tables III and IV, respectively.

Asthma exacerbations and biologic administration during SARS-CoV-2 infection

Among patients infected from SARS-CoV-2, biologic treatment administration was delayed for 7 days in 2 patients, both of them on therapy with mepolizumab according to their treating physicians' personal decision, because there was no official guideline for such a practice. The first case concerned a 71-year-old male patient who had clinical symptoms of asthma exacerbation (defined as asthma control deterioration requiring treatment with systemic corticosteroids) and who also required hospital admission and supplemental oxygen administration due to COVID-19 pneumonia. The second case regarded a 58-year-old female patient who also had symptoms of asthma exacerbation but did not require hospital admission. In all other infected patients, the dose of the biologic was administered in their scheduled time, whereas it is important to mention that 2 of the hospitalized patients received their dose during hospital stay timely and without any complication. Of the patients who experienced symptoms of asthma exacerbations, only 1 was using nasal corticosteroids, and this patient did not require hospital admission.

Finally, except from the 2 aforementioned patients, 3 more patients (in total 5 of PCR+ patients, 19.2%) experienced an

asthma exacerbation; however, no hospital admission was required.

DISCUSSION

In our study, we have shown that treatment with biologics was not associated with an increased risk of SARS-CoV-2 infection compared with the general population. However, once infected, these patients seem to be at greater risk of hospital admission due to COVID-19 complications, whereas some also seem to lose asthma control and to experience symptoms of an asthma exacerbation. From the clinical experience in our country, we suggest that the scheduled dose of the biologic therapy could be administered on time, regardless of SARS-CoV-2 infection, as such a practice does not seem to result in adverse outcomes. Finally, all patients admitted to the hospital were under treatment with mepolizumab.

In our study, we showed that 26 of 591 patients (4.4%) in our cohort had a SARS-CoV-2 infection during the first 14 months of the pandemic, a prevalence which is in line with the estimated prevalence of COVID-19 in Greece at that time period (which varied between 1.9% and 6.01% depending on the season and lockdown imposition). Our findings are in accordance with previous studies showing a lower probability of the disease among asthmatics compared with the general population,^{10,20,21,24,25} suggesting that severe asthmatics treated with biologics are not at higher risk of getting infected. Potential reasons for this observation might include self-protection measures such as social distancing, lockdown restrictions, and hygiene rules, mainly due to awareness of viruses acting as a trigger for exacerbations.^{26,27} Another possible explanation is that the use of biological therapies results in better asthma control in patients with severe disease, thus avoiding the chronic or recurrent use of systemic corticosteroids, which is a predisposal factor

TABLE IV. Comparison of patients infected from SARS-CoV-2 according to the requirement of hospital admission

Variable	Infected patients requiring hospital admission (N = 9)	Infected patients not requiring hospital admission (N = 17)	P value
Age (y)	55.0 (51.0, 71.0)	56.0 (46.0, 65.5)	.458
Sex (female), n (%)	8 (88.8)	7 (41.2)	.019
Smoking status (current smokers), n (%)	4 (44.4)	4 (23.5)	.272
Pack-years	5.0 (0.0, 20.0)	0.0 (0.0, 11.3)	.488
BMI (kg/m ²)	24.6 (24.4, 33.7)	26.0 (25.0, 30.7)	.628
FEV ₁ (% pred)	65.0 (47.5, 84.0)	76.1 (64.6, 90.5)	.388
Asthma duration (y)	35.0 (23.5, 41.0)	10.0 (6.5, 25.5)	.009
Asthma treatment, n (%)			
LABA	7 (77.8)	12 (70.6)	.694
LAMA	7 (77.8)	6 (35.3)	.039
LTRA	5 (55.6)	4 (23.5)	.102
ICS	9 (100)	17 (100)	1.000
High ICS dose*	9 (100)	15 (88.2)	.284
Use of nasal corticosteroids, n (%)	3 (33.3)	4 (23.5)	.419
Atopy, n (%)	1 (11.1)	9 (52.9)	.097
Duration of treatment with biologics (mo)	19.0 (11.0, 36.5)	11.0 (7.0, 18.0)	.075
Type treatment with biologic			.014
Omalizumab	0 (0.0)	9 (52.9)	
Mepolizumab	9 (100)	7 (41.2)	
Benralizumab	0 (0.0)	1 (5.9)	
OCS maintenance therapy	1 (11.1)	2 (11.8)	.960
OCS dose (mg of prednisolone or equivalent)	5.0 (5.0, 5.0)	5.0 (5.0, 5.0)	1.000

Data are presented as n (%), or median (interquartile range) unless otherwise indicated.

Bold indicates statistically significant differences.

BMI, Body mass index; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; ICU, intensive care unit; LABA, long-acting β-agonists; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonists; OCS, oral corticosteroids.

*ICS dose was calculated according to the GINA report dosing tables.

for SARS-CoV-2 infection, due to decreased innate and acquired immunity.²⁰ Furthermore, it has been hypothesized that inhaled corticosteroids might also prevent or mitigate the development of coronaviruses infections, and thus, asthmatic patients treated with high doses of inhaled corticosteroids (like those included in our cohort) may have been protected from severe SARS-CoV-2 infection.^{6,28-30} Finally, it has been proposed that also mucus hypersecretion, which often exists in severe asthmatics, could possibly prevent distal viral penetration.¹¹

Previous studies, including various reports from different regions, have shown that underlying asthma is reported to account for 0.9% to 17% of hospitalized patients with COVID-19^{31,32} and that asthma severity seems to influence the duration of hospitalization because asthmatic patients treated in step 5 showed significant prolonged admission duration than those with step 1.⁶ In our cohort of severe asthmatics treated with biologics, 9 of the 26 infected patients (34.6%) required hospital admission, an incidence that is much greater than those reported from other severe asthma registries;^{24,33} however, the data on severe asthma and COVID-19 are scarce. Furthermore, because we have not evaluated significant differences in the baseline characteristics between patients who required hospital admission and those who did not, further research is needed to recognize the patients who are at greater risk for more severe COVID-19. In our cohort, only 1 patient, a 66-year-old woman with severe obesity (body mass index: 40.2 kg/m²) and cardiovascular comorbidities, was admitted in the ICU and finally died from COVID-19 complications, an observation that is also in

accordance with previous reports in which the worst outcomes were observed mainly in patients with major comorbidities.^{10,21}

The role of eosinophils in the host defense against viral infection has been widely described.³⁴ In patients with severe COVID-19, Th2 immune response is stimulated and eosinophils may play a central role in precipitating immune derangement and aggravating SARS-CoV-2–induced pneumonia.³⁵ At the beginning of the infection, an active migration of circulating eosinophils from the peripheral blood to target tissues occurs, followed by a decrease in the number of peripheral eosinophils.³⁴ Furthermore, an elevation in the eosinophils stimulating cytokines, such as IL-5 and granulocyte-macrophage colony-stimulating factor, has also been described.³⁶ Several laboratory reports of patients with severe COVID-19 have described a lower number of peripheral eosinophils compared with nonsevere cases,³⁷⁻⁴¹ whereas a retrospective study has suggested that pre-existing eosinophil count greater than or equal to 150/μL was protective from future COVID-19–associated hospitalization.⁴² Interestingly, in our cohort, all patients who were admitted to the hospital were receiving mepolizumab. This association might be related to the eosinophil depletion caused by this biologic, which according to the aforementioned studies might predispose to more severe disease.⁴³ Our observation is in accordance with a previous report from the Dutch Severe Asthma Registry in which 6 of 7 patients who required hospital admission for COVID-19 were treated with anti-IL-5 therapy, and 3 of them required admission in an ICU.⁷ However, we have to admit that patients on the mepolizumab group were older and the 1 patient who

died was obese and had severe comorbidities (obesity, diabetes, and cardiovascular disease), which is in accordance with the aforementioned Dutch cohort in which also the 1 deceased patient had obesity and diabetes.⁷

Five of the 26 SARS-CoV-2–infected patients in our cohort experienced symptoms of exacerbation during infection, 2 of them being hospitalized due to COVID-19 pneumonia, whereas the remaining 3 did not require hospital admission, neither for COVID-19 nor for the asthmatic exacerbation. This finding comes in contrast with reports from previous studies suggesting that SARS-CoV-2 is not a cause of asthma exacerbations;³³ however, as the number of exacerbating patients in our study is small, and the management of exacerbations was based on the by-phone evaluation of patients by the treating physician, the potential of overtreatment with systemic corticosteroids cannot be excluded.

In our study, none of the patients receiving omalizumab required hospital admission after SARS-CoV-2 infection. It has been described that respiratory allergies and allergen exposures are associated with a significant reduction in angiotensin-converting enzyme 2 expression, which is the cellular receptor for SARS-CoV-2,⁴⁴ and thus the virus cannot easily penetrate the respiratory system. Furthermore, although in allergic subjects, IgE receptor cross-linking on plasmacytoid dendritic cells (pDCs) suppresses the antiviral activity of pDCs,⁴⁵ when these patients are treated with omalizumab, the blockage of the circulating IgE leads to a long-lasting reduction of its production and a decrease in the expression of IgE receptors on pDCs, a phenomenon that might generally strengthen the antiviral immune responses.⁴⁶ In this regard, the presence of atopy in combination with omalizumab therapy might have exhibited a somehow protective role against severe COVID-19. On the other hand, nonallergic asthma patients are usually older, and comorbidities such as obesity and diabetes, due to chronic subclinical inflammation as well as chronic systemic corticosteroid use, are more often making these patients more vulnerable to severe COVID-19.⁴⁷ “However, although no significant difference was observed between patients who required hospitalization because of severe COVID-19 compared to those who were not hospitalized, the small number of infected patients and the even smaller number of patients who required hospital admission cannot lead to safe conclusions.”

In our cohort, only 2 patients did not receive their scheduled dose of biologic during SARS-CoV-2 infection on time (they both received it 7 days later). Although there is no official guideline on whether the biologic treatment should be postponed during SARS-CoV-2 infection, it has been suggested that treatments with biologics during the COVID-19 pandemic appear to be safe and can be administered normally, but should be interrupted in cases of confirmed SARS-CoV-2 infection.⁴⁸ At the time of the design of our study, the aforementioned recommendation did not exist and the treating physician was free to decide whether to postpone or not the biologic administration and, in most cases, scheduled administration was decided even in patients who were hospitalized for severe COVID-19. Although we must admit that our data are limited and our study does not include a control arm, it seems that these decisions did not lead to adverse outcomes. Moreover, in our opinion, this strategy might have contributed in maintenance of asthma control during SARS-CoV-2 infection in most patients.

Our study has several limitations. First, molecular tests were performed only in symptomatic patients. According to that, it is possible that a number of patients who were infected but were completely asymptomatic may have not been detected and thus were not included in the study. However, the treating physicians were instructed to perform PCR tests in any patient with symptoms suggestive of SARS-CoV-2 infection, and all patients reported as COVID-19 cases had a confirmed diagnosis. On the other hand, one advantage of our study is that all patients with symptoms had a molecular diagnosis of SARS-CoV-2 infection, and diagnosis was not based only on suggestive symptoms. A second limitation is that only a minority of patients were receiving benralizumab. The reason for this is that benralizumab therapy was not yet approved in our country during the study period and the few patients receiving such treatment were those who received the antibody through a preapproval access program. However, we have decided to include those patients in order to have a more general picture of the outcomes of SARS-CoV-2 infection in patients with severe asthma treated with biologics. Furthermore, although results have not been checked for possible confounders—demographic or clinical—that could be driving the conclusions as has been shown in previous studies,^{49,50} the prospective design of the study provides a general picture of the risk of severe asthmatics treated with biologics regarding the risk of SARS-CoV-2 infection and the infection outcome. Finally, in accordance with previous studies, we have also shown that treatment with biologics in patients with severe asthma does not seem to be related to adverse outcomes from severe COVID-19. However, their possible protective role against adverse COVID-19 outcomes cannot be documented by the data of this study.

In conclusion, our study confirms that the use of biologics for the treatment of severe asthma is safe during the pandemic, and despite the initial concerns, COVID-19 is not more common in asthmatics treated with biologics compared with general population. We believe that it would be interesting to study the outcomes of the same cohort of patients during the vaccination period, when a high coverage of this vulnerable population has been achieved. Although some patients have experienced symptoms of asthma exacerbation during COVID-19, in the great majority, infection did not result in loss of control and scheduled administration of biologics was not interrupted. Clinicians should follow the current guidelines regarding the treatment of severe asthmatics and retain a close monitoring of the infected patients, in order to timely recognize those with more severe COVID-19 who will require hospital admission and special care.

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