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Clinical characteristics in 545 patients with severe asthma on biological treatment during the COVID-19 outbreak

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Clinical Implications

- This study aimed to determine the rate of severe acute respiratory syndrome coronavirus 2 infection in Spanish patients with severe asthma under biological treatment and to examine whether the rates and severity of severe acute respiratory syndrome coronavirus 2 infection differ among several antiasthma biological drugs and between patients with severe asthma without biologicals. With the data from this cohort, we hypothesize that biological treatment for severe uncontrolled asthma does not represent a risk factor for coronavirus disease 2019 infection or its severity and that there are no significant differences among the different biologic drugs used.

On March 11, 2020, the World Health Organization declared the coronavirus disease 2019 (COVID-19) pandemic, caused by a new coronavirus previously unidentified in humans, officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Virus Taxonomy.[1] The presence of chronic obstructive pulmonary disease has been associated with an increased risk of developing a severe infection. There is still-controversial evidence regarding the impact of asthma and its treatment on the clinical course of COVID-19.[2] It is hypothesized that patients with asthma are protected from COVID-19 because of the low expression of angiotensin-converting enzyme 2 (ACE2) in bronchial epithelial cells. Tissues from patients with high-allergy type 2 cytokines were studied to show significantly lower ACE2 expression, with ACE2 expression being inversely correlated with type 2 cytokine levels.[3]

The objective of this study was to determine the rate of SARS-CoV-2 infection in patients with severe asthma under biological treatment and to examine whether the rates and severity of SARS-CoV-2 infection differed among different antiasthma biological drugs and with patients with severe asthma with no biological treatment.

We conducted a multicenter retrospective cohort study of 545 adult patients with severe asthma under biological treatment from 9 university hospitals belonging to the Spanish Network of Asthma. Standard data collection methods were used in all participating research centers. The local clinical research ethics committees in all participating hospitals approved the project. The study was conducted following the principles outlined in the Declaration of Helsinki. The demographic, functional, and clinical characteristics of the included patients are summarized in Table I.

Asthma severity has been assigned according to the classification of the Global INitiative for Asthma.[4] Comparisons between more than 2 groups of Gaussian samples were performed using ANOVA with Bonferroni post hoc test. Kruskal-Wallis with Dunn post hoc test was applied for non-Gaussian distributions. To study whether the frequency of observations is significantly different between 2 or more groups, the exact Fischer test has been used. The possibility that COVID-19 occurs in one treatment group versus the risk that occurs in another treatment group has been expressed as odds ratio (OR). A P value of less than .05 was considered significant. Statistical calculations were performed with GraphPad Prism 8.4 (GraphPad Software Inc, San Diego, Calif).

In this cohort, a total of 545 patients with severe asthma under biological treatment were included between March and June 2020: 263 patients treated with omalizumab (48.3%), 154 with mepolizumab (28.2%), 98 with benralizumab (18.0%), 26 with reslizumab (4.8%), and 4 with dupilumab (0.7%). All patients were treated according to Global INitiative for Asthma guidelines,[4] including high-dose inhaled corticosteroids. The groups were homogeneous in terms of sex, lung function, or body mass index. Statistically significant differences were found in the higher prevalence of older age and hypertension in patients treated with mepolizumab ($P < .001$). Among the 545 patients, 35 (6.4%) were diagnosed with COVID-19. Only those patients who presented with compatible symptoms with COVID-19 (fever, general malaise, increased cough, dyspnea, or diarrhea) were tested. The diagnosis was confirmed in 17 of them by PCR and the remaining 18 were diagnosed using antibodies test and compatible clinical symptoms, because PCR test was not available at the time of initial diagnosis. The characteristics of the patients diagnosed with COVID-19 are summarized in Table II. Eight patients (22.9%) required hospital admission. Among hospital-admitted patients, 7 presented with pneumonia and 2 were severe, with one being treated with omalizumab requiring admission to the intensive care unit and the other, being treated with mepolizumab, dying as a result of COVID-19 complications. This death occurred in an 82-year-old patient with hypertension, diabetes, and ischemic cardiopathy. The OR and beta error were analyzed in the different treatment groups (Table II), finding a higher probability, but not significant, of appearance of COVID-19 infection in the reslizumab group (OR, 1.99; $P = .23$; β error, 0.73). This result may be biased by

TABLE I. Clinical characteristics of patients with severe asthma under biological treatment included in this cohort

Characteristic	Drug					*P* Value
	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	
N (%)	263 (48.326)	154 (28.3)	26 (4.8)	98 (18)	4 (0.7)	
Sex: female, N (%)	164 (63.00)	103 (66)	17 (65)	67 (70)	3 (75.0)	NS
Age (y), mean ± SD	52.108 ± 16.33	58.7 ± 1.5	55 ± 14.4	56.13 ± 10.63	42.0 ± 7.5	<.0001
BMI, mean ± SD	27.41 ± 5.878	27.7 ± 5.4	27.6 ± 5.4	29.11 ± 8.80	30.7 ± 4.3	NS
FEV_1%, mean ± SD	78.107 ± 22.105	79.2 ± 22.3	76.3 ± 13.8	72.435 ± 18.217	93.0 ± 18.7	NS
Arterial hypertension, N (%)	61 (23.219)*	62 (40.3)†	4 (15.4)	27 (27.60)	0	<.01* <.0001†
Diabetes, N (%)	22 (8.437)	9 (5.8)	2 (7.7)	5 (5.10)	0	NS

BMI, Body mass index; *NS*, not statistically significant.
*$P < .01$.
†$P < .0001$.

TABLE II. Clinical and epidemiologic characteristics of patients with severe asthma diagnosed with COVID-19

Characteristic	Drug				*P* Value
	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	
N (%)	14 (5.32)	11 (7.14)	3 (11.54)	7 (7.14)	
Sex: female, N (%)	10 (71.43)	5 (45.50)	1 (33.00)	5 (71.40)	NS
BMI, mean ± SD	26.71 ± 6.30	26.04 ± 4.26	25.73 ± 2.40	27.00 ± 4.70	NS
Age (y), mean ± SD	46.36 ± 12.21	56.45 ± 5.30	49 ± 12.12	60.29 ± 11.30	NS
FEV_1%, mean ± SD	84.52 ± 22.65	83.35 ± 21.02	76.00 ± 2.83	85.97 ± 7.38	NS
Arterial hypertension, N (%)	3 (21.43)	4 (36.40)	0 (0.0)	2 (28.60)	NS
Diabetes, N (%)	0 (0.0)	1 (9.09)	0 (0.0)	0 (0.0)	NS
CRSwNP, N (%)	8 (57.14)	8 (72,73)	3 (100)	3 (42.86)	NS
Hospital admission	1 (11.1)	3 (33.33)	2 (66)	2 (28.60)	NS
ICU admission, N (%)	1 (7.14)	0 (0.0)	0 (0.0)	0 (0.0)	NS
Exitus, N (%)	0 (0.0)	1 (9.09)	0 (0.0)	0 (0.0)	NS
OR	0.70	1.18	1.99	1.15	
P value	.38	.67	.23	.82	
95% CI	0.35-1.38	0.55-2.41	0.60-6.36	0.46-2.74	
β error	0.83	0.92	0.73	0.93	

BMI, Body mass index; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *ICU*, intensive care unit; *OR*, odds ratio; *NS*, not statistically significant.
The possibility that COVID-19 occurs in one treatment group vs the risk that occurs in another treatment group has been expressed as OR. The OR for each group compares that group to all other groups combined.

the low number of patients included on treatment with reslizumab. The OR was also calculated by grouping the 3 biologic drugs with anti−IL-5 action (mepolizumab, reslizumab, benralizumab) versus omalizumab with a result of 1.45 (95% CI, 0.7367-2.938), without finding statistical significance ($P = .30$).

When comparing the characteristics of patients of this cohort with patients with asthma with different severity and without biological treatment hospitalized for COVID-19 in Spain,[5] we did not find differences in terms of severity of COVID-19, presence of comorbidities, intensive care unit admissions, or mortality (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Of note, SARS-CoV-2 seroprevalence in Spain's general population is 5.2%,[6] similar to that found in this cohort (6.4%).

The relationship between asthma and COVID-19 infection is controversial. Some articles suggest a low prevalence of asthma among patients with COVID-19, as well as the lack of a statistically significant relationship between a history of asthma and mortality, irrespective of COVID-19 status.[3,5] However, other studies report that asthma may increase COVID-19 susceptibility and disease severity.[7] Other European reports on patients with asthma with COVID-19 show similar trends as those found in Spain[8] and in other series published in the United States.[9] With the data from this cohort, we hypothesize that biological treatment for severe uncontrolled asthma does not represent a risk factor for COVID-19, in terms of infection or severity, and there are no significant differences among patients treated with different biological drugs.

In conclusion, and to our knowledge, this is the first large sample report that found that patients with severe asthma requiring a biologic treatment do not have an increased risk of COVID-19 infection or greater disease severity and mortality. In addition, there were no differences among biological drugs used for asthma treatment.

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ONLINE REPOSITORY

TABLE E1. Comparison of patients with asthma hospitalized with COVID-19: Patients with asthma treated with biologics in this study and a cohort of patients with asthma with no biologic treatment[E1]

Clinical features	Patients with asthma treated with biologics (n = 8)	Patients with asthma with no biologic treatment (n = 11)
Severe asthma	8	0
Moderate asthma	0	5
Mild	0	6
Age (y), mean ± SD	62.8 ± 13.6	57.7 ± 14.6
Sex: female	21 of 35 (60%)	8 of 11 (73%)
Body mass index	27 ± 3.7	29.9 ± 4.6
Pneumonia	7 of 8 (87%)	9 of 11 (81%)
ICU admission	1 of 8 (12%)	2 of 11 (18%)
Intubation	1 of 8 (12%)	1 of 11 (9%)
Exitus	1 of 8 (12%) (with non-T2 comorbidities)	2 of 11 (18%) (both with non-T2 comorbidities)

ICU, Intensive care unit.

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