Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Clinical Communications

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

Manuel Jorge Rial, MDa,*, Marcela Valverde, MDh,*
Victoria del Pozo, PhDc,a
Francisco Javier González-Barcala, MD, PhDc,d
Carlos Martínez-Rivera, MD, PhDc,e
Xavier Muñoz, MD, PhDc,f,g
José María Olaguibel, MD, PhDc,h
Vicente Plaza, MD, PhDc,j
Santiago Quirce, MD, PhDc,j
José María Olaguibel, MD, PhDc,h
Irina Bobolea, MD, PhDc,l,m,n
César Picado, MD, PhDc,l,m,n
Elena Curto, MDc,i
Carlos Martínez-Rivera, MD, PhDc,e
Javier Domínguez-Ortega, MD, PhDc,i
Joaquín Mullol, MD, PhDc,k,l,m
César Picado, MD, PhDc,l,m,n
Antonio Valero, MD, PhDc,k,l,m,n
Irina Bobolea, MD, PhDc,l,m,n
Ebymar Arismendi, MDc,l,m,n
Paula Ribó, MDc,l,m,n
and Joaquín Sastre, MD, PhDc,l,m,n

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
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, 0.35-2.938), 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, 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%, 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. However, other studies report that asthma may increase COVID-19 susceptibility and disease severity. Other European reports on patients with asthma with COVID-19 show similar trends as those found in Spain and in other series published in the United States. 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.

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

| Characteristic                   | Omalizumab | Mepolizumab | Reslizumab | Benralizumab | Dupilumab | P Value |
|---------------------------------|------------|-------------|------------|--------------|-----------|---------|
| N (%)                           | 263 (48.32) | 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      |
| FEV1%, 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*   |
| 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                   | Omalizumab | Mepolizumab | Reslizumab | Benralizumab | P Value |
|---------------------------------|------------|-------------|------------|--------------|---------|
| 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      |
| FEV1%, 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      |
| Exits, 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; **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 probability and disease severity. Other European reports on patients with asthma with COVID-19 show similar trends as those found in Spain and in other series published in the United States. 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.
Received for publication June 29, 2020; revised August 28, 2020; accepted for publication September 23, 2020. 

Available online October 9, 2020. 

Corresponding author: Manuel Jorge Rial, MD, Allergy Department, University Hospital Fundación Jiménez Díaz, Av. de los Reyes Católicos, 2, 28040 Madrid, Spain. E-mail: manuterial@gmail.com.

2213-2198/C211 © 2020 American Academy of Allergy, Asthma & Immunology 

https://doi.org/10.1016/j.jaip.2020.09.050

REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.

2. Matsumoto K, Saito H. Does asthma affect morbidity or severity of COVID-19? J Allergy Clin Immunol 2020;146:55-7.

3. Kimura H, Francisco D, Conway M, Martinez FD, Vercelli D, Billheimer D, et al. Type 2 inflammation modulates ACE2 and TMPRSS2, mediators of SARS-CoV-2 entry and fusion, in airway epithelial cells. J Allergy Clin Immunol 2020;146:80-88.e8.

4. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2019. Available from: www.ginasthma.org. Accessed July 16, 2020.

5. Barroso B, Valverde-Monge M, Cañas JA, Rodrigo-Muñoz JM, González-Cano B, Villalobos-Violan V, et al. Presenting prevalence, characteristics and outcome of asthmatic patients with T2 diseases in hospitalized subjects with COVID-19 in Madrid, Spain. J Investig Allergol Clin Immunol 2020;30:382-4.

6. Ministry of Science and Innovation and Ministry of Health, Government of Spain. Estudio Ene-COVID19: Segunda Ronda Estudio Nacional de Sero-Epidemiología de la Infección por SARS-COV-2 en España. Available from: https://www.mscbs.gob.es/ciudadanos/enecovid/docs/ESTUDIO_ENE-COVID19_SEGUNDA_RONDA_INFORME_PRELIMINAR.pdf. Accessed July 16, 2020.

7. Hegde S. Does asthma make COVID-19 worse? Nat Rev Immunol 2020;20:352.

8. Domínguez-Ortega J, López-Carrasco V, Barranco P, Illin M, Luna JA, Romero D, et al. Early experiences of SARS-CoV-2 infection in severe asthmatics receiving biologic therapy. J Allergy Clin Immunol Pract 2020;8:2784-6.

9. Chhiba KD, Patel GB, Vu THT, Chen MM, Guo A, Kullaya E, et al. Prevalence and characterization of asthma in hospitalized and non-hospitalized patients with COVID-19. J Allergy Clin Immunol 2020;146:307-314.e4.
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.

REFERENCE

E1. Barroso B, Valverde-Monge M, Cañas JA, Rodrigo-Muñoz JM, Gonzalez-Cano B, Villalobos-Violan V, et al. Presenting prevalence, characteristics and outcome of asthmatic patients with T2 diseases in hospitalized subjects with COVID-19 in Madrid, Spain. J Investig Allergol Clin Immunol 2020;30:382-4.