Clinical features in patients with COVID-19 treated with biologics for severe asthma

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Background: Few studies have reported the clinical features of patients with coronavirus disease 2019 (COVID-19) who were treated with biologics for severe asthma (SA).
Objective: We sought to elucidate the clinical features and mutual interaction between COVID-19 and SA in terms of disease severity during the Omicron epidemic.
Methods: A retrospective study among patients with SA who received any biologic therapy from January 2022 to February 2023 at Jikei University Hospital (Tokyo, Japan) was performed.
Results: Among 99 patients with SA, 22 women and 6 men suffered from COVID-19, and 1 woman was reinfected. The severity of COVID-19 was mild in 26 cases and moderate in 3 cases. The number of vaccinations among patients with mild COVID-19 was significantly higher than that among patients with moderate COVID-19 (3.0 ± 1.4 vs 1.0 ± 1.0; $P = .03$). Asthmatic exacerbations were mild in 9 cases and moderate in 7 cases. The severity of asthmatic exacerbations was significantly associated with the Asthma Control Test score at baseline (no/mild/moderate exacerbation = 23.0 ± 2.3/18.1 ± 5.3/15.0 ± 4.3; $P = .004$; Kruskal-Wallis test). By means of a multivariate logistic regression analysis, a lower number of vaccinations was a significant risk factor for COVID-19 progression (odds ratio, 0.64; 95% CI, 0.46-0.91; $P = .006$).
Conclusions: During the Omicron epidemic, the onset and severity of COVID-19 were related to the number of vaccinations, and the severity of asthmatic exacerbations caused by COVID-19 was associated with the Asthma Control Test score at baseline and the number of vaccinations but not with the use of biologics. (J Allergy Clin Immunol Global 2024;3:100219.)

Key words: *COVID-19, severe asthma, biologics, vaccine, exacerbation, asthma control*

Abbreviations used

ACT:	Asthma Control Test
AEx:	Asthmatic exacerbation
BEC:	Peripheral blood eosinophil count
COVID-19:	Coronavirus disease 2019
FENO:	Fractional exhaled nitric oxide
OCS:	Oral corticosteroid
SA:	Severe asthma
SARS-CoV-2:	Severe acute respiratory syndrome coronavirus 2

Coronavirus disease 2019 (COVID-19), which was first detected in Wuhan, China, in 2019, resulted in a pandemic. According to the World Health Organization, 771 billion confirmed cases, including 6.97 million deaths, had been reported worldwide by October 21, 2023.[1]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of COVID-19, is a single-stranded, positive-sense RNA. It has mutated repeatedly, and its infectivity, virulence, and ability to escape immune system responses continue to change. At the end of 2021, the Omicron variant emerged as the dominant strain of COVID-19. Its virulence, infectivity, and ability to escape immune system responses resulted in an explosive increase in the number of patients and deaths, which were mainly attributed to the worsening of underlying diseases. The following factors have been reported to be associated with the severity and prognosis of COVID-19: advanced age, hypertension, chronic kidney disease, malignancy, immunodeficiency status, obesity, and chronic respiratory disease.[2,3] However, the prevalence of asthma among patients with COVID-19 tended to be lower than the regional asthma prevalence.[4] It has been suggested that eosinophils may act protectively against SARS-CoV-2 infection, and type 2 inflammatory cytokines such as IL-4 and IL-13 may prevent SARS-CoV-2 binding through downregulation of the angiotensin-converting enzyme 2 receptor.[5-8] Accordingly, apart from chronic respiratory diseases such as chronic obstructive pulmonary disease, it is likely that bronchial asthma pathology may not be directly linked to COVID-19 severity.[9] With respect to asthma treatment, it was initially speculated that biologics that suppress type 2 inflammation could adversely affect COVID-19 infection and severity.[10] Recent reports have shown that biologics for severe asthma (SA) may not be related to the risk of COVID-19 infection or disease severity, except in asthmatic patients requiring maintenance oral corticosteroids (OCSs).[11,12] However, the exact role of biologics for SA in the severity of COVID-19 and asthma exacerbation during the Omicron variant epidemic remains obscure, especially in a real-world setting.

We therefore conducted this single-center retrospective study to elucidate the risk factors associated with the onset and severity of COVID-19 and asthmatic exacerbation (AEx) in patients with SA treated with biologics.

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Received for publication August 1, 2023; revised November 8, 2023; accepted for publication November 10, 2023.
Available online January 28, 2024.

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2772-8293

https://doi.org/10.1016/j.jacig.2024.100219

METHODS

Patients

From January 2022 to February 2023, 99 adult Japanese patients with SA who received any biologics at Jikei University Hospital (Tokyo, Japan) were enrolled. At this time, 5 biologics—omalizumab, mepolizumab, benralizumab, dupilumab, and tezepelumab—were available in Japan. We excluded patients who missed visits to our hospital during the study period or who did not receive any biologics from January 2022 to February 2023 (Omicron variant epidemic period). The present study was approved by the Ethics Committee of Jikei University (35-023 [11644]). In addition, this study was conducted in accordance with the Declaration of Helsinki. On the basis of the ethical guidelines of Jikei University, informed consent was not necessary for this retrospective study, but we obtained opt-out consent on the hospital website (https://jikei.bvits.com/rinri/publish.aspx) (Japanese only). The director/administrator of Jikei University Hospital granted us permission to access the medical records. The data used in this study were anonymized before use.

Data collection

We retrospectively examined the following characteristics: sex; age; comorbidities including eosinophilic diseases; smoking status; body mass index; baseline treatments, including biologics; type 2 biomarkers at baseline before biologic treatment and at a stable status on treatment, such as peripheral blood eosinophil counts (BECs), serum IgE levels, and fractional exhaled nitric oxide (FENO); COVID-19 infection and severity; vaccine doses; drug allergy history; Asthma Control Test (ACT) score; number of AExs; exacerbation after COVID-19 infection; and disease severity. Then, we evaluated and analyzed these data between the COVID-19(+) group and the COVID-19(−) group. The FENO level was measured using the NIOX VERO device (CIRCASSIA, Oxford, United Kingdom).

Definition of COVID-19 and AEx severity

The severity of COVID-19 was defined on the basis of the World Health Organization classification: "mild" was defined as asymptomatic or symptomatic; "moderate" was defined as hospitalization with treatment or oxygen therapy; and "severe" was defined as hospitalization with noninvasive ventilation, high flow nasal cannula, or mechanical ventilation.[13] The severity of AExs was defined as follows: a mild exacerbation was a worsening of symptoms requiring short-acting β_2-agonist treatment; a moderate exacerbation was a worsening of symptoms requiring a systemic corticosteroid burst; and a severe exacerbation was a worsening of symptoms requiring hospitalization.[14]

Statistical analysis

All statistical analyses were performed using StatView version 5 (SAS Institute, Inc, Cary, NC). All values are expressed as the means ± SDs or SEs. A P value of less than .05 indicated statistical significance. The factors associated with patient characteristics were analyzed using the Mann-Whitney U test, the Fisher exact test, or the χ^2 test and the Kruskal-Wallis test. Univariate logistic regression was performed with the following variables as risk factors for COVID-19: sex (male), age, smoking, ACT score, BEC before biologic treatment, inhaled corticosteroid doses, maintenance OCS, and the number of vaccine doses. Multivariate logistic regression was then performed to evaluate the variables that achieved a P value of less than .20 in the univariate models.

RESULTS

Patient characteristics

Among 99 patients treated with any biologics, 28 patients suffered from COVID-19, and 1 woman experienced a reinfection. The patient characteristics of the COVID-19(+) and (−) groups are provided in Table I. The ACT scores at baseline and at preinfection status were 19.3 ± 5.1 and 21.2 ± 5.1, respectively (P = .08). The initially administered biologic agents were not significantly different between the 2 groups. Furthermore, there was no significant difference in the kind of biologic agents used during the Omicron epidemic. Most patients had allergic or eosinophilic comorbidities, including 78% with allergic rhinitis and 58% with chronic rhinosinusitis with nasal polyps/eosinophilic chronic rhinosinusitis. Regarding type 2 biomarkers, the BEC before biologic therapy was 933 ± 2149 and 611 ± 907 (/μL), respectively (P = .21). During biologic treatment and preinfection status, the BEC was 262 ± 485 and 134 ± 249, respectively (P = .37). A significant difference was demonstrated only in the total vaccine doses between the positive and negative groups (2.9 ± 1.6 vs 3.8 ± 1.2; P = .008). The number of anaphylaxis cases was 5 among all 347 doses administered (1.4%), and a significant difference was observed in cases with drug allergies (P = .03).

Characteristics of patients with COVID-19

A total of 29 infections in 28 patients occurred during the Omicron epidemic. The patient characteristics are provided in Table II. In terms of COVID-19 severity, there were 26 patients with mild disease and 3 hospitalized patients with moderate disease; however, there were no patients with severe disease who required mechanical ventilation or who died. Among the 3 patients who needed oxygen therapy for the treatment of both pneumonia and AEx, 1 patient had not been vaccinated and the other had not received a booster shot. There was a significant difference in the number of vaccine doses between the mild and moderate groups at diagnosis of confirmed COVID-19 (3.0 ± 1.4 vs 1.0 ± 1.0, respectively; P = .03; Mann-Whitney U test). Among these patients, the number of risk factors for COVID-19 progression was 1.3 ± 1.7 (ranging from 0 to 6), and the most common factors were advanced age (≥65 years) and immunocompromised status, including maintenance OCS use. Among 29 infected patients, 11 received antiviral agents for the treatment of COVID-19.

Severity of AExs

Among 29 infected patients, 16 (55%) experienced AExs, including 7 (24%) moderate AExs requiring an OCS burst (Table II). The ACT scores at baseline were significantly associated with the severity of AExs: the ACT scores in the no/mild/moderate exacerbation groups were 23.0 ± 2.3, 18.1 ± 5.3, and 15.0 ± 4.3, respectively (P = .004; Kruskal-Wallis test) (Fig 1, *A*). However, there was no significant difference between the number of vaccine doses and the severity of AExs: the number of vaccine doses in the no/mild/moderate exacerbation groups was 3.3 ± 1.5, 2.5 ± 1.3, and 2.3 ± 1.6, respectively (P = .35; Kruskal-Wallis test) (Fig 1, *B*). Intriguingly, there was no positive

TABLE I. Patient characteristics in asthmatic patients treated with biologics

Characteristics	COVID-19 (+) (n = 28)	COVID-19 (−) (n = 71)	*P* value
Sex: male	6 (21)	22 (31)	.48
Age (y)	57.3 ± 12.0	58.1 ± 13.5	.81
Onset of asthma (y)	29.6 ± 17.8	34.8 ± 16.5	.25
Duration of asthma (y)	27.6 ± 16.7	23.7 ± 14.1	.30
Start biologics (y)	53.3 ± 11.4	53.7 ± 13.5	.86
BMI (kg/m^2)	23.1 ± 4.4	23.0 ± 3.9	.91
Smoking history (yes)	8 (29)	23 (32)	.90
Drug/food allergy	19 (68)	37 (49)	.15
Total no. of vaccine doses	2.9 ± 1.6	3.8 ± 1.2	.008
Anaphylaxis to COVID-19 vaccine	3 (12)	2 (3)	.13
ACT score in stable status (points) (n = 93)	19.3 ± 5.1	21.2 ± 5.1	.08
ACT score ≥ 20	15 (56) (n = 27)	49 (77) (n = 64)	.08
ICS dose* (μg/d)	986 ± 317	1030 ± 371	.95
LAMA	15 (54)	44 (62)	.59
LTRA	23 (82)	56 (79)	.79
Xanthine derivative	14 (50)	38 (54)	.92
Maintenance OCS use	8 (29)	13 (18)	.39
Biologics use,† n			
Initiation: O/M/B/D/T	8/9/5/6/0	18/25/18/9/1	.73
In 2022: O/M/B/D/T/O + D/O + M/O + T/M + D	5/4/7/11/0/1/0/0/0	7/15/24/20/1/0/1/1/2	.50
No. of switching biologics, n	0.9 ± 1.3 (0-5)	0.8 ± 1.0 (0-3)	.99
0/1/2/3/4/5	16/5/3/3/1	39/13/14/5/0	.43
Comorbidities			
Atopic status	24 (86)	62 (87)	>.99
Allergic rhinitis	22 (79)	55 (77)	>.99
CRSwNP/ECRS	16 (57)	41 (58)	>.99
AERD	8 (29)	21 (30)	>.99
Atopic dermatitis	5 (18)	11 (15)	.77
ABPA	4 (14)	4 (6)	.22
CEP	2 (7)	8 (11)	.72
EGPA	1 (4)	12 (17)	.10
Biomarkers before any biologic			
BEC (/μL)	933 ± 2149	611 ± 907	.21
Serum IgE (IU/mL)	389 ± 644	576 ± 1517	.97
FENO (ppb)	57 ± 46	72 ± 66	.50

Data are presented as n (%) or mean ± SD, unless otherwise stated. Data were analyzed using the Fisher exact test, χ^2 test, or the Mann-Whitney *U* test.
ABPA, Allergic bronchopulmonary aspergillosis; *AERD*, aspirin-exacerbated respiratory disease; *B*, benralizumab; *BMI*, body mass index; *CEP*, chronic eosinophilic pneumonia; *CRSwNP/ECRS*, chronic rhinosinusitis with nasal polyp/eosinophilic chronic rhinosinusitis; *D*, dupilumab; *EGPA*, eosinophilic polyangiitis; *ICS*, inhaled corticosteroid; *LAMA*, long-acting muscarinic antagonist; *LTRA*, leukotriene receptor antagonist; *M*, mepolizumab; *O*, omalizumab; *T*, tezepelumab.
*ICS doses are provides as fluticasone propionate equivalents (μg/d).
†For example, "X + Y" means "X" and "Y" are used alternately or together.

correlation in disease severity between COVID-19 and AExs ($P = .14$; Fisher exact test).

Risk factors for COVID-19

We further assessed the risk for COVID-19 using multivariate logistic regression for 29 diagnoses during the Omicron epidemic (Table III). Only a lower number of total vaccine doses was a significant risk factor associated with contracting COVID-19 (odds ratio, 0.64; 95% CI, 0.46-0.91; $P = .006$). No significant link was demonstrated with the ACT score, inhaled corticosteroid dose, maintenance OCS, or type 2 biomarkers.

DISCUSSION

This single-center retrospective study evaluated the risk factors for COVID-19, severity of COVID-19, and AExs among patients with SA treated with biologics during the Omicron epidemic. With respect to patient characteristics, there was no obvious difference between the findings of the present and previous studies of biologics for SA except for body mass index,[12,15] which may reflect the low prevalence of obesity among patients with SA in Japan.[16] The number of vaccine doses significantly differed between the COVID-19(+) and (−) groups in the present study. Although the protective role of vaccination in preventing SARS-CoV-2 infection has already been well established,[17,18] we believe that our finding is unique in terms of showing vaccine efficacy in patients with SA treated with biologics in a real-world setting. Previous reports have shown that advanced age and comorbidities are related to the severity of COVID-19[3,19]; however, asthma is not associated with COVID-19 severity or a worse prognosis.[20] A recent study reported that asthma was not an independent risk factor for hospitalization for COVID-19 in the Delta or Omicron epidemic period.[21] In this study, the ACT score was not a risk factor for COVID-19. It has also been demonstrated that the risk of COVID-19 for asthmatic patients treated with biologics was no

TABLE II. Characteristics of COVID-19–infected patients

Characteristics	Value
Age (y) at COVID-19 onset	57.0 ± 11.9
Severity of COVID-19, mild/moderate/severe, n	26/3/0
Hospitalization	8 (31)
No. of vaccine doses at COVID-19 onset, n	2.8 ± 1.5 (0-5)
Doses in patients with mild/moderate COVID-19, n	3.0 ± 1.4/1.0 ± 1.0*
Anaphylaxis due to COVID-19 vaccine	3 (11)
Severity risk factors for COVID-19, n	1.3 ± 1.7 (0-6)
0/1/2/3, n	10/10/2/6
Age ≥ 65 y	8 (28)
Hypertension	5 (17)
Diabetes mellitus	4 (14)
Chronic kidney disease	0 (0)
Cardiac disease	2 (7)
Malignancy	1 (3)
Immunocompromised†	8 (28)
Obesity (BMI ≥ 30)	2 (7)
Biologics at COVID-19 infection	
O/M/B/D/O + D	5/4/8/10/1
Antiviral agents use	
None	18 (62)
Remdesivir	5 (17)
Monulpiravir	4 (14)
Nirmatrelvir/ritonavir	2 (7)
Severity of AExs (n = 29)	
None/mild/moderate/severe, n	13/9/7/0

The number of COVID-19–infected patients was 28, and total infection was 29. Data are presented as n (%) or mean ± SD, unless otherwise stated.
B, Benralizumab; *BMI*, body mass index; *D*, dupilumab; *M*, mepolizumab; *O*, omalizumab.
*There was a significant difference between mild and moderate COVID-19 ($P = .03$; Mann-Whitney *U* test).
†All 8 patients received maintenance OCS.

different from that for asthmatic patients who were not treated with biologics.[7] During the study period, the total cumulative number of COVID-19 cases was approximately 4.38 million (an incidence rate of 30%) in Tokyo,[22] and this incidence rate was similar to that observed in the present study (28 of 99 patients), further supporting the notion that SA treated with biologics may not increase the risk of COVID-19. In addition, there was no clear link in terms of disease severity between AExs and COVID-19.

Eosinophils have been demonstrated to possess antiviral properties and may influence susceptibility to COVID-19.[23] Mepolizumab and benralizumab were administered as the initial biologics for most patients, and 44 patients (44%) switched to other biologics, including dupilumab, in the present study. Although mepolizumab and benralizumab decrease the number of blood eosinophils, which may increase the risk of viral infections,[24] the present study found no difference between the different biologics regarding COVID-19 diagnoses. Recently, it has been reported that normalization of eosinophils by anti–IL-5/IL-5 receptor antibodies improves the interferon response during viral infection, suggesting the potential antiviral effect of eosinophil normalization by biologics.[25] Furthermore, type 2 markers, including IgE and FENO, were not significant risk factors by means of logistic regression analysis, suggesting that elevation of type 2 markers may not be directly associated with susceptibility to COVID-19.

Vaccine effectiveness against SARS-CoV-2, including the Omicron variant, is already evident,[17,18,26,27] and the infection prevention rate against the Omicron variant was approximately 40% to 50% in several studies. Consistently, the number of vaccine doses was significantly associated with COVID-19 severity in the present study. However, an increased number of vaccine doses did not tend to attenuate the severity of AExs. We speculate that the number of patients with AExs may not have been sufficient to clarify the efficacy of vaccination in the present study. Although a previous report demonstrated that SA with maintenance OCSs can be a mortality risk during COVID-19[12] and 8 patients with COVID-19 were prescribed maintenance OCSs, no severe COVID-19 was observed in this study, which can be partly attributed to the recent availability of antiviral agents and vaccines and viral variants. In terms of safety concerns, the vaccine has already been reported to be safe in highly allergic patients.[28] The Global INitiative for Asthma guidelines also recommend vaccination,[14] but only a few reports exist for patients with SA undergoing biologic treatment.[29] We attempted to show not only the efficacy in preventing severe COVID-19, but also the safety in allergic adverse events by vaccination, especially in a real-world setting. Vaccine-induced anaphylaxis was observed in 1.4% of all vaccinations and approximately 5% of all patients in this study, with mainly moderate to severe symptoms, all of which improved. In general, vaccination should be determined on the basis of the balance between benefits and adverse events. According to the results in this study, we believe that vaccination can be recommended with acceptable safety concerns in severely asthmatic patients receiving biologic treatment.

The incidence of AExs after COVID-19 was approximately 55%, and the incidence of moderate AExs requiring an OCS burst was 24%, but no severe AExs requiring oxygen therapy or mechanical ventilation were observed in the present study. It has been reported that ACT scores may be associated with AExs.[30,31] We found a consistent and significant difference in the ACT scores at baseline between patients with mild and moderate AExs caused by COVID-19 and patients treated with biologics for SA. Accordingly, to attenuate the severity of exacerbations due to COVID-19, it is likely that clinical remission is desirable even in patients with SA who are being treated with biologics.[32]

There are several limitations in the present study. First, a small number of patients were enrolled in this single-center retrospective study. However, only a few large studies of approximately 100 patients have evaluated the association between biologics and COVID-19. Second, this study is one of several on asthma conducted during the Omicron epidemic, and different virologic characteristics may have affected the results and may make it difficult to compare our observations with those in previous reports. Third, regional and social characteristics in Japan, including social distancing, universal masking, and vaccination rates, had a substantial influence on the prevalence and severity of COVID-19, which may also have affected the clinical characteristics of AExs in this study. However, to our knowledge, this is the first report to clarify the efficacy of vaccination for patients with SA treated with biologics during the Omicron epidemic.

The number of vaccine doses was significantly higher among patients with mild COVID-19 than among patients with moderate COVID-19 who had SA and were treated with biologics. Furthermore, the severity of AExs caused by COVID-19 was affected by baseline asthma control during the Omicron epidemic. Regardless of biologic or OCS therapy,

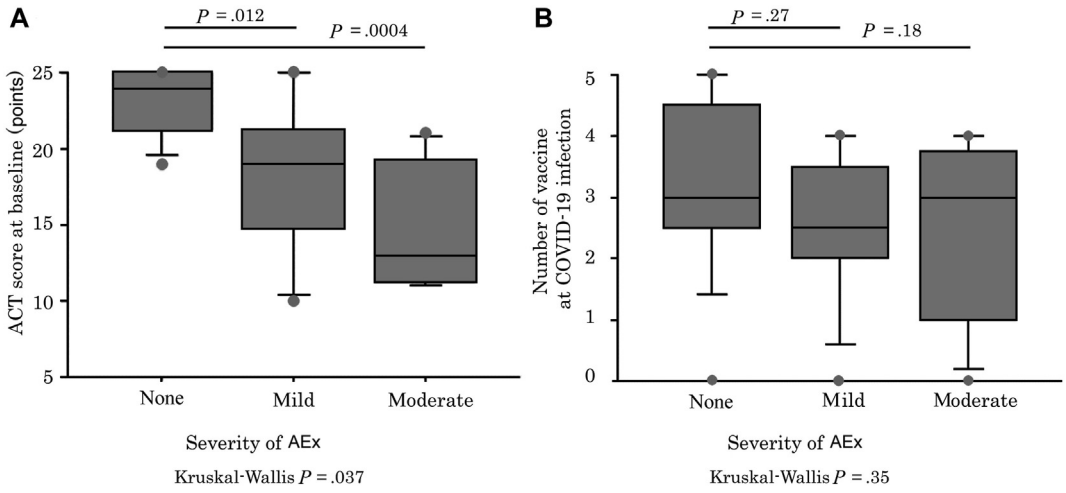

FIG 1. All results are expressed as individual data points, and the boxes represent the medians and interquartile ranges. The upper and lower whiskers represent the 90th and 10th percentiles, respectively. **A,** ACT scores according to the severity of AExs due to COVID-19. The ACT scores among patients without exacerbations were significantly higher than those among patients with mild and moderate exacerbations (comparisons between groups were performed by the Kruskal-Wallis test followed by multiple comparisons using nonparametric analysis with Bonferroni correction). **B,** The number of vaccine doses according to the severity of AExs due to COVID-19. There was no significant difference in the number of vaccine doses in terms of the severity of AExs.

TABLE III. Risk factors for COVID-19 infection by logistic regression analysis

Variables	Odds ratio (95% CI) (univariate)	*P* value	Odds ratio (95% CI) (multivariate)	*P* value
Sex: male	0.61 (0.22-1.71)	.34	—	—
Age (y)	1.00 (0.96-1.03)	.8	—	—
Former or current smoking, yes	0.84 (0.32-2.18)	.71	—	—
ACT score (points)	0.94 (0.86-1.02)	.12	0.97 (0.88-1.06)	.50
BEC before biologic treatment (/μL)	1.00 (1.00-1.00)	.32	—	—
IgE before biologic treatment (IU/mL)	1.00 (0.99-1.00)	.55	—	—
FENO before biologic treatment (ppb)	0.995 (0.987-1.004)	.29	—	—
ICS dose*(μg/d)	1.00 (0.998-1.001)	.57	—	—
Maintenance OCS, yes	1.79 (0.65-4.93)	.26	—	—
Total no. of vaccine doses, n	0.64 (0.47-0.88)	.006	0.64 (0.46-0.91)	.01

ICS, Inhaled corticosteroid.
*ICS doses are provided as fluticasone propionate equivalents (μg/d).

vaccination and baseline asthma control can be important determinants for the severity of COVID-19 and AExs in patients with SA.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Data-sharing statement: The data sets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

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