Received: 18 January 2022 | Revised: 21 April 2022 | Accepted: 27 April 2022

DOI: 10.1111/all.15334

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

LETTER

Covid-19 in the absence of eosinophils: The outcome of confirmed SARS-COV-2 infection whilst on treatment with benralizumab

To the Editors,

Patients with severe asthma have been reported to experience more severe COVID-19 disease outcomes including hospital admission, ICU admission and death.[1] Blood eosinopenia was one of the earliest reported findings in hospitalized patients with COVID-19, opening discussion as to whether eosinophils may have an anti-viral or deleterious role in the immune response against SARS-CoV-2 infection.[2] A number of predominantly pre-clinical studies have suggested a role for eosinophils in anti-viral immunity. For example, eosinophils express several endosomal Toll-like receptors (TLRs) including TLR7 which has been shown to enable eosinophils to recognize single-stranded RNA viruses including coronavirus.[3]

Benralizumab is an anti-IL5R monoclonal antibody licensed for the treatment of severe eosinophilic asthma (SEA), resulting in the near-complete depletion of blood and tissue eosinophils.[4,5] To date, a critical role for the eosinophil in anti-viral defence has been called into question by the absence of safety signals relating to viral infections in the large phase 3 and extension trials of benralizumab in subjects with asthma and COPD.[6,7] However, little is known about the outcomes of SARS-CoV-2 infection in individuals with benralizumab-induced eosinopenia.

We identified patients with SEA established on treatment with benralizumab (treatment commenced prior to April 2021) at Guy's Severe Asthma Centre, London, UK, and contacted them by telephone throughout May and June 2021 to establish whether they had experienced a confirmed PCR-positive SARS-CoV-2 infection since commencing benralizumab. Clinical and demographic characteristics were recorded along with the outcome of infection, including the need for hospitalization and intensive care admission. Patients with severe COVID-19 as defined by the requirement for hospitalization were compared to those experiencing non-severe infections treated in the community. Approval to report observational data for this cohort was granted by the GSTT ethics committee (ref 11999).

Two hundred and sixty-eight patients on treatment with benralizumab were contacted with 24/268 (9%) reporting a confirmed infection with a positive PCR test for SARS-CoV-2. Of 24, 18 (75%) reported non-severe self-limiting infections with the remaining 6 (25%) experiencing more severe infections requiring hospitalization (median length of stay 6 [IQR 1–8] days). No patients required admission to intensive care or needed mechanical ventilation. Of 24, 22 patients in this cohort were unvaccinated at the time of infection. The remaining 2/24 (8.3%) had received a single dose of SARS-CoV-2 vaccine (in both cases Oxford/Astra Zeneca) at least 2 weeks prior to confirmed infection. Of 24, 23 patients had received at least 6 months' treatment with benralizumab at the time of COVID-19 infection. One patient had received 3 doses (at least 8 weeks' treatment).

Comparison of the baseline characteristics of patients experiencing non-severe vs severe infections did not reveal any statistically significant differences (Table 1). However, noteworthy numeric differences consistent with known risk factors for hospitalization with COVID-19 were seen including a higher proportion of male patients (50.0% vs 38.9%) and a higher mean BMI (32.1 vs 29.5) in those that were hospitalized.

Overall, the rate of confirmed infection in our cohort was modest at 9%; however, this is likely to be an underestimate given that other patients may have experienced an asymptomatic infection or not pursued PCR testing in the context of non-severe symptoms only. As such, the true proportion of benralizumab-treated SEA patients with SARS-CoV-2 infection requiring hospitalization is likely to be significantly lower than the 25% we observed herein. A study sampling patients from the UK Severe Asthma Registry across 14 UK severe asthma centres performed one year prior to our data collection found a prevalence of COVID-19 of 6% amongst patients on any anti-IL-5 therapy, with a hospitalization rate of 10%.[8]

A second limitation is that we were not able to collect additional clinical parameters of COVID-19 disease severity such as the degree of respiratory distress and oxygen requirements of the patients. This is relevant as it is conceivable that any threshold for hospital admission based on ventilatory impairment may have been lower for these patients by virtue of their presenting to the emergency room with a diagnosis of severe asthma. Finally, we did not request written proof of the positive PCR as there was no reason for the patient to give inaccurate information in this regard, although accepting this can introduce recall bias.

In summary, we report the outcomes of 24 patients with severe asthma who have had confirmed SARS-CoV-2 infection whilst

TABLE 1 Baseline characteristics of benralizumab-treated patients with severe asthma and confirmed COVID-19 infection according to hospitalization status

	All patients *n* = 24	Hospitalized *n* = 6	Not hospitalized *n* = 18	P value(Hospitalized vs not)
Age, years	46.5 ± 12.6	44.5 ± 32.1	47.2 ± 13.3	0.66
Female subjects, *n* (%)	14 (58)	3 (50)	11 (61)	0.50
BMI, kg/m^2	29.5 ± 5.6	32.1 ± 4.3	28.7 ± 5.8	0.20
Atopic, *n* (%)	19 (79)	4 (67)	15 (83)	0.57
Adult-onset asthma, *n* (%)	13 (54)	2 (33)	11 (61)	0.36
Chronic rhinosinusitis with nasal polyps, *n* (%)	8 (33)	2 (33)	6 (33)	0.70
Smoking history, *n* (%)				
Never smoker	21 (88)	5 (83)	16 (89)	0.72
Ex-smoker	3 (13)	1 (17)	2 (11)	
Current smoker	0 (0)	0 (0)	0 (0)	
Exacerbation rate in year prior to benralizumab	5.2 (4.6)	4.7 (2.9)	5.4 (5.1)	0.74
Annualized exacerbation rate whilst on benralizumab	0.9 (0.8)	0.8 (0.4)	0.9 (0.9)	0.78
Patients on mOCS, *n* (%)	6 (25)	4 (22)	2 (33)	-
FEV1, Litres	1.94 ± 0.62	1.90 ± 0.48	1.95 ± 0.68	0.87
FEV1, % predicted	63.4 ± 16.9	58.0 ± 14.2	65.4 ± 17.7	0.37
ACQ−6 score	2.99 ± 1.43	3.34 ± 1.63	2.91 ± 1.40	0.64
Blood eosinophil count prior to benralizumab, cells × 10^9/L	0.7 (0.6–1.1)	0.6 (0.3–0.7)	0.7 (0.6–1.1)	0.14
Blood eosinophil count on benralizumab, cells × 10^9/L	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	1.0
FENO, ppb	65 (42–102)	73 (47–113)	64 (31–101)	0.63

Note: Data are presented as No. (%), mean ±SD or median (interquartile range).

Abbreviations: ACQ-6, Asthma Control Questionnaire-6; FENO, ractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; mOCS, maintenance oral corticosteroid; ppb, parts per billion.

on treatment with the eosinophil-depleting biologic benralizumab. Although the numbers are small, our finding that 75% did not experience severe COVID-19 suggests that the eosinophil does not appear to have a critical role in defence against SARS-CoV-2 infection. However, this requires additional research.

AUTHOR CONTRIBUTIONS

CHRF and APH drafted the manuscript, APH and DJJ analysed and interpreted the data. CHRF, APH, SR, AT, JD and UA performed the acquisition of data. CHRF, APH, JD, AMN and DJJ revised the manuscript.

CONFLICTS OF INTEREST

DJ reports advisory board and speaker fees and congress travel support from GSK, AstraZeneca, Chiesi, Sanofi Regeneron, Napp and Teva pharmaceuticals. JD reports congress support from Sanofi. AN reports speaker fees from AstraZeneca and congress travel support from Napp. All other authors report no COI.

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