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LETTER

Outcomes of COVID-19 in patients with ANCA-associated vasculitis receiving avacopan

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The complement C5a-C5a receptor (C5aR) signalling axis plays a crucial role in the pathogenesis of both antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and COVID-19. Complement components such as the membrane attack complex, C5a, C3a and factor B are higher in patients with active AAV compared with healthy controls.[1] Similarly, experimental studies have shown abundant expression of C5aR1 and increased levels of soluble C5a in severe COVID-19.[2] Following the ADVOCATE trial, avacopan, a C5aR antagonist, has been approved by the US Food and Drug Administration (FDA) as an adjunct therapy for remission induction in AAV.[3] Similarly, vilobelimab, an anti-C5a monoclonal antibody, was granted Emergency Use Authorization by the FDA for severe COVID-19 based on the results of the PANAMO study.[4] The risk of severe COVID-19 is increased in patients receiving rituximab and high-dose glucocorticoids.[5]

Here, we report the outcomes of eight patients with AAV treated with avacopan who developed COVID-19, which to our knowledge has not been reported to date. We retrospectively identified patients ≥18 years old with AAV at the Johns Hopkins Vasculitis Center in Baltimore, Maryland and the Vasculitis and Glomerulonephritis Center at the Massachusetts General Hospital in Boston, Massachusetts who contracted COVID-19 while on avacopan. Data on ANCA serotype, concomitant immunosuppressive drug use, COVID-19 severity, treatment and vaccination status were retrieved.

Patient characteristics are outlined in table 1. All patients were previously vaccinated against COVID-19. The timing of vaccination in relation to B cell depletion is outlined in table 1. Spike antibody levels prior to this episode of COVID-19 were positive (n=3), negative (n=1) or not tested (n=4). The median (IQR) time from the start of induction therapy to avacopan initiation was 15 (10–30) days. The median (IQR) time from the start of induction therapy to COVID-19 infection was 116 (75–161) days. The median (IQR) time from avacopan initiation to COVID-19 was 78 (59–149) days. In addition to avacopan, induction treatment included rituximab+-cyclophosphamide+glucocorticoids (n=6) and rituximab+glucocorticoids (n=2). Concomitant immunosuppression at the time of COVID-19 infection included rituximab (n=8), prednisone (n=2) and oral cyclophosphamide (n=1). All patients remained on their treatment, but cyclophosphamide was held. Two patients did not receive COVID-19 treatment, while the remainder received nirmatrelvir/ritonavir (n=3), bebtelovimab (n=1), molnupiravir (n=1), and remdesivir and dexamethasone (n=1). The severity of COVID-19 was mild in all patients except for one who was hospitalised and died from acute on chronic respiratory failure secondary to severe COVID-19 on a background of ANCA-related interstitial lung disease. In this patient, the diffusing capacity of the lungs for carbon monoxide was 31% predicted preceding COVID-19. Of the seven surviving patients, all recovered completely from acute COVID-19, and no patient experienced long COVID.

Despite significant immunosuppression, COVID-19 was mild in nearly all patients with AAV receiving avacopan. The one patient with severe COVID-19 had advanced fibrotic lung disease. Larger studies with a

Table 1 Patient characteristics and details of COVID-19

ID	Age, sex	ANCA serotype	Concomitant immunosuppressant at the time of COVID-19	Vaccination status	Spike antibody level*	Prevailing COVID-19 variant	Days from induction treatment to COVID-19	COVID-19 treatment	COVID-19 severity	Outcome	Long COVID
1	83F	MPO	RTX	3 mRNA doses during BCD	Positive	Omicron	165	Nirmatrelvir/ritonavir	Mild	Resolved	No
2	54F	PR3	RTX	3 mRNA doses preceding BCD	NT	Omicron	77	Nirmatrelvir/ritonavir	Mild	Resolved	No
3	71M	PR3	RTX	2 mRNA doses preceding BCD, 1 mRNA dose after BCD	Positive	Omicron	160	Molnupiravir	Mild	Resolved	No
4	81M	PR3	RTX, CYC prednisone 15 mg	3 mRNA doses preceding BCD	NT	Omicron	55	Remdesivir, dexamethasone	Severe	Death	No
5	58F	MPO	RTX prednisone 5 mg	2 mRNA doses preceding BCD	NT	Omicron	123	None	Mild	Resolved	No
6	58F	MPO	RTX	3 mRNA doses preceding BCD	Positive	Omicron	108	Bebtelovimab	Mild	Resolved	No
7	75M	MPO	RTX	2 mRNA doses preceding BCD, 1 mRNA dose after BCD	Negative	Omicron	280	None	Mild	Resolved	No
8	34M	MPO	RTX	3 mRNA doses preceding BCD	NT	Omicron	67	Nirmatrelvir/ritonavir	Mild	Resolved	No

*Positive spike antibody levels preceding this episode of COVID-19 resulted from either vaccination or prior infection during peripheral B cell presence, or through prior receipt of tixagevimab/cilgavimab.
ANCA, antineutrophil cytoplasmic antibody; BCD, B cell depletion; CYC, cyclophosphamide; F, female; M, male; MPO, myeloperoxidase; mRNA, messenger RNA; NT, not tested; PR3, proteinase-3; RTX, rituximab.

comparator arm are needed to confirm the effects of C5aR blockade with avacopan in COVID-19.

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