Tixagevimab and Cilgavimab (Evusheld) in Rituximab-treated Antineutrophil Cytoplasmic Antibody Vasculitis Patients

To the Editor: High mortality rates have been reported among antineutrophil cytoplasmic antibody-associated vasculitis (ANCA-AAV) patients with concomitant COVID-19 infection.[1] Rituximab, an anti-CD20 monoclonal antibody, has been widely used for remission induction and maintenance in AAV. Despite advancements in vaccine strategies to provide protection against SARS-CoV-2, AAV patients on rituximab therapy remain vulnerable with poor humoral response to the SARS-CoV-2 vaccine.[2] In light of these findings, monoclonal antibodies have been developed to provide passive immunity against SARS-CoV-2 in patients with depressed immune systems. Evusheld (tixagevimab-cilgavimab) is a monoclonal antibody that has been shown to reduce the risk of COVID-19 infections in immunocompromised patients. In the original randomized placebo-controlled clinical trial,[3] a total dose of 300 mg (150 mg tixagevimab-150 mg cilgavimab) for pre-exposure prophylaxis was studied. Notably, only 3.2% of the cohort were recipients of immunosuppressive therapy. Because of data that later revealed breakthrough COVID-19 infections in the setting of new SARS-CoV-9 variants, the US Food and Drugs Administration updated their recommendation in February 2022 to increase the Evusheld dose to a total of 600 mg (300 mg tixagevimab-300 mg cilgavimab).[4] Data on the outcomes of this increased dose in patients with AAV and/or those receiving rituximab is currently lacking. Here, we report our experience with 21 AAV patients on rituximab therapy who received an Evusheld dose of 600 mg (300 mg tixagevimab-300 mg cilgavimab) in our center, with particular emphasis on 3 breakthrough COVID-19 cases.

Patients with AAV who were treated with rituximab for remission induction and/or maintenance and received Evusheld between December 2021 and June 2022 were included. All patients had ANCA-associated glomerulonephritis. A review of their electronic health record was completed. Data on the ANCA type, ANCA disease, AAV induction and maintenance therapies, COVID-19 vaccine status, date of Evusheld administration, CD19 and IgG before and after Evusheld administration, and the course of COVID-19 infections were retrieved. This study was approved by the Johns Hopkins Institutional Review Board.

A total of 21 patients were included. The mean (± SD) age was 66 (± 15.5) years. All patients (100%) received the COVID vaccine, and all but one (95%) received a booster dose. Twenty patients (95%) received an Evusheld dose of 600 mg (300 mg tixagevimab-300 mg cilgavimab), and only 1 patient (4.7%) received the lower dose of 300 mg (150 mg tixagevimab-150 mg cilgavimab). The one patient that received the lower Evusheld dose was infected with SARS-CoV-2 122 days after receiving Evusheld. A total of 9 patients received maintenance rituximab after receipt of Evusheld. Interestingly, serum IgG levels before and after Evusheld administration were variable among all patients. Pre-Evusheld, IgG levels were normal (47%), low (47%), and not available (4.7%). Post-Evusheld, IgG levels were normal (28.5%), low (14.2%), and not available (57%). In those with documented pre-Evusheld and post-Evusheld IgG levels, the levels did not change except for one patient with a low post-Evusheld IgG level compared to a normal pre-Evusheld IgG level. In addition, before getting Evusheld, CD19 was depleted (52%), reconstituted (38%), and unavailable (10%) among patients. Post-Evusheld, CD19 was unavailable (66%), depleted (24%), and reconstituted (10%). The median (interquartile range) follow-up time from Evusheld administration to last follow-up was 124 (94–143) days.

Among the 95% of patients who received an Evusheld dose of 600 mg (300 mg tixagevimab-300 mg cilgavimab) (20 of 21), 3 patients (15%) developed breakthrough COVID-19 disease. The patients' characteristics are summarized in Table 1. The mean (± SD) time from Evusheld administration to the onset of COVID-19 disease was 98.6 (± 36.5) days, and the mean (± SD) time from rituximab use to Evusheld administration was 141 (± 64) days. Importantly, 2 of 3 patients received maintenance rituximab at a mean (± SD) time of 29.5 (± 29) days after Evusheld administration and before their COVID-19 diagnosis. All infections were mild and did not require hospitalization. None of the infected patients received Paxlovid, and 2 patients received monoclonal antibody treatment against COVID-19. With regard to AAV, all patients continued on rituximab therapy and remained in remission.

To our knowledge, this is the first retrospective study to look into the outcomes of the most updated dose of Evusheld at 600 mg (300 mg

Table 1. Characteristics of patients receiving Evusheld with breakthrough COVID-19 infection

ID	Age, year	Sex	ANCA type	AAV disease	Induction treatment	Maintenance treatment	Dose of Evusheld (tixagevimab -cilgavimab) (mg)	Serum IgG (mg/dl)		Days from Evusheld administration to COVID-19 infection	Received rituximab between Evusheld and COVID-19 infection	COVID-19 requiring hospitalization
								Before Evusheld	After Evusheld			
1	76	M	MPO	MPA	GC+RTX+AVP	RTX	600 mg (300 mg–300 mg)	Normal	Normal	114	Yes	No
2	37	M	PR3	GPA	GC+RTX	RTX	600 mg (300 mg–300 mg)	Low	Unavailable	57	Yes	No
3	61	M	MPO	GPA	GC+RTX	RTX	600 mg (300 mg–300 mg)	Low	Low	125	No	No

AAV, associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; AVP, avacopan; GC, glucocorticoids; GPA, granulomatosis with polyangiitis; ID, patient identifier; M, male; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase-3; RTX, rituximab.

tixagevimab-300 mg cilgavimab) in ANCA-AAV patients on rituximab. These results highlight 3 patients with breakthrough COVID-19 infections and challenge the idea of adequate passive immunity in immunosuppressed patients. Continued vigilance is required, especially when continuing maintenance rituximab in such patients. Moreover, the exact interplay between the rituximab and monoclonal antibodies remains uncertain. It is now recommended to repeat dosing of Evusheld every 6 months in immunocompromised patients. A more recent study on the antibody kinetics in transplant recipients treated with 150 mg dose of Evusheld demonstrated a decline in antibody titer after 4 to 5 months.[5] This data and our cases of breakthrough COVID-19 infection suggests that the redosing interval may need to be shortened in patients treated with B cell depleting therapy. Further data and larger cohorts are needed to confirm the findings of our study.

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