

## LETTER

# Early experience with tixagevimab/cilgavimab pre-exposure prophylaxis in patients with immune-mediated inflammatory disease undergoing B cell depleting therapy and those with inborn errors of humoral immunity

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Among immunocompromised patients, those with immune-mediated inflammatory diseases (IMIDs) treated with B cell depleting therapies (BCDTs) and those with inborn errors of humoral immunity (IEI) are among the poorest responders to vaccination<sup>1</sup> against SARS-CoV-2. These patients are also more likely to experience severe COVID-19 outcomes, regardless of vaccination status.<sup>2</sup> Although vaccination has not proven to be as efficacious as hoped in this population, the December 2021 emergency use authorisation of tixagevimab/cilgavimab has been greeted with cautious optimism by those providing care for immunocompromised patients. Tixagevimab/cilgavimab consists of two Fc-modified fully human monoclonal antibodies administered by intramuscular injection; it is effective for the prevention of COVID-19 in patients with moderate-to-severe immune compromise who are unlikely to mount an adequate immune response to COVID-19 vaccination (Levin *et al*<sup>3</sup> #2781). In the pivotal trial,<sup>3</sup> however, only 3.3% of patients were receiving immunosuppressive drugs at baseline and no details as to class of agents were provided. It is becoming more and more evident that multiple strategies are required to prevent and treat outpatient COVID-19 in immunosuppressed patients; this includes the use of monoclonal antibodies and antiviral therapies when prevention strategies fail. The practical effectiveness of this multipronged approach in terms of safety, tolerability and effectiveness has yet to be described.

To date, there exist only limited reports of experience with tixagevimab/cilgavimab in patients with compromised humoral immunity and none describing tolerability or clinical outcomes in a real-world setting. Starting 18 January 2022, the Cleveland Clinic has made tixagevimab/cilgavimab available to select high-risk patients including those on BCDT and humoral IEI. Here we report out initial real-world experience with breakthrough infections in combination with standard of care outpatient management of COVID-19.

## METHODS

All Cleveland Clinic healthcare system pharmacy records were electronically searched for patients with IMIDs or IEI who met the criteria to receive tixagevimab/cilgavimab as defined by the Cleveland Clinic COVID-19 Pharmacy & Therapeutics subcommittee. Patients on BCDT or with humoral IEI who had received at least one dose of tixagevimab/cilgavimab and were subsequently diagnosed with COVID-19 were included. Patients receiving BCDT for cancer were excluded. Incident cases were manually reviewed to extract data on COVID-19 infection, vaccination status and outcomes as assessed by an 8-point NIH ordinal scale.

## RESULTS

A total of 412 patients with IMIDs or humoral IEI received tixagevimab/cilgavimab across the rheumatology (n=256), allergy/

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immunology (n=78: 70 common variable immunodeficiency, 2 specific antibody deficiency, 5 BCDT, 1 CD4 lymphopenia) and neurology (n=78) departments between 18 January and 28 May 2022. Of these, 12 patients (2.9%) experienced a breakthrough COVID-19 infection (table 1), all receiving BCDT. Six patients developed infection a median of 19 days (13–84) after receiving 150 mg/150 mg of tixagevimab/cilgavimab. Six patients developed infection a median of 38.5 days (19–72) after either a single dose of 300 mg/300 mg or after their second dose of 150 mg/150 mg. Overall, 11 patients had a mild course and recovered at home (Supplementary file 1). One patient was hospitalised and required high flow oxygen. There were no deaths. All cases had been vaccinated against COVID-19 (five received two vaccines, six received three vaccines, one received four vaccines). In general, tixagevimab/cilgavimab was well tolerated with only one possible serious adverse event (a patient with COVID-19 with immune-mediated thrombocytopenia (ITP) hospitalised soon after receiving tixagevimab/cilgavimab with ITP flare which resolved with intravenous immunoglobulin).

## DISCUSSION

Previous studies have demonstrated the vulnerability of unvaccinated patients with deficits of humoral immunity, including those treated with BCDTs, to severe outcomes of COVID-19.<sup>4 5</sup> A large study performed in the pre-Omicron period and reported by our group revealed that among a cohort of 1696 vaccinated patients with IMIDs undergoing BCDT, 74 developed breakthrough COVID-19 with 29 (39.2%) patients hospitalised, 11 (14.9%) requiring critical care and 6 (8.1%) deaths. Furthermore, in this same study, an exploratory analysis on a comparator group of patients with IMIDs on similar BCDTs revealed no clear evidence of protection from vaccination.<sup>6</sup> Collectively, these data suggest the urgent need for alternative protective strategies for this subpopulation of immunocompromised patients.

This is the first real-world experience describing outcomes of COVID-19 in patients undergoing BCDT for IMIDs who received tixagevimab/cilgavimab as pre-exposure prophylaxis. These results are encouraging as they revealed that of 12 breakthrough infections, disease was mild in 11 with only a single patient experiencing severe (non-fatal) disease. The study is clearly limited by small numbers and a lack of a comparator group. In addition, given that nine patients received additional therapy for COVID-19 which falls within current standards of care for outpatient management in high-risk patients, there is no way to ascribe effectiveness to the individual components of the regimen. Lastly, these cases all fell within the Omicron epoch which may have biased outcomes. Collectively, these early data suggest that pre-exposure prophylaxis with tixagevimab/cilgavimab in combination with aggressive outpatient treatment of COVID-19 may be effective in attenuating disease severity in this highly

**Table 1** Patient characteristics and outcomes (n=12)

Median age	64 years
N (%)	
Female	8 (66.7)
White race	11 (91.7)
Diagnosis	
Vasculitis	8
Rheumatoid arthritis	2
Other*	2
Comorbidities	
Body Mass Index 30+	5 (41.7)
Heart disease†	6 (50.0)
Diabetes	2 (16.7)
Pulmonary‡	5 (41.7)
Chronic kidney disease	3 (25.0)
Malignancy	1 (8.3)
Concomitant immunosuppression	
Glucocorticoid <10 mg/day	4 (33.3)
Glucocorticoid ≥10 mg/day	1 (8.3)
Methotrexate	1 (8.3)
Mycophenolate mofetil	4 (33.3)
Duration of rituximab	
1–3 years	3 (25.0)
>3 years	9 (75.0)
History of prior COVID-19	2 (16.7)
Outcomes in all patients§	
NIH COVID ordinal scale 1–3	11
NIH COVID ordinal scale 4–8	1
Outcomes (treated with mAb¶)	
NIH 1–3	8
NIH 4–8	0
Outcomes (treated with nirmatrelvir/ritonavir)	
NIH 1–3	2
NIH 4–8	0

\*Antisynthetase syndrome, scleroderma.

†Hypertension, coronary artery disease, congestive heart failure.

‡Chronic obstructive pulmonary disease, asthma, interstitial lung disease.

¶, Monoclonal Antibodies: bebtelovimab (n=7), sotrovimab (n=1); §, National Institutes of Health (NIH) COVID Ordinal Scale: 1) Not hospitalized and no limitations of activities 2) Not hospitalized, with limitation of activities, home oxygen (O2) requirement, or both 3) Hospitalized, not requiring supplemental O2 and no longer requiring ongoing medical care 4) Hospitalized, not requiring supplemental O2 but requiring ongoing medical care 5) Hospitalized, requiring any supplemental O2 6) Hospitalized, requiring noninvasive ventilation or use of high-flow O2 devices 7) Hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation 8) Death.

vulnerable population; larger trials with unexposed comparator groups are urgently needed. Such studies are underway.

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