Safety and tolerability of Evusheld in patients with CVID: The Mayo Clinic experience

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Background: The past 2 years of the COVID-19 pandemic brought with it many unknowns for patients with immunodeficiency. Because of the concern for severe infection in those with immunocompromise, patients have been eager for effective prevention, vaccination, and treatment strategies. Preexposure prophylaxis provides another means of prevention in those with immunocompromise. A combination of tixagevimab and cilgavimab (Evusheld [AstraZeneca Cambridge, United Kingdom]) was granted emergency use authorization for preexposure prophylaxis at the end of 2021, but questions remained regarding how this would be tolerated and the side effects associated with its use.

Objectives: Our aim was to evaluate the safety and tolerability of Evusheld in patients with CVID from our tri-site institution.

Methods: We performed an institutional review board–approved, retrospective chart review of patients with common variable immunodeficiency (CVID) who received Evusheld before March 26, 2022.

Results: Of the 45 patients with CVID who received Evusheld, 41 (91%) received the recommended full dose of 600 mg. The majority of patients (39 of 45 [87%]) tolerated Evusheld without adverse events. The adverse events reported included immediate injection site pain, fatigue and cough, an episode of shingles, and chest pain.

Conclusions: This is an initial report on the safety and tolerability of Evusheld injections in patients with CVID. The majority of patients tolerated the injections without adverse events. For patients with reported chest pain, the results of a subsequent cardiac workup were negative. The efficacy of Evusheld could not be evaluated owing to the short median follow-up of this study (19 days). (J Allergy Clin Immunol Global 2023;2:100081.)

Key words: *Evusheld, COVID, CVID, immunocompromise*

Abbreviations used

COVID-19: Coronavirus disease 2019
CVID: Common variable immunodeficiency
ED: Emergency department
EUA: Emergency use authorization
SAE: Serious adverse event
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

INTRODUCTION

Throughout the coronavirus disease 2019 (COVID-19) pandemic, there has been uncertainty regarding the effectiveness of prevention and treatment strategies for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in those with immunodeficiency. This originally stemmed from lack of data on this group of patients, but subsequent studies have shown an increased risk of complications, such as hospitalization in 26% to 63% of patients and a case fatality rate of 9% of reported cases in this population.[1-3] In patients with common variable immunodeficiency (CVID), lower baseline absolute $CD3^+$, $CD3^+CD4^+$, and $CD19^+$ counts, as well as lower trough IgG, levels were associated with increased risk of hospitalization.[1] This may indicate that high circulating levels of SARS-CoV-2 antibodies are important for prevention of severe disease.

The mAbs tixagevimab and cilgavimab (Evusheld [AstraZeneca, Cambridge, United Kingdom]) were the first to be granted emergency use authorization (EUA) for preexposure prophylaxis against COVID-19 infection in those with a contraindication to vaccination, such as allergy to the vaccine or moderate-to-severe immunocompromise. The EUA was granted in the United States on December 8, 2021. Limited information on the safety and tolerability of Evusheld in immunocompromised patients is available, as the studies constituting the basis on which the EUA was granted include patients with varied high-risk conditions such as older age (≥60 years), obesity, and chronic obstructive pulmonary disease. Additionally, only those unvaccinated against COVID-19 and without prior SARS-CoV-2 infection were included.[4,5]

Therefore, we looked to evaluate the safety and tolerability of Evusheld in patients with CVID at our institution. Chart review from our tri-site medical center was performed as part of an institutional review board–approved study. Patients were identified by diagnosis of CVID and an order for tixagevimab and cilgavimab (Evusheld) on or before March 25, 2022. Of the 50 patients identified, 45 were included in the analysis. Four patients were

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

Received for publication June 8, 2022; revised October 12, 2022; accepted for publication November 20, 2022.

Available online February 8, 2023.

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2772-8293

https://doi.org/10.1016/j.jacig.2023.100081

TABLE I. Demographics of patients with CVID who received Evusheld

Characteristic	Value
N	45
Age (y), median (range)	62.0 (15.5-85.8)
Sex (male), no. (%)	17 (37%)
Vaccinated, no. (%)	41 (91%)
Pfizer vaccine	12 (29%)
Moderna vaccine	23 (56%)
Combination mRNA vaccines	4 (10%)
Janssen vaccine	1 (2%)
Janssen mRNA booster	1 (2%)
Received 4 doses of mRNA vaccine, no. (%)	11 (28%)
Pre-Evusheld COVID-19 infection, no. (%)	8 (18%)
Time between COVID-19 infection and Evusheld (d), median (range)	307 (45-463)
Received 600-mg total dose, no. (%)	41 (91%)
Follow-up after Evusheld (d)	19 (0-81)
Adverse events after Evusheld, no. (%)	6 (13%)
Cardiac risk factors, no. (%)	
Hypertension	19 (42%)
Daily aspirin therapy	15 (33%)
Hyperlipidemia	13 (29%)
Diabetes mellitus	6 (13%)
History of myocardial infarction	1 (2%)

excluded, as they had not yet received the injections, and 1 patient declined treatment. Patient demographics are shown in Table I.

RESULTS AND DISCUSSION

The first injections were administered at our institution in mid-January 2022 following the initial EUA approval. After the EUA was modified to a higher dose on February 24, 2022, patients immediately began receiving the recommended dose of 300 mg of tixagevimab and 300 mg of cilgavimab. Of the 45 patients, 41 (91%) received the currently recommended dose of 600 mg in total at either 1 (26 of 41 [63%]) or 2 (19 of 41 [46%]) visits. The remaining 4 of 45 patients were offered the remaining dose but had received only 150 mg of tixagevimab and 150 mg of cilgavimab at the time of analysis. The majority of patients were receiving immunoglobulin replacement (44 of 45 [98%]) and were vaccinated against COVID-19 (41 of 45 [91%]). Among those receiving mRNA vaccines, the median number of vaccine doses received was 3 (range 2-4 doses) and 11 of 39 (28%) were considered fully vaccinated and boosted with 4 total doses. Before receiving Evusheld, 8 of 45 patients (18%) previously had COVID-19 infection at a median of 307 days before Evusheld administration (range 45-463 days); 3 of the 8 (38%) received mAb treatment for COVID-19 infection and none were hospitalized.

No patients developed COVID-19 infection following Evusheld treatment, with a median follow-up time of 19 days (range 0-81 days). Most patients (39 of 45 [87%]) tolerated the injections without adverse events. In the 6 patients who reported adverse events, there were no episodes of anaphylaxis; only 1 patient reported immediate injection site pain after the second dose. One patient reported fatigue and cough starting 1 to 2 days following a single 600-mg dose; both of these conditions were common adverse events in the PROVENT trial. Six days after injection, this same patient presented to the emergency department (ED) with itching, rash, and chest pain. She self-treated with epinephrine at home. The ED evaluation demonstrated normal vital signs aside from mild tachycardia (104-111 beats per minute), a normal electrocardiogram result, and a normal troponin level. Another patient developed shingles 3 days after a 600-mg injection. Notably, 2 patients presented to the ED specifically for chest pain, 1 on day 4 after injection (a 600-mg total dose) and the other on day 23 after the second injection. Both had normal electrocardiogram results, troponin levels, and cardiac stress test results. Both patients were vaccinated with mRNA vaccines, and neither had a history of COVID-19 infection. Neither patient had known cardiac risk factors.

Treatment and prevention strategies for COVID-19 have evolved rapidly over the past 2 years. Patients with immunocompromise, including CVID, have been significantly affected by the pandemic ,with concern about risk of infection despite social distancing, masking, and vaccination. The EUA for Evusheld provides an additional infection mitigation strategy for immunodeficient patients. Although immunoglobulin replacement has been shown to result in increasing quantities of neutralizing SARS-CoV-2 antibodies,[6] whether this will be enough to provide sufficient protection remains unclear at this time. Small patient reports have noted possible benefit of Evusheld in this population of patients despite their also receiving immunoglobulin replacement therapy; for example, Kuster et al reported that 6 of 6 patients with primary antibody deficiency who received Evusheld before SARS-CoV-2 infection did not require hospitalization compared with 6 of the 17 remaining patients, who were hospitalized.[1] However, given the minimal reports on safety and tolerability data in the population of those with CVID, patients and physicians may be hesitant to consider its use, particularly with the concern for adverse cardiac events.

The most commonly reported adverse events with Evusheld in the PROVENT study were headache (6%), fatigue (4%), and cough (3%), the rates of which were similar to those in the

placebo group (rates of 5%, 3%, and 3%, respectively). There was 1 case of anaphylaxis immediately after injection; it was treated with epinephrine.[5] As already mentioned, there was concern regarding the reported cardiac events following Evusheld during these initial studies. In the PROVENT study there was an increased incidence of cardiac serious adverse events (SAEs), such as myocardial infarction, cardiac failure, arrhythmia, and cardiomyopathy, in the treatment group (n = 3461) versus in the placebo group (n = 1736) (rates of 0.6% vs 0.2% respectively), with 1 death due to myocardial infarction in a patient who received Evusheld.[4,5] In the smaller study (STORM CHASER), which examined patients with a lower mean age and fewer baseline cardiac risk factors, there were no reported cardiac SAEs; however, in a separate trial (TACKLE) evaluating Evusheld for the treatment of mild-to-moderate COVID-19 infection there were 4 cardiac SAEs in this trial, 3 from the treatment group (n = 452), including 1 death. There was 1 reported arrythmia in the placebo group for this study.[5] The timing of these events in relation to the Evusheld injections was not provided.

Overall, this report demonstrates the safety and tolerability of Evusheld in a small cohort of patients with CVID, including those with previous infection with or vaccination against COVID-19 as well as with underlying cardiac risk factors. Notably, 2 patients presented to the ED with chest pain, but with a negative cardiac evaluation result and thus without cardiac SAEs comparable to those reported in the PROVENT and TACKLE studies. Our report is unable to adequately evaluate efficacy on account of the short duration of follow-up, which may also have affected the incidence of adverse events reported. Larger studies with longer follow-up periods will be needed to address these issues in the population of those with immunodeficiency.

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