Brief report

Tolerability and outcomes with rollout of tixagevimab-cilgavimab in patients with common variable immunodeficiency

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Background: Tixagevimab-cilgavimab is a combination of 2 mAbs against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In December 2021, the Food and Drug Administration issued Emergency Use Authorization for intramuscular injection of tixagevimab-cilgavimab for prophylaxis against SARS-CoV-2 in immunocompromised patients. Shortly thereafter, our clinic distributed tixagevimab-cilgavimab to patients with common variable immunodeficiency.
Objective: We sought to evaluate the effectiveness and tolerability of tixagevimab-cilgavimab in a common variable immunodeficiency clinic.
Methods: A retrospective chart review from February 1, 2022, to August 1, 2022, of 47 patients with common variable immunodeficiency who were offered tixagevimab-cilgavimab was carried out. Comparative outcomes of treatment and nontreatment groups examined the occurrence of SARS-CoV-2 infection, severity of SARS-CoV-2 infection, and other non–SARS-CoV-2 infections.
Results: Seventy percent of the patients were female; mean age was 49 years. Twenty-three patients received tixagevimab-cilgavimab, and 24 did not receive prophylaxis. In the tixagevimab-cilgavimab group, all were vaccinated for SARS-CoV-2 and 22 were receiving immunoglobulin replacement. One patient was infected with SARS-CoV-2, no patients required emergency care, and 7 patients had non–SARS-CoV-2 infection. In the cohort that did not receive prophylaxis, 21 were vaccinated, and all received immunoglobulin replacement. Two patients tested positive for SARS-CoV-2, 1 patient required emergency care due to SARS-CoV-2 disease severity, and 4 patients had a non–SARS-CoV-2 infection. None of the results showed statistical significance.
Conclusions: Although there is evidence that tixagevimab-cilgavimab can be protective against SARS-CoV-2 in immunocompromised individuals, our data suggest that this benefit may be blunted in patients with common variable immunodeficiency on immunoglobulin replacement. The additional benefit of tixagevimab-cilgavimab in immunocompromised patients already receiving replacement therapy requires further exploration. (J Allergy Clin Immunol Global 2024;3:100293.)

Key words: *Tixagevimab-cilgavimab (Evusheld), common variable immunodeficiency, COVID-19, SARS-CoV-2, primary immunodeficiency, mAb*

INTRODUCTION

Common variable immunodeficiency (CVID) is a disease of absent or diminished humoral immunity from decreased levels of functional immunoglobulins.[1] Those affected are prone to increased infections, especially from respiratory pathogens, and have been suspected to experience increased severity from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. A report by Weifenbach et al[2] found elevated rates of moderate/severe infection and SARS-CoV-2–related complications in patients with CVID compared with the general population. Consequently, patients with CVID were prioritized to receive SARS-CoV-2 vaccines. However, subsequent studies have shown reduced immunologic response to coronavirus disease 2019 (COVID-19) vaccines in patients with CVID, possibly leading to decreased vaccine protection.[1,3] Passive immunity via mAbs is an alternative method for providing immunologic protection in patients with subtherapeutic vaccine response. Immunomodulation with antibodies has been of increasing research interest due to their use in providing effective treatments in cancer, autoimmune diseases, and transplant patients.[4] With SARS-CoV-2, mAbs have been shown to aid in prophylaxis against infection and decrease disease severity.[4] Specifically in the immunocompromised, mAbs can rapidly provide protection against emerging illnesses.

Tixagevimab-cilgavimab is a combination of 2 mAbs against SARS-CoV-2 shown to prevent infection in immunocompromised individuals. In December 2021, it received Emergency Use Authorization from the Food and Drug Administration for COVID-19 prevention.[5,6] Real-world effectiveness of tixagevimab-cilgavimab showed increased protection in multiple patient populations including solid-organ transplant and hematological malignancies.[7-9] With the change of circulating SARS-CoV-2 variants, more recent studies showed decreased effectiveness, which led to the Food and Drug Administration withdrawing the Emergency Use Authorization in January

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Abbreviations used
COVID-19: Coronavirus disease 2019
CVID: Common variable immunodeficiency
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

2023.[6,10] To aid in developing next-generation prophylactic mAbs, thorough understanding of the effectiveness of tixagevimab-cilgavimab is needed. At present, there is limited knowledge about impact on COVID-19 prevention, specifically in patients with CVID. We sought to fill this gap by evaluating the effectiveness and tolerability of tixagevimab-cilgavimab in a CVID clinic.

Upon rolling out tixagevimab-cilgavimab at Penn State Health Milton S. Hershey Medical Center in February 2022, a task force was created to contact patients with CVID receiving care at an Asthma, Allergy, and Immunology clinic and offer tixagevimab-cilgavimab. A list was generated using the CVID diagnosis code, and all patients were contacted via phone and offered tixagevimab-cilgavimab using the same prompts. Patients choosing to receive tixagevimab-cilgavimab were scheduled in clinic. Electronic medical records were reviewed for those contacted between February 1, 2022, and April 1, 2022. Patients were stratified into 2 groups depending on their decision to receive or decline tixagevimab-cilgavimab. Demographics (age, sex, race, ethnicity), current treatment with immunoglobulin replacement therapy, and COVID-19 vaccination status were collected. Records were reviewed for COVID-19 infection, severity, need for oxygen, and positivity for other infections after receiving or being contacted to receive tixagevimab-cilgavimab until August 1, 2022. Charts of patients receiving tixagevimab-cilgavimab were also reviewed for dosage and injection date. Adverse events were recorded including events occurring directly after administration and events reported by patients during the follow-up window.

Descriptive statistics were used to report clinical variables. The median and interquartile range were used to describe continuous variables, and numbers and percentages (%) were used to describe categorical variables. Given small sample size, nonparametic statistics were chosen. For group comparisons, the Mann-Whitney *U* test and Fisher exact tests were used. A *P* value of less than .05 established statistical significance.

RESULTS AND DISCUSSION

Of 47 electronic medical records reviewed, 23 patients elected to receive tixagevimab-cilgavimab and 24 were in the control group. Patients receiving tixagevimab-cilgavimab had their first dose between February 2, 2022, and March 30, 2022, with 13 (56.5%) patients receiving 150 mg/150 mg dosing and 10 (43.5%) patients receiving 300 mg/300 mg dosing. Average duration for follow-up was 150 days. Demographics were similar between the 2 groups (Table I). Of note, 3 control patients (12.5%) were not vaccinated against SARS-CoV-2, but all patients were receiving immunoglobulin replacement therapy. All patients who received tixagevimab-cilgavimab were vaccinated and 22 patients were receiving immunoglobulin replacement therapy.

Overall, there was 1 SARS-CoV-2 infection in the tixagevimab-cilgavimab group compared with 2 in the control group. One patient in the control group required treatment in the emergency department, whereas no patients who received tixagevimab-cilgavimab sought out this treatment. In addition, 4 (16.67%) control patients reported testing positive for other infections during this time compared with 7 (30.43%) in the treatment group. All patients receiving tixagevimab-cilgavimab tolerated the medications with no reported immediate adverse reactions including anaphylaxis or injection-site reactions. No adverse events were reported by patients after leaving the clinic. The difference in dosages is due to the Food and Drug Administration changing its recommendation on February 26, 2022, to increase the initial dosage amount to 300 mg of tixagevimab and 300 mg of cilgavimab.[6,10]

A recent study at Mayo Clinic was the first to assess tixagevimab-cilgavimab use specifically in the CVID population, showing that 87% of patients tolerated injection without adverse events.[11] Although no patients developed COVID-19 in this cohort, median follow-up was only 19 days. There is limited data on the clinical efficacy of tixagevimab-cilgavimab in the CVID population over extended time periods. Our data did not show significant benefit of tixagevimab-cilgavimab in preventing SARS-CoV-2 infection in patients with CVID with a median follow-up of 150 days. Of 3 COVID-19 infections identified in our cohort, only 1 sought out emergency care, and this individual had not received tixagevimab-cilgavimab. We hypothesize that a lack of difference in COVID-19 cases in our study could be due to the presence of protective SARS-CoV-2 antibodies in immunoglobulin replacement (intravenous or subcutaneous immunoglobulin) products. When tixagevimab-cilgavimab debuted in February 2022, immunoglobulin replacement products may have contained SARS-CoV-2 antibodies from the general population from either prior infection or appropriate vaccination. Along with the PROVENT trial having low numbers of immunocompromised patients who were unvaccinated, the data cutoff point occurred in August 2021.[5] Our population was highly vaccinated, which could have provided additional protection despite preliminary studies showing that the vaccine is not as effective in patients with CVID.[1] Literature also suggests that patients with primary immunodeficiency are inherently protected from COVID-19 mortality due to inability to generate a cytokine storm, which is a significant contributor to COVID-19 severity.[2,12]

Our data focus on the use of tixagevimab-cilgavimab in patients with CVID; however, its use in other immunocompromised populations has been studied. In France, Nguyen et al[13] had a similar study window and showed a protective effect of tixagevimab-cilgavimab in solid-organ transplant recipients, stem cell transplant patients, hematologic malignancies, and patients using immunosuppressive medications. The variability speaks to the difficulty of accurately capturing the effectiveness of prophylactic antibodies against a constantly changing novel virus. Increasing available literature of studies with variable designs, study population, and location helps combat this challenge and accurately describes the real-world effectiveness of tixagevimab-cilgavimab.

Passive immunization via mAbs is imperative for immunocompromised patients who have decreased response to COVID-19 vaccination. Our study focuses on patients with CVID, because literature is lacking in this cohort. However, passive immunity is relevant for all patients with significant immunodeficiencies or those unable to receive certain vaccines. It is important to assess safety, tolerability, and rollout in the real world of mAbs. Other

TABLE I. Patients' demographic characteristics

Characteristic	Control group (n = 24)	Tixagevimab-cilgavimab group (n = 23)
Age (y), median (range)	54.5 (16-82)	45.0 (23-70)
Sex, female, n (%)	19 (79.17)	14 (60.87)
Race, White, n (%)	22 (91.67)	21 (95.45)
Ethnicity, Hispanic/Latino, n (%)	0 (0.00)	1 (4.55)
SARS-CoV-2 vaccination status (vaccinated), n (%)	21 (87.50)	23 (100.00)
Receiving immunoglobulin replacement therapy, n (%)	24 (100)	22 (95.65)

preventative mAbs against SARS-CoV-2 (ie, bamlanivimab, casirivimab, imedvimab) have shown variable protection as predominating Omicron variants remain elusive to antibodies.[4] Focusing future research to quickly develop, test, and administer antibodies may be key for enhancing passive immunity in patients especially susceptible to novel pathogens.

Our study is limited by small sample size from a single clinical site, which restricted our ability to conduct a more comprehensive statistical analysis accounting for multiple confounders to elucidate the exact impact of tixagevimab-cilgavimab on COVID-19 infections. This also may contribute to the lack of statistical significance in our study's results because we were unable to provide a more robust analysis. We decided to focus on the process of medication rollout to improve the quality of our system to equitably distribute novel medications. Even though these results may not be broadly applicable to other sites with differing systems, infrastructure, and patient populations, we captured preliminary real-world clinical data during a period when tixagevimab-cilgavimab was shown to have significant neutralization activity against SARS-CoV-2. Our data highlight the need to develop alternative methods of protection in this highly immunocompromised group because they are still extremely susceptible to infection. In addition, our data were collected retrospectively via electronic medical record and some variables were collected from self-reported data. Infectivity and infection severity rates were recorded only if indicated in the chart via positive SARS-CoV-2 test result or patient self-report. This limits the ability to capture all positive infections during the study window, including patients who may be asymptomatic and did not test. Of note, our patients with CVID have frequent follow-ups where physicians record recent infections, which increases the likelihood of self-reported COVID-19 infection. Mitigating this limitation could involve contacting patients after the study window to confirm COVID-19 infections after tixagevimab-cilgavimab administration.

Tixagevimab-cilgavimab was not shown to have significant protection against COVID-19 in our patients with CVID. Currently, tixagevimab-cilgavimab is not authorized for clinical use in the United States due to current literature, including our study, finding lack of neutralization activity with the current predominating COVID-19 variants.[6,10] There remains significant need for the development of protective medications for immunocompromised patients against novel respiratory pathogens. For patients with CVID, adherence to immunoglobulin replacement treatment is strongly advised for protection from bacterial and other infections.[14] Further research can be aimed at increasing the longevity of effectiveness in mAbs, especially against SARS-CoV-2.

DISCLOSURE STATEMENT

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

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