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The Prevention of COVID-19 in High-Risk Patients Using Tixagevimab–Cilgavimab (Evusheld): Real-World Experience at a Large Academic Center

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ABSTRACT

BACKGROUND: Coronavirus disease 2019 (COVID-19) is associated with increased morbidity and mortality among immunocompromised patients. Tixagevimab–cilgavimab (Tix-Cil) is a combination of 2 monoclonal antibodies approved for the prevention of COVID-19 complications in this high-risk group.

METHODS: We retrospectively reviewed the charts of patients who received Tix-Cil during the Omicron variant period (January 17 to April 23, 2022), with a follow-up period until May 24, 2022. We collected data about patient underlying comorbidities and post Tix-Cil COVID-19 infections, deaths, and hospitalizations.

RESULTS: There were 463 patients with a median age of 68 years, of which 51% were male, 79% White, 13.2% Hispanic, 1.7% Black/African American, and 5.8% identified as Other. A total of 18% had undergone a solid organ transplantation or hematopoietic stem cell transplantation. Only 6/98 (6.1%) had severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) detected by polymerase chain reaction (PCR) at a median 48 days (interquartile range [IQR] 27.5, 69) follow-up. Forty-two patients (9.1%) were hospitalized, and 4 (0.9%) died, but none were attributed to COVID-19 or Tix-Cil. One hospitalized patient had an incidental, asymptomatic, positive SARS-CoV 2 by PCR. The median days from Tix-Cil administration to non-COVID-19-related hospitalization and death were 30 (IQR 17, 55) and 53 (IQR 18, 91), respectively.

CONCLUSION: Tix-Cil provides protection against COVID-19 complications in immunocompromised patients with suboptimal immune responses to vaccines.

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KEYWORDS: COVID-19; Immunocompromised host; Tixagevimab–cilgavimab

CLINICAL SIGNIFICANCE

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- Coronavirus disease 2019 (COVID-19) is associated with increased risk of mortality and morbidity in immunocompromised patients, and COVID-19 vaccines are not fully effective in this population.
- Tixagevimab–cilgavimab is a combination of 2 monoclonal antibodies that can prevent COVID-19 complications in at-risk patients.
- Despite the reported benefits of Tix-Cil in multiple studies, greater health care provider awareness is required as many patients are not being offered this important preventative therapy.

INTRODUCTION

Tixagevimab-cilgavimab (Tix-Cil) is a combination of 2 monoclonal antibodies directed against the surface spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) shown to be effective in preventing coronavirus disease 2019 (COVID-19) infection, hospitalization, and mortality among immunocompromised hosts (ICH).

Tix-Cil has proven, in multiple studies¹⁻³ to be effective in reducing hospitalization rates and death from COVID-19 in this population. On December 8, 2021, the US Food and Drug Administration (FDA) approved Tix-Cil under Emergency Use Authorization (EUA) in adults and children aged 12 years or older weighing at least 88 pounds (40 kg) who were moderate to severely immunocompromised for pre-exposure prophylaxis against COVID-19,⁴ with an initial approved dose of tixagevimab 150 mg and cilgavimab 150 mg. However, due to a concern for decreased susceptibility of BA.1 and BA.1.1 subvariants of Omicron (B.1.1.529) variant,^{5,6} the FDA revised the EUA on February 24, 2022 and recommended that the dose of Tix-Cil be increased to 300 mg/300 mg. Since the beginning of the pandemic, interest in finding greater options for the prevention of COVID-19 among the ICH has increased. This is especially evident after recent evidence showing that COVID-19 vaccines did not have a similar effect in reducing hospitalizations or deaths in ICH when compared with immunocompetent patients.⁷ Therefore, Tix-Cil may offer added protection to vaccines in ICH, especially during the Omicron variant period. We aimed to study the real-world effect of Tix-Cil in reducing rates of hospitalizations and deaths from COVID-19 among high-risk ICH who received Tix-Cil in Arizona.

METHODS

The study was conducted in accordance with the Declaration of Helsinki guidelines and was approved by the University of Arizona Institutional Review Board. We retrospectively chart-reviewed ICH who received Tix-Cil in our institution from January 17, 2022 to April 23, 2022, with a follow-up period until May 24, 2022. Data about patients' underlying comorbidities, post Tix-Cil COVID-19 infection, hospitalization, and deaths were collected. During the study period, patients received either 1 or 2 separate administrations of intramuscular injections consecutively to achieve a total dose of 300 mg tixagevimab-300 mg cilgavimab at our designated infusion center at the University of Arizona, Banner University Medical Center in Tucson, Ariz. Patients receiving Tix-Cil therapy were categorized as moderately to severely

immunocompromised with a presumed inadequate immune response to COVID-19 vaccinations. Tix-Cil candidates included those who had received at least one dose of COVID-19 vaccine or were unable to receive COVID-19 vaccinations due to a history of severe reaction to a COVID-19 vaccine. All patients meeting the criteria for therapy did not have a recent exposure or an acute COVID-19 infection.

Due to the initial limited supplies of Tix-Cil, most medical centers developed a system prioritizing the highest-risk patients and nonresponders to vaccines to receive Tix-Cil; however, Tix-Cil became more accessible as greater supplies became more available.

RESULTS

A total of 463 patients were included in the study; they received either a 300-mg/300-mg dose or 2 150-mg doses of Tix-Cil. Patients had a median age of 68 years; 51% were male, 79% White, 13.2% Hispanic, 1.7% Black/African American, and 5.8% identified as Other. A total of 18% had undergone a solid organ transplantation or hematopoietic stem cell transplantation

CLINICAL SIGNIFICANCE

- Coronavirus disease 2019 (COVID-19) is associated with increased risk of mortality and morbidity in immunocompromised patients, and COVID-19 vaccines are not fully effective in this population.
- Tixagevimab–cilgavimab is a combination of 2 monoclonal antibodies that can prevent COVID-19 complications in at-risk patients.
- Despite the reported benefits of Tix-Cil in multiple studies, greater health care provider awareness is required as many patients are not being offered this important preventative therapy.

Table 1 Clinical Characteristics of Patients Receiving Tixagevimab–Cilgavimab (N = 463)

Characteristics	
Age, median (IQR)	68.0 (58.0, 75.0)
Male, n (%)	238 (51.4)
Vaccinated,* n (%)	356 (76.9)
Race/ethnicity, n (%)	
White	367 (79.3)
Black	8 (1.7)
Hispanic	61 (13.2)
Other	27 (5.8)
Underlying disease, n (%)	
Hematologic malignancies	289 (62.4)
Transplant [†]	85 (18.4)
Autoimmune disease	40 (8.6)
Advanced HIV disease	19 (4.1)
Solid tumor on chemotherapy [‡]	19 (4.1)
Other	11 (2.4)
SARS-CoV-2 PCR detected, [§] n (%)	6 (6.1)
Hospitalized, n (%)	42 (9.1)
Deaths, n (%)	4 (0.9)

*Received at least one dose of COVID-19 vaccine; 88 (19%) had missing vaccine information.

[†]Included both solid organ and bone marrow transplant.

[‡]Included primary immunodeficiency and interstitial lung disease.

[§]Available nasopharyngeal samples in 98 patients.

HIV = human immunodeficiency virus; IQR = interquartile range; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome 2 coronavirus 2.

Table 2 Clinical Characteristics Among Hospitalized Patients Receiving Tixagevimab–Cilgavimab (N = 42)

Characteristics	
Age, median (IQR)	67.0 (62.0, 73.8)
Male, n (%)	24 (57.1)
Vaccinated,* n (%)	39 (92.9)
Race/ethnicity, n (%)	
White	29 (69.0)
Black	1 (2.4)
Hispanic	9 (21.4)
Others	3 (7.1)
Underlying disease, n (%)	
Autoimmune disease	2 (4.8)
Hematologic malignancies	26 (61.9)
Advanced HIV disease	2 (4.8)
Solid tumor	3 (7.1)
Transplant [†]	8 (19.0)
Other [‡]	1 (2.4)
Days to hospitalization, median (IQR)	30.0 (17.0, 55.0)
Days to death, median (IQR)	52.5 (18.2, 91.5)
Covid PCR after Tix-Cil, [§] n (%)	
Detected	1 (2.4)
Not detected	38 (90.5)
Missing	3 (7.1)

*Received at least one dose of COVID-19 vaccine; 88 (19%) had missing vaccine information and 19 (4.1%) were not vaccinated due to contraindications.

[†]Included both solid organ and bone marrow transplant.

[‡]Included primary immunodeficiency and interstitial lung disease.

[§]Available nasopharyngeal samples in 98 patients.

HIV = human immunodeficiency virus; IQR = interquartile range; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome 2 coronavirus 2.

(Table 1). The majority (77%) received at least one dose of the COVID-19 vaccine prior to receiving Tix-Cil. None of the patients reported adverse events secondary to Tix-Cil. Only 98 patients had a SARS-CoV-2 test by polymerase chain reaction (PCR) available during the study period, and of those, only 6 (6.1%) had a positive SARS-CoV-2 detected by PCR at a median 48 days (interquartile range [IQR] 27.5, 69) follow-up.

Forty-two patients (9.1%) were hospitalized, and 4 (0.9%) died, but none were attributed to COVID-19. One hospitalized patient had incidental asymptomatic positive SARS-CoV 2 detected by PCR. Among this group, 57% were male, 69% White, 21.4% Hispanic, 2.4% Black/African American, and 7.1% identified as Other. The median days from Tix-Cil administration to non-COVID-19-related hospitalization and death were 30 (IQR 17, 55) and 53 (IQR 18, 91), respectively (Table 2).

DISCUSSION

Our findings show that Tix-Cil was safe and effective in preventing COVID-19-related hospitalizations and death among moderate to severely immunocompromised patients. The study was conducted during the Omicron variant period, which was associated with reduced efficacy of many monoclonal

antibodies.^{5,8} Therefore, due to the concerns of decreased susceptibility of BA.1 and BA.1.1 of the Omicron (B.1.1.529) to Tix-Cil, the FDA revised the EUA and recommended that the dose of Tix-Cil be increased to 300 mg/300 mg. In addition, the lower dose of 150 mg was shown clinically to be associated with breakthrough SARS-CoV-2 in a small cohort of patients with hematological malignancy during the Omicron period.⁹ Several other studies reported in vitro data about decreased susceptibility of Tix-Cil with the BA.1 and BA.1.1 subvariants of the Omicron (B.1.1.529) variant.¹⁰⁻¹²

All our patients received the adjusted higher dose, either once or on 2 separate visits after the recommended dose modification by the FDA. While a recent in vitro study showed reduced antibody neutralization of Tix-Cil against Omicron variants,¹³ this did not have a significant clinical outcome in our study or similar studies during the Omicron variant period.^{9,14,15}

During the study period, we encountered 43 hospitalizations and one death, none of which were attributed to COVID-19. Such a reduction in both COVID-19-related hospitalizations and deaths is significant. A similar report from a study of kidney transplant recipients (KTRs) has indicated that among patients who received Tix-Cil, only 1.2% were hospitalized, as compared with 11.3% in the nontreated group.¹⁴ They also reported one COVID-19-related death in the Tix-Cil group as compared with 2 deaths in the control group. However, our study follow-up period is shorter, and while we included transplant recipients, they constituted 18% of the total cohort. Also, similar to our findings, Kertes et al¹⁵ reported no deaths attributed to COVID-19 in their cohort, who received Tix-Cil with only a 0.1% reported rate of hospitalization in their cohort of ICH. They reported a 92% lower likelihood of hospitalization and death after adjustment for those receiving Tix-Cil¹⁵ despite using a lower dose of tixagevimab 150 mg-cilgavimab 150 mg.

Our cohort's follow-up test positivity percentage of 6.1% is relatively lower than that of the greater community (the Arizona Department of Health Services reported a 19% positivity percentage during a similar period).¹⁶ This was similar to the findings in another study where only 3.5% of the 825 ICH aged 12 years and older who received Tix-Cil were infected with SARS-CoV-2, vs 7.2% in the control group.¹⁵ Additionally, our test positivity rate is similar to the Tix-Cil-treated KTRs who were COVID-19 vaccine nonresponders or low responders, following at least 3 doses of mRNA vaccines at the Bordeaux University Hospital in France. Among the 333 KTRs who received Tix-Cil, 12.3% developed symptomatic COVID-19, as compared with 43.3% of patients who did not receive Tix-Cil.¹⁴ Other studies have also showed a significant reduction in the rates of SARS-CoV-2 positivity after Tix-Cil.^{1,17} Data about SARS-CoV-2 PCR positivity was available for 98 (21%) of the patients who received Tix-Cil in our cohort. We speculate that our cohort's lower test positivity rate may be linked to the proactive preventative measures taken by our severely immunocompromised patients, which include strict masking and social distancing at our center.

Our study has several limitations, including the retrospective design of the study, which can introduce selection bias. Also, while our findings show a reduction in the rates of hospitalizations or deaths secondary to COVID-19, we did not include matched controls to compare such findings. Moreover, not all patients were tested for SARS-CoV-2 by PCR during the follow-up period.

Our study's strengths include a diverse large population of ICH at increased risk of COVID-19-related complications. We provide real-world information about the efficacy of Tix-Cil in preventing COVID-19 hospitalizations and death during the Omicron period, which is reported to have been associated with increased breakthrough COVID-19 infections among vaccinated patients.

In conclusion, Tix-Cil provides an additional tool in the armamentarium of therapies available today by preventing COVID-19 complications in ICH with suboptimal immune responses to COVID-19 vaccines. In addition, as of June 29, 2022, the FDA has recommended that repeat doses of Tix-Cil be administered every 6 months for at-risk individuals.¹⁸ Despite the reported benefits of Tix-Cil, greater health care provider awareness is required because many at-risk patients are not being offered this important preventative therapy. Improved provider awareness is needed to offer such therapies to patients at risk for COVID-19-related complications and death, especially among underserved and resource-limited communities facing barriers to health care.

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