Received: 7 July 2022 | Accepted: 15 July 2022

DOI: 10.1111/tid.13932

TRANSPLANT INFECTIOUS DISEASE

CLINICAL CORRESPONDENCE

Myalgia in liver transplant recipients after receiving tixagevimab/cilgavimab for pre-exposure prophylaxis of COVID-19: A case series

Hanna L. Kleiboeker[1] | **Margaret R. Jorgenson**[1] | **Jeannina A. Smith**[2]

[1]Department of Pharmacy, University of Wisconsin Hospital and Clinics, Madison, Wisconsin, USA

[2]Department of Medicine, Division of Infectious Diseases, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA

Correspondence
Hanna L. Kleiboeker, Department of Pharmacy, University of Wisconsin Hospital and Clinics, 600 Highland Ave, Madison, WI 53792, USA.
Email: hanna.kleiboeker@gmail.com

KEYWORDS
COVID-19, liver transplant, myalgia, tixagevimab/cilgavimab

To the Editor,

Solid organ transplant (SOT) recipients are at increased risk for severe coronavirus disease 2019 (COVID-19) infections, with higher rates of admission to intensive care units and use of mechanical ventilation.[1,2] The Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for tixagevimab with cilgavimab (EVUSHELD) for pre-exposure prophylaxis of COVID-19 in December 2021.[3] Tixagevimab/cilgavimab is approved for use in patients not currently infected with COVID-19; without known recent exposure to an infected individual; and who have moderate-to-severe immune compromise and may not mount adequate immune response to COVID-19 vaccination or for whom vaccination is contraindicated.[3] Based on EUA criteria, tixagevimab/cilgavimab use in SOT recipients has rapidly expanded given the evidence demonstrating diminished responses to COVID-19 vaccination and breakthrough infections in this population at increased risk for severe infections.[4–6]

Tixagevimab/cilgavimab consists of two recombinant human IgG1κ monoclonal antibodies administered intramuscularly that bind to the receptor binding domain of SARS-CoV-2 spike protein simultaneously to neutralize viral particles and prevent infection.[3,7] Warnings and precautions included in the EUA are hypersensitivity reactions, clinically significant bleeding disorders, and cardiovascular events.[3] The mean elimination half-lives of tixagevimab and cilgavimab are 87.9 and 82.9 days, and time to peak drug concentration is 14.9 (range 1.1–86) and 15 (range 1.1–85) days, respectively.[8]

Results from the ongoing phase 3 PROVENT trial investigating the efficacy and safety of tixagevimab 150 mg/cilgavimab 150 mg were recently published.[9] The primary analysis demonstrated a 76.7% relative risk reduction ($p < 0.001$) of symptomatic COVID-19, which improved to 82.8% at extended follow-up.[9] Adverse events were common in patients who received drug, with 35.3% of patients reporting 1+ adverse event (ADE). ADEs were mild-to-moderate in intensity; the most commonly reported was injection-site reaction.[9] Four patients who received tixagevimab/cilgavimab experienced adverse events related to musculoskeletal and connective tissue disorders.[9] Of note, the PROVENT trial utilized original EUA dosing rather than revised dosing currently used in practice of 300 mg.[7] Publication of another phase 3 trial, STORM CHASER, is forthcoming.[10,11]

SOT recipients were screened from 1/11/2022 to 5/1/2022 for receipt of tixagevimab/cilgavimab with subsequent new onset of myalgia. Patients were excluded if another cause of myalgia was identified. We observed three cases of significant myalgia in liver transplant recipients after receiving tixagevimab/cilgavimab. Patient information is available in Table 1.

1 | PATIENT CASE #1

Patient 1 received tixagevimab 150mg/cilgavimab 150 mg 228 days after transplant. Shortly after administration, the patient reported new onset of symptoms including muscle pain and weakness. Four weeks after receiving tixagevimab/cilgavimab, the patient was found to have low level cytomegalovirus (CMV) viremia (viral load, VL, 12,100 IU/ml), which resolved with 2 weeks of valganciclovir therapy. When symptoms had persisted for 5 weeks, a panel of blood tests was ordered

Abbreviations: ADE, adverse drug event; ANA, antinuclear antibodies; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CMV, cytomegalovirus; ESR, erythrocyte sedimentation rate; EUA, Emergency Use Authorization; FDA, Food and Drug Administration; RF, rheumatoid factor; SOT, solid organ transplant; VL, viral load.

TABLE 1 Patient characteristics

	Patient 1	Patient 2	Patient 3
Age at transplant (years)	52	54	56
Gender	Male	Male	Female
Transplant type	Primary DBD Liver	Primary DBD Liver	Primary DBD Liver
Cause of liver failure	Alcoholic cirrhosis	Alcoholic cirrhosis	Alcoholic cirrhosis
Induction immunosuppression	Dexamethasone	Dexamethasone	Dexamethasone
Maintenance immunosuppression	Tacrolimus	Tacrolimus Prednisone taper	Tacrolimus XR Mycophenolate Prednisone
Time from transplant to tixagevimab/cilgavimab (days)	228	40	156
Tixagevimab/cilgavimab dose received	150 mg/150 mg	150 mg/150 mg	150 mg/150 mg
Time from tixagevimab/cilgavimab to myalgia (days)	1	0	29
Additional symptoms reported after tixagevimab/cilgavimab	Muscle weakness Arthralgia Fatigue	Arthralgia	Nausea/vomiting Diarrhea Intermittent fevers Chills Fatigue Malaise
Additional work-up completed after report of myalgia	ESR CRP ANA RF	ESR CRP ANA RF	Blood cultures Urine culture Procalcitonin Lactate
Time from tixagevimab/cilgavimab to resolution of myopathy (days)	Ongoing	Ongoing	47

Abbreviations: ANA, antinuclear antibodies; CRP, C-reactive protein; DBD, donation after brain death; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; XR, extended-release.

to assess for autoimmune diseases. All tests for autoimmune diseases were negative, and the patient reported that his symptoms significantly improved after a prednisone taper, with the exception of ongoing shoulder pain. Liver function tests remained within normal limits for the duration of his symptoms.

2 | PATIENT CASE #2

Patient 2 received tixagevimab 150 mg/cilgavimab 150 mg 40 days after transplant. The patient reported new onset of symptoms including muscle aches with weakness, which began immediately after receiving the product and have persisted for >3 months. Resumption of prednisone, which had been discontinued per protocol, was considered but the patient elected not to resume due to adverse effects. Sulfamethoxaxole-trimethoprim, which was initiated after transplant for *Pneumocystis jirovecii* pneumonia prophylaxis, was held for 1 week without improvement of symptoms. A taper of levetiracetam, which was initiated for posttransplant seizures, was started. After these symptoms had persisted for 7 weeks, a panel of blood tests was ordered to assess for autoimmune diseases; all tests were negative. The patient reports ongoing muscle and joint pain, although these symptoms do not limit his activities of daily living; he has not experienced an elevation of liver function tests since receiving tixagevimab/cilgavimab.

3 | PATIENT CASE #3

Patient 3 received tixagevimab 150 mg/cilgavimab 150 mg 156 days after transplant. Beginning 4 weeks after administration, the patient first reported nausea and vomiting, which resolved, and diarrhea then intermittent fevers with nighttime chills, fatigue, malaise as well as muscle pain and weakness. The patient experienced mild elevation of liver function tests (<2–3× upper limit of normal). After symptoms persisted for 4 weeks, the patient presented to the emergency department for infectious workup. The workup was unremarkable except for low level CMV viremia (VL 2,570 IU/ml). CMV viral load was less than the lower limit of quantification 1 week later, although myalgia persisted. Symptom resolution was not congruous with clearance of viremia. The patient reports all symptoms have resolved except for ongoing mild diarrhea.

It remains unclear why these liver transplant recipients experienced new myalgia after receiving tixagevimab/cilgavimab. The mechanism of tixagevimab/cilgavimab does not seem to convey a risk of myalgia, nor has this adverse effect been widely reported in literature. Additionally, the onset of myalgia did not necessarily correspond with time to peak drug concentration of tixagevimab and cilgavimab, with two patients experiencing myalgia within 1 day of administration and one patient experiencing myalgia over 4 weeks after administration. A limitation of the currently available literature is the small proportion of SOT

TABLE 2 University of Wisconsin transplant recipients who have received tixagevimab/cilgavimab (EVUSHELD) by type of solid organ transplant, as of May 2022

Type of solid organ transplant	Number of patients who have received tixagevimab/cilgavimab
Kidney	139
Lung	101
Liver	77
Heart	48
Simultaneous pancreas-kidney	19
Pancreas	11
Simultaneous liver-kidney	10
Simultaneous intestinal-liver-pancreas-kidney	1
Simultaneous intestinal-liver-pancreas	1
Total	**407**

recipients represented in the data set; in the PROVENT trial, only 3.3% of the total study population was receiving immunosuppressive therapy as the qualifying high-risk factor for severe COVID-19.[9]

All transplant recipients from our center who have received tixagevimab/cilgavimab are shown in Table 2. At our center, three of 77 liver transplant recipients who have received tixagevimab/cilgavimab (3.9%) have reported myalgia; by contrast, 139 kidney transplant recipients and 101 lung transplant recipients have received tixagevimab/cilgavimab without any reports of myalgia. We propose two potential mechanisms that may contribute to this preliminary observation. First, acute myopathy after liver transplant has been reported in literature.[12,13] Perhaps liver transplant recipients are at increased of musculoskeletal adverse effects after receiving tixagevimab/cilgavimab compared to other populations, which constituted the majority of patients studied in the PROVENT trial and largely informed the reported adverse effect profile. If a larger population of SOT recipients, particularly liver transplant recipients, were studied after receiving tixagevimab/cilgavimab, myalgia may emerge as a more commonly reported adverse effect. Second, toxin clearance may be delayed after liver transplant, supported by transient metabolic-toxic central nervous system complications reported in literature.[14] Tixagevimab and cilgavimab undergo metabolism through catabolic pathways, and hepatic clearance of these breakdown products could be delayed in the early post-transplant period, resulting in a serum sickness-like reaction exclusive to liver transplant recipients after receiving tixagevimab/cilgavimab.[3] However, two patients began experiencing myalgias within 1 day of administration, which does not align with true serum sickness where symptoms emerge 1–2 weeks after first exposure.

At this time, tixagevimab/cilgavimab use continues to increase in the SOT population, and the drug is being used at higher doses compared to dosing used in the PROVENT trial due to FDA revision of the EUA. This warrants vigilant monitoring for novel adverse effects in SOT recipients compared to what was observed in the PROVENT trial, including myalgia in liver transplant recipients. Additionally, if a liver transplant recipient experiences new-onset myalgia after receiving tixagevimab/cilgavimab, clinicians may consider drug-induced myalgia in the differential diagnosis. These steps are necessary to ensure tixagevimab/cilgavimab can continue to be used safely to protect this high-risk patient population from severe COVID-19 infections and associated negative outcomes.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

FUNDING INFORMATION

The authors received no specific funding for this work.

ORCID

Hanna L. Kleiboeker https://orcid.org/0000-0003-3149-6558
Margaret R. Jorgenson https://orcid.org/0000-0001-6088-9727
Jeannina A. Smith https://orcid.org/0000-0001-9379-6332

REFERENCES

1. Kates OS, Haydel BM, Florman SS, et al. Coronavirus disease 2019 in solid organ transplant: a multicenter cohort study. *Clin Infect Dis*. 2021;73(11):e4090-e4099. doi: 10.1093/cid/ciaa1097
2. Pereira MR, Arcasoy S, Farr MA, et al. Outcomes of Covid-19 in solid organ transplant recipients: a matched cohort study. *Transpl Infect Dis*. 2021;23(4):e13637. doi: 10.1111/tid.13637
3. FDA. Fact sheet for healthcare providers: emergency use authorization for Evushel (tixagevimab co-packaged with cilgavimab). Accessed April 26, 2022. https://www.fda.gov/media/154701/download
4. Holden IK, Bistrup C, Nilsson AC, et al. Immunogenicity of SARS-CoV-2 mRNA vaccine in solid organ transplant recipients. *J Intern Med*. 2021;290(6):1264-1267. doi: 10.1111/joim.13361
5. Ali NM, Alnazari N, Mehta SA, et al. Development of COVID-19 infection in transplant recipients after SARS-COV-2 vaccination. *Transplantation*. 2021;105(9):e104-e106. doi: 10.1097/tp.0000000000003836
6. Al Jurdi A, Morena L, Cote M, Bethea E, Azzi J, Riella LV. Tixagevimab/cilgavimab pre-exposure prophylaxis is associated with lower breakthrough infection risk in vaccinated solid organ transplant recipients during the Omicron wave. medRxiv; 2022. doi: 10.1101/2022.05.17.22274980. medRxiv
7. Center for Drug Evaluation and Research. FDA authorizes revisions to Evusheld dosing. February 24, 2022. Accessed April 26, 2022. https://www.fda.gov/drugs/drug-safety-and-availability/fda-authorizes-revisions-evusheld-dosing
8. Tixagevimab and Cilgavimab. Lexicomp. Accessed May 12, 2022. https://online.lexi.com/lco/action/doc/retrieve/docid/uofwisconsin_f/7181632?cesid=5bSWTIXlESm&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Devusheld%26t%3Dname%26acs%3Dtrue%26acq%3Devushl#
9. Levin MJ, Ustianowski A, De Wit S, et al. Intramuscular AZD7442 (Tixagevimab–CILGAVIMAB) for prevention of covid-19. *N Engl J Med*. 2022;386(23):2188-2200. doi: 10.1056/nejmoa2116620
10. ClinicalTrials.gov. Phase III double-blind, placebo-controlled study of azd7442 for post-exposure prophylaxis of COVID-19 in adults.

Phase III double-blind, placebo-controlled study of AZD7442 for post-exposure prophylaxis of COVID-19 in adults - full text view - ClinicalTrials.gov. Accessed April 26, 2022. https://clinicaltrials.gov/ct2/show/NCT04625972
11. astrazeneca. Update on AZD7442 STORM CHASER trial in post-exposure prevention of symptomatic COVID-19. June 15, 2022. Accessed June 27, 2022. https://www.astrazeneca.com/media-centre/press-releases/2021/update-on-azd7442-storm-chaser-trial.html
12. Campellone JV, Lacomis D, Kramer DJ, Van Cott AC, Giuliani MJ. Acute myopathy after liver transplantation. *Neurology*. 1998;50(1):46-53. doi: 10.1212/wnl.50.1.46
13. Yilmaz M, Cengiz M, Sanli S, et al. Neurological complications after liver transplantation. *J Int Med Res*. 2011;39(4):1483-1489. doi: 10.1177/147323001103900437
14. Bernhardt M, Pflugrad H, Goldbecker A, et al. Central nervous system complications after liver transplantation: common but mostly transient phenomena. *Liver Transpl*. 2015;21(2):224-232. doi: 10.1002/lt.24035

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kleiboeker HL, Jorgenson MR, Smith JA. Myalgia in liver transplant recipients after receiving tixagevimab/cilgavimab for pre-exposure prophylaxis of COVID-19: A case series. *Transpl Infect Dis*. 2022;e13932. https://doi.org/10.1111/tid.13932