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

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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...
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 | Tacrolimus XR |
|                         | Prednisone taper | Prednisone taper | 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 | Nausea/vomiting |
|                         | Arthralgia | Fatigue   | Diarrhea   |
|                         |           |           | Intermittent fevers |
|                         |           |           | Chills |
|                         |           |           | Fatigue |
|                         |           |           | Malaise |
| Additional work-up completed after report of myalgia | ESR | ESR | Blood cultures |
|                         | CRP | CRP | Urine culture |
|                         | ANA | ANA | Procalcitonin |
|                         | RF  | RF  | 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.

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. Sulfamethoxazole-trimethoprim, which was initiated after transplant for Pneumocystis jiroveci 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 (EVUSHIELD) 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.

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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;24:e13932. https://doi.org/10.1111/tid.13932