Acute Liver Failure Secondary to Remdesivir in the Treatment of COVID-19

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ABSTRACT

Remdesivir has been the mainstay of coronavirus disease 2019 treatment since the start of the severe acute respiratory syndrome coronavirus 2 pandemic. Despite its growing use, safety data are limited. We present the case of an elderly man with obesity and coronavirus disease 2019 who developed acute liver failure after initiation of remdesivir. This report broadens our knowledge of the side effect profile of remdesivir and discusses potential risk factors and an approach to remdesivir-induced liver failure. Our case also highlights the importance of monitoring hepatic function after initiation of therapy with remdesivir.

INTRODUCTION

Since the first reported case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there have been over 60 million cases in the United States, resulting in over 800,000 deaths from coronavirus disease 2019 (COVID-19).1 Remdesivir is currently the only drug approved by the Food and Drug Administration (FDA) for the treatment of hospitalized patients with COVID-19. The FDA recommends remdesivir in the treatment of COVID-19 patients with supplemental oxygen requirements.2

Although safety data on remdesivir for COVID-19 treatment are limited, hepatotoxicity has been reported. Ten percent to 50% of patients can develop a mild-to-moderate increase in serum aminotransferases.3 Less is known about the risk of acute liver failure (ALF) with remdesivir. We present a case of ALF after initiation of remdesivir for COVID-19.

CASE REPORT

An 83-year-old man with obesity (body mass index: 30.2), chronic kidney disease, coronary artery disease status post coronary artery bypass, and prostate cancer status post prostatectomy presented with watery diarrhea, nonproductive cough, and chills for 1 week. He was found to be SARS-CoV-2-positive by polymerase chain reaction testing, with chest x-ray findings consistent with left lower lobe pneumonia. He was placed on nasal cannula for supplemental oxygen support because of mild hypoxemia. Ceftriaxone and azithromycin were started for a superimposed bacterial pneumonia, and he was admitted to the medicine floors.

On admission, his hepatic function test showed an alanine aminotransferase (ALT) level of 27, an aspartate aminotransferase (AST) level of 54, an alkaline phosphatase (ALP) level of 55, and a total bilirubin level of 1.0. His international normalized ratio (INR) for prothrombin time at presentation was 1.15. Three months before his presentation, his AST was 26 and ALT was 17. His acute kidney injury began to improve after intravenous fluids by hospital day (HD) 2 and was resolved by HD 5.

Imaging before admission was only notable for a hepatic cyst seen on computed tomography. This was performed 12 years before assess for malignant spread of his prostate cancer. His medications had not changed in the previous 6 months. He had no history of alcohol use disorder.
On HD 1, he was started on remdesivir and dexamethasone. He was titrated off supplemental oxygen support on HD 2. The patient completed a 5-day course of ceftriaxone and a 3-day course of azithromycin. On HD 6, the patient was noted to have altered mental status without asterixis. His liver function tests showed an elevation in his aminotransferases, with an AST of 3,539 and an ALT of 2,246. His ALP was elevated to 230 and total bilirubin to 2.9. His INR rose to 4.7 with an indirect bilirubin of 0.3. Laboratory test results, including a fibrinogen of 369 and a platelet count of 244, were inconsistent with disseminated intravascular coagulation. A right upper quadrant ultrasound showed a patent portal vein with normal vascular flow and normal biliary ducts. Acute viral hepatitis serologies and autoimmune markers were negative. Remdesivir and dexamethasone were discontinued because of concern for drug-induced liver injury (DILI), and the patient was transferred to the medical intensive care unit. Ceftriaxone, azithromycin, remdesivir, and dexamethasone were the only new drugs administered to the patient.

The patient was started on continuous intravenous N-acetylcysteine (NAC) for a 5-day course. A 3-day course of intravenous vitamin K was administered to reverse his coagulopathy. The patient’s mental status began to improve after initiation of NAC, with return to baseline 2 days after NAC initiation. Given the rapid improvement in mental status, lactulose was deferred for the treatment of hepatic encephalopathy. The patient remained off supplemental oxygen support and was hemodynamically stable during his medical intensive care unit course. He did not require vasoressor support, and his kidney function remained at his baseline. His biochemical abnormalities also began to improve after NAC initiation and continued to improve during his hospital course. He was discharged on HD 23, with an AST of 47 and an ALT of 108.

DISCUSSION

We present a case of an elderly man with SARS-CoV-2 who developed ALF with grade 1 encephalopathy 6 days after initiation of remdesivir that was successfully treated with NAC. This case provides additional knowledge on the safety profile of remdesivir, with implications for patient care and monitoring of hepatic function.

The patient had an acute rise in AST, ALT, and INR after completion of remdesivir. Acute viral, autoimmune, and ischemic etiologies for acute liver failure were ruled out by imaging and serum testing. Aside from remdesivir, other potential causes of DILI include ceftriaxone and azithromycin. However, ceftriaxone is known to induce a cholestatic hepatitis.3 In this case, the elevation of AST and ALT were out of proportion to the rise of ALP.4 The rare reports of azithromycin-induced hepatocellular injury were detected 14 days after treatment, which does not fit our patient’s clinical course.

Treatment with remdesivir is associated with minor aminotransferase elevations usually seen within 1–5 days of remdesivir initiation.1 The risk of more severe liver damage is unclear. Clinical trials report that up to 9% of patients experience aminotransferase elevations greater than 5 times the upper limit of normal.2 However, more recent randomized control studies only saw grade 3–4 AST elevations in 0%–3% of patients.5–7 Our patient experienced an acute, severe rise in AST, ALT, and INR after 6 days of remdesivir. Autoimmune, acute viral, biliary, and ischemic etiologies for ALF were ruled out with serum testing and imaging. Although SARS-CoV-2 may also cause hepatic injury, the degree of hepatic insult was out of proportion to the severity of COVID-19 for this patient who had minimal oxygen requirements. COVID-19 disease severity has been shown to correlate with more severe liver injury.8 Another report describes ALF in 2 patients with COVID-19 treated with remdesivir, with a similar time course of aminotransferase elevation after initiation of remdesivir.9

Although the exact mechanism of remdesivir-induced hepatocellular damage is unknown, it is postulated that p-glycoproteins may play a role.10 P-glycoproteins are commonly found on the cell membrane of hepatocytes and function to move foreign substances to the bile ducts.11 Numerous drugs, including azithromycin, have been shown to inhibit p-glycoprotein activity.12 Our patient was treated with azithromycin for a suspected bacterial infection, which may have led to elevated remdesivir levels within hepatocytes. In vitro studies have shown that remdesivir is toxic to hepatocytes at elevated concentrations.10 Furthermore, this patient’s obesity may have put him at elevated risk for DILI. Remdesivir is metabolized by cytochrome P450 and then renally eliminated.10 Although the exact mechanism has not been elucidated, it is believed that people with obesity have impaired CYP-450 activity leading to toxic metabolite and parenteral drug buildup.13

In conclusion, we would like to increase the awareness among clinicians of this rare but potentially fatal side effect of remdesivir in patients with COVID-19. Currently, the FDA recommends laboratory evaluation of hepatic function and prothrombin before initiation of remdesivir and repeat laboratory testing as clinically indicated. Remdesivir should be discontinued if there are signs of liver inflammation and should be considered for discontinuation if ALT increases to 10 times the upper limit of normal.14 This case highlights the need for close monitoring of liver function when initiating therapy with remdesivir and advocates for the assessment of hepatic function and prothrombin term during treatment. Dedicated studies are needed to expand our understanding of the side effect profile of remdesivir, the patient-level risk factors for remdesivir-associated hepatotoxicity and liver failure, and optimal monitoring and treatment. In addition, this case highlights the need for an easily accessible adverse event-reporting program and postmarketing studies of new therapies because we expect more medications for COVID-19 to be fast-tracked for approval in the near future.
DISCLOSURES

Author contributions: K. Lin: obtaining patient consent, data analysis and interpretation, and writing of the original manuscript draft. V. Gausman: drafting of the manuscript and critical revision of the manuscript. M. Poles: critical revision of the manuscript. V. Popov: data analysis and interpretation of data, critical revision of manuscript, and is the article guarantor.

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REFERENCES

1. COVID Data Tracker: US Center for Disease Control and Prevention. 2021 (https://covid.cdc.gov/covid-data-tracker).
2. National Institutes of Health. Therapeutic management of patients with COVID-19. Therapeutic Management Web site. 2020. Updated December 3, 2020. Accessed February 1, 2021.
3. Remdesivir [Updated 2020 Nov 4]. In LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, 2012 (https://www.ncbi.nlm.nih.gov/books/NBK564049/).
4. Martinez MA, Vuppalanchi R, Fontana RJ, et al. Clinical and histologic features of azithromycin-induced liver injury. Clin Gastroenterol Hepatol. 2015;13(2):369–76.e3.
5. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: A randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395(10236):1569–78.
6. Goldman JD, Lye DC, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med. 2020;383(19):1827–37.
7. Zhai G, Li M, Wang Y, Wu J. Drug-induced liver disturbance during the treatment of COVID-19. Front Pharmacol. 2021;2021:2149.
8. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: Management and challenges. Lancet Gastroenterol Hepatol. 2020;5(5):428–30.
9. Carothers C, Birrer K, Vo M. Acetylcysteine for the treatment of suspected remdesivir-associated acute liver failure in COVID-19: A case series. Pharmacotherapy. 2020;40(11):1166–71.
10. Leegwater E, Strik A, Wilms E, Bosma L, Burger D, Ottens T. Drug-induced liver injury in a patient with coronavirus disease 2019: Potential interaction of remdesivir with P-glycoprotein inhibitors. Clin Infect Dis. 2020.
11. Arias I, Gatmaitan Z, Mazzanti R, Shu H, Kumamoto Y. Structure and function of P-glycoprotein in the normal liver and intestine. Paper presented at: Princess Takamatsu Symposia, 1990.
12. Eberl S, Renner B, Neubert A, et al. Role of P-glycoprotein inhibition for drug interactions. Clin Pharmacokinet. 2007;46(12):1039–49.
13. Ferron P-J, Gicquel T, Megarbane B, Clément B, Fromenty B. Treatments in Covid-19 patients with pre-existing metabolic dysfunction-associated fatty liver disease: A potential threat for drug-induced liver injury? Biochimie. 2020;179:266–74.
14. Remdesivir (veklury) Fact Sheet for Healthcare Providers. Food and Drug Administration: Silver Spring, MD, 2020 (https://www.fda.gov/media/137566/download).

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