

# Acute Kidney Injury Presenting as Hepatorenal Syndrome in the Setting of Glecaprevir/Pibrentasvir Treatment for Hepatitis C

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## ABSTRACT

A 65-year-old man with chronic hepatitis C virus and hepatocellular carcinoma, after surgical resection and chemotherapy, was started on a regimen of glecaprevir and pibrentasvir for treatment of his hepatitis C virus. Ten days later, he developed hepatotoxicity with subsequent progression to hepatorenal syndrome (HRS). On discontinuation of glecaprevir/pibrentasvir and initiation of HRS treatment, he had improvement in his renal and hepatic function. Although there have been recent safety concerns surrounding hepatocellular injury secondary to glecaprevir/pibrentasvir, this is the first case report of HRS secondary to severe hepatotoxicity induced by glecaprevir/pibrentasvir.

## INTRODUCTION

The combined regimen of glecaprevir and pibrentasvir is a highly effective treatment for hepatitis C virus (HCV), with sustained virologic responses (SVR) of over 95%, regardless of HCV genotype.<sup>1</sup> Despite its effectiveness, data from the Food and Drug Administration (FDA) suggest that there can be significant hepatotoxicity with the regimen.<sup>2</sup> We discuss the first published description of hepatorenal syndrome (HRS) secondary to hepatotoxicity from glecaprevir/pibrentasvir.

## CASE REPORT

A 65-year-old man with chronic HCV (genotype 1a), remote alcohol use disorder, hepatocellular carcinoma (HCC), and chronic inactive hepatitis B presented with abdominal distention and jaundice for 1 month. In 2014, he was found to have a 3.9 × 3.3 × 3.4 cm liver mass. On biopsy, HCC was confirmed, and he was treated with surgical wedge resection of segment 4, percutaneous ablation of segment 2, and adjuvant sorafenib. The sorafenib was discontinued 9 months before this admission because of side effects, including diarrhea and bloating. He had been clinically stable without evidence of recurrence on multiphase computed tomography 6 months earlier, and his  $\alpha$ -fetoprotein was 6.8 ng/mL 3 weeks before admission. At the initiation of glecaprevir/pibrentasvir, he had no evidence of chronic kidney disease or chronic kidney disease risk factors such as hypertension or diabetes. His hepatic function was notable for low albumin, elevated transaminases, and elevated alkaline phosphatase (Table 1). He had no previous history of hepatic encephalopathy or ascites suggestive of decompensated cirrhosis and was categorized as Child-Pugh class A.

Ten days after starting glecaprevir/pibrentasvir, he presented to the emergency department with jaundice and abdominal pain. Laboratories were notable for an elevated total (7.7 mg/dL) and direct (5.2 mg/dL) bilirubin with an alkaline phosphatase of 105 U/L and creatinine of 1.1 mg/dL (Table 1). Ultrasound demonstrated moderate ascites, and paracentesis demonstrated a serum ascites albumin gradient of 1.8 and no evidence of spontaneous bacterial peritonitis. He was advised to follow-up as an outpatient.

Two weeks later, he returned to the emergency department with fevers, chills, fatigue, and darkening urine. On examination, he had diffuse jaundice, increased abdominal distension, and right upper quadrant tenderness. His laboratories now showed total bilirubin

**Table 1. Significant laboratory values during clinical course**

	Most recent value before treatment initiation	Value on admission	Value 4 months after discharge
Creatinine (mg/dL)	1.0	1.6	1.1
Total bilirubin (mg/dL)	0.9	25.5	3.7
Direct bilirubin (mg/dL)	0.6	16.1	2.1
International normalized ratio	0.95	1.64	1.71
Albumin (g/dL)	3.2	2.6	2.9
Aspartate aminotransferase (U/L)	113	127	30
Alanine aminotransferase (U/L)	42	55	11
Alkaline phosphatase (U/L)	196	105	109
Platelet count (10 <sup>9</sup> /mL)	112	213	130
Sodium (mEq/L)	138	132	135
MELDNa	11	31	20
HCV viral load (IU/mL)	2,443,203	n/a	<12

HCV, hepatitis C virus; MELDNa, Model for End-Stage Liver Disease Sodium.

of 25.5 mg/dL, direct bilirubin of 16.1 mg/dL, the international normalized ratio of 1.64, and creatinine of 1.6 mg/dL. Abdominal computed tomography and ultrasound showed no evidence of biliary obstruction or portal vein thrombosis. Hepatitis B DNA levels were undetectable, and core IgM was negative. Given his impaired synthetic function, acute decompensated cirrhosis, and rapidly declining renal function, there was a concern for type 1 HRS. He received a 3-day albumin challenge, after which his fractional urinary excretion of sodium decreased from 15% to less than 10%, and his creatinine increased to 2.0 mg/dL. He was subsequently started on octreotide, midodrine, and albumin. Glecaprevir/pibrentasvir was discontinued after 29 days of treatment because of his acute liver decompensation.

Over the following 8 days, the patient's creatinine decreased to 1.3 mg/dL and his total bilirubin decreased from 25.6 to 16.4 mg/dL. Four months after discharge, he has remained clinically stable, with improvement in his renal function and hyperbilirubinemia, but not in his synthetic function (Table 1). Despite discontinuing glecaprevir/pibrentasvir after 29 days, his HCV viral load remained undetectable 4 months later.

## DISCUSSION

In August 2019, the FDA distributed a safety communication outlining serious liver injury in 46 individuals on glecaprevir/pibrentasvir. These patients presented with varying symptoms including hyperbilirubinemia, jaundice, ascites, and hepatic encephalopathy.<sup>3</sup> The communication suggested avoidance of this medication in patients with Child-Pugh class B and C. Although further research is needed on the safety of glecaprevir/pibrentasvir in Child-Pugh class A, this case highlights the importance of regular monitoring of liver and renal function in patients on this regimen. In this case, a more cautious approach and earlier discontinuation at the initial emergency department visit may have helped avoid further complications.

Given this patient's HCC, a regimen without a protease inhibitor may have carried less risk of hepatotoxicity. There are some data to suggest that direct-acting antiviral regimens for HCV genotype 1 that include a protease inhibitor have high SVRs in patients with a previous history of HCC. However, data for regimens including glecaprevir/pibrentasvir are lacking.<sup>4</sup> In part, this is due to HCC being part of the exclusion criteria for many HCV clinical trials. We believe that future clinical trials should seek to assess safety and SVR in this patient population.

Notably, sorafenib was discontinued after 9 months because of gastrointestinal intolerance. There are minimal data on whether to continue sorafenib after achieving a complete response, but the prevailing approach is to continue indefinitely.<sup>5</sup> However, given the side effects in this patient and lack of clinical recurrence, his care team elected to discontinue the medication. It should also be noted that glecaprevir/pibrentasvir may not be the sole precipitant of this patient's decompensation. Although he took no medications with known interactions with glecaprevir/pibrentasvir, the patient had a remote history of alcohol use and reported mild continued drinking up to this admission (3 beers per week).

According to the FDA Adverse Event Reporting System database, 171 adverse hepatocellular reactions have been reported after glecaprevir/pibrentasvir administration since 2017. Of those, 12 patients (7%) developed renal pathology. Six of those required hospitalizations, and 3 led to death.<sup>2</sup> Only 1 previous case report has explored glecaprevir/pibrentasvir-associated liver injury, but that patient had no pre-existing cirrhosis, had elevated transaminases with a milder hyperbilirubinemia, and no kidney injury.<sup>6</sup> To our knowledge, this is the first case report identifying glecaprevir/pibrentasvir-induced HRS secondary to hepatotoxicity. Current glecaprevir/pibrentasvir regimens range from 8 to 12 weeks, yet a 4-week regimen was still effective in virus eradication for this patient. Recent literature has

suggested that a large percentage of patients on glecaprevir/pibrentasvir may be cured with less than 7 weeks of treatment, and a personalized treatment regimen based on viral load may be effective.<sup>7</sup> This could reduce potential side effects and the cost of antiviral therapy.

## DISCLOSURES

Author contributions: All authors contributed equally to this article. M. Poles is the article guarantor.

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Informed consent was obtained for this case report.

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## REFERENCES

1. Zeuzem S, Foster GR, Wang S, et al. Glecaprevir-pibrentasvir for 8 or 12 weeks in HCV genotype 1 or 3 infection. *N Engl J Med*. 2018;378(4):354–69.
2. Center for Drug Evaluation and Research. *FDA Adverse Event Reporting System (FAERS) Public Dashboard*. U.S. Food and Drug Administration: Silver Spring, MD, 2019 ([https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-](https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard)

- reporting-system-faers-public-dashboard). Published December 24, 2019. Accessed May 7, 2020.
3. Center for Drug Evaluation and Research. Risk of liver injury with certain HCV drugs in advanced liver disease. U.S. Food and Drug Administration (<https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-occurrence-serious-liver-injury-use-hepatitis-c-medicines-mavyret-zepatier-and>). Published August 28, 2019. Accessed May 7, 2020.
4. Beste LA, Green PK, Berry K, et al. Effectiveness of hepatitis C antiviral treatment in a USA cohort of veteran patients with hepatocellular carcinoma. *J Hepatol*. 2017;67(1):32–9.
5. Poullenot F, Bioulac-Sage P, Laumonier H, et al. Hepatocellular carcinoma treated by sorafenib with complete radiological response according to mRECIST criteria: Could we stop the treatment? About four cases. *Acta Oncologica*. 2013;53(3):420–3.
6. Hammami MB, Aboushaar R, Alsabbagh E. Glecaprevir/pibrentasvir-associated acute liver injury in non-cirrhotic, chronic HCV infection without HBV co-infection. *BMJ Case Rep*. 2019;12(5):e226622.
7. Dasgupta S, Imamura M, Gorstein E, et al. Modeling-based response-guided therapy for chronic hepatitis C under glecaprevir/pibrentasvir may identify patients for ultra-short treatment duration. *J Infect Dis* 2020; 222(7):1165–9.

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