Case in Point

Possible Simeprevir/Sofosbuvir-Induced Hepatic Decompensation With Acute Kidney Failure

Judith Nwachukwu, PharmD, MPH, HEM; Rena Johnson, FNP-C; and Kenneth Mills-Robertson, MD

A patient with hepatitis C infection and hepatocellular carcinoma developed significant hyperbilirubinemia and acute kidney injury after initiation of a simeprevir and sofosbuvir regimen.

The emergence of hepatitis C (HCV) treatment regimens in the past 5 years has resulted in a major paradigm shift in the management of those infected with this virus. The 2011 approval of boceprevir and telaprevir was associated with a higher virologic response (50% - 75%) and a shorter length of therapy depending on the patient population. Despite these gains, first generation direct-acting antivirals (DAAs) required multiple doses, had a higher pill burden with numerous drug-interactions, and adverse effects (AEs). In addition, viral resistance limited the full use of the first generation DAAs for all genotypes.

Sofosbuvir, simeprevir, and ledipasvir-sofosbuvir (second generation DAAs) boast even higher (> 90%) sustained virologic response rates (SVR) and more tolerable AE profiles especially anemia, depression, and gastrointestinal symptoms compared with the first generation DAAs. At the time of treatment for this case study, sofosbuvir/ledipasvir was not commercially available. Sofosbuvir in combination with simeprevir with or without ribavirin was one of the preferred treatment options for chronic HCV.[1]

Unlike the first generation DAAs, which have been associated with a decline in renal function compared with conventional pegylated interferon and ribavirin, sofosbuvir is extensively renally eliminated by glomerular filtration and active tubular secretion as the metabolite GS-331007. On the other hand, simeprevir is hepatically metabolized.

A PubMed literature search for reports of "simeprevir-induced" or "sofosbuvir-induced with hepatic, renal failure, acute kidney injury" yielded only 1 published case of hepatic decompensation likely related to simeprevir, but no case report of simeprevir and sofosbuvir associated with hepatic decompensation and acute kidney injury.[4] In this article, the authors describe a case of hepatic decompensation and acute kidney injury caused by simeprevir/sofosbuvir initiation for chronic HCV that required intensive care and dialysis.

CASE REPORT

The patient was a 62-year-old African American man with chronic HCV, genotype 1b, TT IL28B, and 4,980,000 IU baseline viral load. He was treatment naïve with biopsy proven compensated cirrhosis, and Child-Turcotte-Pugh class A with a pretreatment model for end-stage liver disease score of 12. His past medical history included hypertension, chronic kidney disease (CKD) (baseline serum creatinine [SCr] 1.4 - 1.8 mg/dL), benign prostatic hypertrophy, depression, obesity (30.6 body mass index, 246 lb), and psoriasis. In addition, the patient was on the following maintenance medications: allopurinol, bupropion, diltiazem, sustained-release and immediate-release morphine, sennosides, and terazosin.

In September 2014, the patient was diagnosed with biopsy-confirmed hepatocellular carcinoma (HCC) Barcelona clinic liver cancer stage B T3aN0M0 stage III. He was considered for transarterial chemoembolization (TACE), but treatment was withheld due

Dr. Nwachukwu is a clinical pharmacy specialist, **Mrs. Johnson** is a gastroenterology nurse practitioner, and **Dr. Mills-Robertson** is a gastroenterologist, all at the Wilmington VAMC in Delaware.

to subsequent increase in liver function tests (LFTs) with total bilirubin (TB) 2.9 mg/dL, direct bilirubin (DB) 1.8 mg/dL, aspartate aminotransferase test (AST) 130 U/L, and alanine aminotransferase test (ALT) 188 U/L (baseline: TB 1.1 mg/dL, AST 69 U/L, and ALT 76 U/L). These results were thought to be the result of worsening hepatic function from untreated HCV, therefore, treatment was initiated.

The patient was started on simeprevir 150 mg orally daily and sofosbuvir 400 mg orally daily with an estimated baseline creatinine clearance of 67 mL/min per Cockcroft-Gault equation.[5] Two days after therapy initiation, the patient presented to the emergency department with the following symptoms: hiccups, nausea, vomiting, and abdominal pain. Laboratory results showed 10.85 mg/dL SCr and 91 mg/dL blood urea nitrogen (BUN), TB increased to 14.6 mg/dL with AST of 325 U/L and ALT 277 U/L. The patient reported no use of acetaminophen, alcohol, nonsteroidal anti-inflammatory drugs, or other nephrotoxic agents.

Upon admission, the patient was diagnosed with drug-induced hepatitis and acute kidney injury (AKI). Simeprevir/sofosbuvir was discontinued along with allopurinol, bupropion, lisinopril, and morphine. An abdominal ultrasound was negative for obstructive uropathy. The patient did not respond to fluid boluses. A nephrologist was consulted, and dialysis was initiated. The patient underwent dialysis for 3 days and his LFTs and SCr levels started trending downward (Figures 1 to 5).

The patient was discharged after 8 days. After 3 weeks, the SCr decreased to 2.29 mg/dL, BUN was 26 mg/dL, TB was 2 mg/dL, DB was 0.9 mg/dL, AST was 73 U/L, and ALT was 81 U/L. Weekly laboratory values continued to improve following discharge but did not return to baseline levels. The patient remained off HCV treatment.

Figure 1. Variation in Serum Creatinine Levels Before and After Treatment Withdrawal

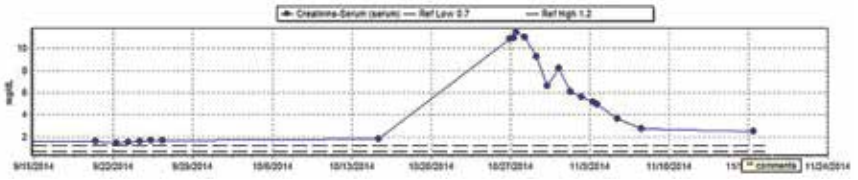


Figure 2. Variation in Total Bilirubin Before and After Treatment Withdrawal

Figure 3. Time Line of Direct Bilirubin

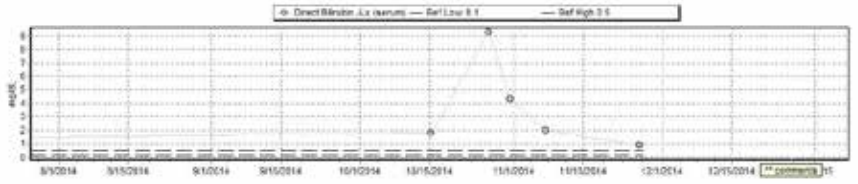
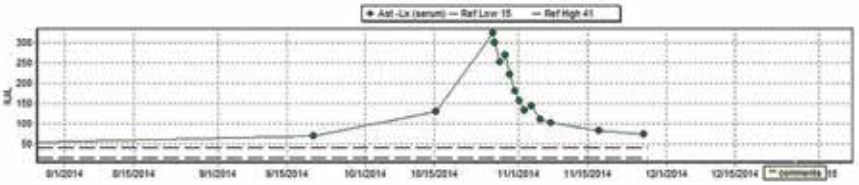


Figure 4. Time Line of Alanine Transaminase

Figure 5. Time Line of Aspartate Aminotransferase



DISCUSSION

The patient had baseline CKD with SCr > 1.5 mg/dL; however, the significant decline in renal function and worsening hepatic function were thought to be the result of

external factors. Although hepatorenal syndrome was considered, the authors suspected that the AKI and hepatic decompensation were related to simeprevir/sofosbuvir regimens due to their presumed relationship and probability analysis. Osinusi and colleagues noted a decline in renal function in a patient who received ledipasvir/sofosbuvir for 6 weeks in an open-label pilot study.[6] Stine and colleagues also reported on cases of simeprevir-related hepatic decompensation.[4]

In this case, the authors employed the Naranjo algorithm adverse drug reaction probability scale to assess whether there was a causal relationship between this event and initiation of simeprevir/sofosbuvir regimen.[7] The Naranjo score was 4, indicating a possible link between simeprevir/sofosbuvir initiation and hepatic decompensation and AKI. This case may be the first postmarketing report of significant hepatic decompensation and AKI related to simeprevir/sofosbuvir.

Unlike simeprevir, which undergoes extensive oxidative metabolism by CYP3A in the liver and has negligible renal clearance with < 1% of the dose recovered in the urine, sofosbuvir is extensively metabolized by the kidneys with an active metabolite, GS-331007, and about 80% of the dose is recovered in urine (78% as GS-331007; 3.5% as sofosbuvir).[8,9] The potential for drug-drug interaction also was assessed because simeprevir is extensively metabolized by the hepatic cytochrome CYP34 system and possibly CYP2C8 and CYP2C19. Clinically significant interactions could have occurred with diltiazem and morphine, because the coadministration of these medications along with simeprevir, an inhibitor of P-glycoprotein (P-gp), and intestinal CYP3A4, may result in increased diltiazem and morphine plasma concentrations.

Of note, because sofosbuvir is a substrate of P-gp, it may have its serum concentration increased by simeprevir. Inducers and inhibitors of P-gp may alter the plasma concentration of sofosbuvir. The major metabolite, GS-331007, is not a substrate of P-gp. Drugs that induce P-gp may reduce the therapeutic effect of sofosbuvir; however, the FDA-labeling suggests that inhibitors of P-gp may be coadministered with sofosbuvir.

According to simeprevir prescribing information, drug interaction studies have demonstrated that moderate CYP3A4 inhibitors, such as diltiazem (although coadministration have not been studied), increased the maximum serum concentration (C_{max}), minumum serum concentration (C_{min}), and AUC of simeprevir.[7] As a result, concurrent use of simeprevir with a moderate CYP3A4 inhibitors is not recommended. Morphine and simeprevir interaction also is possible via the P-gp inhibition of simeprevir. Morphine concentration may have increased and metabolites may have accumulated, leading to urinary retention and elevated creatinine. In addition, decreased oral intake and subsequent nausea/vomiting may have compounded the renal insult.

CONCLUSION

Given that updated HCV treatment guidelines include simeprevir/sofosbuvir as an alternative treatment option, clinicians should be aware of hepatic decompensation with markedly elevated bilirubin and AKI during simeprevir and sofosbuvir treatment. Careful consideration is needed prior to the initiation of simeprevir/sofosbuvir, particularly in patients with advanced liver disease or known HCC and baseline renal impairment. ●

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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