Hepatitis B Virus Reactivation During Successful Treatment of Hepatitis C Virus With Sofosbuvir and Simeprevir

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Treatment of hepatitis C virus with potent, interferon-free, direct-acting antiviral regimens with no activity against hepatitis B virus (HBV) may increase the risk for HBV reactivation in coinfected patients. We present 2 cases of HBV reactivation during treatment with an all-oral regimen of simeprevir and sofosbuvir and discuss strategies to prevent HBV flare.

Keywords. HBV/HCV coinfection; HBV reactivation; acute hepatitis; sofosbuvir; simeprevir.

Sofosbuvir, an NS5B polymerase inhibitor combined with simeprevir, a second-generation protease inhibitor, has been shown to produce a rapid and sustained clearance of hepatitis C virus (HCV) in chronic genotype 1 infection [1]. The increased risk of hepatic cirrhosis and hepatocellular carcinoma in individuals coinfected with hepatitis B virus (HBV) [2] make these patients a priority for treatment with these newer, more effective anti-HCV therapies. However, little is known about the use of direct-acting antiviral medications in HBV/HCV coinfection, as these patients were excluded from recently published clinical trials [1, 3]. HCV is known to cause suppression of HBV replication in coinfected patients [4], and increased HBV replication following successful treatment of HCV with pegylated interferon α (peg-IFN-α) and ribavirin has been reported [5, 6]. As these all-oral anti-HCV therapies have no activity against HBV, the risk for and magnitude of HBV viremia following HCV treatment may be increased. We present 2 cases of HBV viremia during successful treatment of HCV with sofosbuvir and simeprevir.

CASE 1

A 55-year-old man with a history of chronic HBV and genotype 1a HCV coinfection presented for treatment of HCV. Two previous treatment courses with peg-IFN-α and ribavirin failed to produce a sustained virologic response. Magnetic resonance imaging of the abdomen demonstrated evidence of cirrhosis and portal hypertension. Clinically, the patient had compensated cirrhosis with Child-Pugh class A liver disease. The pretreatment HCV RNA viral load (VL) was 1.3 million IU/mL. HBV DNA VL was 2300 IU/mL (all previous HBV VLs were <2000 IU/mL), alanine aminotransferase (ALT) 62 IU/mL, aspartate aminotransferase (AST) 59 IU/mL, total bilirubin 0.7 mg/dL, platelets 135 000 /cm^2, and international normalized ratio (INR) 1.05; hepatitis B e antibody was positive and hepatitis B e antigen (HBeAg) was negative.

Treatment with sofosbuvir and simeprevir was initiated and resulted in a rapid decline in HCV VL. At week 2, the HCV VL was 26 IU/mL and by week 4 was undetectable. After 7 weeks of treatment the patient began to experience malaise, nausea, and epigastric abdominal pain. Physical examination at week 8 revealed significant jaundice with tender hepatomegaly. Liver function tests (LFTs) were now significantly abnormal, with an AST of 1792 IU/L, ALT of 1495 IU/L, total bilirubin of 12.2 mg/dL, and INR of 1.96. Urine toxicology and blood acetaminophen level were negative. Serologies for human immunodeficiency virus and hepatitis E were negative. His antinuclear antibody titer was <1:40 and ferritin was elevated at 1183 ng/mL; α-fetoprotein was elevated at 37.8 ng/mL but stable from pretreatment levels, and abdominal ultrasound revealed only mild hepatomegaly with patent portal and hepatic vessels. HCV VL remained undetectable, but HBV VL was 22 million IU/mL (Figure 1). HCV treatment was discontinued at week 8 and treatment with tenofovir/emtricitabine was initiated for a suspected HBV flare. By week 14 the patient's symptoms resolved and LFTs returned to baseline. At week 28, the HCV VL remained undetectable (20 weeks after sofosbuvir and

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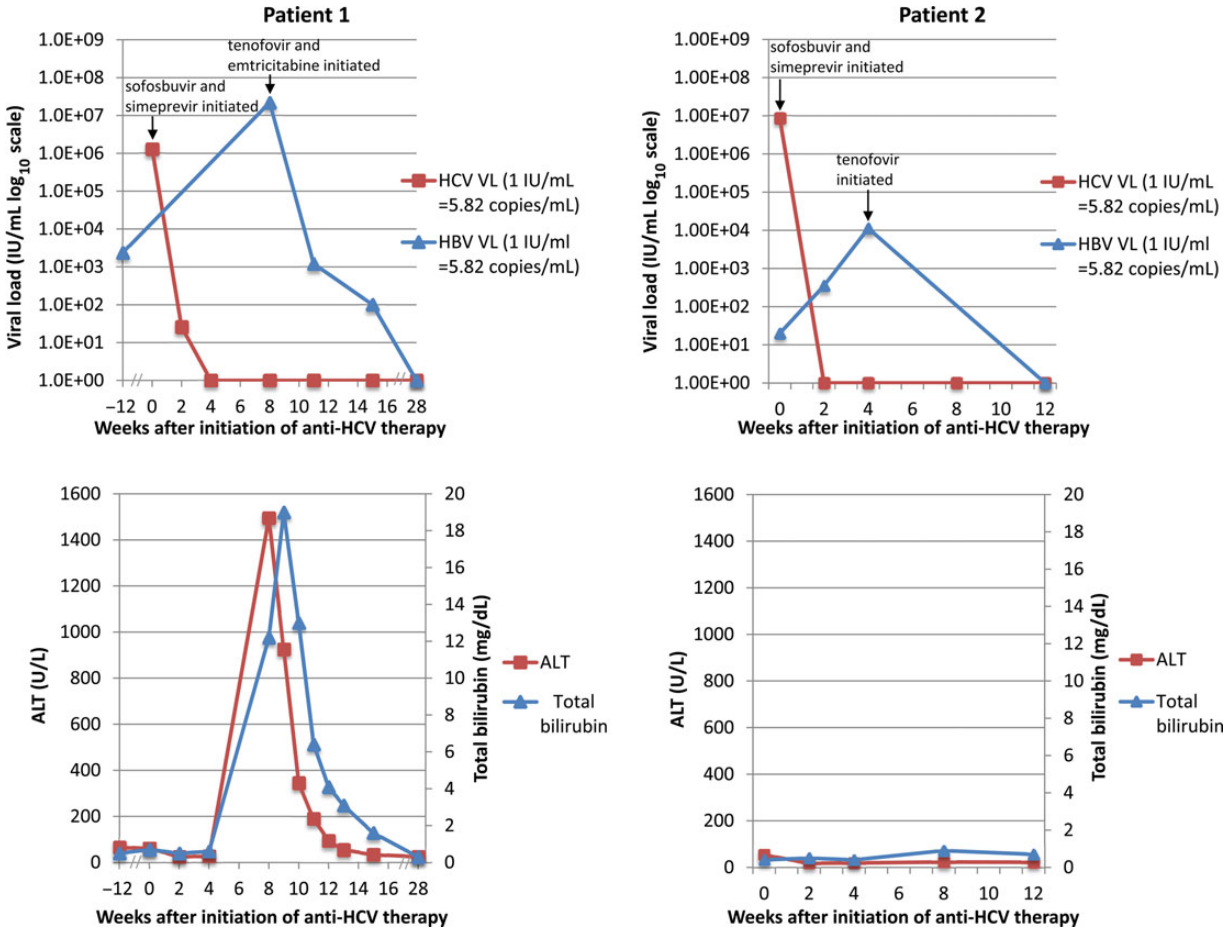

Figure 1. In patient 1, hepatitis B virus (HBV) viral load (VL) was not followed with hepatitis C virus (HCV) treatment, and severe HBV viremia associated with acute hepatitis developed after 8 weeks of treatment with sofosbuvir and simeprevir. In patient 2, HBV VL was followed during HCV treatment and tenofovir was initiated when logarithmic increases in HBV VL were noted at week 4. HBV VL subsequently declined to undetectable levels and no hepatitis was observed. Abbreviation: ALT, alanine aminotransferase.

simeprevir were discontinued), and HBV VL decreased to <20 IU/mL. Tenofovir and emtricitabine were continued for ongoing HBV suppression.

CASE 2

A 57-year-old man with history of chronic genotype 1a HCV infection and no known active hepatitis B viremia presented for HCV treatment. He was treated with peg-IFN-α and ribavirin 5 years prior with no virologic response. Computed tomography of the abdomen and pelvis demonstrated no evidence of liver cirrhosis or portal hypertension. The pretreatment HCV VL was 8.6 million IU/mL. HBV serologic studies revealed a positive hepatitis B core antibody (HBcAb) with a negative hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody (HBsAb). HBV VL was detectable below the lower limit of quantification (20 IU/mL), and ALT was 54 IU/L.

Sofosbuvir and simeprevir were initiated and both HBV VL and HCV VL were monitored at 2-week intervals. At week 2, HCV VL was undetectable and HBV VL had increased to 353 IU/mL. After 4 weeks of treatment, HCV VL remained undetectable and HBV VL increased further to 11 255 IU/mL. LFTs were within normal limits and the patient remained asymptomatic. Sofosbuvir and simeprevir were continued and tenofovir was added for treatment of HBV reactivation. LFTs normalized on HCV treatment, and the HCV and HBV VLs were undetectable after 12 weeks of therapy.

DISCUSSION

Chronic HCV infection has been shown to suppress HBV replication in coinfected patients [4, 7, 8]. Both intrahepatic and peripheral HBV antigen levels are reduced in patients chronically coinfected with HCV compared to individuals with HBV alone

[4]. Similarly, patients with chronic HBV have higher rates of surface antigen clearance following HCV superinfection [7], and viral replication in acute HBV infection may be attenuated in patients with preexisting HCV [8].

Loss of HBV suppression following interferon-based HCV treatment may lead to an increase in HBV replication. A recent meta-analysis showed that 23% of coinfected patients treated with peg-IFN-α and ribavirin experienced an increase in HBV replication [5]. The risk of HBV viremia was increased in cases where the virologic response to anti-HCV therapy was sustained [5]. However, increases in HBV replication following treatment of HCV with peg-IFN-α and ribavirin are typically small [9], and severe hepatitis appears to be rare [6].

Until recently, all HCV treatment regimens included peg-IFN-α, which also has significant activity against HBV [10]. The risk of HBV reactivation may be greater with newer HCV treatment regimens, given their increased potency against HCV and lack of anti-HBV activity. In both of our patients treated with sofosbuvir and simeprevir, suppression of HCV replication was immediate, leading to a nearly undetectable HCV VL after only 2 weeks of therapy. Within weeks of HCV clearance, significant increases in HBV replication were observed. Both patients were previously treated with peg-IFN-α and ribavirin without any demonstrable HBV reactivation. The rapid increase in HBV replication during treatment with sofosbuvir and simeprevir suggests that the risk of reactivation and acute hepatitis may be greater with newer HCV treatment regimens. Even patients with a positive HBcAb but a negative HBsAg and HBsAb appear to be at risk.

However, early recognition and preemptive treatment of HBV reactivation may mitigate the risk of acute hepatitis. In patient 1, HBV VL was not monitored during HCV treatment, and by week 8 severe viremia and acute hepatitis developed. In patient 2, HBV VL was followed closely. When logarithmic increases in HBV replication were observed, anti-HBV therapy was initiated. This suggests that HBV VL should be closely monitored during HCV therapy in coinfected patients. If HBV reactivation is recognized early, prompt initiation of anti-HBV therapy may prevent progression to clinically significant hepatitis.

Current HCV treatment guidelines do not offer specific guidance on treatment and monitoring of patients coinfected with HBV [11]. Although patient 1 was a candidate for HBV therapy with cirrhosis, elevated ALT, and detectable VL, HBV treatment guidelines do not routinely recommend treatment in HBeAg-negative patients with a VL <2000 IU/mL [12]. These cases demonstrate that HBV DNA levels must be closely monitored in coinfected patients during HCV treatment with interferon-free, direct-acting antiviral regimens. In patients with a positive HBcAb but a negative HBsAg and HBsAb, HBV VL should be obtained prior to treatment and monitored during therapy. Early initiation of anti-HBV therapy in the setting of an increasing HBV VL should be strongly considered to prevent significant hepatitis. Further studies are needed to determine whether routine initiation of dual treatment for HCV and HBV should be standard of care for all coinfected individuals when using interferon-free regimens to treat HCV.

Note

Potential conflicts of interest. All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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