Hepatitis B virus reactivation during direct-acting antiviral agent-based therapy for chronic Hepatitis C

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Dear Editor,

The frequency of patients coinfected with hepatitis B virus/hepatitis C virus (HBV/HCV) is unknown and shows varied differences depending on the geographical region. Coinfection Ihas been estimated to be 8.4% in China, while it was reported to be 2.6% in Turkey (1, 2). Viral interference can occur in coinfected patients. Generally, HCV can suppress HBV replication that is mediated by the HCV core protein (1).

The reactivation of HBV infection during the treatment of HCV with a combination of pegylated interferon alpha and ribavirin and with immunosuppressive therapy is well known in coinfected patients (3). Some case series showed that the treatment of HCV with direct-acting antivirals (DAA) (sofosbuvir, daclatasvir, dasabuvir, etc.) may cause the reactivation of HBV. In this letter, we aimed to draw attention to the HBV reactivation in coinfected patients treated with a combination of dasabuvir (Exviera; AbbVie Limited, Illinois, U.S.A) and ombitasvir/paritaprevir/ritonavir (Viekirax; AbbVie Limited) (DOPR).

A treatment-naïve, 58-year-old woman presented to our hospital with anti-HCV, hepatitis B surface antigen (HBsAg) and hepatitis B envelope antibody (anti-HBe) positivity. She was diagnosed with chronic hepatitis due to HBV/HCV coinfection with serum levels of alanine aminotransferase (ALT) of 44 U/L, aspartate aminotransferase (AST) of 42 U/L, HCV RNA of 1,015,251 IU/mL (Genotype 1b), and undetectable HBV deoxyribonucleic acid (DNA). Her vital signs and physical examination on admission were normal. *Moderate inflammation, according to the modified Ishak score (*histological activity index: 7 and fibrosis: 1), was observed on her percutaneous *liver biopsy*. She was classified as an inactive HBV carrier. In July 2017, a combination treatment with DOPR was prescribed for 12 weeks. In August 2017, at the fourth week of treatment, she presented with weakness, and an elevation of HBV DNA (659,947 IU/mL) was documented. HCV RNA was undetectable, and ALT and AST levels were the same as those at the beginning of the treatment. After 1 week of elevation of HBV DNA, an elevation in ALT (747 U/L), AST (542 U/L), total bilirubin (4.93 mg/dL), and direct bilirubin (2.07 mg/dL) was detected. In the second week of the reactivation, serum ALT and AST gradually increased to 1,332 U/L, and 1,009 U/L, respectively. During this period, other tests were in a normal range. Tenofovir disoproxil fumarate (TDF) (Tenribel; Nobel Pharmacy, Istanbul, Turkey) treatment was initiated considering the HBV reactivation. A reduction of HBV DNA and an improvement in ALT and AST levels were detected with this treatment. During the eighth week of TDF treatment, liver function tests were normal.

The second case was a treatment-naïve, 67-year-old woman with HCV genotype 1b. She was also HBsAg positive. She was diagnosed with chronic hepatitis due to HBV/HCV coinfection with serum levels of ALT of 25 IU/L, AST of 32 IU/L, HCV RNA of 1,976,544 IU/mL, and undetectable HBV DNA. Her vital signs and physical examination on admission were normal. Her percutaneous liver biopsy showed moderate inflammation according to the modified Ishak score (histological activity index: 9 and fibrosis: 5). In October 2016, a combination treatment with DOPR was prescribed for 12 weeks. A rapid virological response at the fourth week of treatment was achieved, and the HCV RNA level remained undetectable thereafter. A combination therapy with DOPR was well tolerated, and the patient's adherence to DOPR was 100%. A sustained virological and biochemical response at 12 weeks after the treatment was eventually achieved. In May 2017, 15 weeks after DAA therapy was completed, an elevation in ALT (396 IU/L), AST (486 IU/L), total bilirubin (1.94 mg/dL) with direct bilirubin (0.57 mg/dL) and alpha-fetoprotein

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(102 ng/mL) was detected. At that time, HCV RNA was undetectable again but HBV DNA increased to 4,593,913 IU/L. Among her serological tests, anti-HBe was positive, and the antibody against hepatitis D virus was negative. No pathological findings were found except for hemangiomas in the liver in dynamic magnetic resonance imaging. In June 2017, TDF (Viread; Gilead Sciences) treatment was started with presuming as HBV reactivation. The patient's biochemical tests began to decrease, and at the third month of treatment, ALT, AST and total bilirubin levels were detected as 163 IU/L, 192 IU/L, and 1.71 mg/dL, respectively. HBV DNA reduced to 142 IU/mL in the third month of HBV treatment, and HCV RNA was still undetectable. The patient's HBV therapy is ongoing.

Written informed consent was obtained from patients who participated in this study

In these cases, clinical reactivation (elevation in ALT and bilirubin levels) with nausea and vomiting occurred. The mechanism of HBV reactivation during DAA therapy for chronic hepatitis C (CHC) is still speculative. Cell culture studies showed that HBV and HCV were replicated in the same hepatocyte without evidence of interference. This suggests that HCV suppresses HBV replication through an indirect mechanism. Additionally, in patients coinfected with HBV/HCV with HCV dominance, an overexpression of interferon-stimulated genes and interferon gamma–induced protein 10 (IP-10) occurred, and the level of IP-10 inversely correlated with the decline of HBsAg. This finding suggests that HCV can suppress HBV replication by host immune responses. Therefore, the clearance of HCV infection with DAA could remove immune control on HBV replication and result in HBV reactivation (1).

Unlike most of the published reports, our first case has highly elevated biochemical tests and HBV DNA. ALT was 20 times more than the normal upper limit, and HBV DNA was more than 5 log IU/mL. In other studies, ALT elevation did not occur or increased less than fivefold (4, 5). Our patients showed that in patients with HBV reactivation due to DAA treatment, liver enzymes can be elevated to high values and the clinical condition of the patient may be impaired. Thus, these patients need follow-up.

Our second case is separated from published reports by the time of the reactivation. Until now, almost all of the HBV reactivations had been observed during the DAA treatment (4, 5), which emphasized that patients should be monitored closely for HBV reactivation after DAA treatment is completed.

The current European Association for the Study of the Liver (EASL) guidelines suggest that concurrent HBV nucleoside/nucleotide analogue therapy should be started for patients fulfilling the standard criteria for HBV treatment, and close monitoring should be started if patients are HBsAg positive and if patients do not fullfill the standard HBV treatment criteria (3). Both of our patients did not meet the criteria for starting HBV therapy because the HBV DNA was negative. Therefore, it is our understanding that NA therapy should be initiated in all patients who are HBsAg positive if DAA therapy is initiated, whether or not they meet the criteria.

In conclusion, HBV reactivation can be observed in coinfected patients who are on DAA therapy. Liver function indicators in patients with reactivation may be severely impaired and deteriorate patients' vitals. In our opinion, NA therapy should be initiated in all patients who are HBsAg positive, if DAA therapy is initiated.

MAIN POINTS

- *Doctors who follow chronic hepatitis B and hepatitis C should pay attention to coinfection of these diseases.*
- *Hepatitis B reactivation can be seen in chronic hepatitis C patients receiving direct-acting antiviral therapy.*
- *In chronic hepatitis C patients treated with direct-acting antivirals, if HBsAg is positive, prophylaxis should be initiated to prevent hepatitis B reactivation without considering the level of HBVDNA.*

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