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Case Study

Hepatitis B reactivation with hepatic decompensation after the use of direct-acting antiviral agents in a patient with chronic Hepatitis B and C coinfection

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In recent years, direct-acting antiviral agents (DAAs) have become the major therapy for Hepatitis C virus (HCV) infection and chronic Hepatitis C (CHC). However, Hepatitis B virus (HBV) reactivation (HBVr) remains an important issue among patients with HBV/HCV coinfection when receiving DAAs for CHC. The severity of HBVr-induced Hepatitis may range from a mild to a severe form of liver injury. In this study, we present a rare case of HBVr leading to a decompensated state and jaundice in a 72-year-old man during DAA treatment. His decompensated state subsequent to HBVr, fortunately improved after initiating oral antiviral treatment for HBV. Our case highlights the importance of the pretreatment evaluation of patients for HBV, monitoring potential HBVr, and the initiation of HBV antiviral therapy in HBV/HCV coinfected patients.

Key words: Direct-acting antiviral agents, chronic Hepatitis C, Hepatitis B virus reactivation, decompensation.

INTRODUCTION

Direct-acting antiviral agents (DAAs) have become the major therapy for Hepatitis C virus (HCV) infection and chronic Hepatitis C (CHC) in recent years. However, Hepatitis B virus (HBV) reactivation (HBVr) remains an important issue among patients with HBV/HCV coinfection when receiving DAAs for CHC. The severity of these cases varies in a clinical setting (Bersoff-Matcha et al., 2017; Ende et al., 2015). Nevertheless, HBVr leading to liver decompensation and/or acute liver failure has rarely been reported. In this study, we report a rare case of HBVr induced severe Hepatitis with jaundice and liver decompensation in a patient during his CHC treatment with Paritaprevir+Ritonavir +Ombitasvir plus Dasabuvir.

CASE PRESENTATION

A 72-year-old man had been suffering from chronic Hepatitis B (CHB) and CHC (genotype-1b) for many years. He also had a history of diffuse large B-cell lymphoma,

which achieved complete remission after six cycles of chemotherapy with R-CHOP from February 2016 to May 2016. No HBVr was identified during the period of chemotherapy. He was advised to receive CHC treatment because of his positivity for HCV RNA. He was positive for Hepatitis B surface antigen (HBsAg) but negative for Hepatitis B e-antigen (HBeAg). His HBV DNA level was low (21 IU/mL). Interferon-free DAA treatment with a nonstructural protein 5A (NS5A) inhibitor (Ombitasvir) and the NS3/4A protease inhibitor asunaprevir (Paritaprevir + Ritonavir) plus a NS5B polymerase inhibitor (Dasabuvir) were prescribed. He then received regular visits at 2-week intervals throughout the 12-week treatment period. His HCV RNA level rapidly decreased and became undetectable four weeks after starting treatment. However, jaundice, general malaise and poor appetite developed during the fifth week of DAA therapy, so he visited our outpatient department. Laboratory tests showed markedly increased aminotransferase levels (alanine aminotransferase (ALT) 1212 IU/L, aspartate aminotransferase (AST) 1616 IU/L) and hyperbilirubinemia (total bilirubin 21.07 mg/dL, direct bilirubin 11.94 mg/dL)(Table 1). Physical examination also revealed jaundice. A high HBV DNA level was identified (173,000 IU/mL) in the second week of DAA treatment, during the retrospective examination. Abdominal sonography revealed no evidence of biliary tract obstructive lesions or intrahepatic lesions.

Treatment

Entecavir (1.0 mg per day) was immediately administered for HBVr, DAA treatment was discontinued and liver transplant assessment was also initiated.

Outcome and Follow-up

The levels of aminotransferases and bilirubin decreased gradually upon the initiation of entecavir for HBVr. There was marked improvement in his symptoms within 1 week. This patient was discharged on day 10 in a stable condition. His HBV DNA level checked on the day of discharge was 2180 IU/ml (Figure 1).

DISCUSSION AND CONCLUSIONS

Recently, HBVr has occasionally been reported in patients receiving DAAs for HCV. The mechanism behind HBVr with HCV treatment is unclear. Possible theories are the loss of a direct viral interaction between HBV and HCV that inhibited HBV replication; an increased replication space for HBV; or an interruption of host innate immune responses that affects the control of HBV replication (Balagopal and Thio, 2015). A higher incidence of HBVr in patients receiving DAA-based therapy compared to those receiving Interferon (IFN)-based therapy has been reported (Jiang et al., 2018). This phenomenon can be attributed to an antiviral effect which suppresses HBV replication by IFN, while DAAs do not have any effect on the antiviral immune response.

HBVr is generally defined as HBV DNA recurrence or increase > 1 log. HBVr related to DAA treatment may occur in patients with inactive HBV, occult (HBsAg and Hepatitis B surface antibody (HBsAb) negative with low HBV DNA level) or resolved (HBsAg negative and HBsAb positive) HBV infection (Bersoff-Matcha et al., 2017; Sastre et al., 2019)]. HBVr could occur among HBsAg-positive patients during their DAA treatment for CHC (Yeh et al., 2017; Belperio et al., 2017; Chen et al., 2017; Doi et al., 2017).

One large retrospective cohort study (Serper et al., 2017) that included 17440 HIV-negative, HBV-exposed (IgG antibody against Hepatitis B core antigen (anti-HBc IgG)-positive) patients treated with DAAs from January 2014 to November 2016, showed that clinically significant hepatic events (defined as ALT level increases >100 IU/L with total bilirubin levels >2.5 mg/dL) and HBVr were rare (0.3% and approximately 0.2%, respectively) in HBsAg-negative patients. However, the risk of HBVr was approximately 10% and was associated with 1(1%) clinically significant hepatic event in an HBsAg-positive patient with liver cirrhosis. Another retrospective study (Kawagishi et al., 2017), including 169 patients with HCV infection who received interferon-free DAA therapies, showed a higher prevalence of HBV DNA recurrence (5.9%) in patients with previous HBV infection (HBsAg and HBV DNA-negative, anti-HBc IgG and/or HBsAb-positive). However, no HBV reactivation Hepatitis occurred in these patients. Overall, HBsAg positivity is associated with higher risks of HBVr and subsequent significant hepatic events.

Furthermore, HBV reactivation has been reported not only during but also after DAA treatment. Suda et al. (2017) reported a case of HBV reactivation in a patient with HCV infection and isolated anti-HBc IgG positivity. This patient was treated with daclatasvir/asunaprevir. Twenty-one weeks after DAA treatment ended, the patient developed a Hepatitis flare and became positive for HBsAg. Therefore, they suggested that even after the cessation of DAA treatment, special attention should be given to HBV reactivation until a sustained virological response has been achieved with CHC treatment. Due to the potential risk of HBV reactivation, specific monitoring is necessary to avoid delayed diagnosis and treatment.

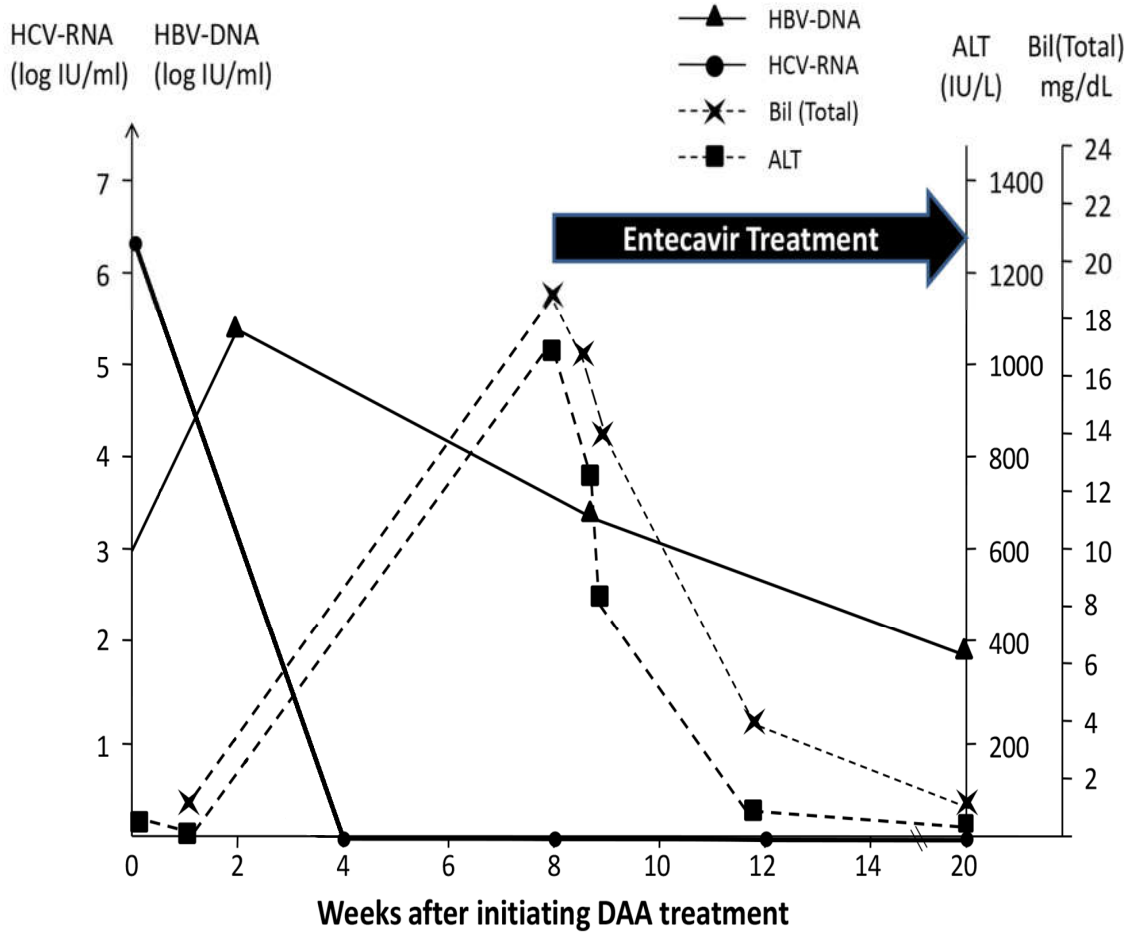
The American Association of the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) recommend that HBV DNA tests should be performed prior to the initiation of HCV therapy for those who are HBsAg-positive. For those who meet the criteria for antiviral treatment for HBV, HBV treatment prior to or at the same time as HCV therapy should be initiated. For those who do not meet the criteria for HBV therapy, monitoring HBV DNA levels at regular intervals (usually not more frequently than every four weeks) during HCV therapy has been suggested. In our case, HBV treatment was not initiated in this patient prior to DAA treatment because of the lack of eligibility for insurance. Nevertheless,

Table 1. Laboratory data on admission

WBC	5,750/μl	AST	1616 IU/L
RBC	4.15 × 106/μl	ALT	1212 IU/L
Hb	13.3 g/dL	T-Bil	21.07 mg/dL
Hct	38.8%	D-Bil	11.94 mg/dL
Plt	219 × 10^3/μl	HCV RNA	<0.03 KIU/ml

WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; Hct, hematocrit; Plt, platelet; AST, aspartate aminotransferase; ALT, alanineaminotransferase; T-Bil, total bilirubin; D-Bil, direct bilirubin

Figure 1: The values of laboratory tests after initiating DAA therapy



Legend: The level of ALT was markedly increased, and the level of HBV DNA had increased from 21 to 173,000 IU/ml. After starting HBV antiviral treatment on admission, his HBV DNA level decreased to 2180 IU/ml four weeks later. The HCV RNA was undetectable four weeks after initiating DAA therapy.

HBV reactivation and the rapid deterioration of the liver were promptly detected by routinely monitoring the ALT and HBV DNA levels. After discontinuing DAAs and starting antiviral treatment for HBV, the patient's decompensated status rapidly improved, and the HBV DNA levels decreased. Our case highlights the importance of monitoring HBV reactivation and administering timely CHB treatment for HBV/HCV patients during DAA treatment for CHC.

Author Contributions

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Conflict of Interest

The authors declare that they have no conflict of interest.

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