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Case Report

Reactivation of hepatitis B virus during interferon-free therapy with daclatasvir and asunaprevir in patient with hepatitis B virus/hepatitis C virus co-infection

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Direct-acting antiviral agents (DAA) for hepatitis C virus (HCV) are not effective for hepatitis B virus (HBV), which may be suggestive of reactivation of anti-HBe hepatitis during interferon (IFN)-free DAA therapy in HBV/HCV co-infected patients with inactive HBV. A 69-year-old male patient was diagnosed with chronic hepatitis due to HBV/HCV co-infection with serum levels of alanine aminotransferase (ALT) of 94 U/L, HCV RNA of 4.2 log IU/mL and HBV DNA of 2.5 log copies/mL. HCV was thought to be responsible for the hepatitis activity because of low level of HBV core-related antigen (3.1 log U/mL). He was treated with combination therapy of daclatasvir and asunaprevir. Serum ALT gradually increased, and reached 237 U/L on day 43 in spite of undetectable HCV RNA. Serum HBV DNA was increasing to 7.0 log copies/mL at that time. The treatment was stopped due to suspicion of drug-induced liver injury and/or HBV reactivation. Administration of entecavir reduced HBV DNA levels, followed by improvement in ALT levels. This report proposes that close monitoring of HBV DNA during the anti-HCV DAA therapy and the commencement of anti-HBV therapy with nucleoside analogs after the increase of HBV DNA should be considered in patients with HBV/HCV co-infection.

Key words: antiviral therapy, co-infection, hepatitis B virus, hepatitis C virus

INTRODUCTION

THE DEVELOPMENT OF interferon (IFN)-free regimens with direct-acting antiviral agents (DAA) has led to new insights into hepatitis C virus (HCV), and recent studies of IFN-free DAA therapy resulted in greater than 80% sustained virological response in patients with genotype 1 of HCV.[1–4] The patients with co-infection of hepatitis B virus (HBV) and HCV are at a high risk of developing liver cirrhosis and hepatocellular carcinoma. They need either or both of the anti-HBV and anti-HCV treatments depending on their viral status by utilizing therapeutic regimens for HBV or HCV mono-infection.[1,2] Because IFN can suppress both HBV and HCV replication, HBV reactivation rarely occurs during IFN-based anti-HCV therapies. By contrast, HCV-specific DAA are not effective for HBV, which may be suggestive of HBV reactivation during IFN-free DAA therapy. We experienced HBV reactivation during combination therapy with daclatasvir and asunaprevir in a patient with HBV/HCV co-infection.

CASE REPORT

A 69-YEAR-OLD MALE patient visited our hospital for abnormal liver function test. The serum alanine aminotransferase (ALT) level was 94 U/L. His HCV was genotyped as 1b with HCV RNA 4.2 log IU/mL. He was also infected with HBV. He had genotype C HBV with negative hepatitis B e-antigen, HBV DNA of 2.5 log copies/mL and hepatitis B core-related antigen (HBcrAg) of 3.1 log U/mL. His imaging studies with dynamic computed tomography denied liver cirrhosis and hepatocellular carcinoma. Then, he was diagnosed with chronic hepatitis due to HBV/HCV co-infection. His low levels of HBcrAg and HBV load suggested that he was classified as an inactive HBV carrier, and HBV treatment was not thought to be necessary for

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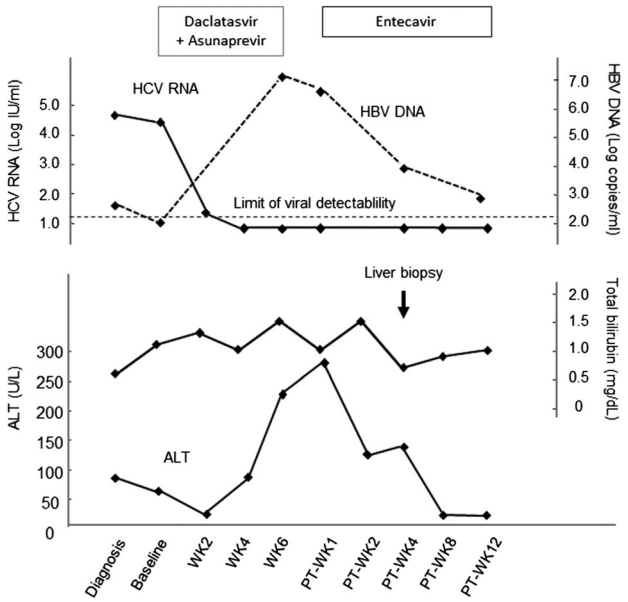

Figure 1 Clinical course of the patient during combination therapy with daclatasvir and asunaprevir. ALT, alanine aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus.

his inactive HBV status according to the treatment guideline of HBV.[4,5] HCV was thought to be responsible for the hepatitis activity, and he was treated with combination therapy of daclatasvir (60 mg daily) and asunaprevir (100 mg twice daily), after confirming the dominance of Y93 and L31 in the HCV NS5A region on his HCV sequence results, as shown in Figure 1 and Table 1.

When visited on day 15, serum ALT became normal and HCV RNA had decreased to an undetectable level. Serum ALT gradually increased thereafter, and reached 237 U/L on day 43. Serum aspartate transaminase was 164 U/L, γ-glutamyltransferase 60 U/L and bilirubin 1.5 mg/dL. Serum HBV DNA was increased to 7.0 log copies/mL at that time. He did not complain about any subjective symptoms. Biliary obstruction was not obvious in his ultrasonography. The treatment was stopped due to suspicion of drug-induced liver injury and/or acute exacerbation due to HBV reactivation of anti-HBe positive hepatitis.

A liver biopsy showed chronic hepatitis with lymphocyte infiltrations and fibrous expansions of some portal areas without zone 3 necrosis (Fig. 2), indicating that the histological appearance was compatible with hepatitis flare induced by HBV reactivation, differently from drug-induced liver injury or autoimmune hepatitis. Entecavir (0.5 mg daily) was started on day 50. Reduction of HBV DNA was followed by improvement in ALT levels. Serum HCV RNA remained undetectable at 12 weeks after cessation of the anti-HCV treatment.

DISCUSSION

AN ANTI-HBE POSITIVE inactive carrier is characterized by very low or undetectable serum HBV DNA levels below 2000 IU/mL and normal serum aminotransferases, and patients should be considered for treatment when they have HBV DNA levels above 2000 IU/mL, serum ALT levels above the upper limit of normal or moderate liver fibrosis.[5,6] As for abnormal ALT levels in HBV/HCV co-infected patients, responsibility of hepatitis is difficult to distinguish between HBV and HCV. The patients with very low or undetectable serum HBV DNA levels below 2000 IU/mL are usually diagnosed as inactive HBV carriers. It has been reported that HBcrAg, reflecting

Table 1 Laboratory data prior anti-HCV therapy

White blood cell	4400	/μL	HBs antigen	(+)		
Red blood cell	485×10^4	/μL	HBe antigen	(−)		
Hemoglobin	15.3	g/dL	Anti-HBe	(+)	99.5	%
Platelet count	13.9×10^4	/μL	Anti-HB core	(+)	11.27	S/CO
Prothrombin time	91	%	HBcrAg	3.1	log U/mL	
Total protein	7.2	g/dL	HBV genotype	C		
Albumin	4.2	g/dL	HBV DNA	2.5	log copies/mL	
Total bilirubin	0.8	mg/dL	Anti-HCV	(+)		
Direct bilirubin	0.1	mg/dL	HCV genotype	1b		
AST	91	IU/L	HCV RNA	4.2	Log IU/mL	
ALT	94	IU/L	AFP	4.4	ng/mL	
γ-GT	72	IU/L	AFP-L3	<0.5	%	
Creatinine	0.84	mg/dL	PIVKA-II	20	mAU/mL	

AFP, α-fetoprotein; AFP-L3, *Lens culinaris* agglutinin-reactive fraction of AFP; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HB, hepatitis B; HBcrAg, hepatitis B core-related antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; PIVKA-II, protein induced by vitamin K absence/antagonist-II; γ-GT, γ-glutamyltransferase.

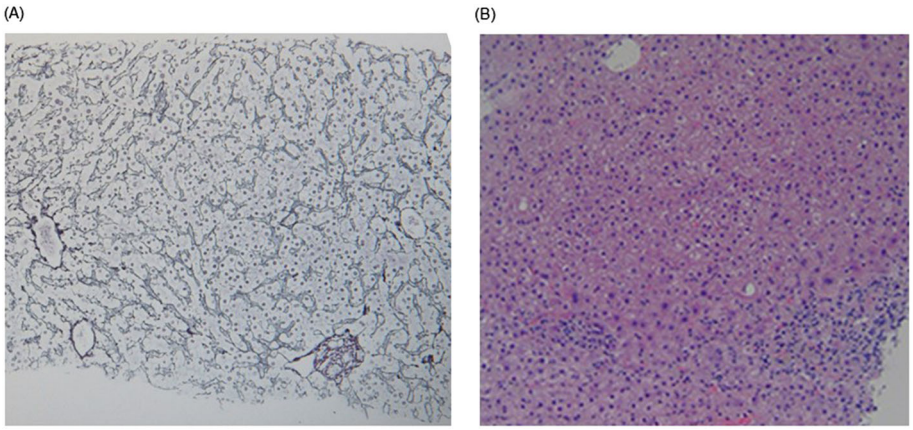

Figure 2 Light microscopic features in the liver of the patient with hepatitis B virus reactivation during combination therapy with daclatasvir and asunaprevir; (a) silver staining (original magnification × 40) and (b) conventional hematoxylin–eosin staining (original magnification × 40).

the transcriptional activity of intrahepatic cccDNA, may help to distinguish between inactive HBV carriers and those with active disease.[7] Then, the patient in the present study showed low levels of HBcrAg and HBV load, suggesting that he should be classified as an inactive HBV carrier.

Because IFN can suppress both HBV and HCV replication, HBV reactivation rarely occurs during IFN-based anti-HCV therapies.[1] However, Liu *et al.* reported that a considerable number of patients revealed an increase of HBV replication in the patients with sustained virological responses to the IFN-based therapy for HCV.[8] HCV-specific DAA are not effective for suppression of HBV replication, and IFN-free DAA therapy may release HBV from HCV suppressive effects, which may be suggestive of HBV reactivation during IFN-free DAA therapy. On the other hand, reactivation of HCV may be possible during and after the anti-HCV therapy in relation to suppression of HBV replication by nucleoside analogs.

The patient in this report had HBV DNA of 320 IU/mL prior to anti-HCV therapy with hepatitis flare by week 6 of treatment. Collins *et al.* reported HBV reactivation during anti-HCV therapy with simeprevir and sofosbuvir in two patients with HBV/HCV co-infection.[9] One patient had HBV DNA of 2300 IU/mL prior to anti-HCV therapy with development of severe viremia and acute hepatitis by week 8 of treatment. The other started anti-HCV therapy with HBV DNA of less than 20 IU/mL, and logarithmic increases in HBV replication were detected at week 2 of treatment with initiation of anti-HBV therapy at week 4 of treatment. HBV reactivation in these patients indicated that close monitoring of HBV DNA during the anti-HCV DAA therapy and the commencement of anti-HBV therapy with nucleoside analogs after the increase of HBV DNA should be considered in HBV/HCV co-infected patients.

Further studies are needed to determine whether simultaneous administration of anti-HBV and anti-HCV drugs, as well as preemptive anti-HBV therapy before anti-HCV therapy, would be possible.

REFERENCES

1 EASL Recommendations on Treatment of Hepatitis C. European Association for the Study of the Liver. *J Hepatol* 2015; **63**: 199–236.
2 Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology. JSH Guidelines for the Management of Hepatitis C Virus Infection: A 2014 Update for Genotype 1. *Hepatol Res* 2014; **44** (Suppl S1): 59–70.
3 Kumada H, Suzuki Y, Ikeda K *et al.* Daclatasvir plus asnaprevir for chronic HCV genotype 1b infection. *Hepatology* 2014; **59**: 2083–91.
4 Mizokami M, Yokosuka O, Takehara T *et al.* Ledipasvir and sofosbuvir fixed-dose combination with and without ribavirin for 12 weeks in treatment-naive and previously treated Japanese patients with genotype 1 hepatitis C: an open-label, randomised, phase 3 trial. *Lancet Infect Dis* 2015; **15**: 645–53.
5 Drafting Committee for Hepatitis Management Guidelines and the Japan Society of Hepatology. JSH Guidelines for the Management of Hepatitis B Virus Infection. *Hepatol Res.* 2014; **44** (Suppl S1): 1–58.
6 Degertekin B, Lok AS. Indications for therapy in hepatitis B. *Hepatology* 2009; **49**: S129–37.
7 Maasoumy B, Wiegand SB, Jaroszewicz J *et al.* Hepatitis B core-related antigen (HBcrAg) levels in the natural history of hepatitis B virus infection in a large European cohort predominantly infected with genotypes A and D. *Clin Microbiol Infect* 2015; **21**: 606.e1–606.e10.
8 Liu CJ, Chuang WL, Lee CM *et al.* Peginterferon alfa-2a plus ribavirin for the treatment of dual chronic infection with hepatitis B and C viruses. *Gastroenterology* 2009; **136**: 496–504.
9 Collins JM, Raphael KL, Terry C *et al.* Hepatitis B Virus Reactivation During Successful Treatment of Hepatitis C Virus With Sofosbuvir and Simeprevir. *Clin Infect Dis* 2015 (in press).