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Caution: Reactivation of Hepatitis B during Hepatitis C Treatment with Direct-Acting Antiviral Therapy

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To the Editor

Direct-acting antivirals (DAAs) have permanently changed the landscape of hepatitis C virus (HCV) treatment, obviating the need for concurrent peginterferon (PEG-IFN). Nonetheless, the DAAs effect on special populations such as those with dual or tri-infection i.e., HCV/ HBV (hepatitis B virus) or HCV/HBV/HIV (human immunodeficiency virus) needs to be examined. Currently, neither the American Association for the Study of Liver Diseases (AASLD) or the Infectious Diseases Society of America (IDSA) offer guidelines on treating HCV/HBV co-infected patients with the recently approved DAAs.

Reported rates of HCV and HBV co-infection vary from 6–30%;⁽¹⁾ and a recent study has shown that up to 61.5% of patients with HCV have evidence of prior exposure to HBV (isolated hepatitis B core antibody (HBcAb)) (1). Reactivation of HBV while undergoing interferon-(IFN)-based antiviral therapy in chronically infected HCV patients has been documented (2), but the exact mechanism is unclear and it is hypothesized that both host and viral factors have a significant role.

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CONFLICT OF INTEREST

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We describe two cases of HBV-reactivation in patients with known chronic HCV, treated with SOF, a NS5B polymerase inhibitor+simeprevir (SMV), a second wave, first-generation NS3/4A protease inhibitor.

Case 1A: a 65-year-old man with genotype 1b HCV and chronic HBV was treated with 12 weeks of SOF/SMV. A 2011 liver biopsy and a recent Fibroscan confirmed stage 3 fibrosis. Patient's pre-treatment labs revealed: HCV viral load (VL) 6,210,000 IU/ml, HBV VL 1,200 IU/ml, negative HIV, alanine aminotransferase (ALT) 18 IU/l, aspartate aminotransferase (AST) 14 IU/l, and total bilirubin (TB) 0.8 mg/dl. At week 8 of treatment, he was noted to have mild scleral icterus. Labs revealed: negative HCV VL, HBV VL 1.3 million IU/ml, TB 2.5 mg/d, and ALT 948. SOF/SMV was discontinued and he was started on entecavir for treatment of his HBV. His liver enzymes normalized, his HCV VL remained undetectable (achieving a 12 week sustained virologic response (SVR)-12) and his HBV became undetectable.

Case 2A: a 57-year-old man with genotype 1a HCV and no known evidence of portal hypertension or cirrhosis presented for antiviral therapy with 12 weeks of SOF/ SMV. Pre-treatment labs showed: HCV VL 8.6 million IU/ml, HBV VL<20 IU/ml, ALT 54 IU/l, positive-HBcAb total, negative hepatitis B surface antigen (HBsAg) and negative hepatitis B surface antibody (HBsAb). At week 2 of treatment, HCV VL was undetectable but HBV VL had increased to 353 IU/ml. At week 4 of treatment, his HBV VL had further increased to 11,255 IU/ml with normal liver enzymes. His SOF/SMV was continued and he was started on tenofovir for treatment of his HBV. Patient achieved a SVR-12 and his HBV VL became undetectable.

Reactivation of HBV in patients with chronic HCV treated with DAAs has only recently been described. Historically, it has been hypothesized that in patients co-infected with HCV and HBV, one virus usually asserts dominance and commonly these patients have active HCV viremia with low or undetectable HBV DNA levels. The mechanism by which chronic HCV may suppress HBV replication has a few possible explanations including (1): HBV antigen levels are reduced in the hepatocytes and in the periphery of chronically co-infected patients (3) (2) patients with chronic HBV have higher rates of surface antigen clearance following HCV superinfection (4), and (3) viral replication in acute HBV infection may be attenuated in patients with pre-existing HCV.(5) Studies have also shown that both HCV and HBV can replicate in the same cell(6) without direct interference, suggesting that viral dominance may be an indirect, rather than direct mechanism, mediated by the host immune system.

In review of the current literature, aside from our recently published series,(7) three additional case reports of hepatitis B reactivation with DAAs have been described(8–10) (see Table 1). While previous IFN-based therapy had treatment effect on both HBV and HCV, DAAs do not offer any antiviral activity against HBV. In our series, both patients had a rapid decline in HCV VL with DAA therapy, and attained a SVR-12. Both patients also responded to HBV antiviral therapy and none of our patients developed irreversible hepatic decompensation.

Our experience emphasizes the importance of not only identifying patients with active hepatitis B viremia but also closely monitoring all patients with prior exposure to HBV (isolated HBcAb) during treatment of HCV with DAAs. We recommend (1): vaccination of all isolated HBcAb-positive patients (2) closely monitoring HBV VL and liver enzymes during HCV therapy in patients who have a positive HBV VL or positive HBcAb, and treating those with ALT increments attributable to a reactivation or recrudescence of HBV infection, and (3) consider treating patients with advanced liver disease (stage 3–4 fibrosis or portal hypertension) with HBV antiviral therapy, while on HCV treatment. Optimal management of these patients involves early identification of HBV exposure and close monitoring of liver enzymes and patient symptoms.

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Table 1

Hepatitis B Flares While Undergoing Non-Interferon Based Hepatitis C Therapy

Author (Reference)	Demographic	Coinfection	HCV GT	Stage	HBV status	HCV therapy	HBV fl are onset (weeks)	Peak ALT (IU/L)	Peak HBV DNA (IU/ml)	HBV Therapy	Symptoms Signs and Outcomes ^a
Pillai <i>et al. (this study)</i>	65M	HCV/HBV	1b	3	Carrier	SOF/SMV	8	948	1.3×10 ⁶	ETV	Jaundice nausea resolved
Collins <i>et al. (7)</i> Pillai <i>et al. (x)</i>	57M	HCV/HBV	1a	Non-cirrhotic	Isolated core Ab	SOF/SMV	2	Normal	11,255	TDF	Asymptomatic
Pillai <i>et al. (x)</i>	52M	HCV/HBV/HIV	2b	2	Isolated core Ab	SOF/RBV	7	1023	845,000	TDF/FTC	Pain nausea jaundice resolved
Collins <i>et al. (7)</i> Pillai, <i>et al. (x)</i>	55M	HCV/HBV	1a	4	Carrier	SOF/SMV	8	1495	22×10 ⁶	TDF/FTC	Pain jaundice resolved
De Monte <i>et al. (8)</i>	53M	HCV/HBV/HIV	4	“low”	Isolated core Ab	SOF/LDV	13 (post-therapy week 1)	1026	960×10 ⁶	TDF	Jaundice fever resolved
Trakayama <i>et al. (9)</i>	61M	HCV/HBV	1b	1	Carrier	ASV/DCV	6	237	7×10 ⁶	ETV	Asymptomatic
Ende <i>et al. (10)</i>	59F	HCV/HBV	1b	2	Isolated core Ab	SOF/SMV	11	2263	29×10 ⁶	TDF	Liver failure olt

AB, antibody; ASV, asunaprevir; DCV, daclatasvir; ETV, entecavir; FTC, emtricitabine; GT, genotype; HBV, hepatitis B; HCV, hepatitis C; HIV, human immunodeficiency virus; LDV, ledipasvir; OTL, orthotopic liver transplant; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TDF, tenofovir disoproxil fumarate.

All patients achieved sustained virologic response for hepatitis C.