

Another Call to Cure Hepatitis B

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Because curing chronic hepatitis B is not yet possible, reactivation of hepatitis B virus (HBV) occurs and is most commonly recognized in the setting of immunosuppression [1]. In this issue of *Clinical Infectious Diseases*, Collins et al give us another setting to monitor for HBV reactivation—curing hepatitis C with direct-acting antiviral agents (DAAs) in HBV/hepatitis C virus (HCV) coinfection [2]. When interferon alfa was the standard of care for HCV treatment, a meta-analysis demonstrated that HBV reactivation occurred in 31% of the patients who experienced a sustained virologic response and only 11% in those without a sustained virologic response [3]. However, interferon alfa is an immunomodulatory drug that affects HBV replication; therefore, it was unclear if HBV reactivation would occur with DAAs that have no activity against HBV. We now have proof that this can occur.

Collins et al describe 2 cases of HBV/HCV coinfection where HBV reactivation occurred during HCV treatment with

sofosbuvir and simeprevir [2]. The first patient was hepatitis B surface antigen (HBsAg) positive with an HBV DNA level of 2300 IU/mL prior to treatment; the second patient was only positive for hepatitis B core antibody (anti-HBc) and had an undetectable HBV DNA level. In both patients, the HCV RNA declined rapidly and was either undetectable or nearly undetectable by week 2. In the first patient, HBV reactivation was detected at week 8 when the patient was clinically symptomatic with an HBV DNA of 22 million IU/mL. The time course of reactivation is unknown as serial HBV DNA tests were not obtained. In the second patient, HBV DNA increased to 353 IU/mL at week 2 and then to 11 255 IU/mL by week 4. As tenofovir disoproxil fumarate was added at week 4, the clinical course without initiation of therapy is not known. In our hepatitis clinic at Johns Hopkins, we cared for a HBV/HCV-coinfected patient who was positive for HBsAg and had undetectable HBV DNA prior to treatment with ledipasvir/sofosbuvir. At week 4 of treatment, HBV DNA increased to 96 IU/mL, and then to 303 IU/mL at 8 weeks, but returned to undetectable without intervention and without a commensurate rise in aminotransferases at week 12. This case illustrates that HBV reactivation during HCV treatment does not always lead to a clinical flare.

When HBV and HCV are chronic in the same host, HCV is usually the dominant virus, with HCV RNA levels higher than HBV DNA levels [4, 5]. Hepatitis B reactivation with immunosuppression is explained by changes in HBV immune control, but why reactivation occurs when HCV is the dominant virus and is eliminated with DAA therapy is not clear. Mathematical models of DAA therapy reveal that the half-life of circulating HCV virions is approximately 45 minutes [6] and that HCV-infected hepatocytes are exponentially cleared; it is likely that the majority of HCV-infected hepatocytes are cleared as early as 4 weeks of treatment. Thus, early in DAA treatment there is disruption of the intrahepatic host-HCV equilibrium that could allow HBV to reactivate. Possible explanations for this reactivation are (1) the loss of a direct viral interaction between HBV and HCV that inhibited HBV replication; (2) an increase in the available replication space for HBV; or (3) a loss of host immune response(s) to HBV.

We will first consider whether HCV interferes with HBV replication through a direct viral interaction. In a human hepatoma cell line, HCV core protein was shown to interfere with HBV gene expression and replication by directly interacting with HBV proteins [7]. However, in a transgenic mouse model, coexpression of HCV core protein did not interfere with HBV

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replication or gene expression [8]. The limitation of these models is that overexpression of HCV proteins rather than replicating virus was used. A more recent study using the HCV replicon system and a replication-competent HBV construct demonstrated that both viruses can replicate in the same hepatocyte in vitro [9]. Similarly, Rodriguez-Inigo et al used fluorescent in situ hybridization on patient samples to show that HCV and HBV can infect the same hepatocyte [10]. Thus, more recent literature does not support direct viral interference between HBV and HCV.

Next we consider whether successful HCV treatment increases the available replication space as a possibility for HBV reactivation. It is plausible that rapid HCV clearance may provide abundant hepatocytes for HBV infection, but several pieces of evidence suggest that HBV replication space is not limited in HBV/HCV coinfection. First, in chronic HCV, 21%–45% of hepatocytes contain HCV RNA [11]. Similarly, in chronic HBV, 21%–27% of hepatocytes were found to have covalently closed circular DNA or to be infected with HBV [12, 13]. Strictly speaking, therefore, as both viruses occupy a minority of hepatocytes, there are ample available hepatocytes to support coinfection. Second, as discussed above, a hepatocyte can be infected with both viruses. Third, the turnover rate of HCV-infected hepatocytes is thought to be short even in the absence of therapy (estimated between 4 and 29 days) [14, 15], so enough new hepatocytes that are susceptible to infection should be available at any given time. Thus, it is unlikely that expansion of the replication space with DAA therapy led to HBV reactivation.

It is most likely that actively replicating HCV produces a host immune state that is favorable for controlling HBV replication and that DAA therapy disrupts this immune state. It seems implausible that HCV directly promoted an HBV-specific T-cell response or enhanced a neutralizing antibody response as this would require freely diffusing HCV proteins to

interact specifically with HBV-specific T or B cells. However, it does seem possible that the innate immune response was altered with elimination of HCV replication. HCV infection stimulates production of interferon-stimulated genes (ISGs) in the liver that are highly expressed during chronic infection [16]. Many ISGs have antiviral effects. These high intrahepatic ISGs are insufficient to suppress HCV replication, but may suppress HBV replication in some cases. Circulating interferon gamma-induced protein 10 (IP-10), an intrahepatic ISG that is strongly associated with intrahepatic ISG expression [17–19], was significantly higher in HBV/HCV-coinfected patients when HCV was the dominant virus and correlated with HCV RNA levels [5]. In both of the patients described by Collins et al, HCV RNA levels were high, suggesting that intrahepatic ISGs may have also been elevated. IP-10 levels drop rapidly with DAAs, showing a 49% decline after 1 week of DAAs in one study [20]. Thus, it is conceivable that the rapid decline in IP-10 heralds the decline of intrahepatic antiviral ISGs, permitting reactivation of HBV as observed by Collins et al. Similarly, natural killer cells, which also show evidence of heightened activation in chronic HCV infection [21, 22], may have altered function after HCV clearance that allows HBV reactivation in some people. It should be emphasized that changes in the innate immune response with HCV control may also have non-specific effects on adaptive immune responses to HBV, further permitting HBV reactivation.

These cases highlight important clinical implications as severe hepatitis can occur with HBV reactivation. All patients starting DAA therapy should be assessed for hepatitis B coinfection with HBsAg, anti-HBc, and hepatitis B surface antibody (anti-HBs), and should receive HBV vaccine if susceptible. If a patient is either HBsAg or isolated anti-HBc positive, then HBV DNA should be obtained prior to DAA therapy. Patients with low

or undetectable HBV DNA should be monitored at least every 4 weeks for HBV reactivation with HBV DNA, and those with HBV DNA levels meeting treatment criteria should initiate HBV therapy [23]. Patients who have evidence of immune recovery (anti-HBs and anti-HBc positive) likely have a low risk of reactivation and can be monitored with HBV DNA at week 4 and, if negative, would likely not require further HBV DNA testing unless a rise in aminotransferases occurs.

The optimal management of HBV reactivation with DAA therapy for HCV is not known. It is likely that not all patients with HBV reactivation need to start treatment for HBV, as illustrated by our case from Johns Hopkins. However, additional studies are needed to determine which patients will benefit from HBV treatment after DAA-induced reactivation. If treatment of HBV is not initiated after initial HBV reactivation, then HBV DNA should be monitored frequently (perhaps every 2 weeks) and treatment initiated if HBV DNA continues to rise.

In summary, HBV reactivation in HBV/HCV-coinfected patients can occur during DAA therapy for HCV, so it is important to check for chronic hepatitis B before starting HCV therapy. Further work is needed to understand the immune mechanisms that are responsible for HBV reactivation in this situation and to determine the optimal management of these patients. These cases clearly add to the list of causes for HBV reactivation and reinforce the need to cure hepatitis B.

Notes

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