HBV Reactivation During DAA Treatment of Chronic Hepatitis C: A Hidden Danger of an Otherwise Major Success Story

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It has been estimated that 250 million and 170 million people worldwide are infected with hepatitis B virus (HBV) and hepatitis C virus (HCV), respectively. Co-infection is relatively common in regions where both viruses are endemic and transmission is facilitated by common routes of exposure. In a recent study of 1287 New York City residents with hepatitis C, most of whom were born in United States, 62% had resolved HBV infection and 6% were HBsAg positive (1.) Dual infection with HBV and HCV leads to accelerated liver disease and a higher risk for cirrhosis and hepatocellular carcinoma. Treatment of co-infected patients is controversial, but it is a common practice to treat the virus that genomic testing reveals to be dominant.

The intracellular interactions of the two viruses are unclear. Cross sectional studies have shown that co-infected individuals often have high levels of HCV RNA, low or non-detectable HBV DNA, anti-HBe reactivity, and lower levels of HBsAg when compared to HBV mono infection.(2) Thus, HCV is most often the primary target of antiviral therapy. However, longitudinal studies have demonstrated that the levels of HBV DNA and HCV RNA may fluctuate with time suggesting that competitive interactions between the two viruses is more dynamic than previously thought.(3)

The recent development of direct-acting antiviral (DAA) drugs that are highly effective in eradicating hepatitis C virus is a milestone achievement. Registration trials have convincingly shown that DAA treatment is far better tolerated than interferon/ribavirin based regimens. However, post approval case series and a compilation of 24 international cases in the FDA Adverse Event Reporting System (FAERS) have demonstrated that HBV reactivation (HBVr) occurs during DAA treatment. (4-6) The recent emergence of this adverse effect of DAAs is explainable by the exclusion of HBV co-infected individuals from registration trials.

As with HBVr during immunosuppressive medications, reactivation with DAA therapy occurs in HBsAg-positive individuals and is less common in persons with resolved infection (HBsAg negative, anti-HBc positive with or without anti-HBs).(5, 7) Predictive factors have not been identified, but there is no apparent association of HBVr with the type of DAA therapy or HCV genotype. Frequent biochemical evidence of hepatitis in the reported cases, with liver injury severe enough to require liver transplantation in a few instances, as well as rare case fatalities have resulted in an FDA box warning for these agents. Both EASL and the AASLD/IDSA Guidance Panel have recommended HBV screening with HBsAg, anti-HBc, and anti-HBs prior to initiation of HCV treatment.(8,9) The Guidance Panel recommends that all HBsAg-positive patients should be tested for HBV DNA and individuals who meet criteria for antiviral therapy (> 2,000 IU) should be given HBV therapy whereas HBsAg carriers with low or nondetectable HBV DNA should be monitored with regular HBV DNA testing during DAA treatment. A paucity of data prevented the Guidance Panel from making specific recommendations for individuals with resolved hepatitis B. These recommendations are likely to change as further information is acquired.

Two articles in the current issue of Hepatology provide further clarity on the relative risk of HBVr during DAA therapy in patients with active and resolved hepatitis B.(10, 11) The studies are important because they allow us to better evaluate the adequacy of the current treatment guidelines. In the paper by Belperio and associates, the authors used the VA Cooperate Data Warehouse to review data on 62,000 HCV infected patients who had undergone treatment with DAA therapy.(10) The study

cohort included 377 HBsAg positive and 7,200 anti-HBc positive patients. Of this number, 9 cases (8 HBsAg positive, 1 with resolved infection) met the virologic criterion for HBVr of a greater than 3 log increase in HBV DNA. One of the 8 HBsAg positive reactivations was associated with a severe ALT elevation (1540 U), and this case was the only one in which pre therapy HBV DNA exceeded 2,000 IU. Twelve additional HBsAg-positive patients demonstrated a 1.32 to 2.95 log increase in HBV DNA during treatment. Peak on treatment ALT levels in these cases were either normal or minimally elevated, and pre-therapy HBV DNA was either non-detectable or less than 100 IU. Reactivation was rare in the resolved hepatitis B patients, with only 1 meeting the virologic criterion for reactivation and none of 390 tested for HBsAg during treatment becoming positive. Although this timely study gives us an important glimpse at reactivation in a large hepatitis C cohort with active or resolved hepatitis B, the observed frequency of HBVr was likely to be an underestimate. Hepatitis B virus DNA testing was only done in 84 (22%) of the 377 HBsAg-positive individuals, and testing for HBV DNA and HBsAg in the group with resolved infection were available in a small minority of patients (2.4% and 5.3%, respectively). Also, the virologic criterion used to diagnose HBVr was considerably more stringent than the 1 log increase in HBV DNA used that is frequently used in the published literature.

The second study in this issue by Chen and colleagues is a systematic review and meta analysis of 29 interferon and 7 DAA studies with a primary objective of determining the efficacy and safety of interferon and DAA treatment of hepatitis C.(11) The authors found that the rate of occurrence of (12-14%) was comparable with interferon and DAA therapy but as they point out, the level of confidence in the pooled incidence rates of HBVr is reduced by substantial heterogeneity of the virologic and ALT criteria used to define reactivation and associated hepatitis. Severe hepatitis was more frequently reported with DAA treatment and reactivation was not recorded in interferon treated patients with occult infection (HBsAg negative, anti-HBc positive). As with the study by Belperio, baseline HBV DNA level was not associated with reactivation in either HBsAg positive or occult infected patients.

The operative mechanisms behind HBVr during DAA therapy of hepatitis C are currently unclear. However, examination of the contrasting clinical features of the cases reported with interferon and DAA treatment provide clues to possible pathogenetic mechanisms. As emphasized in the paper by Chen, HBVr occurs earlier during DAA therapy when compared to interferon. The slower emergence of HBVr with interferon, often occurring after discontinuation of treatment, can be explained by the drug's anti-HBV properties and a slower and weaker effect on HCV replication that provides less momentum toward reciprocal dominance by HBV. In contrast, HBVr first emerges during DAA therapy coincident to the disappearance of HCV RNA at week 4 to 8 of treatment. Investigations in DAA treated patients have shown that this is a time when there is a major change in the hepatic immunologic environment with a steep decline in interferon signaling genes and proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interferon gamma-induced protein 10 (IP-10), each of which could favor enhanced HBV replication (12, 13). Eradication of HCV would also be anticipated to result in the disappearance of the HCV core protein that has been shown to impede HBV replication in vitro and in vivo.(14) In addition, a recent study using peripheral mononuclear cells and hepatic tissue have shown a rapid loss of NK cell activation markers during DAA treatment of hepatitis C (15).

The most pressing clinical issue currently is how to best prevent HBVr during DAA treatment. Prevention requires that all patients who will be placed on DAA treatment should be scrupulously tested for at least HBsAg and anti-HBc before treatment initiation followed by HBV DNA assessment in individuals found to be HBsAg positive. Early initiation of treatment with entecavir or tenofovir is indicated in HBsAg carriers meeting standard criteria for antiviral therapy. However, as noted in the FAERS and the two papers in this issue, a baseline finding of nondetectable or low level HBV DNA in

HBsAg-positive patients does not adequately safeguard that HBVr will not occur during DAA therapy. Thus, it is my belief that anti-HBV prophylaxis also should be given to *all* HBsAg-positive patients who fail to meet treatment criteria, as we currently do with immunosuppressive drug therapy. Until we have more information, prophylaxis should probably be continued until a sustained virologic response can be documented at post treatment week 12. Those failing to achieve a sustained virologic response with DAA therapy may be less likely to have a lower risk for HBVr after treatment, but more information is needed. Routine testing for HBV DNA in resolved HBV infection is not recommended at the current time because of significant costs involved (particularly from a global perspective) and the relative rarity of HBVr in these individuals. (5, 7, 10) Instead, these patients should have regular ALT monitoring with reflexive HBV DNA testing for unexplained ALT elevations.

Reactivation of hepatitis B is an infrequent but not rare complication of DAA therapy in HBV/HCV co-infected patients. The availability of curative treatments for hepatitis C has placed increased emphasis on diagnosing and treating this condition. This is an apt time, however, to also remind ourselves of the importance of screening all HCV infected patients for HBV. As with immunosuppressive drug therapy, HBV screening and early treatment are the key elements in preventing HBVr during DAA therapy.

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