Letter

Hepatitis B reactivation in chronic hepatitis C patients during treatment with ledipasvir and sofosbuvir

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We read with strong interest the article by Gane et al. [1] that evaluated ledipasvir (90 mg/day) and sofosbuvir (90 mg/day) combination therapy of hepatitis C infection in patients coinfected with hepatitis B. They reported all enrolled patients reached the primary end point of HCV RNA <15 IU/ml 12 weeks after treatment. In seven of eight patients (88%), serum HBV DNA levels increased during treatment, but none of the increases were associated with clinical HBV flares or required treatment.

However, there are some concerns related to the conclusion that the new direct-acting antivirals (DAAs) induced HBV reactivation. The evidence confirmed that most HBV–HCV-coinfected patients appear to have active HCV and inactive HBV replication, but some patients also have alternating phases of dominance of one virus over the other [2,3]. It is well-known that HCV is the dominant virus, and may inhibit HBV replication in HBV–HCV-coinfected patients. Some studies revealed that the HCV core gene protein and NS5A proteins may inhibit HBV replication [4,5]. When the HCV barrier is removed, HBV can become the dominant virus and be reactivated more easily.

Recently, cases of hepatitis B reactivation in new DAA-based anti-HCV therapy emerged [6–10]. All the reported cases had very low or even no HBV replication before DAA therapy, some patients even had negative HBsAg and positive HBcAb, and reactivated after suppression of HCV replication. HBV reactivation is often coupled with increased alanine aminotransferase levels and increased HBV DNA copies, and most patients recovered after anti-HBV therapy. However, there are some concerns related to this issue. Firstly, the viral interactions between HBV and HCV in the coinfected patients remain unknown. Secondly, when DAAs are administered to HBV–HCV-coinfected patients, can all reactivation recover without anti-HBV treatment? In addition, when should anti-HBV treatment be initiated appropriately if it is necessary?

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References


Author reply to: Hepatitis B reactivation in chronic hepatitis C patients during treatment with ledipasvir and sofosbuvir

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We are very interested to read the comments from Ou and Chen [1]. They are concerned about the patients included in this study [2], all of whom had active viral replication selection. It is important to note that one inclusion criterion was evidence of chronic HBV infection (that is, HBsAg-positive for at least 6 months) without an indication for commencing antiviral therapy for chronic hepatitis B (that is, HBV DNA <2,000 IU/ml).

Our patient cohort reflected the typical coinfected patient – either Asian or Polynesian infected with HBV as an infant via either vertical or early horizontal transmission and superinfected with HCV in adulthood – all had HCV GT 1 infection typical for Asia-Pacific. All patients were HBeAg-negative and had low HBV DNA at time of study entry. Half had HBV DNA levels below the level of quantitation (LLOQ). Yet HBV DNA levels rose in seven of eight patients (that is, three of four patients who were <LLOQ at baseline, had at least one HBV DNA level >LLOQ during the study period, whilst all four patients with HBV DNA between LLOQ and 2,000 IU/ml had a mean increase of 1 log. The highest HBV DNA recorded during treatment was 14,290 IU/ml but this rapidly fell to baseline (<2,000 IU/ml) after treatment. With HCV suppression, alanine aminotransferase (ALT) normalized during treatment in all patients so none ever met criteria for starting oral antiviral therapy for chronic hepatitis B (CHB).

Our results confirm that HCV suppression does lead to reactivation of HBV (as defined by increase in HBV replication). However, in this pilot study, the effect of HCV suppression on HBV replication was transient and HBV DNA levels fell back to the low baseline levels during post-treatment follow-up and no patient developed ALT elevation and no patient ever required antiviral therapy.

We do not think that our study supports universal antiviral prophylaxis during HCV DAA therapy in all HBsAg+ patients. However, we agree with recommendations that all patients with HBV–HCV coinfection should have their HBV infection monitored during and following HCV DAA therapy and that oral antiviral therapy for HBV should be considered in anyone who meets established starting criteria for starting treatment for CHB (HBV DNA>2,000 IU/ml and either ALT >2×ULN or evidence of severe fibrosis) [3].

Disclosure statement

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References