Hepatitis B reactivation after HCV treatment with sofosbuvir/ledipasvir in a HIV-coinfected patient with previous positive anti-HBs antibody: a case report and a review of literature

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Abstract

Chronic hepatitis B (HBV) and C (HCV) coinfection are frequently observed in clinical practice. The interaction between HCV and HBV is complex and not completely understood, and usually results in the suppression of hepatitis B replication by HCV superinfection or coinfection. Cases of hepatitis B reactivation during and after HCV treatment with direct acting antivirals (DDA) have been described, and it is recommended to screen all patients starting DAA therapy for HBV infection markers and to monitor those that have positive markers of HBV infection. HBs antigen (HBsAg) positivity is the main risk factor for HBV reactivation, and this phenomenon is rarer in those with “resolved” HBV infection (negative HBsAg, positive HBeAb and anti-HBs antibody (HBsAb) positive or negative). The authors present a case of HBV reactivation after HCV treatment with sofosbuvir/ledipasvir that occurred in a 54-year-old male that was HIV-coinfected and had “resolved” hepatitis B infection (negative HBsAg, positive HBeAb and positive HBsAb). Our case reinforces the need to screen all patients who will start DAA therapy for hepatitis C infection, and alerts clinicians to the need to closely monitor patients with evidence of previous HBV infection no only during treatment but also after HCV treatment with DAAs.

Key words: DAA, HCV, HBV reactivation.

Introduction

Due to their shared routes of acquisition, coinfection with human immunodeficiency virus (HIV) and hepatitis B (HBV) and/or hepatitis C (HCV) is common. The World Health Organization (WHO) estimates that 2-15% of HIV-infected people worldwide (and up to 90% of those who acquired the infection through intravenous drug usage) are coinfected with HCV (approximately 2.75 million people), and that chronic HBV coinfection affects 5-20% of HIV-infected patients (approximately 2.6 million) [1]. The interaction between HBV and HCV in patients coinfected with both viruses usually results in the predominance in of one of the viruses over the other, and hepatitis B replication may be suppressed by HCV superinfection or coinfection [2].

There have been reports of hepatitis B reactivation after chronic HCV treatment with pegylated-interferon (pegINF) and ribavirin (RBV), in spite of the fact that these drugs are active against HBV, especially when sustained virological response (SVR) was achieved [3, 4]. The new direct anti-
HBV reactivation with DAA treatment in an HIV patient

He was diagnosed with HIV/HCV coinfection acquired by intravenous drug use in 1995. He initiated antiretroviral therapy (ART) in 1999 with stavudine (d4T) plus didanosine (ddI) that was changed in 2002 to d4T, lamivudine (3TC), and nevirapine (NVP). He abandoned follow-up and therapy in 2004, but reinitiated ART in 2014 with abacavir (ABC), 3TC, and efavirenz (EFV) that he was still taking with good adhesion at the time of referral. Analytically, he had 521 CD4/mm³ and undetectable HIV RNA.

Regarding HCV infection, he was a genotype 1a with baseline HCV RNA of 9,230,000 UI/ml (6.97 log). At baseline, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were 3.5 times the upper normal limit (122 and 125 UI/l, respectively), and he had an interleukin 28-B genotype CC. He had a transitory hepatic elastography (FibroScan®) of 19.0 KPa, a Child-Pugh score A (5 points), and a MELD score of 7 points. He was treatment naive, as he always refused treatment with pegylated-interferon and ribavirin; the abdominal ultrasound showed hepatosplenomegaly and signs of hepatic steatosis. The upper endoscopy showed no signs of portal hypertension.

Current HCV treatment guidelines advise the need to check for HBV serostatus in those initiating HCV treatment with DAs and warn about the risk of HBV reactivation, but provide no guidance on how to monitor these patients [18-20].

The authors present one case of hepatitis B reactivation after HCV treatment and review the published literature on this topic.

Case report

A 54-year-old male was presented in our department with HIV-1 infection, and for chronic hepatitis C evaluation and treatment.

He was diagnosed with HIV/HCV coinfection acquired by intravenous drug use in 1995. He initiated antiretroviral therapy (ART) in 1999 with stavudine (d4T) plus didanosine (ddI) that was changed in 2002 to d4T, lamivudine (3TC), and nevirapine (NVP). He abandoned follow-up and therapy in 2004, but reinitiated ART in 2014 with abacavir (ABC), 3TC, and efavirenz (EFV) that he was still taking with good adhesion at the time of referral. Analytically, he had 521 CD4/mm³ and undetectable HIV RNA.

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Case report

A 54-year-old male was presented in our department with HIV-1 infection, and for chronic hepatitis C evaluation and treatment.
At the time of HIV/HCV diagnosis (1995), he had markers of a “resolved” hepatitis B infection – Hbs antigen (HBsAg) negative, anti-HBc antibody (HBeAb) positive, anti-HBs antibodies (HBsAb) negative, anti-HBe antibody (HBeAb) positive. In 2009, these markers were repeated and confirmed the “resolved” infection (HBsAg negative, HBeAb positive, HBsAb – 75.42 UI/l).

He also had a history of chronic alcoholism (he was abstinent of alcohol for 3 months, but he used to consume more than 70 g/day) and was a smoker (21 pack-years). He was receiving lorazepam for anxiety but had no other co-medications.

Before treatment, screening tests for other causes of chronic hepatitis were performed and were negative, including auto-immune hepatitis, Wilson’s disease, and hemochromatosis.

He was treated with sofosbuvir/ledipasvir for 24 weeks without any intercurrents. By the second week of treatment, aminotransferases had normalized (AST 24 U/l, ALT 17 U/l) and he had a still positive but unquantifiable HCV viral load. At the end of the treatment, the patient had normal aminotransferases, HCV RNA and HIV RNA were undetectable, CD4 cell count was 934 cells/mm³. Liver ultrasound was repeated showing no new alterations.

He was reevaluated 4 and 12 weeks after the end of treatment: he remained asymptomatic and his blood tests showed no abnormalities; he achieved sustained SVR12. His ARV medication was altered to ABC/3TC and dolutegravir (DTG) because of neuropsychiatric complaints that were attributed to EFV. He was reevaluated 6 weeks after this change was made and no abnormality was detected.

At his 24 weeks post-treatment visit, in spite of having no symptoms, there was a steep increase in aminotransferases level (AST 375 U/l, ALT 678 U/l). There was no history of acute infections, use of new drugs or herbal products, alcohol consumption, or illicit drugs use. His HCV RNA remained undetectable and the study of autoimmune hepatitis, Wilson’s disease, and hemochromatosis was repeated and showed HBs antigen reverse seroconversion: HBsAg negative, HBeAb negative, HBeAg positive. ARV medication was altered to tenofovir/emtricitabine and DTG (he had a drug susceptible genotype D HBV virus). We assisted to a normalization of his liver enzymes.

At the time of writing this paper, approximately 17 months after the HBV reactivation, the patient remains asymptomatic. His AST level is normal (18 U/l), HBV DNA is undetectable (less than 10 UI/ml), as is HCV RNA (less than 15 UI/ml).

The evolution of analytical parameters during treatment and follow-up are shown in Figure 1.

**Discussion**

Hepatitis B reactivation after treatment of chronic hepatitis C with pegylated-interferon and ribavirin has been described and was mostly attributed to the end of the HCV suppressive effect on HBV replication after SVR achievement [4, 21]. Some authors believe that this phenomenon was less likely to occur with the interferon-based treatments due to the anti-HBV effect of these drugs that DAAs do not possess [21]. Besides not being active against HBV, DAAs achieve high SVR12 rates and very steep decreases in HCV RNA [7, 22], which may predispose to an increase in the number of HBV reactivations occurring after HCV treatment.

From 22 November 2013 to 15 October 2016, 29 cases of HBV reactivation related to DAA treatment were reported to the U.S.F.D.A. Adverse Event Reporting System [15]. Other case reports have also been published [6-14], whose main characteristics are shown in Table 1.

In most cases described so far, hepatitis B reactivation occurred either during treatment or immediately after. In case 3, there is an evidence of increased HBV replication as soon as two weeks after the beginning of treatment [7], indicating that HBV replication increases shortly after DAAs initiation. Likewise, in the review of cases reported to the FDA, the median time from DAA starting to HBV reactivation was 53 days, and HBV reactivation usually occurred 4-8 weeks after DAA initiation [15]. However, our case shows that the risk of reactivation is maintained after treatment, since our patient showed analytical alterations 6 months after the end of treatment, which also occurred in case 7 [11]. The risk of late HBV reactivation had already been demonstrated in a small study by Wahlke et al. of a cohort of 10 HCV/HBV coinfected patients from a hemodialysis center. The study showed that after HCV treatment with pegylated-interferon and ribavirin, most HBV reactivations occurred at a late stage (mean time, 22 ± 9 months) [23].

Despite these reports, HBV reactivation risk in patients treated with DAAs seems to be low and most frequent in HBsAg positive patients. Sulkowski et al. analyzed retrospectively blood samples of 103 HCV patients with HBeAb positivity and found no HBV reactivation cases [24]. Similarly, a retrospective analysis of 62,290 HCV-infected veterans treated with DAAs, of which 377 had a positive HBsAg and 18,426 were HBeAb positive, found only 9 HBV reactivation cases (8 in HBsAg positive cases and 1 patient with an isolated HBeAb). Of note, this analysis excluded HBsAg positive patients who were considered to have a low-risk of reactivation [25]. Liu et al. presented a prospective cohort study of 81 HBsAg negative and 12 HBsAg positive HBV/HCV co-infected patients, in which only two of the 12 HBsAg positive (16.7%) and none of the 81 HBsAg negative patients had HBV reactivation [26]. These results confirmed the observations of several studies. Wang et al. evaluated 327 DAA treated patients and identified 3 cases of HBV reactivation in 10 HBsAg positive patients and no cases of reactivation in 124 HBsAg negative patients with positive HBV DNA [27]. Londoño et al. evaluated 10 HBsAg positive and 64 HBeAb positive patients, and HBV reactivation rates were 50% (n = 5) and 1.6% (n = 1), respectively [28]. Another study by Yue et al. showed similar results: 4 out of 7 HBsAg positive patients had HBV reactivation, but none of the 57 HBeAb
positive patients had a reactivation [29]. It should be noted, however, that these studies only followed-up patients for 12 weeks after treatment and, as demonstrated in our case, the event may happen after this time period.

Due to the persistence of HBV in the form of cccDNA in hepatocytes and other tissues, the reactivation of hepatitis B is a well known possibility in the setting of immunosuppression [30]. Although the potential protective role of the anti-HBs antibodies is controversial, the risk of HBV reactivation is considered lower than in those without HBsAb [21, 30]. Our case and case 7, both describe HBV reactivation in HBsAb positive patients, which means that clinicians should moni-

Table 1. Cases of HBV reactivation after HCV treatment with direct antiviral agents

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, gender</th>
<th>HBV status</th>
<th>HCV</th>
<th>Cirrhosis</th>
<th>HIV</th>
<th>DAA regimen</th>
<th>Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69 yo, male</td>
<td>Inactive chronic hepatitis</td>
<td>G1a</td>
<td>No</td>
<td>No</td>
<td>DCV + ASU</td>
<td>W4 HCV treatment: aminotransferases elevation</td>
<td>ETC</td>
</tr>
<tr>
<td>2</td>
<td>55 yo, male</td>
<td>Inactive chronic hepatitis</td>
<td>G1a</td>
<td>Child A</td>
<td>No</td>
<td>SOF + SIM</td>
<td>W7 HCV treatment: malaise, nausea, epigastric pain, jaundice, tender hepatomegaly</td>
<td>TDF/FTC</td>
</tr>
<tr>
<td>3</td>
<td>57 yo, male</td>
<td>Occult infection</td>
<td>G1a</td>
<td>No</td>
<td>No</td>
<td>SOF + SIM</td>
<td>W2 and W4 HCV treatment: asymptomatic; detectable HBV DNA</td>
<td>TDF</td>
</tr>
<tr>
<td>4</td>
<td>59 yo, female</td>
<td>“Resolved” infection</td>
<td>G1b</td>
<td>No</td>
<td>No</td>
<td>SOF + SIM</td>
<td>W7 HCV treatment: liver failure</td>
<td>TDF, liver transplantation</td>
</tr>
<tr>
<td>5</td>
<td>59 yo, male</td>
<td>“Resolved” infection</td>
<td>G4d</td>
<td>No</td>
<td>Yes</td>
<td>SOF/LDV</td>
<td>W1 PT: dizziness, fever and fatigue; elevated aminotransferases</td>
<td>TDF</td>
</tr>
<tr>
<td>6</td>
<td>83 yo, female</td>
<td>HBsAg negative</td>
<td>G1b</td>
<td>Yes</td>
<td>No</td>
<td>DCV + ASU</td>
<td>W20 PT: elevated transaminases</td>
<td>ETC</td>
</tr>
<tr>
<td>7</td>
<td>54 yo, female</td>
<td>“Resolved” infection</td>
<td>G4</td>
<td>No</td>
<td>Yes</td>
<td>SOF/LDV</td>
<td>W12 PT: nausea, vomiting, jaundice, abdominal pain</td>
<td>ETC</td>
</tr>
<tr>
<td>8</td>
<td>62 yo, female</td>
<td>“Resolved” infection</td>
<td>G2</td>
<td>No</td>
<td>No</td>
<td>SOF + RBV</td>
<td>W24 PT: nausea and fatigue</td>
<td>TDF</td>
</tr>
<tr>
<td>9</td>
<td>53 yo, male</td>
<td>Inactive chronic hepatitis</td>
<td>G1b</td>
<td>Unknown</td>
<td>No</td>
<td>SOF/LDV</td>
<td>W4 HCV treatment: malaise, choluria, elevated transaminases</td>
<td>ETC</td>
</tr>
<tr>
<td>10</td>
<td>46 yo, female</td>
<td>Inactive chronic hepatitis</td>
<td>G2a</td>
<td>Unknown</td>
<td>No</td>
<td>SOF + RBV</td>
<td>EOT: asymptomatic HBV DNA increase</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>64 yo, female</td>
<td>Inactive chronic hepatitis</td>
<td>G1b</td>
<td>Unknown</td>
<td>No</td>
<td>OBV/PTV/r</td>
<td>Asymptomatic HBV DNA increase during treatment</td>
<td>None</td>
</tr>
</tbody>
</table>


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tor patients with serological markers of “resolved” HBV infection. In both cases of reactivation with anti-HBs antibody, patients were HIV-coinfected, and studies have shown that HIV-related immunosuppression plays a deleterious role on HBV infection with higher rates of chronicity, positive antinuclear antibodies, chronic liver disease, and even HBV reactivation [21, 31]. Fabbrì et al. (case 7) describe a case of an immunocompromised HIV patient with low values of anti-HBsAb when he started ART without any HBV active drug (boosted darunavir and etravirine). Six months later, he had unmeasurable HBsAb levels, and DAA treatment for HCV was started; the patient had HBV reactivation [11]. However, in this case, the authors draw attention to the fact that in immunocompromised HIV patients, many factors may play a role besides DAA treatment, namely immune reconstitution syndrome [11]. However, HIV was well controlled in our patient and in patient from case 5; CD4+ lymphocyte count was above 500 mm$^3$ in both cases.

Reports of reactivation of HBV during or after treatment of hepatitis C with DAs have prompted both EMA and FDA to recommend screening for all patients initiating hepatitis C treatment with these drugs, and close surveillance of patients with markers of hepatitis B previous infection [16, 17]. Similarly, both European and American guidelines on HCV treatment suggest caution when treating HCV infection in patients with serological evidence of previous HBV infection [19, 20]. The AASLD/IDSA guidelines recommend performing HBV DNA testing in patients with positive HBsAg, and starting HBV therapy at the same time or before DAA initiation in those that meet HBV treatment criteria and to regularly monitor those with low or undetectable HBV DNA [20]. However, none of these documents provides guidance on how to monitor those who are HBsAg negative, which markers of active HBV disease (aminotransferases, HBV DNA, or HBs antigen) should be used to monitor these patients, at which intervals, or for how long.

In addition, how to manage patients after an HBV reactivation is not fully clarified. EMA and FDA report guidelines to each disease [16, 17] but some authors advocate initiation of preemptive therapy in those still asymptomatic with analytical evidence of reactivation [7]. This seems to be the most usual attitude described in clinical cases reports [6-13]; however, only 52% of the cases reported to FDA received HBV therapy with entecavir or tenofovir [15]; Sato et al. reported two cases of spontaneous HBV remission [14]. Despite these reports, there have been cases of fulminant hepatic failure, liver transplantation, and death in patients with HBV reactivation related to DAA treatment [8, 22].

We know from literature that the interaction between HCV and HBV is complex and not completely understood [2, 21]. With the tolerability of DAs and their high SVR rates, many HCV/HBV-coinfected patients will be cured of HCV infection and therefore, as an unintended consequence, the immunosuppressive effects of HCV on HBV will be lost and there will be room for HBV reactivation. Due to the potential severity of HBV reactivation that can lead to hepatic failure and hepatic transplantation, clinicians should both be aware and closely monitor patients with evidence of previous HBV infection.

**Conflict of interest**

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**References**