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BRIEF REPORT

# No Evidence of Reactivation of Hepatitis B Virus Among Patients Treated With Ledipasvir-Sofosbuvir for Hepatitis C Virus Infection

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Postmarketing cases of hepatitis B virus (HBV) reactivation during hepatitis C treatment have been reported. We analyzed serum samples from patients in a clinical trial of ledipasvir-sofosbuvir in Taiwan and Korea. Of the 173 patients enrolled, 103 (60%) had been previously infected with HBV. None showed evidence of HBV reactivation.

**Keywords.** ALT flare; HBV reactivation; HCV/HBV coinfection.

Reactivation of hepatitis B is "a well-characterized syndrome marked by the abrupt reappearance or rise of hepatitis B virus (HBV) DNA in the serum of a patient with previously inactive or resolved HBV infection" [1]. This increase in viral replication in patients with HBV reactivation is often accompanied by elevations in alanine aminotransferase (ALT) [2]. HBV reactivation, which occurs most commonly among patients receiving immunosuppressive therapy and certain types of cancer treatment, is frequently subclinical, but it can be severe, leading to acute liver failure and even death [1, 2].

Three cases have recently been reported of patients with resolved HBV infection (all were negative for hepatitis B surface antigen) who experienced reactivation of HBV during treatment for hepatitis C virus (HCV) infection with interferon-free combination regimens of direct-acting antiviral agents (DAAs). In one case, a 59-year-old woman with a history of Burkitt lymphoma who was receiving simeprevir, sofosbuvir, and ribavirin for genotype 1b HCV infection developed fulminant hepatic failure due to HBV reactivation and underwent liver transplantation despite initiating treatment for HBV [3]. The second case involved a 57-year-old man receiving simeprevir and sofosbuvir for genotype 1a HCV infection. This patient's HBV DNA, which was detectable below the lower limit of quantification (20 IU/mL) at baseline, rose to 11 255 IU/mL by week 4 of treatment without ALT elevation. Initiation of tenofovir HBV treatment led to subsequent HBV virologic suppression [4]. The third case involved a 53-year-old man coinfected with human immunodeficiency virus (HIV) and HCV who had previous HBV infection with anti-HBs seroconversion in 1995. After finishing a 12-week regimen of ledipasvir-sofosbuvir, he experienced dizziness, fever, and jaundice. Liver aminotransferases were elevated, HBV DNA was 8.9 $\log_{10}$ IU/mL, and hepatitis B surface antigen (HBsAg) was positive [5]. This patient's reactivated HBV was suppressed by tenofovir treatment.

These cases have led some to call for the screening of all persons initiating interferon-free HCV treatment and the initiation of simultaneous HBV treatment in patients with evidence of HBV coinfection—whether active or resolved [6, 7]. This raises questions concerning the necessity of pretreatment HBV testing for all patients in regions where HBV in endemic, given that some patients with resolved HBV infection may be unaware of having previously been infected.

The current analysis had 2 objectives: (1) to determine the prevalence of resolved HBV infection in patients enrolled in a clinical trial of ledipasvir-sofosbuvir for the treatment of HCV infection in countries with endemic HBV infection, and (2) to assess if those patients had evidence of reactivation of HBV in the setting of HCV treatment.

## METHODS

We analyzed serum samples from patients participating in an open-label, phase 3b clinical trial conducted in 12 sites in Taiwan and 15 sites in Korea (ClinicalTrials.gov identifier NCT02021656). The study evaluated 12 weeks of the fixed-dose combination of ledipasvir-sofosbuvir in treatment-naive and treatment-experienced patients with chronic genotype 1 HCV infection, including patients with compensated cirrhosis. The primary efficacy endpoint of the trial was sustained virologic response 12 weeks after the end of treatment ($SVR_{12}$). Of the 178 patients enrolled and treated, 175 (98%) achieved $SVR_{12}$. The primary results of this trial have been previously reported [8, 9].

This trial excluded patients with active HBV coinfection. Specifically, patients were tested for HBsAg at screening and only enrolled if HBsAg negative. Patients were not, however, tested at screening for antibodies to hepatitis B core antigen or HBsAg. Given that the study was conducted in regions where HBV infection is endemic, a high proportion

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of patients with evidence of prior HBV infection could be expected.

For this analysis, we tested samples collected at posttreatment week 24 for the presence of hepatitis B core antibody (HBcAb), as indicative of resolved HBV infection. Samples positive for HBcAb were further tested for HBV DNA. Samples with detectable HBV DNA were tested for HBsAg. In addition, we examined data collected during the trial for differences between patients with and without HBcAb in ALT, adverse events, or laboratory abnormalities that might be indicative of HBV reactivation. All adverse events and laboratory abnormalities were graded according to a standardized scale. Liver tests were performed at screening, at baseline, at weeks 1, 2, 4, 6, 8, 10, and 12 during treatment, and at posttreatment week 4.

## RESULTS

Posttreatment serum samples that were still within the 1-year stability limit were available for all but 5 of the 178 patients who were enrolled and treated in this trial. Of these 173 samples, 103 (60%) were positive for HBcAb. Baseline characteristics of patients positive and negative for HBcAb were similar—the majority of patients in both groups were women (56% overall), with genotype 1b HCV (92%) and with a mean body mass index of 24 kg/m$^2$. Patients positive for HBcAb were slightly older than patients without HBcAb (58 vs 52 years), and slightly more patients with HBcAb had cirrhosis (18% vs 10%). Median baseline ALT was 58 U/L in both groups, but mean baseline ALT was higher among patients positive for HBcAb (86 vs 68 U/L). A slightly higher proportion of patients with HBcAb had baseline ALT >1.5 times the upper limit of normal (53% vs 49%). Baseline characteristics of the patients with HBcAb are given in Table 1.

**Table 1. Baseline Demographics and Disease Characteristics**

| Characteristic | Patients Positive for HBcAb (n = 103) | Patients Negative for HBcAb (n = 70) |
|---|---|---|
| Age, y, median (range) | 58 (36–75) | 52 (20–74) |
| Male sex | 43 (42) | 33 (47) |
| Race | | |
| Korean | 51 (50) | 40 (57) |
| Taiwanese | 51 (50) | 29 (41) |
| Chinese | 0 | 1 (1) |
| Taiwanese-Chinese | 1 (1) | 0 |
| HCV genotype | | |
| 1 | 1 (1) | 0 |
| 1a | 8 (8) | 4 (6) |
| 1b | 94 (91) | 66 (94) |
| Cirrhosis | | |
| No | 84 (82) | 63 (90) |
| Yes | 19 (18) | 7 (10) |
| HCV RNA, $\log_{10}$ IU/mL, median (range) | 6.8 (3.7–7.4) | 6.9 (5.2–7.6) |
| ALT, U/L | | |
| Mean (SD) | 86 (80.9) | 68 (43.1) |
| Median (range) | 58 (11–619) | 58 (13–189) |
| HCV treatment experience | | |
| Naive | 49 (48) | 37 (53) |
| Previously treated | 54 (52) | 33 (47) |

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ALT, alanine aminotransferase; HBcAb, hepatitis B core antibody; HCV, hepatitis C virus; SD, standard deviation.

In the posttreatment samples of all 103 patients positive for HBcAb, HBV DNA was <20 IU/mL; however, in 2 patient samples HBV DNA was detected below the lower limit of quantification (HBV DNA <20 IU/mL, target detected). Both of these patients were negative for HBsAg and both had elevated ALT at baseline, which declined to near-normal levels during treatment.

The overall rates of adverse events and laboratory abnormalities, including ALT levels, were similar in patients positive and negative for HBcAb. ALT declined from baseline levels through posttreatment week 4 (the last time point at which ALT was measured) in all but 1 HBcAb-positive patient. This patient, a 44-year-old Korean woman with grade 2 ALT level at baseline, had a grade 3 ALT level in the first week of treatment, which returned to a grade 2 elevation at every subsequent visit.

## DISCUSSION

It has long been known that HCV infection can suppress HBV viral replication in patients coinfected with HBV and HCV. The mechanism of this effect is not fully understood, but may be due to direct suppression of HBV by HCV, or it may be related to HCV-induced intrahepatic immune activation that inhibits HBV replication [7, 10]. Suppression of HCV in patients coinfected with HBV may have the unintended consequence of creating a permissive environment for HBV replication, leading to clinical flare or reactivation.

Reactivation of HBV has previously been described following successful treatment with interferon-based regimens, but has not been well studied in the setting of DAA combination therapy. In a recent pilot trial, 8 patients coinfected with HBsAg-positive HBV and genotype 1 HCV were treated with ledipasvir-sofosbuvir. All achieved $SVR_{12}$ [11]. In 7 of the 8 patients, serum HBV DNA levels increased during treatment, but none were >20 000 IU/mL, and HBV DNA returned to baseline levels during follow-up. None of these patients developed clinical HBV flares or required HBV treatment.

No prospective studies of HBV reactivation have been conducted in patients with resolved HBV infection (ie, those negative for HBsAg and HBV DNA, and positive for HBcAb). As the elimination of HBV DNA from hepatocytes is not thought to occur in all persons with resolved HBV, it may be the case that most, if not all, patients who have been previously infected are at least potentially at risk for HBV reactivation. However, available evidence—including the results of the current

analysis—suggests that the risk is low. Trials of DAAs for the treatment of HCV typically exclude patients with active HBV infection, but a substantial proportion of participants are known to have acquired HCV infection through previous injecting drug use. Given the shared routes of transmission of HBV and HCV, many of these patients are positive for HBcAb [12]. Despite this, no cases of acute HBV reactivation have been reported in any clinical trials evaluating DAA combination regimens in HCV-infected patients.

Interpretation of these results is limited by the relatively small sample size and the retrospective nature of the analysis. Because on-treatment HBV DNA levels were not assessed (due to these time points being outside of the assay stability parameters), we cannot be certain that asymptomatic elevations of HBV DNA did not occur during therapy. Given that the population consisted only of Asian patients, generalizability of these results to patients of Western European background cannot be assumed.

To conclude, we found no evidence of HBV reactivation in this cohort of 103 patients positive for HBcAb who received treatment with ledipasvir-sofosbuvir for chronic HCV infection. These data suggest that, although it has been observed, HBV reactivation in coinfected patients with HBcAb without HBsAg is uncommon. Further data concerning possible HBV reactivation in patients receiving sofosbuvir-containing regimens are being collected in an ongoing study in Taiwan, in which 100 patients with active HCV/HBV coinfection are being treated with ledipasvir-sofosbuvir for 12 weeks. The impact of effective HCV treatment on concurrent HBV infection and HBV disease progression will be evaluated throughout treatment and for a follow-up period of 2 years after treatment completion.

## Notes

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