Black Box Warning for Possible HBV Reactivation During DAA Therapy for Chronic HCV Infection

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Keywords
Hepatitis B virus reactivation, direct-acting antiviral therapy, hepatitis C virus, fulminant hepatitis

Abstract: In 2016, the US Food and Drug Administration issued a warning about the risk of hepatitis B virus (HBV) reactivation in some patients receiving direct-acting antiviral (DAA) therapy for hepatitis C virus (HCV) infection. HBV reactivation can occur soon after the start of DAA therapy; thus, monitoring liver enzymes during DAA therapy is important in patients at risk. The clinical outcomes of HBV reactivation in this patient population may resemble the outcomes seen in immunosuppressed patients receiving chemotherapy. Each drug combination regimen has demonstrated risk for HBV reactivation and, therefore, contains a black box warning stating that all HCV-infected patients pending treatment should be tested for evidence of current or prior infection with HBV before initiating treatment. Both the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver guidelines have been updated accordingly.

Direct-acting antiviral (DAA) agents have been used successfully for the treatment of chronic hepatitis C virus (HCV) infection in many patients. DAA therapy has evolved from a combination regimen with interferon that had significant toxicity to a once-daily pill that is typically taken for 8 to 12 weeks with very few side effects. However, as a large number of patients worldwide continue to be treated with these drugs, the US Food and Drug Administration (FDA) monitoring system has detected reports of hepatitis B virus (HBV) reactivation.[1,2] This article reviews cases of HBV reactivation in patients receiving DAA therapy for HCV infection and discusses the effect that HBV reactivation has had on treatment initiation and monitoring.

Initial Reports of Reactivation

In 2016, the FDA issued a detailed Drug Safety Communication warning about the risk of HBV reactivation (defined by the FDA as an increase greater than 1000 IU/mL in HBV DNA or detection of hepatitis B surface antigen [HBsAg] in a person who was previously

Table. Characteristics From the 29 HBV Reactivation Cases Collected by the US Food and Drug Administration

Age in Years	Mean, 60.7; median, 58.0; range, 36.0-85.0
Sex	Male (n=13); female (n=16)
Country of Report	United States (n=5); Japan (n=19); Other (n=5)
Days to Event	Mean, 53; median, 46; range, 14-196
Treatment Delay	Yes (n=7)
	Possible (n=7)
	No delay (n=2)
	No treatment given or treatment not started (n=13)
HCV Genotype	Genotype 1 (n=16); other genotype (n=2); not reported (n=11)
Baseline HBV Viral Parameters	HBsAg-positive (n=13)
	HBsAg-negative (n=4)
	HBsAg not reported (n=12)
	Anti-HBc–positive (n=6)
	Anti-HBc not reported (n=23)
	Anti-HBs–negative (n=3)
	Anti-HBs not reported (n=26)
	HBV DNA undetectable (n=16)
	HBV DNA detectable (n=9)
	HBV DNA baseline either not reported or detectability status unclear (n=4)
Outcomes	Death (n=2); liver transplantation (n=1); hospitalization (n=6); other (n=20)
DAA Therapy	Discontinued (n=10); completed (n=13); not reported (n=6)
Treatment for HBV	Entecavir (n=9); tenofovir (n=6); tenofovir/emtricitabine (n=1); not reported (n=6); no treatment (n=7)

Anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; DAA, direct-acting antiviral; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.

Modified from Bersoff-Matcha SJ, et al.[2]

negative) in some patients being treated with DAA therapy for HCV infection.[1,2] The detailed data of the HBV reactivation cases collected by the FDA were first presented in a late-breaking poster[1] at the 2016 American Association for the Study of Liver Diseases meeting and were subsequently published in *Annals of Internal Medicine*.[2] Twenty-nine cases were collected overall, with the majority coming from Japan and the United States.[2] The Table lists the main baseline characteristics available from the collected patient cases. The median time from initiation of treatment to occurrence of HBV reactivation was 46 days, underscoring the speed at which HBV reactivation can occur and the importance of monitoring liver enzymes in patients at risk who are undergoing DAA therapy.[2] The clinical outcomes of HBV reactivation in this patient population, however, may resemble the outcomes seen in immunosuppressed patients receiving chemotherapy, including death, liver transplantation, and hospitalization.[3,4]

The risk for HBV reactivation during DAA therapy is general rather than drug-specific, as HBV reactivations occurred in patients with different HCV genotypes receiving various DAA therapy combinations.[2] Most patients with HBV reactivation were already known to have chronic HBV infection and were HBsAg-positive. However, 3 of the 29 patients were hepatitis B core antibody (anti-HBc)-positive only, without HBsAg, as a sign of exposure to HBV infection and residual intrahepatic disease.[2] These patients subsequently developed HBV reactivation. All 3 subjects were undetectable for HBV DNA at baseline, making occult HBV infection unlikely.[2] Importantly, HBV screening in HCV-infected patients has been recommended by most guidelines,[5,6] and a risk of HBV reactivation was present during the interferon era in patients with a positive HBsAg.[7,8]

Hepatitis B Virus Reactivation in Other Settings

HBV reactivation in other clinical settings is seen most often in patients receiving immunosuppressive chemotherapy, particularly therapy containing rituximab (Rituxan, Genentech), for hematologic malignancies and in patients undergoing stem cell transplantation.[9,10] Patients who experience HBV reactivation in these settings often develop severe and/or fatal liver injury due to cytopathic viral injury of infected hepatocytes.[3,7,8,10] Antiviral treatments are usually ineffective in such cases, as liver failure and death occur before the viral replication can be adequately suppressed.[10] Hence, this is a complication in patients receiving chemotherapy or B-cell–depleting therapies that should always be prevented.

Recent Studies on Hepatitis B Virus Reactivation

A recent study evaluated 62,920 US veterans who were treated with oral DAA therapy.[11] Before beginning DAA therapy, 53,784 patients (85.5%) underwent testing for HBsAg, and 53,237 patients (84.6%) underwent testing for hepatitis B surface antibody. Significantly

more patients were hepatitis B surface antibody–positive compared to those who were HBsAg-positive (22,479/53,237; 42.2% vs 377/53,784; 0.70%, respectively). Overall, 9 of 62,920 patients experienced HBV reactivation while receiving DAA therapy; 8 patients were HBsAg-positive and 1 was anti-HBc–positive but HBsAg-negative before therapy was started.[11]

Wang and colleagues evaluated 327 HCV-infected patients on a panoral DAA regimen in HBV-endemic areas of China.[12] Ten patients were HBsAg-positive, and 124 patients had occult HBV infection, defined as a measurable HBV DNA and anti-HBc in the absence of HBsAg before therapy. Serum samples containing HBV DNA and HBsAg were collected every 2 weeks throughout treatment, and every 4 weeks following treatment until week 12. Overall, 10 patients (3.1%; all of whom were HBsAg-positive at baseline) had hepatitis; 3 cases were related to HBV reactivation.[12] The remaining 7 cases were associated with other causes. No reactivation was seen in patients with isolated anti-HBc positivity.[12]

In a systematic review and meta-analysis of 28 studies, Chen and colleagues compared rates of HBV reactivation in patients who were coinfected with HCV and overt or occult HBV who received interferon-based therapies or DAA therapies.[13] HBV reactivation occurred earlier and was clinically more significant in patients receiving DAA therapy compared to patients treated with interferon-based therapy, and it was suggested that interferon may have had an antiviral effect on HBV.[13] The authors concluded that all patients should be screened for overt or occult HBV infection and managed during DAA therapy.[13] The prevalence of occult HBV infection (ie, anti-HBc positivity without HBV DNA data) has been estimated to range from 11.9% to 44.4% in HCV-infected patients worldwide and is likely highest in patients from countries in which HBV infection is endemic.[14] However, the prevalence of a positive anti-HBc in HCV patients in the United States is estimated to be 50% to 62%, largely because the acquisition of both HBV and HCV via intravenous drug use or sexual transmission was common.[15-17] The typical adult would be likely to clear HBV and remain anti-HBc–positive lifelong (indicating residual HBV DNA in the liver cell nucleus as covalently closed circular DNA), but become chronically infected with HCV.

The underlying mechanisms of HBV reactivation during panoral DAA therapy for HCV are poorly understood. However, de novo HCV superinfection in the setting of HBV has been reported to result in hepatitis B e antigen seroconversion and, in some cases, clearance of HBsAg, which may suggest that HCV infection can suppress HBV replication; therefore, clearance of HCV could allow reactivation.[18]

Effects on Treatment Initiation and Monitoring

HCV treatment initiation and monitoring is complicated by the new HBV screening algorithm (Figure). The FDA recommends that patients with a positive anti-HBc should be monitored more closely during antiviral therapy, with liver panel testing performed at least at weeks 4, 8, and 12, and after the end of treatment until sustained virologic response is achieved.[2] Therefore, patients also require testing for anti-HBc as well as HBsAg and HIV antibody prior to treatment.[5,6] Because of the significant morbidity and mortality that may be associated with HBV reactivation, the FDA has mandated an update in prescribing information for all DAA regimens with a black box warning.[19]

Each DAA drug or combination regimen currently contains a black box warning stating that all HCV-infected patients pending treatment should be tested for evidence of current or prior infection with HBV before initiating treatment.[20] The warning further states that some cases have resulted in fulminant hepatitis, hepatic failure, or death in patients who were not receiving antiviral therapy for HBV; therefore, all patients with evidence of coinfection with HCV and HBV require monitoring for a hepatitis flare during HCV treatment and prompt, appropriate management for HBV infection if it is present. Posttreatment follow-up is recommended, but a specific amount of time is not provided.

Updated Guidelines

The current guidelines of the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America have been updated to include testing for current HBV infection or previous HBV exposure before initiating HCV treatment, and monitoring of HBV DNA levels and/or DAA therapy for patients who are HBsAg-positive.[5] The European Association for the Study of the Liver guidelines have been updated in a similar fashion and further suggest that HBsAg-positive patients undergoing DAA therapy should be considered for concomitant HBV antiviral prophylaxis until week 12 post–DAA treatment, and then monitored closely.[6] Both guidelines recommend monitoring for HBV DNA titers in cases in which the alanine aminotransferase levels become elevated during therapy.[5,6]

Summary

HBV reactivation may occur during DAA therapy for chronic HCV infection and has been reported from a number of sources. Although HBV reactivation is rare,

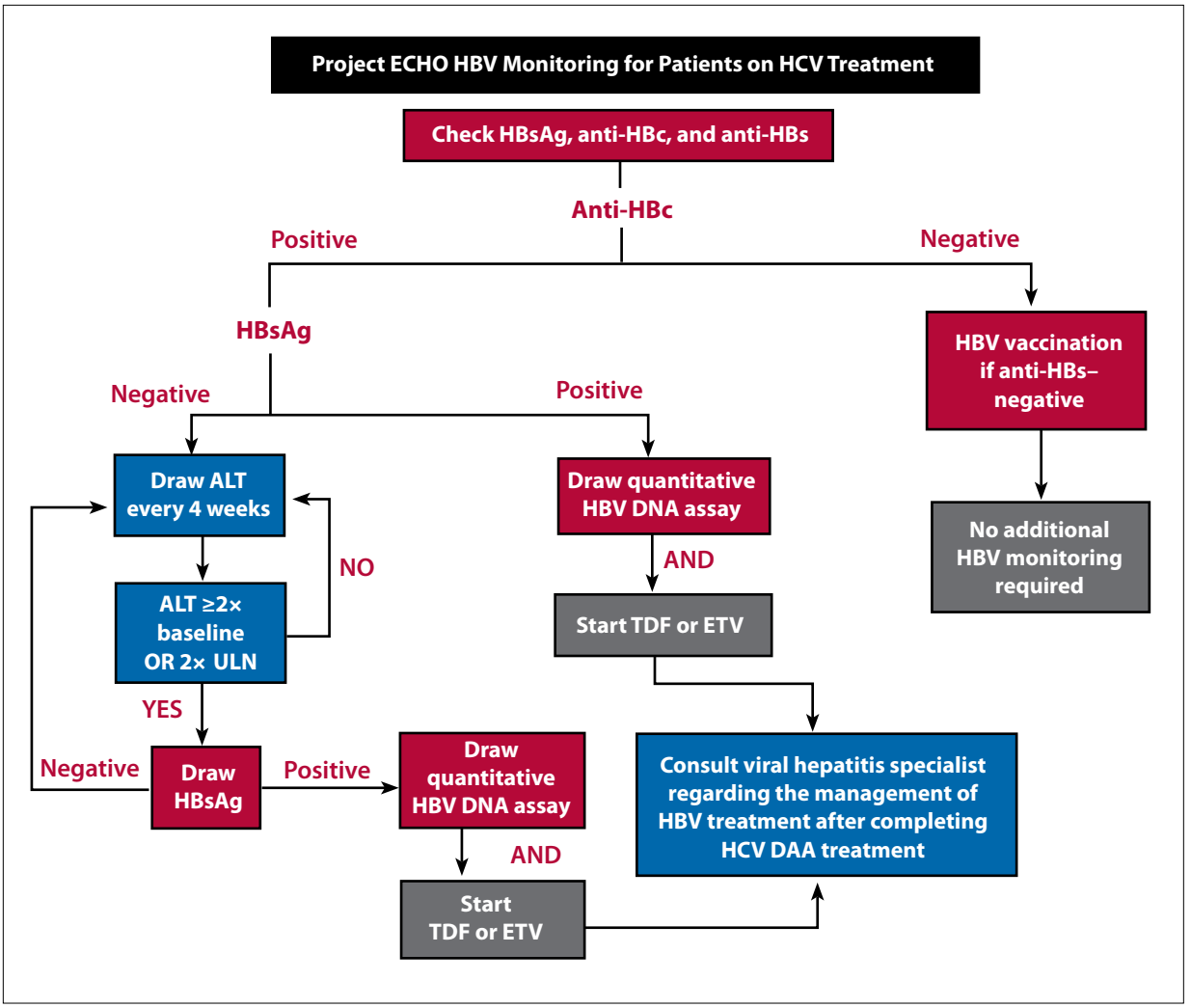

Figure. A proposed algorithm for HBV monitoring for patients on HCV treatment.

ALT, alanine aminotransferase; anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; DAA, direct-acting antiviral; ECHO, Extension for Community Healthcare Outcomes; ETV, entecavir; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

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patients can experience liver failure and/or death in rare cases. New guidelines recommend that all patients be screened for past or present HBV infection prior to initiating DAA therapy and be monitored and/or treated to prevent HBV reactivation.

Dr Pockros has no relevant conflicts of interest to disclose.

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