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HBV/HCV Coinfection and Possible Reactivation of HBV Following DAA Use

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G&H How does coinfection affect hepatitis B and C virus? Are the diseases more severe or resistant?

RG When a person has active hepatitis B virus (HBV) infection and active hepatitis C virus (HCV) infection, one of the viruses usually dominates, typically HCV. Thus, individuals who have active HBV and HCV infections—who probably account for 200,000 to 400,000 people in the United States today—are likely to be HCV-dominant with a high HCV viral load and low or undetectable HBV DNA levels. However, if their HCV infection is suppressed, their HBV can become more active, reactivate, or become more aggressive with high HBV DNA levels and low HCV RNA quantification. In general, coinfection with HBV and HCV is more likely than monoinfection to develop into cirrhosis, cancer, the need for liver transplantation, and death.

G&H In patients with active infection of both HBV and HCV, which disease is treated first?

RG The rule is to treat the dominant disease first, so HCV infection has traditionally been treated first because HCV is usually dominant. However, with the new information regarding the risk of HBV reactivation, HBV is now being treated prophylactically with oral nucleos(t)ide therapy even if there is low activity or inactive disease. With the current knowledge regarding the risk of reactivation, even if a patient is hepatitis B surface antigen (HBsAg)-positive only and HBV DNA–negative, many (potentially most) health care providers would now consider HBV treatment during HCV direct-acting antiviral (DAA) therapy to prevent the HBV infection from becoming more active. That treatment may be short term, or it may be long term, depending upon the patient and the clinical scenario, although guidelines from the American Association for the Study of Liver Diseases recommend monitoring, not treatment.

However, if a patient's HBV infection is dominant, meaning that his or her HBV DNA levels are high using quantitative polymerase chain reaction and his or her HCV viral load is low or undetectable, the HBV infection would be treated first or in combination with HCV if the patient's HCV RNA is positive. Then the provider would recheck the patient's HCV status during HBV treatment to see whether the HCV reactivated or became more active.

G&H In general, how common is reactivation of HBV infection?

RG If a person is infected with HCV, is placed on HCV treatment, and is HBsAg-positive, the risk of HBV reactivation is very high (probably 30%-50%). If the patient is HBsAg-negative but hepatitis B core antibody (anti-HBc)–positive, the risk of reactivation is probably between 1:1000 and 1:10,000, although a recent publication suggested that the risk might be even slightly higher. That estimate comes from data collection by the US Food and Drug Administration (FDA) and my expert estimate of the total US patient population treated to date with DAA agents.

G&H What are the most common risk factors for HBV reactivation?

RG If a patient is undergoing chemotherapy or immunosuppression and is HBsAg-positive, especially if he or she is HBV DNA–positive, the patient is at moderate to high risk of reactivation, especially if (1) a regimen containing rituximab is used; (2) the patient undergoes conditioning therapy for stem-cell transplantation; (3) the patient is being treated with a doxorubicin-based chemotherapy; and (4) high-dose prednisone is used for a prolonged period of time, typically in combination with other immunosuppression. In my practice, I follow the rule that 20 mg or more of prednisone per day for more than 20 days would place a patient at moderate to high risk of reactivation if the patient is HBsAg-positive.

In patients who are HBsAg-negative but anti-HBc–positive, the risk of reactivation is lower but not zero, and rituximab-containing regimens might pose a reactivation risk as high as 30% in anti-HBc–positive patients, as well as in the other 3 settings listed above. Thus, the risk of reactivation depends upon the patient's serostatus and HBV DNA status. Approximately 7% of anti-HBc–positive patients who are HBsAg-negative have measurable HBV DNA at low levels and may be at higher risk of reactivation than patients who are HBV DNA–negative by sensitive polymerase chain reaction assays. A technical review and guidelines for HBV reactivation during immunosuppressive therapy were published in the January 2015 issue of *Gastroenterology*.

G&H Could you discuss the cases that led to the black-box warning regarding possible reactivation of HBV infection after HCV treatment with DAA agents?

RG Twenty-nine cases of HBV reactivation were reported to the FDA and from the published literature of HBV/HCV-coinfected patients treated with DAA agents between November 2013 and July 2016. Only cases reported to the FDA were included in this number, so there are likely other cases as well. Among the reported cases, 2 patients died and 1 patient needed a liver transplant. The clinical trials submitted for approvals of the DAA agents did not include reactivation of HBV infection as an adverse event because the trials excluded HBV/HCV-coinfected patients. This exclusion was made so that the safety of DAA agents, including their effects on the liver, could be assessed specifically in the presence of only HCV and not another virus that affects the liver.

In the United States, over 600,000 people have been treated for HCV infection with DAA agents, but it is not possible to perform a direct calculation to determine the frequency of HBV reactivation because underreporting is probable. However, it is reasonable to say that the frequency is quite low. Nevertheless, the FDA issued a black-box warning that all patients who are being treated with DAA agents for HCV infection must undergo HBV panel testing that includes HBsAg and total anti-HBc, and then have their results listed in their chart. Hepatitis B surface antibody (anti-HBs) testing is usually performed as part of the panel, but anti-HBs does not protect against reactivation of HBV infection, so it is not possible to vaccinate someone who is anti-HBc–positive and state that the patient will have a higher level of protection if his or her anti-HBs level is higher.

G&H Was HBV reactivation more common with certain DAA agents?

RG There was no pattern among the DAA agents; all of them have had reports of reactivation through the FDA. Manufacturers have not necessarily seen reactivation of HBV infection in their databases, but the FDA is collecting real-world information, not just from clinical trials. Thus, this black-box warning is included across the entire DAA class of HCV medications.

G&H Have there been instances of HBV reactivation due to HCV treatment before these cases?

RG In an observational, prospective study of Chinese patients with chronic HCV infection who were taking DAA agents, 10 of the 327 patients screened developed hepatitis. In 3 of the 10 HBsAg-positive patients, the hepatitis was due to HBV reactivation. However, among 124 HBsAg-negative/anti-HBc–positive patients, none had hepatitis because of HBV reactivation. There have also been several case reports in the literature of HBV reactivation of patients on various DAA combinations.

Reactivation of HBV infection has also been described with interferon therapy, with the first reports coming in the mid-1990s. However, interferon suppresses HBV in some patients, so reactivation was less frequent with interferon than it seems to be with DAA agents due to the anti-HBV effect of interferon on HBV replication.

What is different about the recent cases of HBV reactivation with DAA agents is that these agents do not suppress the immune system. As mentioned previously, HCV infection usually dominates HBV infection when a patient is coinfected with both viruses. When the HCV infection is cured, viral competition is eliminated for HBV infection, and the HBV takes over. The cellular machinery is then available for HBV to replicate and break through, even though there has been no change

that we know of specifically in the immune system that is HBV-linked.

G&H Are there any other possible theories to explain why DAA agents can cause reactivation of HBV infection?

RG An additional theory is that when a patient is infected with HCV, he or she has a very active immune system. When the patient is cured of HCV, his or her immune system is not suppressed; it is just less active, which means that the HBV may then be able to supersede the patient's immune control.

G&H What specific adjustments should doctors make in their management of patients coinfected with HBV and HCV?

RG Before treating patients with DAA agents for HCV infection, as well as before using immunosuppressants or chemotherapy, it is now standard of care to check the patient's HBV panel, including HBsAg, total anti-HBc, and anti-HBs. When these 3 tests are checked, the health care provider needs to determine whether the patient is immune to HBV, exposed to HBV, or has active HBV infection. The serum test for anti-HBc is the one that indicates exposure; because HBV infection is not curable, any person with anti-HBc has to be assumed to have occult HBV or "resolved" HBV with, universally, a remnant of HBV covalently closed circular DNA in the liver if his or her HBsAg is negative. In contrast, clinical occult HBV refers to patients who are anti-HBc–positive, are HBsAg-negative, and have measurable HBV DNA levels, accounting for between 7% and 15% of anti-HBc–positive patients. Measuring quantitative HBV DNA levels in anti-HBc–positive patients is controversial and is not considered standard of care at this time, although some providers do follow this practice and use this information to guide prophylaxis.

It is important to note that anti-HBc–positive blood tests have been misinterpreted on various Web sites, including the one for the Centers for Disease Control and Prevention. A patient has sometimes been said to have "natural immunity" when his or her HBsAg is negative and anti-HBs is positive; however, this term is an oxymoron because HBV is incurable. Once a person is exposed to the virus, he or she has residual disease for his or her lifetime, such as with cytomegalovirus, herpes simplex virus, or Epstein-Barr virus. These individuals cannot have any natural protection because they are already infected, so the term natural immunity should not be used.

It should also be emphasized that patients who are anti-HBc–positive do not need HBV vaccine. There is no evidence that boosting anti-HBs provides any clinical benefit to the patient, although it may make the provider or patient feel better to see a response or increase in anti-HBs.

G&H Should any HBV/HCV-coinfected patients completely avoid using DAA agents because of the black-box warning?

RG Coinfected patients should avoid DAA agents until they have been assessed by a liver or hepatitis specialist, the aforementioned HBV tests are performed, and the correct interpretation and linkage to care take place. Then the patients should start their HCV treatment because all patients infected with HCV are indicated for treatment.

G&H Are there any special considerations that should be kept in mind when managing these coinfected patients?

RG If a provider decides not to use HBV medication during HCV treatment and the patient is either HBsAg– or anti-HBc–positive, the patient needs to undergo liver panel testing, including aspartate aminotransferase and alanine aminotransferase levels, every month. If the levels of these liver enzymes increase, the patient's HBV status should be immediately reassessed with HBsAg. If positive, then the quantitative HBV DNA level should be measured, and, if clinically indicated, the patient should be placed on HBV therapy.

G&H What are the next steps in research in this area?

RG One main area of research is what to do with anti-HBc–positive patients who are HBV DNA–positive and HBsAg-negative. Researchers will likely start looking at these individuals to see whether the presence of HBV DNA in an HBsAg-negative patient predicts a higher risk of reactivation and a reason to treat the patient with HBV prophylactic medicine.

Dr Gish has received grants/research support from AbbVie, Gilead, and Merck; has performed as consultant and/or advisor to Abbott, AbbVie, Access Biologicals, Alexion, Arrowhead, AstraZeneca, Bayer AG, Bristol-Myers Squibb, Cocrystal, ContraVir, Eiger, Enyo, Genentech, Gilead, Hoffmann-La Roche, Humabs, Intellia, Intercept, Ionis, Janssen, MedImmune, Merck, Nanogen, Novira, Spring Bank, Theranos, and Vital Therapies; has served on the Scientific or Clinical Advisory Boards of AbbVie, Access Biologicals, AstraZeneca (MedImmune), Arrowhead, ContraVir, Genentech, Gilead, Intercept, Ionis, Intellia, Eiger, Enyo, Humabs, Janssen, Merck, Nanogen, and Quest; has been involved in

clinical trials for Immuron, Intercept, Novo Nordisk, and Oceta; has served as Chair of the Clinical Advisory Board of Arrowhead; has served on the Data and Safety Monitoring Boards of Ionis, Novira, and Presidio; has a speakers contract to do promotional talks for AbbVie, Alexion, Bayer, Bristol-Myers Squibb, Gilead, Merck, and Salix/Valeant; is a minor stock shareholder (liver space noted only) of Alexion, Cocrystal, Kinex, and Riboscience; and has stock options for Arrowhead.

Suggested Reading

Bersoff-Matcha S, Cao KY, Jason M, et al. Hepatitis B reactivation associated with direct acting antiviral therapy for hepatitis C: a review of spontaneous post-marketing cases. Presented at: The 67th Annual Meeting of the American Association for the Study of Liver Diseases; November 11-15, 2016; Boston, Massachusetts. Abstract LB-17.

Chen G, Wang C, Chen J, et al. Hepatitis B reactivation in hepatitis B and C coinfected patients treated with antiviral agents: a systematic review and meta-analysis [published online February 13, 2017]. *Hepatology*. doi:10.1002/hep.29109.

Collins JM, Raphael KL, Terry C, et al. Hepatitis B virus reactivation during successful treatment of hepatitis C virus with sofosbuvir and simeprevir. *Clin Infect Dis*. 2015;61(8):1304-1306.

De Monte A, Courjon J, Anty R, et al. Direct-acting antiviral treatment in adults infected with hepatitis C virus: reactivation of hepatitis B virus coinfection as a further challenge. *J Clin Virol*. 2016;78:27-30.

Ende AR, Kim NH, Yeh MM, Harper J, Landis CS. Fulminant hepatitis B reactivation leading to liver transplantation in a patient with chronic hepatitis C treated with simeprevir and sofosbuvir: a case report. *J Med Case Rep*. 2015;9:164.

FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C. US Food and Drug Administration. https://www.fda.gov/Drugs/DrugSafety/ucm522932.htm. Published October 4, 2016. Accessed April 7, 2017.

Gish R. Reactivation of hepatitis B virus after treatment with direct acting antivirals for hepatitis C: what you need to know. Viral Hepatitis Blog, US Department of Health and Human Services. https://www.hhs.gov/hepatitis/blog/2017/1/17/hbv-reactivation-during-hcv-treatment.html. Published January 17, 2017. Accessed April 7, 2017.

Hayashi K, Ishigami M, Ishizu Y, et al. A case of acute hepatitis B in a chronic hepatitis C patient after daclatasvir and asunaprevir combination therapy: hepatitis B virus reactivation or acute self-limited hepatitis? *Clin J Gastroenterol*. 2016;9(4):252-256.

Kwak MS, Kim YJ. Occult hepatitis B virus infection. *World J Hepatol*. 2014;6(12):860-869.

Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology*. 2015;148(1):221-244.e3.

Raimondo G, Allain JP, Brunetto MR, et al. Statements from the Taormina expert meeting on occult hepatitis B virus infection. *J Hepatol*. 2008;49(4):652-657.

Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT; American Gastroenterological Association Institute. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology*. 2015;148(1):215-219; quiz e16-e17.

Takayama H, Sato T, Ikeda F, Fujiki S. Reactivation of hepatitis B virus during interferon-free therapy with daclatasvir and asunaprevir in patient with hepatitis B virus/hepatitis C virus co-infection. *Hepatol Res*. 2016;46(5):489-491.

Wang C, Ji D, Chen J, et al. Hepatitis due to reactivation of hepatitis B virus in endemic areas among patients with hepatitis C treated with direct-acting antiviral agents. *Clin Gastroenterol Hepatol*. 2017;15(1):132-136.

Yeh ML, Huang CF, Hsieh MH, et al. Reactivation of hepatitis B in patients of chronic hepatitis C with hepatitis B virus infection treated with direct acting antivirals [published online February 23, 2017]. *J Gastroenterol Hepatol*. doi:10.1111/jgh.13771.