Published in final edited form as:

Ann Intern Med. 2017 November 21; 167(10): 759–760. doi:10.7326/L17-0476.

Possible Role of Hepatitis D Virus in Severe Hepatitis Related to Hepatitis B Virus Reactivation After Therapy for Chronic Hepatitis C

Parag Mahale, MBBS, PhD, MPH¹, Jeffrey S. Glenn, MD, PhD^{2,3}, Thomas R. O'Brien, MD, MPH¹

¹Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland ²Department of Medicine, Division of

Gastroenterology and Hepatology, Stanford University School of Medicine, Palo Alto, California

³Department of Microbiology and Immunology, Stanford University School of Medicine, Palo Alto, California

Keywords

hepatitis B virus; hepatitis C virus; hepatitis D virus; treatment; viremia

TO THE EDITOR

We read with interest Bersoff-Matcha and colleagues' article on 29 cases of hepatitis B virus (HBV) reactivation among persons co-infected with HBV/hepatitis C virus (HCV) who attained sustained virologic response after direct-acting antiviral (DAA) therapy for HCV infection (1). Among these patients, all but 1 of whom were reported to the U.S. Food and Drug Administration Adverse Event Reporting System, 2 died and 1 required liver transplantation. These important findings highlight viral interactions that can develop in persons who are chronically infected with multiple hepatitis viruses (2). Bersoff-Matcha and colleagues' article provides details on HBV infection variables for these patients but no information about whether hepatitis D virus (HDV) infection was present, perhaps reflecting inherent limitations of the reporting system. We suggest that this infection, which causes the most aggressive form of human viral hepatitis, might play a role in patients diagnosed with HBV reactivation.

Hepatitis D virus is an incomplete virus that requires hepatitis B surface antigen (HBsAg) for virion assembly and replication (3). Hepatitis B, C, and D viruses have common routes of infection, and patients with chronic HBV infection often have triple infection (3); in some cohorts of U.S. injection drug users, more than one third of those with detectable HBsAg were co-infected with HDV (4) (Mahale P. Unpublished data.). Hepatitis D virus infection

has been associated with fulminant hepatitis and more rapid progression to cirrhosis, hepatic decompensation, and death than is seen in persons who only have HBV infection (3).

Reports of HBV reactivation after successful treatment of chronic HCV infection show that the latter may suppress HBV replication. Complex interactions have been reported in persons who are triply infected with HBV, HCV and HDV, with some reports suggesting that HCV plays a dominant role overall (2). If HCV does, indeed, dominate HBV and HDV, treatment for HCV infection with DAAs may enhance replication not only of HBV but also HDV, with a potential for consequent rapid progression of the underlying liver disease.

Recent HCV treatment guidelines recommend that all HCV-infected patients starting DAA therapy be evaluated for HBV co-infection (1); however, patients with positive results on HBsAg testing are often not evaluated for HDV infection. For example, among 25 603 veterans with positive results on HBsAg testing, only 8.5% were tested for HDV infection (5). We suggest that patients about to undergo DAA therapy for HCV infection with positive results on HBsAg testing also be tested for HDV infection.

Acknowledgments

This work was supported by the Intramural Research Program of the National Institutes of Health (National Cancer Institute, Division of Cancer Epidemiology and Genetics). The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

References

1. Bersoff-Matcha SJ, Cao K, Jason M, Ajao A, Jones SC, Meyer T, et al. Hepatitis B Virus Reactivation Associated With Direct-Acting Antiviral Therapy for Chronic Hepatitis C Virus: A Review of Cases Reported to the U.S. Food and Drug Administration Adverse Event Reporting System. *Ann Intern Med*. 2017.
2. Lin L, Verslype C, van Pelt JF, van Ranst M, Fevery J. Viral interaction and clinical implications of coinfection of hepatitis C virus with other hepatitis viruses. *Eur J Gastroenterol Hepatol*. 2006;18(12):1311–9. [PubMed: 17099381]
3. Hughes SA, Wedemeyer H, Harrison PM. Hepatitis delta virus. *Lancet*. 2011;378(9785):73–85. [PubMed: 21511329]
4. Kucirka LM, Farzadegan H, Feld JJ, Mehta SH, Winters M, Glenn JS, et al. Prevalence, correlates, and viral dynamics of hepatitis delta among injection drug users. *J Infect Dis*. 2010;202(6):845–52. [PubMed: 20701536]
5. Kushner T, Serper M, Kaplan DE. Delta hepatitis within the Veterans Affairs medical system in the United States: Prevalence, risk factors, and outcomes. *J Hepatol*. 2015;63(3):586–92. [PubMed: 25962883]