Making Do With What We Have

After approval of a new class of drugs, such as direct-acting antiviral (DAA) agents against hepatitis C virus (HCV), unanticipated effects are likely. In 2015, the first 2 cases of hepatitis B virus (HBV) reactivation in patients receiving an all-oral DAA regimen for HCV were published (1). In their *Annals* article, Bersoff-Matcha and colleagues (2), from the U.S. Food and Drug Administration (FDA), describe data submitted to the FDA Adverse Event Reporting System (FAERS) on 29 patients receiving DAA-based HCV treatment who had HBV reactivation (2). Eight of these patients were hospitalized; 2 of them died, and 1 required liver transplantation. The FDA found enough evidence that these outcomes were associated with reactivated HBV in the setting of HCV treatment that it required a "boxed warning" on all DAA product labeling about the risk for HBV reactivation (3). The article provides a detailed view of the process involved in a postapproval drug safety reporting system.

On the basis of the FAERS data, exactly which patients are at risk for HBV reactivation during and after HCV treatment is unclear. One at-risk group is patients with chronic HBV infection as indicated by a positive result on hepatitis B surface antigen (HBsAg) testing. According to 2 comprehensive surveys, the prevalence of HBsAg in patients with active HCV infection (that is, those with a detectable HCV RNA level) in the United States is 3% to 5.8%, and an estimated 240 million people worldwide have chronic HBV infection (4–6). In this FDA report, only 17 of the 29 patients had HBsAg test results reported, and 13 of those 17 (or 45% of the total cohort) were known to have HBsAg positivity. Only 2 of the 8 hospitalized patients had documented HBsAg positivity. We know remarkably little about DAA treatment of HCV infection in patients with HBV co-infection. All the registration clinical trials of DAAs against HCV excluded patients with HBsAg positivity. Only 1 report was published of DAA treatment in patients with HBsAg positivity; of the 8 patients in that study, 7 had increases in HBV DNA levels during DAA treatment (although none had clinical HBV flares) (7).

An equally problematic question is how much of an HBV reactivation risk is posed for patients who have been exposed to HBV and have negative HBsAg and positive hepatitis B core antibody (HBcAb) test results with or without positive hepatitis B surface antibody (HBsAb) results. Worldwide, approximately 2 billion people have been exposed to HBV, and a large overlap exists between endemic HBV and HCV (6). In the United States, the prevalence of HBcAb in patients with active HCV infection in 2 comprehensive surveys was 62%, and in 1 cohort, 50% of the patients had isolated HBcAb (with negative HBsAg and HBsAb test results) (4, 5). In the cases reported to the FDA, isolated HBcAb was detected in 3 patients, all of whom had undetectable HBV DNA levels before starting DAA treatment. Two of the 3 patients were hospitalized after HBV reactivation, 1 of whom required liver transplantation. Because FAERS and case reports do not have a denominator, how frequently reactivation occurs in patients with HBsAg negativity and HBcAb positivity cannot be determined. One post hoc analysis of 103 patients receiving DAA treatment who had serologic evidence of HBV exposure showed that none had HBV reactivation (8). Although a relatively infrequent adverse event likely will go undetected in HCV clinical trials, it may occur many times once a regimen has been used to treat hundreds of thousands of patients, as in the case of poastapproval DAAs.

The data reported to the FDA via FAERS frequently have many gaps, as demonstrated in this report. These data bear no resemblance to those of the clinical trials, and the FDA has a difficult job in determining whether a previously unrecognized safety event is occurring. In addition, much of the data clinicians require to understand an event's effect on clinical management are unavailable. The HCV guidelines of the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (AASLD-IDSA) now recommend that patients receive testing for HBsAg, HBsAb, and HBcAb before beginning HCV treatment (9). These guidelines recommend that patients who have positive results on HBsAg testing undergo a full evaluation of their HBV status (including hepatitis B e antigen status and HBV DNA levels). If a patient meets the criteria for HBV treatment, he or she should receive it before beginning HCV therapy. Otherwise, HBV DNA should be monitored during HCV treatment; if, while receiving HCV treatment, a patient meets criteria for HBV treatment, it should be initiated. Only 2 of the 8 patients reported as hospitalized had documented HBsAg positivity, and whether the AASLD-IDSA recommendations would have prevented severe liver outcomes is unclear from the FDA data. Also of concern is that for patients with negative HBsAg test results who have been exposed to HBV, AASLD-IDSA recommends that HBV reactivation be considered "in the event of unexplained increases in liver enzymes during and/or after completion of DAA therapy." Because all-oral DAA regimens have become more potent and easier to administer, the trend has shifted from close laboratory monitoring; therefore, future guidelines will have to reconcile these FDA data with clinical practice.

The National Academies of Sciences, Engineering, and Medicine recently released the second part of its analysis on eliminating HBV and HCV in the United States (10). One barrier it notes is the lack of specialist providers in rural and other underserved communities, underscoring the need to train primary care providers and other nonspecialists in HCV care and treatment. Mentorship to primary care colleagues embarking on HCV treatment facilitates recognition of unexpected

This article was published at Annals.org on 25 April 2017.

events, such as HBV reactivation, and helps fill gaps left by summaries of FAERS and society guidelines. We are part of a global medical community, and efforts to report unexpected events may help patients around the world. A key lesson is that no one pharmaceutical company will be able to address all clinically important questions; therefore, continued funding for the FDA and nonindustry clinical research is vital to help keep our patients safe.

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Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M17-0907.

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Ann Intern Med. 2017;166:850-851. doi:10.7326/M17-0907

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