



Medical Interventions Associated with HBV Reactivation: Common and Less Common

Justin A. Reynolds, M.D., Richard A. Manch, M.D., and Robert G. Gish, M.D.

Hepatitis due to hepatitis B virus (HBV) reactivation is a potentially serious cause of liver injury that may be induced by immunosuppressive drugs and treatments. Liver damage occurs as a result of impaired immune control over viral replication, which often results in a hepatitis flare. These flares can be significant and lead to jaundice, liver failure, and death. The incidence of HBV reactivation is poorly defined, which is due in part to the lack of standardized nomenclature and definitions of what constitutes HBV reactivation. A recent consensus conference has now proposed criteria for HBV reactivation and exacerbation. Efforts are currently underway to standardize definitions that may help guide future studies and recommendations.¹

Many factors contribute to HBV reactivation, including host characteristics, baseline hepatitis B e-antigen status, and the level of HBV DNA at baseline. The immunosuppressant or treatment received also plays a large role in the development of HBV reactivation. As immunosuppressive agents are used more widely across a variety of medical fields, drug-induced HBV reactivation will become a more common clinical entity facing a broader range of medical personnel. Early recognition of patients at risk for HBV reactivation and initiation of antiviral prophylaxis will undoubtedly prevent many cases of liver injury and death. The major classes of immunosuppressive agents, and their risks of HBV reactivation, will be discussed further below (Table 1).

Corticosteroids

Corticosteroids such as prednisone are commonly used medications and a mainstay of many chemotherapeutic regimens. They have also been shown to increase the risk of

HBV reactivation in many patient populations when used alone, and particularly when given in combination with another immunosuppressant. This reactivation of HBV replication is thought to be mediated by suppression of cytotoxic T-cell function and direct stimulation of a glucocorticoid-responsive element within the HBV genomic sequence. In one study of HBsAg-positive patients exposed to long-term prednisolone (10 mg) versus placebo, there was earlier viral relapse after steroid discontinuation; delay in biochemical remission; and an increased frequency of complications, including death.² In a separate randomized controlled study of corticosteroid use in patients undergoing CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) for lymphoma versus the same regimen without steroids, HBV reactivation was seen in 73% of patients versus 38% in the group who did not receive corticosteroids ($P = 0.03$).³ Thus, corticosteroid use for both short-term and long-term duration is an independent and additive risk factor of HBV reactivation in HBsAg-positive patients. The effect of corticosteroids in patients who are HBsAg-negative and anti-hepatitis B core (HBc)-positive, however, is not well characterized.

Antimetabolites

Azathioprine or 6-mercaptopurine, when used as monotherapy, appears to have very little risk of HBV reactivation. Most prior studies implying a risk of HBV reactivation with these agents have included patients treated with glucocorticoids concomitantly. Very few isolated cases of HBV reactivation have been reported; thus, the risk associated with these agents alone is likely quite low. Methotrexate has numerous reports of HBV reactivation associated with its

Abbreviations: DNA, deoxyribonucleic acid; FDA, U.S. Food and Drug Administration; HBc, hepatitis B core; HBV, hepatitis B virus; TACE, transarterial chemoembolization; TNF, tumor necrosis factor.

From the St. Joseph's Hospital and Medical Center, Center for Liver & Hepatobiliary Disease Phoenix, AZ

Potential conflict of interest: Nothing to report.

View this article online at wileyonlinelibrary.com

© 2015 by the American Association for the Study of Liver Diseases

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

doi: 10.1002/cld.413



TABLE 1 Risk of HBV Reactivation by Drug Type

Level of Risk	HBsAg(+)	HBsAg(-) and anti-HBc(+)	Antiviral Therapy
Very high risk	B-cell depleting agents (rituximab and ofatumumab)	B-cell depleting agents (rituximab and ofatumumab)	Prophylaxis
High risk	Anthracycline derivatives (systemic chemotherapy and TACE) Corticosteroids (> 4 weeks)	Anthracycline derivatives (systemic chemotherapy and TACE)	Prophylaxis
Intermediate risk	Anti-TNF agents Other biologic agents (cytokine and integrin inhibitors)	Anti-TNF agents Other biologic agents (cytokine and integrin inhibitors)	Prophylaxis or preemptive monitoring
Low risk	Corticosteroids (< 4 weeks) Azathioprine or 6-MP Methotrexate	Corticosteroids (> 4 weeks) Corticosteroids (< 4 weeks) Azathioprine or 6-MP Methotrexate	No prophylaxis indicated

use. However, nearly every case reported involved the use of other immunomodulators concurrently. In one isolated case of methotrexate-induced HBV reactivation, withdrawal of low-dose therapy was associated with an increase in liver enzymes and evidence of HBV replication, presumably from immune reconstitution and clearance of HBV-infected hepatocytes.⁴ However, given its long history of use and the few reported isolated cases of HBV reactivation, the risk of reactivation with methotrexate has likely been overemphasized.

Tumor Necrosis Factor-Alpha Inhibitors

Tumor necrosis factor (TNF)-alpha inhibitors (infliximab, adalimumab, certolizumab, golimumab, and etanercept) have all been associated with HBV reactivation. Reactivation has been observed in as many as 39% of HBsAg-positive patients and 5% of HBsAg-negative-anti-HBc positive patients receiving anti-TNF therapy.⁵ In this study, both infliximab use and the concomitant use of other immunosuppressant drugs were more commonly associated with HBV reactivation. This prompted the U.S. Food and Drug Administration (FDA) to insert a warning regarding HBV reactivation for the use of infliximab; however, this increased risk is likely a class effect given the similar mechanism of action with other anti-TNF agents. Sparse data exist on the safety or risk of HBV reactivation in HBsAg-negative and anti-HBc-positive patients.

B-Cell Depleting Agents and Other Biologic Antibodies

Rituximab is an anti-CD20 monoclonal antibody that depletes B cells and has been highly associated with HBV reactivation. In combination with CHOP therapy for non-Hodgkin's lymphoma, reactivation may occur in up to 25% of patients with resolved infection as late as 12 months after therapy has been complete.⁶ Importantly, high rates of HBsAg seroreversion may also be seen in patients with anti-HBc who subsequently reactivate viremia. A recent meta-analysis found that, among case series of anti-HBc-positive patients with an associated non-rituximab-treated control

group, there was a significantly higher rate of HBV reactivation in those patients who received rituximab.⁷ The FDA now requires that all anti-CD20 antibodies (including rituximab and ofatumumab) carry a boxed warning recommending anti-HBc and HBsAg screening tests prior to initiating therapy. Antiviral prophylaxis significantly reduces the risk of reactivation.⁸ Other biologic agents, including cytokine and integrin inhibitors such as ustekinumab, natalizumab, alemtuzumab, and ibritumomab, have few reports of HBV reactivation in the published literature; however, given their mechanism of action, they would also be expected to have at least a low to moderate risk of HBV reactivation.

Locoregional Therapy for Hepatocellular Carcinoma

Transarterial chemoembolization (TACE) may result in HBV reactivation from systemic exposure to anthracycline derivatives (e.g., doxorubicin) via arteriovenous shunting or other means of systemic exposure.⁹ A randomized, controlled study of HBsAg-positive patients with HCC undergoing TACE found that a substantially higher proportion of patients with HBV reactivation was seen in the control group versus those who received antiviral prophylaxis (41% vs. 3%). A significant difference in severe transaminemia was also seen (30% vs. 8%). These findings imply that TACE is a risk factor for HBV reactivation, and antiviral prophylaxis might be needed in some cases.¹⁰

Systemic Chemotherapy

HBV reactivation has been studied the most extensively in patients being treated with chemotherapy for non-Hodgkins lymphoma. In an early prospective study in Hong Kong, 100 patients who had serum HBV DNA levels at baseline were followed prospectively while undergoing chemotherapy for lymphoma.¹¹ Prior to treatment, 27 patients were HBsAg-positive, 51 were HBsAg-negative and anti-HBc-positive and/or anti-HBs-positive, and 22 were negative for all three HBV serologic markers. Hepatitis due to HBV reactivation occurred in 48%, 4%, and 0% of patients,



respectively, and reactivation-related liver failure occurred in 7%, 2%, and 0% of patients, respectively. HBV reactivation has also been reported in patients receiving chemotherapy for treatment of solid tumors such as breast, colon, and lung cancer. Anthracycline-based chemotherapy regimens with or without corticosteroids have the highest risk of HBV reactivation and are frequently used for the treatment of lymphoma or breast cancer.¹²

Conclusion

HBV reactivation is a potentially serious disorder frequently caused by immunosuppressive therapy. Future stud-

ies aimed at understanding the gradient of risk associated with certain immunosuppressive classes and stratifying host and viral factors will allow for antiviral treatment and close monitoring to prevent or mitigate the severity of HBV reactivation. As the development of new biologic agents continues at an unprecedented pace, the list of therapies associated with HBV reactivation is likely to continue to expand in the future.

CORRESPONDENCE

Justin A. Reynolds, M.D., St. Joseph's Hospital and Medical Center, Center for Liver & Hepatobiliary Disease, 500 W. Thomas Road, Ste.980, Phoenix, AZ 85013. E-mail: justinaaronreynolds@gmail.com.

References

1. American Association for the Study of Liver Diseases Emerging Trends Conference, Reactivation of Hepatitis B, Arlington, VA: March 21-22, 2013.
2. Lam KC, Lai CL, Trepo C, Wu PC. Deleterious effect of prednisolone in HBsAg-positive chronic active hepatitis. *N Engl J Med* 1981;304:380-386.
3. Cheng AL, Hsiung CA, Su IJ, Chen PJ, Chang MC, Tsao CJ, et al. Steroid-free chemotherapy decreases risk of hepatitis B virus (HBV) reactivation in HBV-carriers with lymphoma. *Hepatology* 2003;37:1320-1328.
4. Flowers MA, Heathcote J, Wanless IR, Sherman M, Reynolds WJ, Cameron RG, et al. Fulminant hepatitis as a consequence of reactivation of hepatitis B virus infection after discontinuation of low-dose methotrexate therapy. *Ann Intern Med* 1990;112:381-382.
5. Pérez-Alvarez R, Díaz-Lagares C, García-Hernández F, Lopez-Roses L, Brito-Zerón P, Pérez-de-Lis M, et al. Hepatitis B virus (HBV) reactivation in patients receiving tumor necrosis factor (TNF)-targeted therapy: analysis of 257 cases. *Medicine (Baltimore)* 2011;90:359-371.
6. Yeo W, Chan TC, Leung NW, Lam WY, Mo FK, Chu MT, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. *J Clin Oncol* 2009;27:606-611.
7. Evens AM, Jovanovic BD, Su YC, Raisch DW, Ganger D, Belknap SM, et al. Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. *Ann Oncol* 2011;22:1170-1180.
8. Kim SJ, Hsu C, Song YQ, Tay K, Hong XN, Cao J, et al. Hepatitis B virus reactivation in B-cell lymphoma patients treated with rituximab: analysis from the Asia Lymphoma Study Group. *Eur J Cancer* 2013;49:3486-3496.
9. Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, et al. Prospective randomized study of doxorubicin-eluting bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. *Cardiovasc Intervent Radiol* 2010;33:41-52.
10. Jang JW, Choi JY, Bae SH, Yoon SK, Chang UI, Kim CW, et al. A randomized controlled study of preemptive lamivudine in patients receiving transarterial chemo-lipiodolization. *Hepatology* 2006;43:233-240.
11. Lok AS, Liang RH, Chiu EK, Wong KL, Chan TK, Todd D. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. *Gastroenterology* 1991;100:182-188.
12. Yeo W, Zee B, Zhong S, Chan PK, Wong WL, Ho WM, et al. Comprehensive analysis of risk factors associating with Hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. *Br J Can* 2004;90:1306-1311.