HBV Treatment in a Patient Who Will Be Receiving Immunosuppressive Therapy

Jordan J. Feld, M.D., M.P.H.

Despite an effective vaccine, hepatitis B virus (HBV) infection remains an enormous global public health problem with up to 400 million people chronically infected and as many as 2 billion people with evidence of exposure to the virus worldwide.^{1,2} The virus is noncytopathic, with hepatic injury occurring as a result of the host immune response against the virus.¹ As a result, the interaction between HBV and the immune system is critical in determining the outcome of infection.

After perinatal or early childhood infection, >90% of individuals will progress to chronic infection, initially characterized by normal liver tests and histology despite high levels of HBV replication, the so-called immunotolerant phase of infection.² Patients eventually develop an immune response against HBV, leading to flares of hepatitis with the potential for progressive liver damage. Ultimately, most immunocompetent patients will gain immune control of HBV, with suppression of viral replication, normalization of liver enzymes, and loss of circulating HBeAg.² Persistence of this inactive carrier state depends on immune function. Even those with undetectable HBV DNA in the serum continue to harbor replication-competent HBV in infected liver cells. With immunosuppression, immune control may be lost, resulting in reactivation of HBV replication with the potential for severe flares of hepatitis, often at the time of restoration of immune function. Reactivation has variable clinical consequences ranging from asymptomatic increases in serum HBV DNA to potentially fulminant and even fatal flares of hepatitis.^{3,4} Reactivation may also lead to interruptions or premature discontinuation of immunosuppressive therapy, including cancer chemotherapy with potential negative consequences.⁵

The risk of reactivation relates to the potency of the immunosuppressive regimen and specific patient factors. Patients with detectable HBV DNA, particularly those with HBV DNA >1,000 IU/mL, are at increased risk of reactivation, and as with most clinical outcomes in HBV, men have a higher risk of reactivation than women.⁶ Although HBV reactivation has been reported more frequently with hematological malignancies than solid tumors, this is likely due to the chemotherapy regimens used rather than the type of cancer. Systematic reviews of published data suggest that the incidence of reactivation in hepatitis B surface antigen (HBsAg)-positive patients with lymphoma is approximately 50%, with higher rates reported since the introduction of rituximab.^{7,8} Although reactivation seems to be less frequent in patients with solid tumors, with careful monitoring, reactivation has been reported to occur in up to 41% of HBsAg-positive breast cancer patients, leading to interruptions or premature termination of chemotherapy in 35% of individuals.⁵

Reverse Seroconversion

Patients who are HBsAg-negative but have antibodies to HBV core antigen (anti-HBc-positive) are often referred to as having resolved HBV. However, this term is somewhat of a misnomer, because although these patients are unlikely to have consequences of HBV infection, most, if not all, continue to harbor traces of HBV DNA in their livers. The clearance of HBsAg is an indication of potent immune control, and therefore it is only in the setting of severe immunosuppression that HBV may again become problematic. Re-emergence of active HBV infection with reappearance of HBsAg (reverse seroconversion) may occur with severe immunosuppression such as occurs with bone marrow or peripheral stem cell transplantation and advanced human

Abbreviations: anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; ASCO, American Society of Clinical Oncology; CHOP-R, cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; TNF, tumor necrosis factor.

From the Toronto Western Hospital Liver Center, Sandra Rotman Centre for Global Health, University of Toronto, Toronto, Ontario, Canada

Potential conflict of interest: Nothing to report.

View this article online at wileyonlinelibrary.com

© 2013 by the American Association for the Study of Liver Diseases

doi: 10.1002/cld.157

immunodeficiency virus infection.^{9,10} Reverse seroconversion may cause severe acute flares of HBV or alternatively may lead to chronic progressive liver disease.¹¹ More recently, reverse seroconversion has been reported in patients receiving biologics, and the risk has been found to be particularly high in those treated with rituximab, a monoclonal antibody against CD20 that leads to long-lasting depletion of B cells.¹² In the only prospective study, Yeo et al.¹² found that 5 of 21 (24%) HBsAg-negative, anti-HBc-positive patients developed reverse seroconversion during CHOP-R chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab) for diffuse large B cell lymphoma. All five cases caused severe hepatitis, including one death. No patients (0 of 25) receiving CHOP alone experienced reverse seroconversion. Other retrospective studies have reported lower rates of reverse seroconversion with rituximab-based chemotherapy, and uncertainty remains regarding the true risk associated with this agent.^{13,14} Given the high prevalence of anti-HBc positivity, particularly in HBV-endemic regions, and the increasing use of rituximab for many conditions, clarifying the risk and appropriate management strategy for patients receiving rituximab needs to be a priority.

HBV Reactivation in Nononcologic Settings

Loss of immune control from any cause may lead to HBV reactivation. The development of biologic agents with varying degrees of immunosuppressive effects has led to reports of HBV reactivation in many areas of medicine, particularly rheumatology, dermatology, and gastroenterology. Clear data on the risk of reactivation with specific agents are lacking, with the literature consisting largely of case reports and small case series leading to widely variable risk estimates. Reactivation has been best studied with inhibitors of tumor necrosis factor (TNF) α and has been reported to occur in both HBsAg-positive and HBsAg-negative, anti-HBc-positive patients. A recent review of reported cases found that reactivation occurred in 39% (35 of 89) of HBsAg-positive individuals including four fatal cases of acute liver failure and reactivation occurred in 5% (9 of 168) of those who were HBsAg-negative, anti-HBc-positive before starting anti-TNF therapy, including 1 fatal case.¹⁵ Most studies have found the risk to be highest in patients receiving infliximab compared with etanercept or adalimumab.^{15,16} Reactivation has also been reported with azathioprine, 6-mercaptopurine, and methotrexate used in nononcologic settings.¹⁷ There have been individual case reports with targeted kinase inhibitors¹⁸ but no published reports of HBV reactivation with inhibitors of vascular growth endothelial factor.

Prevention of HBV Reactivation

Although HBV reactivation may be severe and even fatal, it is largely a preventable problem. Preemptive therapy with

well-tolerated oral antivirals has been shown to prevent most cases of HBV reactivation. Two small, randomized controlled trials have shown that starting antiviral therapy (lamivudine) prior to or concomitant with chemotherapy is more effective than treating reactivation if it occurs.^{19,20} A meta-analysis showed a survival benefit to this approach.⁷ Unfortunately, by the time reactivation is recognized, it is often too late for effective intervention; therefore, the American Association for the Study of Liver Disease, European Association for the Study of the Liver, Centers for Disease Control and Prevention, and Institute of Medicine all recommend prophylactic therapy for all HBsAg-positive patients starting immunosuppressive therapy.^{21–23} Importantly, chemotherapy or other necessary immunosuppressive therapy should not be delayed while waiting for HBV investigations. Reactivation usually takes many weeks and often months to occur; therefore, although it is preferable to start HBV therapy before or with immunosuppressive therapy, short delays are likely safe.

For patients with undetectable or low HBV DNA at baseline, lamivudine is likely adequate therapy. For those with HBV DNA above 2,000 IU/mL or those scheduled to receive immunosuppressive therapy for longer than 1 year, the AASLD guidelines recommend using a more potent antiviral agent with a higher barrier to resistance, such as entecavir or tenofovir.²² Cases of fatal reactivation due to lamivudine-resistant HBV have been reported, including two recent cases in patients with low level HBV DNA at baseline receiving rituximab.²⁴ If lamivudine is used, careful monitoring to identify resistance is required, and it may be prudent to use a more potent agent in any patients receiving rituximab with detectable HBV DNA at baseline. Currently, it is recommended to continue antiviral therapy for 6 months after the end of all immunosuppressive therapy.²² For patients receiving rituximab, it may be prudent to continue antiviral therapy for 12 months or longer after rituximab treatment because of the long delay in recovery of B cell function. Patients must be monitored carefully after stopping antiviral therapy because withdrawal flares (including some fatal cases) have been reported.²⁰

Management of Anti-HBc-Positive Patients

The risk of reverse seroconversion and HBV reactivation is low in HBsAg-negative, anti-HBc-positive patients receiving standard solid tumor or CHOP chemotherapy.¹² Serial monitoring of liver enzymes and possibly HBsAg without prophylactic antiviral therapy is adequate in this setting. However, if patients are to receive more intensive immunosuppression, management is less clear. The risk of reverse seroconversion is clearly significantly increased with the use of rituximab or myeloablative chemotherapy (bone marrow transplantation) and appears to be higher with anti-TNF therapy as well.²⁵

TABLE 1: Strategies for Testing and Management of HBV During Immunosuppressive Therapy

Test	Population to Be Screened	Significance of Positive Result	Action
HBsAg	All patients scheduled to receive immunosuppressive therapy	HBV infection	Antiviral prophylaxis indicated
Anti-HBs alone	None	Immunity to HBV	None
Anti-HBc± anti-HBs	All patients scheduled to receive myeloablative, rituximab, or TNF inhibitor-containing therapy	Exposure to HBV infection	If HBsAg-positive: as above If HBsAg-negative: low risk for standard chemotherapy If BMT/rituximab/anti-TNF: monitoring essential; consider antiviral prophylaxis
HBV DNA	All HBsAg-positive and anti-HBc-positive patients	1. Undetectable 2. <2,000 IU/mL 3. ≥2,000 IU/mL	1. Lamivudine adequate 2. Lamivudine adequate 3. Consider agent with higher barrier to resistance

Although antiviral therapy is likely effective in this setting, data supporting this approach are lacking. As a result, uncertainty remains about the best management strategy for this relatively large group of patients. The risk appears to be higher in older patients and patients without antibodies to hepatitis B surface antigen (anti-HBs).¹³ Anti-HBs titers may decline or even disappear during chemotherapy, and there is some evidence that this is associated with an increased risk of reactivation; however, the data are limited. Patients with detectable HBV DNA are at particularly high risk and should probably receive preemptive antiviral therapy. For other patients, options include preemptive treatment or careful monitoring. Although HBsAg reappears in most patients before the onset of severe reactivation, cases have been described with rises in HBV DNA despite remaining HBsAg-negative.²⁶ The optimal frequency of HBsAg, anti-HBs, and HBV DNA testing during therapy is not clearly established. If compliance with monitoring is likely to be an issue, prophylactic therapy should be considered. Clearly, better data on the best strategy for managing HBsAg-negative, anti-HBc patients are required.

Screening for HBV

With inexpensive, reliable screening tests and effective, well-tolerated treatment, HBV reactivation fits the criteria for population screening. As a result, the Centers for Disease Control and Prevention recently recommended screening for HBV infection for all patients scheduled to undergo chemotherapy.²¹ However, the American Society of Clinical Oncology (ASCO) responded to this recommendation with a provisional clinical opinion, stating that “evidence is insufficient to determine the net benefits and harms of routine screening for chronic HBV infection in individuals with cancer who are about to receive cytotoxic or immunosuppressive therapy.”²⁷

Concerns raised by ASCO included the potential for delays in chemotherapy, misinterpretation of HBV serology, toxicity of antiviral therapy, and cost of screening. The first two issues are amenable to educational interventions, and fortunately oral nucleoside and nucleotide analogues for HBV are

extremely well tolerated and have no known drug interactions with chemotherapeutic agents. The final issue of cost has recently been addressed. Zurawska et al.⁸ recently evaluated different screening strategies for patients with lymphoma. They found that screening all patients for HBsAg was not only more cost-effective but was actually cost-saving compared with screening only those patients with risk factors for HBV or screening no one. Although the analysis was done for patients receiving CHOP-R chemotherapy with curative intent, their sensitivity analysis showed that the results extend to other regimens and to indolent lymphoma. Notably, screening was cost-saving even in regions with low HBV prevalence. In endemic areas, the results would be much more favorable. This analysis adds further weight to the recommendation that all patients should be screened for HBsAg prior to starting therapy for lymphoma.

What about solid tumors? Because of a lower risk of reactivation with solid tumors, the benefit of screening for HBV in this setting might be lower. A recent analysis by Day et al.²⁸ found that screening for HBsAg in patients receiving adjuvant chemotherapy for breast cancer was cost-effective. Unfortunately, their report focuses on the fact that screening with HBsAg and anti-HBc in all patients was not cost-effective, leading many readers to incorrectly interpret that HBV screening in general is not cost-effective for patients with breast cancer. Because the risk of reactivation of HBV in response to breast cancer treatment is very low in patients whose only manifestation of HBV is the presence of anti-HBc, the additional cost and associated monitoring for this large group of patients significantly increases costs without adding much clinical benefit, if any. The Day et al. study shows that HBsAg screening is cost-effective and highlights the uncertainty of management for patients who are lone anti-HBc-positive. Collectively, the cost-effective analyses show that all patients should be screened for HBsAg prior to starting chemotherapy for any type of tumor, regardless of their risk factors for HBV infection.

What to do with anti-HBc screening and screening in other areas of medicine remains less clear. Until there are

clear management strategies for HBsAg-negative, anti-HBc-positive patients, it is difficult to advocate widespread screening. Anti-HBc testing is not necessary for patients receiving standard solid tumor chemotherapy. For patients receiving rituximab, myeloablative chemotherapy, or anti-TNF agents, screening is likely prudent, provided there is a strategy for monitoring positive patients (Table 1).

Conclusion

HBV reactivation is a potentially fatal but largely preventable problem. All patients scheduled to receive immunosuppressive therapy should be screened for HBsAg, and all HBsAg-positive individuals should receive prophylactic anti-

viral therapy. Awareness of HBV reactivation among oncologists and other medical practitioners remains a major issue. Hopefully, recent data showing that screening and prophylactic therapy are not only effective but also cost-saving will encourage revised guidelines and ultimately increased HBV screening. In the meantime, better data are clearly needed regarding the risk of HBV reactivation with newer agents and on the most appropriate management strategies for patients who are lone anti-HBc-positive. ■

CORRESPONDENCE:

J. J. Feld, M.D., M.P.H., Toronto Western Hospital Liver Center, Sandra Rotman Centre for Global Health, University of Toronto, Toronto, Ontario, Canada. E-mail: Jordan.Feld@uhn.ca.

References

1. Yim HJ, Lok AS. Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. *Hepatology* 2006;43: S173–S181.
2. Feld JJ, Heathcote EJ. Hepatitis B e antigen-positive chronic hepatitis B: natural history and treatment. *Semin Liver Dis* 2006;26:116–129.
3. Hoofnagle JH, Dusheiko GM, Schafer DF, Jones EA, Micetich KC, Young RC, et al. Reactivation of chronic hepatitis B virus infection by cancer chemotherapy. *Ann Intern Med* 1982;96:447–449.
4. 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.
5. Yeo W, Chan PK, Hui P, Ho WM, Lam KC, Kwan WH, et al. Hepatitis B virus reactivation in breast cancer patients receiving cytotoxic chemotherapy: a prospective study. *J Med Virol* 2003;70:553–561.
6. Yeo W, Johnson PJ. Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. *Hepatology* 2006;43:209–220.
7. Loomba R, Rowley A, Wesley R, Liang TJ, Hoofnagle JH, Pucino F, et al. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med* 2008;148:519–528.
8. Zurawska U, Hicks LK, Woo G, Bell CM, Krahn M, Chan KK, et al. Hepatitis B virus screening before chemotherapy for lymphoma: a cost-effectiveness analysis. *J Clin Oncol* 2012;30:3167–3173.
9. Rouphael NG, Talati NJ, Rimland D. Hepatitis B reverse seroconversion in HIV-positive patients: case series and review of the literature. *AIDS* 2007;21: 771–774.
10. Knoll A, Boehm S, Hahn J, Holler E, Jilg W. Reactivation of resolved hepatitis B virus infection after allogeneic haematopoietic stem cell transplantation. *Bone Marrow Transplant* 2004;33:925–929.
11. Kempinska A, Kwak EJ, Angel JB. Reactivation of hepatitis B infection following allogeneic bone marrow transplantation in a hepatitis B-immune patient: case report and review of the literature. *Clin Infect Dis* 2005;41:1277–1282.
12. 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: 605–611.
13. Koo YX, Tay M, Teh YE, Teng D, Tan DS, Tan IB, et al. Risk of hepatitis B virus (HBV) reactivation in hepatitis B surface antigen negative/hepatitis B core antibody positive patients receiving rituximab-containing combination chemotherapy without routine antiviral prophylaxis. *Ann Hematol* 2011;90: 1219–1223.
14. Matsue K, Kimura S, Takanashi Y, Iwama K, Fujiwara H, Yamakura M, et al. Reactivation of hepatitis B virus after rituximab-containing treatment in patients with CD20-positive B-cell lymphoma. *Cancer* 2010;116:4769–4776.
15. 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.
16. Carroll MB, Forgiione MA. Use of tumor necrosis factor alpha inhibitors in hepatitis B surface antigen-positive patients: a literature review and potential mechanisms of action. *Clin Rheumatol* 2010;29:1021–1029.
17. Roche B, Samuel D. The difficulties of managing severe hepatitis B virus reactivation. *Liver Int* 2011;31(suppl 1):104–110.
18. Shiba S, Kondo S, Ueno H, Morizane C, Ikeda M, Okusaka T. Hepatitis B virus reactivation during treatment with multi-tyrosine kinase inhibitor for hepatocellular carcinoma. *Case Rep Oncol* 2012;5:515–519.
19. Lau GK, Yiu HH, Fong DY, Cheng HC, Au WY, Lai S, et al. Early is superior to deferred preemptive lamivudine therapy for hepatitis B patients undergoing chemotherapy. *Gastroenterology* 2003;125:1742–1749.
20. Hsu C, Hsiung CA, Su IJ, Hwang WS, Wang MC, Lin SF, et al. A revisit of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in non-Hodgkin's lymphoma: a randomized trial. *Hepatology* 2008;47: 844–853.
21. Weinbaum CM, Williams I, Mast EE, Wang SA, Finelli L, Wasley A, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep* 2008;57:1–20.
22. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 2009;50: 661–662.
23. European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *J Hepatol* 2012;57: 167–185.
24. Win LL PJ, Shah H, Feld JJ, Wong DK. Death from liver failure despite lamivudine prophylaxis during R-CHOP chemotherapy due to rapid emergence M204 mutations. *Hepatology* 2012: Abstract 435.
25. Hwang JP, Vierling JM, Zelenetz AD, Lackey SC, Loomba R. Hepatitis B virus management to prevent reactivation after chemotherapy: a review. *Support Care Cancer* 2012;20:2999–3008.
26. Yamagata M, Murohisa T, Tsuchida K, Okamoto Y, Tsunoda S, Nakamura M, et al. Fulminant B hepatitis in a surface antigen and hepatitis B DNA-negative patient with diffuse large B-cell lymphoma after CHOP chemotherapy plus rituximab. *Leuk Lymphoma* 2007;48:431–433.
27. Artz AS, Somerfield MR, Feld JJ, Giusti AF, Kramer BS, Sabichi AL, et al. American Society of Clinical Oncology provisional clinical opinion: chronic hepatitis b virus infection screening in patients receiving cytotoxic chemotherapy for treatment of malignant diseases. *J Clin Oncol* 2010;28:3199–3202.
28. Day FL, Karnon J, Rischin D. Cost-effectiveness of universal hepatitis B virus screening in patients beginning chemotherapy for solid tumors. *J Clin Oncol* 2011;29:3270–3277.