Preventing Hepatitis B Reactivation Due to Immunosuppressive Drug Treatments

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Reactivation of the hepatitis B virus (HBV) can cause severe liver injury resulting in jaundice, liver failure, and death.1 This outcome continues to occur in patients receiving immunosuppressive drug therapy (ISDT) despite the ability to identify persons at risk with readily available and inexpensive blood tests for hepatitis B surface antigen (HBsAg) and antibody to hepatitis B core antigen (anti-HBc). Importantly, prophylactic antiviral therapy has been shown to be highly effective in preventing HBV reactivation.

Viral and Host Factors That Determine Risk

The rate of HBV reactivation among patients who are HBsAg-positive and receiving chemotherapy is 40% and, among those with reactivation, the risk of liver failure is 13% and risk of mortality is 16%.2 Reactivation of HBV during ISDT is less likely to develop in persons who are HBsAg-negative and anti-HBc-positive who have clinically resolved HBV infection although HBV DNA persists in the liver. The rate of HBV reactivation in persons who are HBsAg-negative and anti-HBc-positive has been reported to be 0% to 5% with tumor necrosis factor α inhibitors (anti-TNF) and 3% to 41% with R-CHOP (a combination of rituximab and cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone).1,3 Most persons with resolved HBV infection have detectable neutralizing antibody to HBsAg (anti-HBs), which reduces but does not eliminate the risk of HBV reactivation particularly in the face of B-cell depletion therapy and aggressive forms of cancer chemotherapy.1 Reappearance of HBsAg, “reverse seroconversion,” has been described in bone marrow or hematopoietic stem cell transplant recipients and those given B-cell depletion therapy. Reactivation risk tends to parallel the potency of the immunosuppressive regimen and patients with detectable serum HBV DNA are more vulnerable.

Reactivation of HBV has been most frequently observed in patients who are HBsAg-positive and treated for non-Hodgkin lymphoma; in these patients, rates of reactivation of up to 50% are routinely reported.1 The use of R-CHOP therapy has been associated with a higher risk of HBV reactivation than CHOP alone. In a prospective study of 63 patients who were HBsAg-negative and anti-HBc-positive undergoing rituximab-containing chemotherapy for lymphoma, the 2-year cumulative rates of HBV reactivation were 34.4% (11 of 49 patients) among those with baseline anti-HBs and 68.3% (8 of 14 patients) among those without.3 Treatment of breast cancer with anthracycline-based therapy is the leading cause of HBV reactivation in patients with solid organ malignancies, occurring at rates of up to 40%.4 Reactivation has also been observed with chemotherapy administered for multiple other types of malignancies.

The list of immunosuppressive agents implicated in HBV reactivation continues to expand as novel cancer therapeutics and biologic agents are used across medical specialties for nonneoplastic indications. After corticosteroids, anti-TNF agents are likely the most frequent noncancer drugs associated with HBV reactivation because these agents are broadly used, have moderate immunosuppressive potency, and are generally given longterm.

Current Management Recommendations

The Centers for Disease Control and Prevention,5 the American Association for the Study of Liver Diseases, the Asian Pacific Association for the Study of the Liver, the European Association for the Study of the Liver, and the American Gastroenterological Association6 endorse a policy of screening for HBsAg and anti-HBc in patients undergoing ISDT. Prophylactic antiviral therapy is recommended for all patients who are HBsAg-positive and for selected patients who are HBsAg-negative and anti-HBc-positive who receive B-cell-depleting agents or other highly aggressive chemotherapy. Alternatively, patients who are HBsAg-negative and anti-HBc-positive receiving rituximab-based therapies may be monitored and antiviral therapy initiated when there is evidence of HBV reactivation. However, this approach requires frequent (every 3-4 weeks) monitoring of HBV DNA and does not completely prevent HBV-related hepatitis. It is recommended that therapy be continued at least for 6 to 12 months after discontinuation of ISDT.

Support for antiviral prophylaxis can be found in systematic reviews that demonstrated lamivudine, compared with no therapy, was associated with an 80% decrease in HBV reactivation.2 Randomized clinical trials showed that antiviral therapy administered before or at the start of ISDT is more effective than frequent HBV DNA monitoring and deferred treatment after reactivation is diagnosed.3 The use of lamivudine has largely been superseded by entecavir and tenofovir, which have significantly lower rates of HBV resistance and have been shown to be safe and effective in preventing HBV reactivation.6

Iatrogenic HBV reactivation continues to occur due to failure to screen patients at risk of HBV reactivation and initiate prophylactic antiviral therapy to those who test positive for HBV. A preliminary analysis of the postmarketing data from the US Food and Drug Administration Adverse Event Reporting System found 109 cases of rituximab- or ofatumumab-associated fatal HBV-related acute liver failure between market approval of these drugs in 1997 (rituximab), 2009 (ofatumumab), and August 2012 (both drugs). This prompted a box

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warning recommending screening for HBsAg and anti-HBc before starting treatment with anti-CD20 agents and referral to a hepatitis B expert for any positive test results.

Areas Where Change Is Needed Specialty Practice Recommendations. Regular HBV screening has been adopted by only a small proportion (<20%) of oncologists. The 2010 American Society of Clinical Oncology provisional guidelines indicate that there is insufficient evidence to determine the net benefits and harms of routine screening for chronic HBV in patients undergoing cancer chemotherapy. The guidelines recommended that screening may be considered if highly immunosuppressive regimens are used as in lymphoma or bone marrow transplantation, but no recommendation was made about other groups of patients.

The National Psoriasis Foundation recommended in 2014 that all patients who are candidates for TNF inhibitors, ustekinumab, cyclosporine, or methotrexate should be screened for HBV. The 2012 American College of Rheumatology (ACR) guidelines for patients with rheumatoid arthritis warned against the use of biologic agents in patients with untreated hepatitis B but there was no recommendation for HBV screening.

Clinician Awareness of Drug Risk. Another barrier to HBV screening is the misperception that HBV reactivation rarely occurs in Western countries and that all persons who are HBV-infected have recognizable risk factors. There is also incomplete recognition that biologic agents can induce HBV reactivation. A survey of 1000 ACR members indicated that only 69% performed universal screening prior to the use of biologic disease-modifying antirheumatic agents and, depending on the agent selected, as many as 53% were unaware of the manufacturers’ warnings of HBV reactivation within drug package inserts.

Limited Cost-effectiveness Data. Other barriers to HBV screening include concerns about the cost of HBV tests and antivirals. A key issue is whether all patients or only high-risk patients should be screened. Risk-based screening fails to identify many infected patients because patients are often unaware of their risks and clinicians often do not properly evaluate hepatitis risks in clinical practice. Blood tests for HBsAg and anti-HBc are simple and the cost of these tests is relatively low compared with the cost of cancer chemotherapy or biologic agents. The costs of HBV screening and antiviral prophylaxis must be balanced against the costs of managing patients who experience HBV reactivation as well as the risk of increased mortality from liver failure and cancer progression due to interruption of chemotherapy.

Approach to Management. Hepatitis B reactivation induced by ISDT can have serious consequences but is preventable. Screening for HBV markers is the first critical step toward prevention, but ambiguity in practice guidelines may be limiting the implementation of preventive measures on a broader scale. HBV screening and antiviral therapy for those at risk has the potential to prevent HBV reactivation and the associated risks of liver failure and death. However, important questions remain regarding how to most efficiently accomplish this. Targeted screening (eg, only screening those with identified risk factors for HBV infection) may be appropriate when populations with a low (<2%) prevalence of infection are given ISDT with a low to moderate risk of inducing HBV reactivation; in such settings, screening with HBsAg alone may suffice. Universal screening, on the other hand, may be more appropriate in high-prevalence populations exposed to high-risk therapy, and for these patients both HBsAg and anti-HBc screening would be important. A possible approach for evaluation and management of patients with chronic or past HBV infection prior to and during ISDT has been proposed but has not been evaluated and validated.

Development and implementation of standardized policies will require collaborative research and educational efforts across specialties. The increasing availability of novel biologic therapies for malignant and nonmalignant disorders underscores the importance in addressing these issues and eliminating barriers to prevention of this potentially serious complication of ISDT.