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Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Overview of Hepatitis B Virus Reactivation

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G&H How is hepatitis B virus reactivation defined?

RP Hepatitis B virus (HBV) reactivation is a clinical syndrome that is characterized by a sudden increase in the level of serum HBV DNA that is most often associated with moderate to marked elevation of serum alanine aminotransferase (ALT) levels. Reactivation occurs in individuals with past HBV (hepatitis B surface antigen [HBsAg]-negative, antibody to hepatitis B core antigen [anti-HBc]-positive) as well as chronically infected individuals (HBsAg-positive, anti-HBc–positive). It is generally considered to reflect a failure of immunologic control over HBV replication, and may occur either spontaneously or whenever an individual with serologic evidence of past or chronic HBV infection becomes immunologically compromised.

There is no standardized criterion for the level of increase in HBV DNA that justifies the diagnosis of reactivation, but at least a 2-log or 100-fold increase is often used in the medical literature. The term HBV reactivation is more properly considered as a virologic event, and transient episodes have been shown to rarely occur without a significant rise in serum aminotransferase levels. However, the frequency of such mild events is unknown. Most observational studies utilize at least a 2- or 3-fold increase in serum ALT levels above baseline as a threshold indicator of HBV reactivation.

HBV reactivation also can be diagnosed when a previously hepatitis B e antigen (HBeAg)- or HBsAg-negative patient undergoes seroreversion for these viral markers. This is most often observed in patients who are undergoing routine evaluation of HBV markers or are participating in clinical trials of antiviral therapy.

G&H Which patients are most at risk for HBV reactivation?

RP Several large studies have shown that HBeAg-positive patients with a greater-than-4-log HBV DNA level are at elevated risk. HBV reactivation tends to more frequently occur in immunologically suppressed individuals. For this reason, reactivation has been frequently described in untreated HIV-1–infected patients. Currently, the most important clinical setting for HBV reactivation is when patients receive immunosuppressive drug therapy (ISDT) such as cancer chemotherapy, biologic agents for the treatment of chronic autoimmune disorders, or prolonged glucocorticoid therapy in moderate (20 mg) or higher doses.

Although HBV reactivation is generally far less common in patients with past or resolved HBV, this is a numerically important group because 2% to 3% of the general US population, and as many as 30% of Asian Americans, have serologic evidence of anti-HBc positivity with or without accompanying neutralizing antibody to hepatitis B surface antigen (anti-HBs). If such individuals are given highly immunosuppressive medication such as rituximab without the benefit of antiviral prophylaxis, as many as 10% to 20% may develop reactivation. These individuals remain at risk for reactivation because sterilizing immunity does not occur after resolution of HBV. Instead, such individuals harbor the presence of small amounts of the HBV minichromosome or genomic template (covalently closed circular HBV DNA) in the nucleus of infected

hepatocytes. Thus, a decline in host immune control may lower the immunologic barrier to viral transcription and enhanced levels of HBV replication.

G&H How should the risk for reactivation be assessed?

RP The best way to assess risk is to test for all 3 serologic markers of HBV—HBsAg, anti-HBc (total or immunoglobulin [Ig] G), and anti-HBs—in all patients who are about to embark on ISDT or who have newly diagnosed immunosuppressive medical disorders such as diabetes, HIV-1 infection, or cirrhosis. HBsAg-positive patients have a higher risk of HBV reactivation compared with those who are HBsAg-negative but anti-HBc–positive. In a variety of clinical settings, individuals with resolved HBV who are positive for both anti-HBc and anti-HBs appear to be at lower risk for reactivated HBV when compared with those with isolated anti-HBc alone.

Unfortunately, the vast majority of clinical observational studies of HBV reactivation have used qualitative rather than quantitative testing for anti-HBs. In my clinical practice, I use quantitative anti-HBs testing at the time of initial serologic testing in individuals who are about to undergo ISDT in order to assess the relative risk for HBV reactivation. This is particularly important in patients placed on B-cell depletion therapy because there are emerging data that patients with high titers (>100 mIU/mL) appear to have a lower risk for HBV reactivation when treated with CD20 monoclonal antibodies.

G&H What are the typical clinical manifestations of reactivated HBV?

RP Many cases are not accompanied by clinical symptoms, but hepatocellular injury can occasionally be severe and lead to hepatic decompensation (jaundice, prolongation of prothrombin time, hepatic encephalopathy) that requires liver transplantation. It is not unusual to find ALT and aspartate aminotransferase elevations from 20 to 100 times the upper limit of normal (ULN) in such individuals. Milder elevation of serum aminotransferase levels may be observed in decompensated individuals with previously unsuspected cirrhosis.

G&H How can HBV reactivation be differentiated from flare?

RP HBV reactivation is one of several reasons for what is generally referred to as an ALT flare. In current usage, flares always require the background setting of chronic HBV infection (HBsAg-positive) and may be associated with increases or decreases in viral HBV DNA level. There are several types of flares, including those that are viral-mediated, host-induced, antiviral therapy–related, and those that occur because of superinfection with another virus.

Viral-mediated flares meet the definition for HBV reactivation in that a sudden increase in viral replication stimulates the innate host immune response to HBV, which, in turn, results in hepatocellular injury and leakage of aminotransferase enzymes into the blood. In theory, this could be because of the emergence of a replication-fit viral variant when an overt cause of immune suppression is not evident. This was commonly seen with first-generation nucleoside analogues such as lamivudine, in which case flares could be explained by a high frequency of drug-resistant viral mutants. Fortunately, this is no longer seen with high genetic barrier nucleos(t)ide analogues unless the patient has been nonadherent.

However, flares also occur during pegylated interferon therapy in 20% to 30% of cases and are more common in HBeAg-positive patients. Interferon is an immunomodulatory agent, and ALT flares during treatment are thought to represent an augmentation of cellular immunity to HBV because they are associated with a decline in HBV DNA as well as accelerated clearance of viral antigens such as HBsAg and HBeAg. Rarely, treatment with nucleoside analogues has been associated with similar ALT flares that are most often transient and can be associated with a decrease in quantitative HBeAg. ALT flares induced by drug withdrawal have also been observed after discontinuation of long-term nucleoside analogue therapy and prolonged suppression of HBV DNA. These flares reflect virologic relapse and occur in 30% to 50% of patients withdrawn from therapy. Resumption of antiviral medication may be required.

Host-induced flares refer to those that occur in association with a decline in HBV DNA and can herald a positive virologic outcome such as impending HBeAg loss. This may occur spontaneously or coincident with HBeAg loss induced by antiviral therapy.

Finally, another cause for ALT flares is superinfection with another virus such as hepatitis A virus, hepatitis C virus, or hepatitis delta virus. Of note, a decline in HBV DNA has frequently been reported when this occurs because of viral interference in which one virus often becomes genomically dominant.

G&H How is reactivation diagnosed in clinical practice situations where baseline data are limited?

RP Often, the initial diagnosis of HBV reactivation may not be straightforward because of lack of previous serologic and HBV DNA testing. Therefore, this situation

requires an index of suspicion. In my clinical practice, patients are often referred to me because of abrupt changes in ALT accompanied by a positive test for HBsAg. In such instances, it is important that a careful search be performed of the patient's medical records to see what his or her ALT has been in the past and whether HBsAg or other viral markers were previously recorded. HBeAg and HBV DNA should always be drawn upon presentation, and if the ALT level is severely elevated, treatment with an oral antiviral should be started immediately while awaiting the viral test results. Prompt treatment initiation is particularly important if there are clinical grounds to suspect the presence of cirrhosis. In the absence of previous HBV DNA testing, HBV reactivation can be assumed to be present when an HBsAg carrier presents with an HBV DNA level of at least 100,000 IU accompanied by moderate or severe ALT elevation (≥5 × ULN or ≥10 × ULN, respectively). If acute HBV is a possibility, then a negative test for IgM anti-HBc can be helpful in confirming HBV reactivation.

G&H What prophylactic measures should be used to lower the risk of reactivation and in which patients?

RP At the current time, the American Association for the Study of Liver Diseases recommends that all HBsAg-positive patients who are to undergo ISDT be placed on oral antiviral therapy prior to or soon after initiation of the drug. However, there are several immunosuppressive medications and regimens that are associated with a particularly high risk of HBV reactivation. One of the earliest to be implicated in causing HBV reactivation was glucocorticoid therapy, including prednisone, prednisolone, and dexamethasone. In addition to the generalized T-cell inhibition that these agents cause, HBV has a glucocorticoid-responsive element in its genome that, once activated, results in enhanced viral transcription and increased viral replication. Short durations of corticosteroids (eg, <4 weeks at doses of 10 mg or less) are not much of a threat, but HBsAg-positive individuals taking these agents for more than 4 weeks at a moderate dose of 20 mg or more should be given antiviral prophylaxis. I prefer to do the same whenever the patient has isolated anti-HBc without concomitant anti-HBs.

Perhaps the most notorious regimen for HBV reactivation is rituximab plus cyclophosphamide, doxorubicin, vincristine, and high-dose prednisone or prednisolone (R-CHOP) treatment for non-Hodgkin lymphoma. The frequency of HBV reactivation may be as high as 50% to 60% in HBsAg-positive patients and 10% to 20% in those with serologic evidence of past infection when antiviral prophylaxis has not been initiated.

The risk of HBV reactivation appears to be much lower in patients taking biologic agents for chronic inflammatory disorders such as psoriasis or rheumatoid arthritis. Examples of these drugs include inhibitors of tumor necrosis factor or interleukins. In this situation, antiviral prophylaxis is recommended for HBsAg carriers because the frequency of HBV reactivation varies between 5% and 10%. Corresponding rates of HBV reactivation in individuals who are HBsAg-negative but anti-HBc–positive vary from 0% to 5% of cases.

It is important to recognize that new biologic agents are being developed every year, and because clinical trials with these agents exclude patients with serologic evidence of HBV infection, the safety of these drugs in patients with positive HBV markers cannot be determined until the drugs are broadly used in phase 4 studies. Providers are informed of the need to report suspected or proven cases of HBV reactivation to the US Food and Drug Administration, but this does not provide adequate assurance of safety because of underreporting. Also, it should be noted that the risk of any one agent may be relatively small, but if given with other immunosuppressive agents, the risk for HBV reactivation may be amplified.

G&H How long should antiviral prophylaxis be used in patients on immunosuppressive therapy?

RP Ideally, antiviral prophylaxis with high genetic barrier nucleos(t)ide analogues should be started no later than 1 week after the initiation of ISDT. The length of the antiviral prophylaxis is based on the duration of exposure to the agent(s) plus a posttreatment interval that varies from 6 to 12 months depending on the type of ISDT.

Biologic therapy for rheumatoid arthritis, psoriasis, or autoimmune-like illnesses is generally administered on a long-term basis, so HBsAg-positive patients need to be given antiviral prophylaxis for the duration of treatment. However, it is not clear how long antiviral prophylaxis needs to be maintained in HBsAg-positive patients if these agents are discontinued. Recommendations have been made to continue antiviral prophylaxis for a minimum of 6 months after cancer chemotherapy and for at least 12 months after the use of rituximab because of slow recovery of adequate B-cell function and isolated reports of late HBV reactivation after discontinuation. The same recommendation applies to R-CHOP–treated patients who are HBsAg-negative but anti-HBc–positive.

G&H How should reactivated HBV be treated?

RP Any of the high genetic barrier nucleos(t)ide analogues (entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide) may be used to treat reactivation. It

is important to initiate antiviral prophylaxis as soon as a diagnosis of reactivation has been made or suspected, even in situations where the ALT level is only mildly elevated (<5 × ULN). On-demand treatment started when both HBV DNA and ALT criteria for reactivation are met has been shown to be associated with less desirable virologic and clinical outcomes.

HBV reactivation should be presumed to meet criteria for long-term antiviral therapy. It has been my practice to only attempt treatment discontinuation 12 or more months after HBeAg seroconversion to antibody to HBeAg in patients who initially presented with reactivation in the context of mild disease and stage 1 or 2 fibrosis. I do not attempt to withdraw antiviral therapy despite similar virologic endpoints being reached in patients with more advanced liver disease, nor do I discontinue treatment when the episode of reactivation was clinically severe or ALT levels were in excess of 1000 IU. Loss of HBsAg allows treatment discontinuation in the previous groups, but I vaccinate these individuals if anti-HBs is not detectable.

G&H What are the priorities of research involving reactivation of HBV?

RP Because HBV reactivation represents a change in viral-host interaction, it is important to understand both the early virologic and immunologic changes that occur. More studies are needed in this area. This remains a challenge because it requires serial harvesting of peripheral mononuclear cells from HBV-infected patients and cellular immunologists with expertise in viral hepatitis. Unfortunately, experts in cellular immunity to HBV often have limited access to clinical samples from infected patients, which can be a serious limiting factor. Furthermore, carryover of the early changes in immune response may no longer be evident by the time the patient presents with HBV reactivation. It also is currently unknown whether viral variants capable of suppressing innate immune responses might serve as a cofactor for HBV reactivation. Thus, future progress in understanding why and how reactivation occurs is likely to require close collaboration of the hepatology community, cellular immunologists, and molecular virologists.

Also needed are clinical research studies on whether HBV vaccination has any role to play in preventing HBV reactivation. This is particularly apt for individuals with resolved HBV who are to be placed on ISDT, a group for whom current recommendations are either long-term monitoring for HBV or antiviral prophylaxis. A large observational database has demonstrated that detection of anti-HBs is associated with a significantly reduced frequency of HBV reactivation in anti-HBc–positive individuals treated for hematologic malignancies. Further exploration needs to be done to assess the extent to which humoral immunity may protect against HBV reactivation in other clinical settings. If this proves to be the case, clinical benefit may potentially be derived from vaccination of anti-HBc–positive patients with a commercially available, immune-adjuvanted HBV vaccine (Heplisav-B, Dynavax Technologies). Early studies are currently underway at my institution.

Disclosures

Dr Perrillo has no relevant conflicts of interest to disclose.

Suggested Reading

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