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THE MANAGEMENT OF VIRAL HEPATITIS IN IMMUNOSUPPRESSED PATIENTS: WHAT THE DERMATOLOGIST SHOULD KNOW

With a growing array of immunomodulatory and biologic therapies available for common and rare skin disorders, prescribing dermatologists increasingly need to be aware of the potential adverse effects of these medications. One serious potential adverse effect is the reactivation of viral hepatitis, which can lead to significant morbidity and mortality.[1] The reactivation risk of Hepatitis B virus (HBV) infection can be minimized by careful evaluation prior to initiating immunosuppressive therapy.

Case Example

A 46-year-old man of Chinese descent is referred for evaluation of psoriasis that is not responding to topical agents. After a detailed evaluation, you recommend adalimumab. The patient is sent for screening bloodwork prior to initiation of therapy, which demonstrates that he has chronic HBV infection (HBsAg positive, anti-HBs Ab negative, anti-HBc positive). How do you proceed?

Natural History of HBV Infection

Chronic HBV infection is most commonly acquired after exposure at birth. Globally, there are estimated to be close to 300 million infected persons, of whom only 10% are diagnosed.[2] After exposure at birth, the infection progresses to an immunotolerant stage characterized by high viral load, normal alanine aminotransferase (ALT), and no liver fibrosis. After the immunotolerant phase, patients will typically experience a phase of immune clearance characterized by fluctuating viral load and ALT, and possible accumulation of fibrosis.

Following immune clearance, patients may enter a phase of immune control characterized by low viral load, normal ALT and host immune response that prevents liver fibrosis.[3] Adult patients usually present in this latter stage.

Understanding HBV Reactivation

HBV is non-cytopathic, and the outcome of infection is determined by adaptive T and B cell responses.[4] Inflammation is the result of the immune response. Despite developing immune control, patients will retain a reservoir of persistent HBV, either as whole virus or as covalently closed circular DNA (cccDNA) which is sometimes called resolved or latent HBV. Medications that suppress general immune function or specific host pathways that alter the immune control of HBV can impair this immune control and result in clinical reactivation.

Reactivation is defined as a rapid increase in HBV DNA level by at least 100-fold in those with previously detectable DNA, or the reappearance of HBV viremia in those who did not previously have viremia. When this occurs, it can be followed by a rise in the ALT and aspartate aminotransferase (AST) and clinical outcomes include spontaneous resolution or persistent liver injury and acute liver failure. While most patients will spontaneously recover, the risk of acute liver failure and resultant death means that attention needs to be given to this serious event.

Screening Evaluation for Viral Hepatitis

All patients who receive immunosuppressive therapy should be screened for viral hepatitis prior to initiation of treatment. Screening should include HBsAg (Hepatitis B surface antigen), anti-HBs Ab (Hepatitis B surface antibody), anti-HBc Ab (Hepatitis B core antibody), and anti-HCV Ab (Hepatitis C antibody). Interpretation of the HBV screening test results is found in **Table 1.**

Patients who test negative for all HBV markers should be referred to their primary care provider or public health authority for vaccination. Patients who test positive for only Anti-HBc Ab have been previously exposed to HBV but do not have active infection. Patients who test positive for HBsAg have active infection and should be referred to specialty care for evaluation of the infection and determination of the need for therapy irrespective of immunosuppression.

HBV Clinical State	HBsAg	Anti-HBs Ab	Anti-HBc Ab
Infected	+	-/+	+
Immune (from vaccination)	-	+	-
Resolved (Natural Immunity)	-	-/+	+
Non-Infected Non-immune	-	-	-

Table 1. Interpretation of HBV screening tests

Patients who test positive for anti-HCV Ab should have a follow-up HCV RNA PCR performed and be referred on for treatment of HCV infection. While HCV RNA levels can slightly rise in a person taking immunosuppressive therapy, it does not cause clinical signs or symptoms.[5]

Risk Matrix for Decision to Prescribe Prophylactic Therapy to Prevent HBV Reactivation

Patients who test positive for HBsAg are high-risk patients for reactivation. These patients should receive prophylactic therapy to prevent reactivation when receiving medications that attribute any risk of reactivation.[6] High-risk patients receiving high-risk therapies have a possibility of reactivation that is higher than 10% and, in some studies, higher than 50%.

Patients who test negative for HBsAg but positive for anti-HBc Ab are low risk for reactivation. These patients should receive prophylaxis only when receiving medications that carry a very high risk of causing reactivation, as shown in **Table 2.**

Choice and Duration of Antiviral Prophylaxis

Patients who qualify for prophylactic therapy should have it initiated prior to, or when starting, immunosuppressive therapy. Baseline lab testing including ALT, AST, international normalized ratio (INR), bilirubin, albumin, hepatitis B e-antigen (HBeAg), anti Hepatitis B e-antibody (anti-HBe Ab), and HBV DNA should be obtained in all patients and HBV DNA should be monitored every 3-6 months while patients are on antiviral therapy.

The same nucleoside/nucleotide analogues used for the treatment of chronic HBV infection can be used for prophylaxis. In a published systematic review, the authors demonstrated that lamivudine can significantly reduce

Very high risk of reactivation	Rituximab, ofatumumab, ustekinumab, natalizumab
High risk of reactivation	High-dose corticosteroids Anthracyclines Potent TNF-α inhibitors including infliximab, adalimumab, golimumab
Moderate risk of reactivation	Systemic chemotherapy Etanercept Tyrosine-kinase inhibitors including imatinib Moderate-dose corticosteroids
Low risk of reactivation	Antimetabolites Azathioprine, 6-mercaptopurine, methotrexate Short-term low-dose corticosteroids

Table 2. Risk profile of common immunosuppressive therapies

the risk of reaction, HBV-related hepatitis, and HBV-related acute liver failure in patients receiving cancer chemotherapy.[7] The authors of this systematic review analyzed fourteen studies (2 randomized controlled trials; 8 prospective cohort studies; and 4 retrospective cohort studies) which met the predefined criteria for analysis. There were 275 patients in the preventive lamivudine group and 475 control participants for the primary end point of HBV reactivation. With preventive lamivudine, the relative risk for both HBV reactivation and HBV-related hepatitis ranged from 0.00 to 0.21. None of the patients in the preventive lamivudine group developed HBV-related hepatic failure (0 of 108 patients vs. 21 of 162 patients), and only 4 deaths were attributable to HBV (4 of 208 patients vs. 27 of 394 patients) in the preventive lamivudine group. Lamivudine was well tolerated, and no adverse effects were noted.[7]

Despite the accumulated evidence, lamivudine is generally not considered the preferred agent due its low potency and low barrier of resistance. More recently, entecavir and tenofovir have become the preferred agents.[8]

Specifically as it relates to the use of entecavir, a recent study comparing the efficacy of entecavir and lamivudine in preventing HBV reactivation in patients seropositive for the hepatitis B surface antigen with untreated diffuse large B-cell lymphoma receiving chemotherapy treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) was conducted. The primary efficacy endpoint was the incidence of HBV-related hepatitis. The secondary endpoints included rates of HBV reactivation, chemotherapy disruption due to hepatitis, and treatment-related adverse events. The results show that the incidence rates were significantly lower for the entecavir group vs the lamivudine group for HBV-related hepatitis (0% vs 13.3%, respectively; difference between groups, 13.3% [95% CI, 4.7% to 21.9%]; P = .003), HBV reactivation (6.6% vs 30%; difference, 23.4% [95% CI, 10.2% to 36.6%]; P = .001), and chemotherapy disruption (1.6% vs 18.3%; difference, 16.7% [95% CI, 6.4% to 27.0%]; P = .002). Of the 61 patients in the entecavir group, 15 (24.6%) experienced treatment-related adverse events. Of 60 patients in the lamivudine group, 18 (30%) experienced treatment-related adverse events (difference between entecavir and lamivudine groups, 5.4% [95% CI, -10.5% to 21.3%]; P = .50).[8]

While prophylaxis can start just prior to the initiation of immunosuppression, it should continue for at least 6 months after the last dose of immunosuppression. Since the risk of reactivation is highest during the immune reconstitution phase following immunosuppression, the patient must receive prophylaxis through this period to be protected. Clinicians should note that there is some evidence that reactivation risk after rituximab can persist for 2 years, so in the case of this therapy, prophylaxis must be given for a longer period of time.[6]

Follow-up and Monitoring of Patients

The risk of reactivation is not eliminated by prophylactic therapy. All patients should be monitored for serologic evidence of reactivation with laboratory testing every 3-6 months that includes HBsAg, HBV DNA and ALT. Patients who are HBsAg positive should also be assessed for fibrosis and there is need for ultrasound surveillance of hepatocellular carcinoma.

Conclusion

Reactivation of viral hepatitis is an uncommon event but can cause severe morbidity and even death when it does occur. It is essential to screen all patients receiving immunosuppression for HBV and HCV and manage them appropriately with collaboration from liver specialists where needed.

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