Hepatitis B Virus Reactivation

What Is the Issue, and How Should It Be Managed?

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KEYWORDS

• Hepatitis B virus • Reactivation • Immunosuppression • Hepatitis flare
• Antiviral prophylaxis

KEY POINTS

- Hepatitis B virus (HBV) reactivation is not uncommon in patients receiving immunosuppressive therapy, which can then lead to serious complication such as hepatitis flare, hepatic decompensation, and hepatic failure.
- Prevention of HBV reactivation by antiviral prophylaxis in patients who are planned to receive immunosuppressive agents is an effective strategy to reduce morbidity and mortality caused by HBV reactivation.
- Risk of HBV reactivation can be classified into low- (<1%), moderate- (1%–10%), and high-risk (>10%) groups according to HBV serologic status and types of immunosuppressive therapy.
- All patients who are candidates for chemotherapy or immunosuppressive therapy should be screened for HBV serologic status before initiating treatment. Patients with moderate-to-high risk for HBV reactivation should be considered for antiviral prophylaxis.
- Every immunosuppressed patient who develops HBV reactivation (with or without hepatitis flare) should be treated with a high barrier to resistance antiviral agent as early as possible. However, despite initiation of antiviral treatment, some patients may still develop hepatic decompensation or hepatic failure.

INTRODUCTION

Hepatitis B virus (HBV) reactivation can be precipitated following the use of immunosuppressive agents and chemotherapy and can be a serious manifestation. HBV

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Clin Liver Dis 24 (2020) 317–333
https://doi.org/10.1016/j.cld.2020.04.002
liver.theclinics.com

reactivation commonly occurs in hepatitis B surface antigen (HBsAg)-positive patients, but also can be encountered in those with a positive antibody to hepatitis B core antigen (anti-HBc) while they are HBsAg-negative.[1] Although there is lack of consistency on the definition of HBV reactivation, it can be defined as virologic, biochemical, or clinical, although most often there is an overlap of various features. Reactivation initially is characterized by a sudden rise of HBV DNA, which can be followed by a hepatitis flare (defined by an elevation of alanine transaminase [ALT] levels ± bilirubin) several weeks after.[2] Therapeutic interventions that can induce HBV reactivation have increased over the past few years, while B cell-depleting agents, such as rituximab, remain the cornerstone for their frequent association with HBV reactivation. Corticosteroid is another drug that is commonly used in combination with immunosuppressive regimens, although the dosage and duration of corticosteroid treatments may affect the risk of HBV reactivation. In addition, a non-cancer drug class such as tumor necrosis factor (TNF) inhibitors can also induce HBV reactivation, a concern among physicians when treating inflammatory bowel disease or rheumatologic diseases.[3] As a consequence of HBV reactivation, there is associated severe morbidity and high mortality because of hepatic decompensation and hepatic failure.[4] Prevention of HBV reactivation is necessary in order to reduce the risk of morbidity and mortality in patients who are targeted to receive immunosuppressive agents. This article discusses the heterogeneous definitions, the risk of reactivation with a spectrum of immunosuppressive and cancer chemotherapeutic agents, the risk with targeted biologics, guideline recommendations for the prevention of HBV reactivation, and the prognosis and management of HBV reactivation.

DEFINITION OF HEPATITIS B VIRUS REACTIVATION

The updated American Association for the Study of Liver Diseases (AASLD) guideline recommendation on prevention, diagnosis, and treatment of chronic hepatitis B 2018 defined HBV reactivation in HBsAg-positive, anti-HBc positive patients as any of the following[2]: (1) at least 2 log (or 100-fold) increase in HBV DNA compared with the baseline level, (2) HBV DNA at least 3 log (or 1000) IU/mL in a patient with previously undetectable HBV DNA, or (3) HBV DNA at least 4 log (or 10,000) IU/mL if the baseline level is not available.

For HBsAg-negative, anti-HBc positive patients, HBV reactivation is defined as[2] detectable HBV DNA or reverse HBsAg seroconversion or reappearance of HBsAg. A clinical hepatitis flare is defined as an ALT rising to at least 3 times the baseline level and greater than 100 U/L.

Some individuals with HBV reactivation are asymptomatic with a normal hepatic biochemical profile, while some can have a flare of HBV infection with increased aminotransferase levels. However, a hepatitis flare can be with or without clinical signs and symptoms (such as nausea and vomiting), but severe flare can be associated with hepatic decompensation, jaundice, and poor outcome, especially in patients with underlying cirrhosis.[5]

NATURAL HISTORY OF HEPATITIS B VIRUS REACTIVATION

Hepatitis B virus (HBV) can infect individuals and lead to acute infection or chronic infection and the latter especially when exposed to the virus in infancy and childhood. HBV virus enters the hepatocytes via the sodium-taurocholate cotransporter (NTCP) receptor.[6] After viral entry, it releases double-stranded viral genomes that are then transported into the nucleus. In the nucleus, viral genomes are repaired by polymerase enzymes into covalently closed circular DNA (cccDNA). The cccDNA is stabilized in

HBV-infected hepatocytes that can then persist as a latent state and serve as a reservoir for HBV reactivation despite evidence for recovery as denoted by the development of anti-HBs.[7] Treatment with nucleoside/nucleotide analogue (NA) can suppress HBV DNA, but cccDNA still remains after several years of treatment.[1,8]

Specific CD4+ and CD8+ T cells target HBV infected cells for viral elimination via cytopathic mechanisms and suppress viral replication via noncytopathic cytokine-mediated pathways.[9] The activated B cells produce neutralizing antibodies that contribute to viral clearance. Although these immune responses can control active HBV replication, they are not potent enough to eliminate cccDNA. Thus, these infected cells serve as a reservoir for HBV reactivation when the immune mechanisms are suppressed.[1] The various types of chemotherapies and immunosuppressive agents may variably be associated with potential risks of reactivation differently.

The evolution of HBV reactivation can be classified into stages[1]:

- Viral replication: After immunosuppression, HBV DNA may increase and patient may still be asymptomatic and without aspartate transaminase (AST) or alanine transaminase (ALT) elevation.
- HBV-reactivation related hepatitis (hepatitis flare): A few days to weeks after viral replication, AST and ALT levels start rising up to 5 to 10 times from baseline levels. Patients may experience constitutional symptom and jaundice; however, some may remain asymptomatic.
- Resolution: Some patients can have spontaneous improvement after hepatitis flare after cessation of immunosuppressive agents. However, if HBV reactivation is recognized, starting antiviral therapy can also lead to decline in HBV DNA levels, amelioration of immune-mediated injury of HBV infected hepatocytes, and subsequent resolution of hepatitis flare.
- Liver failure: A minority of patients may have progressive decline in hepatic function and end up with hepatic decompensation or liver failure despite initiation of antiviral agents. These clinical manifestations may lead to significant morbidity and mortality. Unfortunately, liver transplantation, although it would be considered the logical rescue strategy, might present a contraindication because of the uncertain course and prognosis of the underlying conditions of lymphoma or other malignancy, which are the basis for immunosuppressive treatment that has led to HBV reactivation (**Fig. 1**).

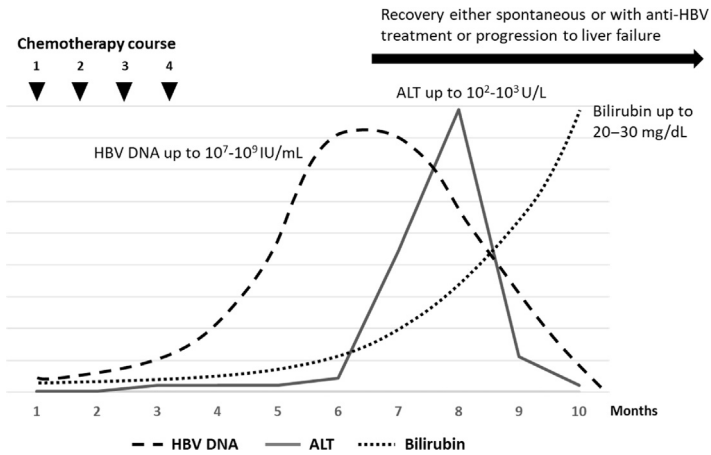

Fig. 1. Natural disease progression of HBV reactivation after immunosuppressive therapy.

A recent retrospective multicenter study (n = 156) from the Acute Liver Failure Study Group (ALFSG) noted that 18% of HBV-associated acute liver failure (ALF) occurred after receiving immunosuppressive therapy. Survival beyond 21 days in patients with HBV-associated ALF after immunosuppression was significantly lower than in nonimmunosuppression HBV-associated ALF.[10] Another systematic review and meta-analysis in patients with solid tumors receiving chemotherapy had demonstrated that without prophylaxis, there was a 23% (range 2%–60%) risk of HBV-related hepatitis and chemotherapy interruption, a 2% (range 1%–20%) risk of HBV-related acute liver failure, and a 2.3% (range 0.4%–20%) mortality risk.[11]

RISK STRATIFICATION OF HEPATITIS B VIRUS REACTIVATION

Status of Hepatitis B Serology

HBsAg-positive

Patients who are HBsAg positive are at higher risk for HBV reactivation than those with HBsAg-negative and anti-HBc positive serologic status. HBsAg-positive patients with HBeAg-positive and/or high baseline HBV DNA levels may have highest risk of hepatitis B virus reactivation, with the highest risk being in those with an HBV DNA of greater than 10^5 copies/mL (approximately 10^4 IU/mL).[12]

HBsAg-negative with anti-HBc positive

These are patients with resolved HBV infection who may also present a risk for reactivation when receiving immunosuppressive therapy, especially including a regimen containing an anti-CD20 (eg, rituximab)[13] or from hematopoietic stem cell transplantation with high predictors of HBV reactivation that include age of at least 50 years (P=.004, hazard ratio[HR] = 8.2) and chronic graft-versus-host disease (P=.010, HR = 5.3).[14]

Of note, based on available data, it is unclear if anti-HBs is protective against HBV reactivation.[15] However, it does appear that patients with detectable anti-HBs have a lower risk of reactivation.[15,16] A prospective study from Taiwan on chemotherapy-induced HBV reactivation in lymphoma patients with resolved HBV infection had noted that HBV reactivation occurred in 9 of 116 (7.8%) patients with positive anti-HBs, and in 8 of 34 (23.5%) patients with negative anti-HBs.[15] Another prospective study from Taiwan also found that quantification of anti-HBc and anti-HBs may help predict HBV reactivation risk in patients with lymphoma; patients with both high anti-HBc ($\geq$6.41 IU/mL) and low anti-HBs (<56.48 mIU/mL) at baseline had higher risk of reactivation (HR = 17.29; P < .001).[16]

Types of Immunosuppressive Therapy

Anti-CD20 agents (eg, rituximab and ofatumumab)

Anti-CD20 agents (eg, rituximab and ofatumumab) are B cell-depleting agents used to treat hematologic malignancies. Rituximab is a CD20-directed cytolytic monoclonal antibody indicated for the treatment of various conditions, including non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), and rheumatoid arthritis (RA) in combination with methotrexate in adult patients with moderately to severely active RA who have inadequate response to one or more TNF antagonist therapies, and granulomatosis with polyangiitis (GPA) (Wegener granulomatosis) and microscopic polyangiitis (MPA), in adult patients in combination with glucocorticoids.[17] Ofatumumab is indicated in combination with chlorambucil, for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate, recurrent or progressive CLL, or patients with CLL refractory to fludarabine.[18] According to an US Food and Drug Administration (US-FDA) warning,

rituximab and ofatumumab are associated with increased risk of HBV reactivation in patients with HBsAg-positive and/or anti-HBc positive serologic status. The incidence of HBV reactivation following rituximab use has ranged from 3% to 55%.[19] Risk factors that are associated with high probability of HBV reactivation include HBsAg-positivity with active HBV replication (positive HBV DNA), male sex, HBeAg positivity, lack of anti-HBs, anthracycline/steroid use, younger age, and pre-existing hepatic biochemical test abnormalities.[19–21] The overall mortality rate from reactivation is reported to be as high as 30% to 60%.[20,22] A recent study from Japan in HBsAg-negative, anti-HBc positive patients receiving obinutuzumab or rituximab-containing immunochemotherapy (n = 326) (phase 3 GOYA and GALLIUM studies) noted HBV reactivation in around 8.2% of cases, occurring at a median of 125 days (IQR 85-331) after the first dose.[23] In 232 patients without prophylactic NA, 10.8% had HBV reactivation, while in 94 patients with prophylactic NA use, 2.1% had HBV reactivation. Prophylactic NA was significantly associated with a reduced risk of HBV reactivation (adjusted HR = 0.09; 95% confidence interval [CI] 0.02-0.41; *P*=.0018).[23]

Anthracyclines (eg, doxorubicin and epirubicin)

Anthracycline-containing chemotherapy regimens are commonly used in treatment for breast cancer, ovarian cancer, lymphoma, and Kaposi sarcoma.[24] This drug class has been associated with a significant risk of HBV reactivation in chronic hepatitis B.[3] The mechanism is believed to be associated with regulatory factor X box 1 gene (RFX1) expression[25] and the activation of ataxia-telangiectasia mutated (ATM), ATM-, and RAD3-related (ATR) transcription.[26] An increasing trend for surveillance and HBV prophylaxis started after Yeo W and colleagues demonstrated HBV reactivation risk in HBsAg-positive breast cancer patients (n = 41) receiving cytotoxic chemotherapy (anthracycline-containing regimens were also included).[27] Forty-one percent developed HBV reactivation, and 71% of the patients who developed reactivation encountered premature termination of chemotherapy.[27] Lamivudine prophylaxis in HBV carrier breast cancer patients receiving adjuvant chemotherapy (n = 165) (80% anthracycline-containing regimens) was associated with significantly lower incidence of hepatotoxicity than in those who were not on prophylaxis (2.7 vs 14.1%, *P*=.011) and with fewer premature terminations of planned adjuvant chemotherapy (0 vs 10.9%, *P*=.004).[28] Accordingly, the American Gastroenterological Association (AGA) guideline recommends antiviral prophylaxis for chronic hepatitis B patients treated with anthracycline derivatives as they are deemed to be at high risk for HBV reactivation.[3,29]

Glucocorticoids

Corticosteroids enhance HBV replication by 2 mechanisms: depressed cytotoxic T-cell function and direct stimulation of HBV genomic sequence.[3] Once glucocorticoids are administered, HBV replication tends to increase, while serum aminotransferase tends to decline.[30] Subsequently when glucocorticoids are withdrawn, HBV replication declines (presumably because of immune system rebound), while serum aminotransferase increases (often peaking at around 4 to 6 weeks after withdrawal).[30,31] In HBsAg-positive individuals receiving corticosteroids, there is evidence of HBV reactivation in both moderate-to-high dose and rapidly tapered-to-prolonged regimens, but reactivation occurs less in patients receiving low-dose regimens (prednisone < 10 mg/d) even after prolonged use.[3,29] As such, short periods of corticosteroid use of less than 1 week regardless of dosage were believed to present a low risk for HBV reactivation; however, a recent study from Hong Kong to evaluate an impact of dose and duration of corticosteroid on the risk of hepatitis flare in patients

with chronic hepatitis B (5254 chronic hepatitis B patients)[32] had shown that peak daily dose of greater than 40 mg compared with less than 20 mg prednisolone equivalents (adjusted HR = 1.64, $P<.001$) was an independent risk factor of hepatitis flare. Risk of hepatitis flare started to increase in those receiving corticosteroid of peak daily dose greater than 40 mg prednisolone equivalents even for less than 7 days (adjusted HR = 1.55, $P=.026$); the risk further increased with increasing duration of use for 7 to 28 days and greater than 28 days (adjusted HR = 1.90 and 1.64, $P<.001$). Thus, short courses of high-dose corticosteroid may also increase the risk of HBV flare in chronic hepatitis B patients, and thus, starting antiviral prophylaxis in this patient would be a consideration, although one would have to take into consideration the cost/benefit ratio of such an intervention.[32] A more recent study from the same group (n = 12,997) also reported that HBsAg-negative/anti-HBc positive individuals who received high peak daily doses of corticosteroids had an increased risk of hepatitis flare, but not HBsAg seroreversion (patients with anti-HBc positive only had 1-year incidence risk of HBsAg seroreversion of 1.8%), and liver failure rate was low, with no deaths identified.[33] Thus, HBV prophylaxis in this group would not appear to be cost -effective.

Tumor necrosis factor-α inhibitors (eg, infliximab, etanercept, adalimumab, certolizumab, and golimumab)

TNF-α inhibitors are also associated with HBV reactivation when used in patients with Crohn disease, RA, and psoriasis.[34–36] Patients who are HBsAg-positive may have risk of reactivation of around 1% to 10%. However, reactivation risk is less common in HBsAg-negative, anti-HBc positive patients (1%).[3] Recent systematic review and meta-analysis to assess the incidence of HBV reactivation among patients treated with anti-TNF-α estimated a pooled incidence of HBV reactivation of 4.2% (95% CI 1.4%–8.2%). The pooled incidence of reactivation was 3.0% (95% CI 0.6%–7.2%) for patients with occult infection compared to 15.4% (95%CI 1.2%–41.2%) in those with overt infection. The incidence of reactivation was 3.9% for etanercept and 4.6% for adalimumab.[37] In contrast, in patients with rheumatologic conditions with previously resolved HBV infection (HBsAg-negative, anti-HBc positive), long-term biologic therapy (n = 146/179 patients with anti-TNF-α) was not associated with HBV reactivation, suggesting that prophylaxis is not indicated in those on anti-TNFs when the patients are anti-HBc alone positive.[38] A large retrospective study (n = 8887) in patients on long-term treatment with TNF antagonists for autoimmune diseases found HBV reactivation in 39% of patients who were HBsAg-positive before therapy, but not in any patients who were HBsAg-negative/anti-HBc positive before therapy, indicating that HBsAg-positive patients should receive prophylactic antiviral therapy, but not HBsAg-negative/anti-HBc positive patients.[39] Another study in resolved HBV infection (HBsAg-negative, anti-HBc positive, HBV DNA negative) with RA (n = 152) treated with biological disease-modifying antirheumatic drugs (bDMARDs) found reactivation rate around 4.6% and that the absence of anti-HBs may be a risk factor for HBV reactivation in resolved HBV patients.[40] It is important to appreciate that in the net aggregate, the risk of reactivation in those who are HBsAg-negative/anti-HBc positive while on anti-TNFs is negligibly low to none, and thus HBV prophylaxis is not indicated in such patients while they are monitored for hepatic biochemical flare on therapy.

Cytokine inhibitors, monoclonal antibodies, and integrin inhibitors (eg, abatacept, ustekinumab, mogamulizumab, natalizumab, and vedolizumab)

Abatacept is a drug indicated for the treatment of moderate-to-severe RA. It is a fusion receptor protein that is fused to the extracellular domain of CTLA-4 and

prevents T cell activation by binding to CD80 and CD86 molecules.[41] HBV reactivation was reported in a patient with RA and with HBsAg-negative and anti-HBc positive state and treated with abatacept. After 2 years of treatment, HBV DNA levels became detectable and with abnormal hepatic biochemical tests, at which time the drug was stopped and lamivudine treatment was introduced. After 1 month of lamivudine, HBV DNA became undetectable and with normalized hepatic biochemical profile.[42]

Belatacept, an example of another fusion protein indicated for the prevention of acute rejection after kidney transplant (KT) in adult patients, has also been reported to cause HBV reactivation in a HBsAg-negative/anti-HBc positive/anti-HBs positive patient who underwent KT for HIV-associated nephropathy (HIVAN) and after 2 years of belatacept treatment. However, after entecavir initiation, HBV DNA became undetectable, and there was a favorable outcome.[43]

Ustekinumab is a human interleukin-12 and -23 antagonist indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis, active psoriatic arthritis, and moderate-to-severe active Crohn disease who have failed or were intolerant to treatment with immunomodulators or corticosteroids, or intolerant to treatment with 1 or more TNF blockers.[44] A study from Taiwan using ustekinumab in the treatment of patients with psoriasis and concurrent hepatitis B (14 patients) found few cases of HBV reactivation in HBsAg-positive patients. Among HBsAg-positive patients, 2 of 7 patients (29%) who did not receive HBV prophylaxis experienced reactivation (one was an inactive carrier, the other had chronic hepatitis B and was HBeAg-negative). No reactivation was found in HBsAg-negative/anti-HBc positive patients. No significant increase in aminotransferase levels were observed in those with reactivation.[45] Another prospective study from Taiwan included 93 psoriasis patients receiving ustekinumab (54 inactive HBV carriers, resolved HBV infection, or isolated anti-HBc positivity); only 3 patients experienced HBV reactivation, and none had liver failure.[46] Although there is paucity of data, it is estimated that ustekinumab-associated risk of reactivation, at most, is at the lower end of moderate-risk category (1%–10%).[3]

A case report from Japan noted fatal HBV reactivation in a HBsAg-positive patient with detectable HBV DNA and adult T-cell leukemia-lymphoma (ATL) receiving the anti-CC chemokine receptor 4 (CCR4) monoclonal antibody, mogamulizumab. Despite concomitant entecavir treatment with mogamulizumab, HBV reactivation occurred and progressed into liver failure.[47]

Experience in HBV-infected patients has thus far not been reported with natalizumab and vedolizumab.[3]

Tyrosine kinase inhibitors (eg, imatinib, sunitinib, gefitinib, erlotinib)

Tyrosine kinase inhibitors (TKIs) are commonly used in the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumor (GIST). Imatinib and nilotinib are reportedly associated with moderate risk for HBV reactivation in chronic hepatitis B patients.[48,49] A large single-center retrospective study evaluating the incidence of HBV reactivation in CML patients who were HBsAg-positive and treated with TKIs (n = 1817, HBsAg-positive 4.2%) found a reactivation rate of 26% in patients without antiviral prophylaxis. This would strongly support routine screening for HBV serologic status prior to initiation of TKI therapy and following with antiviral prophylaxis in HBsAg-positive patients receiving TKIs.[50] Another multicenter retrospective study to evaluate HBV reactivation in CML patients receiving TKIs (n = 702, HBsAg-positive 6.1%) found an HBV reactivation rate of 34.9% in HBsAg-positive patients without antiviral prophylaxis. Median time to HBV reactivation was 9.3 months (range 2.3–

68.8 months). Nonuse of prophylactic strategy and HBV DNA levels at diagnosis were significantly associated with HBV reactivation (P=.011 and P=.036, respectively). This study also suggested the importance of antiviral prophylaxis to prevent HBV reactivation during TKI treatment.[51]

Immune checkpoint inhibitors

Immune checkpoint inhibitors target key regulators of immune system. Programmed cell death 1 (PD-1) is a transmembrane protein expressed on T-cells, B-cells, and NK cells. PD-1 is an inhibitory molecule that binds to programmed death-ligand 1 or 2 (PD-L1 or PD-L2); PD-L1 is usually expressed on many tumor cells. The binding between PD-1 and PD-L1/2 on the tumor cells can inhibit apoptosis of the tumor cells that the tumors use as an escape mechanism. PD-1 and PD-L1 inhibitors are immunotherapies that were developed in order to prevent this escape mechanism of tumor cells and facilitate restoration of T-cells' immune function. Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is implicated as a negative regulator of T-cell activation, and inhibition of CTLA-4 can lead to T-cells activation and immune surveillance of cancers. Stimulating immune systems may lead to immune-related adverse events, including flare of viral hepatitis. There are few case reports on HBV reactivation related to immune checkpoint inhibitors (**Table 1**).

Programmed cell death protein-1 inhibitors

Nivolumab There is a case report on HBV reactivation after nivolumab treatment in a patient with known human immunodeficiency virus (HIV) infection who was HBsAg-negative, anti-HBc positive, and HBV DNA negative. He was on antiretroviral therapy with dolutegravir and abacavir and with undetectable HIV viral load. He experienced HBV reactivation (HBsAg-positive seroreversion with high HBV DNA) while on nivolumab treatment for stage IIIa poorly differentiated carcinoma of the lung. The patient was then switched from abacavir to tenofovir disoproxil fumarate (TDF), and finally HBV DNA decreased while hepatic biochemical profile returned to normal.[52] A pilot study using nivolumab in virally suppressed chronic HBV patients evaluating the hypothesis that increasing T-cell activity may provide durable control of HBV infection found that in HBeAg-negative patients who were virally suppressed by prior antiviral agents, adding nivolumab was well-tolerated and led to HBsAg decline in most patients.[53]

Table 1
Immunotherapeutic agents with reported cases of hepatitis B virus reactivation

Immune Checkpoint Inhibitors	HBsAg Positive/Anti-HBc Positive	HBsAg Negative/Anti-HBc Positive
PD-1 inhibitors		
• Nivolumab	✓[55]	✓[52]
• Pembrolizumab	A report with unknown baseline HBV status[54]	A report with unknown baseline HBV status[54]
PD-1 inhibitors		
• Atezolizumab, Avelumab, Durvalumab	Not available	Not available
CTLA-4 inhibitors		
• Ipilimumab	✓[55]	Not available

Pembrolizumab There is a case report of a patient with stage IV poorly differentiated adenocarcinoma of the lung (no hepatitis panel at baseline) who started on pembrolizumab; subsequently there was HBV reactivation attributed to the drug (newly elevated transaminases and HBV DNA, negative autoimmune profile). After the initiation of TDF, transaminases returned to normal range within 10 weeks, and HBV DNA became undetectable. Therefore, immunotherapy may possibly lead to HBV reactivation, and screening for chronic hepatitis B before initiating therapy is a justified strategy.[54]

Programmed death-ligand 1 inhibitors: atezolizumab, avelumab, and durvalumab Atezolizumab is the first drug in this class that received initial FDA approval for metastatic urothelial carcinoma and has since been approved for metastatic nonsmall cell lung cancer (NSCLC). Avelumab is approved for Merkel cell carcinoma, while durvalumab is approved for urothelial carcinoma and stage III NSCLC. Currently there are no reported cases of HBV reactivation from these agents. Of note is that clinical trials using these immunotherapeutic agents have usually excluded patients with chronic hepatitis B infection (HBsAg-positive). More data are needed, particularly in those with anti-HBc alone positive status, before any conclusions on the risk of HBV reactivation from this drug class.

Cytotoxic T-lymphocyte antigen-4 inhibitors

Ipilimumab A patient with malignant melanoma and HBsAg-positive state (normal ALT, no baseline HBV DNA) was treated with ipilimumab and was then switched to nivolumab and was believed to have HBV reactivation after treatment (ALT elevation, anti-HBc IgM positive, increased HBV DNA with the negativity of all autoimmune markers). The patient started treatment with TDF, and also remained on nivolumab treatment. Eventually, HBV DNA levels significantly decreased after 2 months of TDF.[55] A retrospective study from China to determine the safety of immune checkpoint inhibitors in melanoma patients receiving ipilimumab or pembrolizumab (n = 23) noted hepatic biochemical test abnormalities from immune-related adverse events in 22%; most toxicities were mild and easily managed. No toxicity was observed in 11 patients with previous HBV infection (antiviral drug was started in patients who were HBsAg-positive with or without detectable HBV DNA before receiving ipilimumab or pembrolizumab).[56]

Traditional immunosuppression

There is no convincing evidence of HBV reactivation from azathioprine or 6-mercaptopurine (active metabolite of azathioprine) when used as single agents. The AGA guideline assessment is that this is a low-risk group for reactivation (<1% risk) in both HBsAg-positive and HBsAg-negative, anti-HBc positive patients.[3]

Data from a prospective study from Japan evaluated reactivation of HBV in patients with RA who received immunosuppressive therapy (n = 50). HBV reactivation occurred in 2 out of 5 patients who were HBsAg-positive and in 1 out of 45 patients without HBsAg. Screening for HBV reactivation and prophylactic therapy with entecavir were effective in preventing HBV-associated hepatic failure in patients who were HBsAg-positive and in those who were anti-HBc positive in the background of receiving immunosuppression.[57] On the contrary, in a cross-sectional study evaluating long-term use of methotrexate in RA patients (n=173; 1 patient [0.58%] who was HBsAg-positive, 65 patients [37.6%] had anti-HBc immunoglobulin G [IgG] alone positive serology), none had HBV reactivation during 9.9 years of methotrexate treatment.[58] Because there are small numbers of case reports of HBV reactivation from methotrexate monotherapy (predominantly in HBsAg-positive patients), the AGA

Guideline assessed methotrexate use to present a low-risk group (<1% risk) for reactivation.[3]

Of note, apart from HBV reactivation, the differential diagnosis of patients receiving immunosuppressive therapy with increased aminotransferase levels should include drug-induced hepatotoxicity, infection by other viruses, and other causes of liver disease. Patients who are suspected to have drug-induced hepatotoxicity would have ALT elevation without an elevation of HBV DNA levels. Other viral-induced hepatitis (such as hepatitis A, C, D, E, cytomegalovirus, and herpes viruses) should be considered, and investigations should be sent, particularly in those who are immunocompromised. Further, other causes of liver disease such as ischemic hepatitis, hepatic veno-occlusive disease, and tumor infiltration should also be considered in the differential diagnosis.

Direct-acting antivirals

DAAs are not considered as immunosuppressive agents; however, there are some reports of HBV reactivation in HCV-infected patients treated with DAAs. The FDA reported 29 cases of HBV reactivation in patients receiving DAAs from 2013 to 2016, and this raised concern, particularly in patients with HBV-HCV coinfection treated with DAAs.[59] A report from a clinical trial of ledipasvir-sofosbuvir treatment in HCV-infected patients in Taiwan and Korea (103 of 173 patients [60%] with previous HBV infection [anti-HBc positive]) noted that none had evidence of HBV reactivation.[60] Recent systematic review and meta-analysis of HBV reactivation in HBV-HCV coinfected patients treated with antiviral agents demonstrated that among HCV patients with overt HBV (HBsAg-positive) (n = 779), the pooled HBV reactivation rate was 14.1%; HBV reactivation was reported to occur much earlier in those treated with DAAs (4–12 weeks during treatment) than in those treated with interferon (most at the end of treatment and some during follow-up).[61] However, HBV reactivation occurred less frequently in HCV patients with occult HBV infection (HBsAg-negative with positive HBV DNA), and sustained virologic response (SVR) was not affected by HBV reactivation.[61] An interesting study to evaluate potential risk of HBV reactivation in patients with resolved HBV infection (HBsAg-negative, undetectable HBV DNA, anti-HBc positive) undergoing DAA for HCV treatment found that anti-HBs titer was significantly decreased early on after DAA treatment, and patients with negative anti-HBs or very low titer of anti-HBs at baseline were at risk of transient detectable HBV DNA during HCV treatment.[62] As such, EASL Guideline recommends that patients who are HBsAg-positive and undergo DAA therapy be considered for concomitant NA prophylaxis until 12 weeks after DAA, and patients with HBsAg-negative/anti-HBc positive serology and undergoing DAA be monitored for HBV reactivation.[5]

Risk Categorization

HBV reactivation risk is categorized into high risk (>10% reactivation risk), moderate risk (1%–10% reactivation risk), and low risk (<1% reactivation risk) (**Table 2**).[3,29] Recommended HBV prophylaxis and treatment algorithm for chemotherapy candidates are described in (**Fig. 2**).

TREATMENT AND PROGNOSIS OF HEPATITIS B VIRUS REACTIVATION

Immunosuppressed patients who develops HBV reactivation (with or without hepatitis flare) should be treated with nucleoside/nucleotide analogue (NA) as early as possible regardless of ALT levels. Severe hepatitis and hepatic failure can develop in 25% to 50% of patients with HBV reactivation.[63] Tenofovir or entecavir should be the

Table 2
Hepatitis B virus reactivation risk according to Hepatitis B virus status and immunosuppressive agents and guideline recommendation for prevention of Hepatitis B virus reactivation

Risk Group	HBsAg-Positive/Anti-HBc Positive (% Risk)	HBsAg-Negative/Anti-HBc Positive (% Risk)
High risk (>10%)	• B cell-depleting agents such as rituximab and ofatumumab (30%–60%) • Anthracycline derivatives such as doxorubicin and epirubicin (15%–30%) • Corticosteroid therapy for $\geq$ 4 weeks (moderate-high dose[a]) (>10%)	• B cell-depleting agents such as rituximab and ofatumumab (>10%)
Recommendation	Antiviral prophylaxis regardless of HBV DNA levels and anti-HBs status, and prophylaxis should be continued to at least 18 months in B cell-depleting agents until after cessation of immunosuppression.	
Moderate risk (1%–10%)	• TNF-α inhibitors: etanercept, adalimumab, certolizumab, infliximab (1%–10%) • Other cytokine inhibitors and integrin inhibitors: abatacept, ustekinumab, natalizumab, vedolizumab (1%–10%) • Tyrosine kinase inhibitors: imatinib, nilotinib (1%–10%) • Corticosteroid therapy for $\geq$ 4 weeks (low dose) (1%–10%)	• TNF-α inhibitors: etanercept, adalimumab, certolizumab, infliximab (1%) • Other cytokine inhibitors and integrin inhibitors: abatacept, ustekinumab, natalizumab, vedolizumab (1%) • Tyrosine kinase inhibitors: imatinib, nilotinib (1%) • Corticosteroid therapy for $\geq$ 4 weeks (moderate-high dose) (1%–10%) • Anthracycline derivatives: doxorubicin and epirubicin (1%–10%)
Recommendation	Antiviral prophylaxis regardless of HBV DNA levels.	Monitoring of HBsAg, HBV DNA and ALT 3 months. Pre-emptive therapy when HBsAg seroreversion or detectable HBV DNA noted, regardless of ALT levels.
Low risk (<1%)	• Traditional immunosuppressive agents: azathioprine, 6-mercaptopurine, methotrexate • Intra-articular corticosteroids • Corticosteroid therapy for $\leq$ 1 week	• Traditional immunosuppressive agents: azathioprine, 6-mercaptopurine, methotrexate • Intra-articular corticosteroids • Corticosteroid therapy for $\leq$ 1 week • Corticosteroid therapy for $\geq$ 4 weeks (low dose)

(*continued on next page*)

Table 2
(*continued*)

Risk Group	HBsAg-Positive/Anti-HBc Positive (% Risk)	HBsAg-Negative/Anti-HBc Positive (% Risk)
Recommendation	In HBsAg-positive/anti-HBc positive patients, monitor HBV DNA levels and ALT every 3–6 months as routine practice. Viral suppressive therapy is recommended at baseline or during follow-up as per guidelines based on HBV DNA and ALT levels. In HBsAg-negative/anti-HBc positive patients, if biochemical flare noted, work-up for HBV reactivation is to be initiated, and treatment is indicated if HBsAg seroreversion or elevated HBV DNA noted.	

Abbreviations: ALT, alanine transaminase; DNA, deoxyribonucleic acid; HBV, hepatitis B virus; TNF, tumor necrosis factor.
[a] Corticosteroid: prednisone (or equivalent); low dose (<10 mg), moderate dose (10–20 mg), high dose (>20 mg).
Data from Refs.[2,3,5,29]

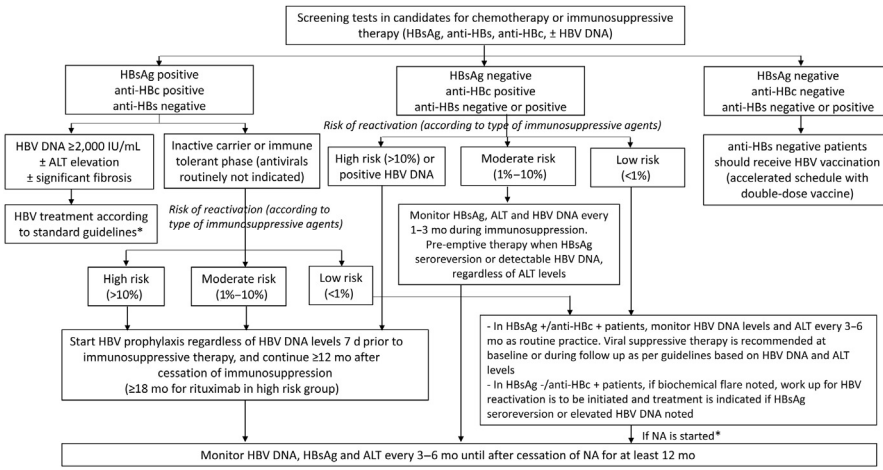

Fig. 2. Recommended HBV prophylaxis, follow up, and treatment algorithm (authors' modifications) for chemotherapy candidates. * High resistant barrier NA (e.g. entecavir, TDF, TAF) should be preferred over low-barrier NA (e.g. lamivudine). HBV, Hepatitis B virus; DNA, Deoxyribonucleic acid; ALT, Alanine transaminase; NA, Nucleoside/nucleotide analogue; TDF, Tenofovir disoproxil fumarate; TAF, Tenofovir alafenamide. (*Data from* Refs.[2,5,66])

treatment of choice once diagnosed with HBV reactivation, because lamivudine (LAM) may be associated with greater risk of drug resistance. Tenofovir is preferred rather than entecavir in patients who have history of prior LAM therapy. Data on efficacy of antiviral agents in reducing morbidity and mortality in patients with HBV reactivation are insufficient, and there are no trials that allow direct comparison of the effectiveness between third-generation antiviral drugs and earlier-generation therapies in patients with HBV reactivation during immunosuppressive therapy.[29] However, there is indirect evidence from randomized controlled trials (RCTs) noting lower drug failure rates and lower viral resistance from third-generation drugs compared with LAM in nonimmunosuppressed patients. Accordingly, the AGA Guideline recommends antiviral drugs with a high barrier to resistance over LAM in patients with HBV reactivation during immunosuppressive therapy.[29]

There are case reports demonstrating clinical improvement after antiviral treatment in patients with HBV flare, especially when early treatment was initiated.[64,65] However, some patients may develop severe flare despite antiviral therapy, which then leads to unnecessary interruption of chemotherapy for the patient's underlying condition, and some may progress to liver failure and with high mortality.[15,64] Thus, initiation of antiviral therapy is essential as early as possible in the HBV reactivation phase and before a clinical flare occurs.

SUMMARY

HBV reactivation in patients with immunosuppressive therapy can result in severe morbidity and mortality. Therefore, testing for HBV serology is suggested in all patients who are candidates for immunosuppressive therapy. High-risk patients for reactivation should be started with antiviral prophylaxis before initiating immunosuppressive regimen. To date, there are many newer agents used in autoimmune and oncologic patients such as biologics and immunotherapies that have been variably reported to lead to HBV reactivation; however, more data are needed in order to estimate their risk for

HBV reactivation and the role on antiviral prophylaxis. Further, when HBV reactivation is recognized during immunosuppressive therapy, prompt initiation of antiviral treatment is essential. While monitoring for resolution during reactivation, some patients may encounter hepatic decompensation, which leads to high morbidity and mortality.

DISCLOSURE

S. Ekpanyapong has nothing to disclose. K.R. Reddy is on the Advisory Board of Gilead, Merck and received grant support from Gilead, BMS, Merck.

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