Review Article

Hepatitis B Reactivation with Novel Agents in Non-Hodgkin's Lymphoma and Prevention Strategies

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Abstract

Hepatitis B virus (HBV) infection remains an endemic disease in most parts of the world despite available prophylactic vaccines. Non-Hodgkin's lymphoma is the most common hematological malignancy, and certain patients undergoing therapy are at increased risk of HBV reactivation. Rituximab, a monoclonal antibody, is well studied in HBV reactivation, but newer agents have been implicated as well. Here, we review novel agents suspected in HBV reactivation and effective strategies to prevent HBV reactivation. Fifteen years of literature were reviewed in order to better understand the reactivation rates of hepatitis B in patients with non-Hodgkin's lymphoma. Anti-CD20 antibodies continue to be the main medications that can lead to HBV reactivation, and HBV reactivation rates have decreased with increased awareness. HBV reactivation is uncommon when using other novel agents. Entecavir and lamivudine remain the agents of choice to prevent HBV reactivation in high risk patients. In conclusion, the immunosuppressive effect of NHL and its therapy provide a pathway for HBV reactivation, especially in patients treated with anti-CD20 antibody. Since many HBV positive patients are often excluded from clinical trials of novel agents in NHL, more aggressive post-market surveillance of new agents, well-designed best practice advisories, and timely case reports are needed to reduce the incidence of HBV reactivation. Lastly, large prospective investigations coupled with well-utilized best practice advisories need to be conducted to understand the impact of more potent novel NHL therapy on HBV reactivation.

Keywords: Hepatitis B virus; HBV reactivation; Non-Hodgkin's lymphoma; Rituximab; Anti-CD20 antibody; Best practice advisories.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ACIP, Advisory Committee on Immunization Practices; AGA, American Gastroenterological Association; ALT, alanine aminotransferase; anti-HBc, HBV core antibody; APASL, Asian-Pacific Association for the Study of the Liver; ASCO, American Society of Clinical Oncology; BTK, Bruton's kinase; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CLL, chronic lymphocytic leukemia; CPOE, computerized physician order entry; DLBCL, diffuse large B-cell lymphoma; EASL, European Association for the Study of Liver Disease; FDA, Food and Drug Administration; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HR, hazard ratio; NCCN, National Comprehensive Cancer Network; NHL, non-Hodgkin's lymphoma; OR, odds ratio; PI3Kδ, phosphatidylinositol 3-kinase delta inhibitors; RR, risk ratio.

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Introduction

Hepatitis B virus (HBV) is a DNA virus that resides exclusively in human reservoirs and is transmitted through body fluids. The infective form remains prevalent globally despite available prophylactic immunization. Endemicity is present in Asia, Africa, the Middle East, parts of Eastern Europe, and South America, and up to 400 million people are chronically infected.[1] Although the United States is non-endemic for HBV, up to 1 million people have chronic HBV, and the risk of acute infection persists. Estimated age-adjusted prevalence in the US is 4.7% for core antibody (anti-HBc) and 0.27% for surface antigen (HBsAg).[2] In addition, HBsAg prevalence rate is thought to be 0.75% in those who receive immunosuppressive therapy and is highest among those with co-infection of the human immunodeficiency virus (HIV).[3] Vaccination efforts have contributed to the decrease in anti-HBc prevalence rate from 1.9% in 1999 to 0.6% in 2006 for those aged 6 to 19 years. Among adults older than 50 years of age, the prevalence rate decreased marginally from 7.7% in 1999 to 7.2% in 2006.[2] Moreover, HBV has been implicated in the incidence of non-Hodgkin's lymphoma (NHL),[4–7] which increases with advancing age for all race and gender subgroups.[8,9]

NHL is one of the most prevalent hematological malignancies globally and contributed to over 190,000 deaths in 2008.[10] NHL is also common in the US, where almost 20,000 patients will die from this disease each year, despite available chemotherapy.[11] Cytotoxic chemotherapy, which is highly immunosuppressive, has been linked to reactivation of HBV infection in seropositive and seronegative cases (undetectable anti-HBc and anti-HB surface antigens).[12–18] The mechanisms underlying HBV reactivation in NHL therapy include the active roles of acquired viral genomic mutations, chronic viral infection, immunosuppression, and exaggerated immune response following cessation of chemotherapy.[7,19–21] The definition of HBV reactivation can vary, but it must include a 10-fold rise in HBV DNA in a patient with past or latent HBV infection and/or levels > 10,000 copies/mL (4 log copies/mL).[7,22,23] A serum transaminase level three times the upper limit of normal or alanine aminotransferase (ALT) over 100 IU/L[7,19,24] in a patient with known HBV seropositivity may also be considered HBV reactivation.[22] HBV reactivation is important in patients treated for NHL, as it increases the likelihood of stopping therapy, may lead to liver failure, and can increase the risk of mortality.[24–26]

Chemo-immunotherapy induced HBV reactivation can be preventable if detected early. A vast majority of the NHL literature on HBV reactivation has focused on rituximab. With

the advent of newer immunotherapy agents, less is understood about the incidence and prevention of HBV reactivation. This review aims to summarize recent data on the reactivation of HBV with novel agents in NHL therapy and effective methods to prevent HBV reactivation in these patients.

Review Criteria

Relevant articles for this review were identified by searching PubMed, Embase, Ovid Medline, and Scopus using the following terms, alone and in combination: "Hepatitis B reactivation", "novel agents", "Non-Hodgkin's lymphoma", "immunosuppression", "immunocompromised host", "immunosuppressive agents", "hepatitis B", "hepatitis B virus", "HBV", "reactivation", "management" and "prevention". Full text articles of all selected studies were retrieved, and if a paper was selected for inclusion, the bibliographic references were scrutinized to identify additional relevant studies. The period of the search was restricted to a 15 year period to limit the search to novel agents in the treatment of NHL (2000–2015).

Hepatitis B reactivation in NHL therapy

Hepatitis B reactivation in susceptible individuals has been linked with chemotherapy through amplification of viral replication and immune function recovery following chemotherapy induced-immunosuppression.[20,21,26,27] Reactivation is also attributable to profound immunosuppression induced by lymphocytotoxic monoclonal antibodies[27,28]. In the largest study (10,729 patients) on HBV reactivation in patients receiving chemotherapy, predictors included male gender, race (Asian, Black), rituximab use, and presence of hepatitis B risk factors. The risk of reactivation was high in individuals with anti-HBc or anti-HBs and even higher in those with seropositive HBsAg.[28]

The severity of chemotherapy-induced HBV reactivation in NHL has been categorized as *low risk* with azathioprine and methotrexate *moderate risk* with commonly used cytotoxic chemotherapy, such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), high-dose corticosteroids (prednisolone > 20 mg), and fludarabine. Patients who received anti-CD20 monoclonal antibodies, such as rituximab, were at the *highest risk* for HBV reactivation.[29,30]

Among the monoclonal anti-CD20 antibodies, rituximab-associated HBV reactivation has been the most commonly reported event.[7,20,26] Two meta-analyses have demonstrated more than a five-fold increased risk of HBV reactivation with rituximab chemotherapy based on HBcAb serum level (risk ratio (RR) of 5.52, 95% confidence interval (CI) 2.05–14.85, $p < 0.001$)[12] and odds ratio (OR) of 5.73, 95% CI 2.01–16.33; $Z = 3.33$, $p < 0.001$.[13] The first published meta-analysis reported a 55% liver failure rate,[13] while another reported that 43% of participants developed adverse hepatic-related events.[7] In addition, early studies on HBV reactivation rates from rituximab combined chemotherapy reported rates up to 56%, especially in HBV endemic regions.[22,31,32] However, more recent studies have reported lower reactivation rates (< 2.7%) and lower mortality rates,[14,15,33,34] even in high prevalent regions. This discrepancy may be explained by improved defined criteria and awareness of HBV reactivation.[14,35] In addition, reactivation rates may be reduced due to early diagnosis and increased knowledge of the management of chronic hepatitis B and the associated HBV reactivation in oncologic therapy.[30,36]

In addition to rituximab, ofatumumab was included in the Food and Drug Administration (FDA) reactivation warning 4 years after its approval in 2009.[24,37] A search of the FDA Adverse Event Reporting System database yielded 32 cases of rituximab-associated HBV reactivation and one case associated with ofatumumab (http://www.fda.gov/Drugs/DrugSafety/ucm366406.htm). Data in support of ofatumumab in HBV reactivation is still sparse, and a recent European Phase IV trial in advanced chronic lymphocytic leukemia (CLL) categorically reported no case of HBV reactivation in patients treated with ofatumumab.[38] Obinutuzumab, recently approved by the FDA for CLL in 2013, has a black box warning for HBV reactivation. However, no published data exist to support this report.[39,40] A search from the FDA Adverse Event Reporting System database did not yield any data to support this report (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111085.htm#O; http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm373263.htm). A Japanese Phase I study of obinutuzumab in refractory B-cell NHL excluded patients with seropositive HBV status,[41] thereby precluding the usefulness of identifying adverse events through clinical trials.[42]

Although there is no FDA warning yet, few case reports of HBV reactivation have been reported with other monoclonal agents used to treat NHL. Alemtuzumab (anti-CD52) therapy, mainly used in CLL, increased HBV DNA level to 7.3 log copies/mL in one patient,[43] while mogamulizumab in adult T-cell leukemia-lymphoma increased HBV DNA to a range of 2.1 to 9.1 log copies/mL during therapy for four different patients.[44,45] Other novel agents, such as the small molecule inhibitors [Bruton's kinase (BTK) inhibitors and phosphatidylinositol 3-kinase delta inhibitors (PI3Kδ)], have been linked to the occurrence of autoimmune hepatitis, but it is unclear if HBV reactivation can occur.[20,46,47] Idelalisib, a potent, small-molecule inhibitor of PI3Kδ has demonstrated favorable treatment response in patients with indolent NHL who are refractory to rituximab and other previous chemotherapy.[48,49] Asymptomatic elevated transaminase levels was reported in 47%–48% of such patients, and 13%–25% had grade 3 elevations, although most cases resolved following dose reduction.[48,49] It is unclear if these are negligible laboratory abnormalities or an indication that patients with HBV risk factors treated with PI3Kδ inhibitors may develop overt HBV reactivation.[50,51] Clinical trials of these agents in combination with rituximab are underway, and the outlook in regard to HBV reactivation is guarded until more post-market surveillance data emerge.[42,52] Table 1 summarizes confirmed and suspected novel agents with HBV reactivation sequela.

Prevention Strategies

HBV screening, best practice advisories, and HBV vaccination

Screening for both HBV reactivation and HBV risk factors is the first step in preventing reactivation in patients undergoing therapy for NHL.[28,30,53] Organizational policies on screening have significantly increased screening rates over the last 6 years from 20% to 90% at large oncology centers in the US.[24,28] Policies on screening modalities are also gradually shifting from a targeted approach to a universal approach.

A targeted screening approach for patients undergoing chemo-immunotherapy on the basis of HBV risk status is limited since chronic hepatitis may be asymptomatic, and

Table 1. Novel agents and HBV reactivation status

[a]Agent	Target	Indication	HBV reactivation Status	Data source	References
Monoclonal antibodies					
Rituximab*	CD20	Relapsed or refractory indolent lymphoma maintenance therapy in B-cell NHL	FDA boxed warning	FDA AERS	13–15,30,31,37
Ofatumumab*	CD20	Relapsed/refractory CLL	FDA boxed warning	FDA AERS	37,38
Obinutumumab*	CD20	Rituximab-refractory patients	FDA boxed warning	FDA AERS	39–41
Alemtuzumab§	CD52	Refractory B-CLL	+HBVr but no FDA warning yet	Case reports	27,43
Mogamulizumab§	CC chemokine receptor	Aggressive adult T-cell leukemia-lymphoma (ATL) and peripheral T-cell lymphoma	+HBVr but no FDA warning yet	Case reports	44,45
Small molecule inhibitors					
Ibrutinib§	BTK inhibitors	Low-grade NHL	Immune hepatitis	Clinical trials	46,47
Idelalisib§	PI3Kδ inhibitors	Relapsed/Refractory low-grade NHL	Immune hepatitis/ Transaminitis	Clinical trials	46,47

[a] Agent – Confirmed* and suspected§ agents with HBV reactivation sequela

Abbreviations: B-CLL, B-cell chronic lymphocytic leukemia; BTK, Bruton's kinase; FDA, Food and Drug Administration; FDA AERS, FDA Adverse Event Reporting System; HBV, hepatitis B virus; NHL, non-Hodgkin lymphoma; PI3Kδ, phosphatidylinositol 3-kinase delta inhibitor.

sufficient information may not be elicited during initial patient encounters to adequately assess the risk of HBV infection.[54,55] On the other hand, universal HBV screening for all patients newly diagnosed with cancer who require chemo-immunosuppressive therapy results in a more direct reduction in reactivation rates.[24] In the US, hospital-enforced universal screening policies in some large cancer treatment centers provide evidence that increasing pre-therapy screening and prophylaxis for HBV can result in zero-to-minimal cases of HBV reactivation.[28,53] Currently, the National Comprehensive Cancer Network (NCCN) recommends that all patients receiving an anti-CD20 antibody should be screened for HBV prior to exposure to the agent.[56] Screening should be for both HBsAg and anti-HBc since HBV DNA undetected in serum can persist in tissues[11,56,57] and the antigen may be absent in indolent cases of HBV.[58] Patients who are found to be positive for either should be considered for HBV prophylaxis prior to chemo-immunosuppressive therapy.

According to clinical opinion in the oncologic literature, there is clear consensus on adopting screening to identify patients who are at high risk of HBV and also candidates for anti-CD20 monoclonal antibody. There are differences in opinion regarding the necessity to screen all patients who will receive chemotherapy irrespective of HBV risk status. Guidelines from the American Gastroenterological Association (AGA),[26] the European Association for the Study of Liver Disease (EASL),[59] the American Society of Clinical Oncology (ASCO),[53] and the Asian-Pacific Association for the Study of the Liver (APASL)[60] recommend that low and high risk patients receiving chemotherapy or immunotherapy should be considered for testing and prophylaxis. On the other hand, the NCCN[57] and the American Association for the Study of Liver Diseases (AASLD)[61] suggested excluding from screening, patients with low risk of HBV and candidates for cancer therapy associated with low risk of reactivation, because supporting evidence was insufficient. A tenable explanation for the disparity in screening approach may be consideration given to patients from regions with high HBV prevalence. At this time, clinicians should determine if screening for HBV is needed in each individual patient receiving chemotherapy. In the future, we hope that better data are available to help allocate resources for patients in need of HBV screening prior to chemotherapy.[53]

Improved coordination of primary care and specialist healthcare professional services is required to screen promptly all patients at risk of HBV infection irrespective of negative cancer status. Screening prescription by healthcare professionals to patients, prior to immunosuppressive therapy still needs to be enhanced.[54,55,62] Improved screening rates to prevent HBV reactivation can be achieved with improved data management and alert systems integrated into existing electronic medical records.[55,63] Between 2012 and 2013, a cancer center study showed the role of a best practice advisory (alert system) incorporated in the computerized physician order entry (CPOE) application in increasing HBV screening rates prior to therapy. At the end of the program, the study reported an improved screening rate for patients treated with biologic agents from < 50% to > 85%.[63]

Since prior HBV infection prior HBV infection is a baseline risk factor for HBV reactivation, prevention efforts need to maintain a clear distinction between identifying risk factors for HBV reactivation and for HBV infection.[28,36] Notable risk factors for HBV infection include groups such as healthcare workers, injecting drug users, recipients of blood products or dialysis, household contacts of people with chronic HBV infection, incarcerated persons, people with multiple sex partners, men who have sex with men, and unvaccinated or partially vaccinated travelers to high endemic regions.[36] Low and intermediate endemic countries require catch-up immunization targeted at these high risk groups. In addition, programs that mandate HBV vaccination for entry into schools, colleges, and work-places remain an effective strategy to reduce HBV infection in low-intermediate endemic regions.[36]

The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control (CDC) recommends universal vaccination of individuals, especially male adults, who test positive, since the risk of hepatitis B remains highest in this group.[36] This recommendation is important because adult males have a higher incidence of NHL compared to women of the same age group.[8,9,64] For children, universal vaccination at childbirth with follow-up remains appropriate for high endemic (>8%) regions. On a global scale, newborns who received a birth dose of HBV vaccine increased from 27% to 38% between 2006 and 2014. Birth cohorts who received three doses in 2008 and 2014 increased from 69% to 82%. Although these data indicate that HBV vaccination rates are rising, there is still room for improvement in high endemic areas.[1,65] Since the last two decades, the CDC has recommended routine post-vaccination tests for anti-HBs and annual booster doses for sustained immunity among high risk groups and immunocompromised persons.[66] Therefore, targeted and universal vaccination efforts should not wane, because the risk of exposure to HBV continues to persist.

Reactivation prophylaxis and therapy

HBV seropositive individuals who require chemotherapy or anti-CD20 antibody therapy should be started on antivirals in a timely manner. Globally, lamivudine has been the most utilized nucleos(t)ide analogue for the prevention of HBV reactivation during chemo-immunotherapy.[33,67–70] Prognosis of patients with lamivudine following HBV reactivation remains favorable, despite few cases of viral resistance.[71] Newer nucleos(t)ide are now favored in reactivation management.[71–75] Newer nucleos(t)ide analogues, such as entecavir, adefovir, and tenofovir, have been used because of their lower viral resistance.[27,57] In a notable study, Li and others compared entecavir with lamivudine as prophylaxis for hepatitis B reactivation in lymphoma patients undergoing chemotherapy. The entecavir group exhibited a significantly lower rate of HBV reactivation (0% vs 12.4%, $p = 0.024$) and a lower incidence of aborted chemotherapy compared to the lamivudine group (5.9 vs 20.2%, $p = 0.042$).[74]

The stage of NHL disease is a useful criterion when considering use of nucleos(t)ide analogues. Studies have shown that the efficacy of entecavir is higher than that of lamivudine, especially in advanced disease.[72,76] In advanced diffuse large B-cell lymphoma (DLBCL), Huang and colleagues compared entecavir and lamivudine and demonstrated that there was a lower reactivation rate (6.6% vs 30%; difference, 23.4% [95% CI, 10.2% to 36.6%]; $p = .001$) and premature chemotherapy cessation (1.6% vs 18.3%; difference, 16.7% [95% CI, 6.4% to 27.0%]; $p = .002$) with entecavir compared to lamivudine.[72] Importantly, despite the lower risk of viral resistance with tenofovir, adefovir, and entecavir compared to lamivudine,[77] these newer agents on rare occasions were associated with mild renal dysfunction with long-term use.[20,78,79] Therefore, dosage of these agents needs to be adjusted in renal impairment, and renal function should be assessed at least every 3 months.[57,79]

Another study that explored steroid-free chemotherapy in the prevention of HBV reactivation in NHL reported a lower incidence and severity of reactivation when compared to steroid-containing chemotherapy.[80] Despite the overall survival rate, which was higher in the steroid-containing group, a limitation of this approach may be deciding between survival following rituximab-containing therapy and the risk of HBV reactivation. Finally, more studies are needed to understand the efficacy of antivirals when both rituximab and steroids are used.[81]

Therapeutic intervention for HBV reactivation in aggressive lymphomas/NHL is indicated in instances such as missed HBV status and failed or interrupted prophylactic therapy.[27,82–84] Failure of prophylactic lamivudine may result in withdrawal hepatitis, viral breakthrough, or mortality from liver failure.[85,86] Predictors of lamivudine failure in a study include: elevated baseline HDV DNA titer ($\geq$ 2,000 IU/mL) (hazard ratio [HR], 9.94; $p = 0.0063$) and the use of rituximab (HR, 3.19; $p = 0.027$) for viral breakthrough, while for withdrawal hepatitis, a high baseline HBV DNA titer (HR, 5.90; $p = 0.007$), liver cirrhosis (HR, 10.4; $p = 0.002$), and distant metastasis (HR, 5.14; $P = 0.008$) were independent risk factors.[86] Therapeutic interventions also depend on the presence of secondary liver failure and prognosis of the lymphoma. Newer antivirals may be used where liver failure is absent.[27,75] For patients with HBV reactivation resulting in liver failure, the AGA recommends liver transplantation.[26,75] Favorable outcomes were recorded in patients who underwent liver transplantation and antiviral therapy, having established prior complete remission of disease and a favorable prognosis of the lymphoma type.[75,87]

Based on better outcomes from recent data, recent ASCO and NCCN guidelines on HBV reactivation recommend, when possible, that patients who are HBV positive (HBsAg-positive and/or anti-HBc positive) and require chemo-immunotherapy should be placed on prophylaxis with entecavir for the duration of treatment.[53,61] Other agents, including tenofovir and lamivuidine, can also be used, but there may be more resistance to lamivudine therapy. Newer antiviral medications are readily favored considering the relatively high barrier to viral resistance compared to lamivudine for both prophylactic and therapeutic purposes. The literature suggests that prophylaxis against rituximab associated HBV-reactivation should be extended up to 12 months following oncologic therapy and should be combined with HBV viral load surveillance every 3 months.[30,53,57] Although NCCN warns against lamivudine as a routine prophylactic agent due to risk of viral resistance, AASLD, EASL, ASIF, and APASL recommend lamivudine as a viable prophylactic agent based on its pharmacoeconomic and safety profiles.[59–61,88] Specifically, the AASLD endorses lamivudine when the planned duration of chemotherapy is less than 12 months and entecavir or tenofovir for chemotherapy lasting beyond 12 months.[20,61,89] In addition, the EASL advocates for use of baseline HBV DNA < 2,000 IU/mL for initiating lamivudine while values > 2,000 IU/mL are indications for prescribing entecavir or tenofovir.[59] In addition, the APASL and ASIF recommend lamivudine for

Table 2. Modalities for preventing HBV reactivation

Reactivation Prevention Modality	Key Characteristics		References
	Indication/Advantages	Drawbacks	
Pre-NHL therapy screening			
Targeted screening	Screen NHL patients receiving anti-CD20 antibody with + HBV risk status	Missed cases (asymptomatic HBV infection)	53,61,62
Universal screening	Screen all patients receiving anti-CD20 antibody irrespective of HBV risk status	False HBV positive cases Added cost to therapy	26,59,60,63
Best Practice Advisory (EHR alert system)	Increase HBV screening rates	Implementation cost	56,64
HBV Vaccination			
Catch-up vaccination	Low NHL endemic regions Reduced HBV reactivation rates	Missed cases	36,54,66
Universal vaccination	High endemic regions Reduced HBV reactivation rates	Surveillance cost	1,36,54,66
Reactivation Prophylaxis			
Entecavir	Agent of choice in advanced disease. Least viral resistance	Expensive Renal insufficiency (rare)	61,72,73,74,78
Lamivudine	Most used and studied agent. Cheapest	Withdrawal hepatitis Lamivudine failure (Viral resistance, viral breakthrough)	31,32,33,34,55, 68,71,85,89
Adefovir	Less viral resistance	Expensive Renal dysfunction (rare) Hypophosphatemia (rare)	27,76,80,81
Tenofovir	Least viral resistance	Expensive Renal dysfunction (rare) Hypophosphatemia (rare)	19,27,70,71
Low dose/steroid free chemo-immunotherapy	Reduced incidence of reactivation	Potentially adverse survival outcomes from undertreated NHL disease	83,84
Reactivation Treatment			
Lamivudine	Most used agent globally	Risk of acquired viral resistance	33,59,60,69,70,91
Newer antivirals (Entecavir, Adefovir, Tenofovir)	Lamivudine failure. Liver failure must be absent	Depends on prognosis of lymphoma type	27,53,61,68,77
Liver transplantation	If liver failure is present with HBV reactivation	Depends on cost, disease prognosis and post-transplant sequelae	26,75

BPA- Best Practice Advisory is synonymous with Electronic Health Records (EHR) alert system.

treatment-naïve patients with evident or impending hepatic derangement.[60,88] We urge clinicians to follow HBV seropositive patients closely while using novel agents for NHL, to ensure that reactivation does not occur. Clinicians should also remember to screen patients for HBV who are receiving chemotherapy without rituximab, if they are at high risk for reactivation. If a patient is positive for HBV, then prophylaxis should be initiated. The literature remains unclear at this time whether universal screening for HBV should be done in all patients receiving chemotherapy.

There are groups of patients in whom routine antiviral therapy may not be indicated. These groups include patients who do not meet the criteria for reactivation (the rise in HBV DNA < 10-fold in patients with past or latent infection, ALT level < three times the upper limit of normal), younger patients in the immune-tolerant phase (normal ALT levels despite positive HBsAg and HBV DNA and minimal hepatic inflammation), and patients in the inactive carrier phase. In addition, patients are considered low risk with agents such as low dose corticosteroids or immunosuppressive agents (e.g., azathioprine and 6-mercaptopurine), and may be excluded

from routine antiviral prophylaxis. Further research is needed to assess the risk in these patients.[30,53,90]

Lastly, critical consideration should be given to factors that may impact the potential outcomes of prophylactic and therapeutic interventions for HBV reactivation. These factors include cost of newer antivirals, liver transplant cost, medication adherence, development of mutant HBV, adverse effects of therapy, and a prolonged monitoring period.[68,83,84,91] Further studies are needed to better understand these issues. Table 2 provides a summary of the modalities for preventing HBV reactivation.

Conclusion

The immunosuppressive effect of NHL and from its therapy provides a pathway for HBV reactivation, especially in those patients treated with anti-CD20 antibody. This effect emphasizes chronic hepatitis B virus infection and reactivation as important public health issues that are preventable, especially among immunosuppressed populations. Because HBV seropositive individuals are often excluded from clinical trials of new agents, there is a paucity of data to measure the risk of morbidity and mortality from novel agent-induced HBV reactivation. Therefore, more aggressive post-market surveillance of new agents, well-designed best practice advisories, and timely case reports are needed to reduce the incidence of HBV reactivation. In addition, large prospective investigations coupled with well-utilized best practice advisories should be performed to understand the role of the more potent novel NHL therapies in HBV reactivation. Sustained HBV vaccination of children and especially adults can reduce the future risk of reactivation in patients with NHL, but this association requires further investigation.

Conflict of interest

None

Author contributions

Conceived the topic of the review article (SD, LS), collected and reviewed pertinent articles (OOO, SD), wrote the manuscript and reviewed the final version (OOO, LS, SD), created the tables (OOO).

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