

# Hepatitis B Reactivation in the Treatment of Non-Hodgkin Lymphoma

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## Abstract

Chronic active hepatitis B infection (HBV) has been implicated in lymphomagenesis of non-Hodgkin lymphoma (NHL). Treatment of cancer including NHL with chemotherapy or immunotherapy can lead to HBV reactivation in previously infected patients. Serological testing of HBV prior to initiation of this therapy is recommended by several national and international medical agencies and expert panels. Patients with positive hepatitis B surface antigen (HBsAg) and anti-hepatitis B core antibody (anti-HBc ab) need to start antiviral therapy with entecavir or tenofovir prior to initiation of chemotherapy or immunotherapy and continue this treatment for 6 to 12 months after completion of cancer therapy to avoid late HBV reactivation. Monitoring of HBV DNA viral load and liver function tests should be done during cancer therapy in infected patients. Hepatitis B infection vaccination resulted in decreases prevalence of HBV virus carriers and decreased incidence of virus-induced malignancies.

## Keywords

hepatitis B, non-Hodgkin lymphoma, antiviral therapy, chemotherapy, rituximab

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## Introduction

The hepatitis B virus (HBV) is a DNA virus and member of the Hepadnaviridae family. This small virus replicates through an RNA intermediate and possesses the ability to integrate into the host DNA. Hepatitis B virus can cause both acute and chronic hepatitis and has an established link with hepatocellular carcinoma.<sup>1</sup> Hepatitis B virus is transmitted via exposure to bodily fluids, such as semen, blood, and vaginal fluid. The most common ways in which the virus is transmitted include mother-to-infant, blood transfusion, sexual contact, and hazardous injection practices.<sup>2,3</sup> The number of people chronically infected with HBV ranges from 240 million to 350 million, with the regions of the world with the greatest prevalence (affecting more than 8% of the population) being the Asia Pacific and sub-Saharan Africa.<sup>3</sup> In the United States, the prevalence of HBV has declined greatly due to routine immunization practices but is estimated that 850 000 to 2.2 million people have chronic HBV infection.<sup>4</sup>

The non-Hodgkin lymphomas (NHLs) are a varied subset of lymphoproliferative malignancies that typically arise from lymphoid tissues.<sup>5</sup> Non-Hodgkin lymphoma is one of the most prevalent hematological malignancy worldwide, accounting for 3% of the global cancer burden.<sup>6</sup> In 2017, it is estimated

that the number of new NHL cases in the United States will total 72 240 and the number of deaths attributable to the disease will reach 20 140.<sup>5</sup> Many of the NHL subtypes have strong geographical associations, for instance, follicular lymphomas tend to occur more often in North America and Western Europe, while adult T-cell lymphoma frequently occurs in East Asia.<sup>7</sup> Certain NHL subtypes are also associated with various infectious diseases. For example, Epstein-Barr virus has been linked to Burkitt lymphoma, extranodal NK/T-cell lymphoma, and NHL in the immunosuppressed patients, while bacterial agents such as *Helicobacter pylori* (gastric mucosa-associated lymphoid tissue lymphoma) and *Borrelia burgdorferi*

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(cutaneous mucosa-associated lymphoid tissue lymphoma in Europe) have established relationships as well.<sup>2,7,8</sup>

Of the many potential NHL associations to explore, the one that will be the focus of this review is its relation to HBV. Previous epidemiological studies have shown that HBV-infected patients (hepatitis B surface antigen positive) have a 2 to 3-fold higher risk of developing NHL than noninfected patients.<sup>9</sup> In addition to the associative role that HBV plays with regard to NHL, the virus is frequently reactivated in patients with lymphoma being treated with immunosuppressive agents.<sup>10</sup> The complex nature of the relationship between HBV and NHL makes it an important topic of study for clinicians tasked with treating either of the disease processes.

### **Incidence of Reactivation and Why We Need to Prevent It**

Hepatitis B virus reactivation occurs broadly across a spectrum of malignant and nonmalignant disease processes with a number of immunosuppressive drugs implicated. There is a well-established risk of hepatitis B surface antigen (HBsAg)-positive patients with regard to HBV reactivation. This risk was established in the pre-rituximab era as HBsAg-positive patients receiving immunosuppressive therapy developed reactivation at rates of 24% to 53%.<sup>11</sup> In HBsAg-positive patients with NHL receiving steroid-containing chemotherapy without HBV prophylaxis, reactivation rates as high as 85% have been reported, with HBV-related death rates reaching 50%.<sup>12</sup> For HBsAg-positive patients with NHL being treated with rituximab-based therapy in the absence of antiviral prophylaxis, retrospective studies have demonstrated reactivation rates of 40% to 80%.<sup>13</sup> Despite prompt antiviral treatment following reactivation, 31% of patients experienced acute liver failure and died.<sup>13</sup> Use of HBV prophylaxis can significantly reduce the rates of reactivation and chemotherapy disruption, but the risk still remains.<sup>14</sup> The risk of reactivation is not exclusive to patients with HBsAg-positive serology, and numerous cases of reactivation have been reported in those who are HBsAg negative with undetectable serum HBV DNA. Tang et al, in a meta-analysis of 1312 HBsAg-negative/HBcAb-positive patients with lymphoma treated with a rituximab-containing chemotherapy regimen, found a HBV reactivation rate of 9%.<sup>15</sup> These findings demonstrate the necessity for HBV serological testing in patients undergoing immunosuppressive therapy or chemotherapy and the need for HBV prophylaxis in susceptible individuals. Additionally, in HBsAg-negative patients, close monitoring for seroconversion and liver enzyme changes is recommended as these patients are still at risk of reactivation even with low-serum HBV DNA levels, and this risk is especially present for those receiving rituximab-containing therapy but appears to be diminished in rituximab-free regimens.<sup>10</sup>

### **Biological Reasons for Hepatitis Reactivation With Anti-CD20 ABs or Chemotherapy**

To fully understand the mechanisms contributing to HBV reactivation, it is useful to review the molecular biology of the

virus. The virus uses a liver-specific receptor, the sodium-taurocholate cotransporter, to enter the host's hepatocytes. Upon gaining entry, a nucleocapsid containing the partially double-stranded viral genome is imported into the nucleus for further modification. The viral genome is repaired by viral polymerase to form a full-length, covalently closed circular DNA (cccDNA). The highly stable cccDNA can remain in infected hepatocytes for years after the patient has fully recovered from the initial HBV infection.<sup>16</sup> The inability of the host to completely clear HBV DNA forms the basis for HBV's impressive capacity for reactivation.

In patients with fully functioning immune systems, HBV will cause acute hepatitis. The host's immune system will direct its efforts at the infected hepatocytes, causing a gradual decrease in HbsAg and serum HBV leading to the complete resolution of the hepatitis. The bout of viral hepatitis and progression to complete resolution is the biological norm for healthy, immunocompetent adults. In spite of what may appear to be complete resolution of HBV, the virus may persist in the liver with continual low levels of HBV replication occurring years after the episode of acute hepatitis.<sup>11</sup> This is due to the nature of the circular DNA that HBV possesses, allowing it to reside in hepatocytes, awaiting its next opportunity to replicate. For chemotherapy to be efficacious, it must suppress the body's immune system, one possible sequelae of this suppression is reactivation of previously controlled viruses. It is believed that the initiating driver of HBV reactivation is the loss of immune control of viral replication, leading to an increase in viral load and infection of hepatocytes.<sup>17</sup> Reactivation of HBV has been reported in individuals previously deemed as having resolved infections.<sup>11,17</sup> Once chemotherapy is stopped and the patient regains their immune function, these cells will attack the reinfected hepatocytes, leading to immune-mediated liver damage and viral hepatitis reactivation.<sup>11,17</sup>

Reactivation of HBV can be broken down into 5 general phases. In the first phase, the virus will increase in replication upon exposure to the immunosuppressive therapy, while the patient will likely remain asymptomatic. The patient may never progress beyond the first stage and may never truly develop HBV reactivation hepatitis.<sup>16</sup> The hallmark of the second stage is a rise in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. This elevation in liver enzymes typically closely follows the increase in HBV-DNA levels, occurring within weeks of the viral replication. The serum ALT and AST levels may reach values 10 times as high as their baseline, this is known as the hepatic flare or HBV reactivation hepatitis. The clinical profile of patients in the second stage of reactivation can range from asymptomatic to jaundice and right upper quadrant tenderness.<sup>16</sup> The third stage may include spontaneous improvement in liver enzymes levels or nonspontaneous improvement due to the initiation of antiviral therapy upon reactivation recognition. The fourth stage is liver injury and acute liver failure. Individuals who reach the fourth stage may exhibit increasing bilirubin levels and loss of liver function, which will be evident based on prolonged prothrombin time. These patients may develop hepatic decompensation

requiring liver transplant and inability to identify these patients may result in liver failure and possibly death. The majority of individuals reach the fifth stage with complete recovery, typically after antiviral therapy or immunosuppressive therapy cessation.<sup>16</sup> Patients may not progress linearly through the stages, and the severity of HBV reactivation is highly variable.<sup>16</sup> Although no consensus exists for defining or diagnosing HBV reactivation, several criteria are often cited by various organizations including HBV DNA level increases and the resurfacing of a positive HBsAg.<sup>18</sup> In HBsAg-negative, anti-HBc-positive patients, the 2017 European Association for the Study of the Liver clinical practice guidelines cite seroreversion (HBsAg reappearance) as the seminal diagnostic feature of reactivation.<sup>19</sup> When using HBV DNA levels to define reactivation, a 10-fold increase or greater from the patient's baseline is often cited as definitive.<sup>20</sup>

Highlighted in the progression of HBV reactivation is the intimate relationship between the virus and the host's immune system. This relationship can be dramatically influenced depending on the therapy being instituted. Hepatitis B infection is mediated by adaptive T and B cells; clearance of the virus is associated with a vigorous CD4+ and CD8+ T-cell response, along with a strong B-cell response and production of anti-HBs antibodies.<sup>16</sup> Chemotherapy agents such as anthracyclines, alkylating agents, and antimetabolites all cause diminished lymphocyte proliferation, opening the door for viral reactivation. Steroids suppress cell-mediated immunity through inhibition of interleukins, which function to signal for T- and B-cell proliferation. The risk with steroids appears to be dose and time dependent; studies have shown that patients receiving more than 10 mg of prednisone daily for 4 weeks or longer had the greatest risk.<sup>18</sup> Rituximab is a monoclonal antibody against CD20, thereby depleting the host's B-cell population, the cells needed to produce the HBV neutralizing antibodies and prevent viral spread.<sup>16</sup> The immunosuppressive agents can be stratified by risk of reactivation; those with the highest risk of reactivation ( $\geq 10\%$  incidence of HBV reactivation) include the B-cell diminishing therapies such as rituximab and ofatumumab, anthracycline derivatives, chronic prednisone therapy, and tumor necrosis factor (TNF- $\alpha$ ) inhibitors.<sup>16</sup>

## Current Guidelines for Treatment and Prevention of Reactivation

### Screening

Prevention of HBV reactivation begins with patient screening. In the United States, screening strategy should be targeted with the aim of establishing the patient's HBV status and risk of reactivation and screening should consist of both HBsAg and anti-HBc.<sup>21</sup> Among the various cancer governing groups, there is a consensus that all individuals who are deemed high risk of HBV or receiving anti-CD20 agents should be screened prior to beginning therapy.<sup>21-23</sup> Despite an emphasis on the need to screen high-risk patients for HBV, screening rates still leave much to be desired. A recent analysis of nearly 12 000 adult

patients with cancer found that of those receiving B-cell depleting therapy, only 41.1% were screened for HBV.<sup>24</sup> Some debate remains whether or not all patients receiving chemotherapy should be screened for HBV, given the availability of HBsAg testing relative low cost, but at this time the National Comprehensive Cancer Network does not advise this due to a lack of evidence.<sup>21,23,25</sup> (see Table 1). It is important to note that many patients may be unaware of their chronic HBV status, and it is estimated that 35% of patients with chronic HBV in the United States are oblivious to their disease state.<sup>28</sup>

Should a patient test positive for either HBsAg or HBcAb, the patient should follow-up with quantitative hepatitis B viral load by polymerase chain reaction (PCR) and surface antibody.<sup>21</sup> HBsAg-positive patients should receive antiviral therapy and have their viral load monitored monthly during treatment and every 3 months following treatment cessation.<sup>21</sup> If the viral load fails to decrease or worse yet, the PCR becomes positive, and anti-CD20 therapy should be terminated and should consult hepatology.<sup>21</sup>

Therapy should be dictated according to level of the patient's risk, anticipated length of chemo or immunotherapy, HBV-DNA level, and previous antiviral usage. Previously lamivudine was used for HBV prophylaxis, but recent studies have shifted favor to tenofovir and entecavir as first-line agents. Timing of therapy is an important consideration as high-risk patients receiving immunosuppressive agents should preferably receive antiviral therapy beforehand or simultaneously with their immunosuppressive regimen.

### Risk Stratification of HBV Reactivation

Stratification of HBV reactivation risk should begin with the patient's HBV biomarkers and the type of immunosuppressive therapy used.<sup>23</sup> Based on a systematic review of the literature, several factors have been identified that would place patients at risk of developing HBV reactivation: high HBV DNA level, use of systemic corticosteroids, use of certain tyrosine kinase inhibitors, lymphoma and breast cancer, HBsAg-positive status, anthracycline use, and use of anti-CD20 monoclonal antibodies.<sup>25</sup> In HBsAg-positive patients, the presence of hepatocellular carcinoma and absence of antiviral prophylaxis have been found to be independent risk factors for reactivation.<sup>15</sup> Analysis of 1676 patients with hematological malignancy found the following to be independent risk factors for seroconversion: diabetes mellitus, liver cirrhosis, positive anti-HBc, and low anti-hepatitis B surface antibody (anti-HBs Ab) titer values.<sup>15</sup> Patients receiving anti-CD20 agents have the highest risk of reactivation and seropositive patients should receive antiviral therapy for the duration of their treatment and a minimum of 12 months following conclusion of therapy.<sup>23</sup> Patients who are positive for HBsAg or anti-HBc and receiving anti-CD20 agents (rituximab, obinutuzumab, or ofatumumab) have an estimated HBV reactivation risk  $>20\%$ .<sup>29</sup> Other agents that fall into high risk of reactivation ( $\geq 10\%$ ) include anthracyclines, chronic prednisone therapy (for more than a 4-week duration), and TNF- $\alpha$  inhibitors.<sup>16</sup>

**Table 1.** Comparison of Professional Guidelines for HBV Reactivation and Management.

Association Guidelines	HBV Screening	Screening Tests	HBsAg-Positive Patients	HBsAb Negative, Anti-HBc-Positive Patients	Antiviral Drug Recommended	Antiviral Treatment Duration
ASCO <sup>25</sup>	Risk-based screening strategy	HBsAg, anti-HBc, HBV DNA if serology positive	Prophylactic antiviral therapy	Antiviral prophylaxis may be considered if cancer therapy associated with high risk of reactivation	Entecavir, tenofovir	Minimum of 6 months after therapy cessation, longer than 12 months for patients receiving anti-CD20 agents
NCCN <sup>21</sup>	Only patients receiving anti-CD20 antibodies	HBsAg, anti-HBc, HBV DNA, and surface antibody if serology positive	Prophylaxis with entecavir	Prophylactic antiviral therapy preferred	Entecavir, tenofovir, avoid lamivudine	Up to 12 months after oncological treatment ends
EASL <sup>26</sup>	All potential patients receiving chemotherapy or immunosuppressive therapy	HBsAg, anti-HBc, HBV DNA if serology positive	Prophylactic antiviral therapy, test for HBV-DNA level	Test for HBV DNA; provide prophylactic antiviral therapy if detectable HBV DNA; monitor ALT and HBV DNA levels if no detectable HBV DNA	Lamivudine if HBV DNA <2000 IU/mL for short treatment course, for longer courses entecavir or tenofovir or if HBV DNA is high	Twelve months after therapy ends
AGA <sup>27</sup>	High-risk reactivation (>10%) and moderate risk of HBV reactivation (1%-10%)	HBsAg, anti-HBc, HBV DNA if serology positive	Prophylactic antiviral therapy	Antiviral prophylaxis instead of monitoring in patients receiving high/moderate reactivation risk chemotherapy	Therapies with high barrier to resistance preferred over lamivudine	Six months after cessation of therapy and at least 12 months for B-cell depleting drugs

Abbreviations: AGA, American Gastroenterology Association; ASCO, American Society of Clinical Oncology; EASL, European Association for the Study of the Liver; HBV, hepatitis B virus; NCCN, National Comprehensive Cancer Network.

### Choice of Antiviral

Patients with lymphoma having chronic HBV are primarily treated with entecavir, tenofovir, and lamivudine, but the treatment plan may differ from patient to patient and inclusion of a hepatitis specialist may be warranted.<sup>30</sup> Current National Comprehensive Cancer Network guidelines state that HBV-seropositive patients (HBsAg+ and/or anti-HBc positive) requiring chemotherapy should receive entecavir prophylactically for the duration of their treatment.<sup>21</sup>

Lamivudine is a cost-effective option, but entecavir has superior viral suppression and lower levels of resistance.<sup>25,31</sup> Although lamivudine is tolerated by most patients, viral resistance to the drug has emerged making other options more appropriate to prevent viral reactivation. Huang et al conducted a randomized clinical trial comparing the efficacy of entecavir to lamivudine in hepatitis B surface antigen-positive patients being treated for diffuse large B-cell lymphoma with a R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). The trial showed that patients receiving entecavir developed HBV-related hepatitis at a rate of 0% compared to 13.3% in the lamivudine group, experienced HBV reactivation at 6.6% compared to 30% in the lamivudine group, and chemotherapy was only disrupted in 1.6% compared to 18.3% in the lamivudine group.<sup>32</sup>

Shang et al demonstrated a similar superiority of entecavir to lamivudine, but in a population of allogeneic hematopoietic stem cell transplant recipients.<sup>33</sup> In the group of patients receiving lamivudine, rates of HBV reactivation at 6, 12, and 24 months following transplant were 3%, 7%, and 24%, while reactivation rates of the entecavir group at 6, 12, and 24 months were 0%, 0%, and 2%.<sup>33</sup> Additionally, the authors found entecavir-receiving patients incurred lower rates of hepatitis due to HBV reactivation and fewer mutations causing drug resistance, and overall, the authors concluded that entecavir may be the better prophylaxis choice to prevent HBV reactivation in HBsAg-positive allogeneic hematopoietic stem cell transplantation recipients.<sup>33</sup>

### Duration of Therapy

Duration of antiviral therapy should at a minimum reach 6 months postchemotherapy, while regimens for patients receiving or having received anti-CD20 agents (rituximab) should be lengthened to 12 months.<sup>25,30</sup> Due to the prolonged immunosuppressive effects of the anti-CD20 agents, patients should be monitored for reactivation even after antiviral therapy is completed.<sup>31</sup> Liu et al analyzed a group of HBsAg-positive patients being treated for diffuse large B-cell lymphoma with chemotherapy. The median time of withdrawal of the prophylactic antiviral therapy from the conclusion of chemotherapy was 6.1 months. It was found that 21.7% of the HBsAg-positive experienced delayed HBV reactivation, while none of the patients with a HBsAg-negative/anti-HBc-positive status experienced reactivation.<sup>34</sup> This may illustrate the need for longer duration of prophylaxis, especially in HBsAg-positive patients.

The need for longer duration of antiviral prophylactic therapy is of even greater importance for those receiving anti-CD20 agents. Numerous cases have been reported of hepatitis B reactivation occurring after 12 months of antiviral therapy following rituximab therapy. Muraishi et al reported a case of a 68-year-old man with occult hepatitis B who experienced reactivation 27 months after completion of a rituximab-containing regimen for malignant lymphoma.<sup>35</sup> Reactivation occurred in this patient despite prophylactic entecavir during chemotherapy and 14 months of postrituximab prophylaxis.<sup>35</sup> This further demonstrates the need for close monitoring of patients with serological evidence of previous hepatitis B infection receiving anti-CD20 therapy and the need for prospective studies evaluating the ideal length of postchemotherapy antiviral prophylaxis.

### Conclusions

Patients undergoing treatment for NHL have an increased risk of HBV reactivation, this risk is amplified in those receiving anti-CD20 antibodies such as rituximab. Current guidelines recommend screening any patients receiving anti-CD20 antibodies for HBV, and any patients found to be seropositive for HBV (HBsAg and/or anti-HBc) should be treated prophylactically and for 6 to 12 months till after cessation of anti-CD20 therapy. Recent trials have demonstrated greater efficacy of entecavir and tenofovir as first-line antivirals for the prevention and treatment of HBV reactivation. As novel agents for NHL treatment come to market, additional studies will need to be conducted to ascertain the risk of HBV reactivation in these new agents.

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