

Hepatitis B virus reactivation with a rituximab-containing regimen

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Conflict-of-interest statement: The authors indicated no potential conflict of interest in this article.

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Received: April 20, 2015
Peer-review started: April 22, 2015
First decision: July 25, 2015
Revised: August 19, 2015
Accepted: September 7, 2015
Article in press: September 8, 2015
Published online: September 28, 2015

Abstract

Rituximab is currently used not only in the treatment of B-cell lymphoma but also for various other diseases, including autoimmune diseases, post-transplant graft vs host disease, and rejection following kidney transplants. Due to rituximab's widespread use, great progress has been made regarding research into complications that arise from its use, one of the most serious being the reactivation of hepatitis B virus (HBV), and efforts continue to establish guidelines for preventive treatment against this occurrence. This report discusses preventive measures against rituximab-induced HBV reactivation and future objectives.

Key words: Rituximab; Hepatitis B virus; Reactivation; Nucleoside analog; Non-Hodgkin's lymphoma

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Core tip: For preventive measures against hepatitis B virus (HBV) reactivation during rituximab treatment, hepatitis B surface (HBs) antigen positive and HBc antibody positive/HBs antibody negative patients are subject to prophylactic treatment with nucleoside analogs. During rituximab treatment, the HBV-DNA levels of patients who are HBc antibody positive (HBs antibody positive or negative) are ideally monitored with PCR once a month. If the PCR results are positive, the administration of nucleoside analogs is initiated. However, since monitoring HBV-DNA levels is expensive, it might be preferable to follow the HBs antibodies instead. Due to wide differences in the insurance situations in each country, including the follow-up intervals, further research must determine ideal follow-up intervals. However, no standard exists for the timing of this treatment's termination. For HBs antigen negative patients who also receive nucleoside analog treatment, it

will be necessary in the future to evaluate the possibility of switching to a vaccine when a patient becomes HBs antibody positive.

Tsutsumi Y, Yamamoto Y, Ito S, Ohigashi H, Shiratori S, Naruse H, Teshima T. Hepatitis B virus reactivation with a rituximab-containing regimen. *World J Hepatol* 2015; 7(21): 2344-2351 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v7/i21/2344.htm> DOI: <http://dx.doi.org/10.4254/wjh.v7.i21.2344>

INTRODUCTION

Rituximab, which improves the prognosis of CD20-positive B-cell lymphoma, is generally indispensable for the treatment of B-cell lymphoma^[1-3]. Rituximab inhibits the production of various antibodies by targeting CD20 positive B-cells and is effective for a range of conditions, including idiopathic thrombocytopenic purpura, chronic rheumatoid arthritis, multiple sclerosis, and cryoglobulinemic vasculitis with applications to other diseases as well^[4-7]. On the other hand, extensive studies have also recently been conducted on rituximab's side effects, which include reports not only of typical infusion reactions but also various infectious diseases due to its immune suppressive effects: Cytomegalovirus, progressive multifocal leukoencephalopathy, parvovirus infection, and Herpes zoster^[8-11]. Although hepatitis B virus (HBV) reactivation has been previously reported to be a complication of chemotherapy^[12-16], this phenomenon has drawn greater attention due to reports that argue that the frequency of reactivation is higher in patients treated with rituximab than those who only received chemotherapy^[17-24]. The best way to deal with HBV reactivation is to prevent it^[25,26]. In this review, we describe the prevention and treatment of HBV reactivation based on previous reports and discuss a summary and future objectives.

Principle of HBV reactivation during rituximab treatment

After HBV infection, HBV-DNA synthesis is initially suppressed by cytokine production from NK and other cells. A subsequent cytotoxic T-cell (CTL) reaction occurs due to the presence of CD8-positive T lymphocytes. Because hepatitis is triggered by CTLs, a time lag likely exists between the HBV infection and the manifestation of hepatitis^[27,28]. On the other hand, rituximab induces CD4 lymphopenia^[29,30]. In a mouse model, B-cell depletion reduced the number and the fraction of CD4 memory T-cells and impaired immunity against virus infection^[31]. A reduction in CD20 B-cells shifted the CD4 effector phenotype to that of enhanced interferon- γ , interleukin (IL)-2, and tumor necrosis factor. Perhaps the depletion of CD20 positive B-cells reduces the production of IL-7 and IL-15, both of which are critical for memory T-cell survival, from monocytes or stromal cells^[31]. Furthermore, HBV replication is likely accelerated by the indirect effects of B-cell depletion on immune globulin

production. It has been reported that rituximab treatment induces a change in CD8 distribution^[30]. This might reduce the number of CD8-positive cells and the subsequent acceleration of HBV replication. Once the number of CD8-positive T-cells recovers, cells are produced that specifically target HBV. However, since memory T-cells are impaired by their reduced numbers, CD8-positive T-cells randomly attack HBV, resulting in severe hepatitis^[31].

Rituximab not only affects B-cells but T-cells as well and accelerates HBV replication. This is a primary factor in the induction of HBV reactivation by the administration of rituximab alone.

Epidemiology of HBV reactivation

When combined with chemotherapy, the HBV reactivation rate during rituximab treatment has been reported to be 20%-55% overall and 3% in hepatitis B surface antigen (HBsAg) negative patients^[32-36]. HBV reactivation can be caused by chemotherapy alone. However, rituximab more easily induces HBV reactivation independently upon combined treatment with chemotherapy or steroid treatment^[18,26]. The frequency of HBV reactivation is also higher with combination treatments including rituximab compared to chemotherapy alone or a combination chemotherapy and steroid treatment^[18,37]. Risk factors for HBV reactivation in patients receiving chemotherapy include being male, lack of HBs antibody, HBs antigen positivity, presence of a precore mutant, HBV-DNA level, anthracycline/steroid use, transplantation, second/third line treatment, youth, and the presence of lymphoma^[35,37-39]. However, when rituximab is used, the risk factors for HBV reactivation are narrowed to a lack of HBs antibody, youth, and being male^[37]. All the above reports are retrospective analyses of patients who were HBs antigen positive and who therefore were subject to prophylactic nucleoside analog therapy. In the future, patient groups must be identified who tend to experience reactivation even when receiving such therapy.

Many remaining problems must be addressed. One is whether the attending physician performs antibody or DNA tests before initiating chemotherapy or a rituximab/chemotherapy combination. This issue is rather basic; yet a surprising report by Méndez-Navarro *et al.*^[40] in 2011 showed that serological screening of HBV is only done in less than 40% of cases before treatment. In some cases, HBV reactivation went undetected because no HBV screening was conducted. Zurawska *et al.*^[41] analyzed the effect of HBsAg screening by dividing patients into three groups: screening, non-screening, and only screening of high-risk patients. Their results showed that the group that was screened before treatment had the highest prevention rate of HBV reactivation (10-fold); screening the high-risk patient group was the most cost effective measure. When comparing the screening and non-screening groups, the former was more cost effective. Screening prevents HBV reactivation.

Another problem is the screening method. Some patients were diagnosed as Hbc antibody negative

when using the EIA method (AxSYM Assay: Abbot Laboratories, Chiba, Japan, 2005), but they were diagnosed as HBc antibody positive with the CLIA method (Architect Assay: Abbott Laboratories, Chiba, Japan, 2013). Thus, in the past, we overlooked an HBV reactivation risk factor since our treatment was based on AxSYM results. Therefore, reports on HBV reactivation cannot be compared since the results were biased by the screening method. This affects the evaluation of risk factors and prophylactic administration. International standardization of screening methods is needed.

The risk factors for HBV reactivation include being male, lack of HBs antibody, HBs antigen positive, presence of precore mutant, HBV-DNA level, anthracycline/steroid combination therapy, transplantation, second/third line treatments, youth, and the presence of lymphoma; When rituximab is used, the risk factors are narrowed down to a lack of HBs antibody, youth, and being male; Currently, the screening rate for HBV is only 30%-40%; Standardization of screening methods is a future task.

HBV-DNA mutations

HBV-DNA mutations must be considered when assessing the potential difficulties in the treatment of HBV using nucleoside analogs. Pelizzari *et al.*^[42] reported that the mutation rate in HBV-DNA with lamivudine is lower than the rate during treatment for hepatitis B. However, in their study, the observation period was short and they analyzed too few cases. Several mutations were reported in HBV reactivated patients. Main of these mutations were developed in immune-active HBsAg regions, such as M103I-L109I-T118K-P120A-Y134H-S143L-D144E-S171F. In other patients, C48G-V96A-L175S-G185E-V190A mutations were observed whose function escaped the T-cell-mediated responses for HBV. An N-linked glycosylation site was observed in a major hydrophilic loop in HBV reactivated patients without HBsAg^[43]. Compared to treatment with standard chemotherapy with or without rituximab, the mutation rate during the prophylactic treatment of HBV-DNA with lamivudine was approximately 15%-20%. Therefore, this indicates no significant difference in the HBV-DNA mutation rate with lamivudine between the prophylactic and standard HBV hepatitis treatment periods^[44,45]. A fatal case was also described in which HBV reactivation was caused by HBV-DNA mutation during R-CHOP treatment, although not at an early stage^[46]. Recently, encouraging results have been reported on the effectiveness of entecavir in the prevention of HBV reactivation^[47]. Due to the low frequency of the emergence of a resistant HBV strain with entecavir use, this is the first choice for the prophylactic treatment of patients with high viral load or patients who require a long prophylactic treatment period^[47].

Lamivudine resistance was induced early when a nucleoside analog such as fludarabine was used with rituximab^[48]. Similar reports have been noted for the induction of HBV-DNA mutations by nucleoside

analogs when steroids or fludarabine were used with rituximab^[49]. Note that the combined use of such purine analogs as fludarabine and cladribine with rituximab tends to induce HBV-DNA mutations. A report on HBV reactivation with bendamustine (an alkylating agent) as well as a nucleoside analog has also been published. However, HBV-DNA mutations with these agents were not evaluated and their effectiveness in this regard remains unknown^[50].

With regard to HBV-DNA mutations, entecavir is desirable for prophylactic treatment in the event of HBV reactivation due to its poor ability to induce mutations in HBV-DNA. However, its cost is problematic, and measures must be enacted that are suitable for different countries.

The presence of HBV mutations corresponds to the frequency of the emergence of resistant strains with standard nucleoside analogs.

Perhaps HBV mutations will increase with a combination treatment of steroids or anti-cancer drugs such as purine analogs that have a strong immune suppressive effect.

HBs antigen positive cases

There is an international consensus that nucleoside analog administration is necessary in HBs antigen positive patients since prophylactic treatment is effective for the prevention of HBV reactivation and reduces mortality in this group^[51-53]. Guidelines for each analog are shown in Table 1. When referring to the guideline treatments for HBs antigen positive chronic hepatitis, entecavir use is desirable when the HBV-DNA concentration exceeds 20000 IU/mL, while lamivudine use is adequate if the HBV-DNA concentration falls under 20000 IU/mL. In addition, in HBV-DNA-positive cases, the possible existence of YMDD mutations must be determined beforehand. If such mutations are detected, using tenofovir or the combined use of two nucleoside analogs might become necessary. As mentioned previously, entecavir is more desirable for the prevention of HBV reactivation due to its low induction of resistant strains during treatment. Ideally, it is desirable to start prophylactic treatment two weeks after the administration of nucleoside analogs since the drugs are most effective during this period. However, there is no standard protocol regarding the starting time for treatment since the specific condition of each individual patient often plays a role. In our clinic, steroids are not used on patients who are HBs antigen positive. A fatality was previously observed in a group of patients who were receiving steroid/rituximab combination therapy that caused HBV-DNA mutation and HBV reactivation even though the patient was HBs antigen negative. We believe that the use of steroids should be avoided, at least in HBs antigen positive patients^[47].

For HBs antigen positive patients, treatment with nucleoside analogs is necessary to prevent HBV reactivation.

Although from the point of view of preventing drug

Table 1 Guidelines for chemotherapy or immunosuppressive drug therapy

AASLD	Subject to preventive treatment if HBsAg positive or anti-HBc positive and HBV-DNA positive. If HBV-DNA concentration is less than 20000 IU or for a shortened treatment (< 1 yr), lamivudine or telbivudine is desirable. If HBV-DNA concentration exceeds 20000 IU and long-term treatment is necessary, entecavir or tenofovir is desirable. If HBV-DNA concentration remains less than 2000 IU six months after the completion of treatment, the treatment should be discontinued; otherwise treatment shall continue (2009)
APASL	There are no guidelines (2005)
EASL	HBsAg cases are subject to treatment, and HBV-DNA is measured in these cases, although there is no defined value in which treatment recommendations can be made. Lamivudine is most commonly used; however, it is best used in cases with low HBV-DNA concentration or when resistant strains are less likely to emerge. In high HBV-DNA concentration cases or when there is a high risk of resistance, entecavir is desirable. Careful follow-up of HBV-DNA concentration and liver function is necessary for HBsAg negative, Anti-HBc positive, and HBV-DNA negative cases. Vaccination is recommended in HBV seronegative cases (2009)
JAPAN	Subject to nucleoside analog treatment if HBsAg positive or if HBsAg negative, and anti-HBs or Hbc positive plus HBV-DNA positive. If HBV-DNA is negative, HBV-DNA is monitored monthly and nucleoside analogs are administered when HBV-DNA becomes positive. Entecavir is recommended as the nucleoside analog. The timing of the termination of the nucleoside analog treatment shall be determined in accordance with the treatment for type B chronic hepatitis if HBsAg is positive. If the patient is anti-HBs or anti-HBc positive, a nucleoside analog is administered for 12 mo after the completion of immunosuppressive therapy or chemotherapy. During this time, nucleoside analog treatment will be discontinued if HBV-DNA is negative and ALT is normal. Patients are closely observed for 12 mo after treatment with nucleoside analogs (2009)

HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; ALT: Alanine aminotransferase.

resistant HBV emergence, using entecavir as the initial treatment is advantageous, due to its excessive cost, substitution with lamivudine is acceptable.

Treatment based on the guidelines might be helpful.

HBc antibody positive/HBs antigen negative/HBs antibody negative

The Hbc antibody positive/HBs antigen negative serotype is further divided into naïve (HBs antibody positive) and occult types (HBs antibody negative). However, since HBV reactivation is often observed in Hbc antibody positive/HBs antigen negative cases, it may be preferable to divide Hbc antibody positive/HBs antigen negative cases based on whether they are positive or negative for HBs antibodies. For Hbc antibody positive patients, perhaps HBV reactivation is induced by rituximab. Although Hui *et al.*^[36] reported a 3%-25% reactivation rate, prophylactic treatment may be desirable since the mortality is relatively high (30%-38%) after reactivation occurs^[36,54-56]. In 2013, Huang *et al.*^[47] conducted a randomized controlled trial to evaluate the effect of the prophylactic administration of entecavir on the frequency of HBV reactivation in Hbc antibody positive patients. In their report, unlike in retrospective analyses, the prophylactic administration of entecavir was the most important factor, at least for Hbc antibody positive patients^[47]. Furthermore, Seto *et al.*^[57] recently reported frequent reactivation of HBV in patients with 10 mIU/mL HBs antibody prior to rituximab treatment. In Hbc antibody positive patients, prophylactic treatment is necessary, at least for those who are antibody negative prior to rituximab treatment (occult type). We believe that the prophylactic administration of a nucleic acid analog is preferable in Hbc antibody positive/HBs antigen negative/HBs antibody negative cases.

HBc antibody positivity can cause HBV reactivation. Attention is required since mortality is high after reactivation occurs.

Patients who are both Hbc antibody positive and

HBs antibody negative are subjected to prophylactic treatment with nucleoside analogs.

HBc antibody positive/HBs antigen negative/HBs antibody positive

There are reports of HBV reactivation in Hbc-ab negative/HBs-ag positive/HBs-ab positive cases^[21,32,36], and reactivation occurred in 6.9% of them^[43]. HBV reactivation in Hbc antibody negative/HBs antigen negative/HBs antibody positive cases has also been reported (albeit in small numbers)^[21,36], and reactivation was reported in 3.4% of them^[43].

We previously reported decreased HBs and Hbc antibodies as well as induced reactivation after combination rituximab/chemotherapy in HBs antibody positive patients^[17,24,25,58-60]. HBs antibody in particular decreased in patients with < 300 mIU/mL and disappeared in patients with < 100 mIU/mL after combination therapy with rituximab and chemotherapy^[58-60]. For patients who were originally Hbc antibody positive/HBs antibody positive but became HBs antibody negative after continuous treatment with rituximab, perhaps HBV reactivation can be induced by maintenance therapy with rituximab. Therefore, the possibility of HBV reactivation must be evaluated for group receiving maintenance therapy with rituximab. Since a case has been documented in which HBV reactivation occurred even though the patient had an HBs antibody titer of 868 mIU/mL, monthly follow-ups must be conducted during treatment for HBV-DNA positive patients^[20]. However, such prophylactic treatment is expensive and HBV reactivation remains a possibility. At present, HBV-DNA follow-up is deemed adequate if the follow-up of HBs and Hbc antibodies is extended to once a month. We must identify those who require prophylactic treatment from among Hbc antibody positive/HBs antigen negative/HBs antibody positive and Hbc antibody negative/HBs antigen negative/HBs antibody positive patients.

Particular attention must be paid to patients with

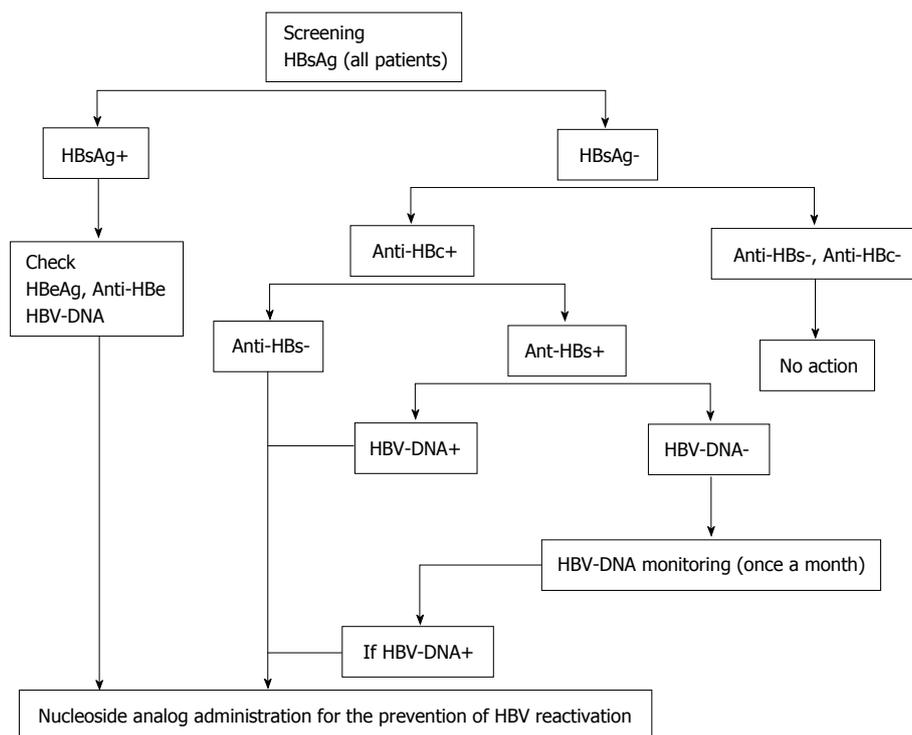


Figure 1 The review is summarized as schematics. The treatment direction described here is based on the assumption that all patients are screened in advance. HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus.

< 300 mIU/mL of HBs antibody during maintenance treatment with rituximab since the HBs antibody status might become negative (follow-up of HBs antibody concentration is required).

Since HBV reactivation was reported even in patients with a high HBs antibody titer, HBs antibody follow-up is not sufficient for detecting the occurrence of reactivation. Monthly follow-up for the presence of HBV-DNA is necessary during treatment.

Administration of nucleoside analogs upon HBV reactivation

As for the prophylactic administration to prevent HBV reactivation, low HBV drug resistance is desirable. Although different guidelines exist, 0.5 mg of entecavir might be desirable with regard to both effectiveness and minimizing drug resistance. Depending on the cost of the drug and individual financial circumstances, 100 mg of lamivudine is also acceptable, although drug resistant strains are induced more easily. In this case, various guidelines are helpful in the selection of appropriate prophylactic drugs^[51-53]. If HBV reactivation occurs, the patient should be dealt with based on the treatment of acute hepatitis B. Although the first choice for treatment is 0.5 or 100 mg of lamivudine, interferon is usually employed as well for acute hepatitis since nucleoside analogs do not take effect immediately upon HBV reactivation. However, in the case of HBV reactivation, interferon is difficult to apply since reactivation occurs after rituximab or chemotherapy treatment and prolonged bone marrow suppression might occur. Interferon's administration is also undesirable because

it can exacerbate liver damage^[61]. In our clinic, liver protective drugs (glycyrrhizic and ursodeoxycholic acids) are used together, although they might remain insufficient. If resistance develops to entecavir or lamivudine, 10 mg of adefovir or 200 mg of tenofovir should be used^[52,53,61,62]. However, great caution is required since switching treatment drugs may induce further HBV drug resistance^[63]. Tenofovir has been reported to be effective for lamivudine as well as adefovir resistant HBV strains^[64-66].

We must evaluate whether to discontinue nucleoside analog administration in patients receiving those drugs that promote HBV reactivation. Since HBs antibody might become negative during rituximab treatment, discontinuation should be considered after the treatment's completion. An additional problem exists with regard to determining the duration of the discontinuation period. Cases of HBV reactivation even after long periods of discontinuation have been documented. For example, even after HBs antibody became temporarily positive, it disappeared later and HBV reactivation was induced^[60,67]. If nucleoside analog treatment is given to HBs antibody negative patients who later become antibody positive, such treatment can be discontinued^[53]. On the other hand, HBV vaccination is unable to suppress HBV reactivation^[68]. If rituximab is administered continuously, HBs antibody may not be induced even after HBV vaccination. It is necessary to evaluate not only the induction of HBs antibody after HBV vaccination but also diseases that are appropriate for the discontinuation of nucleoside analog treatment. Based on the above discussion, Figure 1 shows the modified guidelines from

the Ministry of Health, Labour and Welfare.

Although entecavir is the first choice for prophylactic treatment against HBV reactivation, the decision to use it might also be based on financial conditions, and the guidelines should be referred to when selecting the appropriate drug.

When lamivudine resistance emerges, the treatment drug should be switched to adefovir or tenofovir.

Since nucleoside analogs do not take effect immediately upon HBV reactivation, combination treatment with interferon should be considered. However, bone marrow suppression must be considered for patients with hematological disorders.

The discontinuation of nucleoside analogs must be considered in the future. For HBs antigen negative patients, the discontinuation of nucleoside analog treatment may be possible through a vaccine.

CONCLUSION

Regarding the prevention of HBV reactivation, based on results from clinical studies conducted so far, not only HBs antigen positive patients but also those who are HBs antibody negative/HBc antibody positive might be eligible for prophylactic treatment. By employing combination rituximab/chemotherapy, safer treatment for malignant lymphomas is possible. On the other hand, HBV reactivation during maintenance therapy with rituximab must be considered. The discontinuation of nucleoside analog treatment may be possible through combined administration of an HBV vaccine in patients who are receiving nucleoside analogs as a preventive treatment against HBV reactivation (primarily for antibody negative cases).

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