



Reactivation of Hepatitis B Virus and Its Prevention in Patients with Rheumatic Diseases Receiving Immunosuppressive Therapy

Eun-Jung Park¹, Kyu-sik Choi², Byung-Cheol Song¹

¹Department of Internal Medicine, ²Jeju National University School of Medicine, Jeju, Korea

Introduction of biologic agents to treat patients with rheumatic diseases and cancer has improved clinical outcomes. However, this advance increases the risk of hepatitis B virus (HBV) reactivation in hepatitis B surface antigen carrier and even in resolved HBV infection, which can lead to liver failure and even death. In particular, the risk of HBV reactivation is heightened by the use of B-cell depleting agents such as rituximab, high dose corticosteroid, and anti-tumor necrosis factor- α . Therefore, identification of individuals at risk, and understanding the mechanism of HBV reactivation are essential to preventing HBV reactivation before initiating immunosuppressive therapy. Here, we review the mechanism, incidence, and prevention of HBV reactivation in the setting of immunosuppression. (*J Rheum Dis* 2017;24:261-270)

Key Words. Hepatitis B reactivation, Immunosuppressive agents, Rheumatic diseases

INTRODUCTION

Hepatitis B virus (HBV) infection is a serious global health problem with 2 billion infected people worldwide. Approximately 5% (350 millions) of the world's population is affected by chronic HBV infection. Chronic HBV infection increases the risk of progression to liver cirrhosis, development of hepatocellular carcinoma, and results in liver-related death—500,000 to 1.2 million deaths per year [1]. In Korea, about 5% of Korean people are infected with chronic HBV infection and about 50% of the Koreans have resolved HBV infection (hepatitis B surface antigen [HBsAg]-negative and anti-hepatitis B core [HBc]-positive) [2,3]. Therefore, many Koreans are exposed to risk of HBV reactivation especially if they received immunosuppressive therapy.

The reactivation of HBV commonly occurs in patients with cancer, rheumatic diseases, inflammatory bowel diseases, dermatologic diseases such as psoriasis, and other diseases, who were treated with chemotherapy, im-

munosuppressive agents, glucocorticoid, biologic agents including anti-tumor necrosis factor- α (anti-TNF) and B-cell depleting agents. Clinical courses of HBV reactivation varies from asymptomatic to fatal liver failure or even death [4].

Recent meta-analyses have shown that prophylactic antiviral therapy can prevent the development of HBV reactivation, HBV-related hepatitis, hepatic failure and death in patients receiving immunosuppressive therapy [5-7]. However, up to 50% of clinicians did not screen for HBV before immunosuppressive therapy [8,9]. In this review, we would like to review the mechanism, incidence, and prevention of HBV reactivation in the setting of immunosuppression.

MAIN SUBJECTS

Definition and mechanism of HBV reactivation

Definition of HBV reactivation varies according to studies, but generally refers to as follows; 1) detectable HBV

Received : June 30, 2017, **Revised :** September 11, 2017, **Accepted :** September 11, 2017

Corresponding to : Byung-Cheol Song, Department of Internal Medicine, Jeju National University School of Medicine, 15 Aran 13-gil, Jeju 63241, Korea. E-mail : drsong8177@naver.com

Copyright © 2017 by The Korean College of Rheumatology. All rights reserved.

This is a Open Access article, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

DNA in individuals who previously had undetectable HBV DNA, 2) ≥ 10 -fold increase in individuals who previously had detectable HBV DNA, 3) reverse HBsAg seroconversion, which HBsAg-negative becomes HBsAg-positive [10-12]. HBV-related hepatitis usually develops from several weeks to months after stopping immunosuppressive agents. HBV reactivation-related hepatitis is defined as ≥ 3 -fold increase in alanine aminotransferase (ALT) compared to upper normal limit or rise more than 100 IU/L from baseline [4,13].

Natural course of chronic HBV infection depends on balance between viral replication and host immune response. Immune control of HBV is usually mediated by cytotoxic T cell and B cell [14]. HBV reactivation in patients during immunosuppressive therapy is related to inhibition of function and proliferation of lymphocytes, which indirectly promotes replication of HBV [15]. Glucocorticoid directly increases viral replication via binding to glucocorticoid responsive element in HBV genome. Anthracycline derivatives (doxorubicin, epirubicin et al.) also directly promote replication of HBV [16,17]. In addition, some studies showed that TNF- α promoted HBV clearance and decrease of HBV transcription [18]. Thus, inhibition of TNF- α might have an effect on enhancing HBV replication [4,18,19].

Increased HBV replication related to immunosuppressive therapy results in over-production of viral antigen, which is exposed on surface of hepatocyte. Cessation of immunosuppressive agents makes cytotoxic T cells restore

their function that reacts to overexpressed viral antigens, and causes liver injury. During immunosuppressive therapy, an increase in HBV DNA generally precedes the elevation of serum ALT [4,20].

HBV reactivation is also occurred in individuals with resolved HBV infection (HBsAg-negative/anti-HBc-positive) because covalently closed circular HBV DNA (cccDNA) in the nucleus plays as a template for HBV replication during natural course of HBV, and the cccDNA is quite stable and persists for decades even after HBV infection resolved [21-23].

Incidence and clinical outcomes of HBV reactivation in cancer patients receiving chemotherapy

Table 1 summarized the incidence of HBV reactivation in HBV carriers with immunosuppressive therapy [5-7, 24-63]. The incidences of HBV-related hepatitis, liver failure and death in cancer patients receiving chemotherapy have been reported to be 2%~60%, 6.7%~33% and 0.4%~20%, respectively [5,7].

Risk of HBV reactivation is the most frequent (48% to 72%) in patients treated with chemotherapy for hematologic malignancy including lymphoma, hematopoietic stem cell transplantation, and solid organ transplantation. In particular, patients receiving chemotherapy which contains glucocorticoids or B cell depleting agents (i.e., rituximab, ofatumumab) are the highest risk group of HBV reactivation [5,7,10,24-32]. Several studies revealed 9% to 42% of incidence of HBV reactivation in lymphoma pa-

Table 1. Incidence of HBV reactivation without antiviral prophylaxis in various diseases

| Diseases | HBV reactivation without antiviral prophylaxis (%) | | References |
|---|--|------------------------|-------------------|
| | HBsAg-positive | Resolved HBV infection | |
| Bone marrow/hematopoietic stem cell transplantation | 66~81 | 6~10 | 40~42 |
| Solid organ transplantation | 50~90 | 0.9~5 | 15 |
| Lymphoma | 18~72 | 9~41.5 | 5, 7, 10, 24~32 |
| Leukemia | 61 | 2.8~12.5 | 39, 43 |
| Breast cancer | 21~68 | NA | 7, 13, 33~38 |
| Head and neck cancer | 19.3~29.4 | NA | 7, 13 |
| Hepatocellular carcinoma (systemic chemotherapy) | 36 | 11 | 44 |
| Hepatocellular carcinoma (trans-arterial chemoembolization) | 20.5~29.7 | 9.3~11 | 45~47 |
| Gastrointestinal cancer | 6.9~18.1 | NA | 7, 13 |
| Lung cancer | 14.2~23 | NA | 7 |
| Rheumatic diseases receiving anti-TNF therapy | 6.9~39 | 0~5 | 49~52, 59, 61, 62 |
| Inflammatory bowel diseases receiving anti-TNF* | 36 | 0.7 | 60, 63 |

HBV: hepatitis B virus, HBsAg: hepatitis B surface antigen, TNF: tumor necrosis factor, NA: not applicable. *Case reports or small case series reporting HBV reactivation.

tients who even had resolved HBV infection during chemotherapy including rituximab [28,31,32]. Recent meta-analysis showed that HBV reactivation occurred in 25% (4% to 68%) of HBsAg-positive solid cancer patients who received chemotherapy without antiviral prophylaxis, while HBV reactivation developed in 0.3% to 9.0% of individuals with resolved HBV infection treated with standard chemotherapy [7]. The incidence of HBV reactivation during chemotherapy was higher in patients with breast cancer, which showed 21% to 68% [7,13,33-38] than in those with other solid cancers, which revealed as 4% to 30% [7,13]. High risk of HBV reactivation in patients with breast cancer has been associated with anthracycline-based chemotherapy (doxorubicin, epirubicin containing regimen) [13,16,35].

Incidence and clinical outcomes of HBV reactivation in patients receiving biologic agents including anti-TNF

Patients with rheumatic diseases are most likely exposed to various immunosuppressive agents, such as traditional immunosuppressive agents (azathiopurine, methotrexate, cyclophosphamide, mycophenolate mofetil, cyclosporine, and tacrolimus), anti-TNF (infliximab, adalimumab, etanercept, certolizumab, and golimumab), B-cell depleting agents (rituximab, ofatumumab, belimumab et al.), T-cell inhibitor (abatacept), or interleukin (IL)-6 inhibitor (tocilizumab).

In 2003, Michel et al. [64] and Ostuni et al. [65] reported cases of HBV reactivation in patients with rheumatic diseases who had treated with infliximab. Many case series, small-sized retrospective or prospective studies, have shown that HBV reactivation also developed frequently in patients who were receiving anti-TNF for treatment of various rheumatic diseases, inflammatory bowel diseases, psoriasis and so on [48-50,66]. However, there are no well-designed prospective studies or randomized controlled trials (RCT) in regard to HBV reactivation or antiviral prophylaxis in rheumatic patients receiving anti-TNF. In addition, it is difficult to estimate the precise incidence of HBV reactivation or clinical course in patients with rheumatic disease due to diversity of prophylactic agents or of initiation times of medications.

In a systemic review of 38 published studies in patients treated with anti-TNF, Pérez-Alvarez et al. [50] reported that HBV reactivation occurred in 39% of HBsAg-positive patients (n=89, individual data were not available in 7) and 5% of individuals with resolved HBV infection (n=168).

Twenty-two of 44 patients with HBV reactivation treated with antiviral agents (lamivudine in 12, adefovir in 2, entecavir in 8, lamivudine+tenofovir in 1). Six of 44 patients with reactivation developed hepatic failure and 5 (4 of HBs-positive patients and 1 of patient resolved HBV infection) of those resulted in death. All 6 patients with hepatic failure had received infliximab. Of 5 patients with death, 3 patients were treated with lamivudine, 1 patient was treated with entecavir, and 1 patient did not receive any antiviral agents with stopping anti-TNF. HBV reactivation was frequently observed in the patient with detectable HBV DNA prior to treatment. HBV-related hepatitis or hepatic failure was more frequent in patients who received infliximab than those received etanercept. However, this study is considered to overestimate the incidence of HBV reactivation because of the inclusion of many case reports. In another systemic review of 23 studies regarding to anti-TNF therapy, Carroll and Forgiione [19] reported that symptomatic HBV reactivation which defined as jaundice, malaise or weight loss, occurred in 6 (17.1%) of 35 HBsAg-positive patients (received infliximab in 17, etanercept in 12 and adalimumab in 6). All 6 patients having HBV reactivation received infliximab. Two of 6 patients died. Of 35 HBsAg-positive patients, 11 were treated with lamivudine after receiving anti-TNF, 4 did while starting anti-TNF, and 3 had antiviral prophylaxis with lamivudine prior to anti-TNF therapy. In a systemic review of 9 studies (2 prospective, 7 retrospective studies) of HBsAg-positive rheumatic patients (n=122, including 48 patients with antiviral prophylaxis) who received anti-TNF and disease modifying anti-rheumatic drugs, Lee et al. [49] reported that HBV reactivation developed in 15 patients (12.3%). In 10 (9 patients without antiviral prophylaxis) of 15 patients with HBV reactivation, individual data were available. Four of 10 patients showed severe hepatitis (≥ 10 -fold increase from reference range of ALT). Seven of 10 patients were treated with antiviral agents (entecavir in 5, lamivudine in 1, adefovir in 1) and 3 did not receive antiviral agents because of normal ALT or mild elevation of ALT. All patients showed favorable clinical outcomes without any mortality. Ryu et al. [51] retrospectively analyzed HBV reactivation in patients with rheumatoid arthritis or ankylosing spondylitis (n=49) who received anti-TNF. Twenty patients received prophylactic antiviral therapy (entecavir in 5, lamivudine in 15). HBV reactivation developed in 1 (5.0%) patient who received lamivudine, whereas none of patients who received entecavir developed HBV reactivation. Of 29 pa-

tients without antiviral prophylaxis, HBV reactivation occurred in 2 (6.9%) and recovered with antiviral treatment. In a prospective study of Lan et al. [54], 18 of 88 patients who received anti-TNF therapy were HBsAg-positive. Of 18 patients, HBV reactivation did not occur in 10 patients with prophylactic antiviral therapy, while HBV reactivation occurred in 5 (62.5%) of 8 patients without antiviral prophylaxis. All 5 patients recovered after treatment of lamivudine.

A recent prospective study [58] investigated the incidence of HBV reactivation in inflammatory arthritis patients with HBV infection using anti-TNF therapy and evaluated the efficacy of antiviral therapy. Among the 6 chronic hepatitis B patients (defined by HBV DNA $> 2 \times 10^4$ IU/mL, elevated ALT), HBV reactivation occurred in two patients (33.3%) without antiviral prophylaxis and no HBV reactivation was observed in the other 4 patients with antiviral prophylaxis. In the 31 inactive HBsAg carriers (defined by HBV DNA $< 2 \times 10^3$ IU/mL, normal ALT), HBV reactivation developed in 6 of 22 (27.3%) patients without antiviral prophylaxis and there was no HBV reactivation in the other 9 patients with antiviral prophylaxis. This study suggested that antiviral prophylaxis could effectively decrease the risk of HBV reactivation in patients with HBsAg-positive patients using anti-TNF.

Pérez-Alvarez et al. [50] reported that HBV reactivation occurred in 9 (5.4%) of 168 resolved HBV infection who received anti-TNF therapy. However, Lee et al. [49] reported that HBV reactivation occurred in 1.7% among 468 rheumatic patients with resolved HBV infection during anti-TNF therapy. Ye et al. [58] reported that HBV reactivation was not found in the 50 patients with resolved HBV infection. Recent prospective study also demonstrated that none of 146 rheumatic patients with resolved HBV infection who received anti-TNF developed HBV reactivation during 56 months follow-up periods. Therefore, HBV reactivation is rare in patients with resolved HBV infection during anti-TNF therapy. Although it is not clear whether the risk of HBV reactivation is different according to type of anti-TNF agents, it is considered that the risk might be higher in patients receiving infliximab than in those with other anti-TNF agents.

There are few studies of HBV reactivation in HBsAg-positive rheumatic patients treated with B-cell depleting agents, while HBV reactivation is particularly high in lymphoma patients treated with those agents [26-29,31,32]. It is assumed that the risk of reactivation may be high in

HBsAg-positive rheumatic patients. However, the incidence of HBV reactivation is less than 1% with resolved HBV infection in rheumatic patients who received rituximab [52,56,57].

T cell inhibitor (abatacept), IL-6 inhibitor (Tocilizumab), or kinase inhibitor (imatinib, nilotinib) are also related to moderate risk (1% to 10%) of HBV reactivation [10,53], while disease modifying anti-rheumatic drugs, traditional immunosuppressive agents such as azathioprine, short-course of corticosteroids < 1 week, or intra-articular steroid injection showed low risk ($< 1\%$) of HBV reactivation [10].

Incidence and clinical outcomes of HBV reactivation in patients receiving glucocorticoid

Among HBsAg-positive patients receiving glucocorticoid, HBV reactivation frequently occurred in patients with prolonged period (≥ 4 weeks) [67,68] or with co-administration of chemotherapy regimen [10]. Cheng et al. [24] reported that the incidence of HBV reactivation (72% vs. 37.5%, $p=0.02$), HBV-related hepatitis (60% vs. 33%, $p=0.069$), and severe hepatitis defined by over 10-fold of ALT elevation (44% vs. 13%, $p=0.02$) was higher in patients receiving combination with chemotherapy and high-dose glucocorticoid than those treated with chemotherapy alone.

In a RCT [67] to treat chronic hepatitis B patients with glucocorticoid for 4 weeks (prednisolone 60 mg/day for 2 week, then 30 mg/day for 2 week), HBV reactivation and HBV-related hepatitis occurred after 4 to 10 weeks of withdrawal of prednisone. In another study [68] to investigate whether ALT rebound (defined by over 5 times of ALT elevation) following glucocorticoid priming (30 mg/day for 3 weeks, 15 mg/day for 1 week, no treatment for 2 weeks) enhances response to lamivudine therapy, ALT rebound occurred in 67% of 2 to 6 weeks after withdrawal of prednisolone. However, no ALT rebound was observed in control groups. Serum HBV DNA was high ($> 20,000$ IU/mL) in all patients in these 2 studies. In a prospective, open-label cohort study in inactive HBsAg carrier (defined by HBsAg-positive, undetectable HBV DNA) with idiopathic nephrotic syndrome, patients were assigned to standard prednisone regimen ($n=22$) (1 mg/kg/day) or oral mycophenolate mofetil combined with the lower dose of prednisone ($n=19$) (0.5 mg/kg/day) to compare the complete remission of idiopathic nephrotic syndrome. The planned duration of treatment was 36 weeks with gradual tapering of agents

according to clinical response. The incidence of HBV reactivation (defined as detectable HBV DNA) was higher in patients with high dose of prednisone when compared with lower dose of prednisone (63.6% vs. 36.8%; $p=0.047$). In a retrospective study [69], 198 HBsAg-positive patients with asthma or chronic obstructive pulmonary disease were treated with either inhaled glucocorticoid ($n=126$) or systemic glucocorticoid ($n=72$). HBV reactivation occurred in 11% of the patients treated with systemic glucocorticoid and 3.2% in the patients treated with inhaled glucocorticoid ($p=0.032$). The study also showed that HBV reactivation occurred in 15.8% who received systemic treatment for ≥ 3 months ($n=53$) compared with 9.4% in those who received systemic treatment for < 3 months ($n=19$). The incidence of HBV reactivation was significantly higher in the patients with systemic treatment for ≥ 3 months than in those with inhaled glucocorticoid group ($p=0.048$). However, there was no significant difference between the inhaled glucocorticoid group and those with continuous systemic treatment for < 3 months ($p=0.127$), nor between those with systemic treatment for < 3 months and continuous use of systemic treatment for ≥ 3 months ($p=0.427$). HBV reactivation occurred in 14% in the continuous dosing at \geq prednisolone or equivalent 20 mg daily when compared with 4.5% in the lower dose (< 20 mg daily). There was a significant difference in HBV reactivation between the inhaled glucocorticoid group and continuous use of systemic dosing at ≥ 20 mg daily ($p=0.014$). There were no significant differences among the other groups because of small sample size. However, there are few studies to evaluate the risk of HBV reactivation in patients who received various doses of glucocorticoid for < 4 weeks or low-dose glucocorticoid (< 10 mg of pre-

dnisolone per day). A case of death related to hepatic failure was reported in inactive HBsAg carrier with rheumatoid arthritis who received prednisolone 2.5 mg/day for prolonged period [70]. Recently, Lin et al. [71] reported that fifteen (39.5%) of 38 HBsAg-positive patients developed hepatitis B flare (defined as a five-fold increase in serum ALT of upper normal limit, no information about HBV DNA change) in systemic lupus erythematosus patients who received low to moderate dose of prednisolone for long-term with or without immunosuppressive agents (azathioprine, cyclophosphamide, mycophenolate mofetil). Five patients of 38 patients received prophylactic or preemptive antiviral therapy (if HBV DNA rise, initiate antiviral therapy) and none of them developed hepatitis B flares. Three (1.9%) of 157 patients with resolved HBV infection experienced HBsAg seroreversion. Three patients (2 in HBsAg-positive and 1 in resolved HBV infection) died due to hepatic failure even though lamivudine therapy was initiated as rescue therapy. No mortality was observed in patient receiving entecavir as rescue therapy. A daily dose of prednisolone > 5 mg was only an independent risk factor for hepatitis B flare. Therefore, even in low to medium dose of prednisolone for long-term therapy might increase the risk of HBV reactivation in some rheumatic diseases.

Prophylaxis of HBV reactivation

To prevent HBV reactivation, screening for HBsAg, anti-HBc in all patients prior to receive immunosuppressive agents is recommended. HBsAg-positive and/or anti-HBc-positive patients receiving immunosuppressive agents need to check liver function test and HBV DNA every 3 months for monitoring HBV reactivation. High risk patients with HBV reactivation need to be treated with

Table 2. Prospective, randomized trials of antiviral therapy to prevent HBV reactivation

| Studies | Patients (number) | HBV status | Diseases | Treatment | Antiviral agents | HBV reactivation (%) | | p-value |
|-------------------|-------------------|----------------------------|---------------|-----------------------------------|--------------------------|----------------------|----------|---------|
| | | | | | | Prophylaxis | Control* | |
| Lau et al. [75] | 30 | HBsAg (+) | Lymphoma | Chemotherapy | Lamivudine | 0.0 | 53.0 | 0.002 |
| Hsu et al. [25] | 52 | HBsAg (+) | Lymphoma | Chemotherapy | Lamivudine | 11.5 | 56.0 | 0.001 |
| Long et al. [76] | 42 | HBsAg (+) | Breast cancer | Chemotherapy | Lamivudine | 0 | 28.6 | 0.021 |
| Huang et al. [77] | 80 | HBsAg (-) /anti-HBc (+) | Lymphoma | Rituximab-containing chemotherapy | Entecavir | 2.4 | 17.9 | 0.027 |
| Huang et al. [78] | 121 | HBsAg (+) | Lymphoma | Rituximab-containing chemotherapy | Entecavir vs. Lamivudine | 6.6/30.0 | NA | 0.001 |

HBV: hepatitis B virus, HBsAg: hepatitis B surface antigen, HBc: hepatitis B core, NA: not applicable. *Control patients either remained untreated or had delayed treatment only after HBV reactivation.

prophylactic antiviral therapy before initiating immunosuppressive therapy [72-74].

Many studies have shown the effect of lamivudine as a prophylactic antiviral therapy on HBV reactivation (Table 2) [75-77]. In a meta-analysis, prophylactic lamivudine therapy prior to chemotherapy in cancer patients decreased the risk of HBV reactivation (4% vs. 37%),

HBV-related hepatitis (4% vs. 33%), liver failure (0% vs. 13%), and mortality (2% vs. 7%) compared to placebo [5]. However, resistance to lamivudine increased up to 23% after 1 year and 80% after 5 years of lamivudine treatment [72].

In a RCT [78] to compare the effect of prophylactic antiviral treatment between entecavir (n=60) and lam-

Table 3. The risk of HBV reactivation and policy for antiviral prophylaxis in HBsAg-positive or anti-HBc-positive patients who received immunosuppressive therapy

| Risk group | HBV reactivation estimates | Antiviral prophylaxis [85] |
|--------------------------|---|--|
| High-risk (> 10%) | 1. B cell-depleting agents such as rituximab and ofatumumab - HBsAg positive: (A) - HBsAg negative/anti-HBc positive: (A) | ≥ 12 months |
| | 2. Anthracycline derivatives such as doxorubicin and epirubicin - HBsAg positive: (A) | ≥ 6 months |
| | 3. Corticosteroid therapy (moderate/high dose) for ≥ 4 weeks - HBsAg positive: (B) | ≥ 6 months (strong recommendation) |
| Moderate-risk (1% ~ 10%) | 1. TNF-alpha inhibitors: infliximab, etanercept, adalimumab, certolizumab - HBsAg positive: (B) - HBsAg negative/anti-HBc positive: (C) | 6 months - The American gastroenterological association (AGA) suggests antiviral prophylaxis over monitoring for patients at moderate risk undergoing immunosuppressive drug therapy. |
| | 2. Other cytokine inhibitors and integrin inhibitors: abatacept, ustekinumab, natalizumab, vedolizumab - HBsAg positive: (C) - HBsAg negative/anti-HBc positive: (C) | - Patients who place a higher value on avoiding long-term use of antiviral therapy and the cost associated with its use and a lower value on avoiding the small risk of reactivation (particularly in those who are HBsAg negative) may reasonably select no prophylaxis over antiviral prophylaxis. |
| | 3. Tyrosine kinase inhibitors: imatinib, nilotinib - HBsAg positive: (B) - HBsAg negative/anti-HBc positive: (C) | |
| | 4. Corticosteroid therapy for ≥ 4 weeks - HBsAg positive (low dose): (C) - HBsAg negative/anti-HBc positive: (C) (moderate/high dose) | |
| | 5. Anthracycline derivatives: doxorubicin and epirubicin - HBsAg negative/anti-HBc positive: (C) | |
| Low-risk (< 1%) | 1. Traditional immunosuppressive agents: azathioprine, 6-mercaptopurine, methotrexate - HBsAg positive/anti-HBc positive: (A) - HBsAg negative/anti-HBc positive: (A) | The AGA suggests against routinely using antiviral prophylaxis in patients undergoing immunosuppressive drug therapy who are at low risk for HBV reactivation |
| | 2. Intra-articular corticosteroids - HBsAg positive/anti-HBc positive: (A) - HBsAg negative/anti-HBc positive: (A) | |
| | 3. Corticosteroid therapy for ≤ 1 week - HBsAg positive/anti-HBc positive: (B) - HBsAg negative/anti-HBc positive: (A) | |
| | 4. Corticosteroid (low dose) therapy for ≥ 4 weeks - HBsAg negative/anti-HBc positive: (B) | |

Confidence in evidence was graded as follows: (A) high confidence that the estimate lies within group risk boundaries, (B) moderate confidence that the estimate lies within group risk boundaries, (C) little or no confidence that the estimate lies within group risk boundaries. Glucocorticoids: prednisone (or equivalent): low dose, < 10 mg; moderate dose, 10 ~ 20 mg; high dose, > 20 mg. HBV: hepatitis B virus, HBsAg: hepatitis B surface antigen, HBc: hepatitis B core. Adopted from the article Perrillo et al. (Gastroenterology 2015;148:221-244.e3) [10] with original copyright holder's permission.

ivudine (n=61) in 121 lymphoma patients who received chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), entecavir was superior to lamivudine in terms of HBV reactivation (6.6% vs. 30%, p=0.001), HBV-related hepatitis (0% vs. 13.3%, p=0.003), and chemotherapy disruption (1.6% vs. 18.3%, p=0.002). Chen et al. [79] retrospectively analyzed that entecavir prophylaxis was more effective in preventing HBV reactivation compared to lamivudine (0% vs. 7.0%), while the incidence of HBV-related hepatitis was similar in 213 solid cancer patients treated with prophylactic therapy (entecavir 70, lamivudine 143). Subgroup analysis demonstrated that HBV reactivation occurred in 15.9% of patients with serum HBV DNA levels $\geq 2,000$ IU/mL, while HBV reactivation did not occur in patients with serum HBV DNA levels $< 2,000$ IU/mL (p=0.01). Incidence of HBV-related hepatitis and cessation of chemotherapy related to hepatitis was not significantly different between two groups (5.9% vs. 12.9% and 2.9% vs. 9.7%, respectively). There is no RCT of prophylactic antiviral treatment with tenofovir. Zhang et al. [6] reported that entecavir and tenofovir are the most effective in prophylaxis of HBV reactivation in meta-analysis. Thus, entecavir or tenofovir are preferentially recommended for prophylactic treatment of HBV reactivation [80,81]. However, patients with long-term therapy with tenofovir should beware of kidney toxicity [82,83]. If the cost is a major hindrance to anti-viral prophylaxis, lamivudine may be considered in patients with serum HBV DNA levels $< 2,000$ IU/mL because HBV reactivation had not occurred in patients with serum HBV DNA levels $< 2,000$ IU/mL regardless of antiviral agents [76].

Even though the duration of prophylactic antiviral treatment is controversial, the treatment should be maintained for at least 6 to 12 months after withdrawal of immunosuppressive agents. And the treatment should be maintained for at least 12 months after stopping B cell depleting agents such as rituximab because there is a lag in the recovery of B cell function which results in HBV reactivation even 1 to 2 years after withdrawal [84]. Table 3 shows the guideline of the American gastroenterological association to prevent HBV reactivation according to the level of HBV reactivation risk, which includes high risk ($> 10\%$), moderate risk (1%~10%) and low risk ($< 1\%$) [85].

CONCLUSION

Identification of the individuals at risk, and understanding the mechanism of HBV reactivation is essential to prevent HBV reactivation before initiating immunosuppressive therapy. Most studies of the epidemiology and prophylaxis for HBV reactivation are from chemotherapy for cancer patients. Thus, large-sized, prospective, multi-center studies regard on HBV reactivation should be considered in rheumatic patients who received anti-TNF or glucocorticoids according to dose or duration of treatment.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. *J Viral Hepat* 2004;11:97-107.
2. Joo KR, Bang SJ, Song BC, Youn KH, Joo YH, Yang SK, et al. Hepatitis B viral markers of Korean adults in the late 1990s: survey data of 70,347 health screenees. *Korean J Gastroenterol* 1999;33:642-52.
3. Song EY, Yun YM, Park MH, Seo DH. Prevalence of occult hepatitis B virus infection in a general adult population in Korea. *Intervirology* 2009;52:57-62.
4. Loomba R, Liang TJ. Hepatitis B reactivation associated with immune suppressive and biological modifier therapies: current concepts, management strategies, and future directions. *Gastroenterology* 2017;152:1297-309.
5. Loomba R, Rowley A, Wesley R, Liang TJ, Hoofnagle JH, Pucino F, et al. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med* 2008;148:519-28.
6. Zhang MY, Zhu GQ, Shi KQ, Zheng JN, Cheng Z, Zou ZL, et al. Systematic review with network meta-analysis: Comparative efficacy of oral nucleos(t)ide analogues for the prevention of chemotherapy-induced hepatitis B virus reactivation. *Oncotarget* 2016;7:30642-58.
7. Paul S, Saxena A, Terrin N, Viveiros K, Balk EM, Wong JB. Hepatitis B virus reactivation and prophylaxis during solid tumor chemotherapy: a systematic review and meta-analysis. *Ann Intern Med* 2016;164:30-40.
8. Tran TT, Rakoski MO, Martin P, Poordad F. Screening for hepatitis B in chemotherapy patients: survey of current oncology practices. *Aliment Pharmacol Ther* 2010;31:240-6.
9. Day FL, Link E, Thursky K, Rischin D. Current hepatitis B screening practices and clinical experience of reactivation in patients undergoing chemotherapy for solid tumors: a nationwide survey of medical oncologists. *J Oncol Pract* 2011;7:141-7.

10. Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 2015;148:221-44.e3.
11. Yeo W, Johnson PJ. Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. *Hepatology* 2006;43:209-20.
12. Wands JR, Chura CM, Roll FJ, Maddrey WC. Serial studies of hepatitis-associated antigen and antibody in patients receiving antitumor chemotherapy for myeloproliferative and lymphoproliferative disorders. *Gastroenterology* 1975;68:105-12.
13. Yeo W, Zee B, Zhong S, Chan PK, Wong WL, Ho WM, et al. Comprehensive analysis of risk factors associating with Hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. *Br J Cancer* 2004;90:1306-11.
14. Rehermann B, Nascimbeni M. Immunology of hepatitis B virus and hepatitis C virus infection. *Nat Rev Immunol* 2005;5:215-29.
15. Hwang JP, Lok AS. Management of patients with hepatitis B who require immunosuppressive therapy. *Nat Rev Gastroenterol Hepatol* 2014;11:209-19.
16. Hsu CH, Hsu HC, Chen HL, Gao M, Yeh PY, Chen PJ, et al. Doxorubicin activates hepatitis B virus (HBV) replication in HBV-harboring hepatoblastoma cells. A possible novel mechanism of HBV reactivation in HBV carriers receiving systemic chemotherapy. *Anticancer Res* 2004;24:3035-40.
17. Xu L, Tu Z, Xu G, Wang Y, Pan W, Zhan X, et al. Epirubicin directly promotes hepatitis B virus (HBV) replication in stable HBV-expressing cell lines: a novel mechanism of HBV reactivation following anticancer chemotherapy. *Mol Med Rep* 2014;9:1345-50.
18. Tzeng HT, Tsai HF, Chyuan IT, Liao HJ, Chen CJ, Chen PJ, et al. Tumor necrosis factor- α induced by hepatitis B virus core mediating the immune response for hepatitis B viral clearance in mice model. *PLoS One* 2014;9:e103008.
19. Carroll MB, Forgione MA. Use of tumor necrosis factor α inhibitors in hepatitis B surface antigen-positive patients: a literature review and potential mechanisms of action. *Clin Rheumatol* 2010;29:1021-9.
20. Di Bisceglie AM, Lok AS, Martin P, Terrault N, Perrillo RP, Hoofnagle JH. Recent US Food and Drug Administration warnings on hepatitis B reactivation with immune-suppressing and anticancer drugs: just the tip of the iceberg? *Hepatology* 2015;61:703-11.
21. Murakami Y, Minami M, Daimon Y, Okanoue T. Hepatitis B virus DNA in liver, serum, and peripheral blood mononuclear cells after the clearance of serum hepatitis B virus surface antigen. *J Med Virol* 2004;72:203-14.
22. Lioriot MA, Marcellin P, Walker F, Boyer N, Degott C, Randrianatoavina I, et al. Persistence of hepatitis B virus DNA in serum and liver from patients with chronic hepatitis B after loss of HBsAg. *J Hepatol* 1997;27:251-8.
23. Rehermann B, Ferrari C, Pasquinelli C, Chisari FV. The hepatitis B virus persists for decades after patients' recovery from acute viral hepatitis despite active maintenance of a cytotoxic T-lymphocyte response. *Nat Med* 1996;2:1104-8.
24. Cheng AL, Hsiung CA, Su IJ, Chen PJ, Chang MC, Tsao CJ, et al. Steroid-free chemotherapy decreases risk of hepatitis B virus (HBV) reactivation in HBV-carriers with lymphoma. *Hepatology* 2003;37:1320-8.
25. Hsu C, Hsiung CA, Su IJ, Hwang WS, Wang MC, Lin SF, et al. A revisit of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in non-Hodgkin's lymphoma: a randomized trial. *Hepatology* 2008;47:844-53.
26. Kim SJ, Hsu C, Song YQ, Tay K, Hong XN, Cao J, et al. Hepatitis B virus reactivation in B-cell lymphoma patients treated with rituximab: analysis from the Asia Lymphoma Study Group. *Eur J Cancer* 2013;49:3486-96.
27. Lau GK, He ML, Fong DY, Bartholomeusz A, Au WY, Lie AK, et al. Preemptive use of lamivudine reduces hepatitis B exacerbation after allogeneic hematopoietic cell transplantation. *Hepatology* 2002;36:702-9.
28. Matsue K, Kimura S, Takanashi Y, Iwama K, Fujiwara H, Yamakura M, et al. Reactivation of hepatitis B virus after rituximab-containing treatment in patients with CD20-positive B-cell lymphoma. *Cancer* 2010;116:4769-76.
29. Nakamura Y, Motokura T, Fujita A, Yamashita T, Ogata E. Severe hepatitis related to chemotherapy in hepatitis B virus carriers with hematologic malignancies. Survey in Japan, 1987-1991. *Cancer* 1996;78:2210-5.
30. Yeo W, Chan PK, Zhong S, Ho WM, Steinberg JL, Tam JS, et al. Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. *J Med Virol* 2000;62:299-307.
31. Yeo W, Chan TC, Leung NW, Lam WY, Mo FK, Chu MT, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. *J Clin Oncol* 2009;27:605-11.
32. Seto WK, Chan TS, Hwang YY, Wong DK, Fung J, Liu KS, et al. Hepatitis B reactivation in patients with previous hepatitis B virus exposure undergoing rituximab-containing chemotherapy for lymphoma: a prospective study. *J Clin Oncol* 2014;32:3736-43.
33. Dai MS, Wu PF, Shyu RY, Lu JJ, Chao TY. Hepatitis B virus reactivation in breast cancer patients undergoing cytotoxic chemotherapy and the role of preemptive lamivudine administration. *Liver Int* 2004;24:540-6.
34. Tsai SH, Dai MS, Yu JC, Ho CL, Chen YC, Wu YY, et al. Preventing chemotherapy-induced hepatitis B reactivation in breast cancer patients: a prospective comparison of prophylactic versus deferred preemptive lamivudine. *Support Care Cancer* 2011;19:1779-87.
35. Yeo W, Chan HL. Hepatitis B virus reactivation associated with anti-neoplastic therapy. *J Gastroenterol Hepatol* 2013;28:31-7.
36. Yeo W, Chan PK, Hui P, Ho WM, Lam KC, Kwan WH, et al. Hepatitis B virus reactivation in breast cancer patients receiving cytotoxic chemotherapy: a prospective study. *J Med Virol* 2003;70:553-61.
37. Yun J, Kim KH, Kang ES, Gwak GY, Choi MS, Lee JE, et al. Prophylactic use of lamivudine for hepatitis B exacerbation in post-operative breast cancer patients receiving anthracycline-based adjuvant chemotherapy. *Br J Cancer* 2011;104:559-63.
38. Zhong S, Yeo W, Schroder C, Chan PK, Wong WL, Ho WM, et al. High hepatitis B virus (HBV) DNA viral load is an important risk factor for HBV reactivation in breast cancer patients undergoing cytotoxic chemotherapy. *J Viral Hepat*

- 2004;11:55-9.
39. Chen CY, Huang SY, Cheng A, Chou WC, Yao M, Tang JL, et al. High risk of hepatitis B reactivation among patients with acute myeloid leukemia. *PLoS One* 2015;10:e0126037.
 40. Locasciulli A, Bruno B, Alessandrino EP, Meloni G, Arcese W, Bandini G, et al. Hepatitis reactivation and liver failure in haemopoietic stem cell transplants for hepatitis B virus (HBV)/hepatitis C virus (HCV) positive recipients: a retrospective study by the Italian group for blood and marrow transplantation. *Bone Marrow Transplant* 2003;31:295-300.
 41. Mikulska M, Nicolini L, Signori A, Rivoli G, Del Bono V, Raiola AM, et al. Hepatitis B reactivation in HBsAg-negative/HBcAb-positive allogeneic haematopoietic stem cell transplant recipients: risk factors and outcome. *Clin Microbiol Infect* 2014;20:O694-701.
 42. Nakamoto S, Kanda T, Nakaseko C, Sakaida E, Ohwada C, Takeuchi M, et al. Reactivation of hepatitis B virus in hematopoietic stem cell transplant recipients in Japan: efficacy of nucleos(t)ide analogues for prevention and treatment. *Int J Mol Sci* 2014;15:21455-67.
 43. Totani H, Kusumoto S, Ishida T, Masuda A, Yoshida T, Ito A, et al. Reactivation of hepatitis B virus (HBV) infection in adult T-cell leukemia-lymphoma patients with resolved HBV infection following systemic chemotherapy. *Int J Hematol* 2015;101:398-404.
 44. Yeo W, Lam KC, Zee B, Chan PS, Mo FK, Ho WM, et al. Hepatitis B reactivation in patients with hepatocellular carcinoma undergoing systemic chemotherapy. *Ann Oncol* 2004;15:1661-6.
 45. Jang JW, Kim YW, Lee SW, Kwon JH, Nam SW, Bae SH, et al. Reactivation of hepatitis B virus in HBsAg-negative patients with hepatocellular carcinoma. *PLoS One* 2015;10:e0122041.
 46. Jang JW, Choi JY, Bae SH, Kim CW, Yoon SK, Cho SH, et al. Transarterial chemo-lipiodolization can reactivate hepatitis B virus replication in patients with hepatocellular carcinoma. *J Hepatol* 2004;41:427-35.
 47. Peng JW, Lin GN, Xiao JJ, Jiang XM. Hepatitis B virus reactivation in hepatocellular carcinoma patients undergoing transcatheter arterial chemoembolization therapy. *Asia Pac J Clin Oncol* 2012;8:356-61.
 48. Cho YT, Chen CH, Chiu HY, Tsai TF. Use of anti-tumor necrosis factor- α therapy in hepatitis B virus carriers with psoriasis or psoriatic arthritis: a case series in Taiwan. *J Dermatol* 2012;39:269-73.
 49. Lee YH, Bae SC, Song GG. Hepatitis B virus reactivation in HBsAg-positive patients with rheumatic diseases undergoing anti-tumor necrosis factor therapy or DMARDs. *Int J Rheum Dis* 2013;16:527-31.
 50. Pérez-Alvarez R, Díaz-Lagares C, García-Hernández F, Lopez-Roses L, Brito-Zerón P, Pérez-de-Lis M, et al. Hepatitis B virus (HBV) reactivation in patients receiving tumor necrosis factor (TNF)-targeted therapy: analysis of 257 cases. *Medicine (Baltimore)* 2011;90:359-71.
 51. Ryu HH, Lee EY, Shin K, Choi IA, Lee YJ, Yoo B, et al. Hepatitis B virus reactivation in rheumatoid arthritis and ankylosing spondylitis patients treated with anti-TNF α agents: a retrospective analysis of 49 cases. *Clin Rheumatol* 2012;31:931-6.
 52. Barone M, Notarnicola A, Lopalco G, Viggiani MT, Sebastiani F, Covelli M, et al. Safety of long-term biologic therapy in rheumatologic patients with a previously resolved hepatitis B viral infection. *Hepatology* 2015;62:40-6.
 53. Kim PS, Ho GY, Prete PE, Furst DE. Safety and efficacy of abatacept in eight rheumatoid arthritis patients with chronic hepatitis B. *Arthritis Care Res (Hoboken)* 2012;64:1265-8.
 54. Lan JL, Chen YM, Hsieh TY, Chen YH, Hsieh CW, Chen DY, et al. Kinetics of viral loads and risk of hepatitis B virus reactivation in hepatitis B core antibody-positive rheumatoid arthritis patients undergoing anti-tumor necrosis factor alpha therapy. *Ann Rheum Dis* 2011;70:1719-25.
 55. Lee YH, Bae SC, Song GG. Hepatitis B virus (HBV) reactivation in rheumatic patients with hepatitis core antigen (HBV occult carriers) undergoing anti-tumor necrosis factor therapy. *Clin Exp Rheumatol* 2013;31:118-21.
 56. Mitroulis I, Hatzara C, Kandili A, Hadziyannis E, Vassilopoulos D. Long-term safety of rituximab in patients with rheumatic diseases and chronic or resolved hepatitis B virus infection. *Ann Rheum Dis* 2013;72:308-10.
 57. Varisco V, Viganò M, Batticciotto A, Lampertico P, Marchesoni A, Gibertini P, et al. Low risk of hepatitis B virus reactivation in HBsAg-negative/Anti-HBc-positive carriers receiving rituximab for rheumatoid arthritis: a retrospective multicenter italian study. *J Rheumatol* 2016;43:869-74.
 58. Ye H, Zhang XW, Mu R, Fang LK, Gu JR, Lin J, et al. Anti-TNF therapy in patients with HBV infection--analysis of 87 patients with inflammatory arthritis. *Clin Rheumatol* 2014;33:119-23.
 59. Chung SJ, Kim JK, Park MC, Park YB, Lee SK. Reactivation of hepatitis B viral infection in inactive HBsAg carriers following anti-tumor necrosis factor-alpha therapy. *J Rheumatol* 2009;36:2416-20.
 60. Loras C, Gisbert JP, Saro MC, Piqueras M, Sánchez-Montes C, Barrio J, et al. Impact of surveillance of hepatitis b and hepatitis c in patients with inflammatory bowel disease under anti-TNF therapies: multicenter prospective observational study (REPENTINA 3). *J Crohns Colitis* 2014;8:1529-38.
 61. Viganò M, Degasperis E, Aghemo A, Lampertico P, Colombo M. Anti-TNF drugs in patients with hepatitis B or C virus infection: safety and clinical management. *Expert Opin Biol Ther* 2012;12:193-207.
 62. Xuan D, Yu Y, Shao L, Wang J, Zhang W, Zou H. Hepatitis reactivation in patients with rheumatic diseases after immunosuppressive therapy--a report of long-term follow-up of serial cases and literature review. *Clin Rheumatol* 2014;33:577-86.
 63. Loras C, Gisbert JP, Mínguez M, Merino O, Bujanda L, Saro C, et al. Liver dysfunction related to hepatitis B and C in patients with inflammatory bowel disease treated with immunosuppressive therapy. *Gut* 2010;59:1340-6.
 64. Michel M, Duvoux C, Hezode C, Cherqui D. Fulminant hepatitis after infliximab in a patient with hepatitis B virus treated for an adult onset still's disease. *J Rheumatol* 2003;30:1624-5.
 65. Ostuni P, Botsios C, Punzi L, Sfriso P, Todesco S. Hepatitis B reactivation in a chronic hepatitis B surface antigen carrier with rheumatoid arthritis treated with infliximab and low dose methotrexate. *Ann Rheum Dis* 2003;62:686-7.
 66. Esteve M, Saro C, González-Huix F, Suarez F, Forné M, Viver JM. Chronic hepatitis B reactivation following in-

- fliximab therapy in Crohn's disease patients: need for primary prophylaxis. *Gut* 2004;53:1363-5.
67. Hoofnagle JH, Davis GL, Pappas SC, Hanson RG, Peters M, Avigan MI, et al. A short course of prednisolone in chronic type B hepatitis. Report of a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1986;104:12-7.
 68. Liaw YF, Tsai SL, Chien RN, Yeh CT, Chu CM. Prednisolone priming enhances Th1 response and efficacy of subsequent lamivudine therapy in patients with chronic hepatitis B. *Hepatology* 2000;32:604-9.
 69. Kim TW, Kim MN, Kwon JW, Kim KM, Kim SH, Kim W, et al. Risk of hepatitis B virus reactivation in patients with asthma or chronic obstructive pulmonary disease treated with corticosteroids. *Respirology* 2010;15:1092-7.
 70. Bae JH, Sohn JH, Lee HS, Park HS, Hyun YS, Kim TY, et al. A fatal case of hepatitis B virus (HBV) reactivation during long-term, very-low-dose steroid treatment in an inactive HBV carrier. *Clin Mol Hepatol* 2012;18:225-8.
 71. Lin WT, Chen YM, Chen DY, Lan JL, Chang CS, Yeh HZ, et al. Increased risk of hepatitis B virus reactivation in systemic lupus erythematosus patients receiving immunosuppressants: a retrospective cohort study. *Lupus* 2017;961203317711009.
 72. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2016;10:1-98.
 73. European association for the study of the liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *J Hepatol* 2012;57:167-85.
 74. Korean association for the study of the liver. KASL clinical practice guidelines: management of chronic hepatitis B. *Clin Mol Hepatol* 2016;22:18-75.
 75. Lau GK, Yiu HH, Fong DY, Cheng HC, Au WY, Lai LS, et al. Early is superior to deferred preemptive lamivudine therapy for hepatitis B patients undergoing chemotherapy. *Gastroenterology* 2003;125:1742-9.
 76. Long M, Jia W, Li S, Jin L, Wu J, Rao N, et al. A single-center, prospective and randomized controlled study: Can the prophylactic use of lamivudine prevent hepatitis B virus reactivation in hepatitis B s-antigen seropositive breast cancer patients during chemotherapy? *Breast Cancer Res Treat* 2011;127:705-12.
 77. Huang YH, Hsiao LT, Hong YC, Chiou TJ, Yu YB, Gau JP, et al. Randomized controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B. *J Clin Oncol* 2013;31:2765-72.
 78. Huang H, Li X, Zhu J, Ye S, Zhang H, Wang W, et al. Entecavir vs lamivudine for prevention of hepatitis B virus reactivation among patients with untreated diffuse large B-cell lymphoma receiving R-CHOP chemotherapy: a randomized clinical trial. *JAMA* 2014;312:2521-30.
 79. Chen WC, Cheng JS, Chiang PH, Tsay FW, Chan HH, Chang HW, et al. A comparison of entecavir and lamivudine for the prophylaxis of hepatitis B virus reactivation in solid tumor patients undergoing systemic cytotoxic chemotherapy. *PLoS One* 2015;10:e0131545.
 80. Marcellin P, Heathcote EJ, Buti M, Gane E, de Man RA, Krastev Z, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med* 2008;359:2442-55.
 81. Kitrinou KM, Corsa A, Liu Y, Flaherty J, Snow-Lampart A, Marcellin P, et al. No detectable resistance to tenofovir disoproxil fumarate after 6 years of therapy in patients with chronic hepatitis B. *Hepatology* 2014;59:434-42.
 82. Chen TM, Lin CC. Letter: tenofovir is associated with higher probability of acute kidney injury compared with entecavir. *Aliment Pharmacol Ther* 2014;40:406-7.
 83. Tsai MC, Chen CH, Tseng PL, Hung CH, Chiu KW, Wang JH, et al. Comparison of renal safety and efficacy of telbivudine, entecavir and tenofovir treatment in chronic hepatitis B patients: real world experience. *Clin Microbiol Infect* 2016;22:95.e1-7.
 84. Ceccarelli L, Salpini R, Sarmati L, Svicher V, Bertoli A, Sordillo P, et al. Late hepatitis B virus reactivation after lamivudine prophylaxis interruption in an anti-HBs-positive and anti-HBc-negative patient treated with rituximab-containing therapy. *J Infect* 2012;65:180-3.
 85. Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT; American Gastroenterological Association Institute. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 2015;148:215-9.