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EDITORIAL

# Hepatitis B virus reactivation during immunosuppressive therapy: Appropriate risk stratification

Wai-Kay Seto

Wai-Kay Seto, Department of Medicine, the University of Hong Kong, Queen Mary Hospital, Hong Kong, China
Wai-Kay Seto, Department of Medicine, the University of Hong Kong-Shenzhen Hospital, Shenzhen 518053, China
Wai-Kay Seto, State Key Laboratory for Liver Research, the University of Hong Kong, Hong Kong, China
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Correspondence to: Dr. Wai-Kay Seto, Department of Medicine, the University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong, China. wkseto@hku.hk
Telephone: +852-2-2553994
Fax: +852-2-8162863
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## Abstract

Our understanding of hepatitis B virus (HBV) reactivation during immunosuppresive therapy has increased remarkably during recent years. HBV reactivation in hepatitis B surface antigen (HBsAg)-positive individuals has been well-described in certain immunosuppressive regimens, including therapies containing corticosteroids, anthracyclines, rituximab, antibody to tumor necrosis factor (anti-TNF) and hematopoietic stem cell transplantation (HSCT). HBV reactivation could also occur in HBsAg-negative, antibody to hepatitis B core antigen (anti-HBc) positive individuals during therapies containing rituximab, anti-TNF or HSCT.For HBsAg-positive patients, prophylactic antiviral therapy is proven to the effective in preventing HBV reactivation. Recent evidence also demonstrated entecavir to be more effective than lamivudine in this aspect. For HBsAg-negative, anti-HBc positive individuals, the risk of reactivations differs with the type of immunosuppression. For rituximab, a prospective study demonstrated the 2-year cumulative risk of reactivation to be 41.5%, but prospective data is still lacking for other immunosupressive regimes. The optimal management in preventing HBV reactivation would involve appropriate risk stratification for different immunosuppressive regimes in both HBsAg-positive and HBsAg-negative, anti-HBc positive individuals.

**Key words:** Hepatitis B virus; Antibody to hepatitis B core antigen; Hepatitis B surface antigen; Rituximab; Antigen CD20; Hematopoietic stem cell transplantation; Antibody to tumor necrosis factor; Occult



**Core tip:** Hepatitis B virus (HBV) reactivation not only occurs in hepatitis B surface antigen (HBsAg)-positive, but also in HBsAg-negative, antibody to hepatitis B core antigen positive individuals. Immunosuppressive therapies with increased risk of HBV reactivation include corticosteroids, anthracyclines, rituximab, antibody to tumor necrosis factor and hematopoietic stem cell transplantation. The decision between prophylactic antiviral therapy *vs* routine clinical monitoring would involve appropriate risk stratification for individual types of immunosuppressives regimes.

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## INTRODUCTION

The introduction of nucleoside analogue therapy has revolutionized the management of chronic hepatitis B (CHB). The current first-line therapies of entecavir and tenofovir, if taken long-term, can bring about potent virologic suppression[1], improve liver histology[2,3], and reduce cirrhotic complications[4,5], with low risk of resistance development[6,7]. Nonetheless, the efficacy of nucleoside analogue therapy remains suboptimal in one distinct clinical entity: hepatitis B virus (HBV)-related acute-on-chronic liver failure[8], in which the 3-mo survival rates were only 40%-57%[9,10]. Reactivation of HBV during immunosuppressive therapy, if caught unaware, could present as acute-on-chronic liver failure, signifying the importance of management strategies directed towards preventing HBV reactivation.

The dangers of HBV reactivation are not only limited to hepatitis B surface antigen (HBsAg)-positive patients, but could also involve HBsAg-negative, antibody to hepatitis B core antigen (anti-HBc) positive individuals. Unfortunately, despite the accumulating evidence in this field, the global oncology community remains divided on the need of routine screening of HBV serology prior to immunosuppressive therapy[11,12]. This editorial aims to provide a literature update as well as management recommendations for preventing and controlling HBV reactivation during immunosuppressive therapy.

## IMMUNOSUPPRESSIVE THERAPIES WITH INCREASED RISK OF HBV REACTIVATION

Not all immunosuppressive therapies have been proven to be associated with HBV reactivation - the association is in fact limited to a selected few regimens. Corticosteroids is a well-known risk factor, in which the presence of prednisolone in chemotherapy regimens for HBsAg-positive lymphoma patients would increase the risk of HBV reactivation by 36%[13]. HBV reactivation is also possible in patients treated with steroids for non-malignant conditions, especially when the therapy duration is at least 3 mo or when the steroid dose is equivalent to 20 mg of prednisolone per day[14]. The monoclonal antibodies against B cell surface antigen CD20 (anti-CD20), rituximab and ofatumumab, could also enhance the chances of HBV reactivation, with rituximab resulting in more than five-fold increase[15]. More importantly, HBV reactivation could occur up to one year or more after cessation of rituximab[16,17].

Other biologics, including monoclonal antibodies against tumor necrosis factor (anti-TNF), *e.g.*, infliximab, adalimumab and etanercept have been demonstrated to have a 35% HBV reactivation rate in HBsAg-positive patients with rheumatoid arthritis, inflammatory bowel disease and other non-malignant conditions[18]. Other agents proven to increase the risk for HBV reactivation include transarterial chemo-embolization (TACE) for hepatocellular carcinoma[19], hematopoietic stem cell transplantation (HSCT)[20], methotrexate[21], anthracyclines[22], and other biologic agents including tyrosine kinase inhibitors[23] and ustekinumab[24] (Table 1).

## HBSAG-NEGATIVE, ANTI-HBC POSITIVE HBV REACTIVATION

HBV reactivation is also possible in HBsAg-negative individuals who have occult HBV infection - defined as HBsAg-negativity but with detectable HBV DNA in serum or liver[25]. Such individuals could had CHB, achieved HBsAg seroclearance, but with intrahepatic HBV DNA remaining[26]. They may or may not possess serum antibody to the hepatitis B surface antibody (anti-HBs), with the only positive serologic marker being anti-HBc, indicating past HBV exposure.

HBV reactivation in HBsAg-negative, anti-HBc positive patients has been extensively reported in rituximab-containing chemotherapy (Table 2). Previous retrospective studies reported a reactivation rate of 8.9% to 23.8%[17,27,28]. This large variability could be due to the lack of regular serologic and virologic monitoring, with only HBV reactivation noted when biochemical hepatitis (a late event) occurred. Two recent prospective studies described the risk of HBV reactivation in better detail. The first, when using multiple virologic endpoints, found the rate of reactivation to vary from 11.3% to 18.9%[29]. The second, when defining detectable HBV DNA (> 10 IU/mL) as HBV reactivation, found the cumulative 2-year reactivation rate to be 41.5%. This second study also found patients with negative anti-HBs to have a higher cumulative rate of reactivation than those with positive anti-HBs (68% *vs* 34% at 2 years respectively)[16]. Patients with detectable HBV DNA all responded well to entecavir, with no cases of hepatitic flares.

HBV reactivation has also been reported in HBsAg-negative anti-HBc-positive patients undergoing HSCT. Retrospective studies again found variable rates of reactivation (8.9% to 19.7%)[30-32], again limited by the lack of routine clinical monitoring. Nonetheless, HBV reactivation could occur many months (up to 47 mo) after HSCT, indicating prolonged clinical monitoring would be needed post-HSCT to ensure early detection of HBV reactivation. The preliminary results of an ongoing prospective study found HBsAg-negative, anti-HBc positive HSCT recipients developing graft-*vs*-host disease to have an increased chance of HBV reactivation[33] - these results would need further validation.

Anti-TNF therapy could also increase the risk of

**Table 1 Immunosuppressive regimens known to increase risk of hepatitis B virus reactivation**

| HBsAg-positive | HBsAg-negative Anti-HBc positive |
|---|---|
| Corticosteroids | Anti-CD20 (*e.g.*, rituximab) |
| Anti-CD20 (*e.g.*, rituximab) | HSCT |
| HSCT | Anti-TNF |
| Anti-TNF | TACE for hepatocellular carcinoma |
| Anthracyclines | Methotrexate |
| TACE for hepatocellular carcinoma | |
| Methotrexate | |
| Ustekinumab | |
| Tyrosine kinase inhibitors | |

HBsAg: Hepatitis B surface antigen; Anti-HBc: Antibody to hepatitis B core antigen; Anti-CD20: Antibody against CD20; Anti-TNF: Antibody against tumor necrosis factor; TACE: Transarterial chemo-embolization; HSCT: Hematopoietic stem cell transplantation.

HBV reactivation in HBsAg-negative, anti-HBc positive patients, although when compared to HBsAg-positive patients, reactivation rates were much lower (1.7% to 5%)[18,34]. Other regimens known to be associated with HBV reactivation among HBsAg-negative, anti-HBc positive patients include TACE for hepatocellular carcinoma[35] and methotrexate[21] (Table 1).

## RECOMMENDED STRATEGY TO MANAGE HBV REACTIVATION

### *Screening for HBsAg and anti-HBc prior to immunosuppressive therapy*

Despite the lack of consensus among the global oncology community[11,12], current guidelines from international liver societies[36,37] recommend mandatory screening for serum HBsAg and anti-HBc prior to all forms of immunosuppressive therapy. Screening would be particularly important in HBV-endemic regions, and is cost-effective[38].

### *Prophylactic nucleoside analogue therapy for HBsAg-positive individuals*

The provision of concomitant nucleoside analogue therapy at the commencement of immunosuppression has been demonstrated to be effective in reducing the risk of HBV reactivation for both hematological malignancies and solid-organ tumors[39]. For most immunosuppressive regimes, nucleoside analogue therapy should be kept until at least 6 mo after the last dose of immunosuppressive therapy. The exception is rituximab, with nucleoside analogue therapy continued until at least 12 mo after completion of rituximab-containing chemotherapy[15].

In terms of the choice of nucleoside analogue for prophylactic therapy, lamivudine has been used most extensively, achieving a 79% risk reduction on HBV reactivation[40]. The disadvantage of lamivudine is its low genetic barrier to resistance[4], such that it is no longer a recommended first-line treatment for CHB. Hence, the two first-line therapies, *i.e.*, entecavir or tenofovir, both with a high genetic barrier to resistance should be used instead[6,7]. This is supported by a recent randomized controlled trial demonstrating entecavir to be superior to lamivudine in the prevention of HBV reactivation among HBsAg-positive individuals undergoing rituximab-containing chemotherapy[41].

Prophylactic nucleoside analogue therapy with a finite therapy duration should be only for CHB patients with quiescent disease, as indicated by baseline HBV DNA < 2000 IU/mL. For CHB patients with baseline HBV DNA ⩾ 2000 IU/mL, long-term nucleoside analogue therapy should be considered to reduce the risk of liver-related complications associated with high viral loads[42,43].

### *Monitoring HBsAg-negative, anti-HBc positive individuals*

Defining the optimal management strategy for HBsAg-negative, anti-HBc positive individuals is more difficult. A randomized controlled trial did demonstrate the efficacy of prophylactic nucleoside analogue therapy during rituximab-containing chemotherapy[44]. Nonetheless, within the HBsAg-negative anti-HBc positive population, HBV reactivation seemed to occur only among specific immunosuppressive regimes (Table 1). The risk of HBV reactivation among certain therapies is also low (*e.g.*, < 5% during anti-TNF therapy). Another factor to consider is the seroprevalence of anti-HBc, which could be > 40% among HBV-endemic regions in East Asia[45,46]. Hence, the universal provision of prophylactic nucleoside analogue therapy for all immunosuppressive regimens might not be cost-effective.

Currently, the regular monitoring of serum HBV DNA would probably be the preferred strategy. The optimal interval of monitoring is uncertain - a suggestion would be for every 1-3 mo[36], although there is no high-quality data to support this. Prophylactic nucleoside analogue therapy can still be considered for specific population groups, *e.g.*, anti-HBs negative patients undergoing rituximab-containing chemotherapy[16].

## FUTURE DIRECTIONS

More studies would be needed for risk stratification. Can the current data in HBsAg-positive patients be extrapolated to all forms of immunosuppressive therapy? There is a paucity of data concerning HBV reactivation among traditional immunomodulators, *e.g.*, azathioprine, thalidomide or methotrexate. Other immunosuppressive agents lacking HBV reactivation data include non-steroid or anthracycline-containing chemotherapeutic regimens, monoclonal antibodies other than anti-CD20 or anti-TNF, epidermal growth factor receptor inhibitors and proteasome inhibitors. If current guidelines continue to emphasize prophylactic HBV therapy for all forms of immunosuppression, then cost-effective studies would be

**Table 2 Rates of hepatitis B virus reactivation during rituximab-containing chemotherapy in hepatitis B surface antigen-negative, antibody to hepatitis B core antigen positive individuals as described by various studies**

| Study region | Study nature | No. of patients | HBV reactivation rate | Definition of HBV reactivation |
|---|---|---|---|---|
| Hong Kong[17] | Retrospective | 23 | 23.8% | HBsAg seroreversion |
| Japan[27] | Retrospective | 56 | 8.9% | HBsAg seroreversion |
| Asia-Pacific[28] | Retrospective | 178 | 9.6% | HBsAg seroreversion |
| Taiwan[29] | Prospective | 150 | 11.3%-18.9% | Multiple virologic endpoints |
| Hong Kong[16] | Prospective | 63 | 41.5% | Detectable HBV DNA |

HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus.

needed to justify their usage.

For HBsAg-negative, anti-HBc positive individuals undergoing rituximab-containing chemotherapy, the discrepancies in reactivation rates from previous studies (Table 2) could indicate not all cases of HBV reactivation, when defined as detectable serum HBV DNA, would end up being clinically relevant. In addition, prospective data is still needed to clearly define the risk of HBV reactivation among HSCT and anti-TNF therapy, as well as to identify additional risk factors besides anti-HBs status.

Hopefully, future studies in these directions would help in stratifying the risk of HBV reactivation among different immunosuppressive regimes and improve disease outcomes of HBV-infected individuals undergoing immunosuppressive therapy.

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