Prevention of Hepatitis B reactivation in the setting of immunosuppression

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INTRODUCTION

Hepatitis B is a disease prevalent globally, with approximately 2 billion people exposed to hepatitis B and of these, 240 million are chronically infected (chronic hepatitis B, CHB). This review will highlight the impact of concomitant hepatitis B virus (HBV) infection amongst patients with malignant, inflammatory and autoimmune conditions who undergo immunosuppression. It is apparent that immunosuppression for a range of disease states may be associated with HBV reactivation in susceptible individuals. HBV reactivation leads to a spectrum of clinical outcomes, the most concerning being symptomatic hepatitis, liver failure and death. Clinicians must be aware of such potential adverse outcomes, and screen for and manage HBV accordingly in conjunction with the immunosuppressive regime prescribed for the primary disease. Current recommendations and the existing evidence base for these recommendations will be presented in this review.

Abbreviations:
AGA, American gastroenterological association; ALT, alanine aminotransferase; Anti-HBC, hepatitis B core antibody; Anti-HBs, hepatitis B surface antibody; BMT, bone marrow transplant; CHB, chronic hepatitis B; DNA, deoxyribonucleic acid; EASL, European association for the study of the liver; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBV reactivation, hepatitis B virus reactivation; HDV, hepatitis D virus; HSCT, hematopoietic stem cell transplant; IL, interleukin; LPAM, lymphocyte Peyer's patch adhesion molecule; OR, odds ratio; R-CHOP, rituximab-cyclophosphamide, hydroxydaunorubicin (doxorubicin or adriamycin), oncovin (vincristine) and prednisolone; R-CHEOP, rituximab-cyclophosphamide, hydroxydaunorubicin (doxorubicin or Adriamycin), etoposide, oncovin (vincristine) and prednisolone; RR, risk ratio; RNA, ribonucleic acid; SLE, systemic lupus erythematosus; TNF, tumour necrosis factor

Keywords: Hepatitis B reactivation; Prophylaxis; Chemotherapy; Immunosuppression; Guidelines

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HOW AND WHY DOES HBV REACTIVATION OCCUR WITH IMMUNOSUPPRESSION?

HBsAg positive patients

Chronic HBV infection is characterised by the interaction between the virus, the immune system and the liver. Serologically, the presence of hepatitis B surface antigen (HBsAg) defines CHB. Observing the natural history of HBV infection, there are four phases of infection depending on the interaction between the virus and the host immune system; immune tolerance, immune clearance, immune control or immune escape. Any modulation to the immune system may disrupt the interaction between virus and host and contribute to HBV reactivation. Clinically, this has been observed in pregnant women who likely owing to peri-partum changes in the immune system may experience post-partum flares of hepatitis B infection. A case of HBV reactivation with liver failure due to excess endogenous adrenocortical activity due to an adrenal tumour (Cushing’s syndrome) has also been reported.

Of concern are the iatrogenic effects of chemotherapy and immunosuppression for malignant, inflammatory and autoimmune diseases on individuals with CHB. The interaction between the immune system and HBV may be disrupted by drug-induced modulation of the immune system resulting in HBV reactivation, which has the potential to cause significant liver injury.

Liver injury resulting from HBV reactivation in the setting of immunosuppressive therapy may occur through 2 mechanisms. Uncontrolled viral replication may occur during immunosuppression. Rapid rises in hepatitis B viral particles may cause direct cytolytic destruction of hepatocytes. After chemotherapy or immunosuppression has been ceased, immune reconstitution may cause severe immune-mediated injury to infected hepatocytes. An exaggerated immune response against hepatocytes expressing viral proteins may occur, leading to necrosis of liver cells. The delayed reactivation associated with immune reconstitution may occur up to six months after cessation of immunosuppression, and in the case of certain immunosuppressive agents (eg rituximab) can occur as late as 12 months post-treatment due to a prolonged immune reconstitution phase observed for more potent immunosuppressive drugs.

Iatrogenic HBV reactivation due to immunosuppression can result in asymptomatic biochemical hepatitis or more concerning, acute symptomatic hepatitis that in severe cases can lead to fulminant liver failure and death.

HBsAg negative, anti-HBc positive patients

Patients with serological evidence of past infection with HBV by far outnumber those with CHB across the globe. Patients with previously documented CHB may experience spontaneous clearance of HBsAg at a rate of 0.5% per year. Individuals may alternatively have serological evidence of past HBV exposure, both scenarios leading to an HBsAg negative/hepatitis B core antibody (anti-HBc) positive state. These patients remain at risk of HBV reactivation in the setting of immunosuppression owing the persistence of the HBV in the form of cccDNA in hepatocytes and other tissues.

Anti-HBs positive patients

There is limited evidence to date that the presence of anti-HBs protects against HBV reactivation. Anti-HBs antibodies may develop in HBsAg negative/anti-HBc positive individuals indicating the development of natural immunity. In a cohort of HBsAg negative/anti-HBc positive patients with lymphoma, patients who were anti-HBs negative prior to rituximab-based chemotherapy were observed to have a higher 2-year cumulative incidence of HBV reactivation than those who were anti-HBs positive (68.3% vs. 34.4%; \( P=0.01 \)). In a study of 29 patients with lymphoma, a threshold anti-HBs titre >100 IU/mL was associated with 0% HBV reactivation, and lower anti-HBs titre was independently associated with HBV reactivation. Cho et al similarly observed 0% HBV reactivation in patients with pre-chemotherapy anti-HBs titres >100 IU/mL, but incidence of HBV reactivation of 8.3% at 6-months and 17.3% at 24 months post-chemotherapy in those with anti-HBs titres below this threshold. In patients receiving hematopoietic stem cell transplantation, the donor anti-HBs titre was associated with a decreased risk of HBV reactivation. These findings are yet to be validated. Until then, the presence or titre of anti-HBs cannot be used to assess risk of HBV reactivation, nor guide decisions on the use of antiviral prophylaxis for HBV reactivation.

WHAT ARE THE NON-HEPATIC CONSEQUENCES OF HBV REACTIVATION?

The occurrence of HBV reactivation may influence the clinician to interrupt immunosuppression or chemotherapy to mitigate the severity of the reactivation and prevent liver failure or mortality. Treatment interruption occurred in 71% of breast cancer patients.
who experienced HBV reactivation in comparison with only 33% of patients in whom HBV reactivation did not occur \( (P=0.019) \).\textsuperscript{14} The potential outcome of any treatment interruption is a higher morbidity or mortality associated with the primary diseases process. Although data is limited as to the magnitude of the impact of treatment interruption on morbidity and mortality in relation to HBV reactivation across diseases states, these outcomes also form part of the rationale for HBV screening and prophylaxis in patients receiving any form of immunosuppression.

**HOW DO WE DEFINE HBV REACTIVATION?**

HBV reactivation has been variably defined across the existing studies, which makes the interpretation and direct comparison of some studies challenging. Across studies, the HBV DNA assays used have varied in their lower limits of detection, potentially underestimating the prevalence of HBV reactivation and delaying the timepoint at which HBV reactivation may be first detected.  

"Hepatitis" has been variably reported as alanine aminotransferase (ALT) elevation above upper limit of normal, or by "fold" increase from baseline; whether the hepatitis is symptomatic or asymptomatic is inconsistently documented. Suggested definitions for HBV reactivation are listed beneath, however a consensus is yet to be reached for the purposes of future studies:

1. In HBsAg positive patients:
   - Detectable HBV DNA in individual who previously had undetectable HBV DNA by highly sensitive assay (lower limit of detection, <20 IU/mL).
   - ≥1 log rise in HBV DNA in individual who previously had a detectable HBV DNA.\textsuperscript{15}
   - Biochemical hepatitis (ALT flare):
     - ≥3 fold rise in ALT from baseline levels exceeding the reference range or an absolute ALT ≥100 IU/mL,\textsuperscript{15} preceded by a rise in HBV DNA.
     - Consensus is needed as to a grading of the severity of biochemical hepatitis and associated clinical symptoms for the purposes of reporting in future studies.\textsuperscript{16}

2. In HBsAg negative/anti-HBc positive patients:
   - Seroreversion (or reverse seroconversion) has been described in which an individual undergoing immunosuppression develops detectable HBsAg, HBV DNA and/or biochemical hepatitis as a result of reactivation of occult infection.\textsuperscript{17}

3. In conjunction with the serological and biochemical changes, the occurrence of jaundice, liver failure or

| Disease                                      | Incidence of HBV reactivation without HBV prophylaxis | References |
|----------------------------------------------|--------------------------------------------------------|------------|
| Lymphoma                                    | 18-73, 34-68                                          | 6, 10, 33, 51-53 |
| Acute leukaemias                            | 61, 2.8-12.5                                          | 31, 32     |
| Chronic leukaemias                          | NA, NA                                               |            |
| Multiple myeloma                            | NA, 6-8                                              | 24, 47     |
| Bone marrow/haematopoetic stem cell         | 66-81, 6-10                                          | 13, 59, 61 |
| transplantation                             |                                                       |            |
| Breast cancer                               | 21-41, NA                                             | 14, 134, 157, 158 |
| Nasopharyngeal cancer                       | 33, NA                                               | 66         |
| Hepatocellular cancer (systemic chemotherapy)| 36, 11                                               | 68, 159    |
| Hepatocellular cancer (trans-arterial       | 21-30, 9.3                                            | 71-73      |
| chemoembolization)                          |                                                       |            |
| Rheumatoid arthritis                        | 12.3, 3-5                                            | 160-163    |
| Psoriasis/psoriatic arthritis               | NA, NA                                               | NA         |
| Inflammatory bowel disease                  | 36, 0-7                                              | 80, 81     |
| Autoimmune diseases                         | NA, 17                                               | 92         |
| Renal Transplantation                       | 45-70, 0.9                                           | 93, 97-99  |

HBV, hepatitis B virus; NA, not available.
*Case reports or small case series reporting HBV reactivation.
death may be considered clinical endpoints resulting from HBV reactivation.

HOW COMMON IS HBV REACTIVATION?

Immunosuppression has been associated with clinically significant reactivations of HBV in patients with both malignant disease and non-malignant inflammatory or autoimmune diseases. A range of immunosuppressive drugs and drug classes has been implicated in HBV reactivation. A broad range of prevalence of HBV reactivation is reported in the literature, largely due to the fact that the majority of the studies reporting the rates of HBV reactivation are case reports or small case series using variable definitions of HBV reactivation. Furthermore, reports in the literature arise from populations with varying prevalence of chronic HBV and HBV exposure, thereby influencing the absolute numbers of cases of HBV reactivation observed. In a recent systematic review, the observed rate of HBV reactivation in patients receiving chemotherapy for solid tumours without HBV prophylaxis was 4-68% (median 25%). Table 1 lists the range of rates of HBV reactivation reported for specific diseases.

Haematological malignancies

The greatest body of evidence for HBV reactivation in the setting of immunosuppression arises from patients treated for haematological malignancies. Reactivation of HBV has been reported in patients treated for lymphoma, leukaemia and multiple myeloma (see Table 1).

The HBV itself may be a risk factor for the occurrence of non-Hodgkin’s lymphoma, and thereby it makes this subgroup of patients particularly at risk of HBV reactivation when treated for their malignancy. In one cohort of patients with lymphoma the prevalence of CHB was 26%, but the prevalence of CHB could be even higher in other populations where HBV is endemic. HBV reactivation can occur in 18-73% of HBsAg positive patients being treated for lymphoma.

Higher HBV reactivation rates have been observed in patients receiving treatment regimens that utilize high dose corticosteroids and/or rituximab. HBV reactivation also occurs in lymphoma patients who have achieved remission; fulminant liver failure due to HBV reactivation requiring liver transplantation in 3 HBsAg-negative/anti-HBc positive patients has been reported.

Amongst patients treated for acute or chronic forms of leukaemia, regimens which include (but not limited to) imatinib and erlotinib (tyrosine kinase inhibitor class drug) appear to be associated with HBV reactivation in susceptible individuals. A similar association between the tyrosine kinase inhibitor bortezomib and HBV reactivation has been observed in cases of multiple myeloma.

Haematopoetic stem cell and bone marrow transplantation

Patients who receive a bone marrow (BMT) or haematopoetic stem cell transplant (HSCT) for haematological malignancy are a particularly at-risk population that experience prolonged immunosuppression during the conditioning chemotherapy leading up to the transplant, post-transplant immunosuppressive therapy and a protracted immune deficiency phase while engraftment occurs. Fatal HBV reactivation has been observed in HBsAg positive patients, as well as HBsAg negative/anti-HBc positive patients. In a multicenter retrospective study including 33 patients with CHB receiving both autologous and allogeneic stem cell transplantation, the rates of HBV reactivation at 2 years post-transplant were 66% and 81% respectively; the majority of the reactivations occurred within the first 12 months post-transplant. The incidence of HBV reactivation is observed to be lower, albeit not insignificant in patients with past exposure to HBV infection (HBsAg negative/anti-HBc positive). Amongst 764 patients who received a haematopoetic stem cell transplant, 137 (18%) were HBsAg negative/anti-HBc positive; HBV reactivation was observed in 14 cases (10%) within a median of 19 (range 9-77) months after stem cell transplantation.

Solid tumours

Amongst oncology patients, the prevalence of CHB has been reported in 12% of those with solid tumours. Without antiviral prophylaxis, approximately 20% of patients with CHB being treated for malignancy will experience HBV reactivation. Amongst women being treated for breast cancer who were also positive for HBsAg prior to treatment, 41% have been observed to develop HBV reactivation. HBV infection may be a carcinogenic risk factor for nasopharyngeal carcinoma thereby potentially contributing to a higher prevalence of HBV exposure and chronic infection in this subgroup of oncology patients. Not unexpectedly, HBV reactivation has been reported in patients who received chemotherapy for nasopharyngeal...
HBV reactivation has been reported in patients receiving immunosuppression for rheumatoid arthritis (see Table 1). In a cohort of HBsAg negative/anti-HBc positive patients with rheumatoid arthritis, 5% experienced HBV reactivation, and the incidence of reactivation was significantly higher amongst those who received etanercept (86% vs 36%, \( P=0.008 \)). Numerous case reports of HBV reactivation (some with fatal liver failure) have been published with the use of methotrexate, B-cell depleting agents and tumor necrosis factor (TNF)-alpha inhibitors. The contribution of specific drug classes in the development of HBV reactivation will be discussed further later in this review.

Patients with psoriasis and psoriatic arthritis with positive serological markers for past exposure to- or for CHB have also been reported in multiple case reports to experience HBV reactivation, however authors of small case series have concluded that patients with psoriasis have a negligible risk of HBV reactivation even with the use of biological agents. The latter results should be interpreted with caution, owing to the significant episodes of HBV reactivation associated with the use of biological agents in patients other diseases. These patients should still be considered at risk of HBV reactivation and be screened and managed according to current guidelines.

**Rheumatological diseases**

HBV reactivation has been reported in patients receiving immunosuppression for rheumatoid arthritis (see Table 1). In a cohort of HBsAg negative/anti-HBc positive patients with rheumatoid arthritis, 5% experienced HBV reactivation, and the incidence of reactivation was significantly higher amongst those who received etanercept (86% vs 36%, \( P=0.008 \)). Numerous case reports of HBV reactivation (some with fatal liver failure) have been published with the use of methotrexate, B-cell depleting agents and tumor necrosis factor (TNF)-alpha inhibitors. The contribution of specific drug classes in the development of HBV reactivation will be discussed further later in this review.

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**Inflammatory bowel disease**

The prevalence of HBV amongst patients with inflammatory bowel diseases (IBD, including Crohn’s disease and ulcerative colitis) ranges from 0.6-17% for HBsAg positive patients and 1.6-42% for HBsAg negative/anti-HBc positive patients and appears to correlate with prevalence in HBV in the general population. One multicenter study of patients with IBD treated with immunosuppression observed a HBV reactivation rate of 35% in HBsAg positive patients, but 0% reactivation in HBsAg negative/anti-HBc positive patients. In a subsequent study, 2/29 (7%) of patients who were HBsAg negative/anti-HBc positive developed detectable HBV DNA during treatment with anti-TNF-alpha agents without associated clinical or biochemical hepatitis. Treatment for IBD may include high dose corticosteroids and/or anti-TNF-alpha agents, both of which have been associated with cases of HBV reactivation; contrary to the observations of Lorers et al., cases of clinically significant HBV reactivation have been reported in HBsAg negative/anti-HBs positive patients, and some have been associated with fatal liver failure. Whether patients with inflammatory bowel diseases and serological markers of HBV are at lower risk of HBV reactivation under immunosuppression compared with other diseases and malignancies has been a subject of contention in the literature. This is due in part to the relatively low volume of data available on HBV reactivation in IBD patients. However, it is clear from available data that HBV is still common amongst patients with IBD, and clinically significant HBV reactivation may occur under immunosuppression. Therefore IBD patients should be screened for serological markers of HBV at the time of diagnosis of IBD, and a prophylactic treatment and/or monitoring plan for HBV reactivation instituted prior to immunosuppression according to current guidelines.

**Autoimmune diseases**

Patients with autoimmune conditions such as systemic lupus erythematosus (SLE), vasculitis, polymyositis/dermatomyositis, idiopathic thrombocytopenic purpura and autoimmune haemolytic anaemia may also receive immunosuppressive regimes, which in the setting of HBV may put them at risk of HBV reactivation. Rituximab, the B-cell depleting agent which has been associated with HBV reactivation when used for haematological malignancies is also a potential therapy in SLE, Sjogren’s syndrome, vasculitis, dermatomyositis, neurological diseases (multiple sclerosis, neuromyelitis optica, antibody-mediated paraneoplastic syndromes and IgM-mediated polyneuropathy), endocrinopathies (type 1 Diabetes and Graves disease), dermatological conditions (autoimmune blistering diseases) and non-malignant haematological conditions such as immune thrombocytopenic purpura and autoimmune haemolytic anaemia. Cases of HBV reactivation have been reported in patients immunosuppressed for a
range of autoimmune conditions however due to low numbers of cases, the true incidence of HBV reactivation is not clear. In a cohort of 35 patients with a range of such autoimmune conditions and concomitantly HBsAg negative/anti-HBc positive, 6 patients (17%) were observed to have HBV reactivation (detectable HBV DNA) 4-8 weeks after initiation of immunosuppressive treatment. Notwithstanding the limitations of the available data, patients with autoimmune conditions receiving immunosuppression should be considered at risk of HBV reactivation and managed accordingly.

Solid organ transplantation

Similar to patients who have undergone BMT, patients who have solid organ transplantation are prescribed long-term immunosuppression to prevent organ rejection. The need for pre-transplant HBV evaluation and prophylaxis in these patients must be emphasized as these patients are not only susceptible to the hepatic consequences of HBV reactivation, but are also at risk of morbidity and mortality due to graft loss.

Renal transplantation

HBV reactivation has been clearly documented in patients in the setting of renal transplantation (see table 1), some cases resulting in death due to liver failure. Furthermore, patients with pre-existing chronic HBV infection who undergo renal transplantation experience higher rates of cirrhosis and hepatocellular carcinoma than those in the general population, indicating more rapid progression of HBV-related liver disease in these patients, if untreated.

Liver transplantation

Patients who have undergone liver transplantation for cirrhosis due to chronic HBV or HBV-related hepatocellular carcinoma are at particular risk of a fulminating form of HBV reactivation; fibrosing cholestatic hepatitis. The latter is a rapidly progressive form of HBV reactivation that can result in graft loss, liver failure and death. Management guidelines for HBV infection in this special population have been provided by the American Association for the Study of Liver Disease.

Although it is beyond the scope of this review to provide a detailed discussion on the prevention and management of HBV reactivation amongst these patients, it is important to recognize that these patients will need long-term HBV prophylaxis co-administered with their immunosuppressive regime.

WHAT ARE THE FACTORS ASSOCIATED WITH HBV REACTIVATION?

The patient’s virological and serological status, the specific immunosuppressive drug or class of drug prescribed, and the duration of immunosuppression contribute to the risk of HBV reactivation in patients receiving immunosuppression.

Virological and serological status

The virological and serological risk factors associated with HBV reactivation (in descending order of risk) are detectable HBV DNA, HBsAg, hepatitis B e antigen (HBeAg) and anti-HBc.

Patients positive for HBsAg are up to 8 times more likely to experience HBV reactivation than HBsAg negative/anti-HBc positive patients. Amongst HBsAg positive patients, HBeAg positive patients are more likely to experience HBV reactivation than HBeAg negative patients.

Mutations of the HBsAg may confer risk of HBV reactivation. In a recent study of 93 patients with CHB (29 of whom developed HBV reactivation) the HBsAg genetic-features were analyzed. Seventy-six percent of HBV-reactivated patients (vs. 3.1% of the 64 control-patients, P<0.001) carried HBsAg mutations localized in immune active HBsAg regions. Of the 13 HBsAg mutations found in these patients, 8 are known to hamper HBsAg recognition by humoral response and the remaining 5 were localized in Class-I/II-restricted T-cell epitopes, suggesting a role in HBV-escape from T-cell mediated responses.

These observations suggest that patients infected with HBV expressing such HBsAg mutations may have enhanced capability to evade the immune response may be more susceptible to HBV reactivation with chemotherapy. Colson et al observed HBsAg and HBV-reverse transcription mutations in patients who were initially HBsAg negative/anti-HBc positive who experienced reverse sero-conversion.

Sequencing of HBV DNA after HBV reactivation in patients who were initially HBsAg negative/anti-HBc positive patients demonstrated that the reactivated virus is characterized by low genetic heterogeneity, with the wild-type G1896 or G1896A variant prevalent.

These findings taken together speak to the possible mechanisms of HBV reactivation in susceptible individuals, however the clinical applications are yet to be determined.

Immunosuppression drug class

The therapy of malignant, inflammatory and autoimmune conditions continues to evolve with novel and targeted agents being
developed for a range of disease states. Many of these novel immunosuppressive agents have been associated with clinical evidence of HBV reactivation as outlined above. The risk of HBV reactivation attributed to specific drug classes has been estimated by the American Gastroenterological Association (AGA) based on a comprehensive review of the literature, bearing in mind the limitations of the available data (mainly case reports or series for some drugs; Table 2).\textsuperscript{109,110}

The B-cell depleting agents appear to have a potent and durable immunosuppressive effect and are thereby associated with the highest risk of HBV reactivation. Rituximab and ofatumumab are two agents within this class largely used to treat haematological malignancy, however rituximab has been used a range of non-malignant diseases as discussed.\textsuperscript{91,111} Both HBsAg positive and HBsAg negative/anti-HBc positive patients who receive these agents are susceptible to HBV reactivation. The rate of HBV reactivation with these agents in HBsAg negative/anti-HBc positive patients has been reported at 16.9%, and seroreversion rate of 20-40%.\textsuperscript{92,108,112} HBV reactivation has occurred up to 12 months after cessation of B-cell depleting drugs (and some cases occurring beyond 12 months) indicating the durability of the immunosuppressive effect of this drug class likely due to a prolonged immune reconstitution phase. Amongst 63 HBsAg negative/anti-HBc positive patients with haematological malignancy who received rituximab without antiviral prophylaxis, the 2-year cumulative rate of HBV reactivation was 41.5%, occurring at a median of 23 weeks (range, 4 to 100 weeks) after rituximab treatment.\textsuperscript{10} These observations would indicate that extended antiviral prophylaxis and monitoring is required in patients receiving these agents.

TNF-alpha inhibitors such as infliximab, etanercept and adalimumab are used to treat inflammatory bowel disease, rheumatological disease, psoriasis and autoimmune diseases. Drugs of this class have been associated with HBV reactivation.\textsuperscript{113} A large study of 257 cases exposed to anti-TNF agents for a variety of indications reported HBV reactivation in 39% in HBsAg positive patients, 7 times higher than the incidence of HBV reactivation in HBsAg negative/anti-HBc positive patients in this cohort.\textsuperscript{114}

Cytokine and integrin inhibitors have also been associated with HBV reactivation. Drugs of this class and their target molecules are listed in table 2. Evidence of role of these drugs in HBV reacti-
viation exist largely as case reports however the risk of HBV reactivation associated with these agents may be attributed to their known relative potency of immunosuppression according to the agents’ mechanism of action.\textsuperscript{10,116}

Tyrosine kinase inhibitors including imatinib and nilotinib are considered moderately immunosuppressive and have been associated with HBV reactivation in the setting of chronic myeloid leukaemia and gastrointestinal stromal tumours amongst other diseases.\textsuperscript{37-40,54,55,117}

Corticosteroids are very commonly used immunosuppressive drugs across many disease processes. Corticosteroids directly affect T-cell function but also promote HBV DNA replication through interacting with the HBV glucocorticoid responsive element (a transcriptional regulatory element)\textsuperscript{118} Corticosteroids are prescribed at a range of dosages and durations according to indication, however it has been observed that a 4-week course of prednisone is associated with HBV reactivation after drug withdrawal (immune-reconstitution phase) and worsened liver histology.\textsuperscript{119} In patients with chronic airways disease, long-term steroid use is associated with HBV reactivation in 11.1% of those treated with oral steroids and 3.2% of those treated with inhaled steroids.\textsuperscript{120} Continuous oral corticosteroid therapy (>3 months) and high-dose (defined as >20 mg prednisone/day) was associated with HBV reactivation with odds ratio (OR) of 5.7 and 4.9 respectively, when compared with HBV reactivation in those receiving inhaled corticosteroids.\textsuperscript{120} Prednisone at a dose of <10mg/day (or equivalent), short term (<2 weeks) administration of oral (systemic) corticosteroids, intraarticular injection and topical therapies may be considered low immunosuppressive risk therapies as these have not been associated with HBV reactivation. It is therefore apparent that corticosteroids have the potential to induce HBV reactivation, but that the risk varies according to the dose, duration and route of administration.

Traditional immunomodulating drugs such as azathioprine, 6-mercaptopurine and methotrexate appear to have the lowest potential for HBV reactivation. There are no documented cases of HBV reactivation associated with the use of azathioprine or 6-mercaptopurine alone. Cases of HBV reactivation have been reported with methotrexate, however corticosteroids or other immunomodulators were co-administered in most instances, compounding the risk of HBV reactivation.\textsuperscript{121,122}

**Hepatitis B and Delta co-infection**

To date, only a single case report of hepatitis delta virus (HDV) reactivation in association with HBV reactivation exists.\textsuperscript{123} This patient was co-infected with hepatitis C virus (HCV RNA positive), HBV (HBsAg positive, HBV DNA undetectable at baseline) and had evidence of cleared HDV infection (anti-HDV positive). A rituximab-CHEOP regime was prescribed to treat lymphoma; HBV DNA became detectable during chemotherapy and HDV RNA was positive at 77.6 million copies/mL 15 months after chemotherapy. The patient was managed successfully with lamivudine, which was subsequently switched to emtricitabine/tenofovir. Given the singularity of this report, currently no evidence-based guide for the management of hepatitis B and delta co-infection in the setting of immunosuppression or cancer chemotherapy and patients should be managed according to their HBV status.

**HOW DO WE MANAGE HEPATITIS B REACTIVATION?**

The role of antiviral therapy once HBV reactivation is already established has been examined by several studies. Lamivudine therapy started at the time of ALT elevation did not appear to change the natural course of chemotherapy-associated HBV reactivation in a prospectively followed cohort of patients treated for non-Hodgkin’s lymphoma; 2 patients in this cohort died despite lamivudine use at the onset of HBV reactivation.\textsuperscript{3} Numerous case reports and series describe death due to liver failure despite the introduction of lamivudine at the onset of HBV reactivation.\textsuperscript{124-128} Only a few cases of successful treatment of HBV reactivation with entecavir or tenofovir have been published.\textsuperscript{41,129-131} Despite the paucity of data regarding the efficacy of entecavir and tenofovir to treat established HBV reactivation, the ability of these drugs to rapidly reduce HBV DNA make them attractive alternatives to lamivudine in patients who experience HBV reactivation to potentially abrogate the risk of liver failure and mortality. Ideally, these adverse outcomes should be avoided through prophylaxis of HBV reactivation.

**“PREVENTION IS BETTER THAN CURE”: HOW DO WE PREVENT HEPATITIS B REACTIVATION?**

Given the significant rates of HBV reactivation with immunosuppression and the poor outcomes observed when antiviral treatment is introduced only once HBV reactivation is already established, the role of antiviral prophylaxis must be considered in
susceptible patients who will receive immunosuppressive therapy. A systematic review and metaanalysis of 5 randomised controlled trials,\textsuperscript{19,71,132-134} comparing antiviral prophylaxis to treatment at the onset of HBV reactivation concluded that the overall risk ratio (RR) favoured the prophylactic use of antivirals over no antivirals, with RR 0.13 (95% confidence interval [CI], 0.06-0.30).\textsuperscript{109} In a systematic review of patients being treated with immunosuppressive chemotherapy for solid tumours, antiviral prophylaxis reduced the risk for HBV reactivation (OR, 0.12; 95% CI, 0.06-0.22), HBV-related hepatitis (OR, 0.18; 95% CI, 0.10-0.32), and chemotherapy disruption (OR, 0.10; 95% CI, 0.04-0.27).\textsuperscript{18}

The World Health Organization (WHO) published guidelines on the management of CHB in 2015.\textsuperscript{1} The WHO provided limited recommendations stating that CHB patients who were either eAg positive or anti-HBe positive can experience HBV reactivation precipitated by immunosuppression from chemotherapy or renal transplantation, and that these patients should receive antiviral therapy.\textsuperscript{2}

The current AGA recommendations (published in 2015) are based on the HBV reactivation risk stratification according to the combination of serological markers of HBV and the chemotherapy/immunosuppression regimen prescribed and are more detailed and specific with regard to the patient risk groups in whom antiviral prophylaxis should be considered (Table 3).\textsuperscript{108,110}

**Table 3. Summary of American Gastroenterology Association guidelines on the prevention and treatment of hepatitis B reactivation during immunosuppressive drug therapy\textsuperscript{108,110}**

| Population at risk of HBV reactivation | Screening test | Is antiviral prophylaxis recommended? | Antiviral drug recommended for prophylaxis | Monitoring in untreated HBsAg negative/anti-HBc positive patients |
|----------------------------------------|---------------|--------------------------------------|------------------------------------------|------------------------------------------------------|
| High risk of HBV reactivation (>10%)   | HBsAg and anti-HBc; HBV DNA if serology +ve | Yes (B1) if taking: B-cell depleting agents, Anthracycline derivatives, Drug with high barrier to resistance is favoured over lamivudine (B2). | Drug with high barrier to resistance is favoured over lamivudine (B2). | No recommendation provided |
| Moderate risk of HBV reactivation (1-10%) | HBsAg and anti-HBc; HBV DNA if serology +ve | Yes (B2) | Drug with high barrier to resistance is favoured over lamivudine (B2). | No recommendation provided |
| Low risk of HBV reactivation (<1%)    | Routine screening not recommended. Screen for HBV as per CDC guidelines; manage accordingly | Not recommended (B2) | Not applicable | No recommendation provided |

Evidence grade A: high quality; B: moderate quality; C: low quality. Recommendation grade 1: strong; 2: weak.

HBV, hepatitis B virus; CDC, center for disease control.
Which antiviral drug should be used for prophylaxis of hepatitis B Reactivation?

The nucleos(t)ide analogue antiviral drugs lamivudine, adefovir, telbivudine, entecavir and tenofovir may all be of potential use in the prevention of HBV reactivation in patients undergoing immunosuppression. The majority of reports concern the use of lamivudine or entecavir for the prophylaxis of HBV reactivation. Both drugs appear to reduce the incidence of HBV reactivation in immunosuppressed individuals. Entecavir (and potentially tenofovir) may be superior to lamivudine because of more potent viral suppression and lower risk of antiviral resistance (and therefore lower risk of viral breakthrough/reactivation) than lamivudine, resistance occurring in up to 20% of patients on lamivudine after just one year of use. Fatal HBV reactivation despite lamivudine prophylaxis owing to the development of the M204 drug resistance mutation has been reported in a patient who received R-CHOP for lymphoma.\textsuperscript{135} The data regarding adefovir and telbivudine in the prevention and management of HBV infection is limited to the liver transplantation setting and is outside of the scope of discussion of this review. These drugs are not recommended as first line drugs for prophylaxis of HBV reactivation in the context of chemotherapy or immunosuppression.\textsuperscript{90,110}

Lamivudine

A systematic review of lamivudine prophylaxis in chemotherapy patients determined that prophylaxis was associated with a relative risk of 0.0 to 0.21 for HBV reactivation and a relative risk of 0.0 to 0.2 for HBV-related death when compared without lamivudine prophylaxis.\textsuperscript{136} In patients with breast cancer, prophylactic lamivudine was superior to HBV treatment once HBV reactivation was established in reducing HBV recurrence (OR, 0.12; 95% CI, 0.04-0.31), HBV-related hepatitis (OR, 0.13; 95% CI, 0.04-0.37) and the rate of chemotherapy interruption (OR, 0.37; 95% CI, 0.23-0.60).\textsuperscript{137} Patients given lamivudine prophylaxis during chemotherapy have an 87% decrease in HBV reactivation compared to patients not given prophylaxis, the number not recommended to treat to prevent one reactivation being just 3 patients.\textsuperscript{138} Lamivudine prophylaxis is associated with a 92% reduction in treatment delays and premature terminations of chemotherapy due to HBV reactivation.\textsuperscript{138} A single study compared lamivudine to adefovir prophylaxis in chemotherapy patients. Amongst 70 HBsAg positive patients who received chemotherapy, HBV reactivation was observed in 13/35 (37.1%) on lamivudine was not significantly different to the incidence in patients 10/35 (28.6%) on adefovir (P=0.611).\textsuperscript{139} Taken together, these studies indicate that lamivudine significantly reduces but does not necessarily abrogate the risk of HBV reactivation in the setting of immunosuppression.

The use of lamivudine prophylaxis has been demonstrated to be cost-effective, owing to the reduced number and severity of HBV reactivations. Reduced numbers of cancer deaths in patients who receive prophylaxis have been observed, presumably due to a reduced need for withholding chemotherapy.\textsuperscript{140}

Lamivudine may have a role where total chemotherapy and post-chemotherapy follow-up duration spans less than 12 months (thereby reducing risk of drug resistance and virological breakthrough), the HBV DNA is undetectable at baseline and the patient is not receiving any of the “high risk” treatment regimes. The latter approach requires further evaluation, but may be an attractive strategy e.g. in countries with high prevalences of HBV where the cost of the more potent antivirals may be prohibitive.

Entecavir

There are seven studies to date comparing entecavir to lamivudine or no prophylaxis in patients with haematological malignancy, lymphoma alone, stem cell transplantation and solid tumours.\textsuperscript{132,134,144} Lower rates of HBV reactivation are generally observed with the use of entecavir in these studies, however these studies vary in their design (ranging from retrospective audit to randomized-controlled study) and hence the strength of their findings. In the single randomized controlled study (published in abstract form), 61 patients who received entecavir prophylaxis were compared to 60 patients who received lamivudine.\textsuperscript{132} Entecavir was associated with a relative risk reduction of 0.22 (0.08-0.61) for HBV reactivation and had significantly fewer chemotherapy interruptions (1.6% vs. 18.3%).\textsuperscript{132} In a retrospective study of 213 patients HBsAg positive patients who received chemotherapy for solid tumours, HBV reactivation was observed in 0% of the 70 patients on entecavir compared with 7% of the 143 patients in the lamivudine group (P=0.02).\textsuperscript{144} Amongst 216 HBsAg positive patients who underwent allogeneic stem cell transplantation, the cumulative incidence rates of HBV reactivation at 6, 12 and 24 months following transplantation were 3.0%, 7.0% and 24.0% in the 119 lamivudine patients, and 0%, 0% and 2.0% in the 97 entecavir patients, respectively.\textsuperscript{145} Taken together, these data suggest that entecavir is superior to lamivudine in prevention of HBV reactivation in the setting of immunosuppression.

Tenofovir

There is only one case series report to date examining the role
of tenofovir in prevention of HBV reactivation. In a heterogeneous cohort of 25 patients who received tenofovir prophylaxis prior to immunosuppression, 0% experienced HBV reactivation. Despite the paucity of data on the use of tenofovir for HBV prophylaxis in immunosuppression, it is of theoretical benefit due to the potency of its antiviral effect and low drug resistance profile.

The cost-effectiveness of entecavir and tenofovir for the prophylaxis of HBV reactivation has to date not been studied.

**How long should antiviral prophylaxis be prescribed?**

For most immunosuppressive regimes, current guidelines suggest that antiviral prophylaxis should be prescribed continuously until at least 6 months after the cessation of chemotherapy or immunosuppression and for at least 12 months for those receiving B-cell depleting agents (Table 3).

In the absence of antiviral prophylaxis, HBV reactivation has been observed in some patients as late as 6-12 months after cessation of chemotherapy in both HBsAg positive and HBsAg negative/anti-HBc positive patients, and also when the antiviral prophylaxis has been curtailed to just 2 months post-completion of antiviral therapy. Patients who have receive B-cell depleting agents appear to be susceptible to delayed HBV reactivation (up to 12 months post-treatment and beyond). This is likely because agents of this class have potent and durable immunosuppressive effects with a prolonged immune reconstitution phase, during which time patients remain susceptible to HBV reactivation. Subsequent monitoring for delayed HBV reactivation after cessation of antiviral prophylaxis is essential.

Recipients of BMT or HSCT are a special population that must be considered. Both lamivudine and entecavir have been used with the aim of preventing HBV reactivation in these cases. Whether antiviral prophylaxis can be withdrawn is unclear. HBV reactivation has been observed as early as 12 weeks post-discontinuation of lamivudine in the BMT setting. HBV reactivation has been diagnosed as late as 4 years after transplantation in a patient who was anti-HBs positive at baseline. In these patients, entecavir (or tenofovir) may be more suitable than long-term lamivudine due to the higher barrier to drug resistance conferred by entecavir. The European Association for the Study of Liver Disease (EASL) guidelines (2009) provide a recommendation for this patient population: that nucleos(t)ide analogue prophylaxis is recommended for anti-HBc positive patients receiving bone marrow or stem cell transplantation (grade of recommendation C2); a duration of therapy is not specified. As these patients are potentially at risk of HBV reactivation for years after the transplant, long-term antiviral therapy may need to be considered at the clinician’s discretion.

**HOW SHOULD SCREENING FOR HBV PRIOR TO IMMUNOSUPPRESSION BE PERFORMED?**

It is essential for clinicians caring for patients at risk of HBV reactivation under immunosuppression to be aware of this risk and screen for HBV in order to institute appropriate prophylactic therapy and/or monitoring. Screening may also uncover previously undiagnosed chronic HBV infection and potentially the presence of associated cirrhosis and/or hepatocellular cancer. These liver-related complications of chronic HBV infection require specific management and may influence how the underlying disease process is managed.

There are several approaches to screening for HBV in this patient population:

a. Screen all patients prior to chemotherapy/immunosuppression. This strategy would identify patients who would potentially benefit from:
   - Antiviral prophylaxis
   - HBV serology and HBV DNA monitoring (without antiviral prophylaxis)
   - Immunisation against HBV
   - Evaluation for complications of CHB
   - Contact tracing of family members for CHB and their subsequent management.

b. Screen only patients at risk of HBV according to CDC “high risk” groups.

c. Screen only patients who, if serological testing was positive, would be prescribed antiviral prophylaxis.

Consideration must also be given to which serological test(s) are to be used for screening:

a. Test HBsAg, anti-HBc and anti-HBs. Test HBV DNA if HBsAg or antiHBc are positive (the latter in case of occult HBV infection).

b. Test HBsAg, anti-HBc only. The role of anti-HBs in HBV reactivation is unclear. Furthermore, immunization against HBV may not be efficacious during immunosuppression. Therefore, one may argue that anti-HBs status may not be relevant prior to chemotherapy.

c. Test anti-HBc only. If positive, proceed to test for HBsAg and HBV DNA.
There is a paucity of data on the best and most cost-effective approach to screening for HBV in patients at risk of HBV reactivation. The AGA recommends HBV serological screening in patients with “moderate to high risk” according to their risk stratification paradigm (Table 3).109,110 The clinical decision on who and how to screen will likely be influenced by the characteristics of the population being managed and the resources available to the individual, the institution and nation to fund the serological testing and manage positive results.

HOW SHOULD WE MONITOR HBsAg NEGATIVE/ANTI-HBc POSITIVE PATIENTS WHO DO NOT RECEIVE ANTIVIRAL PROPHYLAXIS?

The data summarized in this review and the current clinical guidelines109,110 indicate that not all HBsAg negative/anti-HBc positive patients will benefit from antiviral prophylaxis e.g. patients with undetectable HBV DNA who are prescribed lower potency or limited duration immunosuppressive drug regimes. In those who do not receive antiviral prophylaxis, monitoring for the rare cases of HBV reactivation is advised, however there is a lack of evidence as to how this monitoring should be carried out. The EASL recommends ALT and HBV DNA testing every 1-3 months and treatment upon any evidence of HBV reactivation, but this is based on a weak level of evidence (C1).152 The current AGA guidelines do not give a recommendation on this point. An alternative approach may be to test for the reappearance of HBsAg in HBsAg negative/anti-HBc positive patients, which may occur prior to HBV DNA elevation or biochemical hepatitis. In the absence of evidence based monitoring guidelines, clinicians will need to be guided by the prevalence of HBV and HBV reactivation in their populations, the cost-effectiveness of serial serological and biochemical testing as well as the access to testing and follow-up that may vary across different countries.

HOW DO WE MONITOR PATIENTS AFTER THE CESSATION OF ANTIVIRAL PROPHYLAXIS?

Some patients who receive antiviral therapy at the initiation of chemotherapy or immunosuppression may need to remain on antivirals long term if there is underlying chronic liver disease and ongoing treatment criteria for CHB are met.152,153,157 In those who receive antiviral prophylaxis without otherwise meeting ongoing treatment criteria for CHB, specific guidelines as to how to perform post-prophylaxis monitoring are not available owing to a paucity of evidence. Clinical intuition and the available evidence would suggest that these patients should be monitored for at least 12 months, if not, long-term, particularly if there is a likelihood for the relapse of their underlying disease process requiring resumption of immunosuppression, and reinstitution of antiviral prophylaxis is required. Monitoring for HBsAg seroreversion, HBV DNA and/or ALT elevation could form part of the post-prophylaxis monitoring, however the time interval required between testing is unclear due to a lack of evidence base. Intuitively, more frequent monitoring may be required soon after cessation of antiviral prophylaxis (eg 3-monthly for the first year) and less frequent testing may be required beyond this.

CONCLUSIONS

Awareness of the potential for iatrogenic HBV reactivation as a complication of immunosuppression is essential. Those at risk for HBV reactivation must be screened serologically according to current evidence based-guidelines. Prophylaxis for HBV reactivation with antiviral nucleos(t)ide analogues should be commenced in susceptible individuals before the initiation of chemotherapy to abrogate the risk of HBV reactivation and the associated adverse clinical outcomes.

Conflicts of Interest

The author has no conflicts to disclose.

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