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MINIREVIEWS

Management of hepatitis B reactivation in immunosuppressed patients: An update on current recommendations

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Abstract

The proportion of hepatitis B virus (HBV) previously exposed patients who receive immunosuppressive treatment is usually very small. However, if these individuals are exposed to potent immunosuppressive compounds, the risk of HBV reactivation (HBVr) increases with the presence of hepatitis B surface antigen (HBsAg) in the serum. Chronic HBsAg carriers have a higher risk than those who have a total IgG anticore as the only marker of resolved/occult HBV disease. The loss of immune control in these patients may results in the reactivation of HBV replication within hepatocytes. Upon reconstitution of the immune system, infected hepatocytes are once again targeted and damaged by immune surveillance in an effort to clear the virus. There are different virological scenarios, and a wide spectrum of associated drugs with specific and stratified risk for the development of HBVr. Some of this agents can trigger a severe degree of hepatocellular damage, including hepatitis, acute liver failure, and even death despite employment of effective antiviral therapies. Currently, HBVr incidence seems to be increasing around the world; a fact mainly related to the incessant appearance of more powerful immunosuppressive drugs launched to the market. Moreover, there is no consensus on the length of prophylactic treatment before the patients are treated with immunosuppressive therapy, and for how long this therapy should be extended once treatment is completed. Therefore, this review article will focus on when to treat, when to monitor, what patients should receive HBV therapy, and what drugs should be selected for each scenario. Lastly, we will update the definition, risk factors, screening, and treatment recommendations based on both current and different HBV management guidelines.

Key words: Anti-tumor necrosis factor-α drugs; Acute liver failure; Biologic therapy; Immunosuppressive therapy; Hepatitis B

Core tip: Chronic hepatitis B surface antigen carriers have a high risk to develop hepatitis B virus (HBV) reactivation (HBVr) when exposed to immunosupresive therapy. The loss of immune control in these patients may results in an increase in HBV replication. There is a wide spectrum of associated drugs with specific and stratified risk for the development of HBVr. Currently, HBVr incidence seems to increase worldwide, mainly due to the appearance of more powerful immunosuppressive drugs. This review article focus on when to treat, when to monitor, what patients should receive HBV therapy, and what drugs should be selected in each scenario. We updated here current HBV management guidelines.

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INTRODUCTION

Hepatitis B virus (HBV) infection is a major public health problem worldwide; roughly, 30% of the world population shows serological evidence of current or past infection[1], and it is largely considered that there are 350 million chronic carriers globally[2,3]. Although chronic infection can lead to progressive liver injury, most patients (60%-85%) are asymptomatic, and therefore the infection remains unrecognized until the appearance of signs or symptoms of chronic liver disease/cirrhosis[4,5]. Even though a small percentage of patients who were previously in contact with HBV will probably require immunosuppression as treatment of different illnesses (malignant, autoimmune, chronic rheumatic diseases) or to avoid post-transplantation rejection. However, treatment with such agents raises the risk of HBV reactivation (HBVr). This holds particularly true for patients with previously undetected chronic HBV infection, but also for those with resolved or occult infection [hepatitis B surface antigen (HBsAg)-negative, antibody to hepatitis B core antigen (antiHBc)-positive, with or without antibody to hepatitis B surface antigen (antiHBs)-positive serology][6-10]. These events are referred to as HBVr; they were first described 40 years ago as a complication of renal transplantation and cancer chemotherapy. Since then, HBVr has become well recognized in numerous immunosuppression (IS) settings. Despite of that, HBVr due to IS continues to cause severe hepatitis, liver failure, and even death in spite of the availability of effective HBV vaccines, easily available and cheap tests to define patients at risk, and safe and effective antiviral therapies. A more worrisome issue is that the occurrence of this severe clinical event appears to increase around the globe[11]; perhaps, this is due to the permanent changing landscape of IS agents involved, the heterogeneous screening, definition and treatment guidelines, and the multiple available therapeutic options[12]. This revision aims to update HBVr definition, risk factors, screening, and treatment recommendations based on the currently published evidence.

HOST AND VIRAL INTERACTION: HBVR CLINICAL FEATURES

Hepatocellular inflammation and injury in HBV infection is suggested to be directly related to the intensity of host immune response[13]. In the initial phase of immune tolerance, infected children have high levels of viral replication, with no associated liver injury. As the immune system matures, the infected person enters a phase of immune clearance, in which the hepatocytes infected with HBV are targeted and damaged, resulting in hepatitis flares. In most individuals, the immune system is eventually able to control viremia, leading to hepatitis B e antigen clearance, suppression of HBV DNA levels, and normalization of liver biochemical test. The immune control phase usually endures; however, in cases of iatrogenic or natural IS, the loss of immune control results in reactivation of HBV replication inside hepatocytes. Upon reconstitution of the immune system, these hepatocytes are once again targeted and damaged by immune surveillance, in an effort to clear the virus[5,14,15]. HBVr has been described as a three-phase event (Figure 1). Initially, an increase in HBV DNA levels in an HBsAg positive person, or a reappearance of either HBsAg (seroreversion) or HBV DNA occurs; this period is usually asymptomatic. When the following phase takes place, HBV DNA levels show a sustained increase in viral load, accompanied by concomitant elevations in aminotranferase levels, which may also be associated to the development of severe hepatocellular damage; to note, even acute liver failure and ultimately death may occur. The aforementioned events result from a reconstitution syndrome of the host immune response. Finally, liver damage resolves due to recovery of the immune system strength (spontaneously or as a result of immunosuppressive therapy suspension) or due to the administration of antiviral drugs. This event may result in complete resolution of hepatic inflammation, or in fewer cases, a higher HBV DNA viral load in previously HBsAg positive patients can be observed[3,14,15]. Despite the fact that HBVr is usually found in chronically infected patients; it has also been reported in patients with resolved or occult HBV infection (*i.e.*, HBsAg negative, antiHBc positive), since these individuals still have traces of HBV DNA replication in their liver.

The reactivation risk depends on a combination between the degree and duration of IS[4,16] Reactivation of HBV replication during IS can occur in an indirect fashion, through abolition of specific T-cell control, but also in a straightforward manner, when stimulation of a glucocorticoid-responsive element in the HBV

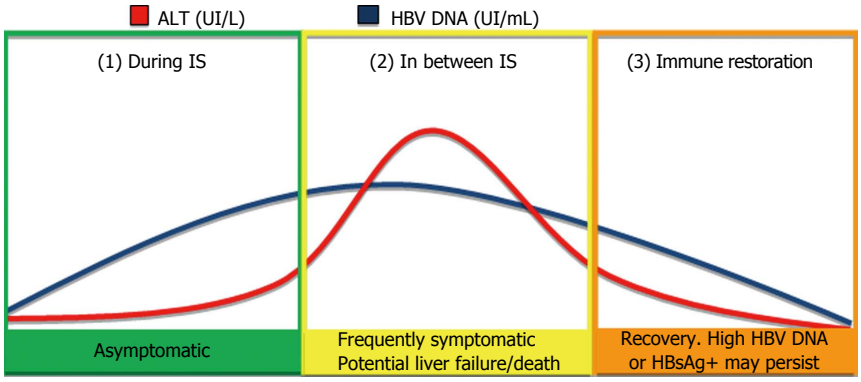

Figure 1 Hepatitis B reactivation phases. In the initial phase, there is an increase in HBV DNA levels, usually with an asymptomatic evolution. In the second phase, both ALT and HBV DNA are elevated; symptoms are frequently present, and they may be severe. The third phase is determined by resolution, although HBsAg (if reappeared), or elevated HBV DNA, may persist[3,17,55]. IS: Immunosuppression; HBV: Hepatitis B virus; ALT: Alanine aminotransferase; HBsAg: Hepatitis B surface antigen.

genome occurs, leading to up regulation of HBV gene expression[17].

HBVR DEFINITIONS: A HETEROGENEOUS GROUP

One of the major difficulties assessing the impact of HBVr is the different diagnostic criteria found in the literature[16]. Although reports of HBVr and its consequences are not scarce, the data are often difficult to contrast, because of the different definitions used. Some studies consider HBV DNA level elevations[18], some evaluate reappearance of HBsAg[19], and others evaluate episodes of hepatitis syndrome, utilizing different grading (severity) systems[4]. Consensus has not been reached, even in the major clinical guidelines; both the European Association for the Study of the Liver (EASL) and Asian Pacific Association for the Study of the Liver (APASL) chronic hepatitis B guidelines, when addressing HBVr, considers HBsAg seroreversion and rise in HBV DNA levels as diagnostic criteria[20,21], whereas the American Association for the Study of Liver Diseases (AASLD) defines HBVr as reappearance of active necroinflammatory disease of the liver in an individual at an inactive HBsAg carrier state or who was known to have resolved hepatitis B[5]. Recently, at the Reactivation of Hepatitis B AASLD meeting held in 2013, the first attempt to establish a standardized nomenclature was made. Reactivation of HBV replication was defined as a marked increase in HBV replication ($\geqslant$ 2 log increase from baseline levels or a new appearance of HBV DNA to a level of $\geqslant$ 100 IU/mL) in a person with previously stable or undetectable levels. The types of reactivation were described as reverse HBsAg seroconversion (reappearance of HBsAg), or appearance of HBV DNA in serum in the absence of HBsAg. The severity of reactivation, defined by the presence or absence of jaundice and liver failure; and its outcome (return to baseline status or persistence in an activated state, need for liver transplantation or death) should also be reported[2,17]. A universal grading system that also includes the consequences related to the IS therapy was recently proposed by Visram *et al*[4], in an additional effort to standardize HBVr grading and its consequences.

MEDICAL INTERVENTIONS ASSOCIATED WITH HBVR

Several agents have been associated with the risk of HBVr, depending on the type and intensity of IS caused by these medical interventions[2]. The most relevant ones are described below, and displayed according to the risk of HBVr in Figure 2.

Antimetabolites

HBVr during IS with low doses of azathioprine or methotrexate, when used as monotherapy, is uncommon[3,22]. In a thorough review recently published, no report was found in which azathioprine used alone was documented to cause HBVr[12]. Similarly, although several reports associated with methotrexate-induced HBVr are available, most of them involved the concomitant use of other immunomodulators[22]. Indeed, this antimetabolite has been in clinical use for more than 50 years, and only a small number of cases have been described in published reports in which HBVr was attributable to this agent when used alone. Based on these findings, they are considered to be drugs with low risk of HBVr[12,23].

Tumor necrosis factor-α inhibitors

Tumor necrosis factor-α (TNF-α) is a pro-inflammatory and immunoregulatory cytokine involved in the pathogenesis of several inflammatory disorders. The inhibition of TNF-α signaling can lead to increased HBV replication and reactivation[2,24]. Anti-TNF-α agents are approved to treat rheumatoid arthritis, intestinal inflammatory diseases and psoriasis; in this context, several (*e.g.*, infliximab, adalimumab, certolizumab, golimumab and etanercept) have been associated with HBVr[22]. In a meta-analysis published by Lee *et al*[25] evaluating the risk of HBVr in 468 isolated antiHBc patients with rheumatic conditions treated with different anti-TNF-α

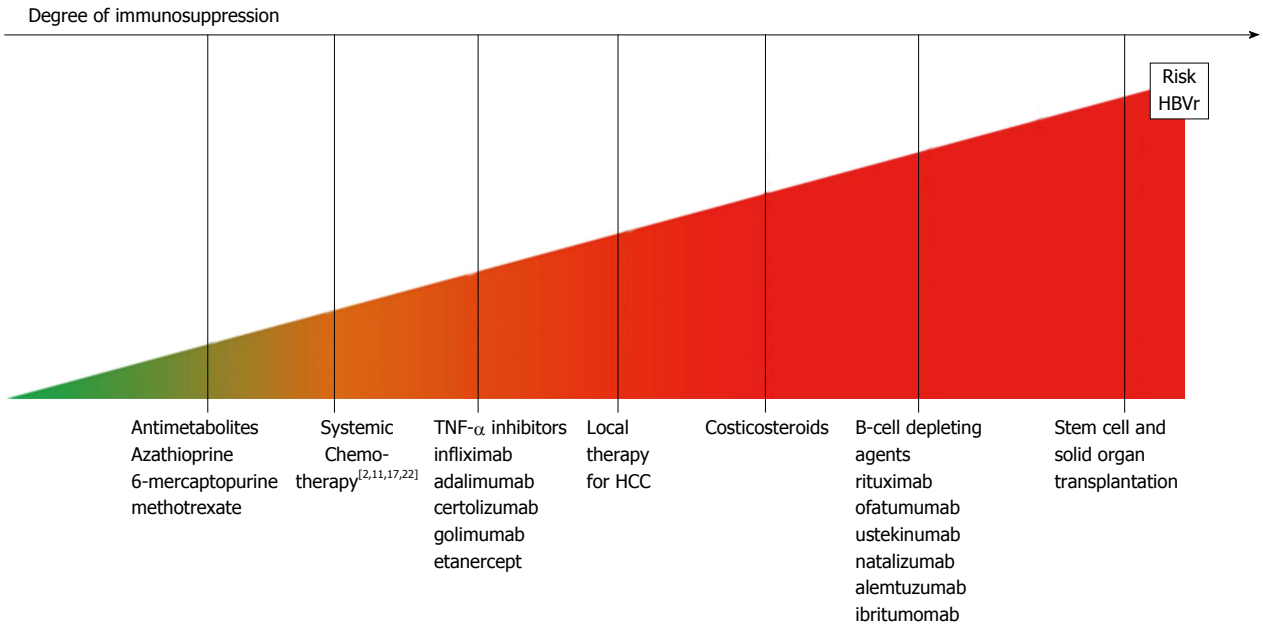

Figure 2 Immunosuppressing agents and related risk of hepatitis B reactivation. HCC: Hepatocellular carcinoma; TNF-α: Tumor necrosis factor-α; HBVr: Hepatitis B virus reactivation.

(mostly etanercept), HBVr was found in 1.7% of the cases. The same author reported much higher rates of HBVr in HBsAg-positive patients (12.3%) in a similar cohort of rheumatic patients[26]. Additionally, several severe HBVr have been communicated, particularly following infliximab administration[3,27]. However, it is unclear whether the risk of HBVr is the same with every TNF-α inhibitor. Most cases have been associated with the more potent IS drugs such as infliximab or adalimumab rather than etanercept. Comparative risk assessment between these agents is doubtful when incidence is derived from case report and retrospective rather than well-designed prospective studies. Therefore, a moderate level of confidence can be given to estimation that the risk of HBVr during anti-TNF-α monotherapy is between 1% and 10% in HBsAg carriers, and quite lower in isolated antiHBc[12].

Locoregional therapy for hepatocellular carcinoma

Several therapeutic strategies for hepatocellular carcinoma (HCC) have been inferred to cause HBVr[28,29]. Transarterial chemoembolization (TACE) has been directly associated with an increased rate of HBVr[30]. Even though this procedure has little systemic effect due to the administration of chemotherapeutic agents directly into a branch of the hepatic artery[2], it may cause systemic symptoms if arterio-venous shunts or peritumoral microcirculation are present; this is why host immune system is often compromised. Additionally, anthracyclines (*i.e.,* doxorubicin) are frequently used as part of intra-arterial chemotherapy. In experimental models, anthracyclines have stimulated HBV DNA secretion from HCC cell lines; this mechanism may help to explain the higher risk of HBVr in patients treated with doxorubicin-containing TACE[12]. HBVr during radiotherapy, with or without TACE, has also been examined in several studies[27,31]. In a prospective study conducted by Huang evaluating 69 HBV patients with HCC treated with conformal radiotherapy, almost 25% of them suffered HBVr, and 21.7% HBVr induced hepatitis[32]. HBVr in patients who underwent HCC surgical resection and local ablation therapy have also been extensively reported[27,30].

Corticosteroids

Prednisone is the cornerstone of several chemotherapeutic regimens, and an important agent to induce remission in inflammatory bowel disease[2]. This and other corticosteroids have been associated with an increased risk of HBVr (both in monotherapy and especially when combined with other IS drugs)[22]. The HBVr is thought to be mediated by abolition of specific T-cell control, and also by direct viral stimulation. The risk of infection has been stratified according to the dosage and time of exposure to the corticosteroid[33]. Based on these variables, in a meta-analysis that included every well-documented report on HBVr, a risk stratification score was proposed: HBsAg positive patients who received more than 10 mg/daily of prednisone for 4 wk or longer were included in the high-risk group (> 10% chance of HBVr); HBsAg positive patients that received less than 10 mg/daily of prednisone or HBsAg-negative, antiHBc positive patients that were treated with less than 20 mg/daily of prednisone for less than 4 wk are included in the moderate-risk group (1%-10% risk of HBVr). Finally, antiHBc positive patients treated with less than 10 mg/daily of prednisone for less than 4 wk, and patients with local steroid treatment (such as intra-articular infusion) were included in the low risk group[12]. Therefore, corticosteroid use is an independent risk

factor for HBVr[12,22].

Systemic chemotherapy

This is one of the therapeutic interventions more frequently related with HBVr; not only associated with the degree of immunosuppression but also with the type of malignancy treated[14,16,34]. HBsAg-positive chronic carriers with hematologic diseases are at the highest risk of developing HBVr during IS, reaching an incidence of 40%-50%, or even higher, according to different series[12,27]. One of the most frequently cited study is related to the risk of HBVr in lymphoma patients, with reactivation rates reaching almost 50%, and an associated mortality of 4%[14,17,18,22,35]. Other studies report on an incidence of HBVr in this setting between 24%-67%, and an elevated mortality rate of 4%-41%. One of the reasons for this elevated risk relies on the intensive chemotherapy necessary for lymphoma treatment, especially when most chemotherapies schemes include high doses of steroids and/or rituximab. It may also be due to the rather high prevalence of HBV observed in this cohort of patients[14,36]. HBVr has also been described in patients receiving chemotherapy for treatment of solid tumors (*i.e.*, breast, colon and lung cancer)[21,22,37]. These patients fall within the intermediate risk category (HBVr chance of 10%-30%). Finally, the low risk group includes patients with gastrointestinal malignancies receiving 5-fluorouracil based therapy[27].

Biologic antibodies

Rituximab is considered a high-risk factor for HBVr[38]. This cytolytic monoclonal antibody is directed against the CD20 antigen of immature and mature B cells; it is used for the treatment of numerous hematological malignancies, severe rheumatic conditions, and (off-label) solid organ transplantation (in the latter scenario, as an adjunctive agent to mitigate humoral allograft response)[13]. When combined with standard-of-care chemotherapy for non-Hodgkin's lymphoma, HBVr has been observed in up to 25% of patients with resolved infection; this reactivation may occur even 12 mo after the therapy has been completed; including those patients with isolated antiHBc[22,39]. A preliminary analysis of the post marketing data from the Food and Drug Administration (FDA) Adverse Event Reporting System found 109 cases of HBV-related acute liver failure associated with rituximab and ofatumumab (another anti-CD20 monoclonal antibody). They occurred during the 13 years of rituximab and 3 years of ofatumumab commercialization[17]. Due to these reports, in the year 2013 a boxed warning was included in the label issued by the FDA for both drugs, describing HBVr resulting in "fulminant hepatitis, hepatic failure and death". This advisement underlines the potential for HBVr especially in chronically infected patients, but also in those who have resolved a previous HBV infection[13,17]. Due to these events, all antibodies directed against CD20 have been compelled by the FDA to add HBVr to the boxed warning; recommending HBV screening tests before initiation of therapy and therapy when positive results are found[17]. Other biologic agents, such as specific tyrosine kinase inhibitors imatinib and nilotinib, have been implied in well-documented cases of HBVr; however, newly developed drugs including cytokine and integrin inhibitors such as ustekinumab, natalizumab, alemtuzumab and vedolizumab, have few or no reports of HBVr as yet. Since they all share the same mechanism of action, it is expected for them to convey at least a low to moderate risk of this complication[12,22].

Stem cell and solid organ transplantation

Patients undergoing stem cell/bone marrow transplantation are at the highest HBVr-risk position followed closely by those receiving solid organ transplantation.

Bone marrow/stem cell transplanted patients typically get intense chemotherapy to induce remission of the underlying malignancy, followed by additional chemotherapy and radiation therapy to ablate bone marrow[17,40]. The profound IS and loss of pre-existing HBV-specific immunity allows for HBVr in the liver to occur, and the return of active viral replication[19]. In this setting, the HBVr rate reaches 50% in both HBsAg-positive and isolated antiHBc-positive patients. In the latter group, antiHBs titles below 10 mUI/mL were a predictor of HBsAg seroreversion[17]. Due to the considerable delay in immune system reconstitution that typically occurs in this subset of patients, the risk of seroreversion can endure for several years; furthermore, these patients are prone to develop chronic infection once the virus is reactivated[19]. In a retrospective study that evaluated 137 HBsAg negative and antiHBc positive patients who underwent hematopoietic cell transplant patients, the prevalence of HBVr reached 10%, occurring within 9 to 77 mo after transplantion[40].

When considering solid organ transplantation, HBVr risk has been known to reach 50%-90% in HBsAg-positive patients after kidney transplantation. In these cases, reactivation has the potential to cause liver failure, progression to cirrhosis, HCC, and increased liver-related mortality. Other solid transplant recipients (*e.g.*, heart, lung) have been the subject of similar reports[17].

WHOM TO CHECK: UNIVERSAL SCREENING *VS* HIGH-RISK PROFILING

The key to prevent HBVr is the timely identification of HBV-infected patients prior to immunosuppressive therapy[41,42]. The proportion of patients ignorant of their chronic HBV infection reaches 35% in United States; this proportion is far higher (90%) in the European Union[4,17], whereas in Latin America the figures are unknown. To note, HBV screening is mandatory in high-risk groups in only 15% of the countries located of this region[43]. Lack of standardized risk factor assessment, the fact that many patients are not aware (or might not acknowledge)

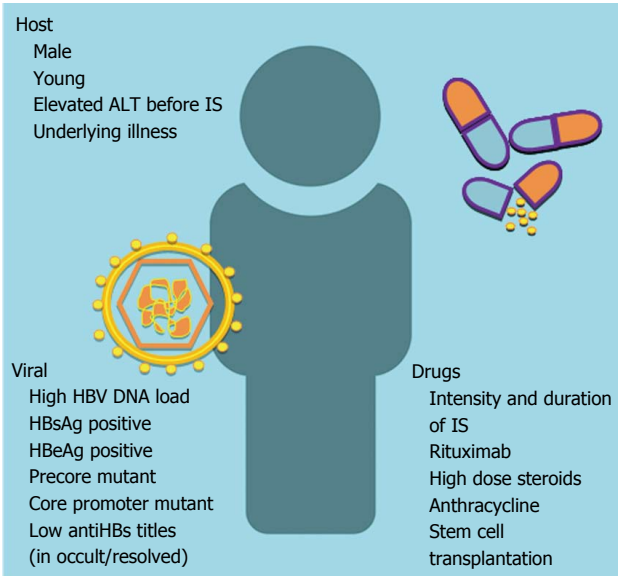

Figure 3 Risk factors for hepatitis B reactivation in patients with current/past hepatitis B infection. ALT: Alanine aminotransferase; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; IS: Immunosuppression[2,4,27,56,57].

that they have had risk behaviors, and the scarce time dedicated by most physicians to systematically screen their patients for HBV risk factors when they are about to start immunosuppressive therapy worsen the situation[14,17,44]. Risk factors for HBV infection are well-known (patients born in areas with intermediate-high HBV prevalence, patients who use intravenous drugs, patients that have had multiple sexual partners, patients with sexually transmitted diseases, *etc.*)[5,20], but factors associated with HBVr have been less described; these are relevant for the decision and timing of HBV treatment. The most relevant ones are shown in Figure 3.

The combination of several of these risk factors has been suggested to stratify patients into high-, intermediate-, and low-risk for HBVr[6,12]. The relevance of risk assessment relies on the screening strategy adopted by the physician. Several HBV diagnostic consensus statements suggest universal screening, including the Centers for Disease Control and Prevention recommendations, as well as the EASL and the APASL guidelines[6,20]. The benefits of this approach are not only the identification of every chronically infected HBV patient, but also the recognition of patients previously exposed to the virus, thus eliminating the possibility of missing patients without clearly identified risk factors. The alternative screening strategy involves testing only patients at high risk for HBV infection; these recommendations are endorsed by the AASLD, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network[6,17,45]. This targeted approach has been praised in relation to its lower cost, however, it may fail to identify chronic HBV carriers and previously exposed patients, and perhaps more importantly, it has been challenging for physicians to accomplish[6].

Table 1 Diagnostic tools suggested for hepatitis B screening prior to immunosuppression therapy by different major guidelines

Recommendations	Hepatitis B screening tests before immunosuppression			
	HBsAg	AntiHBc	HBV DNA	AntiHBs
CDC	Yes	Yes	No	Yes
AASLD	High risk	High risk	No	No
EASL	Yes	Yes	No	No
APASL	Yes	No	No	No
ASCO	High risk	High risk	No	Yes[1]

[1]Only suggested in antiHBc-positive patients. CDC: Center for Disease Control; AASLD: American Association for the Study of Liver Disease; EASL: European Association for the Study of the Liver; APASL: Asian Pacific Association for the Study of the Liver; ASCO: American Society Clinical Oncology; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; AntiHBc: Antibody to hepatitis B core antigen; AntiHBs: Antibody to hepatitis B surface antigen.

SCREENING TOOLS: HETEROGENEOUS RECOMMENDATIONS

Currently, there are no universally accepted screening tests adopted into clinical practice. Again, lack of consensus regarding testing for hepatitis B current/resolved infection complicates the picture[2]. Recommendations of different serologic testing for HBV screening prior to IS are shown in Table 1. HBsAg testing is endorsed by all major societies without consensus regarding risk evaluation, as already stated[6]. AntiHBc is not a required test by the APASL due to the high prevalence of HBV in this region (up to one third of the population)[46]. Whether to include antiHBs and HBV DNA testing among antiHBc-positive subjects is still controversial, since it is not based on prospective data[6,46]. Finally, regarding the moment for testing, it has been suggested that the major benefit is reached when it is done prior to initiation of therapy[16,27,47].

TREATMENTS FOR HBVR: SEVERAL MATTERS TO ADDRESS

The rationale for the identification of patients infected by HBV is to allow proper antiviral therapy, if needed, or otherwise to undertake careful monitoring[17]. Once again, several decisions have to be made by physicians on this point, some of which have different endorsements according to the consulted guideline. The decision-making stages are the following ones.

When to treat

Several definitions have been used to classify treatment initiation timing. Treatment prophylaxis refers to antiviral therapy started before or concurrently as the initiation of immunosuppressive therapy, and before aminotransferase or HBV DNA levels rise occurs. On the other hand, in pre-emptive treatments, the occurrence of serum HBV DNA or aminotransferase elevation deter-

Table 2 Recommendations for treatment and follow-up in different clinical scenarios, according to Asian Pacific Association for the Study of the Liver, American Association for the Study of Liver Disease and European Association for the Study of the Liver guidelines

	Recommendations in different clinical scenarios				
	HBsAg (+) HBV DNA ⩾ 2000 U/mL	HBsAg (+) HBV DNA < 2000 U/mL	HBsAg (-) antiHBc (+)	HBsAg (-) antiHBc (-) antiHBs (-)	HBV-HCC TACE
Action	Treat	Treat	Close mon/treat if HBV DNA (+) or rituximab/stem cell transplant[1]	Vaccination	Treat[3]
Onset	Before IS	Before IS	Before IS	-	Before IS
Duration	6-12 mo (except CI)	6-12 mo (except CI)	6-12 mo	-	-
Drug	Short IS: LAM (LdT) preferred ETV/TDF	Short IS: LAM (LdT) (ETV/TDF)	Short IS: LAM (LdT) (ETV/TDF)	-	LAM (ETV/TDF)
Follow-up	-	-	Every 1-3 mo/treat if HBV DNA (+)[2]	-	-

In HBsAg-positive patients, duration could be determined by CI as in immunocompetent patients. A 12-mo treatment was only endorsed by EASL. Drug selection depends on treatment duration and clinical setting. [1]In isolated antiHBc-positive patients when treated with biologic agents, close follow-up and treatment, if necessary, is suggested by AASLD/APASL; however, EASL proposes that isolated antiHBc-positive patients, if HBV DNA-positive, antiHBs-negative or undergoing rituximab/stem cell transplantation, should be treated with the same strategy as HBsAg positive patients; [2]When monitored, treatment should start when HBV DNA becomes positive, before ALT rise (EASL); [3]Treatment in all HBV-related HCC patients undergoing TACE is suggested by APASL guidelines. CI: Clinical indication; IS: Immunosuppression; HBsAg: Hepatitis B surface antigen; AntiHBc: Hepatitis B core antibody; AntiHBs: Hepatitis B surface antibody; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolization; LAM: Lamivudine; ETV: Entecavir; TDF: Tenofovir; LdT: Telbivudine (only listed as an option in AASLD guidelines); AASLD: American Association for the Study of Liver Disease; APASL: Asian Pacific Association for the Study of the Liver; EASL: European Association for the Study of the Liver.

mine the initiation of antivirals (before symptoms, if any, appear)[17]. The latter definition has been included in what referred to as "deferred treatment" in more recent publications[12]. Regarding HBsAg-positive patients, most treatment guidelines recommend prophylactic treatment; such as the AASLD (initiation of antivirals at the onset of IS), and the APASL guidelines (initiation of antivirals one week prior to chemotherapy)[5,30] (Table 2). The EASL mentions the "pre-emptive" treatment strategy, but defines it as antiviral administration during therapy regardless of HBV DNA levels, similar as the aforementioned guidelines[20].

Several studies have compared these starting-point strategies. In the technical review by Perrillo *et al*[12] where results of two randomized controlled trials of antiviral prophylaxis with lamivudine in HBsAg-positive patients undergoing chemotherapy were evaluated, an HBVr rate of 55% was found in the untreated group. There was biochemical evidence of hepatitis in 86% of these patients, which resulted in hepatic failure in 10% of the cohort[12]. In a recent meta-analysis published by Zheng *et al*[48] where the efficacy of prophylactic use of lamivudine in HBsAg-positive patients undergoing chemotherapy for breast cancer was evaluated, the rate of HBVr was diminished by 91%, and there was a similar reduction in chemotherapy disruption in the prophylactic lamivudine group. HBsAg-negative and antiHBc-positive patients, when compared with HBsAg-positive patients, appear to have a lower risk of HBVr when exposed to moderate-risk immunosuppressive drugs. This would explain why certain scientific societies such as APASL suggest close monitoring and treatment in this patient's population only when reactivation occurs[30]. In contrast, when high-risk agents such as rituximab are used in isolated antiHBc-positive patients, high rates of reactivation in excess of 10% occur, and antiviral prophylaxis can be expected to result in similar absolute risk reduction, as described for HBsAg-positive patients[5,12,30].

Whom to treat and what antiviral to choose

Most guidelines agree on recommendations for HBsAg-positive patients[49]. In this group, the choice of antiviral and lenght of therapy will depend on the clinical status of the HBV infection. When considering HBsAg-positive patients, antiviral therapy should commence in the context of immunosuppression. If the patient has clinical indications for HBV treatment (*i.e.*, HBV DNA > 2000 IU/mL), either tenofovir or entecavir should be chosen, and therapy should be maintained until they reach therapeutic endpoints for chronic hepatitis B. Otherwise, prophylactic therapy could be initiated with lamivudine, although more powerful antiviral could be chosen as well[5,20,30,50]. This rule also applies to all HBV-related, HCC patients who are to undergo TACE[30]. Lamivudine will only be sufficient in a finite and short-term course of immunosuppressive therapy. Elseways, in those patients with elevated HBV DNA viral load and/or in those receiving prolonged cycles of IS, protection with entecavir or tenofovir is preferred, due to their higher potency and stronger barrier of resistance[20,51-53]. Lamivudine resistance increases according to treatment duration, reaching a 10%-20% rate in the first year, and increasing longitudinally with time (especially with high initial HBV DNA viremia). In addition, given that drug-resistant variants are archived and reemerge quickly on re-exposure to the antiviral drug, patients with a history of prior lamivudine or telbivudine treatment would be best treated with tenofovir, as this is the most effective drug for patients with prior resistance. The recommendation of both entecavir and tenofovir are based on the evidence of efficacy of these drugs in treating chronic HBV patients outside the prophylaxis setting, since their utility in the immunosuppressive

scenario has been less studied. There are no studies of tenofovir use, but several cohort studies and a randomized trial using entecavir[12,54]. Preliminary results of 121 patients with lymphoma treated with R-CHOP (chemotherapy treatment including rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) randomized to lamivudine and entecavir prophylaxis, HBVr was seen in 8% of the lamivudine-treated patients and none among the entecavir-treated patients. Recommendations for tenofovir use must be based on anticipated parallel benefits to entecavir, as both drugs are of high antiviral potency and have low risk of resistance with prolonged therapy[49].

There is no consensus regarding the duration of treatment; AASLD and APASL societies suggest 6 mo of maintenance after IS cessation, whereas EASL recommends its extension to 12 mo[5,20,30]. Both AASLD and APASL guidelines consider that in HBsAg-negative but antiHBc- and antiHBs-positive patients, and in those with isolated antiHBc, reactivation is infrequent. Therefore these patients should be monitored and antiviral therapy initiated when HBVr occurs[5,30]. However, EASL suggests that this subgroup of patients should be tested for HBV DNA, and if present, they should be treated similarly as HBsAg-positive patients. Furthermore in antiHBs negative patients and/or when close monitoring of HBV DNA is not guaranteed, this guideline recommends prophylaxis therapy with antivirals in patients receiving rituximab, bone-marrow or stem-cell transplantation and/or combined regimens for hematological malignancies. The optimal duration of prophylaxis for these indications is unknown[20].

CONCLUSION

Ambiguity on the nomenclature of HBVr is a major problem that has led to the uncertain estimation of its incidence. A proper standardization of both terminology and definitions are required to reach better estimates of the frequency and associated risk factors of HBVr in different clinical settings. Furthermore, this standard definitions should be employed in safety and efficacy trials for new IS agents.

HBV screening before starting immunosuppressive therapy is a key factor to prevent HBVr. We need consensus on how and when to screen HBV in patients at high risk for HBVr. The call for large, collaborative, population-based studies is eagerly awaited to determine with confidence the efficiency of the HBV screening methods, and the consequent optimal antiviral prophylaxis, aimed to HBVr prevention.

Many HBV-infected patients are unconscious of their disease or risk factors. An appeal from scientific societies for physicians to spend enough time to assess patients for HBV risk factors prior to begin immunosuppression therapy is mandatory.

Finally, to make progress in this field, consensus from major societies composing the scientific hepatology community in the construction of clear guidelines to define HBVr management (*i.e.,* antiviral selection, treatment onset and duration) and follow-up are essential.

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