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TOPIC HIGHLIGHT

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Management of hepatitis B virus infection after liver transplantation

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Abstract

Chronic hepatitis B virus (HBV) infection is responsible for up to 30% of cases of liver cirrhosis and up to 53% of cases of hepatocellular carcinoma. Liver transplantation (LT) is the best therapeutic option for patients with end-stage liver failure caused by HBV. The success of transplantation, though, depends on receiving prophylactic treatment against post-transplant viral reactivation. In the absence of prophylaxis, liver transplantation due to chronic hepatitis B (CHB) is associated with high rates of viral recurrence and poor survival. The introduction of treatment with hepatitis B immunoglobulins (HBIG) during the 1990s and later the incorporation of oral antiviral drugs have improved the prognosis of these patients. Thus, LT for CHB is now a universally accepted option, with an estimated 5 years survival of around 85% *vs* the 45% survival seen prior to the introduction of HBIG. The combination of lamivudine plus HBIG has for many years been the most widely used prophylactic regimen. However, with the appearance of new more potent oral antiviral agents associated with less resistance (*e.g.*, entecavir and tenofovir) for the treatment of CHB, new prophylactic strategies are being designed, either in combination with HBIG or alone as a monotherapy. These advances have allowed for more personalized prophylaxis based on the individual risk profile of a given patient. In addition, the small pool of donors has required the use of anti-HBc-positive donors (with the resulting possibility of transmitting HBV from these organs), which has been made possible by suitable prophylactic regimens.

Key words: Hepatitis B virus; Liver transplantation; Recurrence; Prophylaxis; Hepatitis B immunoglobulin

Core tip: The current success of liver transplantation in patients with chronic hepatitis B (CHB)-related cirrhosis is mainly due to the use of prophylaxis with hepatitis B immunoglobulins (HBIG) and oral antivirals against post-liver transplant recurrence of CHB. The combination of low-dose HBIG plus antivirals forms the current standard prophylaxis. The use of newer antivirals (entecavir and tenofovir), coupled with better understanding of the predisposing factors for recurrence of CHB, has led to new perspectives for prophylaxis regimens, aimed at withdrawal of HBIG or the use of HBIG-free regimens, oriented toward a strategy of individualized prophylaxis.

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INTRODUCTION

Chronic hepatitis B virus (HBV) infection is responsible for up to 30% of cases of liver cirrhosis and up to 53% of cases of hepatocellular carcinoma[1]. Liver transplantation (LT) is the best therapeutic option for patients with end-stage liver failure caused by HBV. The success of transplantation, though, depends on the need to receive prophylactic treatment against post-transplant viral reactivation. In the absence of prophylaxis, LT due to chronic hepatitis B (CHB) is associated with high rates of viral recurrence that negatively influence survival[2,3]. The introduction of treatment with hepatitis B immunoglobulins (HBIG) during the 1990s[4] and the later incorporation of oral antiviral drugs have led to improvements in the prognosis for these patients, resulting in LT for CHB now being a universally accepted option, with an estimated 5 years survival of around 85% *vs* the 45% survival seen prior to the introduction of HBIG[2,3,5]. The combination of lamivudine (LAM) plus HBIG has for many years been the most widely used prophylactic regimen. However, with the appearance of new more potent oral antiviral agents associated with less resistance [entecavir (ETV) and tenofovir (TDF)] for the treatment of CHB, new prophylactic strategies are being designed, either in combination with HBIG or even alone in monotherapy. This has resulted in the development of more personalized prophylaxis based on the individual risk profile of a given patient[6]. In addition, the small pool of donors has required the use of anti-HBc-positive donors (with the resulting possibility of transmitting HBV from these organs), which has been made possible by suitable prophylactic regimens[7]. Table 1 reflects the risk of recurrence of hepatitis B in recipients of anti-HBc-positive organs according to the serological status of the recipient.

Table 1 Risk of de novo hepatitis B in recipients of anti-HBc-positive organs

Recipient status	Naive	AntiHBc$^+$ AntiHBs$^-$	AntiHBc$^+$ AntiHBs$^+$	AntiHBc$^-$ AntiHBs$^+$
No prophylaxis	> 40%	13%	< 2%	10%
With prophylaxis	12%	< 4%	< 2%	< 2%
	High risk	Intermediate risk	Low risk	Intermediate risk

PROPHYLAXIS FOR HBV RECURRENCE AFTER LT

Various strategies have been suggested to aid in the prevention of HBV recurrence after LT.

HBIG monotherapy

HBIG was the first effective drug used as prophylaxis for recurrence of CHB in transplant patients. It led to great advances, as it reduced the rates of recurrence to around 20%-30% and significantly improved survival rates[4]. However, the use of HBIG as prophylaxis in monotherapy has certain complications, such as the potential for mutations in the surface gene that determines resistance and loss of efficacy, the inability to reach sufficiently protective anti-HBs titers in all patients[8,9], and the high economic cost and difficulties associated with their parenteral administration[10]. These inconveniences, together with the appearance of new oral antiviral nucleos/tide analogues (NAs) and the confirmation of their synergistic effect, mean that HBIG is no longer used in monotherapy, and the standard treatment for prophylaxis against CHB recurrence is now combined therapy with HBIG plus NAs[10].

NAs in monotherapy

LAM: LAM was the first effective oral antiviral used against CHB. Its safety and efficacy, even in patients with decompensated hepatic cirrhosis, enabled patients to have a negative viremia at LT, thus reducing the probability of post-LT viral recurrence[11].

Perrillo *et al*[12], using LAM monotherapy both before and after LT, reported a recurrence rate of around 30%, very similar to that seen with HBIG monotherapy[4]. Furthermore, it was also noted that most recurrences were due to the development of HBV DNA polymerase mutations that led to drug resistance. These patients who experienced recurrence had higher viral loads at the time of LT than those who did not have recurrence, similar to patients treated with HBIG monotherapy.

Because of the high rate of resistance with LAM after prolonged use the resulting risk of recurrence, and the introduction of ETV and TDF with their high genetic barrier to resistance, LAM monotherapy has fallen into disuse.

Adefovir: The commercialization of adefovir (ADV) in 2003 represented an alternative for patients with resistance to LAM. Schiff *et al*[13] studied a group of 60 patients, of whom 24 received ADV with or without LAM with no HBIG as prophylaxis against post-LT hepatitis B, and found that none developed recurrent hepatitis B after a follow-up of 36 mo. However, because of the potential nephrotoxic effect associated with ADV and the risk of developing resistance ADV is not the first choice for prophylaxis against post-LT CHB recurrence.

ETV and TDF: The recent availability of these highly effective, well-tolerated antivirals with their high genetic barrier to resistance has resulted in changes in the approach to CHB in relation to LT. Accordingly, prophylactic strategies are now being reconsidered (see below).

Combined prophylaxis with HBIG plus oral antivirals

Various studies and meta-analyses[14-18] on the synergic effect of combination HBIG and NAs in prophylaxis for CHB recurrence have found general recurrence rates < 10%, which is noticeably lower than those seen with HBIG or NAs in monotherapy. This reduction in recurrence has led to combined prophylaxis (mainly HBIG plus LAM) becoming the standard of care in LT due to CHB. The possibility of resistance with long-term use of LAM encouraged a trial on the use of combination HBIG and ADV. A systematic review by Cholongitas *et al*[19] found that the combination of HBIG plus ADV was more effective than prophylaxis with HBIG plus LAM (2% *vs* 6.1%, $P = 0.024$).

However, relatively few studies have examined combined prophylaxis with HBIG plus ETV or TDF. Overall, these studies have found recurrence rates ranging from 0% to 4%[20-26]. Nevertheless, no randomized studies have yet compared the efficacy of combined prophylaxis with HBIG + LAM *vs* HBIG + ETV or TDF, although a recent systematic review noted a higher recurrence rate with the combination HBIG + LAM than with HBIG + ETV/TDF (6.1% *vs* 1%, $P = 0.0004$)[27].

Prophylaxis with alternative dosing schedules of HBIG

The high economic cost of prophylaxis schedules combining HBIG plus oral antivirals, together with the high efficacy and safety of the more recent oral antivirals (ETV/TDF), have led to the study of different prophylactic strategies aimed at lowering or eliminating HBIG in order to reduce costs and the inconveniences associated with its administration.

Additionally, other possible routes of administration of HBIG have been assessed. Several studies[28,29] have shown that low-dose intra-muscular (IM) administration of HBIG when combined with NAs is a cost-effective alternative to its intravenous (IV) administration. Recently the subcutaneous administration of HBIG has been found equally effective, well-tolerated, and accepted by patients[30,31].

HBIG dose reduction: Two differing strategies have been tried: (1) Low-dose IM administration of HBIG (400-500 IU) at fixed intervals with oral antivirals. Two studies endorse these results; Gane *et al*[29] found recurrence rates of 1% during the first year and 4% in the fifth year, using doses of 400-800 IU per day for the first week and then monthly in combination with LAM. Zheng *et al*[32] used doses of 800 IU at first weekly and then monthly, recording recurrence rates of 15% at 2 years. In both studies, the rates of recurrence were significantly higher in those patients with HBV-DNA values > 10^5 copies/mL at the time of transplantation; and (2) "On demand" use of HBIG doses to maintain anti-HBs titers between 50-100 IU/L, considered protective when administered together with oral antivirals. Although this strategy can be more cost effective, it requires repeated monitoring of anti-HBs titers, as the amount of HBIG needed to reach a certain level of anti-HBs varies greatly from patient to patient. Using this strategy plus LAM, Jiang *et al*[33] found recurrence rates of 2.3% the first year, 6.2% the third year, and 8.2% the fifth year. As before, pretransplant HBV-DNA levels > 10^5 copies/mL were associated with greater recurrence.

These studies[29,32,33], therefore, show that IV administration of high doses of HBIG is neither necessary nor cost-effective when given together with oral antivirals and also highlight the importance of pretransplant levels of HBV-DNA as a predictive factor for recurrence.

Withdrawal of HBIG after combined prophylaxis: Studies of this strategy vary greatly in design, type of antiviral agent used, and time from LT to HBIG withdrawal. In addition, most of the studies are observational and from a single center[34-44], with just three randomized studies[45-47]. The overall rates of recurrence in these studies ranged from 0% to 17%[34-47].

Using this strategy, it is necessary to note that although the results during the initial years after withdrawing HBIG are good, the risk of recurrence can increase over time due to the appearance of resistance and, in particular, to lack of adherence[48]. The problem of the appearance of resistance may be of little importance if high genetic barrier oral antivirals are used, such as ETV or TDF. To date, only four studies have been published[34,37,42,43], none randomized, analyzing recurrence after withdrawal of HBIG using

TDF or ETV. A systematic review by Cholongitas *et al*[27] that included the patients in these four studies found a recurrence rate of 3.9% *vs* 1% in the case of combined prophylaxis with HBIG and ETV/TDF, although the difference was not significant (P = 0.17).

This therapeutic strategy seems to be associated with a greater risk of recurrence in those patients with high HBV-DNA levels at the time of transplantation. One study found that detection of low and transitory HBV-DNA levels was not necessarily associated with recurrence, and only those patients who had persistently high hepatitis B surface antigen (HBsAg) and/or HBV-DNA levels had a high risk of experiencing recurrence[44].

Prophylaxis without HBIG: Experience using regimens of prophylaxis without HBIG and just oral antivirals is very limited[25,49-54]. Fung *et al*[52] studied 80 patients who received ETV monotherapy as prophylaxis, and the rate of HBsAg positivization was 22.5%, where only one patient (1.2%) was positive for HBV-DNA after the 26 mo follow-up period. Likewise, they found that the patients with HBV-DNA < 5 log copies/mL and HBsAg values < 3 log IU/mL pretransplant had an accumulated rate of HBsAg negativization at 18 mo of 100% *vs* 78% in the patients who did not fulfill these criteria. A more recent study by these same authors[53] showed that recurrence in patients treated with ETV (n = 142) was 0% at 3 years, whereas recurrence in those patients treated with LAM (n = 176) was 17% (P < 0.001). A study by Wadhawan *et al*[49] using different antivirals in regimens without HBIG (ETV, n = 42; LAM + ADV, n = 19; TDF, n = 12; and ETV + TDF, n = 2) noted recurrence (defined as HBV-DNA positivity) in 6/75 (8%) patients, five of these related to lack of treatment adherence. Cholongitas *et al*[34], in a systematic review, noted a significantly higher recurrence rate among patients who received prophylaxis completely free of HBIG, using ETV or TDF, compared with those who received combined therapy with HBIG plus LAM, with recurrence defined as HBsAg positivity [26% (29/112) *vs* 5.9% (109/1834), P < 0.0001]. Considering recurrence as HBsAg positivity and detectable DNA, the recurrence rates were 0.9% with HBIG-free therapy *vs* 3.8% with combined therapy, although the difference was not statistically significant (P = 0.11). No differences were found in relation to the antiviral used or the use of double-antiviral prophylaxis.

No studies are yet available concerning the combined use of two ANs (*e.g*., ETV + TDF or TDF plus emtricitabine) as prophylaxis without HBIG.

Vaccination against HBV

Active immunization with recombinant anti-HBV vaccines could be an attractive alternative to the indefinite administration of HBIG, particularly in patients with a low risk of recurrence. However, the few studies available provide contradictory results; and, at the present time, their generalized use cannot be recommended, at least as an isolated prophylactic strategy for post-LT CHB[55,56].

Individualized prophylaxis against HBV

In recent years, growing scientific evidence supports the possibility of reducing or even completely withdrawing HBIG from prophylaxis regimens against post-LT HBV, especially in patients with a low risk of recurrence. When considering the prophylactic regimen, it is necessary to consider all those factors that may affect viral recurrence, including virus-dependent factors [DNA-HBV and HBsAg levels at the time of transplantation, antiviral resistance, coinfection with hepatitis delta virus (HDV), human immunodeficiency virus], patient-related factors (treatment adherence, coexistence of hepatocarcinoma), or those related with the particular antiviral used (antiviral potency, genetic barrier). The pretransplant DNA-HBV levels and the existence of antiviral resistance are considered the most important predictive factors for post-transplant recurrence[29,53,57]. The presence of pretransplant hepatocarcinoma, especially if there is post-transplant recurrence of CHC, is associated with a greater risk of HBV recurrence[58,59]. On the other hand, fulminant hepatitis B is associated with a low risk of HBV recurrence[60], as is coinfection with HDV[10].

Thus, those patients considered to be at low risk for recurrence (negative pretransplant viremia, prior absence of antiviral resistance) could be considered for HBIG-free prophylaxis or with HBIG just given for a limited time (1-6 mo), using antivirals with a high genetic barrier (ETV/TDF) and provided there are no treatment adherence problems. On the other hand, patients at high risk for recurrence, as well as those with limited options for treatment if prophylaxis fails (*e.g*., patients with delta coinfection) would benefit more from a long-term regimen based on the combination of HBIG plus antivirals.

ANTI-CORE-POSITIVE DONORS

The imbalance between the high demand for transplant organs and the paucity of donors has necessitated the use of serum HBV-positive organs (anti-HBc positive, HBsAg negative). These represent the main risk factor for the *de novo* development of hepatitis B in transplant patients[7]. Several studies have shown equal survival for anti-HBc positive and anti-HBc negative organ recipients[61-63]. The risk of developing *de novo* hepatitis B in anti-HBc-positive organ recipients depends mainly on the serological status of the recipient at the time of transplantation and the adoption of effective prophylactic measures. A systematic review by Cholangitas *et al*[7] found that if recipients were negative for both anti-HBc and anti-

HBs the risk of recurrence was 48%, if the recipient was anti-HBc positive the risk was 13%, and if the recipient was anti-HBc positive and anti-HBs positive, the risk was reduced to < 2%. With prophylaxis, the risks were 12%, < 4%, and < 2%, respectively (Table 1). This prophylaxis is specifically for: (1) patients with no immunity against the virus (HBsAg negative, anti-HBc negative, anti-HBs negative); (2) patients with acquired immunity (vaccinated: anti-HBs positive, anti-HBc negative and HBsAg negative); and (3) patients who are anti-HBc positive and anti-HBs negative. Prophylaxis is not generally advisable in patients with natural acquired immunity (HBsAg negative, anti-HBc positive with anti-HBs positive) given the minimum or null risk of reinfection[7,64].

Prophylactic strategies for *de novo* hepatitis B in recipients of anti-HBc organs have traditionally consisted of HBIG with or without LAM. Diverse studies have shown that HBIG monotherapy is inferior to that of HBIG combined with LAM, and that combination therapy with HBIG and LAM is no more efficient than monotherapy with LAM to prevent resistance[7]. The systematic review by Cholongitas *et al*[7] found that the rate of *de novo* hepatitis B with monoprophylaxis with LAM was < 3%. The high cost of prophylaxis with HBIG and the introduction over recent years of new antivirals with a high genetic barrier (ETV/TDF) has resulted in many transplant centers ceasing to use HBIG as passive prophylaxis[7,64,65]. Nevertheless, the heterogeneity of studies concerning prophylactic strategies with the use of anti-HBC positive organs necessitates large, well-designed multicenter studies to provide a high level of scientific evidence.

TREATMENT OF POST-LIVER TRANSPLANT HEPATITIS B

Hepatitis B in the LT patient can appear through transmission from a risk contact, transmission from an anti-HBc positive organ with no adequate prophylaxis (*de novo* hepatitis B), or by reactivation of a prior hepatitis B when prophylaxis fails (recurrent hepatitis B). Whatever the reason, treatment of established hepatitis B in the LT patient is based on the same recommendations as for immunocompetent patients.

The most commonly accepted definition of recurrent hepatitis B is the reappearance of circulating levels of HBsAg after transplantation, with or without HBV-DNA positivization or histological evidence of disease. Nonetheless, a few authors, such as Lenci *et al*[66], suggested that the definition of recurrence should include one or more of the following at some time after transplantation: (1) HBsAg positivity; (2) detectable serum levels of HBV-DNA; (3) detectable levels of covalently closed circular DNA in liver tissue; (4) increase in alanine aminotransferase; or (5) liver damage seen in a liver biopsy. Whilst this definition would seem more useful from the practical point of view, it is not yet universally accepted. Those patients who, years after transplantation, are still HBsAg-positive with negative HBV-DNA may have a high risk for a clinical, histological, and biochemical recurrence of hepatitis B. Accordingly, it is not advisable to stop HBIG in these patients.

CONCLUSION

LT for patients with hepatic cirrhosis due to CHB is now a universally accepted treatment. The magnificent results have been made possible in great measure by the use of HBIG and oral antivirals for prophylaxis against post-LT recurrence of CHB. The combination of low-dose HBIG plus antivirals is now considered the standard prophylaxis for post-LT recurrence of hepatitis B. The use of the newer antivirals (ETV and TDF), together with our better understanding of the factors that predispose patients to recurrence of CHB, has allowed for new focus to be placed on prophylaxis regimens. These efforts are aimed at withdrawing HBIG or the use of HBIG-free regimens from the outset, using only oral antivirals, especially in patients at low risk of recurrence, thus applying a strategy of individualized prophylaxis. In addition, the efficacy of these prophylactic regimens has enabled the use of grafts from anti-HBc positive donors without these being considered a risk, thereby increasing the donor pool.

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