Prevention of Hepatitis B Virus Reinfection in Liver Transplant Recipients

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Key Words

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Abstract

Antiviral therapy using newer nucleos(t)ide analogues with lower resistance rates such as entecavir or tenofovir could suppress hepatitis B virus (HBV) replication, improve liver function, delay or obviate the need for liver transplantation in some patients, and reduce the risk of HBV recurrence. The combination of long-term antiviral and low-dose hepatitis B immune globulin (HBIG) can effectively prevent HBV recurrence in more than 90% of transplant recipients. Some form of HBV prophylaxis needs be continued indefinitely after transplantation. However, in patients with a low risk of HBV recurrence (i.e. HBV DNA levels undetectable before transplantation), it is possible to discontinue HBIG and maintain long-term antiviral therapy. A more cautious approach to prophylaxis regimen is necessary for those patients with high pretransplant HBV DNA levels, those with limited antiviral options if HBV recurrence occurs (i.e. HIV or HDV coinfection, preexisting drug resistance), those with a high risk of hepatocellular carcinoma recurrence, and those with a risk of non-compliance to antiviral therapy.

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Introduction

In the USA and Europe, 5–10% of patients undergoing liver transplantation (LT) have hepatitis B virus (HBV)-associated chronic or fulminant liver disease. In Asia, 80% of patients are transplanted for HBV-associated disease. Historically, the spontaneous risk for HBV reinfection was about 80% and the 5-year survival rate was low (between 40 and 60%). The advent of long-term intravenous (IV) hepatitis B immune globulin (HBIG) administration and the introduction of new antiviral agents were a major breakthrough in the pre- and post-LT management of these patients. Nucleos(t)ides agents can suppress HBV replication and improve liver function in patients with decompensated cirrhosis [1–4], delay or obviate the need for LT in some patients [5], and decrease the risk of HBV recurrence after LT. Lamivudine (LAM) and adefovir (ADV) are no longer considered as an optimal first-line therapy due to a high rate of resistance development, and the latest guidelines suggest using new antiviral agents with a higher efficacy and a low rate of resistance development such as entecavir (ETV) or tenofovir (TDV) as primary antiviral agents [6, 7]. The use of nucleos(t)ide agents before LT and the combination of prophylaxis with antiviral and HBIG after LT prevents HBV recurrence in 90–100% of patients,

with survival rates at 5 years over 80% [8]. There is a consensus regarding the use of lifelong HBV prophylactic therapy supported by the detection of low levels of HBV DNA in serum, liver and peripheral blood mononuclear cells, or the presence of total and covalently closed circular HBV DNA in liver tissue transiently after LT in the absence of a positive HBsAg [9, 10]. However, this long-term prophylaxis using IV HBIG is expensive and inconvenient for patients. This has led to the development of alternative strategies aiming to change the route of administration of HBIG, reduce the dose or duration of HBIG, or avoid the use of HBIG. A more cautious approach to prophylaxis regimen is necessary for those patients with a high risk of HBV recurrence: high pretransplant HBV DNA levels, those with limited antiviral options if HBV recurrence occurs (i.e. HIV or HDV coinfection, preexisting antiviral drug resistance), those with a high risk of hepatocellular carcinoma (HCC) recurrence, and those with a risk of non-compliance to antiviral therapy.

In this review, we will describe the significant improvements in the prevention of recurrence after LT for HBV-related liver disease.

Diagnosis, Mechanisms, and Risk Factors for HBV Recurrence after LT

Recurrence of HBV infection after LT is commonly defined as the reappearance of circulating hepatitis B surface antigen (HBsAg) with or without detectable HBV DNA. However, only patients who develop persistently detectable HBV DNA are shown to be at risk for clinical disease and graft loss [11]. HBV reinfection is the consequence of an immediate reinfection of the graft by circulating HBV particles, or a later reinfection from HBV particles coming from extrahepatic sites such as peripheral blood mononuclear cells, or both.

Whatever the prophylaxis used, there is a direct relationship between HBV viral load at transplantation (i.e. $>10^5$ copies/ml) and the rate of HBV recurrence [8, 12, 13]. Thus, the use of antivirals before transplantation to achieve undetectable HBV DNA levels aiming at reducing the risk of HBV recurrence is a consensus. Other factors associated with low rates of recurrence are surrogate markers for low levels of viral replication and include negative hepatitis B e antigen (HBeAg) status, fulminant HBV, and HDV coinfection [8, 13].

In addition, several studies have reported that HCC at LT, HCC recurrence, or chemotherapy used for HCC are independently associated with an increased risk of HBV

recurrence [14]. The detection of cccDNA in HCC cells suggests the possibility of viral replication in tumor cells, which would then act as a viral reservoir [14].

After the removal of the major viral reservoir, the use of HBIG at the anhepatic phase is aimed at inhibiting entry by neutralizing viral determinants of attachment. Evaluation of patients failing HBIG prophylaxis indicates that early recurrence of HBV is typically related to insufficient dosing of HBIG and is more frequent in patients with a high level of pre-LT HBV replication, whereas late recurrences are usually caused by the emergence of mutations involving the 'a' determinant of the HBV surface protein [15].

In patients receiving LAM monoprophyllaxis, HBsAg remains positive, progressively declining over a period of a few months after transplantation to become undetectable. In compliant patients, recurrence is most often associated with HBV polymerase mutations [1, 16]. In patients without overt recurrence, persistence or reappearance of HBsAg positivity without detection of HBV DNA can be observed [1, 16, 17].

In patients receiving combination prophylaxis, reduction of the pretransplant viral load with antivirals may decrease the risk that selection of variants with mutations of the 'a' determinant of the HBV surface protein due to immune pressure occurs. Antiviral therapy may inhibit replication of virus particles which escaped neutralization by HBIG, allowing a reduction in the HBIG dosage. As a complement, blocking the infectivity of HBV particles by HBIG may reduce the residual replication on antiviral therapy and thus decrease the risk of developing resistant mutants.

Whatever the prophylaxis used, measurable low levels of HBV DNA have been reported after LT in serum, peripheral blood mononuclear cells, and in liver – both total and/or cccDNA – in a significant proportion of patients without detectable HBsAg and without evidence of chronic hepatitis on liver graft [9, 10]. These findings suggest that occult HBV reinfection occurs in some HBV recipients and implies a risk for overt HBV recurrence if prophylaxis is stopped. Conversely, for the few patients who are negative for HBV DNA and cccDNA in all compartments, the discontinuation of HBV prophylaxis could be discussed [10]. However, assays for quantitation of total HBV DNA and cccDNA within cells are not standardized.

Prevention of HBV Recurrence

Since the study by Samuel et al. [13], HBIG has been the cornerstone of prophylaxis against HBV recurrence after LT. This study demonstrated a dramatic reduction

in the rate of HBV recurrence, from 75% in patients receiving no or short-term therapy with HBIG to 33% in those receiving long-term IV HBIG treatment ($p < 0.001$), and was associated with improved graft and patient survival. Recurrence of HBV occurred in 67% of patients who underwent transplantation for HBV cirrhosis, 32% of patients who underwent transplantation for HDV cirrhosis, and 17% of patients who underwent transplantation for fulminant hepatitis B. Whatever the mechanism(s) by which HBIG protects the transplanted liver against HBV reinfection, there is evidence for a dose-dependent response to HBIG treatment [18].

The advent of antiviral therapy further changed the landscape of post-LT prophylaxis and the standard of care is now to combine HBIG with a nucleos(t)ide analogue. Several meta-analyses have shown that combination prophylaxis was significantly superior to antivirals or HBIG alone in preventing HBV recurrence [18–20].

Protocols for the Administration of HBIG

In conventional protocols, HBIG is used at high dose during the anhepatic phase and the first postoperative week (i.e. generally 10,000 IU/day) to neutralize HBsAg [13]. In the early posttransplant period, some studies reported that high IV HBIG dosage ($\geq 10,000$ IU/day) versus low HBIG dosage ($< 10,000$ IU/day) was associated with a lower frequency of HBV recurrence [18]. In the medium- and long-term follow-up, IV HBIG has been administered in two different ways: at a frequency dictated by the maintenance of specific anti-HBs levels (i.e. 100 IU/l), or on a fixed schedule. The latter approach is simpler and requires less monitoring, but is more expensive [21]. The target levels for anti-HBs titers decrease with time after LT: generally anti-HBs levels were maintained > 500 IU/l during 1–3 months, > 250 IU/l until 6–12 months, and > 100 IU/l thereafter. The optimal anti-HBs titer needed to prevent recurrence in the medium and long-term follow-up is unknown, but is probably reduced if potent antiviral therapy is associated with HBIG.

The use of IV HBIG has limitations, namely the high cost, parenteral administration, limited supply, need for frequent clinic visits and laboratory monitoring, lower effectiveness in patients with high levels of HBV replication before LT, and the potential selection of HBsAg escape mutants. Alternative approaches have been studied, which include the use of low-dose intramuscular (IM) HBIG [22], subcutaneous HBIG [23], withdrawal of HBIG after a finite period or prophylaxis regimens without HBIG. The ability to achieve undetectable HBV DNA before LT in the majority of patients using potent anti-

virals allows the use of prophylaxis regimens minimizing the dose or duration of HBIG.

Combination protocols are heterogeneous with regard to the dosing, duration, and routes of HBIG administration. The most cost-effective regimen reported to date is a very low IM HBIG plus LAM regimen [22]. Combination prophylaxis with low-dose IM HBIG (400–800 IU IM) decreases costs by more than 90% as compared with an IV regimen with a recurrence rate as low as 4% at 4 years [22]. More recently, subcutaneous regimens of HBIG administered 6 months after LT have proven effective as well, with some advantage in tolerability and possibility of self-administration by patients at home [23]. Degertekin et al. [8] analyzed data from 183 patients receiving combination prophylaxis with antiviral therapy (mostly LAM monotherapy) plus HBIG given either IV high-dose (25%, 10,000 IU monthly), IV low-dose (21.5%, 3,000–6,000 IU monthly), IM low-dose (39%, 1,000–1,500 IU every 1–2 months), or for a finite duration (14.5%, median duration 12 months). Cumulative rates of HBV recurrence at 1, 3, and 5 years were 3, 7, and 9%, respectively. Multivariate analysis showed that positivity for HBeAg and high viral load at transplant, but not the posttransplant HBIG regimen, were associated with HBV recurrence.

The role and the safety of newer nucleos(t)ide analogues (ETV or TDF) have not yet been adequately evaluated [20, 24]. Cholongitas and Papatheodoridis [20] reported that the combination of HBIG and a newer nucleos(t)ide analogue was superior than the combination of HBIG and LAM in reducing the risk of HBV recurrence (1 vs. 6.1%, $p = 0.0004$).

Prophylaxis Protocols with HBIG Discontinuation

Indefinite combination therapy with HBIG plus a nucleos(t)ide analogue may not be required in all liver transplant recipients.

Studies of hepatitis B vaccination as an alternative to long-term HBIG in LT recipients have shown that successful hepatitis B vaccination and discontinuation of HBIG are feasible only in a small group of selected patients; however, the optimal vaccine protocol has not been established [25, 26].

Another strategy is HBIG withdrawal after a defined period of combination prophylaxis [10, 11, 27–31]. In a study of 29 patients, high-dose HBIG and LAM were used in the first month, after which the patients were randomized to receive either LAM monotherapy or LAM plus IM HBIG at 2,000 IU monthly [27]. None of the patients developed HBV recurrence during the first 18 months, but

later recurrences developed in 4 patients after 5 years of follow-up, which was related to poor LAM compliance [28]. An alternative approach is to switch from HBIG/LAM to a combination of LAM/ADV [29] or a combination of emtricitabine/TDV [30]. Several studies have demonstrated cases of seroconversion to positive HBsAg associated with undetectable HBV DNA [29, 31]. A proposed mechanism for this is that HBsAg is produced at low levels during HBIG therapy and becomes detectable after HBIG cessation. Longer follow-up of these patients is necessary to determine whether these patients will clear HBsAg or whether they are at future risk of viral breakthrough. Drug compliance during long-term antiviral therapy may be a very important issue for transplant patients who feel healthy but have a lifelong risk of HBV recurrence.

Another approach was to evaluate the safety of complete and sustained prophylaxis withdrawal in liver transplant recipients at low risk of HBV recurrence. Lenci et al. [10] evaluated a cohort of 30 patients at a low risk of recurrence treated with combination HBIG and LAM for at least 3 years. Using the absence of intrahepatic total HBV DNA and cccDNA in sequential liver biopsies as a guide, HBIG and then antiviral therapy was withdrawn in a stepwise fashion. After a median of 28.7 months off all prophylactic therapy, 83% of the cohort remained without serologic recurrence of HBV infection. Five patients developed HBsAg recurrence, but only 1 patient showed evidence of HBV disease (HBV DNA positive). This strategy needs sequential liver biopsies, and assays for quantitation of total HBV DNA and cccDNA within tissues are not standardized.

The studies to date highlight several key issues to consider with the discontinuation of HBIG posttransplantation. First, the risk of HBV recurrence after cessation of HBIG may increase with time off HBIG either due to the development of viral resistance or due to nonadherence to antiviral therapy. The role of antiviral combination or antivirals such as ETV or TDV with a high genetic barrier to resistance should be better evaluated. Second, the patients with high levels of HBV DNA at the time of transplantation appear to be a higher risk group for recurrence when HBIG is discontinued. Third, HBV DNA persists in serum, liver, or peripheral blood mononuclear cells even 10 years after LT in a proportion of HBV transplanted patients who are HBsAg-negative. These reservoirs may serve as a source of HBV reinfection in the future, supporting the use of long-term prophylactic therapy in most patients. Finally, we currently lack the ability to identify patients who may have cleared HBV after transplantation.

HBIG-Free Prophylactic Regimens

LAM has been evaluated as a prophylactic monotherapy, with the drug started before transplantation and continued after transplantation without HBIG. The outcome at 1 year showed a 10% recurrence rate [16]. However, with longer follow-up, rates of recurrence reached 22–41% at 3 years after LT due to the emergence of escape mutations in the YMDD motif of the polymerase gene. Recurrence was observed mainly in patients with a high level of HBV replication prior to drug exposure [1, 16]. Schiff et al. [2] reported 61 LAM-resistant patients treated with ADV in the wait-list who underwent LT. Forty percent of these patients received ADV plus/minus LAM prophylaxis without HBIG. Interestingly, no patient had recurrent HBV infection. Recently, Gane et al. [31] reported the results of a combination prophylaxis using LAM and ADV without HBIG in 18 patients who had HBV DNA below 3 log₁₀ IU/ml before LT. No cases of HBV recurrence were observed after a median follow-up of 22 months. The combination of LAM and ADV is cost-effective as compared with low-dose IM HBIG and LAM (USD 8,290 vs. 13,718 per year). The availability of more potent antivirals with a higher barrier to resistance could increase the proportion of patients with undetectable HBV DNA before transplantation and decrease the risk of recurrent disease after transplantation [11]. Fung et al. [17] investigated the efficacy of ETV as monoprophyllaxis in 80 patients. A total of 18 patients (22.5%) had persistent HBsAg positivity after transplant without seroclearance (n = 8) or reappearance of HBsAg after initial seroclearance (n = 10). One of these patients had a very low HBV DNA level. The pre-LT HBsAg level was significantly higher in those who had HBV recurrence/persistence compared with those who did not.

Guidelines and Future Prospects for Prevention of HBV Reinfection

The principles in strategies to prevent HBV recurrence should be to maximize antiviral potency while minimizing the risk for viral resistance, costs, side effects, and inconvenience to patients. Viral suppression is the goal in every wait-listed patient. ETV, TDV, or a nucleoside/nucleotide combination should be used in preference to LAM or ADV. There is a consensus regarding the need for a lifelong prophylactic therapy supported by the detection of HBV DNA in both hepatic and extrahepatic sites in patients who are HBsAg-negative on posttransplant HBIG and antivirals. In the early posttransplant period, some studies reported that a high IV HBIG dosage (≥10,000 IU/day) versus a low HBIG dosage (<10,000 IU/day) was associated with a lower frequency of HBV recurrence. In the

Fig. 1. Prophylaxis for prevention of HBV graft recurrence following LT: proposal for a guideline. ^a Shortening the duration of HBIG administration in HDV/HBV patients could have detrimental consequences as reinfection in the case of HDV latency may lead to chronic hepatitis B and delta. ^b High-dose IV HBIG during the first post-operative week could be associated with a lower frequency of HBV recurrence.

long term, low-dose IM (or subcutaneous) HBIG in combination with a potent nucleos(t)ide analogue is the most cost-effective prophylaxis. Patients with undetectable HBV DNA levels at the time of transplant are eligible for protocols using short-term low-dose IV or IM HBIG and an antiviral, and then switched to antiviral mono- or combination therapy (fig. 1). A more cautious approach to prophylaxis regimen is necessary for those patients with high pretransplant HBV DNA levels, those with limited antiviral options if HBV recurrence occurs (i.e. HIV or HDV coinfection, preexisting drug resistance, or intolerance), those with a high risk of HCC recurrence, and those with a risk of noncompliance to antiviral therapy. In this group, HBIG-free prophylaxis cannot be recommended.

Use of Liver Grafts from Anti-HBc- or HBsAg-Positive Donors

The growing organ shortage and the improved possibilities of HBV therapy favors the use of marginal grafts such as grafts from anti-HBc-positive donors. Anti-HBc is a marker of past HBV infection. However, after a resolved infection, the viral genome can persist as cccDNA in the liver and may reactivate during immunosuppressive therapy after transplantation. The prevalence of anti-HBc is low in developed countries, ranging from 3 to 15%, but it may exceed 50% in highly endemic areas. In the absence of HBV prophylaxis, the probability of de novo HBV infection after LT with grafts from anti-HBc-positive donors is

around 50% in HBV-naïve recipients [32]. This risk is reduced to 15% in recipients with serological markers of past HBV infection and to 12% using posttransplant HBV prophylaxis such as HBIG and/or LAM [32]. Conversely, the risk of HBV recurrence was not reported to be higher in HBsAg-positive recipients of anti-HBc-positive grafts using posttransplant prophylaxis as compared to those of anti-HBc-negative grafts. Thus, such liver grafts should be first offered to patients transplanted for HBV-related liver disease, as they require lifelong HBV prophylaxis.

The experience with HBsAg-positive liver grafts for HBsAg-positive recipients is far more limited. A recent Chinese study showed that the use of these grafts did not reduce posttransplant graft and patient survival [33].

Conclusion

During the past two decades, major advances have been made in the management of HBV transplant candidates. The advent of long-term HBIG administration and efficient antiviral drugs used before and after transplantation as a prophylaxis against HBV recurrence were major breakthroughs in the management of patients preventing HBV recurrence in more than 90% of transplant recipients. Some form of HBV prophylaxis needs to be continued indefinitely after transplant. However, in patients with low HBV DNA levels before transplantation, discontinuation of HBIG, with continued long-term nucleos(t)ide analogue(s) treatment is possible.

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