



2016 Hepatitis B virus: Global view

Prophylactic managements of hepatitis B viral infection in liver transplantation

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Abstract

Liver transplantation (LT) is a considerably effective treatment for patients with end-stage hepatitis B virus (HBV)-related liver disease. However, HBV infection often recurs after LT without prophylaxis. Since the 1990s, the treatment for preventing HBV reinfection after LT has greatly progressed with the introduction of hepatitis B immunoglobulin (HBIG) and nucleos(t)ide analogues (NAs), resulting in improved patient survival. The combination therapy consisting of high-dose HBIG and lamivudine is highly efficacious for preventing the recurrence of HBV infection after LT and became the standard prophylaxis for HBV recurrence. However, mainly due to the high cost of HBIG treatment, an alternative protocol for reducing the dose and duration of HBIG has been evaluated. Currently, combination therapy using low-dose HBIG and NAs is considered as the most efficacious and cost-effective prophylaxis for post-LT HBV reinfection. Recently, NA monotherapy and withdrawal of HBIG from combination therapy, along with the development of new, potent high genetic barrier NAs, have provided promising efficacy, especially for low-risk recipients. This review summarizes the prophylactic protocol and their efficacy including prophylaxis of *de novo* HBV infection from anti-HBc antibody-positive donors. In addition, challenging approaches such as discontinuation of all prophylaxis and active immunity through hepatitis B vaccination are discussed.

Key words: Liver transplantation; Hepatitis B infection; Prophylaxis; Nucleos(t)ide analogue; Anti-hepatitis B immunoglobulin

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Core tip: Combination therapy consisting of high-dose hepatitis B immunoglobulin (HBIG) and lamivudine has been the standard prophylaxis for hepatitis B virus recurrence after liver transplantation. Currently, after development of more potent high genetic barrier nucleos(t)ide analogues (hgbNAs), such as entecavir and tenofovir disoproxil fumarate, combination therapy using low-dose HBIG and hgbNA is considered as the most efficacious and cost-effective prophylaxis. In addition, monotherapy with hgbNAs and withdrawal of HBIG following combination therapy of HBIG and hgbNAs could be promising approaches, especially for low-risk patients and those receiving grafts from hepatitis B core antibody-positive donors. This review discusses those approaches including other challenging therapeutic options.

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INTRODUCTION

Liver transplantation (LT) is a highly effective treatment for patients with cirrhosis, liver cancer, or fulminant hepatitis caused by hepatitis B virus (HBV). However, the recurrence of HBV infection and subsequent severe disease, including an atypical, aggressive HBV recurrence pattern known as fibrotic cholestatic hepatitis (FCH), is a concern for patients with HBV-related diseases. In an era without effective prophylaxis, LT for HBV-related disease was a relative contraindication by the mid-1990s. Samuel *et al*^[1] reported that the rate of HBV recurrence was 67% ± 4% among LT recipients with HBV-related cirrhosis and 83% ± 6% among those with positive post-LT serum HBV-DNA in the absence of any prophylaxis.

Several prophylaxis strategies for recurrent HBV have greatly progressed since the mid-1990s with the use of anti-hepatitis B immunoglobulin (HBIG) and nucleos(t)ide analogues (NAs). Therefore, LT outcomes for HBV-related diseases have markedly improved. Currently, combination therapy consisting of HBIG and NAs is widely used in most liver transplant centers. However, various issues exist with long-term combination therapy with HBIG and NAs after transplantation. In this article, we review present and future possible strategies, based on the previous

history of prophylaxis, for preventing recurrent post-LT HBV infection. These include vaccine strategies that involve active immunization after LT.

INDICATIONS FOR LT AND PREOPERATIVE ANTI-VIRAL THERAPY FOR PATIENTS WITH HEPATITIS B AND RISK FACTORS FOR HBV RECURRENCE

LT is indicated for patients with irreversible hepatic failure due to HBV infection, which occurs through acute exacerbation of chronic hepatitis, cirrhosis, or fulminant hepatitis. The Child-Pugh score is widely used to evaluate the severity of cirrhosis. The one-year survival rate is 100% for patients with a Child-Pugh score of less than 6 points (Class A), while it is as poor as 50% for patients with a Child-Pugh score of 10 points or more (Class C). If a patient's clinical severity falls into Grade B or C (a score of 7 or above), LT may be required. The one-year survival rate after LT is as high as 80% to 90%, even for patients with Child-Pugh scores of 8 points or more. The model for end-stage liver disease (MELD) score is useful for predicting the short-term prognosis of patients with cirrhosis^[2]. When the MELD score is below 14 points, patients have limited benefits from LT^[3], while the risk of the transplantation itself increases when the score is too high. Thus, transplantation is considered optimal when the MELD score is above 15 points, but not after it becomes too high. In practice, the indications for transplant will be comprehensively determined by the patient's activities of daily living, complications, and the presence or absence of liver cancer or infectious diseases, among other indicators. In patients with HBV-related disease, several factors are considered as risks for HBV recurrence after LT^[4-7]. High-risk patients include those who are hepatitis B e antigen (HBeAg) positive, as well as those who have high serum HBV-DNA levels at LT and anti-viral drug-resistance before LT^[6]. On the other hand, low-risk patients include those with fulminant HBV, co-infection with hepatitis D virus^[1], and low/negative serum HBV-DNA levels, which occur due to spontaneous or therapeutic features^[8]. Among them, high serum HBV-DNA level at LT is a common significant risk factor that occurs regardless of protocol and is reported by many groups. Therefore, it is important to clear the virus from the blood or to reduce levels as much as possible by administering NAs before transplantation. Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are new potent agents that are recommended for the first-line treatment of NA-naïve patients due to low rates of drug resistance. For patients with renal disorders, which is often complicated by cirrhosis, ETV might be preferable compared to TDF because of the risk for nephrotoxicity. Currently, there are several

reports of patients developing resistant strains, such as the YMDD motif mutation, following long-term administration of lamivudine (LAM) among patients who are being considered for transplantation^[9-11]. However, there is cross-resistance between LAM and ETV because a resistant mutation of LAM (*e.g.*, rtM204V/I and rtL180M) is also necessary in order to develop resistance to ETV^[12]. In fact, many patients with LAM resistance have already acquired cross-resistance to ETV^[13]. Therefore, ETV should not be used in patients with LAM resistance^[14,15]. In this case, adding adefovir (ADV) or TDF to LAM, or switching to TDF but not ETV, is recommended. It should be noted that possible severe lactic acidosis might occur when ETV is used in patients with decompensated cirrhosis^[16]. Interestingly, hepatocellular carcinoma (HCC) is believed to be a risk factor for HBV recurrence^[17-19]. Saab *et al.*^[18] reported that 12 out of 175 patients (6.9%) developed HBV reinfection after LT despite combination therapy with HBIG and NAs. Among the 12 patients with HBV reinfection, 10 (83.3%) had HCC prior to LT and 5 (50%) developed HCC recurrence after LT^[18]. Multivariate analyses revealed that pre-LT HCC and post-LT recurrence of HCC were independent risk factors for post-LT HBV reinfection. Although the mechanism remains unknown, close monitoring of virological status in patients with HCC is important.

PROPHYLAXIS OF RECURRENT HEPATITIS B IN HBSAG-POSITIVE RECIPIENTS AFTER LT

Monotherapy with HBIG or LAM

Prophylaxis of recurrent HBV infection with HBIG or LAM monotherapy has been performed since the 1990s for HBsAg-positive recipients. Several breakthrough studies demonstrated a reduction in reinfection and improvement of graft survival using HBIG^[1,5,20,21]. Moreover, high-dose and long-term HBIG administration was shown to be most effective^[1,20,21]. After the development of LAM, several groups investigated its use as a monotherapy without HBIG^[22-25]. Perrillo *et al.*^[24] described the results of a multicenter US-Canadian trial where 25 out of 42 (60%) transplanted patients were HBsAg-negative at least three months post-transplantation. Patients also exhibited superior survival rates in comparison to a historical control group, which were similar to patients who were treated with long-term HBIG monotherapy^[24]. However, monotherapy with either of HBIG or LAM resulted in the recurrence of HBV infection in 30% to 40% of patients, which was still a considerable rate despite the fact that graft survival greatly improved in most studies^[1,21-24]. It is well known that amino-acid mutations in the predominant epitope of the HBs-Ag results in lower-binding affinity

of anti-HBs Ab (*i.e.*, escape mutation). A significant correlation has been reported between the duration of HBIG monotherapy and the development of such mutants, indicating that mutations of the S gene were induced or selected by immune pressures exerted by HBIG^[26]. Currently, long-term HBIG monotherapy is outmoded and not recommended for prophylaxis.

Combination therapy with HBIG and NAs

Following monotherapy with HBIG or LAM, a group from the University of California, Los Angeles, reported a landmark trial of combination therapy involving high-dose HBIG and LAM^[27]. First described in 1998, this therapy successfully prevented the recurrence of HBV infection in almost all patients. In this trial, 14 patients who underwent LT for HBV-related decompensated liver disease received high-dose HBIG intra- and post-operatively in combination with pre- and post-operative LAM therapy as prophylaxis. Using polymerase chain reaction (PCR), all 13 surviving patients did not have detectable serum HBV-DNA at a median of 346 d (130-525 d) following LT. Similar high efficacy was demonstrated by other groups using this strategy^[28,29]. Therefore, combination therapy consisting of high-dose HBIG and LAM became the gold standard for treatment and was rapidly introduced in many liver transplant centers. A recent meta-analysis revealed that combination therapy was superior in preventing reactivation of the virus when compared with monotherapy using HBIG or LAM alone^[30].

Combination therapy with low-dose HBIG and NAs, and withdrawal of HBIG

Although the combination therapy consisting of high-dose intravenous HBIG and NAs is very effective, it is very expensive. Additionally, HBIG is not available in some countries. The first year and subsequent yearly treatment costs more than United States \$100000 and United States \$50000^[31], respectively. In cost-effectiveness analysis, the cost-effectiveness is most sensitive to the cost of HBIG^[32]. Therefore, optimizing the protocol by reducing the dose and duration of HBIG has been previously attempted. This concept is utilized in two strategies. One involves combination therapy with low-dose intramuscular HBIG and LAM, while the other includes the withdrawal of HBIG from combination therapy^[33]. There are two more options in the combination therapy with low-dose HBIG involving either fixed low-dose or on-demand low-dose HBIG protocols.

For the fixed-dose protocol, Angus *et al.*^[34] showed that the combination of low-dose HBIG and LAM provides effective prophylaxis for post-LT HBV recurrence (Table 1). In this study, 400 or 800 IU of HBIG was administered intramuscularly (im) daily for 1 wk after transplantation and monthly thereafter, in combination with daily LAM (100 mg). Only 1 out of 32 patients was HBsAg positive and all 32 patients were

Table 1 Main results of published studies using combination therapy of low-dose hepatitis B immunoglobulin and nucleos(t)ide analogues and withdrawal of hepatitis B immunoglobulin from combination therapy

Ref.	Patients (n)	Median follow-up (mo)	NAs (dose)	HBIG protocol	HBV recurrence
Angus <i>et al</i> ^[34] , 2000	32	18.4	32 LAM (100 mg/d)	400 IU or 800 IU/d im for 1 wk and then 400 IU or 800 IU/mo	1/32 (3.1%) HBsAg+ 0/32 (0%) HBV-DNA+
Gane <i>et al</i> ^[35] , 2007	147	62	147 LAM (100 mg/d)	400 IU or 800 IU/d im for 1 wk and then 400 IU or 800 IU/mo	5/147 (3.4%) actuarial risk of HBV recurrence was 1% at 1 yr and 4% at 5 yr
Karademir <i>et al</i> ^[36] , 2006	35	16	33 LAM 2 LAM + ADV	6000 IU im intraoperatively, 2000 IU/d until HBsAb > 200 IU/L, and then 1200 to 2000 IU im on-demand if HBsAb < 100 IU/L, thereafter	2/35 (5.7%) Two HBV recurrent case had LAM resistance at LT
Iacob <i>et al</i> ^[38] , 2008	42	21.6	42 LAM	10000 IU im in anhepatic phase and 10000 IU/d im for first 1 wk, and then 2500 IU im on-demand if HBsAb < 50 IU/L, thereafter	2/48 (4.8%)
Jiang <i>et al</i> ^[37] , 2010	254	41.2	254 LAM	2000 IU im in anhepatic phase, followed by 800 IU/d for the next 6 d and weekly for the rest of 3 wk in the first postoperative month and 800 IU monthly or biweekly im on-demand if HBsAb < 100 IU/L, thereafter	14/254 (5.5%) The 1-, 3- and 5-yr HBV recurrence rates were 2.3%, 6.2% and 8.2% 5 of 14 recurrent cases had YMDD mutants at recurrence
Nath <i>et al</i> ^[41] , 2006	14	14.1	14 LAM + ADV	10000 IU HBIG iv in anhepatic phase and 10000 IU/d for first 1 wk, and then HBIG was withdrawn and replaced with oral ADV	1/14 (7.1%) HBV recurrent case showed normal liver function.
Angus <i>et al</i> ^[42] , 2008	34	21	18 LAM + HBIG 16 LAM to LAM + ADV	Randomized trial All patients were treated with low-dose im HBIG + LMV ≥ 1 yr post-LT 18 patients continued HBIG vs 16 patients discontinued HBIG and ADV was added (LMV + ADV)	0/18 in HBIG + LMV 1/16 (6.3%) in LMV + ADV (HBIG withdrawal group) Recurrent case was HBsAg+/HBV-DNA-
Saab <i>et al</i> ^[43] , 2011	61	15	19 LAM to LAM + ADV 41 LAM to LAM + TFV 1 ETV to ETV + ADV	All patients were treated with low-dose im HBIG + LMV ≥ 1 yr post-LT. All patients discontinued HBIG, and ADV or TDF was added as described left	2/61 (3.3%) Both recurrent case was HBsAg+/HBV-DNA- without liver dysfunction

HBV: Hepatitis B virus; NAs: Nucleos(t)ide analogues; HBIG: Hepatitis B immunoglobulin; LT: Liver transplantation; HBsAb: Hepatitis B surface antibody; LAM: Lamivudine; ADV: Adefovir; ETV: Entecavir; TDF: Tenofovir disoproxil fumarate; im: Intramuscularly.

HBV DNA negative at the latest follow-up visit (mean follow-up period, 18.4 mo). Subsequently, Gane *et al*^[35] reported the long-term results of an expanded population, including high-risk patients from the same group of HBV-DNA positive patients, at LT (85%) (Table 1). One hundred and forty-seven patients were analyzed and the actuarial risk of HBV recurrence was 1% and 5% after 1 and 5 years, respectively. The high HBV-DNA titer at LT was associated with HBV recurrence.

Karademir *et al*^[36] previously reported on the efficacy of the on-demand protocol (Table 1). Patients received 6000 IU intra-operatively, 2000 IU daily, and 2000 IU as on-demand maintenance medication for life, respectively, in order to keep the serum level at 100 IU/L. Two of the 35 patients who had experienced HBV recurrence (5.7%) after a median follow-up of 16 mo were HBV-DNA positive at the time of LT, despite preoperative LAM administration due to LAM resistance. The mean cumulative dose of HBIG, that was administered within the first, second, and third years were 34014, 5258, and 5090 IU, respectively. Jiang *et al*^[37] evaluated the low-dose,

on-demand protocol in a larger population (Table 1). Two hundred and fifty-four adult patients received LAM (100 mg/d orally) and HBIG (2000 IU, im) in the anhepatic phase, which was followed by 800 IU daily for the next 6 d, and weekly for the rest of 3 wk in the first postoperative month. This was followed by the administration of 800 IU monthly or biweekly, in order to maintain hepatitis B surface antibody (HBsAb) levels at 100 IU/L. Their 1-, 3-, and 5-year HBV recurrence rates were 2.3%, 6.2% and 8.2%, respectively, after a mean follow-up period of 41.2 mo. Fourteen patients experienced post-transplant HBV recurrence. High pre-transplant HBV-DNA levels (> 10⁵ copies/mL) at LT and post-transplant prednisone withdrawal times (> 3 mo) were associated with recurrences. Regarding the optimal target HBsAb titer, Iacob *et al*^[38] reported successful prophylaxis for 42 patients with lower HBsAb maintenance levels (10000 IU within the anhepatic phase and daily within the first postoperative week, followed by 2500 IU on demand if HBsAb titers fell below 50 IU/L) (Table 1). The HBV recurrence rate was 4.8% with a median follow-up period of 1.8 years. Currently, the optimal target

HBsAb titer of 50-100 IU/L is most accepted, although it depends on the involved institutions. This low-dose, on-demand protocol was also effective in living donor liver transplantation^[39,40].

The withdrawal of HBIG from combination therapy is another strategy that was reported by several groups. Nath *et al*^[41] evaluated the efficacy of this protocol. Fourteen patients with HBV-related disease received intravenous HBIG (10000 IU) administration during the anhepatic phase at LT, and daily for 7 d in combination with LAM. HBIG was subsequently discontinued and replaced with the oral administration of ADV. One patient experienced an HBV recurrence (7.1%) with a mean follow-up of 14.1 mo. Angus *et al*^[42] reported a multicenter randomized study of ADV substitution for low-dose intramuscular HBIG. In this study, 34 patients without HBV recurrences at least 12 mo post-LT were randomized to either the ADV replacement (16) and HBIG continuation (18) groups. Although one patient in the ADV group (6.2%) had a HBV recurrence, HBV-DNA was undetectable in the subsequent 20 mo. Saab *et al*^[43] also reported low recurrence rates (3.3%) in 61 patients who changed their regimen from low-dose HBIG and nucleoside analogue therapy to nucleoside and nucleotide analogue therapies, respectively.

Both Combination therapy consisting of low-dose intramuscular HBIG and NAs and the withdrawal of HBIG, were more cost-effective compared to the combination therapy consisting of high-dose, indefinite HBIG, and NAs.

In most studies that utilized the HBIG withdrawal protocol, HBIG was replaced with a nucleotide analogue (mostly ADV) in combination with LAM and this likely resulted in favorable outcomes. Furthermore, it has been reported that HBV recurrence was associated with low HBIG dose during the first week post-LT in patients receiving low-dose HBIG and LAM suggesting that perioperative, high-dose HBIG administration might compliment the low efficacy of LAM^[44]. These facts would also imply that usage of new and emerging, more potent high genetic barrier NAs (hgbNAs) such as ETV or TDF could increase the efficacy of these protocols. In fact, in the combination therapy of low-dose HBIG and NAs, ETV has been recognized as superior to LAM^[44-46]. In their systematic review of 519 HBV liver transplant recipients from 17 studies, Cholongitas *et al*^[44] recently indicated that patients who were treated with HBIG and LAM developed HBV recurrence significantly more frequently, compared to patients who were treated with HBIG and ETV or the TDF combination (6.1% vs 1.0%, $P < 0.001$). They also showed that hgbNA administration, along with HBIG discontinuation, was not inferior to the combination of HBIG and hgbNA [3.9% (4/102) vs 1.0% (3/303), $P = 0.17$]. Furthermore, it has been reported that HBIG dose and duration had no impact on HBV recurrence rate

if combined with hgbNAs (ETV or TDF)^[7]. This result might support the concept of NAs monotherapy for HBV prophylaxis, as described in following section.

Prophylaxis without HBIG (NA monotherapy)

As mentioned above, LAM monotherapy without HBIG after LT is partially effective but is not sufficient as prophylaxis for recurrent HBV infection^[22-24]. Therefore, it has been rapidly replaced with the combination therapy involving HBIG and LAM/other NAs.

However, along with development of more potent hgbNAs such as ETV or TDF, the necessity of HBIG for prophylaxis and efficacy of monotherapy with hgbNAs has been the subject of much discussion. Four reports, including three retrospective cohort studies^[47-49] and a prospective cohort study^[50] on hgbNA monotherapy have been published to date. Cholongitas *et al*^[46] conducted a systemic review of 112 patients who received hgbNAs without HBIG prophylaxis. Cholongitas *et al*^[46] showed that the post-LT HBV recurrence rate was higher in patients with mono-prophylaxis using hgbNAs than in those who were taking a combination of HBIG and LAM [26% (29/112) vs 5.9% (109/1834), $P < 0.001$] when HBV recurrence was defined as being HBsAg positive. However, HBV-DNA was detectable in only one patient in the mono-prophylaxis group and the recurrence rates in both groups were comparable (0.9% vs 3.8%, $P = 0.11$) when HBV recurrence was defined as the presence of serum HBV-DNA.

More recently, Gane *et al*^[51] reported that the combination of LAM and ADV, without HBIG was a safe and effective prophylaxis for post-LT HBV recurrence. Eighteen patients with pre-LT serum HBV-DNA ($< 3 \log_{10}$ IU/mL) suppression were selected to receive HBIG-free prophylaxis with LAM and ADV and did not show any HBV recurrences after a median post-LT follow-up of 22 mo. Fung *et al*^[47] reported the long-term outcomes of 362 patients who were receiving post-LT NA monotherapy without HBIG. The authors showed that the virological relapse rates at 3 years for the LAM, ETV, and combination groups (predominantly LAM + ADV) were 17%, 0% and 7%, respectively ($P < 0.001$). The majority of patients with virological relapses were in the LAM and combination groups and had the YMDD mutation. No resistance mutations were identified in the ETV group. These results imply that NA monotherapy without HBIG using either single potent hgbNA or the combination of nucleoside and nucleotide analogues, which have been associated with a very low rate of virologic breakthroughs, might suffice in the prophylaxis of HBV infections. In the current era, increasing the use of potent NAs before LT and NA monotherapy for post-LT prophylaxis is expected. The studies described above suggest the satisfactory and promising prophylactic efficacy of hgbNA monotherapy. Nonetheless, the preoperative administration of hgbNAs in the current age can achieve HBV-DNA negativity in many LT candidates, and such low risk

patients were included in studies described above. Therefore, low-risk patients should be selected for NA monotherapy. Furthermore, the inconsistencies between the HBsAg and HBV-DNA appearances have also been seen in NA monotherapy. HBsAg-positive and HBV-DNA-negative patients receiving hgbNA monotherapy had normal graft function without any sign of hepatitis. Long-term, larger, and randomized studies are needed in order to re-evaluate the clinical impact of HBsAg and HBV-DNA levels in this setting.

Interestingly, it has been reported that prophylactic HBIG prevents acute rejection after LT^[52-54]. Kwekkeboom *et al*^[52] reported that recipients receiving HBsAg-positive liver grafts and treated with prophylactic HBIG ($n = 40$) showed a significantly lower incidence of acute rejection compared to recipients without viral hepatitis ($n = 147$) (12% vs 34%, $P = 0.012$). Furthermore, HBIG suppressed functional maturation of human blood-derived dendritic cells (DCs) and cytokine production as well as alloantigen- and lectin-stimulated peripheral T cell proliferation *in vitro* at concentrations similar to that during HBIG treatment. These findings suggest that HBIG still has a significant role as an allo-immunosuppressant as well as a prophylactic agent.

Discontinuation of all prophylaxis

How long a prophylactic treatment should be continued has been previously debated. Cheung *et al*^[55] reported occult post-LT HBV infection of both donor and recipient origins despite NA prophylaxis. In this study, 31 patients who received post-transplant NAs prophylaxis remained seronegative for HBsAg for a median of 44.5 mo. Nineteen of these recipients (61%) had received anti-HBcAb positive grafts. Intrahepatic total HBV DNA and levels were quantified, and the sequence was analyzed. Intrahepatic total HBV DNA and covalently closed circular DNA were detected in 26 (84%) and 16 (52%) of the 31 recipients, respectively, although none of them had detectable serum HBsAg and HBV-DNA. A phylogenetic analysis of the isolated HBV DNA sequence revealed HBV infections of both donor and recipient origins. These results showed that an occult HBV infection after LT from either the recipient or donor could be present despite the absence of serum HBsAg and HBV-DNA after prophylaxis. Lifelong prophylaxis is advocated based on these data. Lenci *et al*^[56] have recently addressed this issue. They investigated the safety of withdrawal of all HBV prophylaxis regimens in selected LT recipients according to a stepwise approach. After receiving a combination of HBIG with LAM (\pm ADV) as prophylaxis, 30 low-risk patients (*i.e.*, HBeAg and HBV-DNA negative at LT) underwent sequential liver biopsies in order to confirm the absence of intrahepatic total and cccDNA. Based on biopsy results, HBIG and then NAs were withdrawn sequentially. Twenty-five patients did not show clinical signs of HBV recurrence after withdrawal of prophylaxis with a

median follow-up period of 28.7 mo, while 5 patients subsequently became HBsAg-positive. All 25 patients who did not have recurrences did not have detectable total/ccc DNA in their liver specimens, while the 5 patients with recurrences had detectable total HBV-DNA in their tissues. This study suggests that a sensitive method using protocol biopsy might be useful for identifying candidates for complete withdrawal of prophylaxis. However, this concept remains challenging and larger studies with longer follow-up are necessary.

It is important to remember that HBV recurrence has been conventionally diagnosed by the persistence or reappearance of serum HBsAg and/or HBV-DNA. PCR assays have demonstrated that HBV-DNA is typically detected prior to HBsAg re-appearance^[57]. However, in this study, 4 out of 5 patients who became HBsAg-positive did not have detectable HBV-DNA in their serum, or experience any clinically relevant events. This inconsistency between HBsAg and HBV-DNA appearances has also been seen in HBIG-free prophylaxis, as described above^[46]. All HBsAg positive and HBV-DNA negative patients receiving HBIG-free prophylaxis with hgbNAs had normal graft functions without any sign of hepatitis. These findings might indicate the necessity for redefining HBV reinfection. Its clinical impact should be confirmed in future studies.

Active immunity through hepatitis B vaccination

Although the virus is cleared after surgery by the aforementioned prophylaxis for HBV recurrence, hepatitis could recur if treatment is discontinued. Prolonging the treatment involves safety issues such as the development of escape mutations and/or emerging resistant strains due to long-term administration of HBIG and NAs, as well as economic issues^[58]. These considerations are also important in the prevention of *de novo* HBV infection that is induced by anti-HBc antibody (HBcAb)-positive donors. Theoretically, the development of natural, long-lasting anti-HBsAb in the recipient through active immunotherapy with a vaccine is the most ideal approach in terms of cost and benefit, in order to avoid the issues that are encountered after LT and HBIG replacement. Nonetheless, this approach has not been used widely because of its low response rate in most trials (Table 2)^[59-62]. This low response rate is caused by the difficulty in introducing active immunity under an immunosuppressed state after transplantation. Newer data suggest the enhancement of vaccination rates with the addition of more effective adjuvants or the administration of third generation recombinant vaccines. Some groups showed that HB vaccine plus more potent adjuvants such as monophosphoryl lipid A was much more effective for post-LT patients^[63-65]. Another group has shown the efficacy of pre-S containing third generation vaccines^[66]. However, as shown in Table 2, the long duration between LT, vaccination, and mono-immunosuppression, especially

Table 2 Main results of published studies using vaccination after liver transplantation

Ref.	Patients (n)	Age, median (yr)	HBV-DNA negative before LT	Duration between LT and vaccination	Momo immunosuppression	Response to vaccination ¹	Vaccination protocol (dose: µg)
Sánchez-Fueyo <i>et al</i> ^[59] , 2000	22	39	100%	33%	63.5	22.7%	40 im/40 im 3 + 3 (/cycle) without HBIG
Angelico <i>et al</i> ^[60] , 2002	17	53	100%	48%	100	11.8%	40 im/10 sc/40 im 3 + 6 + 3 (/cycle) without HBIG
Bienzle <i>et al</i> ^[63] , 2003	20	54	100%	78%	80	80%	20 im or 100 im 5 + 3 (/cycle) with HBIG Adjuvant: MPL + QS21
Stärkel <i>et al</i> ^[64] , 2005	10	49	90%	55%	100	40%	40 im/40 im 5 (/cycle) with HBIG Adjuvant: MPL
Lo <i>et al</i> ^[66] , 2005	52	47	81%	14%	92.3	1.9%	40 im 3 + 3 (/cycle) without HBIG
Rosenau <i>et al</i> ^[62] , 2006	8	50	37.5%	60%	37.5	12.5%	20 im 6 (/cycle) without HBIG
Lo <i>et al</i> ^[66] , 2007	20	52	80%	21%	85	35%	HBs + preS 20 im 3 + 3 (/cycle) without HBIG
Tahara <i>et al</i> ^[69] , 2009	20	53	75%	20%	60	65%	20 im or 40 im unrestraint with HBIG
Di Paolo <i>et al</i> ^[65] , 2010	18	59	100%	73%	89	44%	under immune-monitoring 20 im 6 + 6 (/cycle) HBIG withdraw Adjuvant: MPL

¹Anti-HBsAb level \geq 100 IU/L. HBV: Hepatitis B virus; MPL: Monophosphoryl lipid A; HBIG: Hepatitis B immunoglobulin; QS21: Quillaja saponaria Molina; HBsAb: Hepatitis B surface antibody; LT: Liver transplantation; im: Intra-muscular administration; sc: Subcutaneous administration.

with withdrawal of steroids, seems to be necessary for vaccination to be effective. This suggests the significance of immune-optimization for successful treatment^[59]. In our facility, we are trying to optimize immunosuppression by monitoring immune status using the CFSE-MLR (mixed lymphocyte reaction using carboxyfluorescein succinimidyl ester)^[67,68], in order to achieve a more effective introduction to active immunity and the withdrawal of HBIG therapy through unrestricted HB vaccination. Using these methods, we have seen an increase in anti-HBsAb values in 13 out of 20 patients who received HB vaccination after LT (65%) and have had successful HBIG^[69] withdrawal. When comparing the immunocompromised state during HB vaccination, the responder group was in the anti-donor-specific immunocompromised state, which maintained immunity against the third party, while the non-responder group was in a nonspecific immunocompromised state. Although a reduction in anti-HBsAb levels was observed after withdrawal of HBIG in 8 out of 13 successfully immunized cases, no re-administration of HBIG was required because the

antibody levels increased again after short-term HB vaccine re-administration. According to our results, the proper maintenance of long-term immune status and administration of the HB vaccine for a lengthy period, if needed, is important for successful HB vaccination therapy. The establishment of standardized HB vaccination therapy is expected in the near future, along with the development of a more efficient novel hepatitis B vaccine, although additional large studies will be needed prior to universally recommending this strategy.

PROPHYLAXIS OF *DE NOVO* HBV INFECTION FROM HBCAB-POSITIVE DONORS

Transplantation from HBcAb-positive donors to HBV-uninfected recipients is clinically critical. Ideally, in order to prevent HBV transmission, HBcAb-positive donors should not be accepted. Since a considerable percentage of the population is HBcAb-positive and in

the presence of a chronic and global organ shortage, the use of HBcAb-positive donor livers would expand the donor pool. Nonetheless, *de novo* HBV infection would be a problem, particularly with the combination of HBcAb-positive donor and HBcAb- and HBsAg-negative recipients^[70,71], respectively. Dickson *et al*^[70] evaluated 674 LT patients and reported that *de novo* HBV infection developed in 18 out of 23 recipients of livers from HBcAb-positive donors (78%) compared with only 3 (0.5%) out of 651 recipients of HBcAb-negative donor livers ($P < 0.0001$). Furthermore, LT from HBcAb-positive donors were associated with a decreased four-year survival rate (adjusted mortality hazard ratio of 2.4; 95%CI: 1.4-4.0). Therefore, the establishment of necessary and sufficient prophylaxis for *de novo* HBV infection is an important area for therapeutics in LT cases. An adequate consensus has not been established and prophylactic strategies that are currently used for LT from HBcAb-positive donors vary from the administration of HBIG or NAs alone to combination therapy, depending on the liver transplant centers. Several groups studied the efficacy of HBIG monotherapy for the prophylaxis of *de novo* HBV infection in recipients who received grafts from HBcAb-positive donors. Roche *et al*^[72] showed that HBV infections were observed in 31.6% of HBV-naïve recipients despite HBIG monotherapy. Furthermore, HBIG monotherapy was associated with a significant risk of *de novo* HBV infection and escape mutation. Ueda *et al*^[58] retrospectively analyzed the clinical course of 75 patients who received HBIG prophylaxis for greater than 6 mo after LT with HBcAb-positive donor grafts. In this study, 19 out of 75 patients (25%) developed *de novo* HBV infection and escape mutations were detected in 7 out of 19 patients^[58]. Conversely, Yu *et al*^[73] showed the excellent prophylactic effect of LAM monotherapy for HBsAg-negative patients receiving HBcAb-positive donor grafts (0 out of 9 patients) with no evidence of HBV-DNA in the grafts. Two systematic reviews confirmed these results^[74,75]. Cholongitas *et al*^[74] reported *de novo* HBV infection rates of 19%, 2.6% and 2.8% in HBsAg-negative recipients treated with HBIG, LAM, and their combination, respectively, in their systemic review. These data indicate the sufficient prophylactic potential of LAM monotherapy and the absence of supplementary effects of HBIG for preventing *de novo* HBV infection. However, the necessity of lifelong prophylaxis needs to be elucidated in future long-term studies.

CONCLUSION

LT for patients with hepatitis B has been one of the most successful treatments in the LT field for decades because of several effective prophylaxis treatments, especially the development of potent hgbNAs. Currently, combination therapy using low-dose HBIG and hgbNA is likely the most accepted prophylaxis. Monotherapy with hgbNAs and withdrawal of HBIG

following combination therapy with HBIG and hgbNAs, are promising approaches.

FUTURE PERSPECTIVES

Treatment strategies that involve hgbNA monotherapy or the withdrawal of HBIG are effective and would be accepted in more institutions. However, further studies are required to decide appropriate regimens (timing and duration) and select optimal patient subpopulations for those strategies. Long-term compliance with the administration of anti-HBV drugs including hgbNAs and newly emerging drug resistance are other issues that need to be addressed. Therefore, close monitoring of recipients with NAs prophylaxis is important. Active immunity through hepatitis B vaccination might be another promising measure for resolving these issues after a more effective and standardized hepatitis B vaccination therapy has been established.

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