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TOPIC HIGHLIGHT

2015 Advances in Hepatitis B virus

Change of strategies and future perspectives against hepatitis B virus recurrence after liver transplantation

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Abstract

A few decades ago, liver transplantation in patients with chronic hepatitis B virus (HBV) infection was considered a relative contraindication because of the high rate of graft infections and poor prognosis. Since then, remarkable progress was introduced by using nucleos(t)ide analogues and/or hepatitis B immunoglobulin (HBIg) and liver transplantation for HBV-related disease is now becoming one of the good indication. However, high cost burden is the main problem for this combination prophylaxis for a long time use, and this issue should be emerged to be resolved. In this review, we show the progress of post anti-HBV strategies showing the history from introduction of HBIg and nucleos(t)ide analogues to recent new strategies with hepatitis B vaccine or saving or stopping protocols of HBIg, and clarify and discuss how to do for further improvement of prevention strategies with better quality.

Key words: Liver transplantation; Hepatitis B virus; Prophylaxis; Hepatitis B immunoglobulin; Nucleos(t)ide analogue; Hepatitis B vaccine; Escape mutant

Core tip: Liver transplantation for patients with hepatitis B virus (HBV)-related diseases is made remarkable progress since combination prophylaxis with nucleos(t)ide analogues and hepatitis B immunoglobulin was introduced. This combination prophylaxis is established as the gold standard in these days, however, the biggest problem is the high cost for longer use of these drugs. In this study, we show the history of preventive strategy against HBV after liver transplantation, and discuss what to and how to resolve the issues concerning posttransplant anti-HBV strategies with reported literature.

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HEPATITIS B VIRUS-A LEADING INDICATION FOR LIVER TRANSPLANTATION

Worldwide, 500 million people are estimated to be chronically infected with hepatitis B virus (HBV)[1]. Chronic HBV infection induces liver failure due to liver cirrhosis and/or hepatocellular carcinoma, and accounts for 500000-1000000 deaths annually[2,3]. This trend is especially marked in Asian-Pacific countries, and more than 5000 liver transplants are performed annually in these countries[4]. In Western countries, 5%-10% of liver transplantation is performed for patients with HBV-related liver diseases[5-8], compared with 12.4% in Japan[9], up to 80% in South Korea[10], and up to 90% in China[11]. Therefore, the control of HBV is an important issue for improving long-term survival after transplantation, especially in Asian countries.

Since HBV was identified in 1968, treatment has changed, and, accordingly, anti-HBV strategies before and after liver transplantation have also changed. In this review, we try to summarize past and present peri- and post-operative anti-HBV strategies for liver transplant patients, and discuss future perspectives and issues that should be resolved.

WHY IS THE CONTROL OF HBV DIFFICULT?-THE COMPLICATED HBV LIFE CYCLE AND WEAK IMMUNOLOGICAL RESPONSE IN CHRONIC CARRIERS

HBV is a unique virus in some respects; it infects only humans and apes, and is an incomplete, double-stranded, circular DNA virus with quite a complicated life cycle, in that it is first transcribed into pregenomic RNA, and then back to DNA[12]. As HBV passes through many steps for replication, there are many chances for drug-resistant mutations to arise. Also, HBV-DNA becomes a very stable transcript, covalent circular DNA (cccDNA), in the nucleus of host hepatocytes during its life cycle[12,13].

Because of these unique aspects, treatment for HBV appears to be very difficult and complicated. Nucleos(t)ide analogue therapy is one of the recent standards for treatment of HBV. This agent targets DNA polymerase, which is important for the formation of DNA from pregenomic RNA; inhibition of the polymerase stops HBV-DNA replication very efficiently. On the other hand, if pressure toward a specific site continues, the virus tries to escape for its own survival, and finally becomes drug-resistant[14]. Furthermore, cccDNA, which exists in the nucleus in a very stable form, is not targeted by nucleos(t)ide analogues, and this form can survive stably during the treatment[15]. Thus complete virus eradication is difficult.

Another aspect is the immune response to HBV. In chronic HBV carriers, specific T cell responses against HBV were shown to be narrowly focused[16]. Furthermore, to control viral infection, coordination of innate and adaptive immune responses is necessary, and many steps of this series of immune reactions were proven to be suppressed by many molecular and immunological investigations[17]. In transplant patients, immunosuppressants are necessary to avoid rejection of the grafts, and these drugs target mainly lymphocytes (either T or B cells, or both) through several mechanisms[18]. These situations add to the difficulties with controlling HBV.

HBV-RELATED DISEASE WAS A RELATIVE CONTRAINDICATION FOR LIVER TRANSPLANTATION SEVERAL DECADES AGO

A few decades ago, the prospect of liver transplantation for patients with HBV infection was completely different from recent times. Before prophylaxis for HBV was introduced, the risk of graft reinfection was reportedly 80%-100%[19,20], and patients with a high viral load preoperatively had a higher risk for HBV reinfection[21-23]. Recurrence of hepatitis B after liver transplantation considerably reduced graft and patient survival[19,24-26]. In the short term, patients with recurrence were at risk for fibrosing cholestatic hepatitis or fulminant hepatitis, and, in the long term, for cirrhosis[19,27]. Consequently, the mortality rate was 50% 2 years after liver transplantation[28]. Thus, liver transplantation in patients with chronic HBV infection was considered a relative contraindication in those days. So how did this situation dramatically change in the last 20 years?

DEVELOPMENT OF EFFECTIVE POST-TRANSPLANT HBV PROPHYLAXIS

Anti-HBs hepatitis B immunoglobulin monoprophylaxis

In 1991, Samuel *et al*[23] reported a trial of polyclonal anti-hepatitis B surface antigen antibody [anti-HBs hepatitis B immunoglobulin (HBIg)], and in 1993, they reported the results of a European multicenter study of this prophylaxis regimen[29]. Of 110 HBsAg-positive patients who received liver transplantation and were treated with high-dose HBIg from the anhepatic phase, HBsAg reappearance occurred in only 25 (22.7%) within 2 years, and the overall survival rates improved to 83.6% 1 year, and 74% 2 years,

after transplantation[23]. That effectiveness of long-term HBIg administration was superior for both HBV recurrence and actual survival was confirmed in a European multicenter trial by 17 institutions[29].

From the early 1990's, HBIg monoprophylaxis became a major regimen for prophylaxis of post-transplant HBV recurrence[7,30]. Studies conducted by several groups demonstrated that in long-term follow-up, as long as 10 years, HBV recurrence was 56.5% by maintaining the anti-HBsAb level at > 100-150 IU/l[31], and 16%-35% by maintaining the level at > 500 IU/L[31-35], which seems to be a dose-dependent effect[23-29].

Nucleos(t)ide analogue monoprophylaxis, in the lamivudine era

In the mid-1990's, the first nucleoside analogue, lamivudine, which acts as a reverse transcriptase inhibitor, was approved[36] for use as an effective treatment for both HBeAg-positive[37] and -negative patients[38]. In transplanted patients, this drug was tried first without administration of HBIg. Preliminary results were quite promising, in that only 1 of 10 patients had recurrence of HBV 1 year after transplantation[39]. However, with longer follow-up, several groups reported that the recurrence rate was 22%-50%, and HBV-related death was shown to be 0%-15.3% in these patients[31,40-42]. The main mechanism of recurrence in these patients was emergence of escape mutations in the YMDD motif of the polymerase gene[43], as shown in non-transplant HBV-positive patients; and sometimes these patients had a severe clinical outcome[31,44]. Ultimately, monoprophylaxis with lamivudine for prevention of post-transplant HBV recurrence was quite disappointing.

Nucleos(t)ide analogues in combination with HBIg-the recent gold standard for prevention of post-transplant HBV recurrence

The next conceptual strategy was using the combination of agents that were effective to some extent, as described above; lamivudine and HBIg. Markowitz *et al*[45] first reported the effect of lamivudine administration prior to transplantation and combination with lamivudine and HBIg after transplantation for anti-HBV prophylaxis. First results were excellent in that 13 of 14 (92.9%) patients who received lamivudine prior to transplantation had no detectable HBV-DNA at transplant, and no HBV recurrences were seen during 13 mo of follow-up after transplantation. Since then, several groups have confirmed the effectiveness of this combination treatment, and HBV recurrence was reported to be < 10% 1-2 years after transplantation[31,46-48].

Over 10 years, this combination treatment became the gold standard for prevention of post-transplant HBV recurrence[4,49,50] and currently most transplant centers use this treatment concept.

FUTURE PERSPECTIVES FOR THIS ESTABLISHED PREVENTIVE REGIMEN-ISSUES THAT SHOULD BE RESOLVED

Recent status and future perspectives

As described above, the combination of nucleos(t)ide analogues and HBIg was established as an effective regimen for prevention of post-transplant HBV recurrence. However, this combination treatment has an essential weakness-namely, its high cost.

Basically, high-dose HBIg is necessary in the first postoperative month, and regular HBIg administration is also necessary to maintain a target level of HBsAb titers to prevent recurrence. The costs of representative reported regimens in the first year are shown in Table 1[7,14,31,45-48,51-56]. Basically, around $40000 United States per patient should be spent in the first year. And for each additional year, costs continue at $25000-$40000 United States per year[15,50,57].

In addition, some new nucleos(t)ide analogues with high genetic barriers, other than lamivudine, such as adefovir, entecavir, and tenofovir, have successively appeared in clinical practice, further changing the field of prevention of post-transplant HBV recurrence.

Recent status of nucleos(t)ide use in transplant patients-a focus on genetic barriers

Lamivudine was the main nucleos(t)ide analogue in use until a decade ago, however, it has an essential weakness-development of a high proportion of drug resistant mutations. The most common site is substitution of methionine to valine or isoleucine (rtM204V/I) in the tyrosine-methionine-asparate-asparate (YMDD) motif in the HBV-DNA polymerase region[16]. Resistance can be detected in 14%-32% after 1 year of treatment[1,37,58,59], and increases up to 60%-70% after 5 years of treatment[1,60,61].

In the situation of transplant patients, combination of HBIg with lamivudine dramatically reduced the appearance of drug-resistant mutations after liver transplantation; however, in a recent systematic review, such mutations were detected in 5.7% of patients[62]. Of note, among the patients who had recurrence by this mechanism, pre-transplant existence of this mutation, especially in patients treated for a long time before transplantation, could have been a risk factor for recurrence[63].

Adefovir dipivoxil was reported to have effective in vitro and *in vivo* activity against lamivudine-resistant HBV mutants as well as against wild type virus[64]. Also, in the transplant field, adefovir has recently been used along with lamivudine if drug resistance is discovered[65]. In a recent systematic review, combination therapy of adefovir and HBIg with or without lamivudine was superior in efficacy to combined lamivudine and HBIg and lamivudine alone for preventing post-transplant HBV recurrence

Table 1 Comparison of amounts and costs of hepatitis B immunoglobulin for combination prophylaxis with nucleos(t)ide analogues in previous publications[7,51]

Ref.	Patients (*n*)	Protocol (HBIg)	Follow-up months median or average	HBV recurrence	HBIg amount V/1000IU/3 mo	HBIg cost US dollars
Markowitz *et al*[45]	14	80KIU *iv* 1st month Then 10KIU *iv*/mo	12	0	100	40000
Yao *et al*[52]	10	80KIU *iv* + 3.3KIU *im* x 1 mo Then 1.48KIU *im*/mo	15.6	1 (10)	86.26	34500
Yoshida *et al*[53]	18	43.4KIU *im* 1st month 4.3-6.8KIU *im*/mo thereafter	18	0	52-67	20800-26800
Mazano *et al*[47]	33	46.5KIU *iv* 1st week 5KIU/mo thereafter	30	1 (3)	56.5	23000
Rosneau *et al*[46]	21	45KIU *iv* 1st week HBsAb > 500 until 14POD HBsAb > 200 thereafter	21	2 (9.5)	> 45	> 18000
Roche *et al*[31]	15	80KIU *iv* 1st month 10KIU/month *iv* thereafter	> 120	1 (6.6)	100	40000
Han *et al*[48]	59	80KIU *iv* 1st month 10KIU/month *iv* thereafter	35	0	100	40000
Seehofer *et al*[54]	17	80KIU *iv* 1st month 1.5-2KIU/month to maintain HBsAb > 100	25	3 (18)	83-84	25200-25600
Wong *et al*[55]	21	70KIU *iv* 1st month 10KIU/month *iv* thereafter	25	2 (9.5)	90	36000
Takaki *et al*[56]	18	200IU/kg *iv* for 1 wk HBsAb > 100 following 5 mo HBsAb > 10 thereafter	18	0	47	18800
Buti *et al*[14]		10KIU *iv* anhepatic phase 5KIU *iv* following 6 d 4KIU *im* following 3 wk	18	1 (7.1)	52	20800

For these calculations, 1 US dollar = 100 yen. Estimated cost of HBIg: 400 dollars. HBV: Hepatitis B virus; HBIg: Hepatitis B immunoglobulin.

(2.0% *vs* 6.1%, $P = 0.024$)[30]. Thus, in most cases adefovir was administered supplementary to lamivudine, especially in cases of lamivudine-resistant mutations[66-68].

Recently, anti-HBV drugs with high genetic barriers were successively developed. Two of most frequently used nucleos(t)ide analogues in the transplant field are entecavir and tenofovir. Entecevir was first approved by the FDA in March, 2005. This drug was apparently shown to have a high genetic barrier for drug resistance mutations; that is, the rate was 1.2% after 5 years of continuous use[69,70]. With regard to the transplant field, post-transplant recurrence of HBV was shown to be significantly lower with combined entecavir and HBIg prophylaxis (3/197; 1.5%) compared with lamivudine-based combined prophylaxis regimens (115/1889; 6.1%, $P < 0.001$), as reported in a recent systematic review[15,50,57].

Tenofovir was first approved as an anti-HIV drug in October, 2001, was also shown to have an anti-HBV effect, and was approved as an anti-HBV drug in August, 2008. Resistance to tenofovir was reported as 0% after 5 years of treatment in non-transplant patients[69,70]. HBV recurrence in patients taking tenofovir combined with HBIg as post-transplant HBV prophylaxis was reported as 0% (0/106) in the systematic review mentioned above[67]. There were no apparent differences of recurrence between entecevir and tenofovir combined with HBIg[71]. These data suggest that recent NAs with high genetic barriers should be used in standard treatment regimens.

HB vaccine-attractive alternative for cost savings, but premature

Successful HB vaccine induction was first reported by Sanchez-Fueyo *et al*[72]; 82% of patients after liver transplantation responded to the vaccine. Since then, several transplant centers have attempted to implement this new concept of prophylaxis; however, most results were quite disappointing[73-77]. Overall, HB vaccination after liver transplantation is less effective than expected.

However, some treatment manipulations and careful selection of patients might improve the effectiveness of post-transplant vaccination against HBV. Bienzle *et al*[78] showed an 80% response in HBV carriers to vaccine containing 3-deacetylated monophophoryl lipid A (MPL-A) and natural saponin as an adjuvant. They also showed that a significant cellular immune response inhibited regulatory T cells, which was related to the good response to the vaccine[79]. Tahara *et al*[80] described an interesting method to monitor the recipients' immune status by using the mixed lymphocyte reaction with the CFSE-labeling technique; the immune status of hyporesponsiveness to donor lymphocytes but response to anti-third party lymphocytes was a key point for successful vaccine response, and the response rate was 64.7% in HBV

carriers.

Non-HBV patients who received grafts from HBcAb-positive donors and patients with fulminant hepatitis due to HBV infection have also been populations targeted for prophylaxis against HBV. In both populations, vaccine response was generally good in pediatric[81-83], and adult cases[84,85], and we showed by direct comparison that vaccine response was significantly better in non-HBV patients than in HBV-carriers[86].

In summary, the HB vaccine response of transplanted patients is quite disappointing, but some improvements seem to be pending. At this moment, some treatment manipulations and proper patient selection can be expected to yield a satisfactory level of response.

HBIg-Is lifelong treatment really necessary?

Needless to say, HBIg is one of the most important key drugs for the prevention of HBV recurrence after liver transplantation. However, the biggest issue for using HBIg is the high cost burden for long-term use, as described repeatedly. HBIg is definitely necessary in the early postoperative period for controlling HBV recurrence, but is lifelong treatment really necessary?

The first trial was designed to determine how far an HBIg dose could be saved. One strategy was "on demand" administration of HBIg to maintain a target trough HBsAb level, and then lowering these trough levels; the other was using "intramuscular" low-dose administration of HBIg[50]. In "on demand" protocols, trough HBsAb titers were usually 50-100 IU/L, and the HBV recurrence rate was < 10% in the distant postoperative period[87-90]. Even with trough levels of 10 IU/L more than 12 mo after transplantation, reported in 2/18 patients, and accompanied by transient low-titer HBsAg-positivity, titers became negative after reintroduction of HBIg, during a median follow-up period of 57 mo[56]. Intramuscular administration of HBIg was first reported by Gane *et al*[3]; the dosage was 400-800 IU daily for a week and monthly thereafter, resulting in costs of less than 10% compared with high-dose HBIg regimens, and the recurrence rate was 1% at 1 year and 4% at 5 years. In contrast, Zheng *et al*[91] reported 15.2% recurrence at 2 years and demonstrated that a high serum HBV-DNA level at transplant was a significant risk factor accompanying low-dose intramuscular HBIg administration.

The next trial concerned HBIg withdrawal in the distant postoperative period. Buti *et al*[14] reported a study of use for HBV recurrence prophylaxis after liver transplantation of the combination of HBIg and lamivudine for 1 mo and then randomization to 17 mo of either lamivudine monotherapy or combination therapy in 29 patients. They showed no recurrence of HBV at 18 mo. Wong *et al*[55] reported a retrospective cohort study of 21 patients in whom recurrence rates were 0% at 2 years and 9% at 4 years. One factor lowering the risk for HBIg recurrence after withdrawal of HBIg was pre-transplant viral suppression. Fox *et al*[50] reported in their review of the recent literature that low viral load is definitely an important predictive factor for preventing HBV recurrence after liver transplantation[92,93], and they concluded the best candidates for HBIg withdrawal are patients with enough pre-transplant suppression of HBV[50]. Another issue is the selection of NAs. Fung *et al*[94] showed that among 362 patients, even without HBIg prophylaxis, none who received entecavir had HBV recurrence, compared with 17% recurrence in patients who received lamivudine. And in a recent meta-analysis, HBIg withdrawal in patients who received NAs with high genetic barriers was not inferior to those treated with the combination of HBIg and NAs with high genetic barriers (3.9% *vs* 1.0%, respectively, of HBV recurrence, $P = 0.17$) and was lower than in those treated with the combination of lamivudine and HBIg, although this was not statistically significant (3.9% *vs* 6.1%, $P = 0.52$). Collectively, studies suggest that permanent administration of HBIg is not always necessary for carefully selected patients.

HBs escape mutants; another HBV-related aspect of the care of transplant patients

As described repeatedly, one of the key drugs for prevention of HBV recurrence after liver transplantation is HBIg. In some patients, repeated injection of anti-HBs Ab has led to induction of HBs escape mutants by blocking neutralization of HBV, as with the HB vaccine.

There are two reports that address this issue. Ueda *et al*[95] reported that in patients who received livers from HBsAg-negative, HBcAb-positive donors under prophylaxis with HBIg without NAs, 19 of 75 patients developed *de novo* HBV activation, and among them, 7 patients were confirmed to have anti-HBs escape mutations especially in determinant regions like G145R, G145A, or Q129P[95]. And in another study, we have found that among 8 patients with successful vaccine response who stopped NAs, 4 had HBV viremia after a median of 12 mo, and anti-HBs escape mutants like G145R, T131P, D144A, or S143T were found in 3 patients. In this study, we also showed that reintroduction of entecavir immediately inhibits HBV replication[96]. When considering nucleos(t)ide-analogue free regimens including HBIg monotherapy or stopped after successful vaccine response, it is important to appropriately address the issue of HBs escape mutants.

CONCLUSION

Treatment of HBV-related disease has now become a relatively safe and established indication for liver transplantation. The biggest remaining issues are related to the long term use of HBIg; namely cost and issues with vaccination and development of escape

mutants. Strategies for prevention of HBV after liver transplantation are evolving and improving; along with development of treatments for HBV, including new NAs, new post-transplant strategies should also emerge.

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