Original Article

Prophylaxis of Hepatitis B after Liver Transplantation Using Low-Dose Short-Course Hepatitis B Immunoglobulin Plus Antiviral Drug

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Background: The most common indication for liver transplantation (LT) in South East Asia is hepatitis B virus (HBV)-related liver disease. Without proper prophylaxis, HBV will recur rapidly after LT. Currently, there is no universally accepted regimen, and most transplant centers use high-dose hepatitis B immunoglobulin (HBIG) for prophylaxis, which is costly.

Objective: To review the authors' experience with low-dose short-course HBIG plus antiviral for HBV prophylaxis.

Materials and Methods: Between July 2002 and December 2013, 90 patients who were positive for HBV surface antigen (HBsAg) underwent LT at the authors' institute. The protocol included continuing previously prescribed antiviral drug or giving lamivudine 150 mg orally before the operation in patients who had never received antiviral drug. All patients received 1,200 to 2,000 international units (IU) of HBIG intravenously during anhepatic phase, and 1,200 to 1,600 IU of intravenous HBIG daily for six days postoperatively. Oral antiviral drug was continued postoperatively. HBV recurrence was defined as the reappearance of HBsAg in serum. Cumulative incidence function was used to calculated cumulative recurrence rate.

Results: At the end of follow-up, the post-transplant HBsAg status was positive in six patients (6.7%); two patients at three months, one patient at one year, two patients at seven years, and one patient at ten years after LT. Cumulative HBV recurrence rate was 2.3% at one year, 3.5% at five years, and 11.3% at ten years after LT. The median time-to-recurrence was 49.5 months. All treatments were well tolerated with no serious adverse event.

Conclusion: Combination of low-dose short-course HBIG and long-term oral antiviral drug is effective in preventing HBV recurrence after LT. Since HBIG is very expensive, this low-dose short-course HBIG prophylaxis regimen can reduce the cost of LT without increasing the HBV recurrence rate.

Keywords: Hepatitis B virus, Prophylaxis, Hepatitis B immunoglobulin, Liver transplantation, Recurrence

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Hepatitis B virus (HBV) infection is a common cause of chronic liver disease and one of the top ten causes of death[1]. An estimate of two billion people are infected with HBV worldwide, and approximately 360 million patients have chronic HBV infection and 600,000 of these patients die each year[2]. About 75% of infected patients have been found in Asia, particularly East and South East Asia[3]. Approximately 10% to 15% of HBV infected patients would progress to chronic liver disease[4], and 3% would develop hepatocellular carcinoma (HCC)[5].

Liver transplantation (LT) is currently the standard treatment for patients with end-stage liver disease, including HBV-related liver disease[6]. In the early years of LT, before the use of antiviral prophylaxis, HBV was contraindicated for LT because of the very high HBV recurrence rate of 50% at three years and HBV-related graft injury leading to early graft failure and death. The 3-year survival was only about 44% in HBV recurrence patients[7]. However,

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for the last two decades, the indication for LT for HBV infected patients has changed. After antiviral prophylaxis was used, the 5-year survival has been improving to more than 80% and LT has become the standard treatment for HBV-related liver disease[8].

The introduction of passive immunoprophylaxis with intravenous (IV) hepatitis B immunoglobulin (HBIG) reduced the recurrence rate by 60%[7], but life-long maintenance treatment is required. This is very expensive and inconvenient for patients because they would require regular hospital visits for parenteral administration. The combination of nucleoside or nucleotide analogues with HBIG further reduce the recurrence rate to less than 10%[9]. There is a regimen adapted to use low-dose intramuscular (IM) or subcutaneous HBIG instead of high-dose IV HBIG[10]. The cost is substantially decreased. However, this lifelong HBIG regimen is still inconvenient to patients and expensive. Thus, there were a number of studies reporting the use of short-course HBIG instead of the lifelong regimen[11-21]. Most protocols require HBIG for six to 12 months, with only two studies reporting 7-day regimen of IV or IM HBIG[11,12]. These short-course HBIG regimens showed no higher recurrence rate than the previously recommended lifelong HBIG regimens. Some centers also proposed low-dose HBIG regimens (of less than 2,000 international units [IU]/dose) instead of high-dose HBIG (10,000 IU/dose). These were found to be safe and cost-effective[10,12,22].

Currently, there is no universally accepted regimen for HBV prophylaxis after LT. Majority of transplant programs still use long-term high-dose HBIG. Only a few centers use alternative prophylaxis regimens, such as low-dose or short-course HBIG. The authors have adopted the low-dose short-course HBIG plus antiviral drugs for HBV prophylaxis since 2002. The aim of the present study was to review the experience of the authors' prophylaxis protocol at the liver transplant unit at Siriraj Hospital, Bangkok, Thailand.

Materials and Methods

The present study was a retrospective study using prospectively collected database of 180 patients that underwent LT at Siriraj Hospital between July 2002 and December 2013. Among these, 90 patients were positive for hepatitis B surface antigen (HBsAg) and were included in the analysis. Retransplantation and living donor LT were excluded. The study was approved by the Ethics Committee of the Faculty of Medicine Siriraj Hospital, Mahidol University.

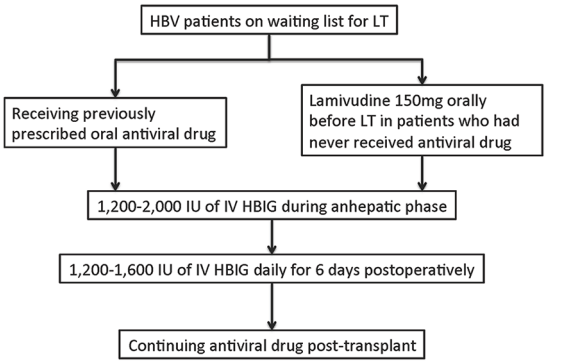

Figure 1. Flow diagram of hepatitis B prophylaxis protocol after liver transplantation at Liver Transplant Unit, Siriraj Hospital.

HBIG: hepatitis B immunoglobulin, HBV: hepatitis B virus, IV: intravenous, IU: international unit, LT: liver transplantation

HBV prophylaxis

The present study HBV prophylaxis protocol included continuing previously prescribed oral antiviral drug (nucleoside or nucleotide analogue) or starting lamivudine 150 mg orally before the transplant operation in patients who had not previously received antiviral drug. The antiviral drug was continued long-term post-transplant indefinitely.

All patients received 1,200 to 2,000 IU (depending on the patient's body weight) of HBIG intravenously during anhepatic phase of their transplant operation. Postoperatively, 1,200 to 1,600 IU of IV HBIG was administered daily for six days only (Figure 1).

Immunosuppression

Post-transplant immunosuppression consisted of calcineurin inhibitor (tacrolimus or cyclosporine) adjusted to blood level, and a short course of prednisolone (tapered off and discontinued around 3-month postoperatively). Some patients might receive mycophenolate or azathioprine to reduce the dosage and serum level of calcineurin inhibitor, depending on their renal function.

All patients were followed up regularly at the liver transplant clinic with standard laboratory test including liver function, renal function, complete blood count, and immunosuppression level. HBsAg status was checked at three months post-transplant and annually thereafter. A liver biopsy was performed when graft rejection was suspected. HBV recurrence was defined as the reappearance of HBsAg in serum.

Statistical analysis

Cumulative HBV recurrence rate was estimated

Table 1. Demographic data of 90 patients with positive HBsAg who underwent LT at Siriraj Hospital

Characteristics	n (%)
Age (year), Mean±SD	54.6±8.8
Sex	
Male	65 (72)
Female	25 (28)
Associated diagnosis	
HCC	57 (63)
HCV	22 (24)
Comorbidity	
Hypertension	23 (26)
Diabetes mellitus	37 (41)
Coronary artery disease	6 (7)
Chronic kidney disease	16 (18)
Laboratory, Mean±SD	
Total bilirubin (mg/dL)	10.9±14.5
Creatinine (mg/dL)	1.8±2.2
INR	1.5±0.6
MELD score	23.7±9.4

HCC=hepatocellular carcinoma; HCV=hepatitis C cirrhosis; INR=international normalized ratio of prothrombin time; MELD=model of end-stage liver disease; SD=standard deviation

using the cumulative incidence function. The reappearance of serum HBsAg was defined as the event of interest, whereas death during follow-up was the competing event. The cumulative incidence function is a more accurate way than the standard Kaplan-Meier function to estimate an incidence that involves competing events such as death during follow-up time[23,24].

All the statistical analyses were performed using Stata version 11.1 (StataCorp, College Station, Texas, USA). A p-value of less than 0.05 was considered statistically significant.

Results

Ninety patients with positive HBsAg status underwent LT at Siriraj Hospital between July 2002 and December 2013. Among these patients, 57 patients (63%) had associated HCC, and 22 patients (24%) had hepatitis C virus (HCV) co-infection. The median (interquartile range; IQR) of the follow-up time was 31 (6.6 to 67.3) months. The demographic data of the study cohort is shown in Table 1.

At the end of follow-up, the post-transplant status of HBsAg was positive in six patients, giving the crude HBV recurrence rate of 6.7%. Three patients were found to have HBV recurrence in the early post-transplant period. Two patients had HBsAg positive at three months post-transplant, and one patient at one year. The remaining three patients achieved the short and medium-term control of HBV infection, but it recurred in the later years. Two patients were found to have HBsAg positive at seven years and one patient at ten years after LT. However, all six patients who had the reappearance of HBsAg showed no serological evidence of active viral replication and no clinical evidence of graft hepatitis or cirrhosis. All patients are still alive at the end of follow-up.

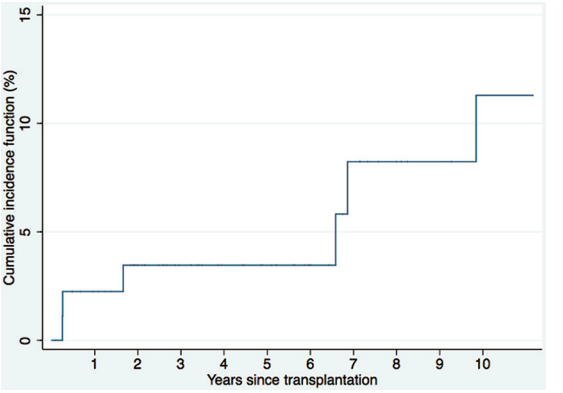

Figure 2. Cumulative incidence of hepatitis B recurrence after low-dose short-course intravenous hepatitis B immunoglobulin plus antiviral drug.

According to the cumulative incidence function, the HBV recurrence rate was 2.3% (95% confidence interval [CI] 0.6 to 8.7) at one year after transplantation. The HBV recurrence rates at five years and ten years post-transplant were 3.5% (95% CI 1.1 to 10.4) and 11.3% (95% CI 4.9 to 25.0), respectively (Figure 2). The median (IQR) time to HBV recurrence was 49.5 (3.1 to 82.4) months.

The authors' hepatitis B prophylaxis protocol was well tolerated, before, during, and after the transplant operations in all patients without any significant adverse event. All patients received the full course of HBIG without any drop out.

Discussion

In the present study, the authors have shown that the proposed low-dose short-course IV HBIG was effective in HBV prophylaxis after LT. The HBV recurrence rate is comparable to other previously reported HBV prophylaxis protocols using long-term or high-dose HBIG.

A number of studies reported various prophylaxis protocols with HBIG discontinuation after a certain period[11-21]. These prophylaxis protocols were

proved to be effective with HBV recurrence ranging from 0% to 17%. These regimens consist of HBIG intravenously or intramuscularly starting at the time of transplant and continuing for a certain period of time, combining with one or two oral antiviral drugs continuously afterwards.

Most regimens involve the duration of HBIG of 12 months or more[13-18]. Only a few previous studies reported using short-course HBIG of seven days with comparable results[11,12]. Nath et al used a prophylaxis protocol of 10,000 IU of IV HBIG during anhepatic phase and 10,000 IU IV HBIG daily for seven postoperative days. Lamivudine was started immediately after transplantation and adefovir was introduced after HBIG was discontinued. They reported 7% of HBV recurrence (1 of 14 patients) over the mean follow-up of 14 months[11]. Gane et al reported using 800 IU of IM HBIG plus lamivudine and adefovir for seven days then only lamivudine and adefovir afterwards in 20 patients. They reported no HBV recurrence with transient detection of HBsAg in one patient with concomitant HCC recurrence[12].

There were two recurrence patterns observed in the present study. The first is the early recurrence within the first few years after transplantation. There is a possibility that this may be related with the inability of low-dose HBIG to completely clear HBV DNA from the patient. There is evidence that low level of HBV DNA is detected in serum, liver graft, and peripheral blood mononuclear cells after LT, even in the case that HBsAg cannot be detected[25]. The early recurrence may be related with a high pre-transplant HBV DNA level or a high risk of HCC recurrence. Unfortunately, this could not be concluded from the data in the present study, and a further study is warranted.

The second pattern of recurrence is the late recurrence after five years. In this group of patients, a possible explanation for HBV recurrence may be antiviral drug resistance. Recurrence is probably due to the escape mutations in the tyrosine-methionine-aspartate-aspartate (YMDD) locus of the HBV RNA-dependent DNA polymerase gene[11]. This was found to be related with lamivudine monotherapy in which some studies reported the resistance to be as high as 14% after 52 weeks of treatment[26]. Unfortunately, the authors could not further confirm the cause of drug resistance in these patients. Lamivudine combining with adefovir in the long term may provide a better control of lamivudine resistance[11,21,27]. However, adefovir has some nephrotoxic effect, and administering together with calcineurin inhibitor may lead to the deterioration of renal function[12]. Newer generation of antiviral drugs such as tenofovir and entecavir are effective and can be used in controlling HBV when lamivudine resistance is suspected.

There are a few limitations in the present study. Firstly, the main limitation of the study was the retrospective nature of the study over the 10-year period. Secondly, the HBIG prophylaxis protocol was consistent in all patients, but antiviral drug was not similar in all patients. In patients who already had pre-transplant HBV treatment other than lamivudine, the authors did not change their antiviral medication, so they might already develop lamivudine resistance. In patients who did not have pre-transplant antiviral drug, lamivudine is still the first-line treatment regarding its safety profile and cost-effectiveness. Thirdly, the present study did not routinely check Hepatitis B envelope antigen (HBeAg) status, serum HBV DNA, or liver biopsy for HBV DNA. Patients with the reappearance of HBsAg with undetectable serum HBV DNA may not develop clinical disease or histological evidence of HBV-related hepatitis on liver biopsy, and, thus, may not have a higher risk of graft loss[28,29]. The presence of intrahepatic HBV DNA may be a novel indicator of clinical recurrence of HBV, but the technique to measure HBV DNA in liver biopsy is still not standardized.

Conclusion

The use of low-dose short-course IV HBIG combining with long-term oral antiviral drug is effective in preventing HBV recurrence after LT. This low-dose short-course HBIG prophylaxis regimen can reduce cost of LT without increasing the HBV recurrence rate.

What is already known on this topic?

Unless effective prophylaxis, hepatitis B recurrence after LT is high and can cause graft failure and poor survival. Regimens for HBV prophylaxis are still not standardized, mostly included high-dose and/or long-term HBIG, which is expensive.

What this study adds?

The low-dose short-course IV HBIG combining with long-term oral antiviral drug is safe and effective in preventing hepatitis B recurrence after LT. This prophylaxis regimen can reduce the cost of LT for HBV cirrhosis.

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Conflicts of interest

The authors declare no conflict of interest.

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