Original Article

Optimal Level of Hepatitis B Surface Antibody for Prevention of Recurrent Hepatitis B Following Liver Transplantation: A Retrospective Study

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Background: The combinative regimens using oral nucleos(t)ide analogs (NA) plus either regular or on-demand low dose hepatitis B immunoglobulin (HBIG) have shown significant decrease in recurrence of post-liver transplantation (LT) hepatitis B, leading to considerable cost saving. Most of the protocols aimed to maintain hepatitis B surface antibody (HBsAb) levels above 100 IU/mL.

Objective: To demonstrate that the maintenance threshold for HBsAb level could be lowered to 50 IU/mL for hepatitis B virus (HBV) prophylaxis during post-LT.

Materials and Methods: The authors conducted a retrospective study of 45 patients that undergone LT for HBV-related diseases between 2003 and 2015. All patients had been followed-up and placed on a post-LT anti-HBV regimen of on-demand low-dose HBIG plus NAs. A fixed dose of 800 U HBIG was given as required to maintain HBsAb levels above 50 IU/mL. HBV recurrence was defined as persistent reappearance of HBsAg.

Results: The mean follow-up was 57.8±38.3 months (range 6 months to 12 years), and no patient experienced HBV recurrence during that period. However, two patients experienced a few episodes of non-sustained HBsAg seropositivity without active disease, which indicated an actuarial risk of recurrence of 4.4%. The mean level of HBsAb in each stratified period was well maintained above 50 IU/mL. The estimated cost of HBIG was approximately 50% of the cost for the regular low-dose regimen.

Conclusion: The present regimen yielded good result and significant cost reduction. The authors propose the maintenance HBsAb level could be reduced to 50 IU/mL without compromising the clinical outcome.

Keywords: Liver transplantation, Hepatitis B, Hepatitis B immunoglobulin, HBsAb level, Nucleoside analog

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End-stage liver disease (ESLD), liver failure, and hepatocellular carcinoma (HCC) are the leading causes of death among hepatitis B patients worldwide, especially in the Asia-Pacific region[1]. Liver transplantation (LT) is the one or often the only therapeutic option in early stage HCC, irreversible decompensated hepatitis B virus (HBV) cirrhosis after treatment with oral antiviral drugs, and acute-on-chronic liver failure (ACLF) from flare-up hepatitis B[2-4]. At one time, LT for hepatitis B-related diseases yielded poor clinical outcomes due to the high incidence of graft failure or death from post-LT severe recurrent hepatitis B[5-8]. However, since the implementation of prophylactic strategy using passive immunization with very high dose hepatitis B immunoglobulin (HBIG), the rate of post-LT recurrence of hepatitis B has significantly declined to at least one-third of the cases[9].

The initial aim of the HBIG prophylactic protocol was to keep the level of hepatitis B surface antibody (HBsAb) above 500 IU/mL during the initial phase of treatment and to at least 100 to 500 IU/mL during the maintenance phase[9,10]. To meet these requirements, a long-term high dosage of HBIG was

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administered during the peri-operative period and as the monthly life-long maintenance[11]. The costs of these prophylactic regimens were considered to be extremely high[11,12]. Moreover, increasing demand for HBIG for this purpose, especially in the Asia-Pacific region, depleted supplies, which inevitably limited the use of the regimen.

In the era of oral antiviral drugs, an HBV prophylaxis strategy of combinative regimen using oral nucleos(t)ide analogs (NA) plus regular low-dose HBIG yielded better results with considerable cost reduction[13]. Historically, most protocols have used varying dosages of HBIG, from 400 to 800 IU, administered via intramuscular injection at regular fixed intervals[14]. In recent years, however, a few on-demand HBIG regimens have been published and showed reasonable good outcomes. The underlying idea was to provide HBIG replacement according to the measured levels of HBsAb, with most regimens aiming to maintain a level above 100 IU/mL during the maintenance phase[15,16].

During the evolution of worldwide HBV prophylactic protocols, the authors developed a protocol of oral antiviral drugs plus on-demand low-dose HBIG, which was able to maintain the HBsAb level at a lower value.

Materials and Methods

Patients and data

All the patients (n = 45) included in the present study were treated at the Center of Excellence in Liver Diseases, King Chulalongkorn Memorial Hospital (Bangkok, Thailand). There were 32 males and 12 females, age ranging from 45 years to 67 years. The medical records of the patients that underwent deceased donor LT for HBV-related ESLD or HCC between January 2003 and December 2015 were reviewed. Each patient required at least six months of follow-up after the transplantation and the last follow-up ended in June 2016. Patients who had received the on-demand low-dose HBIG and NA therapy were included in the present study. Data on patients' demographics, post-LT immunosuppressive regimen, HBIG dosage regimens, and clinical outcomes, including hepatitis B recurrence, HBsAb level, and HBV DNA viral load were collected. The prophylaxis data reported in the present study was limited to the maximum range of seven years, so as to ensure a sufficient number of cases for each follow-up year.

Prophylaxis protocols

Two peri-operative HBIG regimens were used during the evolution of the protocol. The high-dose regimen used 10,000 IU administered intravenously (IV) during the anhepatic phase, followed by 5,000 IU delivered on days 1, 3, 5 and 7. Later on, the protocol was changed to 10,000 IU IV during the anhepatic phase, followed by 800 IU IV delivered daily for seven days. For the maintenance phase, a fixed dose of HBIG 800 IU was administered intramuscularly on-demand when the HBsAb levels fell below or nearly reached 100 IU/mL during the first six months and at the level of 50 IU/mL after six months post-LT. The HBIG used in this protocol was manufactured by the National Blood Centre, Thai Red Cross Society (Bangkok, Thailand).

All the patients were treated with a daily dose of lamivudine (100 mg) or other NAs prior to the LT, and continued indefinitely thereafter. In patients with lamivudine-resistant HBV, a nucleotide analog, adefovir, was added on or switched to tenofovir during the pre-LT period according to standard treatment, and continued indefinitely.

Hepatitis B evaluation

Post-LT blood tests for hepatitis B surface antigen (HBsAg) and HBsAb levels were carried out at the same time as the post-LT follow-up protocol. The patients were seen weekly in the first month, biweekly in the second month, triweekly in the third month, monthly during the fourth to sixth months, and then every four to six weeks during the seventh to twelfth months post-LT. One to two years post-LT, the patients were followed-up in six to eight weeks periods. Three years post-LT, the patients were followed-up in 8 to 12-week periods, depending on their clinical stability. For patients who were followed-up longer than 6 to 8 weeks, blood tests for both HBsAg and HBsAb were performed regularly at 4-week intervals. All HBsAg and HBsAb results were followed and reviewed regularly by a transplant coordinator and recorded in a separate database. HBV viral load was assessed using automated HBV viral load assay (Abbott Molecular, Des Plaines, IL, United States) at the lowest detectable level of 10 IU/mL. Recurrent hepatitis B was defined as persistent HBsAg seropositivity or detectable HBV viral load.

Immunosuppressive regimens

A quadruple regimen protocol was commenced in all patients and included 1 g of methylprednisolone during the reperfusion phase, IL-2 receptor antagonist (basiliximab) at immediate pre-LT and 4-day post-LT, and oral tacrolimus/mycophenolate/prednisolone

(20 mg) during the post-operative period. The steroid was usually weaned-off within three months. Cyclosporine or sirolimus was considered in some cases, according to clinical judgments.

Statistical analysis

The data were collected and analyzed using Excel (version 2016; Microsoft Corp.). The demographic data and clinical characteristics of the patients were expressed as mean ± standard deviation (SD) for continuous data and in number (n) for categorized data. The HBsAb level calculation was divided into post-LT time periods. The results are presented as mean±SD and median. The average lowest HBsAb level was calculated from the lowest level of each individual case in each period and presented as mean±SD and median. The cost of HBIG was calculated as per unit of injection and expressed as percentage in comparison to the fixed dose regimen.

Ethics statement

The present study was reviewed and approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB No. 631/59).

Results

Demographic data

During the 12-year period, 52 patients underwent deceased donor LT for hepatitis B-related diseases. Forty-five patients were included in the present study and seven patients were excluded for the following reasons: previous regular low-dose HBIG plus lamivudine and subsequent relapse of hepatitis B after a few months of discontinuing the HBIG during the recurrence and advanced stage HCC (n = 1); undertaking a different prophylactic protocol after being referred back to another hospital, with current HBsAg status as negative (n = 1); referred to another country and lost to follow-up after the first year (n = 1); death within the first day of operation (n = 1); and received lamivudine mono-therapy without recurrent hepatitis B (n = 3).

The clinical characteristics of the 45 patients included in the present study are summarized in Table 1. During the mean follow-up period of 57.8±38.3 months (range 6 months to 12 years), three patients died from HCC recurrence, at 26, 40, and 72.5 months without recurrent HBV. Five patients were transplanted for severe flare-up hepatitis B with liver failure. The antiviral drugs were started several weeks prior to the LT. Following LT, HBV remained

Table 1. Clinical characteristic of the patients included in the study

Clinical characteristics	n = 45 n (%)
Age at transplantation (years), Mean±SD (range)	56.5±6.1 (45 to 67)
Sex	
Male	33 (73.3)
Female	12 (26.7)
Indication for transplantation	
Cirrhosis	18 (40.0)
ACLF	5 (11.1)
Hepatocellular carcinoma	22 (48.9)
HBeAg status (positive/negative)	5 (11.1)/40 (88.9)
HBV viral load at transplantation	
Undetectable	40 (88.9)
Detectable [HBV viral load as log IU/mL]	5 (11.1) [2.76, 3.31, 3.43, 4.56, 5.25, and 6.93]
Maintenance immunosuppressive drugs	
Tac/MMF, CsA/MMF	23 (51.1), 10 (22.2)
Sir/CsA, Sir/MMF	2 (4.4), 4 (8.9)
Tac/Aza, Tac	1 (2.2), 5 (11.1)
Post-transplant antiviral drugs	
Lamivudine	16 (35.6)
Entecavir	20 (44.4)
Lamivudine/adefovir, adefovir	6 (13.3), 1 (2.2)
Tenofovir	2 (4.4)
HBIG regimens	
Initial high-dose	5 (11.1)
Initial low-dose	40 (88.9)
Follow-up period (months), Mean±SD (range)	57.8±38.3 (6 to 144)

Aza=azathioprine; ACLF=acute on chronic liver failure; CsA=cyclosporine A; HBeAg=hepatitis B antigen; HBV=hepatitis B virus; MMF=mycophenolate mofetil; Sir=sirolimus; Tac=tacrolimus; SD=standard deviation

detectable in five cases (ACLF, n = 4; cirrhosis, n = 1), with the levels ranging from 2.8 to 6.9 log IU/mL. Five patients had lamivudine resistance and had been on lamivudine/adefovir combination therapy for a few years before the LT. For two patients, tenofovir was used post-LT.

HBV recurrence

There was no recurrence of hepatitis B at the end of the study period. All 45 patients remained HBsAg-negative and with undetectable HBV viral load at last follow-up. Two patients showed positive for HBsAg and negative for HBsAb, without detectable HBV virus (Table 2; case 1 and 2). Each of these patients

Table 2. Characteristics of 3 patients who had episodes of HBsAg seropositivity or HBsAb seronegativity

Case	Age (years)	Diagnosis	HBV viral load pre-LT	Follow-up period, weeks (years)	HBsAg	HBsAb	Number of episodes	Time of events, at year	HBsAg/ HBV viral load at last follow-up
1	53	HCC	Undetectable	270 (5.2)	Positive	Negative	5	1, 2, 4	Negative/ undetectable
2	52	ACLF	3.3 log IU/mL	211 (4.1)	Positive	Negative	5	1, 2, 3	Negative/ undetectable
3	56	HCC	Undetectable	79 (1.5)	Negative	Negative	2	1	Negative/ undetectable

ACLF=acute chronic liver failure; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCC=hepatocellular carcinoma; LT=liver transplantation

Table 3. Number of injections and HBsAb level for the patients and mean of the lowest HBsAb level for each case during the post-transplant follow-up period

Follow-up period	Number of cases	Number of injections		HBsAb level		Lowest HBsAb level for each case	
		Mean±SD	Median	Mean±SD	Median	Mean±SD	Median
0 to 3-month	45	0.5±0.9	0	448.8±361.8	312.0	219.5±264.9	104.0
3 to 6-month	45	1.5±1.1	1	109.1±146.5	72.2	72.6±145.5	41.4
6 to 12-month	44	3.2±1.7	3	76.7±104.9	51.8	34.3±25.8	28.5
2nd year	41	5.9±2.4	5	61.1±43.4	49.6	25.6±13.7	24.0
3rd year	31	6.3±1.8	6	55.9±32.1	51.3	24.9±22.7	21.7
4th year	29	6.3±2.4	6	51.7±32.6	45.3	22.8±13.4	20.0
5th year	25	6.3±2.4	6	58.6±37.8	49.1	21.8±7.9	20.4
6th year	19	5.2±2.1	5	65.5±40.8	56.5	24.8±17.6	21.0
7th year	15	5.1±2.1	5	52.6±34.4	43.8	19.7±7.5	19.1

HBsAb=hepatitis B surface antibody; SD=standard deviation

had five episodes of HBsAg positive during the follow-up periods. After increasing the frequency of injections, HBsAg became negative during the final year of the study. Another patient experienced two episodes of HBsAb negativity alone, without HBsAg seropositivity during the 1.5-year follow-up period (Table 2; case 3). HBV viral loads of these three patients were undetectable at the end of the study period. If the two patients who had transient episodes of HBsAg seropositivity during the study period were considered as having recurrent HBV, then the rate of recurrence was 4.4% (2/44).

HBsAb level during the follow-up period

The mean and median levels of HBsAb in each period are shown in Table 3. According to the protocol, HBIG was given in a fixed dosage of 800 IU intramuscularly when the level fell below 100 IU/mL or 50 IU/mL during the post-LT follow-up period of the first six months or after six months, respectively. Though there were varying levels of HBsAb detected for the individual cases, the average levels of HBsAb of the overall cases were kept in line with the protocol.

Lowest HBsAb level

The data of the lowest level for an individual case in each period were selected and calculated to determine the mean and median levels (Table 3). During the first three months, the mean of the lowest HBsAb level remained higher than 100 IU/mL. However, after the three-month period, the mean and median levels were much lower and mostly less than 50% (20 to 25 IU/mL) of the required level in the protocol. The median HBsAb levels after six months varied between 19 to 20 IU/mL before the next injection.

As noted previously, the level of HBsAb declined rapidly within one month in three patients (Table 2). Two of these patients experienced a few episodes of HBsAg seropositivity and HBsAb seronegativity, and the remaining patient had two episodes of HBsAb negativity without HBsAg seropositivity. By increasing the frequency of HBIG injection, the three patients achieved HBsAg seronegativity, HBsAb

Table 4. Number of HBIG injections in each period after transplantation

Regimens	Periods								
	0 to 3-month	3 to 6-month	6 to 12-month	2nd year	3rd year	4th year	5th year	6th year	7th year
Regular (monthly)	3	3	6	12	12	12	12	12	12
On-demand	0.5	1.5	3.2	5.9	6.3	6.5	6.3	5.2	5.1
Number of patients*	45	45	44	41	31	29	25	19	15

Numbers of hepatitis B immunoglobulin (HBIG) injection of the regular regimen were estimated as monthly requirement. The numbers of injections for the on-demand regimen represent the mean value for each period.

* The number of the patients was calculated from the patients who received injections until completion of the time of each period

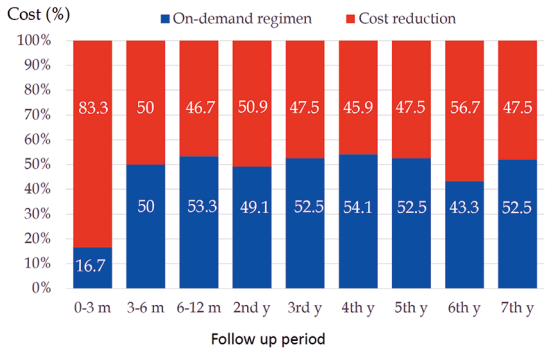

Figure 1. Estimated cost of on-demand low-dose HBIG injection in each follow-up period as compared to the regular low-dose regimen. The percentage was calculated from the ratio of number of injections, as shown in Table 4. Blue represents the percent of the cost of the on-demand regimen compared to the total cost of the regular low-dose regimen. Orange represents the percent of the cost reduction from the estimated cost of the regular low-dose regimen.

seropositivity, and undetectable levels of virus at the end of the follow-up period.

Number of injections

The number of injections varied after the peri-operative period (Table 3, 4). The requirements during the first three months were less, with a mean of 0.5±0.9 and median of zero (range 0 to 3). The requirements after one year ranged between five and six times a year. The mean and median levels of each period were mostly comparable.

Cost reduction

According to the standard regular low-dose regimen, each patient required at least 12 injections per year, with even more during the early post-LT period. The cost reduction in each period of the current study is shown in Figure 1. When the cost of the regular low-dose regimen (calculated according to the number of injections) was set as 100%, the average cost of the on-demand low-dose regimen varied from 17% for the first three months and 42% to 52% after three months and out to year 7. The costs were less during the first three months.

Tolerability

No patient experienced significant adverse effect from the HBIG dosages used in the present protocol. Most patients only reported the usual pain associated with the intramuscular injection.

Discussion

Hepatitis B-related ESLD and early stage HCC are common indications for transplantations worldwide, especially in the Asia-Pacific region[17,18]. Due to the evolution in HBV prophylactic regimens during the last decade, transplant survival for hepatitis B-related diseases has improved substantially[19,20]. The initial protocols using passive immunization with high-dose HBIG reduced the recurrence rate from 75% to 36%[9]. Several of the mono-prophylactic regimens required HBIG at 10,000 IU during the operation, 10,000 IU daily for seven days after, and 10,000 IU as required during the subsequent weeks or months for the life-long prophylaxis. The aim of that strategy was to maintain the HBsAb levels 100 to 500 IU/L. Subsequent data using this aggressive passive immunization demonstrated better outcome in prevention of post-LT HBV recurrence, which varied from 7% to 19%[10,11].

Subsequently, combinative strategies by using lower dose HBIG and NA achieved further reduction in rates of recurrent hepatitis B, to less than 10% reported in most publications, and cutting the costs down to as low as 10% of the previous high-dose HBIG mono-therapy[12,13,20-23]. The HBIG doses of these combinative regimens varied from the regular

high-dose of 10,000 IU to low-dose of 400 to 800 IU. The time courses also varied, from fixed to variable durations depending on the measured HBsAb levels. Most protocols, however, usually gave a standard dose of HBIG 10,000 IU during the anhepatic phase, delivering a daily low-dose of 400 to 800 IU in the first week and weekly thereafter in the early post-operative period and subsequently as monthly to bi-monthly for life-long maintenance[14]. The regular monthly intramuscular injections at the dose of 800 IU provided average levels of HBsAb above 80 IU/mL at 12 months[13]. At this average level, we could postulate that it was enough to prevent the recurrence of HBV. In addition, this regular protocol simplified the need for frequent serological testing for the HBsAb level before making decisions about dosage of HBIG.

In recent years, several studies have shown the regular monthly injection could be reduced by giving on-demand regimens[15,16,20,22,24-26]. These strategies yielded comparable numbers of recurrent cases to that of the regular fixed-dose regimen.

The present study, using on-demand low-dose HBIG plus NA and setting a protocol to maintain HBsAb level above 50 IU/mL during the maintenance phase, demonstrated a good result. Even though the number of patients in the present study was small, but it was quite moderate number as compared to similar long-term studies by others[27]. There was no case of recurrent hepatitis B at the end of the follow-up periods (the mean follow-up was 3.6 years and ranging between 6 months and 12 years). Considering that two patients had some episodes of HBsAg seropositivity during the early and middle periods of follow-up, the recurrent rate was 4.4%, which was rather low and comparable to other studies. These recurrences were successfully overcome by increasing the frequency of HBIG injections. Recently, a larger study that maintained HBsAb level above 100 IU/mL demonstrated a rate of recurrence as 6.2% at 3-year post-LT and 8.2% at 5-year post-LT[15].

During the early period of development of the on-demand protocols, very high doses of HBIG were used and most protocols tended to maintain HBsAb levels above 500 IU/mL[20,22,28]. Subsequently, most studies tended to use lower HBIG dose regimens and set the protocols to maintain HBsAb above 100 IU/mL[15,16,25]. There was no real scientific background to support which levels should be used, apart from the levels set by authorities from past clinical studies. Clinical evidence suggested that oral antiviral drugs reduced the number of virus, resulting in a lower requirement of neutralizing antibodies[29,30]. This explained the low requirement of passive immunization in patients who were given the combined regimens.

By setting the lower level of HBsAb maintenance at 50 IU/mL and giving a fixed dose of HBIG supplement to only those patients whose levels became lower or nearly equal to that level, the mean and median levels in the authors' study were able to be successfully maintained. The only drawback of this protocol was that the patients had to be monitored and wait for the results of HBsAb and HBsAg serological testing for a few hours before making the treatment decision, which translated to two steps in the clinical management process. However, by setting a good management team and clear protocol, these two steps became easily manageable. The advantage of this regimen was that the cost of the serological testing was negligible compared to the cost of the HBIG. The cost of HBIG shown in the current study could be reduced to approximately 50% of the regular low-dose regimen, as estimated from the number of injections. The number of injections was comparable to a previous on-demand study of 11 patients, which set the level of 70 IU/mL and used a higher dose of 2,000 IU, which required 5.6 injections per year[24].

As shown in other studies, there were intra- and inter-patient variations of HBsAb levels[10,11,15,24]. The authors further explored the average levels of the lowest level for the individual cases. These figures gave insight into the lower margin of safety zone that accompanies minimal chance of HBV recurrence. After 6-month post-LT, the mean and median of the lowest levels before the following injection varied from 19 to 34 IU/mL and 19 to 28 IU/mL, respectively. These average lowest levels (Table 3) were approximately less than half of the intended level of 50 IU/mL, and they could represent the safe window for clinical application. In addition, it might be the protective level required to prevent recurrent diseases could be lower than 50 IU/mL or even as low as 20 IU/mL.

Three patients in the present study experienced a few episodes of HBsAb seronegate, and two of these three cases also experienced some episodes of HBsAg seropositive. However, these events were overcome by proper adjustment of the HBIG injection frequencies. Unfortunately, the number of cases in the present study was rather small to demonstrate the association of some risk factors for HBV recurrence. Several previous studies have suggested that the risk of recurrence is associated with high-level viral load prior to transplantation, HBeAg seropositive, prolonged use of steroids (more than three months post-LT),

and development of viral resistance(9,11,13,15,20). Both cases in the current study had none of these risk factors, apart from one having 3.3 log IU/mL prior to transplantation.

The present study involved a long-term single-center experience and a number of patients regarded as moderate in comparison to other relevant studies in the literature. All patients had been carefully followed-up, as per protocol. Most of the cases had undetectable HBV prior to the LT. Moreover, achieving this favorable outcome required appropriate teamwork and coordination. Therefore, application of on-demand HBIG regimen with low HBsAb maintenance level requires a larger study to validate this concept.

In summary, the present study demonstrated an on-demand low-dose HBIG regimen yields good results and significantly reduces the cost of post-LT hepatitis B prophylaxis. We also propose the long-term maintenance level of HBsAb could be reduced to 50 IU/mL without compromising clinical outcome.

What is already known on this topic?

Recurrent hepatitis B after liver transplant is common and cause rapid progressive liver failure or cirrhosis without prophylactic regimens. Combinative prophylactic regimens using NA plus regular low dose HBIG are effective, and previously defied the optimal levels of HBsAb level above 100 IU/mL.

What this study adds?

This regimen yielded a good result and significant cost reduction. Importantly, the maintenance HBsAb level could be reduced to 50 IU/mL without compromising the clinical outcome.

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Conflicts of interest

The authors declare no conflict of interest.

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