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ORIGINAL ARTICLE

Hepatitis B virus vaccine switch program for prevention of *de novo* hepatitis B virus infection in pediatric patients

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Summary

The principal objective of this study was to evaluate the feasibility of Hepatitis B virus (HBV) vaccine switch program after 1-year Hepatitis B immunoglobulin (HBIG) for the prevention of *de novo* HBV (DNHBV) infection in pediatric recipients of hepatitis B core antibody (anti-HBc)-positive grafts. In this study, we enrolled pediatric recipients ($n = 14$), who had undergone living donor liver transplantation with anti-HBc-positive grafts between July 2000 and July 2005 and were followed up for over 24 months after transplantation. HBIG was given daily during the first week and intermittently in order to maintain anti-hepatitis B surface antigen (anti-HBs) titers greater than 200 IU/l until 12 months post-transplantation. Then the HBV vaccine was given intermittently as a substitute for HBIG when anti-HBs titer fell below 200 IU/l. The median follow-up duration after vaccination was 26.5 months, and a median of 2.03 doses of vaccine per year was required for the maintenance of anti-HBs titers greater than at least 100 IU/l. Two of the patients did not start the HBV vaccine due to sustained high anti-HBs titer. Eleven completed the HBV switch, whereas 1 was ongoing. With the HBV vaccine switch program, anti-HBs titers greater than 100 IU/l could be maintained conveniently and effectively.

Introduction

In Korea, an area in which the hepatitis B virus (HBV) infection is highly endemic, hepatitis B core antibody (anti-HBc)-positive rates in the general population were reported to be as high as 62.0% [1]. These situations of restricted graft source, coupled with the general scarcity of deceased-donor organs for transplantation, often leave physicians with no choice but to use anti-HBc-positive grafts for living donor liver transplantation in hepatitis B surface antigen (HBsAg)-negative recipients.

The incidence of *de novo* HBV (DNHBV) infections in recipients who had received liver grafts from anti-HBc-positive donors has been reported to be as high as 38–100% in naïve recipients [2–6]. In certain cases, the graft function of the recipients deteriorated with the progression of DNHBV [7,8]. Some centers have suggested the exclusion of liver transplants from anti-HBc-positive donors or limiting the use to selected recipients [7,9]. However, several observations revealed a low risk of DNHBV infection in recipients positive for anti-HBc or anti-hepatitis B surface antigen (anti-HBs) [2,4,5,10]. In addition, the results of several trials have demonstrated that DNHBV infection in the recipients of anti-HBc-positive liver grafts could be prevented by life-long prophylaxis regimens, and have proposed that transplant patients be treated with hepatitis B immunoglobulin (HBIG), lamivudine, or both (combination therapy) [11–15].

As grafts from anti-HBc-positive donors have been demonstrated to constitute a feasible organ source, it is clearly of great importance to develop a safe, efficient, and cost-effective life-long regimen, which prevents the transmission of HBV to the transplant recipients. Since December 1998, we had experienced DNHBV infection in all of the three pediatric recipients with anti-HBc-positive grafts without any prevention, two of whom were positive for pre-transplant anti-HBs. Thereafter, we initiated an HBIG prophylaxis regimen for the prevention of DNHBV infection in the recipients [16]. However, HBIG administration is inconvenient for life-long or prolonged prophylactic treatment, especially in pediatric recipients, and lamivudine not only carries a risk of emergence of drug-resistant mutant strains, but is not sustainable in Korea as it is in other countries, because the National Health Insurance Program does not cover the use of lamivudine.

Therefore, in July 2000, we applied a new treatment regimen for the prevention of HBV transmission from anti-HBc-positive grafts, which consisted of early postoperative intermittent HBIG administration and switch to HBV vaccine 1 year after transplantation, when the maintenance of a low level of immunosuppression is possible. In this study, we have evaluated the long-term safety and efficacy of our regimen for the prevention of DNHBV infection and the feasibility of HBV vaccine switch program from HBIG one year after transplantation.

Patients and methods

Patients

Between July 2000 and July 2005, a total of 63 pediatric patients underwent living donor liver transplantation at the Samsung Medical Center. Sixteen (25.4%) were HBsAg-negative recipients with grafts of anti-HBc-positive donors. They were managed according to our DNHBV infection prevention regimen and 14 were followed up for at least 24 months after transplantation. These 14 patients were enrolled in this study.

Immunosuppression protocol

Recipients were treated with a dual immunosuppressive regimen consisting of tacrolimus (Prograf®, Astellas, Ireland) and steroids. The tacrolimus levels were measured and adjusted in order to maintain target trough levels in accordance with the established protocols. The steroid treatment was tapered off within 3 months post-transplantation, at the earliest possible, and as soon as liver function tests remained stable without any evidence of acute allograft rejection.

De novo HBV prevention regimen including HBV vaccine

The 14 recipients in this study had been vaccinated three times as scheduled with recombinant HBV vaccination after birth according to the universal immunization program of infants for HBV. At the beginning of the liver transplantation (during the anhepatic phase), 100 IU/kg of HBIG (Hepa-big®, Green Cross Pharmacy, Yongin-si, Kyunggi-do, Korea), was intravenously administered, and then daily up to postoperative 6 days. During the first postoperative year, the anti-HBs titer was maintained at a level greater than 200 IU/l with the intermittent intravenous delivery of 100 IU/kg of HBIG. At 1 year post-transplantation, when it was possible to maintain a low level of immunosuppression and discontinue the steroids, a double-dose of the HBV vaccine (Euvax®, 10μg/0.5 ml, LG Bioscience, Seoul, Korea or Hepavax®-gene TF 10 μg/0.5 ml, Green Cross Pharmacy, Yongin-si, Kyunggi-do, Korea) was intramuscularly injected into the deltoid muscle (20 μg for a body weight of less than 20 kg, or 40 μg for a body weight of greater than 20 kg), instead of HBIG administration. Thereafter, an additional double dose of the HBV vaccine was administered intermittently when anti-HBs titer fell below 200 IU/l. In the case of anti-HBs titers of less than 100 IU/l despite repeated administrations of HBV vaccine, additional HBIG was administered temporarily in order to maintain an anti-HBs titer greater than 100 IU/l at least.

Serologic titer determination and HBV DNA analysis

Serum HBsAg and anti-HBs were measured during every outpatient visit (usually every month within a postoperative period of 1 year, and every 2–3 months thereafter). HBsAg and anti-HBs were assessed via electrochemiluminescence immunoassays (ECLIA) using ELECSYS and MODULAR (Roche Diagnostics, Mannheim, Germany) in accordance with the manufacturer's instructions.

De novo HBV infection was defined as the appearance of HBsAg in the serum of a recipient. In the case of DNHBV infection, HBV DNA quantitation [polymerase chain reaction (PCR)-Hybridization] was accomplished via real-time PCR using the COBAS TaqMan HBV test (Roche Diagnostics, Mannheim, Germany). The purified HBV DNA was directly sequenced for the S region, via the standard protocols established for the ABI 3730 DNA Analyzer (Applied Biosystems, Foster City, CA, USA).

Results

Demographic findings

The demographic information for 14 recipients is shown in Table 1. Their median age at the time of

Table 1. Demographic findings of liver transplant recipients with grafts from anti-HBc-positive donors.

Characteristics	Total recipients (n = 14)	Intermittent HBIG not required (n = 2*)	Vaccine initiated (n = 12‡)
Age (month) (median; range)	17.0 (4–168)	100.5 (33–168)	15.0 (4–120)
Sex (M:F) (case)	9:5	1:1	8:4
Indication for LT (case)			
Biliary atresia	12 (85.7%)	1 (50%)	11 (91.7%)
Fulminanat hepatitis	1 (7.1%)	1 (50%)	0
Congenital hepatic fibrosis	1 (7.1%)	0	1 (8.3%)
Pretransplant serologic status			
Anti-HBs positive (case)	11 (78.6%)	2 (100%)	9 (75.0%)
Anti-HBs titer (median; range, IU/l)	30.0 (0–>1000)	31.0, >1000†	29.0 (0–>1000)
Anti-HBc positive (case)	2 (14.3%)	1 (50%)	1 (8.3%)
Anti-HBe positive (case)	0	0	0
Donor anti-HBs positive (case)	13 (92.9%)	2 (100%)	11 (88.2%)

HBIG, hepatitis B immunoglobulin; anti-HBs, anti-hepatitis B surface antigen; anti-HBc, hepatitis B core antibody; anti-HBe, anti-hepatitis B e antigen.
*Immediate post-transplantation HBIG for 7days was given, but after then intermittent HBIG was not required to maintain anti-HBs titer greater than 200 IU/l.
†Median titer could not be calculated because of one indefinite value of two. Raw data were presented.
‡Twelve recipients were required intermittent HBIG to maintain anti-HBs titers greater than 200 IU/l within 12 months post-transplantation and started HBV vaccine switch at 12 months post-transplantation.

transplantation was 17.0 months (range 4–168) and the median postoperative follow-up duration was 39.0 months (24–85). Among the 14 recipients, 11 were positive for serum anti-HBs (median serum anti-HBs titer 30.0 IU/l, range 0–>1000 IU/l) at the time of transplantation, and two were positive for serum anti-HBc, whose HBV DNA titers were less than detection limit. Each recipient had been vaccinated at birth in accordance with the universal HBV immunization program for infants, but one recipient did not complete all of the three scheduled vaccinations prior to transplantation, as he was younger than 6 months of age at the time of transplantation. Among the 13 recipients who completed the three scheduled HBV vaccinations prior to transplantation, three were negative for pretransplant serum anti-HBs, and one required additional temporary HBIG following vaccine switch initiation.

Profiles of the vaccinated patients

Two of the 14 patients, who were postoperatively followed up for 85 and 24 months respectively, were administered immediate postoperative doses of HBIG for 7 days, as per our protocols, but required no administrations of intermittent HBIG or HBV vaccine to maintain anti-HBs titers greater than 200 IU/l. A total of 12 recipients were vaccinated against HBV at approximately 12 months after transplantation (Table 2). The median interval between transplantation and vaccine initiation was 12.0 months (10–16), whereas the median postvaccine follow-up duration was 26.5 months (14–65). The median number of HBIG doses given prior to vaccination was 5.0 (2–13), with the exception of the 7-day immediate post-transplantation doses. The median anti-HBs titer at the initiation of the HBV vaccine was 158.5 IU (70.2–510.0). After the initiation of vaccine administration, a median of 2.03 administrations (1.0–6.0) of HBV vaccine per year was required in order to maintain anti-HBs titers greater than 100 IU/l at least.

Table 2. Profiles of the vaccinated recipients (n = 12).

Vaccination profile	Total recipients, median (range)
Postoperatively follow-up (month) (median, range)	39.0 (26–81)
Duration before vaccine initiation (month)	12.0 (10–16)
HBIG administration before vaccine initiation (time)	5.0 (3–10)
Anti-HBs titer at vaccine initiation (IU/l)	158.5 (70.2–510.0)
Serum FK level at vaccine initiation (ng/dl)	5.3 (1.5–7.9)
Follow-up duration after vaccine initiation (month) (median, range)	26.5 (14–65)
Vaccine injection time (per year)	2.03 (1.0–6.0)
Vaccine injection time during the first vaccine-switch year	4 (2–6)
Recipients who needed additional HBIG (case)	3
Temporary HBIG administration (case) (times)	2 (3, 4 times)
On-going HBIG administration (case) (times)	1 (7 times)

HBIG, hepatitis B immunoglobulin; anti-HBs, anti-hepatitis B surface antigen.

Response with HBV vaccine switch from HBIG

In 11 of the 12 recipients (91.7%), HBIG had been switched successfully to HBV vaccine with the maintenance of anti-HBs titers greater than 100 IU/l. In nine (75.0%) of the 12, after the HBV vaccine switch, additional HBIG was not required at all. The anti-HBs titer of one of the nine recipients who required no more HBIG after HBV switch is provided in Fig. 1. Two recipients required temporarily as many as 3 or 4 additional HBIG doses during the early period of HBV vaccine switch process (within postvaccine initiation 6 and 9 months respectively), in order to maintain anti-HBs titers greater than 100 IU/l. After then, they required no more administrations of HBIG. The anti-HBs titer profile of one of these two recipients who required additional doses of HBIG temporarily during the early vaccine switch period is provided in Fig. 2. One additional recipient was followed up for 29 months after transplantation and still undergoing the vaccine switch process.

Occurrence of *de novo* HBV infection

Among 14 recipients, one recipient developed DNHBV infection (7.1%) (Fig. 3). HBV vaccine switch was conducted at 12 months after transplantation. During the early period following vaccination, the serum anti-HBs response was not so profound, but 12 months after vaccine switch, the recipient's serum anti-HBs titers were elevated beyond 1000 IU/l. However, at 28 months after vaccine switch, when the patient's serum anti-HBs titer was 361.2 IU/l, DNHBV infection was apparent, as was shown by HBsAg sero-positive conversion. HBV DNA sequencing for the HBV S region was conducted, and several mutations were recognized in the polymerase region, the '*a*' determinant (amino acid 120, 126 and 145), and

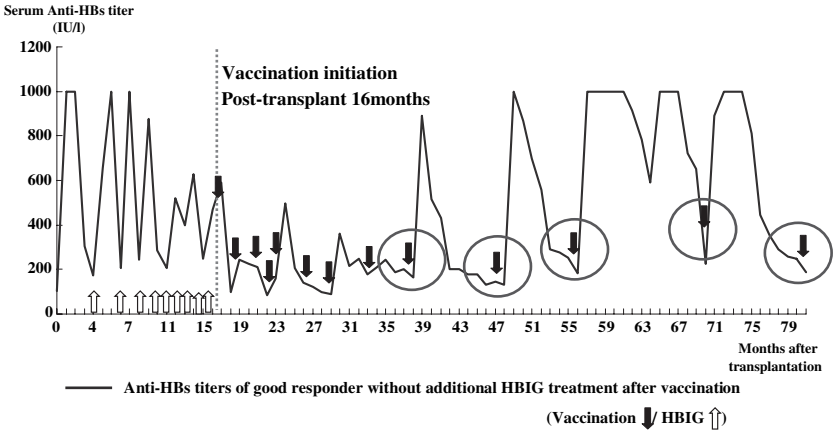

Figure 1 Serum anti-HBs titer profile of one representative case of nine liver transplant recipients who did not receive additional HBIG treatment after vaccination initiation. Preoperative Anti-HBs titer of this recipient was 131.6 IU/l and anti-HBc was negative. She started vaccination at 16 months. Before vaccine initiation, HBIG was given nine times. In the early vaccine switch period, she needed repeated doses of vaccine to maintain antibody titer greater than 100, But finally she just needed 1–2 doses of vaccine per year. The circles show the response of anti-HBs titer with HBV vaccine. Her antibody titer could be successfully maintained by HBV vaccine without additional HBIG administration. Follow-up duration is postoperatively 81 months.

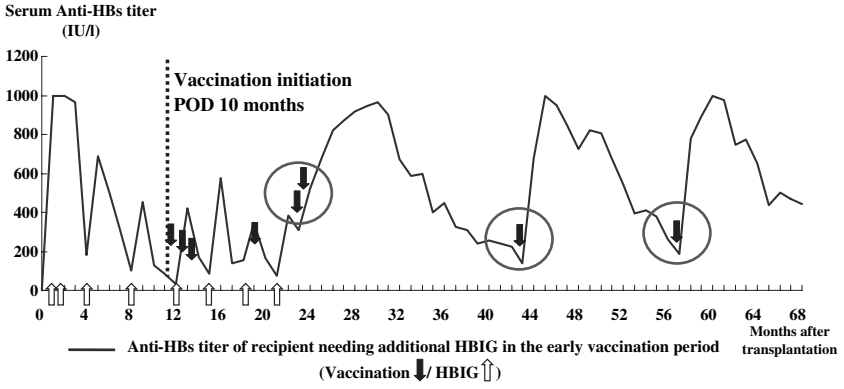

Figure 2 Serum anti-HBs titer profile of one representative case of liver transplant recipients who received additional HBIG treatment after vaccination initiation. This recipient is being followed up for 55 months after vaccination. Although this patient needed 4 additional HBIG doses during the early vaccine switch period, eventually, she could maintain the anti-HBs titer greater than 100 IU/l with intermittent vaccine only.

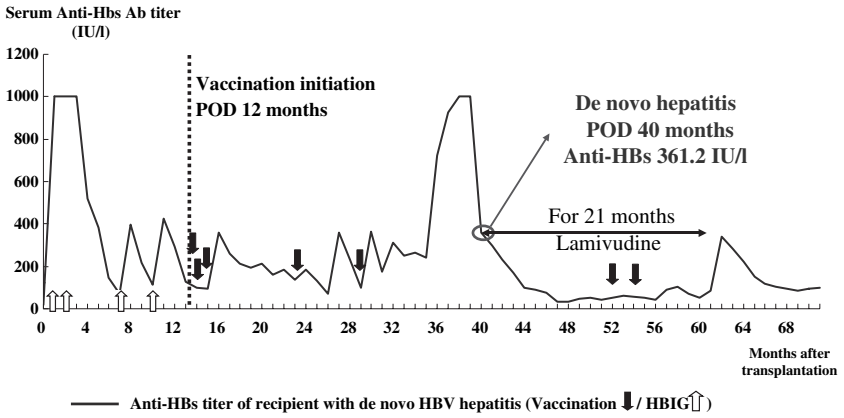

Figure 3 Serum anti-HBs titer profile of one liver transplant recipient who acquired *de novo* hepatitis B infection. This profile is the only recipient with *de novo* HBV infection. This patient's serum tested positive for anti-HBs prior to transplantation. Vaccine switch was started at postoperative 12 months. At 29 months postvaccination seroconversion of HBs Ag occurred and sustained for 21 months. Anti-HBs titer at the occurrence of *de novo* HBV infection was 361.2 IU/l. The patient began lamivudine (Zeffix®, GlaxoSmithKline Inc., Ansan-si, Kyunggi-do, Korea) treatment, and serum HBsAg became negative during the administration of lamivudine treatment.

the pre-S1 (D54E, G55A, I56N, K57Q) and S regions (R24K).

Discussion

Several trials for the establishment of a prophylactic regimen for DNHBV infection in recipients of anti-HBc-positive grafts have been attempted and proposed. These trials utilized different regimens, but consisted principally of passive immunization with HBIG, treatment with an antiviral agent, or both, and were also reported to result in successful HBV infection prevention rates [6,9,11–13]. The various regimens were based on the following facts: (i) serum anti-HBs lowers the risk of DNHBV infection [17] and (ii) antiviral agents actively inhibit HBV replication. However, each regimen has limitations, as the prolonged administration of HBIG is both costly and inconvenient, and long-term lamivudine treatment may result in the emergence of drug-resistant mutant strains. In recipients who undergo transplantation for HBV-related liver diseases and long-term lamivudine treatment, mutations were detected in up to 31.9% of cases within 1–2 years after transplantation [18]. Recently, the emergence of lamivudine-resistant HBV strains was reported in naïve recipients who underwent transplantation with anti-HBc-positive liver grafts and were treated with lamivudine for prevention [19]. The emergence of mutations in naïve pediatric recipients should not be considered as less serious than those in adult recipients with HBV-related liver disease, since the life expectancy in pediatric recipients would be much longer than in adult recipients.

Despite the importance of the prophylaxis regimen, life-long treatment with HBIG or lamivudine for the prevention of DNHBV seems to be distressing for the naïve pediatric recipients. Lamivudine monotherapy is simple, but life-long everyday administration would be troublesome. On the other hand, although frequent doses of HBV vaccine were required in the early vaccination periods, HBV vaccine switch program could maintain anti-HBs titer greater than 100 IU/l conveniently with only 1 or 2 vaccination doses per year in recipients who were followed up for more than 20 or 30 months after vaccination, as is shown in Figs 1 and 2. HBV vaccine switch from HBIG at 1-year post-transplantation would be an alternative strategy convenient and economical for the life-long prevention of DNHBV infection.

The recipient's serological characteristics, including pre-transplant anti-HBs status and post-transplant anti-HBs titer, are known to be an important factor in the incidence of DNHBV infection. Therefore, serum anti-HBs titers should be maintained at levels greater than 100 IU/l at least [11]. Chang *et al.* reported the response with HBV vaccine in pediatric liver recipients including nine who received grafts from anti-HBc-positive donor. They maintained anti-HBs titer above 20 IU/l in the recipients with anti-HBc-positive grafts as well as with naïve grafts [20]. Lin *et al.* in a study concerning DNHBV infection prevention in recipients with grafts of anti-HBc-positive donors classified recipients with serum anti-HBs titers of less than 1000 IU/l as a low-titer group [21]. One of the points of prevention strategy for DNHBV infection in recipients of anti-HBc-positive grafts seemed to be not about achieving a peak level of anti-HBs titer, but about maintenance of anti-HBs titer above effective level. Even in the case of adult liver transplant recipients for HBV-related liver disease, the target level of serum anti-HBs

titers has been recommended at a level of greater than 100–250 IU/l [22] or 100–500 IU/l, depending on the HBV DNA status [23,24]. In our transplant recipients, we maintained serum anti-HBs titers at levels greater than 100 IU/l after HBV vaccine switch, as we previously reported the effective prevention of DNHBV infection with HBIG when the anti-HBs titers were maintained at this level [16]. Serum anti-HBs titers greater than 100 IU/l after 12 months post-transplantation appear to be effective for the prevention of DNHBV infection in recipients of anti-HBc-positive grafts.

Despite HBIG prophylaxis, surface-escape mutations in the recipients were detected in the S region, including the '*a*' determinant [25–28]. In the only child who developed DNHBV infection, the serum anti-HBs titer was 361.2 IU/l at the time of HBsAg-positive detection, and HBV DNA mutations were detected in various regions, including the polymerase, '*a*' determinant, pre-S and S regions. Therefore, the cause of DNHBV infection in the recipient may not be related with an insufficient anti-HBs titer, but rather with the emergence of escape mutants. In the study conducted by Lin *et al.* [21], the incidence of DNHBV infection was 3.3% in 30 recipients of anti-HBc-positive grafts, and the cause of DNHBV infection appeared to be the emergence of mutants. The principal limitation of vaccination, which is similar to HBIG in terms of protective mechanisms, may be the emergence of escape mutants. However, according to the study of Ghany *et al.* most of these mutations reverted after HBIG withdrawal [25].

In this study, the time of vaccination initiation was considered with regard to the immunosuppression level of the recipients. At 12 months after transplantation, it was possible not only to taper off the steroid treatment and to maintain a low level of immunosuppression with a reduced risk of rejection, but also to catch up on growth [29]. Therefore, it appears possible that the response rate can be increased via the repeated administration of the vaccine, or via the augmentation of the dose.

Recently the several studies of the adjuvant-containing HBV vaccine administration in the recipients in the setting of adult liver transplantation for HBV-related liver disease were reported [30,31]. There seemed to be controversies in the feasibility of HBV vaccination for the prophylaxis of HBV recurrence. There are crucial differences between the adult recipients with HBV-related liver disease and the pediatric patients with anti-HBc-positive grafts, in terms of age, pretransplant viral exposure and load in recipients and the primary disease of transplantation. However, the adjuvant-containing vaccination that gave rise to the augmented response can be considered to apply to the naïve pediatric recipients who received anti-HBc-positive grafts.

In conclusion, although temporary additional HBIG doses in the early period of HBV vaccine switch process were required in certain recipients, the maintenance of serum anti-HBs titers greater than 100 IU/l in 11 of 12 patients (91.7%) was achieved by the switch from HBIG to the HBV vaccine after 12 months post-transplantation.

Authorship

KW Lee, SJ Kim, JW Joh, SK Lee, Study concept and design; JB Park, GS Choi, DJ Kim, JM Seo, JW Joh, SK Lee, Acquisition of data; JB Park, CHD Kwon, SK Lee, Writing the manuscript; CHD Kwon, SJ Kim, JW Joh, SK Lee, Critical revision of the manuscript for important intellectual content.

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