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Successful Active Immunization Using a Hepatitis B Virus Vaccination Protocol for a Recipient With Hepatitis B Core Antibody–Positive Liver Graft

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ABSTRACT

Introduction. Donor shortages occasionally necessitate the use of hepatic allografts from hepatitis B core antibody–positive (HBcAb+) donors, with an attendant risk of post-transplantation hepatitis B virus (HBV) infection. The aim of the present study was to develop and evaluate a protocol of active immunization for prevention of post-transplantation de novo HBV infection in patients receiving liver grafts from HBcAb+ donors.

Patients and Methods. Ten patients who had received HBcAb+ liver grafts at Shinshu University Hospital between October 1996 and December 2012 were enrolled. All the recipients were negative for HBV serological tests, and HBV-DNA. Hepatitis B immunoglobulin (HBIG) was given routinely in the peritransplantation and post-transplantation periods, without antiviral drugs. Subcutaneous vaccination with recombinant HBV was given at a dosage of 20 μg in adults and 5 μg in children concomitant with HBIG until acquisition of active immunization. The timing to start HBV vaccination was dependent on the condition of the patient.

Results. The median follow-up period after liver transplantation was 140 months, and the median period after transplantation until the start of vaccination was 7.0 months. Nine patients (90%) acquired active immunity after a median number of 4 (range, 2–13) vaccinations (hepatitis B surface antibody >300 mIU/mL for 1 year, or >100 mIU/mL thereafter), and did not require HBIG administration thereafter. None had any side effects of HBV vaccination or developed hepatitis B infection during the study period. Four fast responders who achieved antibody high titers by active immunization within 9 months received pretransplantation vaccinations, whereas 5 slow responders did not.

Conclusions. Our vaccination protocol provides a new effective strategy for prevention of de novo hepatitis B infection after liver transplantation in recipients with HBcAb+ liver grafts. Pretransplantation HBV vaccination was helpful for the post-transplantation vaccine response.

DONOR organ shortages occasionally necessitate the use of hepatic allografts from donors with antibody positivity for hepatitis B core antigen (HBcAb). However, transplantation of HBcAb-positive (HBcAb+) livers carries a risk of transmitting hepatitis B virus (HBV) to recipients, with an incidence of 25%–95% [1–7]. Although hepatitis B immunoglobulin (HBIG) and/or nucleotide analogue have been used worldwide to prevent de novo HBV infection in recipients with HBcAb+ liver grafts [1,2,8], life-long administration of HBIG is costly and inconvenient. Once patients acquire active immunization by HBV vaccination, they can maintain their hepatitis B surface antibody (HBsAb)

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0041-1345/14/$–see front matter
http://dx.doi.org/10.1016/j.transproceed.2013.12.005

titer for a longer period than after receiving passive immunization, such as HBIG. Active immunization might be a better strategy than the use of HBIG, but previous reports have indicated unsatisfactory vaccination response rates after liver transplantation [9,10]. Recently, good results have been reported for active immunization in pediatric patients with HBcAb+ liver grafts [11,12]. On the other hand, the efficacy of HBV vaccination for HBcAb-negative (HBcAb−) adult recipients with HBcAb+ liver grafts still remains unclear, and the rate of acquisition of active immunization is not satisfactory [13]. The aim of the present study was to develop an active immunization protocol and to evaluate its usefulness for preventing de novo HBV infection in adult and pediatric patients undergoing liver transplantation.

PATIENTS AND METHODS

Between December 1996 and December 2012, liver transplantations were performed for 300 patients at Shinshu University Hospital. Among them, 15 patients obtained liver grafts from HBcAb+ donors. For the purposes of this study, we excluded 5 recipients, 4 of whom had already showed HBcAb positivity at the time of liver transplantation and the remaining 1 was not administered immunosuppressants because of her graft from an identical twin. The remaining 10 patients, comprising 7 adults (age $\geq$ 18 years) and 3 infants, were adopted as the study subjects. Prior to transplantation, all recipients and donors were evaluated for hepatitis B using serological testing for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), HBcAb, hepatitis B envelope antigen (HBeAg), hepatitis B envelope antibody (HBeAb), and HBV-DNA.

Immunosuppression

The immunosuppression protocol for the recipients has been described elsewhere [14]. The initial immunosuppressive regimen consisted of tacrolimus and steroids. Patients who had been rejection-free under a stable tacrolimus-based regimen for 6 months were offered the option of steroid withdrawal.

Post-Transplantation Prophylaxis for HBV Infection

The prophylaxis protocol for HBcAb− recipients with a HBcAb+ liver graft was initiated with HBIG alone. HBIG was intravenously given at 10,000 IU in the anhepatic period during liver transplantation. Postoperatively, the serum HBsAb titer was maintained at >300 mIU/mL for 1 year, and >100 mIU/mL thereafter by administration of HBIG. Subsequently, we added a subcutaneous injection of recombinant HBV vaccine (Bemmugen INJ[Vial]; Astellas, Tokyo, Japan) with a dose of 20 μg in adult cases and 5 μg in pediatric cases while maintaining HBsAb by HBIG. The timing to start HBV vaccination was dependent on the condition of the patient. The interval of the vaccinations was basically longer than 1 month, and depended on the serum HBsAb titer when introducing the HBV vaccination protocol. The HBV vaccine was initially administered together with intravenous HBIG administration. We defined a positive vaccination response as an increase in the serum HBsAb titer more than expected when administering HBIG alone. Nonresponders needed to continue HBIG administration, maintaining their serum HBsAb level. We did not define an upper limit for the frequency of vaccinations in our protocol. We investigated the success rate of vaccination, the periods of introducing HBV vaccination, the frequency of vaccinations to acquire active immunization, and the factors for successful active immunization.

Statistical Analysis

Univariate analysis was performed for categorical variables with the use of the chi-square test. We analyzed continuous variables with a 2-tailed unpaired t test. A $P < .05$ was considered statistically significant.

RESULTS

Characteristics of the recipients and donors at the first medical examination in our hospital are presented in Tables 1 and 2. The median age of the recipients was 41 (range, 0.5–61) years, and 6 of them were women. The underlying diseases for liver transplantation were biliary atresia in 3 cases, primary biliary cirrhosis in 2, hepatitis C in 2 (both had hepatocellular carcinoma concomitantly), familial amyloid polyneuropathy in 2, and autoimmune hepatitis in 1. Seven cases involved transplantation from living donors (3 parents, 3 siblings, and 1 child), and 3 from deceased donors. The median follow-up period after liver transplantation was 140 (range, 74–193) months. At the initial evaluation for liver transplantation, all recipients were negative for HBsAb. All the recipients were negative for HBsAg, HBcAb, HBeAg, HBeAb, and HBV-DNA. All donors were positive for HBcAb and negative for HBsAg, HBeAg and HBV-DNA. Among 4 recipients who were vaccinated against HBV before transplantation, 3 preoperatively showed a positive serum HBsAb titer with a median of 17.3 (range, 16–227) mIU/mL. At the liver transplantation, HBsAb was positive (>10 mIU/mL) in 3 of 9 patients. Vaccination was postoperatively performed in all 10 recipients. Nine patients acquired active immunity with a median number of 4 vaccinations (range, 2–13; HbsAb >300 mIU/mL for 1 year, or >100 mIU/mL thereafter). Vaccination was started 7.5 (range, 2–29) months after transplantation. In 1 nonresponder who was a 54-year-old woman with primary biliary cirrhosis, vaccination was started 16 months after deceased donor liver transplantation and still continued in the interval between outpatient visits. She was administered prednisolone (5 mg/d), tacrolimus, and mycophenolate mofetil (750 mg/d) at the time of observation. No patients showed a conversion to HBsAg+ or HBV-DNA+ postoperatively without HBIG administration in the median follow-up period of 112 months after they had acquired active immunity. The patients have still maintained the HBsAb level >100 mIU/mL by vaccination once or twice per year. No obvious side effects (fever, exanthema, nausea, diarrhea, anorexia, or headache) were seen in our series. One patient died of liver cirrhosis due to recurrent autoimmune hepatitis 5 years after liver transplantation.

In this study, 2 types of response were observed among the patients who acquired active immunity. Four of 9 patients (44%; case 140, 195, 233, and 245) achieved antibody titers >100 mIU/mL within 9 months after induction of