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Prevention of *de novo* hepatitis B virus infection in living donor liver transplantation using hepatitis B core antibody positive donors

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Abstract: Exclusion of liver grafts from hepatitis B core antibody (anti-HBc) positive donors to prevent *de novo* hepatitis B virus (HBV) infection after liver transplantation is not feasible in areas highly endemic for HBV virus like Taiwan, where approximately 80% of adults are anti-HBc(+). The efficacy of lamivudine monotherapy to prevent *de novo* HBV infection after living donor liver transplantation (LDLT) using grafts from anti-HBc(+) donors remains to be elucidated. From June 1994 to August 2000, LDLT was performed in 42 recipients. Twenty-four of the 42 donors were anti-HBc(+) (57%). Pre-transplant HBV vaccination was given to all recipients irrespective of anti-HBc status at monthly intervals for 3 months. Until December 1997, eight recipients received liver grafts from anti-HBc(+) donors without prophylaxis. Since January 1998, prophylaxis with lamivudine monotherapy was given to 16 recipients receiving liver grafts from anti-HBc(+) donors. *De novo* HBV infection occurred in three of the eight recipients (37.5%) who did not receive prophylaxis, while none of the 16 recipients given lamivudine developed *de novo* HBV infection after a mean follow-up of 25 months. Two of the three recipients with *de novo* HBV infection were anti-HBs(–) and one recipient was anti-HBs(+). Lamivudine was well tolerated, and no side effects were noted. These results suggest that lamivudine monotherapy for recipients receiving anti-HBc(+) liver grafts is a simple, relatively inexpensive and effective prophylactic regimen for prevention of *de novo* HBV infection. The additive protection provided by vaccine-induced or natural immunity is uncertain.

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The acquisition of hepatitis B virus (HBV*) infection after liver transplantation in recipients who are hepatitis B surface antigen (HBsAg)-negative pre-transplant has been recognized (1). The possible sources of infection include blood products, donor organs and occult infection in recipients. The incidence of *de novo* hepatitis B from hepatitis B core antibody (anti-HBc)-positive donors may be as high as 72% in naïve recipients (2). Although the clinical course of *de novo* hepatitis B is often benign (3), development of chronic hepatitis or cirrhosis with mortality has been reported (4). Some centres have suggested the exclusion of liver transplants from anti-HBc(+) donors or to limit their use to selected recipients (5). This strategy would not be practical in Taiwan, where 15–20% of the general population is HBsAg(+) and approximately 80% of adults are anti-HBc(+) (6). As the use of grafts from anti-HBc(+) donors cannot be avoided, it is of paramount importance to develop a safe, effective and cost-effective means to prevent HBV transmission

to transplant recipients. Based on its potent suppression of HBV DNA and effectiveness in the treatment of chronic hepatitis B (7, 8), lamivudine monotherapy is a potentially effective prophylactic regimen to prevent *de novo* hepatitis B in recipients receiving liver grafts from anti-HBc(+) donors. In this study, we retrospectively analysed our experience with the prevention of *de novo* hepatitis B with routine HBV vaccination with or without lamivudine monotherapy in living donor liver transplantation (LDLT) using grafts from anti-HBc(+) donors.

Materials and methods

From June 1994 to August 2000, 42 consecutive parent-to-child LDLT were performed at the Chang Gung Memorial Hospital, Kaohsiung Medical Centre. The patients included 42 children with a mean age of 4.3 yr (range, 1.2–17 yr). The diseases of the recipients were biliary atresia (n = 34), glycogen storage disease (n = 5), neonatal hepatitis (n = 2) and Wilson's disease (n = 1). The donors included 33 mothers and nine fathers. Before transplantation, serum samples from all donors and recipients were tested for hepatitis B serological markers (HBsAg, anti-HBs, anti-HBc, HBeAg and anti-HBe), hepatitis C antibody (anti-HCV) and hepatitis delta antibody using radioimmunoassay (Abbott Laboratories Diagnostics Division, Abbott Park, IL, USA). Pre-transplant HBV vaccination with recombinant hepatitis B vaccine (rHBVac, 20 μg Engerix-B; Smithkline Beecham Biologicals, Belgium) was given to recipients who were anti-HBs(–) irrespective of anti-HBc status at monthly intervals for 3 months. Donors and recipients were also tested for serum HBV DNA (Digene Hybrid Capture Assay, Digene Corp., MD, USA). Some samples were tested retrospectively as this test became available in our unit only in August 1997. No prophylaxis was given to recipients receiving grafts from anti-HBc(+) donors before 31 December 1997 (first period). Since 1 January 1998, lamivudine monotherapy (3–4 mg/kg/day for children and 100 mg/day for adolescents) was given to recipients with grafts from anti-HBc(+) donors from post-transplant day 1. Immunosuppressive therapy in all recipients consisted of cyclosporin, azathioprine and corticosteroids. The initial dosage of cyclosporin was 600 mg/m^2/qd, targeting a trough level of 250–300 ng/mL for the first 4 wk, 150–200 ng/mL at 6 months and 100 ng/mL at 1 yr. The azathioprine dosage was 2 mg/kg for the first month, then 1 mg/kg thereafter and complete withdrawal after 6 months. The steroid was tapered from 2 (wk 1) to 0.2 mg/kg/day thereafter and tapering attempted within 4–6 months in order to minimize the replication of occult HBV. After transplantation, recipient HBV serological markers including HBsAg, anti-HBs and anti-HBc were routinely tested every 3 months or when liver function was abnormal.

Results

All 42 recipients are currently alive and well with their original grafts after a mean follow-up of 31 months (range, 14–86 months). All donors were negative for HBsAg, HBeAg, delta antibody and anti-HCV, while 24 (57%) were positive for anti-HBc. In the first period, 14 LDLTs were performed and eight of the 14 donors were anti-HBc(+) (57%). Seven of the eight anti-HBc(+) donors were anti-HBs(+) and serum HBV DNA(–), while one donor was anti-HBs(–) and serum HBV DNA(+). Of the eight recipients who received grafts from anti-HBc(+) donors, three (37.5%) became HBsAg(+) with detection at months 39, 14 and 35, respectively. Five of the eight recipients receiving anti-HBc(+) donors were anti-HBs(+) pre-transplant and one of them developed *de novo* hepatitis B. Two of the three recipients who were anti-HBs(–) pre-transplant became HBsAg(+) after transplantation. The liver function tests of the three patients with *de novo* HBV infection were normal, and they were all treated with lamivudine after HBsAg was detected and the drug became available in Taiwan. Table 1 shows the serological characteristics of the donors and pre- and post-transplant status of the recipients. The mean follow-up for this group of patients is 63 months (range, 45–86 months).

In the second period, 28 liver transplants were performed in 28 recipients. Sixteen (57%) of the 28 donors were anti-HBc(+) and all 16 were also anti-HBs(+). None of the 16 donors was serum HBV DNA(+). Fifteen of the 16 recipients were anti-HBs(+) and two of the 15 anti-HBs(+) recipients were anti-HBc(+) pre-transplant. Only one recipients (LDLT 23) remained anti-HBs(–), despite four doses of rHBVac administered before transplantation. The recipient was anti-HBc(+). Lamivudine monotherapy was given to all these 16 recipients immediately after transplantation. There have been no side effects related to lamivudine. All the 16 recipients who are at least 1 yr post-transplant remain HBsAg(–) and HBV DNA(–) at a mean follow-up of 25 months (range, 14–40 months). Table 2 shows the serological characteristics and pre- and post-transplant status

Table 1. HBV profile of donors and recipients who received anti-HBc(+) donors: first period

			Recipient							
	Donor		Pre-transplant				Post-transplant			
Case no.	Anti-HBs	S DNA[a]	HBsAg	Anti-HBs	Anti-HBc	S DNA	HBsAg[b]	S DNA	ALT[c] (U/L)	Survival (m)
1	–	+	–	–	–		+ (39 m)	+	13	86
3	+	–	–	–	–		+ (14 m)	+	18	70
4	+	–	–	–	+		–	–	123	69
6	+	–	–	+	+		–	–	12	64
7	+	–	–	+	–		+ (35 m)	–	12	63
9	+	–	–	+	–		–	–	31	60
13	+	–	–	+	–	–	–		29	46
14	+	–	–	+	–	–	–	–	9	45

[a] S DNA, serum HBV DNA.
[b] Numbers in parentheses indicate interval in months from transplant to first detection of HBsAg positivity.
[c] ALT, alanine aminotransferase; latest values shown.

of the recipients. All the 16 recipients are alive and well at a mean follow-up of 25 months (range, 14–40 months).

De novo HBV infection has not occurred in the 18 recipients receiving grafts from anti-HBc(–) donors, and they are all alive and well at a mean follow-up of 41 months (range, 14–72 months).

Discussion

The occurrence of *de novo* HBV infection in liver transplantation using liver grafts from anti-HBc(+) donors has been established. HBV DNA may persist in the serum or liver of persons who are HBsAg(–) but anti-HBc(+), and grafts from donors with this serological profile can transmit the virus (9). Occult or latent HBV may be reactivated by post-transplant immunosuppression and cause *de novo* infection in the recipient (10). Donors who test positive for HBV DNA, even when HBsAg(–), will invariably cause disease transmission and recipients of grafts from such donors would therefore require antiviral prophylaxis. Our first recipient received a graft from his mother who was HBsAg(–) but HBV DNA(+), and developed *de novo* HBV infection. Unfortunately, the mother's HBV DNA status was known retrospectively

Table 2. HBV profile of donors and recipients who received anti-HBc(+) liver grafts: second period

			Recipient							
	Donor		Pre-transplant				Post-transplant			
Case no.	Anti-HBs	S DNA[a]	HBsAg	Anti-HBs	Anti-HBc	S DNA	HBsAg	S DNA	ALT[b] (U/L)	Survival (m)
16	+	–	–	+	–	–	–	–	13	40
18	+	–	–	+	–	–	–	–	24	38
19	+	–	–	+	–	–	–	–	12	37
21	+	–	–	+	–	–	–	–	10	33
22	+	–	–	+	–	–	–	–	19	31
23	+	–	–	–	+	–	–	–	22	30
24	+	–	–	+	–	–	–	–	8	26
26	+	–	–	+	–	–	–	–	6	25
29	+	–	–	+	–	–	–	–	7	22
30	+	–	–	+	–	–	–	–	14	21
36	+	–	–	+	–	–	–	–	11	18
38	+	–	–	+	+	–	–	–	36	17
39	+	–	–	+	–	–	–	–	26	17
41	+	–	–	+	+	–	–	–	17	15
42	+	–	–	+	–	–	–	–	16	15
44	+	–	–	+	–	–	–	–	21	14

[a] S DNA, serum HBV DNA.
[b] ALT, alanine aminotransferase; latest values shown.

at a time when the recipient already had *de novo* hepatitis B.

The simplest way to prevent post-transplant *de novo* HBV infection is to exclude anti-HBc(+) individuals as donor candidates for liver transplantation. However, in highly endemic areas for hepatitis B compounded with a marked donor shortage, exclusion of anti-HBc(+) donors is impractical. One potential way of preventing *de novo* HBV infection is pre-transplant induction of active immunity against HBV in naïve recipients by vaccination, as patients who are devoid of HBV antibodies are most prone to *de novo* infection (5). The only two naïve recipients in this series both acquired *de novo* hepatitis B infection after receiving grafts from anti-HBc (+) donor parents. Most of our paediatric transplant candidates are, however, anti-HBs(+) as a consequence of a nationwide hepatitis B vaccination programme for neonates in Taiwan, which began in 1984 and has provided herd immunity for the beneficiaries (11). While induction of active immunity may be effective in the paediatric age groups who mostly have cholestatic end-stage liver disease, adults with parenchymal liver disease respond poorly (12). This was the case with one of our recipients who did not develop anti-HBs despite four doses of rHBVac (LDLT 23). The protection provided by anti-HBs in the recipient pre-transplant is, however, not absolute, as in one of our recipients who was anti-HBs(+) pre-transplant but still developed *de novo* HBV infection after receiving an anti-HBc(+) liver graft (LDLT 7). The possible reasons for HBV infection might be a very low anti-HBs titre to protect the host, the occurrence of another subtype of HBV infection or a virus mutation. Although the risk of *de novo* HBV infection in anti-HBs(+) recipients may be low, we still suggest prophylaxis in this group of patients, contrary to the policy of Pittsburgh group, who suggest no prophylaxis for anti-HBs(+) recipients (5). In our series the prevention of *de novo* HBV infection might be provided by vaccination-induced anti-HBs and lamivudine. One of our recipients in the prophylaxis group were anti-HBs(–) but anti-HBc(+), and the protection might be from lamivudine. Nevertheless, a low risk of *de novo* HBV infection can still be expected if no prophylaxis is provided in isolated anti-HBc(+) recipients who receive anti-HBc(+) grafts.

Contrary to the observation that *de novo* hepatitis HBV infection from anti-HBc(+) grafts usually appears early, i.e. within 6 months of transplantation (5), the three cases reported herein developed disease at an average of 29 months, the earliest being at 14 months post-transplant. These three cases, likewise, have had a benign course thus far while being maintained on lamivudine. While these results are encouraging, it would be ideal to have a larger patient series with longer follow-up in order to verify these findings.

Prophylaxis with hyperimmune hepatitis B immunoglobulin (HBIG) after transplantation was suggested by the Kyoto group, and they report no evidence of *de novo* HBV infection in three recipients after a follow-up of less than 2 yr (13). The disadvantages of HBIG are exceedingly high cost, inconvenient usage, and possible mercury intoxication in some preparations (14). The Pittsburgh group used a combination of lamivudine and HBIG to prevent *de novo* HBV infection in 15 patients. After a 495-day average follow-up period, no *de novo* HBV infection has occurred (5). This combination regimen, however, is a more costly prophylactic treatment strategy.

Lamivudine, a synthetic nucleoside analogue, has potent activity against HBV and is well tolerated by immunosuppressed patients, making it an ideal drug in the transplant setting. Lamivudine has been shown to be effective in the treatment of recurrent HBV infection after transplantation; suppressing HBV replication and reducing liver graft injury in these patients (15). A once daily dosage schedule via the oral route makes administration simple and patient compliance better assured. Lamivudine monotherapy is much less expensive compared with a regimen requiring HBIG. Without prophylaxis the incidence of *de novo* hepatitis B in this series was 37.5%, while lamivudine monoprophylaxis afforded 100% protection in a similar group of patients at a follow-up period of 25 months. A longer follow-up would be necessary to establish the effectiveness of this prophylactic strategy, as *de novo* hepatitis B infection may still occur as an outright lamivudine-resistant YMDD viral mutation. However, there have been no published data truly defining the time that lamivudine-resistant YMDD mutants might develop in the setting of the use of this drug as prophylaxis for anti-HBc(+) grafts vs. its use for chronic hepatitis B infection.

In summary, *de novo* HBV infection occurred in about one-third of the recipients receiving anti-HBc(+) grafts without prophylaxis. Active pre-transplant immunization combined with lamivudine monotherapy immediately after transplantation appears to be effective in preventing *de novo* HBV infection in recipients who receive grafts from anti-HBc(+) donors.

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