ORIGINAL ARTICLE

Liver Transplantation in Hepatitis B Core–Negative Recipients Using Livers From Hepatitis B Core–Positive Donors: A 13-Year Experience

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The use of livers from hepatitis B surface antigen–negative ($HBsAg^-$)/hepatitis B core antibody–positive ($HBcAb^+$) donors in liver transplantation (LT) for $HBsAg^-/HBcAb^-$ recipients is still controversial because of a lack of standard antiviral prophylaxis and long-term follow-up. We present our 13-year experience with the use of $HBcAb^+$ donor livers in $HBcAb^-$ recipients. Patients received prophylaxis with hepatitis B immunoglobulin at the time of LT and then lamivudine daily. De novo hepatitis B virus (HBV) was defined as positive HBV DNA detection. Between January 1999 and December 2010, 1013 adult LT procedures were performed at our center. Sixty-four $HBsAg^-/HBcAb^-$ patients (6.3%) received an $HBsAg^-/HBcAb^+$ liver. All donor sera were negative for HBcAb immunoglobulin M and HBV DNA. The mean follow-up was 48.8 ± 40.1 months (range = 1.2-148.8). Both the patient survival rates and the graft survival rates were 92.2% and 69.2% at 1 and 5 years, respectively. No graft losses or deaths were related to de novo HBV. Nine of the 64 patients (14.1%) developed de novo HBV. The mean time from LT to de novo HBV was 21.4 ± 26.1 months (range = 10.8-92.8 months). De novo HBV was successfully treated with adefovir or tenofovir. In conclusion, $HBcAb^+$ allografts can be safely used in $HBcAb^-$ recipients without increased mortality or graft loss. Lifelong prophylaxis, continuous surveillance, and compliance are imperative for success. Should a de novo infection occur, our experience suggests that a variety of treatments can be employed to salvage the graft and obtain serum HBV DNA clearance. ***Liver Transpl 19:611–618, 2013***. **© 2013 AASLD.**

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The disparity between the liver allograft supply and the demand remains a problem for those caring for patients with end-stage liver disease who require liver transplantation (LT).[1] In response, several strategies, including the use of hepatitis B surface antigen–negative ($HBsAg^-$)/hepatitis B core antibody–positive ($HBcAb^+$) donors, have been used to expand the liver donor pool. This practice varies with the regional incidence of hepatitis B virus (HBV), and such donors represent 3% to 6% of the donor pool in the United States, 8% to 15% of the donor pool in Europe, and 50% to 55% of the donor pool in Asia.[2-5]

The presence of persistent intrahepatic HBV covalently closed circular DNA in $HBcAb^+$ patients has been reported after HBsAg clearance, and constitutes a potential reservoir for viral reactivation.[6,7] In the absence of prophylaxis, the rate of de novo HBV has reached up to 75% to 80% in $HBsAg^-/HBcAb^-$ recipients, 15% to 20% in $HBcAb^+$ or $HBsAg^+$ recipients, and 5% to 10% in $HBcAb^+$/hepatitis B surface antibody–positive ($HBsAb^+$) recipients.[8] There is a consensus that $HBsAg^-/HBcAb^+$ donor livers should be preferentially used in recipients with a diagnosis of HBV because these patients require HBV treatment

Abbreviations: ADV, adefovir; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBcAb, hepatitis B core antibody; HBIG, hepatitis B immunoglobulin; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IgM, immunoglobulin M; LAM, lamivudine; LFT, liver function test; LT, liver transplantation; TDF, tenofovir.

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after LT.[9] The use of these livers in $HBsAg^-/HBcAb^-$ recipients is not a universally accepted practice despite the relative success of using lamivudine (LAM) and/or hepatitis B immunoglobulin (HBIG) to prevent HBV recurrence in recipients with HBV.[10]

Causes of $HBsAg^-/HBcAb^+$ serologies include a false-positive test, an acute HBV infection, and remote exposure to HBV infection with or without persistent viremia.[11] The interpretation of these results is often challenging, especially in the setting of organ donation, in which the documentation of a donor's past medical history is often limited and there is no time for follow-up tests. In this scenario, the use of these organs in LT has the potential for HBV transmission, especially in the setting of posttransplant immunosuppression.

In 1999, our group designed a protocol to use $HBsAg^-/HBcAb^+$ donors for $HBsAg^-/HBcAb^-$ patients. Its rationale, strategy, and preliminary results were published previously.[12,13] Briefly, our protocol includes planned preoperative vaccination, HBIG during the anhepatic phase, and lifelong LAM prophylaxis. Initial reports, first for 6 patients and then for 14 recipients, showed a low incidence (7%) of de novo HBV with a mean follow-up of 33 months. The presence of de novo HBV was associated with poor compliance with LAM and was controlled with appropriate antiviral treatment. On the basis of these preliminary data, the use of $HBsAg^-/HBcAb^+$ donors for $HBsAg^-/HBcAb^-$ patients became a standard practice at our institution. Here we present our 13-year experience with these livers in $HBsAg^-/HBcAb^-$ patients.

PATIENTS AND METHODS

Definitions and Serologies

$HBcAb^+$ donors were $HBsAg^-/HBcAb^+$. $HBcAb^-$ recipients were not naturally exposed to HBV and were $HBsAg^-/HBcAb^-/HBsAb^+$ or $HBsAg^-/HBcAb^-/HBsAb^-$. De novo HBV was defined as the development of detectable HBV DNA.

Study Population

All adult candidates for LT were considered eligible to receive a liver from an $HBcAb^+$ donor, but preference was given to patients who had HBV liver disease or were $HBcAb^+$. All $HBsAb^-$ patients began an accelerated immunization series in the pre-LT period with an HBV vaccine (three 20-μg doses of the Recombivax intramuscular HBV vaccine at monthly intervals). Not all patients completed the immunization regimen before LT, and the development of HBsAb positivity was not required for inclusion. The potential risks of receiving a liver from an $HBcAb^+$ donor were explained to each potential recipient, and consent was obtained at the time of the initial evaluation and confirmed once a liver became available.

This study was approved by our institutional review board protocol and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Donors

All $HBcAb^+$ donors who met our cadaveric donor criteria were considered for donation. Screening for HBcAb immunoglobulin M (IgM) was used to rule out acute HBV infections when it was possible. A liver biopsy sample was obtained at the time of procurement to rule out acute hepatitis and/or chronic liver disease. Serum from the donor was collected for HBcAb IgM serology (if it was not available before LT) and for HBV DNA analysis by polymerase chain reaction.

De Novo HBV Prophylaxis Strategy

According to our protocol (Fig. 1), recipients of $HBcAb^+$ allografts received HBIG (10,000 U) intravenously during the anhepatic phase of transplantation, and indefinite treatment with LAM (150 mg/day) began on postoperative day 1. The LAM dose was adjusted for renal function. Because post-LT HBV DNA polymerase chain reaction and HBcAb IgM findings were negative for each and every patient, arm 2 of our algorithm was never activated. Surveillance consisted of the serial analysis of recipient serum for HBsAg and HBV DNA by polymerase chain reaction (performed weekly for 1 month, monthly for 1 year, and every 3 months thereafter). Additional serum testing, liver biopsy, or both were performed for elevated liver function tests (LFTs). Biopsy specimens were examined by immunohistochemistry for the presence of HBV proteins.

Immunosuppression

Most of the patients underwent induction with methylprednisolone, which was followed by tacrolimus, mycophenolate mofetil, and prednisone. The immunosuppression was tapered to tacrolimus monotherapy within 6 to 8 weeks after LT. In addition to methylprednisolone, some patients underwent induction with thymoglobulin, which was followed by 2 extra doses of steroids. In this group, the immunosuppression was tapered to tacrolimus monotherapy by week 2 after LT. Neither the immunosuppression protocol nor changes in the immunosuppressive regimen were related to the presence of $HBcAb^+$ livers.

Statistical Analysis

Patient and graft survival analyses were performed with Kaplan-Meier plots, with log-rank tests used for differences in survival curves. Chi-square analysis or Fisher's exact test was used for comparisons of categorical data.

RESULTS

Between January 1, 1999 and December 31, 2010, 1013 adult LT procedures were performed at the Ochsner Clinic Foundation. Sixty-four $HBsAg^-/HBcAb^-$ recipients (6.3%) received a liver from $HBcAb^+$ donors. Forty-six of the 64 recipients (72%)

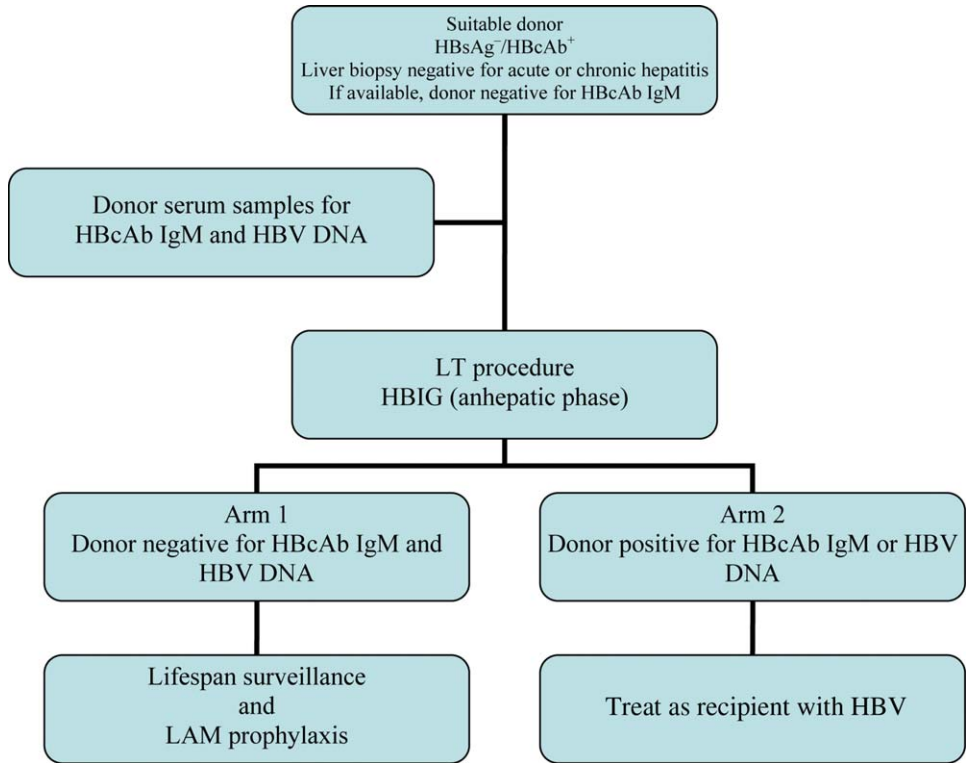

Figure 1. Algorithm for the management of recipients of $HBsAg^{-}/HBcAb^{+}$ livers.

were male, and 18 were female. The mean recipient age at LT was 53.5 years (range = 39-71 years). The etiology of liver disease was hepatitis C virus (HCV) in 34 patients (53.1%), alcohol in 16 patients (25%), nonalcoholic steatohepatitis in 7 patients (10.9%), cryptogenic cirrhosis in 4 patients (6.2%), autoimmune hepatitis in 2 patients (3.1%), and alpha-1-antitrypsin deficiency in 1 patient (1.6%). Hepatocellular carcinoma (HCC) was present in 18 of the patients (28.1%). The mean follow-up period was 48.8 ± 40.1 months (range = 1.2-148.8 months). One patient underwent combined liver-kidney transplantation, and another required retransplantation 7 years after his first transplant because of HCV recurrence.

The study group was compared with 815 adult recipients of primary LT alone who received $HBcAb^{-}$ livers at our center during the same time period. All $HBcAb^{+}$ recipients were excluded from the comparison group. The patient survival rates were 92.1% and 86.4% at 1 year ($P = 0.4$) and 69.2% and 74.8% at 5 years ($P = 0.4$) for the study and control groups, respectively; the graft survival rates were 92.1% and 89.2% at 1 year ($P = 0.5$) and 69.2% and 69.6% at 5 years ($P = 0.5$). No graft losses or deaths were related to HBV disease.

All donors were $HBsAg^{-}/HBcAb^{+}$, and none had a detectable serum HBV DNA level. Three donors had concomitant positive testing for HCV antibodies. Donor liver biopsy samples were reported to be normal in 43 of the cases (67.2%). A mild, nonspecific mononuclear infiltrate in the portal triad was reported in 15 cases (23.4%); mild fibrosis with no inflammation was reported in 2 cases (3.1%) and 1 case 1.6%; 10% to 30% fat infiltration was reported in 2 cases (3.2%); moderate, nonspecific inflammation was reported in 1 case (1.5%); and minimal HCV activity was reported in 1 case (1.5%).

Recipient Surveillance

HBV serology and serum HBV DNA tests were performed by protocol for 63 of the 64 patients (98.4%). For 1 patient, tests were performed irregularly and outside the protocol parameters because of poor patient compliance.

De Novo HBV: Incidence and Potential Risk Factors

De novo HBV, which was defined as HBV DNA detection, occurred in 9 of the 64 patients (14.1%) 21.4 ± 26.1 months (range = 10.8-92.8 months) after LT. HBsAg positivity was observed in 8 of these 9 patients (8/64 or 12.5%) at 16.9 ± 28.5 months (range = 8.9-92.8 months). The conversion to HBV DNA and HBsAg positivity occurred simultaneously in 4 patients (patients 3, 4, 8, and 9); 1 patient (patient 1) never became positive for HBsAg despite being positive for HBV DNA; and in the remaining 4 patients (patients 2, 5, 6, and 7), HBsAg seroconversion

TABLE 1. Pre-LT Information for Patients With De Novo HBV

					HBsAb Status		
Patient Number	Age (Years)	Sex	Primary Disease	HCC	Before LT	After LT	Donor Biopsy
1	50	Male	HCV	No	Negative	Negative	Normal
2	60	Male	HCV	No	Positive	Negative	Minimal triaditis
3	50	Female	Cryptogenic	Yes	Negative	Negative	Minimal triaditis
4	56	Female	HCV	No	Negative	Negative	Normal
5	47	Male	Alcohol	No	Negative	Negative	Normal
6	53	Female	Nonalcoholic steatohepatitis	Yes	Negative	Negative	Minimal triaditis
7	40	Male	Alcohol	No	Negative	Negative	Normal
8	34	Female	Autoimmune hepatitis	No	Negative	Negative	Normal
9	71	Male	Alcohol	Yes	Negative	Negative	Normal

TABLE 2. Information at the Time of the De Novo HBV Diagnosis

	Time to Positivity (Months)		Viral Load		Tests	
Patient Number	HBV DNA	HBsAg	Copies/mL	Titer (IU/mL)	AST/ALT (U/L)	Liver Biopsy/HBV Staining
1	34.2	Negative	418,000	Not available	Normal	Normal/negative
2	34.7	29.1	Positive*	Positive*	Normal	Normal/negative
3	92.8	92.8	9,660,000	1,660,000	Normal	Fibrosis/negative
4	13	13	94,000	Not available	Normal	Normal/negative
5	16.3	8.9	3068	1590	54/112	No rejection/positive
6	14.6	9.4	856	Not available	Normal	Mild triaditis/negative
7	24.3	19.8	>640,200,000	>110,000,000	Normal	No
8	10.8	10.8	12,500	2140	Normal	No
9	10.8	10.8	13,863,100	Not available	125/255	Mild rejection/positive

*Qualitative viral load.

occurred months before HBV DNA detection (Tables 1 and 2).

Fourteen of the patients (21.9%) were positive for HBsAb at the time of LT. Eight of the 50 recipients (16%) who were $HBsAb^-$ before LT and 1 of the 14 recipients (7.1%) who were $HBsAb^+$ before LT developed de novo HBV ($P = 0.67$), although all were $HBsAb^-$ at the time of HBV DNA detection (Tables 3 and 4).

Immunosuppression and rejection episodes were evaluated (Table 3). Thymoglobulin induction was used in 23 of the 64 patients (36%); 5 of them developed de novo HBV, whereas 4 of the 37 patients who received steroid-only induction did ($P = 0.26$). Prednisolone was used for $\leq$60 days in 52 of the 64 patients (81.2%); 7 patients in this group were diagnosed with de novo HBV, whereas 2 out of 12 patients who received prednisolone for $\geq$60 days were ($P = 0.67$). Only 1 patient was receiving prednisolone at the time of the de novo HBV diagnosis for control of autoimmune hepatitis recurrence. Rejection was confirmed in 13 patients (20.3%) at some point after LT; de novo HBV was seen in 3 of these patients and in 6 of the 51 patients who were rejection-free ($P = 0.37$). One patient with poor compliance (patient 9) presented with both de novo HBV and rejection.

Poor compliance with LAM was documented in 5 of the 9 patients with de novo HBV, and a YMDD mutation developed in 2 of the LAM-compliant patients (Tables 3 and 4).

De Novo HBV: Presentation and Treatment

All but 2 patients (patients 5 and 9) presented with normal LFTs, and de novo HBV was detected during routine surveillance. Liver biopsy samples were obtained for 7 of the 9 patients. Only the 2 patients who presented with abnormal LFTs had positive HBV stains, and one of them was also diagnosed with rejection (patient 9). The treatment of de novo HBV was initiated on the basis of HBV DNA detection and varied with the availability of antiviral medications, renal function, and the presence of virus resistance. The immunosuppression protocol was not modified because of the presence of de novo HBV. HBV DNA was undetectable in patients after a mean HBV treatment period of 2.64 ± 4.25 months (range = 0.8-13.4 months), whereas patients were negative for HBsAg at

TABLE 3. Post-LT Information for Patients With De Novo HBV

Patient Number	Thymoglobulin Induction	Prednisolone ≥ 60 Days	Rejection	LAM Compliance	Mutation	HBIG (Months)	Antiviral Therapy	Time of Therapy to Negativity (Months): HBV DNA	Time of Therapy to Negativity (Months): HBsAg	Current HBV DNA Status	Liver Function (Months After LT)
1	Yes	No	No	No	No	No	LAM/ADV	0.8	Always positive	Negative	Good (36.8)
2	No	Yes	Yes	Yes	No	14	LAM	1.9	1.9	Negative	Good (131.5)
3	Yes	No	No	No	No	No	LAM/TDF	3	8.2	Negative	Good (111.2)
4	Yes	No	No	No	No	No	LAM/ADV	3.2	74*	Negative	Good (99)
5	Yes	No	No	Yes	YMDD	32	LAM/TDF	13.4	24.3	Negative	Good (99.1)
6	Yes	No	No	Yes	No	16	LAM/TDF/ADV	1.1	6.5	Negative	Good (79.7)
7	No	No	No	Yes	YMDD	No	TDF	11*	11*	Positive	Good (33.1)
8	No	Yes	Yes	No	No	No	LAM	0.6	2.7	Negative	Good (26.2)
9	No	No	Yes	No	No	No	LAM	6.2	11*	Positive	Good (25.5)

*Still positive.

a mean of 6.78 ± 7.45 months (range = 1.9-24.3 months).

Patients 2, 5, 6, and 7 experienced de novo HBV despite professed compliance with LAM prophylaxis (Table 2). Patient 2 was treated with a combination of HBIG and LAM because of positive HBsAg results and qualitative HBV DNA assays despite a negative quantitative HBV DNA test. Patient 5 presented with mild hepatic enzyme elevations. The liver biopsy sample was positive for HBV stains and did not show other possible causes of inflammation. This patient received HBIG and LAM, but after 8 months of therapy, LAM resistance (YMDD mutation) was confirmed, and tenofovir (TDF) was added to the therapy. Patient 6 received combination therapy with HBIG, LAM, and TDF. TDF was switched to adefovir (ADV) because of adverse side effects of TDF (facial edema). Patient 7 had normal LFTs but presented with LAM resistance/YMDD mutation at the time of the de novo HBV diagnosis and was placed on TDF monotherapy. After 11 months of treatment, this patient had normal LFTs; however, he remained $HBsAg^+$ and $HBV\ DNA^+$, although his viral load showed a 5-log reduction.

In those patients who were noncompliant with LAM prophylaxis (patients 1, 3, 4, 8, and 9), LAM was restarted immediately. Patient 1 presented with positive HBV DNA and negative HBsAg results and received ADV in addition to LAM. For patient 3, TDF was added to LAM therapy because of the persistent presence of HBV DNA, although LAM resistance was not confirmed in multiple tests. Patient 4 received LAM monotherapy and became $HBV\ DNA^-$ after 3.2 months of treatment, but HBsAg positivity persisted with normal LFTs. Because of significant social and economic limitations, this patient was not eligible for other antiviral and/or HBIG therapy; however, the liver function remained normal 99 months after LT. Patient 8 was restarted on LAM and responded very quickly. Patient 9 presented with elevated LFTs and admitted poor compliance with LAM and immunosuppression. A liver biopsy sample showed both mild rejection and positive HBV stains. This patient received antirejection treatment with a steroid bolus and was restarted on LAM with the normalization of his LFTs. He became $HBV\ DNA^-$ after 6.2 months of treatment, but he was still $HBsAg^+$ after 11 months of therapy despite the addition of TDF.

DISCUSSION

In this study, we report our experience with the use of livers from $HBsAg^-/HBcAb^+$ donors in $HBsAg^-/HBcAb^-$ recipients and demonstrate the efficacy of using a long-term prophylaxis and surveillance protocol in terms of graft and patient survival. This has allowed us to expand our donor pool when donor and recipient HBV serology matching before LT is not possible.

Viral replication and HBV DNA can be detected even when HBsAg results are negative (as in 1 of our patients), or, conversely, HBsAg can be detected

TABLE 4. Potential Risk Factors for De Novo HBV

Risk Factor	De Novo HBV (n = 9)	Negative for HBV (n = 55)	*P* Value
$HBsAb^-$ at LT (n)	8	42	0.67
Thymoglobulin induction (n)	5	18	0.26
Prednisolone use ≥ 60 days (n)	2	10	0.67
Rejection (n)	3	10	0.37
LAM compliance (n)	5	Unknown	—*
YMDD mutation (n)	2	0	—*

*The n values were too small to calculate a *P* value or unknown.

before HBV DNA detection (as in 4 of our patients). In order to increase detection and standardize management, a better definition of de novo HBV is required.[14] Studying HBV recipients, Lenci et al.[15] proposed defining HBV recurrence as the presence of 1 or more of the following parameters at any time after transplantation: HBsAg positivity, serum HBV DNA, and hepatic covalently closed circular DNA detectability.

The presence of HBV DNA in the donor liver and HBsAb in the recipient has been used to determine whether $HBcAb^-$ recipients of $HBcAb^+$ livers require HBV prophylaxis.[8] As pointed out by Loss et al.[12] and reported by others,[16,17] there is a wide discrepancy between serum and liver HBV DNA positivity (8.2%-92.8%), and an absence of HBV DNA in the donor's serum and/or liver does not confer protection against HBV. Moreover, we reported that one-sixth of patients with an initial negative donor biopsy sample taken to assess hepatic HBV DNA became positive according to liver biopsy 2 months after LT.[13] Therefore, the use of these livers carries a risk for the potential development of de novo HBV due to latent virus or low-level replication that can be reactivated in the setting of immunosuppression,[18-20] especially in $HBsAg^-/HBcAb^-$ patients, for whom the incidence of HBV recurrence can reach up to 100% without prophylaxis.[10,21,22] The presence of HBsAb before LT decreases, but does not eliminate, the risk of de novo HBV. Although pre-LT HBV vaccination is desirable, it is not always possible or effective. Anergy increases with the progression of liver disease and in patients with cirrhosis, and nearly 90% of those who are $HBsAb^+$ become $HBsAb^-$ within the first year after LT.[13,23,24] An $HBsAb^+$ status before LT does not eliminate the risk of developing HBV in patients receiving $HBcAb^+$ livers.[10,13] Thus, neither the donor's hepatic HBV DNA status nor the recipient's HBsAb status should be used to determine whether post-LT prophylaxis is required in $HBsAg^-/HBcAb^-$ recipients of $HBcAb^+$ donors: all these recipients should receive prophylaxis.

The use of HBIG, alone or in combination with LAM, has also been considered for the prevention of de novo HBV.[25,26] However, in this population, which has no or undetectable levels of circulating virions and is negative for HBsAg, the protective mechanisms of HBIG[27,28] do not seem to be applicable. Its effectiveness has not been proven either. Two systematic reviews[22,29] did not show HBIG-LAM combination therapy to be more effective than LAM-only treatment. In addition, HBIG is expensive, its administration is inconvenient, and its use has the potential for the development of escape mutations.[25,30]

Surprisingly, our incidence of de novo HBV (14.1%) is higher than that reported in previous reviews.[9,22] In the first one,[9] de novo HBV was observed in 3.0% of $HBsAg^-/HBcAb^-$ recipients (1/33) who received LAM monoprophylaxis and in 0% of $HBcAb^-/HBsAb^+$ recipients (0/17) with a median follow-up of 25 months; in the second study,[22] the rates for the same types of recipients were 11% (8/73) and 2% (1/44), respectively. The higher incidence of de novo HBV in our report seems to be related to the development of LAM resistance (2/9 patients) and poor LAM compliance (5/9 patients) in an intense and long-term surveillance program, although it cannot be proved because of the small number of cases. We were unable to find any other significant correlations to explain our higher incidence of de novo HBV.

Adherence to treatment with LAM is essential[31] and is a major factor in HBV reactivation. Patient compliance and long-term insurance coverage for LAM should be carefully evaluated in potential recipients before these livers are used. The duration of prophylaxis has not been established, but indefinite prophylaxis has been recommended,[9,11,32] and our report reinforces long-term prophylaxis because we had 1 patient who seroconverted 92.8 months after LT. Likewise, periodic lifespan surveillance (3-6 months), including HBsAg and HBV DNA, is advised because normal LFTs do not exclude the possibility of HBV reactivation. Although rare, resistance to LAM is another factor for de novo HBV. In contrast to our early belief that LAM "should be effective in preventing de-novo HBV without concerns of emergence of resistance in HBc (+) donors with undetectable HBV-DNA and none or minimal replication,"[12] LAM resistance has been reported.[33,34] To prevent the development of resistance, Chang et al.[35] used ADV monoprophylaxis in 16 $HBcAb^-$ recipients who received an $HBcAb^+$ liver with a median follow-up of 18 months. Although all patients remained $HBV\ DNA^-$, 1 patient became $HBsAg^+$ 52 weeks after transplantation and was switched to TDF; this indicates that ADV prophylaxis does not fully protect against de novo HBV.

Once the appearance of HBV is confirmed, treatment should be initiated to prevent graft damage because spontaneous resolution is unlikely.[3,10,36] Although some centers treat de novo HBV only when LFTs are elevated,[37] we have chosen to treat HBV DNA positivity. Changes in immunosuppression are not required, although the discontinuation of steroids, if it is possible, seems to be reasonable because of the presence of a glucocorticoid-sensitive enhancer in

HBV DNA and its effect on virus replication.[38] In patients with poor compliance, LAM should be reintroduced as soon as possible with a good response in terms of HBV DNA clearance, although the introduction of a second agent is sometimes necessary. In compliant patients, although there is no extensive published literature, TDF and entecavir seem to be the agents of choice because of their antiviral potency, resistance profile, and minimal nephrotoxicity. The effects of new antiviral therapies and antiviral-resistant HBV infections on the course of prophylaxis and/or de novo HBV have yet to be determined, and the long-term cost-effectiveness needs to be evaluated in multicenter studies because of the low number of cases.

In conclusion, $HBsAg^{-}/HBcAb^{+}$ liver allografts can be safely used to expand the donor pool, and their use in $HBsAg^{-}/HBcAb^{-}$ recipients does not increase mortality or graft loss, but the incidence of de novo HBV could be higher than has been previously reported. Lifelong compliance with prophylaxis and permanent surveillance are imperative for success. Should de novo infection occur, treatment strategies vary, but they are ultimately successful in HBV DNA^{-} seroconversion. These livers are an extra source of organs, but patients and transplant centers should realize that their use demands extra effort and a lifelong commitment to antiviral prophylaxis and surveillance.

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