Use of Liver Grafts From Anti-Hepatitis B Core-Positive Donors: A Multicenter Study in Argentina


ABSTRACT

Liver transplantation success is limited by the availability of donors. To overcome this limitation, anti-core-positive donors are increasingly being accepted, but underutilization of this resource still occurs. We performed the current study to determine the prevalence of anti-core-positive donors in our region and to describe the management of these donors and their recipients. Between January 2005 and July 2011, the national transplant database included 2,262 registered liver donors among whom 106 (4.7%) were anti-core-positive including 59 (56%) discarded and 47 (44%) implanted organs. A median of 14.5 offers (range 4 – 60) were rejected before harvesting and implanting the accepted grafts. The only difference between the implanted and the discarded grafts was found for the alanine aminotransferase level, which was higher among the discarded ones (50 ± 9 UI/L vs 25 ± 16, P < .05). Among 40 recipients included in the study, 5 (12.5%) did not receive any prophylaxis; 18 (45%) a nucleos(t)ide analog 11 (25.5%), hepatitis B immunoglobulin and nucleos(t)ide analogs and 6 (15%) pretransplant hepatitis B vaccination. Over a mean follow-up of 871 ± 585 days, 4 de novo hepatitis B cases were identified at 545, 720, 748, and 1,080 days posttransplantation. None of these patients had received any prophylaxis. In all cases entecavir successfully controlled viral replication. We believe that better utilization of these donors and careful management of their recipients represent safe strategies to expand the liver donor pool in Argentina.

Liver transplantation success is limited by the availability of donors. Various strategies have sought to overcome this limitation: living donor liver transplantation and the use of extended criteria after cardiac death donors.1,2 To date, no guidelines clearly define which donors are considered to have extended criteria, in general terms, these individuals confer higher risks for the recipients than ideal donors, which manifest as early graft dysfunction or diseases transmission.3

Liver transplantation with hepatitis B virus (HBV) infected donors has been implemented recently, particularly using donors with serology evidence of resolved infection.4,5 as evidenced by surface HBV antigen (HBsAg) negative, HBV core antibody (anti-HBc) positive and either positive or negative for the HBV surface antibody (anti-HBs). They are usually called anti-HBc-positive donors. The infectious risk of the anti-HBc-positive donors is mainly related to HBV reactivation in the recipient,6 triggered by immuno-

Table 1. Anti-HBc-Positive Donor Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Implanted</th>
<th>Discarded</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>52</td>
<td>50</td>
<td>NS</td>
</tr>
<tr>
<td>Na+ (mEq/L)</td>
<td>154</td>
<td>154</td>
<td>—</td>
</tr>
<tr>
<td>ALT (UI/L)</td>
<td>25</td>
<td>50</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>BMI</td>
<td>25</td>
<td>28</td>
<td>NS</td>
</tr>
</tbody>
</table>

Na+, serum sodium; ALT, alanine aminotransferase; BMI, body mass index; NS, not significant.

From Hepatology Unit (S.M., L.A.G., A.C.G.), Hospital Italiano de Buenos Aires, Argentina; National Institute for Organ Donation and Transplantation (INCUCAI) (L.B.), Buenos Aires, Argentina; Liver Transplant Unit (V.I.D., S.Y.), Hospital Universitario Fundación Favaloro, Buenos Aires, Argentina; Liver Transplant Unit (M.M., M.O.S.), Hospital Universitario Austral, Buenos Aires, Argentina; Liver Transplant Unit (M.A., O.F.O.), Hospital Alemán, Buenos Aires, Argentina; Liver Transplant Unit (O.G., R.T.), Sanatorio Allende, Córdoba, Argentina; Hepatology Unit (J.C.B, O.A.G.), Hospital Italiano de Buenos Aires, Argentina; Liver Transplant Unit (E.d.S.), Hospital Italiano de Buenos Aires, Argentina.

Address reprint requests to Dr Sebastian Marciano, Hospital Italiano from Buenos Aires, Hepatology, Peron 4190, Buenos Aires, Buenos Aires AC1181ACH, Argentina. E-mail: sebastian.marciano@hospitalitaliano.org.ar

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360 Park Avenue South, New York, NY 10010-1710

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suppression, which enhances replication of the covalently closed circular DNA. 

Transmission of HBV from anti-HBc-positive donors has been well documented, a situation termed de novo hepatitis B. Without prophylaxis, as many as 70% of the recipients develop de novo hepatitis B. However the risk of transmission is significantly reduced with prophylaxis. Even in cases of de novo hepatitis B develops, treatment with nucleoside or nucleotide analogs (NUCs) most likely controls the infection.

The risk of de novo hepatitis B relates to the recipient’s serologic status, being greater for anti-HBc-negative/anti-HBs-negative recipients, intermediate for the anti-HBc-positive/anti-HBs-negative recipients and lower for the anti-HBc-positive/anti-HBs-positive recipients.

Even though there are no guidelines to suggest the prophylaxis indicated for each case, lifelong NUC treatment seems appropriate. In this setting, lamivudine has been the most explored antiviral drug. The association of HBV immunoglobulin (HBIG) with the NUC does not seem to add benefit. In Due to the low risk of reactivation, close follow-up without prophylaxis is a possible approach for anti-HBc-positive/anti-HBe-positive recipients. We performed this study to determine the prevalence of anti-HBc-positive donors in our region and to describe the management of these donors and recipients.

MATERIALS AND METHODS

The national database SINTRA (Sistema Nacional de Información de Procuración y Trasplante de la República Argentina; National System of Information of Procurement and Transplant from Argentina) was consulted to extract data between January 2005 and July 2011. All anti-HBc-positive liver donors were included in the analysis. All donors were tested for HBV, hepatitis C (HCV), and human immunodeficiency virus (HIV) with HBsAg, total anti-HBc, anti-HCV, and anti-HIV by chemiluminescent magnetic immunosay.

We defined anti-HBc-positive donors as those negative for HBsAg and positive for anti-HBc. We excluded anti-HBc donors who were HCV- and/or HIV-positive.

The characteristics between the implanted and discarded anti-HBc-positive donors were compared for age, body mass index, alanine aminotransferase (ALT), serum sodium and city of procurement. For the implanted grafts, we recorded the number of offers that were rejected before acceptance and implantation of the graft.

To evaluate the characteristics and evolution of the recipients, we consulted the 5 liver transplant centers that performed the majority of the activity. Only recipients aged over 18 years were included. Pretransplant characteristics were registered, including age, sex, Child-Pugh, and Model for End-stage Liver Disease (MELD) scores, and reason for liver transplantation. Recipient HBV serologic status was recorded as well as the HBV prophylaxis. The occurrence of de novo hepatitis B was evaluated during the follow-up. De novo hepatitis B was defined as the development of HBsAg and/or HBV DNA in a previously HBsAg-negative recipient.

Descriptive analysis was used to characterize the study population. Categorical variables were compared using the chi-square or Fisher exact test. Normally distributed continuous variables were compared using Student t test or Mann-Whitney test. All of which were 2-tailed tests. We accepted a statistical significance of 95% employing SPSS 13.0.2004 software (SPSS, Inc, Chicago, Ill, USA).

RESULTS

Donors

During the study period 2,262 liver donors were registered, of whom 116 tested positive for anti-HBc. We included 106 donors (47) after excluding 10 cases from the dialysis: 6 HBsAg+, 3 HCV+, and 1 HIV+.

Fifty-nine (56%) anti-HBc-positive donors were discarded and 47 (44%) implanted. The only significant difference between the two groups was observed for the ALT level, which was higher among discarded donors: 50 ± 59 UI/L, vs 25 ± 16 (P < .05; Table 1).

There was no difference in relation to the region of procurement between the implanted and discarded donors.

A median of 14.5 offers (range 4–60) were rejected before harvesting and implanting the accepted grafts. For every donor who was rejected at least once, one of the reasons recorded in the database by the transplant centers was related to the anti-HBc-positive status.

<table>
<thead>
<tr>
<th>Table 2. Recipient Characteristics</th>
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<tbody>
<tr>
<td>Reason for Transplantation</td>
</tr>
<tr>
<td>Cirrhosis</td>
</tr>
<tr>
<td>HCV</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>HBV</td>
</tr>
<tr>
<td>PBC/AIH</td>
</tr>
<tr>
<td>Crytocogenic</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Emergency</td>
</tr>
<tr>
<td>HBV</td>
</tr>
<tr>
<td>Hepatic artery thrombosis</td>
</tr>
<tr>
<td>AIH</td>
</tr>
</tbody>
</table>

HCV, hepatitis C virus; HBV, hepatitis B virus; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; HCC, hepatocellular carcinoma.

<table>
<thead>
<tr>
<th>Table 3. HBV Prophylaxis According to the Recipient’s HBV Serologic Status</th>
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</thead>
<tbody>
<tr>
<td>Prophylaxis</td>
</tr>
<tr>
<td>Pretransplant vaccination*</td>
</tr>
<tr>
<td>NUC</td>
</tr>
<tr>
<td>HBIG + NUC</td>
</tr>
<tr>
<td>None</td>
</tr>
</tbody>
</table>

HBV, hepatitis B virus; NUC nucleoside or nucleotide analogs; HBIG, HBV immunoglobuline.

*Considered when pretransplant anti-HBs titer was ≥10 UI/mL.
Recipient

Among the 47 recipients transplanted with anti-HBc-positive grafts, we included 40 in the study, excluding the other 7 recipients. The mean age at transplantation was 55 ± 10 years and 27 (60%) were male recipients.

Thirty-six subjects were electively transplanted based upon a MELD mean score of 25 ± 10; 6 were transplanted emergently: 4 with acute liver failure and 2 with hepatic artery thrombosis. Six recipients (15%) were HBsAg-positive; 2, transplanted for acute liver failure; and 4, due to cirrhosis. Eight of the 40 recipients included in the study had hepatocellular carcinoma at the time of transplantation. The characteristics of the recipients are detailed in Table 2.

There was great variability in relation to the HBV prophylaxis. Five recipients (12.5%) did not receive any prophylaxis: four were at high risk to develop, de novo hepatitis B (anti-HBc-negative/anti-HBs-negative) and 1 was in the low-risk category (anti-HBc-positive/anti-HBs-positive).

The remaining 35 recipients received HBV prophylaxis: 18 (45%) NUCs, 11 (25.5%) HBIG and NUCs, and 6 (15%) pretransplant HBV vaccination with development of anti-HBs titers greater than 10 IU/mL. The selected NUC was lamivudine (n = 2) or entecavir (n = 8). Table 3 details the prophylaxis according to the recipient’s HBV serologic status.

During a mean follow-up of 871 ± 585 days, we identified 4 cases of de novo hepatitis B, at 545, 720, 748, and 1,080 days posttransplantation. All received some prophylaxis. The pretransplant serologic profile was anti-HBc-negative/Anti-HBs-negative in 3 and Anti-HBc-positive/Anti-HBs-positive in 1 patient. Table 4 details the clinical and biochemical characteristics of these patients. All patients started entecavir (0.5 mg per day) after confirming HBV infection. There was no graft loss or significant graft dysfunction.

**DISCUSSION**

The imbalance between available donors and potential liver transplant recipients is a major health problem that is not expected to be solved in the forthcoming years. Extending donor criteria is a strategy that expands the pool but can confer greater risks upon the recipient, which could be manifest either in the immediate posttransplant period as algograft dysfunction, or later in follow-up, as disease transmission.

In our experience, we found that half of the Anti-HBc-positive donors were discarded during the study period. A similar scenario was reported by the Organ Procurement and Transplantation Network from the United States of America in 2010, describing a low use rate of anti-HBc-positive donors. The well-documented risk of de novo hepatitis B after liver transplantation from anti-HBc-positive donors is estimated to be as high as 70%. However, the risk is dramatically reduced or even abolished where administering adequate prophylaxis. The use of NUCs is the most attractive strategy. Lamivudine might be adequate, since the risk of resistance development is expected to be low in the absence of active viral replication. Other NUCs such as entecavir and tenofovir are expected to be at least as effective as lamivudine. In low-risk recipients (anti-HBc-positive/anti-HBs-positive), close follow-up without prophylaxis may be adequate. The great variability in the selected prophylaxis observed in our study can probably be explained by the long period in which patients were included and the available information experience using these donors in each period.

The 4 cases of de novo hepatitis B occurred in patients who did not receive any prophylaxis. Even in these cases, treatment with entecavir satisfactorily controlled viral replication; no graft losses were reported during the follow-up.

After reviewing our own experience, we believe that even in low endemic countries such as Argentina, the better use of Anti-HBc-positive donors will contribute to expand the liver donor pool.

**REFERENCES**