Hypothesis: Hepatic allografts from donors positive for antibody to hepatitis B core antigen (anti-HBc) frequently transmit hepatitis B virus (HBV) infection to recipients. Therefore, most transplantation centers will not use these organs for orthotopic liver transplantation (OLT). Although it is expensive and not always efficacious, hepatitis B immune globulin (HBIG) has been used routinely for indefinite periods to prevent HBV infection in liver allograft recipients. We assessed the effectiveness of long-term use of a nucleoside analog, lamivudine, in preventing HBV transmission by anti-HBc–positive allografts.

Design: Retrospective study.

Setting: A tertiary care center.

Patients: Twelve patients received hepatic allografts from anti-HBc–positive donors at Loyola University Medical Center, Chicago, between February 23, 1998, and March 13, 2001.

Intervention: All patients received 10,000 U/d of intravenous HBIG for 7 days. In addition, they received 300 mg/d of lamivudine in divided doses. Their liver biopsy specimens were tested for HBV DNA, hepatitis B surface antigen (HBsAg), and hepatitis B core antibody (HBcAb). Serum samples from the donor and recipient were tested for HBcAb, HBV DNA, and hepatitis B surface antibody (HBsAb).

Main Outcome Measure: The incidence of HBV infection in recipients who received HBcAb-positive donor livers and lamivudine prophylaxis.

Results: All recipients were anti-HBc negative before OLT. Five of the recipients had HBsAb titers greater than 150 U at the time of OLT. Three of the donor livers were HBV DNA positive and 2 were hepatitis B core antigen positive at the time of OLT. Donor serum was HBcAb positive in all 12 donors. None of the recipients have become infected with HBV with a follow-up of 2 to 38 months.

Conclusion: Perioperative use of HBIG combined with long-term use of lamivudine can prevent HBV infection in recipients who receive hepatic allografts from HBcAb-positive donors.

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The initial orthotopic liver transplantation (OLT) experience for patients with hepatitis B virus (HBV)-induced liver failure was dismal.1,2 These patients often developed recurrent HBV infection after transplantation, resulting in subsequent liver failure and death. Therefore, HBV infection became a contraindication for liver transplantation. This poor initial experience subsequently improved with the use of immunophylaxis, namely, hepatitis B immune globulin (HBIG). This therapy resulted in outcomes for this population comparable to those of patients who underwent transplantation for non-HBV disease. Another drug, lamivudine, has also been shown to be effective in eradicating HBV viremia and has been used as additional prophylaxis for HBV-infected patients undergoing OLT.

Although it is unusual, there is a definite incidence of de novo HBV infection after liver transplantation. Experience has shown that the use of allografts from donors who have positive serologic test results for hepatitis B core antibody (HBCab) is a risk factor for such infection in HBV-naive recipients.3,4 As a result, many liver transplantation centers have not used HBcAb-positive donors for recipients without previous HBV infection. This results in discarding many otherwise normal allografts, which could potentially be transplanted successfully, adding to the already severe organ shortage.

In an attempt to prevent transmission of HBV infection to recipients from...
donors positive for antibody to hepatitis B core antigen (anti-HBc), HBIG has been administered to the recipients almost universally. Many centers use HBIG either continuously or for an indefinite amount of time, usually 2 or more years following OLT.3 The expense of HBIG therapy and the need for parenteral administration have driven the search for a better approach to the prevention of HBV infection in allograft recipients of HBcAb donor organs. Recent studies5 have suggested that lamivudine, a nucleoside analog, can be used in addition to or as an alternative to HBIG in such cases.

In an effort to increase the number of donors available to the transplantation team at Loyola University Medical Center, HBcAb-positive donors have been routinely used for OLT whenever they become available. These donor organs have been used for the sickest patient at the time the donor organ became available. In an attempt to reduce the use of HBIG, lamivudine has been given to recipients of HBcAb-positive donor organs in the immediate postoperative period. This article reviews the experience at Loyola University Medical Center with the use of HBcAb-positive donors and lamivudine prophylaxis for the prevention of recipient HBV infection in recipients of HBcAb-positive donor organs.

### RESULTS

Twelve patients received an allograft from a donor positive for HBcAb. At the time of OLT, all but 1 of the recipients was negative for HBcAb. All 12 received hepatitis B vaccine before transplantation. Five of the 12 recipients had developed HBsAb titers greater than 150 U at the time of transplantation (Table 1).

At the time of OLT, 3 of the 12 donor livers were positive for HBV DNA as determined by polymerase chain reaction (PCR) using primers for the “c” region. Two of the 12 donor livers stained positive for HBeAg with immunohistochemical analysis. All 12 donor organs were negative for HBsAg expression (Table 2).

All 12 recipients have been followed up closely in the postoperative period. None have been lost to follow-up. They have all remained negative for HBeAg, HBV DNA, and HBsAg in the serum and liver, with a follow-up ranging from 2 to 38 months. Of the 12 pa-
tients, 1 died of sepsis, 1 of cardiac arrhythmia, and 1 of lung cancer. At the time of their deaths, they had no evidence for an HBV infection.

Posttransplantation liver biopsy specimens were obtained whenever there was an alteration in liver function and on a protocol basis at 6, 12, and 24 months after OLT. All liver biopsy specimens were assessed for HBsAg, HBcAg, and HBV DNA by PCR. All have been negative for each parameter (Table 3).

**COMMENT**

Traditionally, HBIG has been used in recipients who are HBsAg positive or who have received a HBcAb-positive donor organ to prevent recurrence or activation of HBV infection in the recipient. Long-term HBIG administration is expensive and necessitates parenteral administration. In an effort to reduce costs and patient discomfort associated with parenteral therapy, we instituted a program in which HBIG has been used for a short period (7 days) in combination with long-term lamivudine therapy (2 years).

The nucleoside analog lamivudine is a potent inhibitor of HBV-associated DNA polymerase and is capable of inhibiting HBV DNA replication in chronically infected patients. Lamivudine has been shown to be efficacious in the prevention of recurrent viral infection after liver transplantation. However, its use has been associated with the emergence of a resistant mutant virus, when used without HBIG, as the agent for HBV prophylaxis after liver transplantation.

The mutation is most common in patients who have relatively high titters of HBV DNA. The mutation in the HBV DNA polymerase results in reduced binding affinity of lamivudine, thus resulting in resistance. Mutations characteristically occur in patients who have high titters of HBV DNA before exposure to lamivudine or in patients who have undergone OLT because of the doses of immunosuppressive agents that are used immediately after the procedure. Therefore, we used HBIG for the first 7 days after OLT. After 1 week, the patients completed their steroid taper, and immunosuppressive drug doses were lowered significantly. We did not see any evidence of a resistant mutation with single-agent therapy with lamivudine and believe it is safe to proceed with this therapy in the future.

An attempt was made to vaccinate all recipients before OLT. There are reports that indicate that vaccination with HBsAg preparations may not be successful in most patients with chronic liver disease. By doubling the vaccination dose (40 µg) and performing vaccinations monthly, we have been able to successfully vaccinate some potential recipients before OLT. However, when a transplant recipient with an anti-HBc–positive donor organ was identified, we did not consider the HBV vaccine response, but instead selected the sickest individual with the appropriate blood type.

Twelve patients received an allograft from an anti-HBc–positive donor. No recipient experienced an HBV infection. Five of the 12 recipients had evidence of adequate antibody against hepatitis B (HBsAb) before OLT. However, 7 recipients did not, having no measurable HBsAb. Therefore, these 7 recipients were at high risk for the development of HBV infection as a result of their acceptance of a HBcAb-positive donor organ. All 12 recipients were maintained with long-term lamivudine therapy, and none have developed evidence for an HBV infection. Moreover, no patient has shown any evidence for the development of an HBV mutant as a result of long-term therapy.

### Table 2. Donor Characteristics

<table>
<thead>
<tr>
<th>Donor No.</th>
<th>Liver HBV DNA Status</th>
<th>Liver HBcAg Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
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<td>–</td>
</tr>
<tr>
<td>12</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

*HBV indicates hepatitis B virus; HBcAg, hepatitis B core antigen; minus sign, negative; and plus sign, positive. All donors were positive for serum hepatitis B core antibody and negative for liver hepatitis B surface antigen.

### Table 3. Recipient Outcome

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Transplantation Date†</th>
<th>Follow-up Month</th>
<th>Survival</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9/3/1998</td>
<td>32</td>
<td>Alive</td>
<td>...</td>
</tr>
<tr>
<td>2</td>
<td>3/31/2000</td>
<td>13</td>
<td>Alive</td>
<td>...</td>
</tr>
<tr>
<td>3</td>
<td>8/26/1999</td>
<td>20</td>
<td>Alive</td>
<td>...</td>
</tr>
<tr>
<td>4</td>
<td>10/15/1998</td>
<td>31</td>
<td>Dead</td>
<td>Lung carcinoma</td>
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<tr>
<td>5</td>
<td>2/1/1999</td>
<td>27</td>
<td>Alive</td>
<td>...</td>
</tr>
<tr>
<td>6</td>
<td>2/23/1998</td>
<td>38</td>
<td>Dead</td>
<td>Arrhythmia</td>
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<tr>
<td>7</td>
<td>5/14/1998</td>
<td>36</td>
<td>Alive</td>
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</tr>
<tr>
<td>8</td>
<td>3/13/2001</td>
<td>2</td>
<td>Alive</td>
<td>...</td>
</tr>
<tr>
<td>9</td>
<td>3/21/2000</td>
<td>14</td>
<td>Alive</td>
<td>...</td>
</tr>
<tr>
<td>10</td>
<td>1/24/2001</td>
<td>3</td>
<td>Alive</td>
<td>...</td>
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<td>6/24/1998</td>
<td>34</td>
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<td>...</td>
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<tr>
<td>12</td>
<td>4/5/1998</td>
<td>37</td>
<td>Dead</td>
<td>Sepsis</td>
</tr>
</tbody>
</table>

*All patients were negative for hepatitis B virus DNA posttransplantation. Ellipses indicate not applicable.
†Given as month/day/year.
In conclusion, this retrospective study indicates that liver allograft recipients can receive adequate HBV prophylaxis with long-term use of lamivudine coupled with short-term HBIG administration for only 7 days in the immediate postoperative period. This study is limited by its retrospective routine and small size but suggests that the combination of short-term HBIG coupled with long-term lamivudine therapy is efficacious and cost-effective. Clearly, a larger study needs to be performed to confirm these results. Until such data are available, anti-HBc donor organs should not be rejected for OLT because they can be used with good survival and freedom from HBV infection with the use of HBIG and lamivudine therapy.

This study was presented at the 109th Scientific Session of the Western Surgical Association, San Antonio, Tex, November 14, 2001.

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REFERENCES


DISCUSSION

William C. Chapman, Nashville, Tenn: I had not originally planned to be the first discussant of this paper so my comments will be somewhat limited. This is an important paper and in an important area. Any techniques, as we have heard, to experiments will be somewhat limited. This is an important paper andasis, in most circumstances, is satisfactory to use. But that usegoing to have hepatitis C infection in the posttransplant period. So it is a given that recipients who are hepatitis C positive are going to have hepatitis C infection in the posttransplant period.

Now in terms of the use for the hepatitis B core-positive donors, this has been a difficult area to investigate. As we have heard, most centers have not utilized the hepatitis B core antibody-positive grafts but have restricted those to patients in whom the recipients were chronic hepatitis B carriers. In chronic hepatitis B carriers who undergo transplantation, those patients at the time of transplantation are given hepatitis B immune globulin, and this is generally continued for at least a year along with lamivudine therapy. This study is different in that these grafts were used in patients regardless of their serological status. It’s important because it demonstrates that these grafts can be used even in patients who did not have hepatitis B surface antibody prior to their transplantation.

There are a couple of questions I would like to ask that perhaps the authors could clarify. The strategy of immunizing recipients prior to their transplant while they are on the waiting list was discussed. Some recipients will seroconvert and develop hepatitis B surface antibody. So one issue I would raise is why these hepatitis B core grafts weren’t restricted to only those patients who had surface antibody. In general the assumption is made, although this isn’t always true, that patients who are hepatitis B immune will generally not develop chronic hepatitis B infection following transplantation with hepatitis B core-positive grafts although that has not always been true. So I think that would be one area that could be clarified.

The other area that is perhaps a more difficult question is how long to continue therapy in these patients. This report clearly demonstrates the safety of the technique that has been used here, and it has been presented today that at least the use of HBIG, which is the most difficult and most costly portion of treating these patients, may be able to be discontinued after a relatively short time interval. In these patients, it was proposed that they can receive a short course of HBIG and be continued on lamivudine therapy. The difficulty, of course, is in following these patients with hepatitis B DNA PCR is that in general once those patients develop evidence of infection, it can be difficult to reverse the course at that point. So the second question I would raise is how do you decide when to shorten your therapy and do you predict that in the future shorter courses of therapy may be able to be utilized?

Carlos A. Pellegrini, MD, Seattle, Wash: Could you please confirm for us that none of the patients who received a liver became infected with hepatitis B, even though 3 died? Is there any other evidence in the literature in those who have used this technique; do the authors know if any patients have become infected with hepatitis B?

Donald L. Kaminski, MD, St Louis, Mo: I have 2 questions. If you are preoperatively talking to a patient who is going to receive a liver with hepatitis B, do you have to tell the patient that, and do you have to have their consent to do it? Secondly, a question somewhat related to Dr Chapman’s, have you had any patients who have had their treatment discontinued who developed hepatitis B? In this era of terrorism, what is this mutant that this drug produces and how harmful is it?

Thomas Bichl, MD, Seattle: Maybe I missed this in the presentation. Did any of the recipients have hepatitis B as the cause of their liver failure? If so, how does that play into the use of a donor hepatitis B organ?

Philip E. Donahue, MD, Chicago, Ill: I think it was a very interesting presentation, illustrating the modern surgeon as a virologist. I am very impressed by your successful results with
hepatitis B. I would like to ask how much lamivudine costs per year. The other question is why is it that we can’t get hyper-immune globulin for hepatitis C in contrast to our success with hepatitis B?

Dr Brems: As was mentioned, we did try to immunize all of our patients while they were awaiting transplantation and found by doubling the vaccination dose and by giving monthly injections we are able to vaccinate some of these patients. As far as why we didn’t place these livers into patients who had immunity against hepatitis B, it was really because we have such sick patients on our list. What I didn’t mention was that, and this relates to Dr Kaminski’s question, this went through our IRB and we do have a consent form and every patient we see who is awaiting liver transplantation we offer them this opportunity to be on this list for one of these donors. They all sign a special consent as they are waiting for liver transplantation. It has gone through our IRB, and we have a separate list of patients who will accept one of these donors. When a donor becomes available, we usually put them in the patient who is sickest, and because of being in Chicago with so many programs, usually the patient that we put these livers in is a patient who is in the ICU with a very short time to live. Therefore, we feel it justifies using these organs in these types of patients because they are so sick at the time of liver transplantation.

We continue the lamivudine for 2 years’ time, and all of these patients showed no evidence of hepatitis B virus by DNA PCR, so we stopped the lamivudine at 2 years’ time. We continue to follow these patients beyond that period to see if they develop any evidence of hepatitis B virus. We worry about the risk of developing mutations with this drug. We do have other nucleoside analogs that have just recently come on the market that can be used for hepatitis B, so we figure we do have other treatment strategies if they would develop any evidence of hepatitis B.

Dr Pellegrini asked about whether anybody became infected in our study. Nobody became infected with the hepatitis B virus. There is no other study in the literature talking about stopping HBIG in the perioperative period. The other studies continue HBIG indefinitely, and we felt that this precludes us in many cases from using these organs because of the expense. Lamivudine costs about $2000 a year to use as compared to HBIG, which is about $30000 to use. I mentioned about the informed consent. We do have these patients sign a special informed consent and, as mentioned, we usually do that at the time they go on the list awaiting liver transplantation. We don’t do it at the time an organ becomes available, so we feel that this gives them time to think about it and to ensure that they really want to accept one of these donors.

The mutant is a YMDD mutant. Usually if you stop the lamivudine, a lot of times you can clear the mutant; you can treat these patients with interferon since it is hepatitis B if they are not decompensated to try to clear the mutant. Patients who have developed the mutant are mainly patients who have, as I have mentioned, have very high titer s of hepatitis B DNA at the time they are placed on the lamivudine. We were concerned since they were on immunosuppressive drugs. We were concerned we might see the mutant and that is one of the reasons we put them on HBIG for the first week until we decrease their immune suppression at the end of 1 week.

Dr Donahue talked about a vaccine for hepatitis C. The reason there is no vaccine for hepatitis C is because there are so many different serotypes of hepatitis C. Hepatitis C is a completely different virus. It is an RNA virus, not a DNA virus. There are many different serotypes and genotypes of hepatitis C, so it makes it virtually impossible to come up with any vaccine. It’s a completely different virus than the hepatitis B virus, and I suspect that there probably won’t be any vaccine for hepatitis C in the near future just because of that. What is going to become available for hepatitis C are some of these protease inhibitors, and I think they will be available to treat patients with hepatitis C. The problem is you will need to maintain the patients on these drugs for a lifetime, and they are going to be very expensive drugs to continue the patients on these drugs.

Please read the special articles related to the Generation Gap in Modern Surgery in the March 2002 issue, and then take the poll below:

Recent trends in NRMP matching for categorical positions in surgery show a definite decrease for 2001. This can be attributed best to:
(a) night call and in-hospital work hours
(b) lifestyle issues
(c) duration of training
(d) lack of flexibility in training programs
(e) other

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