Are We Ready for Marginal Hepatitis B Core Antibody–Positive Living Liver Donors?

Robert J. Fontana and Robert M. Merion†*

Adult-to-adult living donor liver transplantation (LDLT) is being performed in the United States with increasing frequency because of the severe shortage of cadaveric donor organs.[1,2] For example, 42 of 89 Organ Procurement and Transplantation Network–certified liver transplant programs (47%) reported having performed at least one adult-to-adult LDLT in 2000, and 355 adult-to-adult LDLTs were performed in the United States in 2002, with the latter accounting for 6.6% of all liver transplantations.[1,3] Patient and graft survival rates in carefully selected adult living donor liver transplant recipients have been similar to those for cadaveric recipients; however the number of patients and duration of follow-up are limited.[4,5] In addition, greater rates of biliary, infectious, and vascular complications have been reported in adult living donor liver transplant recipients compared with cadaveric recipients.[2-5]

Information on outcomes of right-lobe liver donors is limited because of the lack of a standardized follow-up protocol and central registry. However, short-term complications reported in adult living liver transplant donors include blood transfusion (10% to 15%), biliary complications (15% to 30%), and reoperation (5%), among others.[1-7] Although most healthy adult living liver transplant donors regenerate the majority of their liver mass within 1 month of donation, liver failure requiring possible liver transplantation has been reported in three donors, and death, in three others.[1,2,6] Although the need for adult-to-adult LDLT may decline with implementation of the Model for End-Stage Liver Disease liver allocation policy, some critics have called for a moratorium on adult-to-adult LDLT until risks and benefits have been clarified in prospective studies.[2,8,9]

Many US liver transplant programs also have begun to use marginal cadaveric donor livers in selected liver transplant candidates with high medical urgency.[10] Marginal cadaveric livers are variably defined as those with a greater risk for primary nonfunction or the potential to transmit disease. Preliminary data suggest that overall patient and graft survival rates have been acceptable using such carefully selected marginal donors as those older than 50 years and donor livers with less than 30% steatosis on biopsy.[11,12] Conversely, results with non–heart-beating donors and severely steatotic livers have been less favorable.[13,14]

Hepatitis B core antibody–positive ($HBcAb^+$) cadaveric donor livers also are considered marginal because of the 25% to 90% risk for hepatitis B virus (HBV) transmission to the recipient.[15,16] However, outcomes in selected hepatitis B surface antigen $(HBsAg)^+$ and seropositive (i.e., $HBcAb^+$ or antibody to HBsAg $[HBsAb]^+$) recipients generally have been favorable.[15] Transplantation of $HBcAb^+$ cadaveric livers to seronegative recipients is associated with a high rate of HBV transmission, which may lead to severe graft dysfunction in some recipients.[16,17] Use of lamivudine and hepatitis B immunoglobulin (HBIG) immunoprophylaxis in recipients of $HBcAb^+$ cadaveric livers appears to reduce the rate of HBV transmission; however, larger studies with longer follow-up are needed to determine the optimal prophylaxis strategy.[18-20]

In this issue of *Liver Transplantation*, Lo et al[21] present outcomes of 54 consecutive adult living liver transplant donors from Hong Kong who were followed up for a median of 31 months postdonation. Although clinical outcomes of a limited number of recipients of $HBcAb^+$ living donor liver grafts have been reported previously, the short- and long-term safety of partial hepatectomy in $HBcAb^+$ adult living liver transplant donors has not been described previously.[22,23] The majority of right-lobe liver donors in this series were women (65%), and mean donor graft weight was 574 g. The 24 $HBcAb^+$ donors were significantly older than the 29 HBcAb− donors (median age, 42 *v* 31 years). Interestingly, 80% of the HBcAb− group were $HBsAb^+$, suggesting either previous HBV vaccination or exposure to HBV. However, serum HBV DNA was

*From the Divisions of *Gastroenterology and †Transplantation, University of Michigan Medical Center, Ann Arbor, MI.*

Address reprint requests to Robert J. Fontana, MD, 3912 Taubman Ctr, Ann Arbor, MI 48109-0362. Telephone: 734-936-4780; FAX: 734-936-7392; E-mail: rfontana@umich.edu

1527-6465/03/0908-0008$30.00/0

doi:10.1053/jlts.2003.50141

undetectable in all adult living liver transplant donors before surgery.

HBcAb$^+$ donors experienced significantly greater intraoperative blood loss than HBcAb− donors (median, 600 *v* 350 mL). In addition, the incidence of day 7 cholestasis was greater in HBcAb$^+$ donors compared with HBcAb− donors (10% *v* 0%). Intraoperative liver biopsies showed a greater proportion of HBcAb$^+$ donors with hepatic steatosis compared with HBcAb− donors (21% *v* 12%), and the 3 HBcAb$^+$ donors with day-7 cholestasis had evidence of hepatic steatosis. At last follow-up, all 54 adult living liver transplant donors were reported to have normal liver biochemistry test results and no evidence of HBV reactivation, although laboratory data were not provided.

On univariate analysis, donor age and hepatic steatosis were associated with day 7 cholestasis, whereas donor HBcAb status was not. It remains unclear whether HBcAb$^+$ donors are at increased risk for developing postoperative cholestasis or whether HBcAb$^+$ donors are simply older and more likely to develop cholestasis from underlying steatosis with impaired regeneration.[24,25] Unfortunately, no qualitative or quantitative assessment of donor liver regeneration was reported. The greater intraoperative blood loss observed in HBcAb$^+$ donors also may be related to hepatic steatosis because steatosis has been associated with increased intraoperative bleeding in patients undergoing hepatic resection.[26] Furthermore, the presence of hepatic steatosis in 15% of this "thin" group of Asian liver donors with a median body mass index of only 20 kg/m^2 emphasizes the potential importance of liver biopsy in donor assessment.[1,2,27] Previous studies of Western patients have shown a lack of reliable clinical features, such as donor sex, body mass index, and radiological imaging, in identifying living donors with significant hepatic steatosis preoperatively.[27]

This interesting observational cohort study suggests that carefully selected Asian HBcAb$^+$ adults may be suitable donors for adult LDLT. The absence of HBV reactivation in HBcAb$^+$ donors is surprising because one would hypothesize that regenerating donor hepatocytes are at risk for infection from integrated HBV DNA present in the remnant liver. Multiple studies have shown that HBV DNA can be found in livers of HBcAb$^+$ patients with otherwise normal liver biochemistry test results who have completely recovered from previous HBV infection up to 30 years after exposure.[28,29] In addition, HBV DNA was detected in frozen liver tissue of 16 consecutive HBcAb$^+$ adult living liver transplant donors in Japan, which was associated with universal HBV transmission to graft recipients.[22] More recent studies of these healthy HBcAb$^+$ donors also have shown evidence of replicative forms of HBV, including covalently closed circular DNA (cccDNA) and intermediate RNA, in their livers.[30] Unfortunately, data regarding the presence of HBV DNA and hepatitis B e antigen in HBcAb$^+$ donors at 1 and 3 months postdonation are not provided by Lo et al.[21] In addition, the investigators did not perform polymerase chain reaction for HBV DNA from frozen donor liver tissue to look for occult HBV infection.

Although continued and careful follow-up of HBcAb$^+$ living liver transplant donors is needed, it also is important to assess outcomes in recipients of HBcAb$^+$ grafts. Transplantation of cadaveric HBcAb$^+$ livers is more likely to transmit HBV than transplantation of other solid organs (i.e., kidneys), presumably because of the greater number of infectious HBV particles in the donor liver.[16] Previous studies from Japan and Hong Kong show that adult HBcAb$^+$ living donor liver grafts are capable of transmitting HBV to 50% to 100% of seronegative recipients.[22,23,31] Japanese investigators proposed to exclude all HBcAb$^+$ adult living liver transplant donors because of the high rate of HBV transmission to the recipient.[22] However, they and others have shown that the rate of HBV transmission may be reduced with lamivudine and/or HBIG immunoprophylaxis; however, the number of patients treated and duration of follow-up are limited.[22,23]

Recently, the Hong Kong group reported a 90% 1-year patient and graft survival rate in HBsAg$^+$ recipients of 13 cadaveric and 37 adult living donor liver grafts with lamivudine prophylaxis.[30] Surprisingly, transient expression of HBsAb was detected in 21 HBsAg$^+$ recipients (42%) within the first 12 months of transplantation, which was associated with either HBsAb$^+$ or HBcAb$^+$ serostatus in the donor. This novel observation suggests either adaptive immune transfer of protective lymphocytes from the seropositive donor to the recipient or mild self-limited infection of the recipient with donor HBV.[31] Clearly, additional long-term follow-up of all recipients of HBcAb$^+$ and HBsAb$^+$ adult living donor liver grafts is needed to follow up on these intriguing preliminary results.

In the United States, recent review articles advocate excluding HBcAb$^+$ adult living liver transplant donors because of the potential risk for: (1) HBV reactivation in the donor, (2) impaired liver regeneration in the donor, and (3) HBV transmission to the recipient.[1,2] The study by Lo et al[21] suggests that HBV reactivation in carefully selected HBcAb$^+$ Asian donors is unlikely, and adequate regeneration presumably can be achieved in the majority of donors without steatosis.

However, uncertainty persists regarding the risk for HBV transmission and the long-term outcome in recipients of these marginal $HBcAb^+$ living donor liver grafts. The rate of HBcAb positivity is known to parallel the overall rate of HBV infection in the general population. For example, in such a low endemic country as the United States, the lifetime risk for exposure to HBV and having detectable HBcAb is 5%.[32] In such moderately endemic areas as Spain or Hong Kong, where the prevalence of HBsAg positivity is 2% and 10%, the lifetime risk for HBV exposure and having detectable HBcAb may be as high as 12% and 33%, respectively.[21,33] Therefore, the likelihood of encountering an $HBcAb^+$ adult living liver transplant donor during preoperative evaluation will vary substantially among programs in different countries. In most populations, the prevalence of HBcAb positivity also increases with age.[32,33]

Data from the Scientific Registry of Transplant Recipients (SRTR) indicate that the number of $HBcAb^+$ cadaveric livers transplanted in the United States has increased from 175 livers (3.9%) in 1998 to 248 livers (4.9%) in 2002, with a total of 1,036 livers (4.5%) transplanted during that period.[3] Although $HBsAg^+$ patients account for approximately 5% of all liver transplant recipients, the majority (80%) of cadaveric $HBcAb^+$ livers were transplanted into recipients with negative or unknown HBsAg serostatus. During the same period, the number of $HBcAb^+$ adult living liver transplant donors in the United States was 2 donors (2.2%) in 1998, 5 donors (1.4%) in 2002, and 43 donors (2.7%) total during that interval. The majority (81%) of $HBcAb^+$ adult living donor liver grafts also were transplanted into recipients with negative or unknown HBsAg serostatus. Unfortunately, the use of lamivudine and/or HBIG for recipients of either cadaveric or adult living donor $HBcAb^+$ liver grafts is not reported.

The National Institutes of Health recently assembled the Adult-to-Adult Living Donor Liver Transplant study group to determine the long-term safety and outcomes of adult living liver transplant donors and recipients in the United States.[34] The study design of this observational trial includes comparing outcomes of adult living donor liver transplant recipients with those of age-, sex-, and disease severity–matched controls undergoing cadaveric transplantation at the participating centers. Although larger studies on $HBcAb^+$ adult living liver transplant donors are likely to come from endemic areas, the National Institutes of Health Adult-to-Adult Living Donor Liver Transplant study group likely will provide valuable information with the careful prospective evaluation and collection of blood and liver tissue samples in both donors and recipients.

Because the prevalence of steatosis and other factors affecting liver regeneration may be different in American adult living liver transplant donors compared with Asians, we advocate continuing to exclude $HBcAb^+$ adult living liver transplant donors in the United States until risks and benefits of LDLT in this group of marginal donors have become better established. We also recommend that all seronegative adult living liver transplant donors be vaccinated against HBV because they may be at increased risk for adverse outcomes if they were exposed to HBV. Furthermore, vaccinating adult living liver transplant donors for $HBsAg^+$ recipients may enhance the recipient immune response to HBV and improve outcomes; however, additional studies are needed.[31]

In summary, rapid proliferation of adult-to-adult LDLT programs in the United States and abroad during the past 5 years has created substantial concern regarding donor safety.[8,9] However, adult-to-adult LDLT provides a novel opportunity to study and improve the science of liver transplantation in ways that are not feasible with cadaveric liver transplantation. In addition to identifying essential factors involved in liver regeneration, the LDLT model allows us to conduct unique natural history studies of primary viral infection in newly transplanted grafts in a controlled prospective manner. At this time, we believe that US transplant programs offering adult-to-adult LDLT should err to the side of donor and recipient safety and exclude marginal living liver donors who may be at increased risk for having poor outcomes (i.e., older donors, steatotic donors) and those associated with potentially inferior recipient outcomes (i.e., $HBcAb^+$ donors).

Future studies of $HBcAb^+$ adult living liver transplant donors should include protocolized collection of serum, peripheral-blood mononuclear cells, and frozen liver tissue before and periodically after donation for several years. It appears reasonable to target $HBcAb^+$ adult living donor livers to either $HBsAg^+$ or seropositive recipients to minimize the impact of potential HBV transmission. Last, serum, peripheral-blood mononuclear cells, and frozen liver tissue samples also should be collected prospectively in recipients of $HBcAb^+$ living liver grafts to determine the natural history of potential HBV transmission in conjunction with antiviral and HBIG immunoprophylaxis. Although adult-to-adult LDLT poses significant potential risk to the donor, it also provides a unique opportunity to study disease mechanisms and physiological processes in a novel unprecedented manner.

References

1. Brown RS, Russo MW, Lai M, Shiffman ML, Richardson MC, Everhart JE, et al. A survey of liver transplantation from living adult donors in the United States. N Engl J Med 2003;348:818-825.
2. Trotter JF, Wachs M, Everson GT, Kam I. Adult to adult transplantation of the right hepatic lobe from a living donor. N Engl J Med 2002;346:1074-1082.
3. University Renal Research and Education Association. United Network for Organ Sharing Annual 2002 Report of the US Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1992-2001. Available at: http://www.ustransplant.org/annual.html. Accessed April 10, 2003.
4. Bak T, Wachs M, Trotter J, Everson G, Trouillot T, Kugelmas M, et al. Adult-to adult living donor liver transplantation using right-lobe grafts: Results and lessons learned from a single-center experience. Liver Transpl 2001;7:680-686.
5. Marcos A. Right-lobe living donor liver transplantation. Liver Transpl 2000;6(suppl 2):S64-S65.
6. Marcos A, Fisher RA, Ham J, Shiffman ML, Sanyal AJ, Luketic VA, et al. Liver regeneration and function in donor and recipient after right lobe adult to adult living donor liver transplantation. Transplantation 2000;69:1375-1379.
7. Beavers KL, Sandler RS, Shrestha R. Donor morbidity associated with right lobectomy for living donor liver transplantation to adult recipients: A systematic review. Liver Transpl 2002;8:110-117.
8. Cronin DC, Millis JM, Siegler M. Transplantation of liver grafts from living donors into adults—Too much, too soon. N Engl J Med 2001;344:1633-1637.
9. Surman OS. The ethics of partial-liver donation. N Engl J Med 2002;346:1038.
10. Gridelli B, Remuzzi G. Strategies for making more organs available for transplantation. N Engl J Med 2000;343:404-410.
11. Karatzas T, Olson L, Ciancio G, Burke GW, Spire G, Cravero L, et al. Expanded liver donor age over 60 years for hepatic transplantation. Transplant Proc 1997;29:2830-2831.
12. Imber CJ, St Peter SD, Handa A, Friend PJ. Hepatic steatosis and its relationship to transplantation. Liver Transpl 2002;8: 415-423.
13. Adam R, Bismuth H, Diamond T, Ducot B, Morino M, Astarcioglu J, et al. Effect of extended cold ischaemia with UW solution on graft function after liver transplantation. Lancet 1992;340:1373-1376.
14. D'Alessandro AM, Hoffman RM, Knechtle ST, Ororico JS, Becker YT, Musat A, et al. Liver transplantation from controlled non-heart-beating donors. Surgery 2000;128:579-588.
15. Munoz SJ. Use of hepatitis B core antibody–positive donors for liver transplantation. Liver Transpl 2002:8(suppl):S82-S87.
16. Feng S, Buell JF, Cherikh WS, Deng MC, Hanto DW, Kauffman HM, et al. Organ donors with positive viral serology or malignancy: Risk of disease transmission by transplantation. Transplantation 2002;74:1657-1663.
17. Dickson RC, Everhart JE, Lake JR, Wei Y, Seaberg EC, Wiesner RH, et al. Transmission of hepatitis B by transplantation of livers from donors positive for antibody to hepatitis B core antigen. Gastroenterology 1997;113:1668-1674.
18. Yu AS, Vierling JM, Colquhoun SD, Arnaout WS, Chan CK, Khanafshar E, et al. Transmission of hepatitis B infection from hepatitis B core antibody–positive liver allografts is prevented by lamivudine therapy. Liver Transpl 2001;7:513-517.
19. Dodson SF, Bonham CA, Geller DA, Cacciarelli TV, Rakela J, Fung JJ. Prevention of de novo hepatitis B infection in recipients of hepatic allografts from anti-HBc positive donors. Transplantation 1999;68:1058-1061.
20. Roque-Afonso AM, Feray C, Samuel D, Simoneau D, Roche B, Emile JF, et al. Antibodies to hepatitis B surface antigen prevent viral reactivation in recipients of liver grafts from anti-HBc positive donors. Gut 2002:50:95-99.
21. Lo CM, Fan ST, Liu CL, Yong BH, Wong Y, Ng IO, Wong J. Safety and outcome of hepatitis B core antibody–positive donors in right-lobe living donor liver transplantation. Liver Transpl 2003;9:827-832.
22. Uemoto S, Sugiyama K, Marusawa H, Inomata Y, Asonuma K, Egawa H, et al. Transmission of hepatitis B virus from hepatitis B core antibody-positive donors in living related transplants. Transplantation 1998;65:494-499.
23. Rokuhara A, Tanaka E, Yagi S, Mizokami M, Hashikura Y, Kawasaki S, Kiyosawa K. De novo infection of hepatitis B virus in patients with orthotopic liver transplantation. J Med Virol 2000;62:471-478.
24. Fan ST, Lo CM, Liu CL, Yong BH, Chan JK, Ng IO. Safety of donors in liver donor liver transplantation using right lobe grafts. Arch Surg 2000;135:336-340.
25. Sakomoto S, Uemoto S, Uryuhara K, Kim ID, Kiuchi T, Egawa H, et al. Graft size assessment and analysis of donors for living donor liver transplantation using right lobe. Transplantation 2001;71:1407-1413.
26. Behrns KE, Tsiotos GG, DeSouza NF, Krishna MK, Ludwig J, Nagorney DM. Hepatic steatosis as a potential risk factor for major hepatic resection. J Gastrointest Surg 1998;2:292-298.
27. Ryan CK, Johnson LA, Germin BI, Marcos A. One hundred consecutive hepatic biopsies in the workup of living donors for right-lobe liver transplantation. Liver Transpl 2002;8:1114-1122.
28. Brechot C, Thiers V, Kremsdorf D, Nalpas B, Pol S, Paterlini-Brechot P. Persistent hepatitis B virus infection in subjects without hepatitis B surface antigen: Clinically significant or purely occult? Hepatology 2001:34:194-203.
29. Blackberg J, Kidd-Ljunggren K. Occult hepatitis B virus after acute self-limited infection persisting for 30 years without sequence variation. J Hepatol 2000;33:992-997.
30. Marusawa H, Uemoto S, Hijikata M, Ueda Y, Tanaka K, Shimotohno K, Chiba T. Hepatitis B virus infection in healthy individuals with antibodies to hepatitis B core antigen. Hepatology 2000;31:488-495.
31. Lo CM, Fung JT, Lau GK, Liu CL, Cheung ST, Lai CL, et al. Development of antibody to hepatitis B surface antigen after liver transplantation for chronic hepatitis B. Hepatology 2003: 37:36-43.
32. McQuillan GM, Coleman PJ, Kruszon-Moran D, Moyer LA, Lambert SB, Margolis HS. Prevalence of hepatitis B virus infection in the United States: The National Health and Nutrition Examination Surveys, 1976 through 1994. Am J Public Health 1999;89:14-18.
33. Prieto M, Gomez MD, Berenguer M, Cordoba J, Rayon JM, Pastor M, et al. De novo hepatitis B after liver transplantation from hepatitis B core antibody–positive donors in an area with high prevalence of anti-HBc positivity in the donor population. Liver Transpl 2001;7:51-58.
34. Shiffman ML, Brown RS, Olthoff KM, Everson G, Miller C, Siegler M, Hoofnagle JH. Living donor liver transplantation: Summary of a Conference at The National Institutes of Health. Liver Transpl 2002;8:174-188.