LIVER TRANSPLANTATION 12:516-519, 2006

EDITORIAL

# Live Donor Liver Transplantation for Hepatitis C: New Data, Old Story

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Received September 20, 2005; accepted September 22, 2005.

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One of the greatest challenges in liver transplantation is the ever-growing shortage of donor organs. Indeed, over the last decade the increase in organ demand has significantly exceeded the supply, resulting in longer waiting periods and higher death rates on the waiting list. Among other strategies, such as the use of "marginal donors," live-donor liver transplantation (LDLT) has become an important strategy to expand the donor pool.[1] However, as this procedure has developed in the adult population, several questions, both from a clinical and ethical point of view, have been raised.[2] In that sense, one intriguing aspect relates to the outcome of recurrent hepatitis C following live-donor as opposed to deceased-donor liver transplantation. From a theoretical point of view, live donors may offer significant advantages as well as disadvantages in hepatitis C virus (HCV)-infected recipients. Positive circumstances include the flexibility of the waiting period, hence allowing an attempt at pretransplantation antiviral therapy,[3] shortened liver allograft cold ischemic time, younger donor age, and possibly better quality of the organ,[4] all factors previously shown to positively influence recurrent HCV.[5] In contrast, plausible biological mechanisms that might explain worse results in this setting include histocompatibility leukocyte antigen homology between donor and recipient, enhanced HCV proliferation secondary to rapidly proliferating hepatocytes, greater immune suppression as a result of different drug metabolism, and higher rate of biliary complications with may lead to persistent cholestasis,[6,7] a situation that is difficult to differentiate from recurrent hepatitis C or alternatively, which may act synergically with HCV to damage the allograft.[7] After several full published papers, abstracts, and editorials on this topic,[7-18] the conclusions could not be more diverse, from "hepatitis C recurrence is more severe after living donor compared to cadaveric liver transplantation"[7] to "it is therefore apparent that recurrent HCV is not more severe in patients who underwent LDLT".[13]

The answer to the question "Is hepatitis C more severe after living donor than deceased donor liver transplantation," is, however, of paramount importance given the potential impact of hepatitis C in the liver transplant arena.[19] Hepatitis C-infected patients comprise the largest group of patients awaiting liver transplantation, a trend that is expected to rise further in the next decade. Unfortunately, recurrence of HCV viremia or infection is invariable and generally associated with histologically-proven chronic hepatitis, the course of which appears to be accelerated when compared to the nontransplant population, with approximately 20% of patients developing HCV-graft cirrhosis within 5 yr of receiving their organs.[20] If the assertion "recurrence is more severe after LDLT" is true, we should consider whether it is wise to continue to perform LDLT for this indication; in contrast, if the assertion is false, we need to show this with solid data. So, are we ready to solve this conflicting dilemma with current available data?

There are 9 full published studies, including the 1 reported in this issue by Guo et al.,[21] comparing the posttransplantation outcome of live vs. deceased organ donors[7-14,21] (see Table 1). The first report by Gaglio et al.[8] suggested that HCV recurred earlier and was associated with more severe hepatitis, particularly cholestatic hepatitis. Subsequent studies though were unable to confirm these results, and overall showed similar outcome.[9-12] Two recent studies based on protocol liver biopsies had significantly discrepant results.[7,13] In the first study from the United States,[13] none of the patients in the LDLT group developed cirrhosis after a median of 3 yr of follow-

**Abbreviations:** **LDLT**, live-donor liver transplantation; **HCV**, hepatitis C virus.

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DOI 10.1002/lt.20656
Published online in Wiley InterScience (www.interscience.wiley.com).

**TABLE 1. Published Studies Comparing Live Donor to Deceased Donor Liver Transplantation in Hepatitis C Infected Recipients**

| References | N | Protocol biopsies | IS | End-point | LDLT vs. cadaveric LT |
|---|---|---|---|---|---|
| Gaglio et al.[8] | 23 | No | Cyc + MMF + *P* | Rate and timing of histological recurrence, cholestatic hepatitis | Cholestatic hepatitis: 17% vs 0% ($P = .001$). No differences in remainder end-points |
| Van Vlierberghe et al.[9] | 17 | No | Tac + *P* | Rate and timing of histological recurrence, Graft/patient survival at 1 year | Time to recurrence longer in LDLT. No differences in remainder end-points |
| Rodriguez-Luna et al.[10] | 9 | Yes | Tac-*P* | Rate and severity of recurrence at 1 year | No differences |
| Russo et al.[11] | 279 | No | Different regimes | Graft/patient survival at 2 years | No differences |
| Bozorgzadeh et al.[12] | 35 | No | Tac + MMF + *P* | Rate/timing of histological recurrence, Graft/patient survival at 3 years | No differences |
| Garcia Retortillo et al.[7] | 22 | Yes | Different regimes | Severe recurrence: = Cirrhosis on liver biopsy + decompensated liver disease | At 22 months, 45% vs. 22% ($P = .019$) |
| Shiffman et al.[13] | 23 | Yes | CNI + MMF + *P* | Severe recurrence = Cirrhosis on liver biopsy, Graft/patient survival at 4 years | No cirrhosis at 3 years in either group. No differences in fibrosis stage at 3 years. |
| Guo et al.[21] | 15 | Yes | Tac + *P* or MMF | Graft and patient survival at 2 years, histology at 4, 12 and 24 months, viral load | No cirrhosis at 2 years in LDLT vs 5.8% in DDLT. No differences in fibrosis stage at 2 years, nor in viral load, graft and patient survival. |

up. In contrast, in a recent Spanish study,[7] cirrhosis or decompensated liver disease occurred at 2 yr in 45% of LDLT patients compared to 22% in the deceased donor group ($P = 0.01$). In this issue, Guo et al.[21] present a new single center comparison between recipients of living donor (n = 15) and deceased (n = 52) donor transplants for chronic hepatitis C. All comparisons, including survival analysis, post-transplantation viral load, rates of HCV recurrence and severity of recurrence were not significantly different between groups. As with the 2 above-mentioned studies,[7,13] the major strength of the Guo report is the availability of protocol liver biopsies up to 2 yr posttransplantation regardless of the presence of liver function test abnormalities, while the major drawback is the limited number of patients undergoing live-donor transplantation.

How can we reconcile these conflicting findings? There are 2 major reasons for these discrepant results: lack of standardized definitions of post-liver transplantation HCV disease severity, and differences between centers in the presence of potentially relevant variables affecting disease severity. Recurrent hepatitis C is a very complex process with a broad heterogeneity in the morphological, clinical, and pathological pattern of liver damage.[19,20] As stated in the conclusions from the Consensus Development Conference on Liver Transplantation and Hepatitis C, "recurrence of HCV disease occurs at various time points and exhibits a wide spectrum of histological findings, from acute to chronic hepatitis to cholestatic hepatitis, which may occur via different mechanisms of hepatocyte damage."[19] It is hence imperative to apply uniform criteria to define "severe recurrent hepatitis C." While the experts agree on the fact that "the recurrence of HCV disease requires protocol and/or clinically indicated liver biopsies that report both grade and stage of disease,"[19] it is still unclear what is the exact meaning of "severe recurrent HCV disease." Should we define it as "graft loss from HCV," "progression to cirrhosis," or "progression to portal fibrosis"? Should "time-to-cirrhosis" be taken into consideration? Indeed, progression to graft cirrhosis in 1 yr is quite different from progression to cirrhosis in 10 yr. Clearly, differences in the end-points chosen limit the interpretation of published studies (see Table 1). In addition, and as previously demonstrated for deceased donor liver transplantation, when using survival as an end-point, the follow-up must be of sufficient duration to detect differences in outcome.

The second plausible explanation to the controversial data is the existence of differences in risk factors for severe recurrence between centers. Indeed, several determinants of HCV-related disease progression have been proposed,[20] including viral load at transplantation, degree of immunosuppression, donor age, and cytomegalovirus infection. While the exact impact of each of these factors on outcome needs to be defined, prior studies have shown that their distribution in transplant population varies greatly by geographical area. For instance, race, a variable that has been found in a few studies to influence outcome with non-Caucasians doing worse than Caucasians, has a substantial different distribution in U.S. vs. European centers.[22] The same may apply to other variables, such as infecting genotype, donor age, type of cytomegalovirus prophylaxis, or immunosuppression. In fact, differences in these variables were implicated in controversial results regarding the change in the natural history of recurrent hepatitis C over the years using deceased organ donors.[21,23]

In summary, the number of reports on HCV-infected LDLT recipients to date is still small, the post-transplantation follow-up interval is generally too short, the studies using stringent methods and protocol biopsies such as the one published in this issue are limited by low numbers, and there is failure to control for factors potentially affecting the natural history of HCV, present prior to and or following liver transplantation. Despite the difficulty in getting robust data, the majority of studies points toward no differences in 1- and 5-yr graft and patient survival or 1- to 3-yr histological findings. However, as our vision regarding the natural history of recurrent hepatitis C has substantially changed over the year, the same may happen with LDLT and hepatitis C. In the meanwhile, with organ shortage meaning that 5 to 20% of patients die before a liver becomes available, LDLT should continue to be proposed to potential candidates with HCV-cirrhosis provided some criteria are fulfilled: surgical expertise, established indications for liver transplantation, and presence of a restricted cadaveric donor pool. In addition, in centers where patients with HCV fare less well than patients with non-HCV disease following LDLT, a careful analysis of possible contributing factors should be undertaken. The implementation of measures aimed at avoiding or limiting the effect of these factors is likely to lead to better results.[24] Future studies, preferentially multicenter studies based on protocol liver biopsies, such as the A2ALL study, a multicenter study of outcomes in LDLT recipients, should unable us to adequately understand the natural history of recurrent hepatitis C following the use of a partial organ graft.

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