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IMPACT OF HEPATITIS C VIRAL INFECTION IN PRIMARY CADAVERIC LIVER ALLOGRAFT VERSUS PRIMARY LIVING-DONOR ALLOGRAFT IN 100 CONSECUTIVE LIVER TRANSPLANT RECIPIENTS RECEIVING TACROLIMUS

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Background. **There has been concern that adult living-donor liver transplantation (LLTx) for hepatitis C virus (HCV) infection may lead to recurrent disease that is more severe compared with the results of cadaveric LTx (CLTx), because the smaller sized graft in LLTx regenerates and may increase viral replication. This study examines the survival outcome and HCV recurrence in CLTx versus LLTx performed at a single institution.**

Method. **A total of 100 consecutive adult recipients (75 men and 25 women; mean age 49.9±8.4 years) of LTx (65 CLTxs and 35 LLTxs performed July 2000–July 2002) who tested positive for HCV by polymerase chain reaction were examined retrospectively until October 2003. All patients received tacrolimus-based immunosuppression with mycophenolate mofetil and steroids.**

Results. **The overall actual patient survival was 85% (83.1% for CLTx vs. 88.6% for LLTx). The 39-month Kaplan-Meier actuarial patient survivals were 75.1% for CLTx and 88.6% for LLTx. Of 15 deaths, 6 were the result of recurrent HCV (five CLTxs and one LLTx), and of 10 retransplants, 2 were related to recurrent HCV (one CLTx and one LLTx). The rates of recurrence were 72.3% and 77.1%, the hepatitis activity indices were 5.4+2.4 and 6.2+2.8, the fibrosis scores were 1.4±1.4 and 1.5±1.3, and the times to recurrence were 318±269 days and 394±250 days for CLTx and LLTx, respectively. None of the differences between the two groups were significant.**

Conclusion. **No detrimental effect of HCV infection was found in LLTx recipients when compared with contemporaneous CLTx recipients. Patient survival, graft survival, rate of HCV recurrence, severity of HCV recurrence, graft loss from HCV, and interval for recurrence in CLTx and LLTx were similar.**

With the increasing number of patients awaiting liver transplantation (LTx) and the stagnant supply of cadaveric organs, living-donor liver transplantation (LLTx) has emerged as an accepted therapeutic alternative (*1–5*). However, there have been recent suggestions that adult recipients of living-donor allografts (LDAs), whose end-stage liver disease is caused by hepatitis C virus (HCV) infection, may experience worse outcomes compared with adult recipients of cadaveric liver allografts (CLAs) who demonstrate HCV infection. It has been hypothesized that because an LDA is much smaller in size than a CLA, the resultant regenerative process is associated with enhanced viral replication in the LDA. This may potentially adversely affect the smaller-sized graft, resulting in the early and rapid recurrence of HCV disease (*6*, *7*). Although there are a few abstracts on this subject, no published data are available in peer-reviewed journals to support these concerns and they remain speculative (*8–10*). This study examines our institutional experience in 100 consecutive adult LTx recipients with HCV infection who received either a CLA or an LDA.

MATERIALS AND METHODS

Patients and Methods

A total of 100 consecutive adult recipients (aged >18 yr) of LTxs (CLA or LDA, performed July 2000–July 2003) who tested positive for HCV by polymerase chain reaction were retrospectively reviewed with the use of an institutional review board-approved protocol. Recipient demographics; HCV genotype; donor information; preoperative model for end-stage liver disease (MELD) score; incidence of hepatocellular carcinoma; rate, timing, and severity of HCV recurrence; and graft and patient survival were collected. Liver function, as indicated by biochemical profile, and immunosuppression at the last follow-up were recorded. All patients were followed until October 2003.

Immunosuppression

All patients received triple-agent–based immunosuppression consisting of tacrolimus, mycophenolate mofetil, and steroids. Tacrolimus was orally administered at 0.1 mg/kg/d every 12 hr. Target 12-hr trough whole-blood concentrations were 12 ng/mL in the first month, 10 ng/mL in the second month, 8 ng/mL in the third month, and 6 ng/mL beyond 3 months. Mycophenolate mofetil was administered as 1 g twice per day. One gram of methylprednisolone was given before reperfusion of the liver allograft, followed by a steroid taper totaling 600 mg during the next 5 days. By day 6, the patients were receiving 20 mg prednisone daily. Subsequent immunosuppressive adjustments were made based on the individual's clinical course considering the presence of rejection, drug toxicity, or infection.

Liver Biopsy

Percutaneous, ultrasound-guided liver biopsy was performed as clinically indicated when alterations in the biochemical profile were suggestive of hepatic dysfunction. Some patients also underwent protocol liver biopsy after they showed a normal biochemical profile for 12 months but tested positive for HCV with a viral load of more than 500,000 IU/mL. All liver biopsies were graded by an experi-

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enced pathologist, who was blinded to the type of LTx, for the hepatitis activity index (HAI) (0–18) and fibrosis score (0–6) (*11*). When more than one liver biopsy was performed, the higher score was used in each group.

Statistical Analysis

Patient and graft survival were estimated using Kaplan-Meier analysis (SPSS Windows Version 11.5; SPSS Inc., Chicago, IL). Differences in survival were calculated using the log-rank method and the Pearson chi-square test for nonparametric values. Differences in parametric values were analyzed by a two-sided *t* test. Statistical significance was determined when the *P* value was less than 0.05.

RESULTS

Demographics

Of the 100 consecutive patients evaluated, 75 were male and 25 were female. Their mean age at the time of LTx was 50.3±7.0 years (median 49.6 years, range 32.9–72.6 years), and the mean follow-up was 25.0±6.9 months (median 23.9 months, range 14.5–39.3 months). Of these patients, 65 underwent primary whole CLTx and 35 underwent primary right-lobe LLTx consisting of hepatic segments 5, 6, 7, and 8 as previously described (*12–14*). The patients' demographics, MELD scores, and HCV genotypes, when known, are described in Table 1. The mean MELD score was calculated on the basis of the patient's total bilirubin, creatinine, and international normalized ratio values on the day of transplant, without regard for exception scores. Mean donor age, mean MELD score, and male:female ratio were lower, although not statistically significant, in recipients of LLTx compared with recipients of CLTx.

Patient Survival

With a mean follow-up of 25 months, patient actual survival was 85% (83.1% for CLTx and 88.6% for LLTx), whereas the projected (Kaplan-Meier analysis) 39-month actuarial patient survival was 81.7%. Patient survival at 12, 24, and 30 months was 92.3%, 79.5%, and 75.1%, respectively, for CLTx and 91.4%, 88.6%, and 88.6%, respectively, for LLTx (P=0.32 Fig. 1).

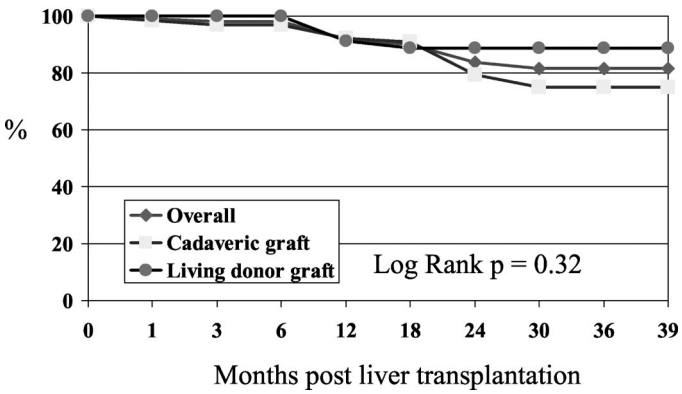

FIGURE 1. Patient survival: overall, cadaveric graft, and living-donor graft over time.

Causes of Death

In all, 15 patients (15%) died during the follow-up period, 11 (16.9%) in the CLTx group and 4 (11.4%) in the LLTx group. These deaths were attributable to recurrent HCV (n=6), cardiac arrest (n=2), portal vein thrombosis, biliary abscess, biliary cast syndrome, short gut syndrome, withdrawal of care, carcinoma of the lung, and bleeding from accidental dislodgement of a dialysis catheter at home. The distribution of these events relative to the type of transplant is shown in Table 2, and the timing of these deaths is shown in Table 3. There was no particular trend noted in either group.

Graft Survival

Graft loss was defined as patients who either underwent retransplantation or died without retransplantation. During the observed follow-up period, nine patients underwent retransplantation, with one patient undergoing retransplantation twice. All patients who underwent retransplantation received cadaveric grafts, and all patients survived. The overall actual graft survival at last follow-up was 76.0% (72.3% for CLTx and 82.9% for LLTx). Kaplan-Meier estimated graft survival at 12, 24, and 39 months was 84%,

TABLE 1. Donor and recipient characteristics

	CLTx	LLTX
Number of patients	65	35
Male/female	52/13	23/12
Age (yr mean±SD)	50.0±7.0	50.7±7.2
MELD score (mean±SD)	15.9±5.3	14.9±4
Donor age (yr mean±SD)	49.2±20.4	34.6±9.7
Presence of hepatocellular carcinoma n (%)	13 (20)	2 (5.7)
Genotype for HCV		
1	8	1
1a	20	17
1b	19	9
1a/1b	1	1
2b	3	1
3a	4	3
5a	1	0
Unknown	9	3

MELD, model for end-stage liver disease; HCV, hepatitis C virus; CLTx, cadaveric liver transplantation; LLTx living-donor liver transplantation.

TABLE 2. Causes of death and retransplantation

Causes of deaths	CLTx	LLTx	Total
Recurrent HCV	5	1	6
Portal vein thrombosis	1	0	1
Biliary cast syndrome/sepsis	2	0	2
Cardiac arrest	1	1	2
Post-resection gangrenous bowel	0	1	1
Withdrawal of support	1	0	1
De novo carcinoma of lung	0	1	1
Hemorrhage from accidental dialysis catheter dislodgement	1	0	1
Total	11	4	15
Causes of retransplantations			
Hepatic artery thrombosis	2	1	3
Primary nonfunction	3	0	3
Recurrent HCV	1	1[a]	2
Biliary cast syndrome	1	0	1
Total	7	2	9

[a] Patient underwent second retransplantation for hepatic artery thrombosis.

TABLE 3. Timing of death and retransplantation

Months from first LTx	0–2	2–4	4–6	6–12	12–18	18–24	>24
Deaths							
CLTx	1	1	1	3	1	3	1
LLTx	0	0	0	3	1	0	0
Total	1	1	1	6	2	3	1
Retransplantation							
CLTx	3	1	2	0	0	1	0
LLTx	0	0	0	2[a]	0	0	0
Total	3	1	2	2	0	1	0

[a] One of them required second retransplantation for hepatic artery thrombosis.

LTx, liver transplantation.

74.4%, and 72.4%, respectively (CLTx 83.1%, 68.3%, and 64.3% vs. LLTx 85.7%, 82.9%, and 82.9%, respectively) (P=0.16 Fig. 2). The causes of graft loss included hepatic artery thromboses in four patients (the first allograft in three patients and the second allograft in one patient), primary nonfunction in three patients, recurrent HCV in two patients, and biliary cast syndrome in one patient. The distribution of graft loss relative to CLTX and LLTx is shown in Table 2, and the timing of retransplantation is presented in Table 3. Neither group demonstrated a particular trend for cause of graft loss.

Hepatitis C Virus Recurrence Leading to Retransplantation or Death

Eight patients (six in the CLTx group and two in the LLTx group) lost their hepatic allograft secondary to HCV recurrence. Six of these patients died before retransplantation at 8 (LLTx), 9 (CLTx), 11 (CLTx), 12 (CLTx), 19 (CLTx), and 24 (CLTx) months posttransplant. One patient in each group underwent retransplantation at 9 months post-LLTx and 21 months post-CLTx. One of the patients (who underwent a first LLTx) lost the retransplanted CLA as the result of hepatic artery thrombosis and received another CLTx.

Rate of Hepatitis C Virus Recurrence Without Graft Loss or Death

Biopsies were performed in the setting of biochemical data indicative of hepatic dysfunction without evidence of vascular or biliary complications. Protocol liver biopsies were performed after 12 months if the HCV load was more than 500,000 copies IU/mL. A total of 81 patients (54 in the CLTx group and 27 in the LLTx group) underwent 145 liver biopsies (1.45/patient; 128 CLAs and 57 LDAs). A total of 70 patients showed evidence of recurrence (47 [72.3%] in the CLTx group and 23 [65.7%] in the LLTx group). The HAIs were 5.4±2.4 and 6.2±2.8 with fibrosis scores of 1.4±1.4 and 1.5±1.3 in the CLTx and LLTx groups, respectively. The mean times to recurrence were 318±269 days (median 221 days) and 394±250 days (median 377 days) in the CLTx and LLTx groups, respectively. None of the differences seen between the CLTx and LLTx groups were significant (Table 4).

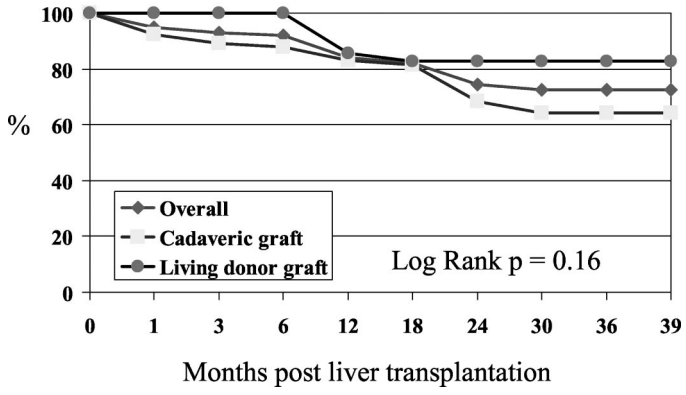

FIGURE 2. Graft survival: overall, cadaveric graft, and living-donor graft over time.

Liver Function

Biochemical profiles indicative of liver allograft function were examined at last follow-up. Total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and gamma glutamyltransferase values are presented in Table 4. No apparent differences were identified between the CLTx and LLTx groups.

Immunosuppression

The mean tacrolimus dose was 4.0±2.3 mg/d (median 4.0 mg/d), providing trough concentrations of 7.0±2.2 ng/mL (median 7.1 ng/mL) in the CLTx group (Table 4) at the last follow-up. In the LLTx group, the mean tacrolimus dose was 4.1±2.5 mg/d (median 4 mg/d), providing a mean trough value of 5.9±2 ng/mL (median 5.3 ng/mL). Three patients in the CLTx group and four patients in the LLTx group were switched to a microemulsion formulation of cyclosporine A (Neoral; Novartis, Basel, Switzerland) because of tacrolimus-induced neurotoxicity, whereas two patients in the CLTx group received rapamycin because of calcineurin-induced nephrotoxicity.

Anti-Hepatitis C Virus Treatment

Prophylactic anti-HCV treatment was not used. Anti-HCV medications were instituted after biopsy-proven HCV recurrence (HAI ≥5 or fibrosis score ≥1) with serum-positive HCV determined by polymerase chain reaction irrespective of liver function determined by biochemical parameters. Pegylated interferon alpha-2b (1.0–1.5 μg/kg/wk) was used in 28 patients (14 CLAs and 11 LDAs), and pegylated interferon alpha-2a (180/μg/wk) and ribavirin (800 mg–1,200 mg/d; adjusted dose for renal dysfunction) were used in 14 patients (11 CLAs and 3 LDAs).

DISCUSSION

LTx is a well-established therapy for end-stage liver disease. The single most common indication for LTx, accounting for more than 30% of the total LTxs performed, is HCV-related end-stage liver disease, the occurrence of which continues to grow steadily (*15*).

Unfortunately, although the number of patients awaiting LTx has grown exponentially in the last decade, the donor pool has remained relatively static (*16–18*). Consequently, the mortality while awaiting LTx has also steadily increased. LLTx has been successfully performed in the pediatric population and is increasingly offered to adults. Although the results of adult CLTx versus LLTx are comparable, one must consider that the two groups of recipients are not necessarily

TABLE 4. Liver function: tacrolimus dose/level and recurrence of hepatitis C virus

		Liver function					Tacrolimus		Recurrence of HCV				
		Total bilirubin mg/dL	ALK U/L	AST U/L	ALT U/L	GGTP U/L	Dose mg/d	Level ng/mL	Days to recurrent HCV	HAI score out of 18	Fibrosis score out of 6	Rate of recurrence n (%)	Graft/death from recurrence n (%)
CLTx	Mean	0.87	249	60	70	226	4.01	7.04	318	5.4	1.4	47 (72.3)	6 (9.2%)
	SD±	0.65	631	44	65	307	2.28	2.23	269	2.4	1.4		
	Median	0.65	124	43	50	140	4	7.1	221	5.0	1		
LLTx	Mean	0.99	251	61	79	153	4.08	5.9	394	6.2	1.5	23 (65.7)	2 (5.7%)
	SD±	1.3	204	61	91	167	2.47	2	250	2.8	1.3		
	Median	0.75	173	41	51	104	4	5.3	377	5.5	1		

ALK, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGTP, gamma glutamyltransferase; HAI, hepatitis activity index.

comparable with respect to age and severity of liver disease at the time of transplantation (*19*).

Currently, there is no satisfactory treatment available to eradicate HCV infection (*20*). Available pharmacotherapy with pegylated interferon in combination with ribavirin has been shown to be efficacious in only one third of the patients treated (*21–23*). A primary consideration when undertaking LTx for HCV-induced ESLD is the recurrence of the disease posttransplantation (*24*). There has been growing concern that living-related LTx adult recipients may be increasingly susceptible to early graft loss from recurrent HCV. After LLTx, there is a compensatory regenerative process in the transplanted segment that is growth-factor driven (*6*, *7*). Gaglio et al. (*10*) showed that 17% of LLTx recipients (n=23) developed cholestatic HCV leading to graft loss, with a recurrence rate of 79% compared with 0% graft loss and 69% recurrence rates in the CLTx group (n=45). Russo et al. (*8*), in a search of the United Network for Organ Sharing database (274 LLTxs and 3,955 CLTxs), found equivalent patient and graft survival for both groups of patients; however, they did not give an account of graft loss related to recurrence of HCV or rate of recurrence.

Our data indicate that there is no need for such a concern. Although mean donor age, mean MELD score, and male: female ratio were lower in LLTx compared with CLTx, it was not statistically significant. In our series, graft and patient survivals are comparable in both groups of recipients with no significant differences noted. Furthermore, there are no significant differences with respect to the cause of graft loss and death. We observed a total of eight graft losses (six in the CLTx group and two in the LLTx group) resulting from recurrent disease. During a 39-month period, two of the patients survived (one in each group) after retransplantation, and the other six patients died. In addition, the rate and severity of recurrence, ascertained by graded biopsies, were similar. Contrary to unsubstantiated concerns, the mean time to recurrence in the LLTx group was actually longer compared with that of the CLTx group in the present series. Overall, our observations may differ from others because of possible differences in baseline immunosuppression or rate of rejection (*25*). Levitt et al. (*10*) and Russo et al. (*8*) did not mention baseline immunosuppression in their studies. At our institution, we use tacrolimus-based immunosuppression, which was found to be superior to cyclosporine A in a U.S. multicenter trial (*26*). A relationship between the rate of rejection and severity of rejection to the recurrence of HCV disease has been suggested (*25*). These are some of the areas that need further evaluation in LLTx recipients.

CONCLUSION

For patients with HCV infection, patient and graft survival for recipients of cadaveric or living allografts were comparable during a 39-month follow-up period. Furthermore, the rate of HCV recurrence, severity of HCV recurrence, and graft loss or death from HCV recurrence were similar for recipients of CLTx and LLTx. The time to recurrence was surprisingly longer in the LLTx group compared with the CLTx group; however, none of the values reached statistical significance. On the basis of our findings, and because of the ongoing shortage of cadaveric organs, HCV-positive recipients should not be excluded from LLTx and may further

benefit from emerging refinements in the management of chronic HCV infection.

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