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KIDNEY TRANSPLANTATION FOR END-STAGE RENAL FAILURE IN LIVER TRANSPLANT RECIPIENTS WITH HEPATITIS C VIRAL INFECTION[1]

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Background. **End-stage renal failure after successful liver transplantation (LTx) has been described in up to 5% of patients. Kidney transplantation (KTx) has been the treatment of choice in these cases. However, in recipients infected with hepatitis C virus (HCV), the augmentation of immunosuppression after KTx may result in an increased viral load. This, in turn, may adversely affect the liver allograft.**

Method. **The present study retrospectively examined the outcome in 17 patients (3 females and 14 males, mean age 51.1±11.3 years) who received KTx after LTx. The mean interval from LTx to KTx was 57.6±32.1 months. The mean follow-up was 41.7 ±20.5 months after KTx, and 99.6±37.7 months after LTx. Sixteen of the 17 patients received tacrolimus-based immunosuppression at the time of KTx.**

Results. **During the follow-up period, one patient underwent combined liver and kidney retransplantation 3.7 years after KTx and 12.7 years after LTx. She subsequently died secondary to primary nonfunction. Four other patients died, two of lung cancer, one of pancreatitis/sepsis, and one of severe depression leading to noncompliance. A total of 29 episodes of biopsy-proven acute renal allograft rejection (1.7 episodes/patient) were encountered and treated with steroids. Seven patients experienced a rise in liver function tests during the period of increased steroid dosage. Four patients received no treatment, and their liver function returned to baseline. The remaining three were treated with interferon. Overall 1- and 3-year actuarial patient and liver allograft survival was 88% and 71% (after renal transplantation); corresponding 1- and 3-year actuarial graft survival was 88% and 61%. Twelve patients are alive with normal liver function. One patient is on dialysis, because of renal allograft loss to noncompliance.**

Conclusion. **In this series, LTx recipients with HCV infection were able to undergo KTx with a reasonable degree of success. KTx should be offered for end-stage renal failure after LTx, even in the presence of HCV infection, to individuals with stable liver function and no signs of liver failure.**

Successful liver transplantation (LTx) can be associated with end-stage renal disease (ESRD) in up to 5% of recipients who are followed beyond 5 years (*1, 2*). LTx recipients with hepatitis C virus (HCV) infection may also have a higher incidence of renal failure because of glomerular disease and/or cryoglobulinemia (*2–5*). Renal transplantation (KTx) for ESRD offers better patient survival and quality of life than dialysis (*6*). However, LTx recipients with HCV infection may be at increased risk after KTx, because the augmented immunosuppression that is required can lead to increased replication of the HCV and inadvertently may affect the liver allograft (*7–10*). The aim of the present study was to examine the outcome in our LTx recipients with HCV infection who underwent KTx for ESRD.

PATIENTS AND METHODS

We identified all patients (n=17) from our institution who were infected with HCV virus who underwent KTx between October 1992 and January 1997 for ESRD after LTx. A diagnosis of hepatitis C infection was established in the 17 patients by detection of anti-HCV antibodies using either a first generation enzyme-linked assay (Ortho Diagnostic, Raritan, NJ) and/or a second-generation enzyme-linked assay (Abbott Laboratory, Abbott Park, IL). Fourteen of the 17 patients were also tested for HCV-RNA (ribonucleic acid) in serum by reverse transcriptase-polymerase chain reaction. This was positive in all 14; quantitative HCV RNA levels were obtained in 12 of these patients. Patient demographics are shown in Table 1. The causes of renal failure were considered primarily to be tacrolimus-related nephrotoxicity and HCV infection. In addition, four patients had hypertension and one patient had insulin-dependent diabetes mellitus as cofactors.

We analyzed patient survival, liver and kidney allograft survival, baseline immunosuppression and additional immunosuppression to control rejection, liver function, hepatitis activity index (HAI) scores (whenever liver biopsies were performed), and renal function.

RESULTS

Mean follow-up was 41.7±20.5 months (median 38, range 14–72) after KTx and 99.6±37.7 months (median 92.8, range 39–177) after LTx. The mean recipient age was 51.1±11.3 years (median 49.5, range 23–64) at the time of KTx. There

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TABLE 1.

Demographics				HCV-RNA	Pre/post KTx Knodell HAI score[a]				IFN treatment			
No	Age at Ktx (yr)	Sex	Months Ltx to Ktx	Quantitative (copies/ml)	Pre-Ktx	Months pre-Ktx	Post-Ktx	Months post-Ktx	Pre-Ktx	Post-Ktx	Acute episodes of Ktx rejection	Clinical outcome current status (post-Ktx months of follow-up)
1	23.3	F	112.1	183×10e5	7	12.3	8	15.4		Yes	9	Renal graft lost: 2.7 yr: noncompliance (65.6)
2	63.5	M	47.6		5	34.3					0	Died from pancreatitis/sepsis: 17 days post-Ktx (0.6)
3	35.8	M	99.4	204×10e5	9	7.3	14	30.2			2	Alive with functioning liver and kidney allografts (44.1)
4	52.1	F	32.9								0	Alive with functioning liver and kidney allografts (54.7)
5	57.7	M	59.2	74×10e5	15.7	5	13.3			1	Alive with functioning liver and kidney allografts (19.0)	
6	63.1	M	74.7		8	51			Yes		1	Alive with functioning liver and kidney allografts (25.4)
7	43.0	M	70.0	43×10e5							2	Alive with functioning liver and kidney allografts (24.9)
8	48.6	M	34.7	43×10e5	3	16.5					3	Alive with functioning liver and kidney allografts (21.4)
9	49.5	M	17.6	892×10e5			10	33.2			1	Alive with functioning liver and kidney allografts (38.8)
10	36.1	F	107.7	2257×10e5	7	75.7	12	0.23			0	Liver + kidney retransplantation 3.7 yr after first Ktx; died 2 mo later (47.7)
11	48.0	M	75.0		7	14.6			Yes		1	Died 9 mo post-Ktx from Ca lung (8.4)
12	61.5	M	43.4	892×10e5	6	37.7	10	9.3		Yes	3	Died 24 mo post-Ktx from Ca lung (23.5)
13	50.6	M	54.7	5×10e5	7	20	11	20.8	Yes		0	Died 34 mo post-Ktx severe depression noncompliance (34.9)
14	64.4	M	15.7						Yes		1	Alive with functioning liver and kidney allografts (73.4)
15	48.7	M	25.3	591×10e5							3	Alive with functioning liver and kidney allografts (13.9)
16	45.5	M	18.3	40×10e5	3	11.5	6	80.7		Yes	2	Alive with functioning liver and kidney allografts (84.9)
17	60.7	M	91.5	54.4×10e5			10	2.7	Yes		0	Alive with functioning liver and kidney allografts (29.4)

[a] Where more than one biopsy, highest score is used.
RNA, ribonucleic, HAI, hepatitis activity index (ref.*11*).

were 14 men and 3 women. The mean interval from LTx to KTx was 57.6±32.1 months (median 54.7, range 17.6–112.2).

Patient and graft survival. During the study period, one patient (case 10) developed recurrent HCV and underwent combined liver and kidney retransplantation 3.7 yr after KTx (12.7 years after the initial LTx). She died of primary nonfunction and sepsis. Four other patients died during the same time period. Two (cases 11 and 12) developed de novo lung cancer (9 and 24 months after KTx, and 67 and 84 months after LTx, respectively), with normal liver and kidney allograft function; both patients had a documented long-standing smoking history. One (case 2) died of pancreatitis and sepsis during the first month after KTx (48 months after LTx). One patient (case 13) developed severe depression and refused all of his medications, he subsequently died of combined hepatic and renal failure 34 months after KTx and 89 months after LTx. Overall actuarial patient and liver allograft survival was 88%, 81%, and 71% at 1, 2, and 3 years after KTx. Actuarial renal allograft survival at 1, 2, and 3 years was 88%, 81%, and 61%, respectively (Fig. 1).

Immunosuppression. Primary immunosuppression was with tacrolimus in all patients except one who was receiving cyclosporine (case 17). Five (31%) of sixteen patients who were on tacrolimus at the time of KTx were originally on cyclosporine and were switched to tacrolimus, before KTx, to control liver allograft rejection (cases 1, 3, 6, 10, and 11).

All patients received 1 g of methylprednisolone followed by a methylprednisolone taper from 200–20 mg/dl over the first 5 days after KTx. The one patient who was on cyclosporine remained on this drug (case 17), while the other recipients were initially given increased doses of tacrolimus after KTx. The mean tacrolimus dose, trough tacrolimus concentration, and prednisone dose before KTx and 1, 3, 6, 12, 24, and 36 months after KTx are shown in Table 2. The mean increase in the tacrolimus and prednisone doses was an average of five times the pre-KTx dose at 1 month and two times at 6 months. Twelve (71%) patients experienced a total of 29 (2.4 per patient) episodes of acute renal allograft rejection, which were treated with steroids.

Liver function. Mean total bilirubin, aspartate aminotransferase, alanine aminotransferase (ALT), and gamma-glutamyltransferase levels, before and at 1, 3, 6, 12, 24 and 36 months after KTx are shown in Table 2. Seven patients (41%) experienced elevations in liver function tests. Four (24%) patients (cases 3, 5, 10, and 11) had a transient rise in liver function tests (LFTs) with augmentation of steroids after KTx. In all four patients, LFTs stabilized when the baseline immunosuppression was restored. None of these patients had evidence of any other viral illness, and no other potential hepatotoxic drug was added during this time. Three patients (17.6%) (cases 1, 12, and 16) received interferon (IFN) therapy, and in all of them the biochemical changes were restored to baseline. Four of the patients who died (cases 2, 11, 12, and 13) had stable liver function, without jaundice. One (patient 10) developed end-stage liver failure 3.7 years after KTx because of recurrent hepatitis C and underwent (unsuccessful) combined liver and kidney retransplantation.

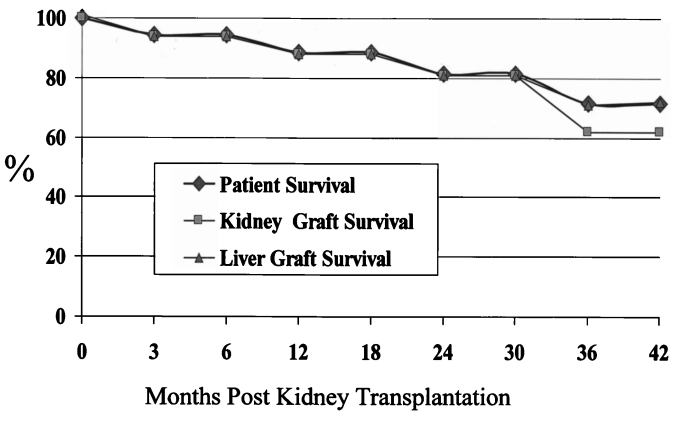

FIGURE 1. Kaplan-Meir actuarial survival of patient and liver plus kidney allografts.

Use of IFN. Pre-KTx IFN-α (1.5–3 million units) was given in the case of five patients (cases 6, 11, 13, 14, and 17) with biopsy-proven recurrent HCV and an increase in ALT to more then twice the upper limit of normal. However after KTx, IFN-α was given to only three patients because of the risk of precipitating renal allograft rejection (cases 1, 12, and 16) with the first rise in LFTs within the first 3 months after KTx. One of these patients (case 1) eventually lost the renal allograft to noncompliance, and is currently on dialysis; she maintains normal and stable liver function. Another patient (case 12) died of lung cancer with normal liver and renal function at the time of death. The other patient (case 16) is alive with stable liver and renal function.

HAI. No protocol liver biopsies were performed before or after KTx. All biopsies were performed when clinically indicated and when elevation in liver function tests was demonstrated. Thirty liver biopsies were performed in 13 patients. Seventeen liver biopsies were performed in 11 patients before KTx, and 13 biopsies were performed in 9 patients after KTx. These were reviewed retrospectively and scored blindly for HAI using the Knodell score by a pathologist who had no knowledge of the clinical course of the patient (*11*). Mean HAI score was 5.3 (range 2–9, n=11) before KTx and 8.6 (range 5–14, n=9) after KTx. Only seven patients had biopsies before and after KTx. In this group, the mean HAI score pre-KTx was 6.4 (range 3–9), whereas post-KTx, the mean HAI score was 8.3 (range 5–14).

Renal function. With the exception of one patient (case 1) all survivors are off dialysis. The mean blood urea nitrogen and creatinine before KTx and at 1, 3, 6, 12, 24, and 36 months after KTx are shown in Table 2. Case 1 had a total of nine episodes of acute rejection, only one of which occurred while on IFN-α. The others rejection episodes were related to noncompliance with immunosuppressive medications.

DISCUSSION

KTx after LTx in HCV-positive patients is controversial, and there are no data available thus far. This is the first report on 17 patients from a single institution, with a mean follow-up of more than 3 years. This retrospective study examined patient survival, graft survival, rate of rejection, and changes in immunosuppression and its impact on liver and kidney function. The 11 patients with functioning kidneys are 3.4±1.9 years (median 2.8, range 1.2–5.4) after kidney transplantation. They all have stable

TABLE 2. Immunosuppression, renal, and liver function

Months post-Ktx	*0*	*1*	*3*	*6*	*12*	*24*	*36*
Immunosuppression[a]							
Tacro. dose mg/day	3.8±2.9	18.5±10	13.3±7.0	8.2±5.0	4.5±3.9	4.0±3.9	4.2±4.0
Tacro. level ng/ml	3.0±4.2	13.4±12.1	12.9±7.2	10.1±7.6	10.6±9.0	5.5±4.5	5.0±4.1
Prednisone mg/day	3.3±2.8	17.9±5.0	11.7±2.2	7.5±3.2	4.0±4.2	2.5±6.6	3.3±6.1
Liver function[a]							
T. Bili. mg/dl	0.64±0.17	0.57±0.16	0.58±0.25	0.65±0.21	0.71±0.24	0.68±0.24	0.78±0.8
AST μ/ml	46±18	44±24	37±26	66±78	45±18	54±36	47±24
ALT μ/ml	47±24	79±55	48±34	93±130	55±32	54±43	55±45
GGTP μ/ml	243±242	388±524	290±476	301±405	254±266	215±135	221±80
Renal function[a]							
BUN mg/dl	68.1±17.7	29±7	30±6	32±10	28±14	30±9	32±12
Creatinine mg/dl	9.1±1.9	1.8±0.3	1.8±0.4	1.8±0.6	1.6±0.4	2.0±0.5	2.3±1.3

AST, aspartate aminotransferase; BUN, blood urea nitrogen; GGTP, gamma-glutamyltransferase; Tacro, tacrolimus; T. Bili., total bilirubin.

[a] Mean value and standard deviation.

liver and renal function. Of the five patients who died, two died of lung cancer with normal liver and renal function. One patient died of pancreatitis with sepsis and another patient died as a result of depression and noncompliance. Despite this, actuarial patient survival is 81% at 2 years after KTx and 61% at 10 years after LTx. Only one patient developed end-stage liver failure 3.7 years after KTx. This patient was maintained on a subtherapeutic dose of baseline immunosuppression because of increased HCV replication. She subsequently died after combined liver and kidney retransplantation from primary nonfunction of the liver and sepsis. There are reports that an increase in immunosuppression can lead to an increase in viral load, which may adversely affect the liver allograft (*6–10*). Unfortunately, there were no serial quantitative HCV polymerase chain reaction results available for this population. Hepatic graft survival, however, did not seem to have been affected by augmentation of immunosuppression. Liver function improved in all patients after baseline immunosuppression was restored, and the initial increase to immunosuppression does not seem to have had any long-term effect on liver allograft function. In the future, protocol serial measurement of HCV viremia may be important to determine the impact of augmented immunosuppression in this setting. Three patients who received IFN-α because of increased LFTs 2 weeks after KTx probably in retrospect could have waited until the effect of augmented immunosuppression resolved before instituting IFN-α. IFN-α did not seem to have caused an increased incidence of liver or kidney allograft rejection (*12*). This observation is in contrast to published data on isolated kidney transplants (*13*). Caution is nevertheless warranted when IFN-α is used after KTx in LTx patients. This is a retrospective study, and all patients did not undergo serial pre- and post-KTx liver biopsies and quantitative HCV RNA studies. However, this does not obscure our observations that KTx can be performed safely in patients who have stable liver function without any evidence of hepatic decompensation. In future protocol of KTx in LTx patients with HCV infection, pre-KTx liver biopsies may be helpful in some patients who may have early cirrhosis related to HCV infection in the absence of abnormal LFTs or any other clinical sign of liver failure; similarly, post-KTx liver biopsies may be useful if liver function does not return to baseline after temporary augmentation of posttransplantation immunosuppression. It is of course unlikely that the liver allograft would experience rejection, because patients are on a considerably higher dose of baseline immunosuppression after KTx compared with before KTx.

In conclusion, this retrospective study suggests that LTx recipients with HCV infection who develop ESRD may be considered for KTx. After KTx these patients may have a transient rise in LFTs coincident with increased doses of steroids that usually subsides when the baseline immunosuppression is restored. Overall, patient and graft survival are reasonable. The presence of a liver allograft should not preclude kidney transplantation when a patient with recurrent hepatitis C develops ESRD , provided there is no sign of hepatic decompensation.

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A WORLDWIDE, PHASE III, RANDOMIZED, CONTROLLED, SAFETY AND EFFICACY STUDY OF A SIROLIMUS/CYCLOSPORINE REGIMEN FOR PREVENTION OF ACUTE REJECTION IN RECIPIENTS OF PRIMARY MISMATCHED RENAL ALLOGRAFTS

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Background. **Despite the various immunosuppressive regimens presently in use, acute rejection in the early postoperative period continues to occur in 20 to 40% of renal transplant patients. In a double-blind, multicentred study, we investigated the ability of two different doses of sirolimus (rapamycin, RAPAMUNE), a new class of immunosuppressant that blocks cell cycle progression, to prevent acute rejection in recipients of primary mismatched renal allografts when added to a regimen of cyclosporine (cyclosporin A, CsA) and corticosteroids.**

Methods. **Between October 1996 and September 1997, 576 recipients of primary mismatched cadaveric or living donor renal allografts were randomly assigned in a 2:2:1 ratio (before the transplant operation) to receive an initial loading dose of either 6 or 15 mg of orally administered sirolimus, followed by a daily dose of either 2 or 5 mg/day, or to receive a matched placebo. All groups received cyclosporine (microemulsion formula, CsA) and corticosteroids. The primary endpoint was a composite of first occurrence of biopsy-confirmed acute rejection, graft loss, or death during the first 6 months after transplantation. Safety data were monitored by an independent drug safety monitoring board.**

Results. **Based on an intention-to-treat analysis of**

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