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Combined liver and kidney transplantation

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Abstract Patients with end-stage renal and hepatic failure may be treated with combined liver and kidney transplantation (CLKTx). We reviewed the indications and outcomes of 16 CLKTx performed at the University of Minnesota between 1980 and 1994. The majority of the recipients (87.5 %) were young patients affected by congenital hepatic anomalies and concomitant end-stage renal failure. Fourteen were treated with cyclosporin-based immunosuppression and had an excellent outcome: with an average of 6 years of follow-up, patient survival was 85.7 %, liver graft survival 85.7 %, and kidney graft survival 72 %. The incidence of rejection episodes was similar to the rate of rejection in our solitary kidney and liver transplants. In conclusion, our experience supports the value of CLKTx in treating patients with simultaneous failure of both organs or with congenital enzymatic hepatic deficits leading to renal failure.

Key words Kidney, liver transplantation · Liver, kidney transplantation

Introduction

For patients with end-stage failure of both liver and kidneys or with enzymatic inherited defects of the liver leading to renal failure, simultaneous transplantation of these organs is the optimal therapy. We reviewed the indications and results of combined liver and kidney transplantation (CLKTx) in 16 recipients at the University of Minnesota.

Materials and methods

Between 1 September 1980 and 1 April 1994, a total of 316 orthotopic liver transplantations were carried out at the University of Minnesota. Of these, 16 recipients (5 %) had a simultaneous kidney transplant (15 primary) from the same donor; 1 recipient with oxalosis had had two previous kidney transplants.

Table 1 summarizes the causes of hepatic and renal failure and the characteristics of the 16 combined transplant recipients. Five patients had alpha 1-antitrypsin deficiency causing liver failure and documented membranoproliferative glomerulonephritis according

Table 1 Combined liver-kidney transplant recipients: characteristics (*MPGN,* membranoproliferative glomerulonephritis; *ESRD,* end-stage renal disease)

Patients ($n = 16$)	Age (years)	Sex	Year of transplantation	Cause of kidney failure	Cause of liver failure	Mode of dialysis
1	28	M	1980	Aminoglycosides toxicity	Extrahepatic biliary hypoplasia	Hemodialysis
2	6	F	1981	MPGN	α 1-antitrypsin deficiency	Hemodialysis
3	18	M	1985	MPGN	α 1-antitrypsin deficiency	Preemptive
4	22	F	1985	Fulminant Wilson disease	Fulminant Wilson disease	Hemodialysis
5	10	F	1985	MPGN	α 1-antitrypsin deficiency	Preemptive
6	28	F	1986	Hepatorenal syndrome	Toxic acute hepatic failure	Hemodialysis
7	26	M	1986	Type I glycogenosis	Type I glycogenosis	Hemodialysis
8	3	F	1988	Congenital dysplastic kidneys	Idiopathic hepatic fibrosis	Hemodialysis
9	8	F	1988	MPGN	α 1-antitrypsin deficiency	Preemptive
10	62	M	1990	Hepatorenal syndrome	Alcoholic cirrhosis	Hemodialysis
11	18	M	1990	Type 4 renal tubular acidosis with ESRD	Alagille syndrome	Peritoneal dialysis
12	24	F	1990	Hepatorenal syndrome	Acute hepatic failure due to hepatitis B	Hemodialysis
13	26	M	1991	MPGN	α 1-antitrypsin deficiency	Preemptive
14	8	M	1992	Primary oxalosis	None	Hemodialysis
15	3	F	1992	Primary oxalosis	None	Hemodialysis
16	8 months	M	1994	Primary oxalosis	None	Hemodialysis

to pretransplant native kidney biopsy. Of these five patients, one was on dialysis at the time of transplant; the other four underwent a preemptive kidney transplant. In all four of these patients, the creatinine clearance was less than 15 cc/min. Given their markedly abnormal creatinine clearance and documented glomerulopathy, we felt they would not tolerate further deterioration of renal function associated with cyclosporin immunosuppression. Another three patients had renal failure due to oxalosis; for them, the liver transplant was done at the time of the kidney transplant to definitively cure the enzymatic deficiency disease. All of these patients had type I primary hyperoxaluria and, at the time of transplant, had no signs of systemic manifestations of the disease besides the renal failure.

Donors were selected only by size and ABO compatibility. None of the recipients was highly sensitized pretransplant (PRA ranging from 0% to 10%); all had negative B- and T-cell crossmatches (done post-transplant on samples obtained before transplantation). The average number of HLA-A, -B, and -DR mismatches was 4.2 ± 0.8. Three of the 16 cases (10%) were performed emergently in the setting of a fulminant hepatic failure.

Operative technique

Patients 1 and 2 underwent an orthotopic liver transplant followed by an orthotopic kidney transplant after native right nephrectomy through a single bilateral subcostal incision. Biliary reconstruction was a cholecystojejunostomy in patient 1 and a choledochojejunostomy in patient 2. In both patients, the transplant ureter was anastomosed end-to-end to the native right ureter.

The other 14 recipients underwent an orthotopic liver transplant via a subcostal incision. Only in adult cases performed after December 1989 was venovenous bypass used. After the liver transplant was completed, the subcostal incision was closed and an extraperitoneal kidney transplant was done through a new lower abdominal incision. Biliary reconstruction consisted of a choledocho-choledochostomy in ten patients and a choledochojejunostomy in the other four. The ureteral anastomosis was done by an extravesicular ureteroneocystostomy in 13 patients and Leadbetter-Politano in 1 (patient 4). One patient received a reduced-size liver graft (segments 2–4); all others received the whole organ.

Immunosuppression

For patients 1 and 2, immunosuppression consisted of 14 days of induction therapy with ALG, then maintenance therapy with prednisone and azathioprine. For the other 14 patients, immunosuppression consisted of cyclosporin, azathioprine, and prednisone; the 7 pediatric recipients (< 14 years old) also received a 14-day postoperative course of ALG or ATG. Cyclosporin (1 mg/kg per day) was started early postoperatively as a continuous IV drip; the dose was increased, as tolerated, during the first 24 h to a target dose of 3 mg/kg per day. Subsequently, oral cyclosporin was given to maintain levels between 200 and 300 ng/ml by HPLC. Azathioprine was started at a dose of 2.5 mg/kg per day and adjusted to avoid bone marrow toxicity. Steroids were started at a dose of 2 mg/kg per day, tapered to 0.25 mg/kg per day 6 months post-transplant and to 0.125 mg/kg per day 1 year post-transplant.

For all 16 patients, a liver graft biopsy was routinely done on postoperative day 7, then once a year by protocol or when clinically indicated. A kidney graft biopsy was done as part of the standard work-up of any renal dysfunction. If rejection in either graft was demonstrated, initial treatment consisted of steroid boluses (Solu-Medrol at 500 mg IV per day for 3 days), then a recycling of the prednisone taper. Steroid-resistant rejection episodes were treated with OKT3 or ALG/ATG.

Results

Precyclosporin era

The first two patients, transplanted in 1980 and 1981, had multiple complications. Patient 1 had prompt function of both organs despite a very difficult transplant operation. Postoperatively, he developed a biliary obstruction at the cholecystojejunostomy; it was successfully treated by conversion to hepaticojejunostomy. Later, he had a large intra-abdominal abscess that required open surgical drainage. After recovery, he enjoyed 6 months with excellent function of both organs. He then developed cerebral aspergillosis that was unresponsive to medical and surgical treatment and he died. Patient 2 had infarction of the transplanted kidney graft requiring nephrectomy 2 weeks postoperatively. She also had a subphrenic abscess (due to *Bacteroides fragilis*) that required surgical drainage. Her liver graft continued to function until her death due to generalized cytomegalovirus (CMV) infection 2 months post-transplant. No rejection was documented in these two initial patients.

Cyclosporin era

Survival

Of the 14 CLKTx recipients who underwent surgery since 1985, 12 are alive and well (85.7 %). Of the two who died, one underwent emergent CLKTx for acute hepatic failure due to a suicide attempt with multiple drugs. At the time of the transplant, she was ventilator-dependent and on hemodialysis because of hepatorenal syndrome. Despite initial good function of both grafts, she rapidly deteriorated and died due to CMV pneumonia and systemic candidiasis. The other underwent CLKTx for alcoholic cirrhosis with hepatorenal syndrome that required hemodialysis. He had a stormy postoperative course and died of a massive myocardial infarction 2 weeks post-transplant; both grafts were working at that time.

Technical complications

Of the 14 recipients, 7 had technical complications. However, no graft loss or patient death resulted.

Four recipients had five technical complications related to the liver transplant. One (patient 14) developed early hepatic artery thrombosis that was treated by embolectomy and reanastomosis the day after the transplant; the hepatic artery is still patent 3 years later. The same patient developed biliary stricture 6 months after transplant; this was successfully managed by percutaneous dilatation and stenting.Two patients (patients 8 and 12) had postoperative bleeding that required laparotomy for control. Another (patient 16) had biliary stricture 3 months post-transplant; this was successfully treated by percutaneous dilatation.

Two recipients had technical complications related to the kidney transplant. One (patient 8) had a leak of the ureteroneocystostomy that was successfully treated by nephrostomy and percutaneous stenting. The other (patient 4) had severe mucormycosis infection of the right lower quadrant incision; this was treated with local debridement and systemic antifungal therapy.

Early graft function

All of the liver grafts had primary function; retransplantation was never required. Of the 14 kidney grafts, 4 (28 %) had acute tubular necrosis post-transplant (patients 8, 10–12), but all recovered function within 1 week.

Long-term function

In the surviving 12 recipients, the liver graft function has been excellent. Current hepatic and renal function, as well as rejection history, are reported in Table 2.

Two kidney grafts (16.6 %) have failed. One recipient stopped immunosuppression and the kidney failed 6 years post-transplant; his liver function continues to be excellent. Another recipient's graft failed due to acute rejection 6 months post-transplant; after 8 months of hemodialysis, she underwent a successful living donor retransplant.

Rejection episodes

Of the 12 long-term survivors, 7 (58.3 %) experienced documented liver graft rejection episodes. All were diagnosed within the first 2 months post-transplant, with a peak incidence at 2 weeks (Table 2). Of the seven patients who experienced rejection episodes, two responded to steroids, while the other five required anti-T-cell treatment (ALG in four recipients and OKT3 in one). No liver rejection episodes occurred more than 2 months post-transplant. All of the protocol biopsies have been normal.

By comparison, the incidence of rejection (at least one biopsy-proven episode) in our solitary orthotopic liver transplant recipients is 61 % (P = NS).

We diagnosed six biopsy-proven kidney graft rejection episodes in 5 of the 12 long-term survivors (41.6 %). As described above, one recipient had a severe tubulointerstitial rejection 6 months post-transplant, causing graft loss. The other five episodes were reversed with steroids ($n = 3$) or antibody ($n = 2$). Only

Table 2 Long-term combined liver-kidney transplant recipients: current hepatic and renal function and rejection episodes (*TIR*, tubulointerstitial rejection, *Tx*, transplant, *VR*, vascular rejection)

Patients ($n = 12$)	Length of follow-up (years)	Liver function			Kidney function (serum creatinine) (mg/dl)	Rejection episodes	
		ALT (U/l)	AST (U/l)	Bilirubin (mg/dl)		Liver	Kidney
3	10	139	99	0.9	1.1	None	Mild TIR 2 months post-Tx
4	10	61	57	2.1	1.5	Moderate VR 2 months post-Tx	None
5	10	37	44	1.6	0.9	Moderate VR 2 weeks post-Tx	None
7	9	16	18	0.8	Failed	Moderate VR 1 week post-Tx	None
8	7	33	24	0.4	Failed	Moderate VR 1 month post-Tx	Severe TIR 6 months post-Tx
9	7	39	33	0.7	1.1	Mild VR 2 weeks post-Tx	None
11	5	30	20	0.5	1.3	None	Moderate TIR 6 months post-Tx
12	5	26	26	0.4	1.0	None	None
13	4	149	129	1.3	0.9	Moderate VR 2 weeks post-Tx	None
14	3	11	26	0.3	0.8	None	None
15	3	87	24	1.0	1.0	Mild VR 2 weeks post-Tx	Moderate TIR 3 weeks & 24 months post-Tx
16	1	108	62	0.9	0.6	None	Severe TIR 1 month post-Tx

patient 13 had two episodes of acute rejection (Table 2). By comparison, the incidence of biopsy-proven rejection in our primary cadaver kidney transplant recipients of comparable age (range 1–28 years) is 42 % (P = NS). We did not find any instance of simultaneous rejection of both the liver and kidney grafts.

CMV disease

Of the 14 recipients treated in the cyclosporin era, 4 suffered from CMV infection (28.5 %). CMV disease always occurred within 3 months post-transplant. CMV pneumonia contributed to the death of patient 6 (along with systemic *Candida* infection). The other three recipients recovered from CMV pneumonia (patient 12) and systemic CMV disease (patients 4 and 14) with ganciclovir treatment.

Discussion

The first published report of CLKTx was in 1984 by Margreiter et al. [8]. It was done in December 1983 for a patient with chronic glomerulonephritis and chronic active hepatitis B. However, our first CLKTx (done by JSN, the senior author of the present article, on 3 September 1980) predates theirs by 3 years. To the best of our knowledge, ours was the first CLKTx ever performed. Since then, it has been successfully carried out in many leading transplant institutions [5–7, 10–12].

Goldstein et al. [6] reported 15 cases of CLKTx performed at Baylor University in Dallas; 12 recipients (80 %) survived, all with excellent long-term kidney and liver graft function. Their incidence of acute rejection was only 3 % for kidneys transplanted with the liver (versus 47 % for kidneys transplanted alone); for the liver it was 59 %. They concluded that CLKTx is the optimal approach for ESRD patients undergoing a liver transplant and that a simultaneous liver transplant decreases the incidence of acute kidney rejection.

Rasmussen et al. [10] recently reviewed the Cambridge experience with 21 CLKTx and found a significantly decreased incidence of kidney graft rejection in CLKTx (9.5 %) versus kidney transplantation alone (37.2 %), as well as a superior kidney graft survival rate for the combined procedure. The liver graft survival and rejection rates were similar for CLKTx and isolated liver transplant recipients. Other authors have also re-

ported no kidney transplant rejection in CLKTx recipients [5, 12].

CLKTx has been thought to protect the kidney graft from hyperacute rejection due to preformed anti-HLA antibodies, even in highly sensitized recipients [3, 4]. However, hyperacute rejection of a kidney transplanted after a liver has been reported in the face of a positive lymphocyte crossmatch [2, 11]. Saidman et al. [11] studied the effect of preformed lymphocytotoxic antibodies in 38 CLKTx done at the University of Pittsburgh between 1983 and 1992. The overall patient survival rate was 68 % (comparable to survival for liver alone). Kidney graft survival was 60 % and liver graft survival 68 %; the length of follow-up was 11 months to 9 years. When subdivided by those with ($n = 6$) versus those without ($n = 32$) a positive crossmatch, patient and graft survival significantly decreased with a positive crossmatch. No information was given about the incidence of kidney or liver graft rejection. The authors concluded that preformed lymphocytotoxic antibodies have a deleterious effect on long-term CLKTx patient and graft survival. However, they stated that a positive crossmatch should not be an absolute contraindication.

Our good results may be because we did not transplant any patient with high PRA or positive lymphocyte crossmatches. Interestingly, our incidence of acute kidney rejection after CLKTx did not decrease compared with kidney transplant alone; however, the numbers are too small to draw valid conclusions. As described by other authors, the liver and the kidney grafts do reject independently.

Our series is unique in its indications for CLKTx. In 13 of our recipients, the indication for liver transplant was inherited defects (Table 1). In other series, the majority of transplants have been done in adults with postnecrotic viral cirrhosis, often acquired while on hemodialysis. We encountered rare causes of hepatic failure, such as Alagille syndrome (congenital paucity of interlobular bile ducts with malformation of the pulmonary artery) and type I glycogenosis. We also encountered several cases of alpha 1-antitrypsin deficiency, which most likely caused both hepatic and renal failure. The association between glomerulonephritis and alpha 1-antitrypsin deficiency causing liver failure is well documented [1, 9, 13]. Davis et al. found a high incidence (37 %) of membranoproliferative glomerulonephritis (MPGN) and focal segmental MPGN in children with alpha 1-antitrypsin deficiency (genotype PiZZ) and liver disease [1]. They recommended native kidney biopsies and creatinine clearance monitoring as part of the pretransplant work-up for children referred for liver transplantation who have alpha 1-antitrypsin deficiency. Our standard pretransplant work-up for such patients includes native kidney biopsies and creatinine clearance measurements. We have identified five children with biopsy-documented MPGN and extremely low creatinine clearance (one already on hemodialysis) and properly treated them with CLKTx. We currently consider for CLKTx patients with alpha 1-antitrypsin deficiency who are already on dialysis or who have biopsy-proven glomerulonephritis and a creatinine clearance below 40 cc/min.

Primary oxalosis is a very well-established indication for CLKTx. The European Study Group on Transplantation in Hyperoxaluria Type 1 recently analyzed the results of 22 CLKTx done in 14 European centers for this disease [14]. They showed that kidney survival rates are better after combined procedures than after kidney transplants alone. They recommended CLKTx for patients with a creatinine clearance below 25 cc/min in order to avoid, as much as possible, life-endangering systemic oxalosis (especially oxalate osteopathy and arteriopathy). The authors also support liver transplant alone in patients with decent renal function as long as the diagnosis is unequivocally established by liver biopsy with measurement of alanine glyoxylate aminotransferase activity in the specimen. A policy of early liver transplantation is also supported by Watts et al. [14]. In their experience, a prolonged period of renal failure in patients with systemic oxalosis is a very poor prognostic indicator.

Our results in three CLKTx recipients with type 1 hyperoxaluria have been excellent; all of the grafts are currently functioning, and recurrent oxalosis of the renal graft has not been documented. Our most recent recipient was 8 months old at the time of the transplant and weighed 7.5 kg; to our knowledge, he is the youngest and smallest CLKTx recipient.

In summary, we support a liberal use of CLKTx for patients with chronic renal failure who need a liver transplant. It is particularly important for pediatric patients who otherwise would have no chance for normal physical and mental development.

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