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Combined liver-kidney transplantation: long-term follow up in 18 patients

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Abstract Since August 1992, 18 patients underwent combined liver and kidney transplantation. Eight patients had lymphocytotoxic antibodies pretransplant and 5 of these patients (27.7%) had a positive crossmatch. Fifteen patients received cyclosporine-based immunosuppression and 3 patients were treated with a tacrolimus-based immunosuppressive protocol. One patient died in the postoperative course due to intractable bleeding episodes after 96 days and one kidney graft was lost due to technical complications. The 1-year survival rate of patients with combined transplantation was 95% vs 87% in patients with liver transplantation alone. None of the patients with a positive crossmatch experienced a hyperacute rejection of the kidney. The long-term patient and graft survival was not impaired in patients with a positive crossmatch. These results suggest that combined liver-kidney transplantation is a safe treatment for end-stage liver and renal disease. A positive crossmatch or positive lymphocytotoxic antibodies are not contraindications for a combined transplantation.

Key words Combined liver-kidney transplantation · Positive crossmatch · Lymphocytotoxic antibodies · Long-term follow up

Introduction

Kidney or liver transplantation are well-established therapeutic procedures for end-stage liver and renal diseases. A number of liver transplant candidates have pre-existing renal failure either due to chronic renal disease, acute renal failure (ARF) or hepatorenal syndrome (HRS). While recovery from ARF and HRS after successfuly liver transplantation can be expected [1, 2], for patients with chronic renal disease or with enzymatic inherited defects of the liver leading to renal failure, simultaneous transplantation of these organs may be the only therapeutic option. The first published report of combined liver and kidney transplantation (CLKTx) was in 1984 by Margreiter et al. [3]. At this time chronic renal disease was seen as a contraindication to liver transplantation. The purpose of this study was to evaluate the long-term patient and graft survival after CLKTx with special regard to the protective effect of a liver graft on the kidney, HLA matching, pre-existing lymphocytotoxic antibodies, and a positive crossmatch.

Patients and methods

Between August 1992 and June 1997, 18 patients underwent CLKTx at our institution. Six recipients had a prior kidney transplantation which failed due to chronic rejection and they were retransplanted. Table 1 summarises the diagnosis of hepatic and renal failure and the characteristics of the 18 simultaneous transplanted patients. Six patients underwent CLKTx due to polycystic liver and kidney disease. Six patients acquired a hepatitis virus (2 HCV, 4 HBV) with progressive liver failure and renal insufficiency due to glomerulonephritis. Two patients suffered from cryptogen cirrhosis combined with diabetic nephropathy or glomerulonephritis. Four patients had primary hyperoxaluria type 1, a metabolic deficiency based in the liver with nephrocalcinosis. The median age of

Table 1 Combined liver-kidney transplant recipients, characteristics (*Tx* Transplant)

Patients	Age (years)	Sex	Year of Tx	Indication for kidney Tx	Indication for liver Tx	Kidney	Dialysis
1	50	M	1992	Pyelonephritis	Hepatitis C	–	5.75
2	55	F	1992	Polycystic disease	Polycystic disease	–	0.3
3	49	M	1993	Polycystic disease	Polycystic disease	–	0.6
4	27	M	1993	Primary oxalosis	None	–	5.5
5	56	F	1993	Diabetic nephropathia	Cryptogen cirrhosis	–	0.2
6	31	M	1994	MPGN	Cryptogen cirrhosis	–	–
7	25	F	1994	Primary oxalosis	None	+	4
8	23	M	1994	Primary oxalosis	None	–	5
9	58	M	1994	Polycystic disease	Polycystic disease	–	–
10	58	F	1994	Polycystic disease	Polycystic disease	–	13
11	53	F	1994	Polycystic disease	Polycystic disease	–	–
12	47	M	1995	Pyelonephritis	Hepatitis C	+	2.2
13	21	M	1995	Primary oxalosis	None	–	0.75
14	55	M	1995	Pyelonephritis	Hepatitis B	+	0.3
15	50	M	1996	MPGN	Hepatitis B	+	0.9
16	56	F	1996	Polycystic disease	Polycystic disease	–	1.25
17	54	M	1997	Pyelonephritis	Hepatitis B	+	7.8
18	40	F	1997	Pyelonephritis	Hepatitis B	+	0.2

patients was 50.7 ± 3.1 years and the male : female ratio was 11 : 7. All patients received a simultaneous liver and kidney transplantation utilizing organs from the same donor. The criteria used for the selection of the donors was ABO compatibility and avoidance of severe size discrepancies.

HLA matching of all donors was done by serology at the donor centers and most of the donors were retyped at the Eurotransplant Reference Laboratory in Leiden. Recipient typing was done in Virchow Clinics [4]. There was no attempt to HLA match donors with the recipients. The match grades are shown in Table 2. For the cytotoxic crossmatch, recipient sera were obtained immediately prior to transplantation. The crossmatch between the donor's isolated T- or B-lymphocytes and the recipient's sera was performed by a standard microcytotoxicity test at 22 and 37 °C. In the case of a positive crossmatch, the sera were treated with dithiothreitol to inactivate IgM antibodies. The reaction was defined as positive when there was more than 20% cell death. The panel reactive antibodies (PRA) assay was performed by standard lymphocytotoxic assay using commercial frozen cell trays for class I antigens. A positive reaction was defined when lymphocytotoxicity was greater than 20%. Five patients (27.7%) had a positive T-cell crossmatch. Eight patients had PRA of the IgG class.

Operative technique

Liver transplantation (OLT) was performed using standard techniques as described before [5] with side to side anastomosis of the bile duct. The kidney was implanted after the OLT through a separate lower abdominal incision and placed retroperitoneally.

Immunosuppression

Fifteen patients were treated with a cyclosporine (CsA)-based immunosuppressive protocol consisting of CsA, prednisolone, azathioprine, and 7 days induction therapy with antithymocyte globulin (ATG) in 12 patients and an anti-interleukin-2 receptor antibody in 2 patients. One patient had CsA triple therapy including CsA, prednisolone, and mycophenolate mofetil. Three patients were treated with a tacrolimus (FK506)-based immunosuppression protocol. One patient had FK506 quadruple therapy, consisting of FK506 prednisolone, azathioprine, and a 7 day induction therapy with ATG. Two patients were given a FK506 dual therapy with FK506 and prednisolone. CsA was started directly postoperatively at a dose of 1–2 mg/kg body weight intravenously every 12 h, and oral administration was started as soon as possible. The dose was adjusted according to whole blood levels measured with a polyclonal FPIA (TDX-Assay, Abbott) to achieve levels between 600–900 ng/ml in the early period after transplantation and 300–400 ng/ml thereafter. FK506 was administered orally from the first day at a dose of 0.05–0.1 mg/kg body weight, and levels were maintained at 10 ng/ml (determined by IMX-Assay). Steroids consisted of 500 mg intravenously prior to reperfusion of the liver graft and 500 mg intravenously directly after transplantation, followed by prednisolone started at 50 mg/day and tapered to 20 mg/day in 1 week.

For all 18 patients a liver biopsy was routinely performed on postoperative day (POD) 7, then after 1, 3, and 5 years by protocol and when clinically indicated. A kidney graft biopsy was done in cases of a significant rise in creatinine. If rejection in either graft was histologically confirmed, the treatment consisted of a steroid bolus therapy (methylprednisolone 500 mg intravenously, daily for 3 days). Steroid-resistant rejections were treated with the murine monoclonal antibody OKT3 (Ortho Pharmaceuticals), 5 mg for 5 days.

Results

Transplant data

The median cold ischemia time of the liver and kidney was 7.9 ± 0.6 and 11.7 ± 0.7 h, and the median warm ischemia time was 58 and 30 min, respectively. Intraoperative blood replacement consisted of a median of 9 ± 1.65 units of red packed cells and 10 ± 1.8 units of fresh frozen plasma.

Table 2 HLA matches

Patients	HLA-A	HLA-B	HLA-DR
1	1	0	1
2	1	0	0
3	0	1	2
4	1	0	0
5	1	0	1
6	1	0	0
7	0	0	0
8	0	0	0
9	1	0	1
10	1	0	0
11	0	0	1
12	2	1	1
13	1	0	0
14	1	0	0
15	1	1	1
16	0	0	2
17	0	0	0
18	0	0	1

Early graft function

All of the liver grafts had primary function. Three patients required supportive hemodialysis after transplantation for several days (1–14 days) until renal function recovered. Three patientss transplanted for primary hyperoxaluria were treated with hemodialysis for 30–60 days to prevent oxalate accumulation in the grafted kidney [6]. The other patients had good function of the kidney graft directly after transplantation and normal values of serum creatinine concentration within the 2nd postoperative week. The median stay in the intensive care unit following transplantation was 24 ± 6 days.

Technical complications

One patient died due to intractable bleeding episodes after 96 days, following nephrectomy of the graft on the 29th POD and several surgical revisions. The cause of these disseminated bleedings remained unclear. Another patient with severe oxalosis lost the kidney graft due to technical problems on the 3rd POD; he underwent kidney retransplantation 6 weeks later. Five patients had to be reoperated on due to bleeding complications in the early posttransplant course.

Rejection episodes

Despite a positive crossmatch and/or positive lymphocytotoxic antibodies in 5 and 8 patients, respectively, no hyperacute rejection of the kidney or liver graft occurred. All patients with a positive crossmatch converted to a negative crossmatch within the 1st week after transplantation. In 2 out of 8 patients with lymphocytotoxic antibodies prior to transplantation, lymphocytotoxic antibodies remained positive in the long-term follow up (Table 3). Nine patients experienced acute rejection episodes of the liver. A slightly higher incidence of acute rejection episodes of the liver graft was found in patients with a positive crossmatch than in patients with a negative crossmatch (3/5 = 60% vs 5/13 = 39%). Five patients had a steroid-resistant rejection of the liver graft, 2 of them with a positive crossmatch. Four underwent successful OKT3 treatment and 1 patient had FK506 rescue therapy. Overall only 1 patient had an acute rejection episode of the kidney graft; this patient had a positive crossmatch and was responding to steroids.

Long-term graft function

In the 17 surviving patients liver function has been excellent. Two patients developed a hepatitis C reinfection and were treated with ribavirin and interferon. One patient had an acute rejection episode of the liver graft 2 years after transplantation and was successfully treated with steroids. The long-term kidney function of the patients with primary hyperoxaluria and those with other indications for combined transplantation are shown in Fig. 1. The patients with primary hyperoxaluria had higher levels of creatinine in the long-term follow up compared to patients with other indications, despite supportive hemodialysis for up to 60 days after transplantation to prevent the recurrence of oxalate deposits in the kidney graft. None of the patients had to be readmitted to hospital due to complications of the kidney transplant. The 1- and 3-year survival of patients who underwent combined transplantation was 95% versus 91% und 87% in patients with liver transplantation alone. In 2 patients lymphocytotoxic antibodies were present in the long-term follow-up. Despite the higher incidence of acute rejection episodes of the liver graft, the long-term patient and graft survival is not impaired in patients with a positive crossmatch and/or lymphocytotoxic antibodies.

Discussion

Liver or kidney transplantation are well established and successful therapeutic procedures in end-stage liver or renal disease. A number of patients have a combined end-stage liver and kidney disease, either due to polycystic liver and kidney disease, metabolic disease (primary hyperoxaluria type I), or acquired hepatitis during hemodialysis. In 1984 Margreiter et al. [3] published the first report about CLKTx. At this time advanced renal disease was seen as a contraindication for a liver transplantation.

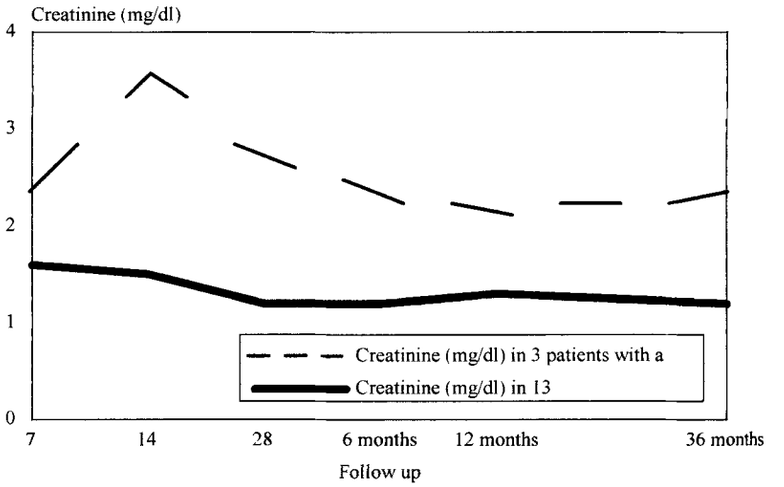

Fig. 1. Creatinine levels during long-term follow up

Liver transplant candidates with pre-existing kidney disease have to be evaluated carefully to distinguish those with chronic renal failure from those with HRS or ARF. The recovery from HRS after successful liver transplantation is documented, as well as a recovery from ARF postoperatively in most of the cases [2, 7]. If progressive renal disease can be ascertained before livewr transplantation, combined transplantation should be considered. Numerous reports from kidney transplantation studies have demonstrated that compatibility in crossmatch and HLA match is associated with higher graft survival [8]. Transplantation across a positive crossmatch is usually associated with predictable hyperacute rejection of a kidney graft [9]. Only a few cases of hyperacute rejection of a liver graft are reported [10]. The effect of HLA incompatibility or of donorspecific positive lymphocytic erossmatch on patient and graft survival are discussed controversially [11–13]. However in CLKTx from the same donor, the liver is reported to protect the kidney from hyperacute rejection despite a positive crossmatch [1, 14–16]. Additionally there is evidence for a decreased number of rejection episodes of the kidney grafts, though this protective effect does not extend to the liver [1, 16, 17].

In our study we could demonstrate that CLKTx is a safe procedure for patients with end-stage liver and kidney disease. Survival data of patients with CLKTx are similar to patients with liver transplantation alone. There was no difference in the number of acute cellular rejection episodes of the liver graft in patients with CLKTx compared to patients with only a liver transplant, but there was a low frequency of renal rejection episodes of the simultaneously grafted kidney. The long-term graft and patient survival of patients with a positive crossmatch was similar compared to patients with a negative crossmatch. None of the patients with a positive crossmatch developed a hyperacute rejection.

The exact mechanism of the resistance of the liver to hyperacute humoral rejection and its protective ability on other grafts remains unexplained. One explanation might be the unique architecture of the liver with a double blood supply and a less vasoreactive venous system, but this would not explain the protection of the donor kidney [18]. Clinical experience and experimental animal models have demonstrated that the liver allograft seems capable not only of resisting hyperacute rejection, but also of acting as a sump to absorb antibodies from the circulation [19, 20]. Additionally it has been postulated that donor soluble HLA class I antigens, exported from the liver graft, bind to antibodies and these complexes are removed by the reticuloendothelial system [21, 22].

The present report of 18 patients lends further support to the notion that combined transplantation is well

Table 3 Rejection episodes depending on positive crossmatch or lymphocytotoxic antibodies

	Acute rejection, liver	Acute rejection, kidney	Steroid-resistant rejection
Positive crossmatch (n = 5)	3 (60%)	1 (20%)	2 (40%)
Negative crossmatch (n = 13)	5 (39%)	0	3 (23%)
Positive lymphocytotoxic antibodies (n = 8)	3 (37.5%)	1 (12.5%)	2 (25%)
Negative lymphocytotoxic antibodies (n = 10)	5 (50%)	0	4 (40%)

tolerated, despite an intentional lack of attention to the degree of HLA matching. Additionally a positive crossmatch is no contraindication for CLKTx. This improved tolerance allows for greater accessibility to donor organs. Furthermore not having to wait for the results of donor/recipient crossmatching can considerably shorten to cold ischemia time and might improve the chances of a favorable outcome.

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