The Renal-Sparing Efficacy of Basiliximab in Adult Living Donor Liver Transplantation

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The purpose of this study is to find out whether basiliximab administration will improve postoperative renal function by delaying the start of tacrolimus and decreasing of dosage requirement for tacrolimus in adult living donor liver transplantation (LDLT). Forty-five adult LDLT recipients were enrolled in the study. The induction group (n = 27) was given basiliximab 20 mg on days 0 and 4; tacrolimus administration was delayed until renal function improved. The control group (n = 18) did not receive basiliximab; tacrolimus was given on the first postoperative day. Trough levels of tacrolimus in the induction and control groups were aimed to be maintained at 5 - 10 ng/ml and 10-15 ng/ml during the first week after transplant, respectively. The median follow-up was 22 months (range 10-34 months). The preoperative conditions were poorer in the induction group (Child C, 56% vs. 33%, $P = 0.01$; UNOS 2a, 15% vs. 0%, $P = 0.02$). The intraoperative blood loss was also higher in the induction group than in the control group (median 2,180 ml vs. 495 ml, $P < 0.01$). The median delay in tacrolimus administration in the induction group was 36 hours (range 24-108 hours). Serum creatinine levels at second and third postoperative months were significantly lower in the induction group. The creatinine clearance rate in the induction group was higher at the third month posttransplant (median 72 vs. 57 ml/minute, $P = 0.04$). The incidence of renal insufficiency was significantly lower in the induction group at the third month posttransplant (26% vs. 67%, $P < 0.01$). Blood cholesterol level at the sixth month posttransplant was lower in the induction group (median 152 vs. 196 mg/dl $P = 0.03$). The incidences of acute cellular rejection, bacteremia, and cytomegalovirus (CMV) infection were similar in both groups. In conclusion, for pretransplant critical patients with more intraoperative blood loss, basiliximab induction could prevent early renal dysfunction by delaying the start of tacrolimus and reducing the dose requirement of tacrolimus without increasing graft rejection and infection. Furthermore, it also improved renal function as well as lowered cholesterol levels within 6 months after transplantation. (*Liver Transpl 2005;11:1258-1264.*)

Living donor liver transplantation (LDLT), driven by organ shortage, has emerged as an effective therapy in the management of end-stage liver disease and has achieved excellent 5-year survival rates.[1,2] However, chronic renal dysfunction has become a recognized long-term complication after liver transplantation, resulting in significant morbidity and mortality.[3,4] Studies report that postoperative acute renal failure is one of the risk factors for chronic renal failure. In our previous study, we reported that the incidences of acute renal failure and hospital-acquired renal insufficiency were 8.7% and 19.3%, respectively, in patients undergoing LDLT.[5,6] The etiologies of early posttransplant renal dysfunction are multifactorial including pretransplant hepatorenal syndrome, intraoperative massive blood loss, and posttransplant drug-related nephrotoxicity such as antibiotics and immunosuppressive agents.

Calcineurin inhibitor (CI), a key component in immunosuppressive regimens for patients undergoing transplantation, has been implicated as a principal cause of posttransplant renal dysfunction, leading to severe tubular atrophy, interstitial fibrosis, and focal hyalinosis of small arteries and arterioles.[7]

Basiliximab, one of the interleukin-2 receptor antibodies (IL-2Rab), is a chimeric anti-CD25 monoclonal antibody that blocks the high-affinity interleukin-2 receptor expressed on alloantigen-reactive T lymphocytes, hence, impeding the immune cascade that elicits acute cellular rejection in solid-organ transplantation.[8-10] Some studies attempted to propose new protocols by adding mycophenolate mofetil (MMF) and IL-2Rab without the initial use of CI to avoid consequent side effects but proved ineffective due to higher steroid-resistant rejection.[11] This study was done to find out whether basiliximab administration will cause delay in starting tacrolimus immunosuppression and

Abbreviations: LDLT, living donor liver transplantation; CMV, cytomegalovirus; CI, calcineurin inhibitor; IL-2Rab, interleukin-2 receptor antibody; MMF, mycophenolate mofetil.

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Received February 3, 2005; accepted May 23, 2005.

Presented at the American Transplant Congress, Boston, 2004.

Supported partly by project grant NHRI-EX 93-9228SP from the National Health Research Institutes, Taiwan.

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Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/lt.20520

decrease its dosage requirement in adult LDLT recipients through improvement in postoperative renal function.

Patients and Methods

Forty-seven consecutive adult LDLT were performed at the Chang Gung Memorial Hospital, Kaohsiung, Taiwan, from February 2001 to December 2003. Forty-five recipients were enrolled in the prospective, open-label, nonrandomized study. These patients were assigned into either the basiliximab group (induction group) or the conventional immunosuppression group (control group). We were inclined to use basiliximab induction in more seriously ill patients and in patients with greater blood loss during operation. Two patients were excluded because other immunosuppressants were used.

The operative procedure for donor and recipient are described in detail elsewhere.[12,13] All patients were ABO compatible and did not undergo venovenous bypass during cavohepatic vein anastomosis. The intraoperative management including fluid resuscitation, blood transfusion, and maintenance of blood pressure during operation was maintained by the same anesthesia team.[14] Postoperatively, prostaglandin E1 (0.01 μg/kg/hr) was routinely administered for two weeks and heparin was started once bleeding parameters were acceptable. Prophylactic antibiotics included ampicillin (50 mg/kg/6 hours) and ceftazedine (30 mg/kg/8 hours). Antibiotic regimens were also tailored according to preoperative cultures. Nephrotoxic antibiotics such as aminoglycosides have never been used. Both groups were administered fluconazole (4 mg/kg/day) to prevent fungal infection for three months and trimethoprim-sulfamethoxazole against pneunocystis carinii. For prevention of cytomegalovirus infection (CMV), hyperimmune CMV globulin (cytotec 1 ml/kg/week) and ganciclovir (5 mg/kg/twice daily) were given routinely for one month. Hepatitis B immunoglobulin (HBIG) and Lamivudine (100 mg/day, Glaxo Wellcome, Middlesex, UK) were routinely used to prevent hepatitis B recurrence in recipients with hepatitis B; Lamivudine was also given to prevent de novo hepatitis B if the grafts were from donors with hepatitis B core antibody positive. Recurrent hepatitis C was not treated. Patients with allograft dysfunction or suspected rejection underwent liver biopsies. Routine liver biopsies were not performed. The median follow-up was 22 months (range 10-34 months).

In the conventional group, oral tacrolimus (0.15 mg/kg/day, Prograf, Fujisawa, Kerry, Ireland) was started within 24 hours postoperatively. Dosage adjustments were based on achieving a trough level of 10-15 ng/ml in the first week. Methylprednisolone (20 mg/kg IV) was administered intraoperatively followed by 2 mg/kg/day IV administration posttransplantation and gradually tapered to oral prednisone (20 mg/daily) on postoperative day 7 until a minimum dose of 5 mg daily was achieved. Patients were started to be weaned off steroids three months after transplantation unless these patients have had rejection episodes or if the indication for transplantation is autoimmune disease. MMF (CellCept, Roche, Humacoa, Puerto Rico) was administered with a starting dose of 1-2 gm/day in select patients for additional immunosuppression.

In the induction group, basiliximab (Novartis Pharma AG, Basle, Switzerland) 20 mg was administered 6 hours after portal vein reperfusion (day 0) and on postoperative day 4. Tacrolimus administration was delayed until renal function improved as evidenced by adequate urine output (1 ml/kg/hour) and decreasing serum creatinine levels. Upon administration of tacrolimus, the dose was adjusted to target trough levels of 5-10 μg/ml during the first week. The dosages of steroids and MMF were identical to those in the control group with the exception that the inductive dose of the steroid was reduced combined with faster and earlier weaning off in the latter period.

The demographic data, operative outcomes, and postoperative clinical parameters in both groups were compared. Acute renal failure was defined as a $\geq$0.5 mg/dl increase in serum creatinine over the baseline value, an increase of $>$50% over the baseline value, a reduction in the calculated creatinine clearance of 50%, or a decrease in renal function requiring dialysis.[15] The creatinine clearance rate was calculated using the Cockcroft-Gault formula. Post-liver transplantation diabetes mellitus was defined as hyperglycemia requiring treatment with insulin or oral hypoglycemic agents.[16]

All continuous data were expressed with a median and statistical analysis of data was performed using the Mann-Whitney U test when comparing two groups. Nominal data were compared by the chi-square test or Fisher's exact test when appropriate. Continuous data repeated tests were compared with repeated measurement of ANOVA, and post hoc multiple comparisons were performed by Bonferroni test. Survival rate was calculated using Kaplan-Meier. Significance was considered with P values < 0.05.

Results

The baseline demographics, indications for liver transplantation, and clinical parameters are described in Table 1. There were no significant differences between induction and control groups based on age, gender, and indications for transplantation. The preoperative serum creatinine levels and presence of diabetes mellitus and hypertension were also similar in both groups. The patients in the induction group had poor preoperative conditions with a greater number of recipients in Child C (56% vs. 33%, $P = 0.01$) and United Network Organ Sharing (UNOS) 2A status (15% vs. 0%, $P = 0.02$) than those in the control group. The MELD scores were also higher (median 14 vs. 10, $P = 0.047$) in the induction group than in the control group. The intraoperative parameters were similar in both groups except blood loss and requirement of blood transfusion. The intraoperative blood loss was significantly higher in

Table 1. Demographics, Indications for Liver Transplantation, and Clinical Parameters for Induction and Control Groups

	Induction (n = 27)	Control (n = 18)	*P* Value
Age	49.3 (34–61.5)	45.5 (25.6–60.5)	NS
Gender (female/male)	5/22	4/14	NS
Body weight (kg)	63.5 (48.8–83.5)	64 (40–86.5)	NS
Diagnosis			
Alcoholic liver disease	2	0	
Hepatitis	21	15	
With tumor	10	10	
Without tumor	11	5	
Primary biliary cirrhosis	3	3	
Cryptogenic	1	0	
Preoperative status			
Child			
A	1	7	
B	11	5	0.01
C	15	6	
UNOS			
2a	4	0	
2b	15	17	0.02
3	8	1	
MELD score	14 (6–40)	10 (6–30)	0.047
Diabetes mellitus	1	0	NS
Hypertension	1	0	NS
Graft weight (gm)	716 (437–960)	686 (400–832)	NS
GRWR (%)	1.10 (0.77–1.66)	1.08 (0.76–1.27)	NS
Blood loss (ml)	2,180 (100–8,050)	495 (115–4,140)	<0.01
Blood transfusion*			
Yes	80.6%	19.4%	<0.01
Red blood cell (gm)	1,908 (0–7,925)	0 (0–2,265)	<0.01
Whole blood (gm)	0 (0–625)	0	0.46
Platelet (gm)	0 (0–250)	0	0.056
Albumin (ml)	2,400 (750–4,000)	1,500 (400–3,500)	0.01
Cold ischemia time (minutes)	68 (35–119)	68 (50–89)	NS
Warm ischemia time (minutes)	50 (31–115)	50 (36–79)	NS
P-A reperfusion time (minutes)	83 (43–2,400)	86 (54–271)	NS
Surgical time (minutes)	684 (535–1,069)	669 (490–786)	NS

Abbreviations: UNOS, united network organ sharing; MELD, model for end-stage liver disease; GRWR, graft recipient weight ratio; P-A reperfusion time, portal—artery reperfusion time; NS, no significance.
* Intraoperative blood transfusion.

the induction group compared with the control group (median 2,180 vs. 495 ml, $P < 0.01$). The percentage of the requirement of intraoperative blood transfusion in the induction group was 80.6%, significantly higher than 19.4% in the control group ($P < 0.01$).

The operative and nonoperative complications are shown in Table 2. The operative complications included one hepatic vein obstruction, two biliary strictures and one peptic ulcer perforation in the control group, and two patients with postoperative bleeding requiring relaparotomy in the induction group. The one-year Kaplan-Meier graft and patient survivals were 100%. One patient in the control group died from recurrent hepatocellular carcinoma more than one year after transplantation, and one patient from the induction group died from recurrent hepatitis C two years after transplantation.

The sequential dosages of immunosuppression and trough levels of tacrolimus are shown in Table 3. The median delay in starting tacrolimus was 36 hours (range 24-108 hours). The dosages and trough levels of tacrolimus were lower within the first month posttransplant in the induction group. There were similar dosages for MMF in both groups. The cumulative dosages of steroid given were significantly lower through the second to sixth month posttransplant in the induction group.

Table 2. Operative and Non-operative Complications in Induction and Control Groups

	Induction (n = 27)	Control (n = 18)	*P* Value
Surgical complication			
Hepatic artery thrombosis	0	0	
Portal vein thrombosis	0	0	
Hepatic vein obstruction	0	1	NS
Biliary complication	0	2	NS
Relaporotomy	2 bleeding	1 PPU	
Infection			
CMV	0	2	NS
Bacteremia	2	1	NS
Drain infection	7	2	NS
Rejection (6 months)	3	5	NS
Post-transplant DM	1	2	NS
Renal insufficiency	7	12	0.007

Abbreviations: CMV, cytomegalovirous; DM, diabetes mellitus; NS, no significance; PPU, perforation of peptic ulcer.
* Compared creatinine levels between third month post-transplant and preoperative.

The sequential renal function tests were shown in Table 4. The serum creatinine levels were significantly higher at the second, third, and sixth months posttransplant than those taken preoperatively in both groups. We further found that the serum creatinine levels at the second ($P = 0.04$) and third ($P < 0.01$) months postoperatively were lower in the induction group compared with those in the control group (Fig. 1). The creatinine clearance rate in the induction group was also at the second month posttransplant (median 72 vs. 57 ml/minute, $P = 0.04$). The incidence of renal insufficiency at the third month posttransplant was significantly lower in the induction group (26% vs. 67%, $P < 0.01$), although the incidence was not significantly lower with the value taken at the first month posttransplant (39% vs. 15%, $P = 0.08$).

The acute rejection rates were 11% and 28% ($P = 0.12$) in the induction and control groups at 6 months, respectively. There were similar incidences for bacteremia, CMV infection, and drain-related infection in both groups. The incidence of posttransplant new-onset diabetes mellitus was also similar. At 6 months posttransplant, the median serum cholesterol level was 152 mg/dl in the induction group; this was significantly lower than the control group with 196 mg/dl ($P = 0.03$). The serum triglyceride levels were comparable at 6 months in the two groups (median 119 vs. 103 mg/dl, $P = 0.32$).

Table 3. Dosages and Levels of Immunosuppressants in Induction and Control Groups

		Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 24
Tacrolimus dosage (mg/day)	Induction	6.0 (2–14)	6.0 (1.5–12)	6.5 (1–12)	6.0 (2–12)	5.5 (1.5–11)	4.5 (1.25–10)	5.0 (1–8)
	Control	5.25 (1–11)	8.0 (1.5–17)	9.0 (2–15)	5.25 (2.5–12)	5.0 (1.5–12)	4.25 (1.5–11)	3.5 (1–10)
	P value	0.27	0.01	0.18	0.83	0.24	0.62	0.38
Tacrolimus trough level (ng/ml)	Induction	11.1 (6.1–18.8)	10.1 (4.3–15.5)	8.0 (5.0–16.8)	8.2 (4.1–15.2)	5.7 (2.9–16.7)	6.1 (2.1–10.4)	4.7 (0.9–10.6)
	Control	12.7 (6.3–24.5)	11.6 (8.7–17.7)	13.5 (9.8–18.8)	11.8 (5.9–19.9)	8.2 (3–13.7)	9.05 (1.5–14.8)	5.6 (2.6–16.6)
	P value	0.01	0.02	<0.01	<0.01	0.13	0.01	0.54
MMF dosage (gm/day)	Induction	0.25 (0–1.5)	1.0 (0–2.0)	1.0 (0–2.0)	1.0 (0–1.5)	1.0 (0–1.5)	1.0 (0–1.5)	1.0 (0–1.5)
	Control	0 (0–1.0)	0.625 (0–2.0)	0.75 (0–2.0)	1.0 (0–2.25)	1.0 (0–2.0)	1.375 (0–2.0)	1.0 (0–2.0)
	P value	0.02	0.33	0.34	0.55	0.18	0.16	0.90
Cumulative steroid dosage (mg)	Induction					1,510 (1,175–2,964)	1,785 (1,325–3,244)	2,120 (1,552–3,729)
	Control					2,543 (1,957–3,240)	2,883 (2,110–3,480)	3,401 (2,370–4,240)
	P value					<0.01	<0.01	<0.01

Abbreviation: MMF, mycophenolate mofetil.

Table 4. Serum Creatinine Levels and Creatinine Clearance Rate 6 Months After Transplantation in Induction and Control Groups

		Pre-op	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 24
Creatinine level (mg/dl)	Induction	0.8 (0.5–3.0)	0.80 (0.5–1.5)	0.9 (0.4–2.4)	0.9 (0.5–1.7)	1.0 (0.6–1.6)	1.00 (0.8–1.5)	1.10 (0.7–1.8)	1.10 (0.7–1.8)
	Control	0.90 (0.6–1.8)	0.9 (0.5–1.10)	0.8 (0.6–1.3)	1.0 (0.8–1.8)	1.2 (0.7–1.9)	1.35 (0.8–2.1)	1.45 (1.1–2.0)	1.25 (1.0–1.7)
	P value	0.92	0.14	0.74	0.12	0.24	<0.05	<0.01	0.09
Creatinine clearance rate (ml/minute)	Induction						69 (39–101)	72 (37–104)	62 (37–109)
	Control						62 (27–100)	57 (22–88)	60 (26–97)
	P value						0.34	0.04	0.27

Abbreviation: pre-op, preoperative.

Discussion

Acute renal failure is identified as a risk factor for morbidity and mortality after liver transplantation. To avoid renal complications, several strategies have been developed to minimize risk factors causing acute renal failure, including renal-sparing immunosuppressant protocols and refinement of surgical technique.[17] Antimetabolites, such as MMF and azathioprine, have frequently been used in renal-sparing protocols, but it may take days or months for the immunosuppressive action to take effect. IL-2Rab, with its high specificity, low toxicity, and limited half-life, appears as an ideal agent for liver transplant recipients.[18,19]

The current study was performed to look into the potential benefits of improving renal function by basiliximab through delay in tacrolimus administration and decreasing dosage requirement for tacrolimus. The preoperative renal functions and risk factors such as diabetes mellitus and hypertension contributing to renal dysfunction were similar. The intraoperative management, including fluid resuscitation, blood transfusion, and maintenance of blood pressure, are maintained by the same team of anesthesiologists. Moreover, the dosages of MMF, another renal-sparing immunosuppressant, are similar throughout the study. The complications that often worsen renal function are also not different in both groups.

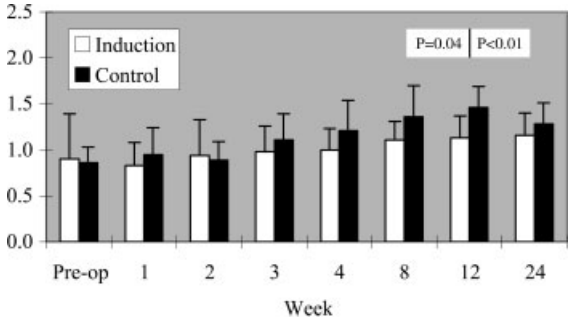

Figure 1. Serum creatinine levels from the preoperative to 6-month posttransplant period in induction and control groups. The serum creatinine levels were significantly higher at the second, third, and sixth months posttransplant than those preoperative in both groups. Preop vs. week 8, $P < 0.01$; preop vs. week 12, $P < 0.01$; preop vs. week 24, $P < 0.01$ in the induction group. Preop vs. week 8, $P < 0.05$; preop vs. week 12, $P < 0.01$; preop vs. week 24, $P < 0.01$ in the control group. The serum creatinine levels at the second ($P = 0.04$) and third ($P < 0.01$) months posttransplant were lower in the induction group compared with those in the control group. Compared with repeated measurement of ANOVA and post hoc multiple comparisons were performed by Bonferroni test. Preop, preoperative.

The patients in the induction group were in poor preoperative condition and consequently experienced more blood loss during the operation, which is a risk factor for acute renal failure. However, our study shows that renal function is significantly better at both the second and third months posttransplant in the induction group with the incidence of renal insufficiency significantly lower three months after transplant (26% vs. 67%, $P < 0.01$). Furthermore, renal function also deteriorates at the second, third, and sixth months posttransplant in both groups. The etiology of renal insufficiency is multifactorial for the majority of patients. The renal insufficiency derives mainly from ischemic renal damage and tacrolimus-related toxicity during the first two months posttransplant. Nevertheless, the authors believed that the differences in creatinine that occurred later (8-24 weeks) were due to the toxicity of relative higher-level CI in the control group because all recipients have already been well. The addition of basiliximab provides a sufficient window for renal function to recover and contributes mostly to short-term benefits in renal improvement for at least 6 months, especially for marginal renal function recipients.[20] Because the effects of IL-2Rab in reducing CD25+ cells last for 4-6 weeks after liver transplant, the trough levels of tacrolimus were significantly lower in the early period after

transplant.[21] Therefore, the benefits provided by basiliximab in renal function beyond 6 months after transplant became insignificant. Our study is similar to that of findings by Echoff et al., who reported that IL-2Rab induction therapy can facilitate improvement in renal function for critically ill patients (UNOS status 1 and 2a).[22] Heffron, however, reported that renal function did not improve in pediatric patients. The reason could be that the problems of renal dysfunction in pediatric patients are not as serious as in adults.[23]

As to acute rejection rate, most studies report that IL-2Rab induction can reduce the acute rejection rate in both renal and liver transplantation. Our study seems to show similar incidence rates for acute rejection 6 months after transplant in both groups. This finding may be due to the fact that the study is not randomized, and we purposely reduced the dose of tacrolimus. Some studies indicate that IL-2Rab induction combined with MMF and steroids would safely delay administration of tacrolimus by one week after transplant and reduce the acute rejection rates during the 30-day posttransplant period in pediatric liver transplantation.[23] Although we did not delay tacrolimus administration to one week, our study shows that administration of tacrolimus can be delayed by as long as 48 hours and maintain it at lower trough levels during early posttransplant period.

The combination of more immunosuppressants can mean more risk for infection. Our study shows that the addition of IL-2Rab did not increase the risk of infection such as bacteremia, CMV infection, and drain-related infections. In other studies, basiliximab induction is used for early steroid withdrawal immediately after transplant in patients undergoing adult LDLT. The majority of these recipients have chronic hepatitis B or C with or without hepatocellular carcinoma and can benefit from this early withdrawal from steroid. Liu et al. proposed a protocol for basiliximab induction with early withdrawal from steroid and reduction in tacrolimus dosage use.[24] The incidence of acute rejection 6 months after transplant is similar in both groups, and the short-term results are promising. Although steroid withdrawal was not done early, the cumulative dosage of steroid is significantly lower in the induction group. This is due to the fact that we reduced the actual dosage on induction and withdrew the steroid rapidly on follow-up. Hyperlipidemia and hypertension have been reported in liver transplant recipients and contributed to an increased risk for ischemic heart disease and cardiovascular death.[25] Together with lower tacrolimus dose and early steroid withdrawal, serum cholesterol levels are found to be significantly lower in the induction group 6 months posttransplant.

The major limitations of the study are the nonrandomized selection of patients, the small number of patients in each group, and the relatively short follow-up. However, since the two groups of patients are comparable in demographics and clinical data and the study focused on early postoperative period, the authors believe that the findings presented in this study maybe valid as a clinical practice guideline.

In summary, the regimen described in this study can significantly improve renal function during the early postoperative liver transplant period. This is particularly beneficial in pretransplant liver patients with renal dysfunction. Moreover, the administration of basiliximab in adult LDLT can safely maintain lower tracolimus dosage at one month after transplantation with similar infection rates. Randomized studies and long-term follow-up are required to evaluate the effects and potential benefits of basiliximab in recipient patients developing chronic renal failure after liver transplantation.

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