Renal-sparing immunosuppressive protocol using OKT3 after liver transplantation: a 19-year single-institution experience

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Different renal-sparing immunosuppressive protocols have been used in liver transplantation. At our institution, muromonab-CD3 (OKT3) is used in patients with acute renal failure (ARF), along with a delay in starting a calcineurin inhibitor. This study was conducted to compare outcomes in liver transplant patients with ARF who received OKT3 and those who did not. From 1988 to 2007, ARF was present in 1685 of 2587 patients (65%). OKT3 was used in 109 patients (OKT3 group). The control group (1416 patients) received a low-dose calcineurin inhibitor. The OKT3 group was more critically ill. In spite of this, the OKT3 group patients who were on renal replacement therapy (RRT) achieved long-term survival similar to that of the control group on RRT. Among the patients who were not on RRT, the OKT3 group had a higher complete recovery rate, but this did not translate into improved long-term survival. Bacterial and fungal infections were more common in the OKT3 group; however, there was no increased risk of malignancy or death from hepatitis C recurrence. The use of OKT3 in patients with ARF allowed more critically ill patients on RRT to achieve survival rates similar to those of patients who did not receive OKT3.

Acute renal failure (ARF), also known as acute kidney injury, has been reported to occur in 14% to 94% of patients after liver transplantation (1–7). Such a wide range is attributed to the lack of a uniform definition of ARF. The risk factors for ARF include preexisting renal dysfunction, diabetes mellitus, extensive intraoperative blood loss, postoperative infection, and calcineurin inhibitor (CNI) nephrotoxicity. In addition to its inherent morbidity, ARF is a known risk factor for chronic kidney disease in liver transplant patients and is associated with decreased long-term survival (7, 8). The incidence of chronic kidney disease in liver transplant patients can be as high as 18% at 5 years (9). A recent study from our institution showed a higher incidence of sepsis and cardiovascular events in patients with ARF, providing a possible explanation for the decreased long-term survival in these patients (7).

Several factors may precipitate ARF in the posttransplant period. CNI nephrotoxicity plays a major role. Different CNI-sparing immunosuppressive regimens have been employed after liver transplantation to minimize further renal injury and to promote renal recovery. At our institution, muromonab-CD3

(OKT3) (Orthoclone, Ortho Biotech, Horsham, PA), a murine monoclonal antibody, is used as a renal-sparing protocol in the early postoperative period for patients with severe ARF. The aims of the study were 1) to review our institution's pattern of OKT3 use in patients with severe ARF; 2) to determine the potential benefits of OKT3 in renal recovery in the postoperative period; 3) to determine the impact on long-term survival and potential drawbacks associated with OKT3 use; and 4) to determine an optimal dose of OKT3 for renal recovery.

PATIENTS AND METHODS

Study design

This retrospective cohort study was conducted from the data obtained from the patient charts and from a prospectively maintained liver transplant database at the Simmons Transplant Institute. This study was approved by the institutional review board. The study was designed to compare outcomes between liver transplant patients with ARF who received OKT3 (treatment group) and those who did not (control group).

Inclusion and exclusion criteria

All patients who received primary liver transplantation at the Simmons Transplant Institute from 1988 to 2007 who had ARF were considered for the study. The patients who experienced ARF after retransplantation were excluded. The definition of ARF was adopted from the RIFLE criteria set by the acute dialysis qualitative initiative (10). Acute renal failure was defined as 1) preoperative creatinine (Cr) >1.5 times the baseline or 1.5 mg/dL (preoperative value obtained on the day of the operation); 2) postoperative Cr >1.5 times the baseline or 1.5 mg/dL; 3) postoperative glomerular filtration rate (GFR) <1.5 times the baseline value; or 4) a need for renal replacement therapy (RRT) (hemodialysis or continuous veno-veno hemodialysis) in the perioperative period (both preoperative and postoperative). The GFR was measured by Glofil-125 (sodium iodothalamate

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I-125) clearance. The treatment group was defined as patients who received OKT3 and a delay of CNI introduction while on OKT3. OKT3 was started at the discretion of the transplant surgeon and was administered to patients who had 1) the need for pretransplant RRT; 2) the need for posttransplant RRT; or 3) oliguric ARF posttransplant, defined as <400 cc per day of urine output for >48 hours. The control group was defined as all other liver transplant patients with ARF after their first liver transplant who did not receive OKT3 but were treated with low-dose CNI in the postoperative period.

A total of 2587 liver transplants were performed in the study period, and 1685 patients (65%) had ARF after transplant. Forty-three patients were excluded because they received OKT3 for reasons other than renal-sparing induction or they received other antibody therapy (e.g., Thymoglobulin) for renal preservation. The patients who received combined liver and kidney transplantation were also excluded, since their pattern of recovery from renal dysfunction would be different from that of patients who had ARF associated with liver transplantation alone. For the study, the control group consisted of 1416 patients and the OKT3 group consisted of 109 patients.

Administration of OKT3

OKT3 was given as an intravenous push at 5 mg per day on consecutive days. The therapy was monitored by absolute lymphocyte counts. The cumulative total dose was expressed as total dose in mg. The duration of therapy was determined by renal recovery at the discretion of the transplant surgeon. OKT3 therapy was stopped and a CNI was introduced when the patient displayed clinical parameters consistent with renal recovery, as defined by urine output >50 cc per hour and a decrease in serum Cr. The patients received cytomegalovirus (CMV) prophylaxis regardless of donor and recipient CMV status, with 2 to 5 mg/kg of intravenous ganciclovir daily, which was adjusted for renal dysfunction. The median cumulative dose was 50 mg (range, 20–80 mg), with a median duration of therapy of 10 days (range, 4–14 days).

Clinical endpoints

Four clinical endpoints were analyzed: 1) rates of renal function recovery; 2) incidence of acute cellular rejection; 3) incidence of infectious complications (bacterial, viral, and fungal); and 4) patient survival. The definition of renal recovery was adopted from the RIFLE criteria (10). For patients who were on RRT such as hemodialysis or continuous veno-veno hemodialysis before or after liver transplant, independence from these modalities was defined as a complete recovery. For patients who did not receive RRT, a complete recovery was defined as a return of serum Cr to a level <1.5 times their baseline value. Partial recovery was defined as a Cr level >1.5 times their baseline value. The patient was considered to have no renal recovery if he or she did not become independent from RRT, died in the early postoperative course while on RRT, or received a kidney transplant. GFR values were analyzed at evaluation for liver

transplant and at 3 months, 1 year, 2 years, and 5 years after liver transplantation.

Statistics

Statistical analysis was performed using SAS software, version 9.1.3 (SAS Institute, Cary, NC). Categorical data were analyzed with Fisher's exact test for 2 × 2 tables and the chi-square test for larger tables. Continuous variables were

Table 1. Demographic characteristics of liver transplant patients with acute renal failure who received OKT3 or low-dose calcineurin inhibitors (control)

Variable	Control (n = 1416)	OKT3 (n = 109)	P value
Recipient age (years)	51 (15–73)	48 (13–68)	0.005
Sex (M:F)	895:521 (63%:37%)	74:35 (68%:32%)	0.4
Etiology			0.2
Hepatitis C virus	530 (37%)	41 (38%)	
Laennec's	217 (15%)	18 (17%)	
Cirrhosis not otherwise specified	200 (14%)	17 (16%)	
Primary biliary cirrhosis	96 (7%)	5 (5%)	
Primary sclerosing cholangitis	59 (4%)	6 (6%)	
Hepatocellular carcinoma	6 (0.4%)	0 (0%)	
Others	308 (22%)	22 (20%)	
Model for End-Stage Liver Disease score	17 (6–40)	33 (8–40)	<0.0001
Donor age (years)	35 (4–82)	36 (11–79)	0.4
Preoperative labs			
International normalized ratio	1.4 (0.9–9.3)	1.8 (1–4.5)	0.0001
Bilirubin (mg/dL)	3.0 (0.2–66.7)	12.2 (0.7–53.8)	<0.0001
Albumin (mg/dL)	2.9 (1.4–6.6)	2.9 (1.3–4.8)	0.8
Aspartate transferase (U/L)	80 (9–6061)	101 (22–25406)	0.004
Cold ischemia time (hours)	8.3 (0.5–31)	8.3 (3–18)	0.2
Intraoperative blood products			
Red blood cells	4 (0–133)	8 (0–233)	0.0001
Fresh frozen plasma	5 (0–42)	9.5 (0–111)	0.0001
Platelets	1 (0–1500)	2 (0–80)	0.001
Cryoprecipitate	5 (0–300)	10 (0–60)	0.02
Length of stay (days)	13 (0–250)	23 (3–142)	<0.0001
Intensive care unit stay (days)	2 (0–196)	8 (1–92)	<0.0001
Patients on renal replacement therapy	94 (6.6%)	42 (38.5%)	<0.0001

Table 2. Demographic characteristics of liver transplant patients with and without renal replacement therapy who were treated with OKT3 vs low-dose calcineurin inhibitors (control)

Variable	Patients on RRT			Patients not on RRT		
	Control (n = 94)	OKT3 (n = 42)	P value	Control (n = 1322)	OKT3 (n = 67)	P value
Recipient age (years)	52 (18–67)	51 (25–68)	0.8	51 (15–73)	47 (13–67)	0.001
MELD score	26 (7–40)	34 (11–40)	0.0009	17 (6–40)	33 (8–40)	<0.0001
Donor age (years)	37 (10–79)	34 (10–62)	0.4	35 (4–82)	36 (11–79)	0.4
Preoperative labs						
INR	1.4 (0.9–4.9)	1.8 (1.3–3.9)	0.004	1.4 (0.9–9.3)	2.1 (1–4.5)	0.0001
Bilirubin (mg/dL)	4.3 (0.2–66.7)	12.5 (1.1–49.4)	0.003	3.0 (0.2–62.9)	11.5 (0.7–53.8)	0.0001
Albumin (mg/dL)	3.1 (1.8–4.8)	2.9 (1.6–4.8)	0.2	2.9 (1.4–6.6)	2.9 (1.3–4.7)	0.8
AST (U/L)	67 (9–1118)	95 (22–25406)	0.009	81 (12–6061)	101 (28–10319)	0.03
CIT (hours)	7.5 (3–19)	7.4 (3–15)	0.9	8.4 (0.5–31)	8.7 (3–18)	0.5
Intraoperative blood products						
Red blood cells	6 (0–47)	9 (0–21)	0.09	4 (0–133)	6.5 (0–233)	0.0001
Fresh frozen plasma	8 (0–42)	12 (0–24)	0.02	5 (0–38)	8.5 (0–111)	0.0001
Platelets	2 (0–1500)	3 (0–30)	0.3	1 (0–365)	2 (0–80)	0.02
Cryoprecipitate	10 (0–40)	10 (0–50)	0.3	5 (0–300)	4 (0–60)	0.09
Length of stay (days)	19.5 (0–230)	25.5 (3–142)	0.03	13 (0–250)	20 (3–117)	0.0001
ICU stay (days)	7 (1–100)	9.5 (1–92)	0.08	2 (0–196)	8 (1–65)	<0.0001
Initial GFR at evaluation	71 (0.7–175)	73 (6–139)	0.9	82 (3–218)	72 (4–189)	0.4
Initial Cr at evaluation	1.3 (0.5–12.6)	1.5 (0.6–6.9)	0.2	1 (0.4–13.4)	1.5 (0.6–6.6)	0.0001
Recovery from RRT	66 (75%)*	35 (83%)	0.4	NA	NA	NA

*Data available for 88 patients only (66/88 = 75%).

RRT indicates renal replacement therapy; MELD, Model for End-Stage Liver Disease; INR, international normalized ratio; AST, aspartate transferase; CIT, cold ischemia time; ICU, intensive care unit; GFR, glomerular filtration rate; Cr, creatinine; NA, not applicable.

reported as median values with ranges and analyzed with the Wilcoxon two-sample test. Patient survival was estimated using the Kaplan-Meier method and compared using the log rank test. *P* values <0.05 were considered significant.

RESULTS

Demographics

The demographic data for the control and OKT3 groups are illustrated in *Table 1*. The OKT3 group patients were younger, had significantly higher Model for End-Stage Liver Disease (MELD) scores (33 vs. 17, *P* < 0.0001), received more blood products, and had longer hospital and intensive care unit stays. Also, a higher proportion of patients in the OKT3 group were dependent on RRT posttransplant (38.5% vs. 6.6%, *P* < 0.0001). Overall, the patients in the OKT3 group were more critically ill than the patients in the control group. This was true when the patients were further divided into those who had RRT around the transplant and those who did not have RRT (*Table 2*).

Renal recovery

The renal recovery in the patients who had RRT was analyzed separately from that of patients who did not have RRT. As illustrated in *Table 3*, in patients who had RRT around the time of transplant, the 1-month, 6-month, and 1-year renal recovery

rates were no different between the control and OKT3 groups. The serum Cr values at the same time points reflect a similar pattern. The postoperative GFR values at 3 months, 1 year, 2 years, and 5 years were not statistically different between the two groups. In patients who did not have RRT around the time of transplant, the use of OKT3 appeared to result in significantly higher complete renal recovery rates at 1 month, 6 months, and 1 year. This was reflected by significantly lower serum Cr values at 1 month in the OKT3 group (1.3 vs. 1.5 mg/dL). This was a significant improvement, in that the same group of patients had significantly higher preoperative serum Cr values (1.9 vs. 1.1 mg/dL) (*P* = 0.0001). The long-term renal function as reported by GFR was no different between the two groups at 1 year, 2 years, and 5 years posttransplant. In addition, although the 6-month and 1-year renal recovery rates were significantly higher in the OKT3 group, the serum Cr and GFR did not reflect this difference. Of the patients who were on RRT, 75% of the patients in the control group and 83% of the patients in the OKT3 group recovered from this modality (*P* = 0.4). *Figure 1* illustrates the precipitous drop in Cr with OKT3 use.

Rejection, infections, and malignancies

As illustrated in *Table 4*, there was no difference in the acute cellular rejection rates in the first year between the two groups.

Table 3. Renal recovery after liver transplantation among patients with and without renal replacement therapy who were treated with OKT3 vs low-dose calcineurin inhibitors (control)

	Patients on RRT			Patients not on RRT		
Variable	Control (n = 94)*	OKT3 (n = 42)†	P value	Control (n = 1322)	OKT3 (n = 67)	P value
Renal recovery rate						
1 month						
Complete	63 (72%)	30 (77%)	0.7	820 (62%)	54 (90%)	<0.0001
Partial	0 (0%)	0 (0%)		454 (34%)	5 (8.3%)	
No recovery	25 (28%)	9 (23%)		48 (4%)	1 (1.6%)	
6 month						
Complete	64 (72%)	30 (71%)	1	774 (51.7%)	47 (70.1%)	<0.0001
Partial	0 (0%)	0 (0%)		439 (33.2%)	3 (4.5%)	
No recovery	24 (28%)	12 (29%)		199 (15.1%)	17 (25.4%)	
1 year						
Complete	64 (73%)	27 (64%)	0.4	686 (52%)	40 (60.6%)	<0.0001
Partial	0 (0%)	0 (0%)		441 (33%)	5 (7.6%)	
No recovery	24 (27%)	15 (36%)		195 (15%)	21 (31.8%)	
Serum creatinine (mg/dL)						
Preoperative	2.3 (0.4–11.9)	2.75 (0.8–8)	0.2	1.1 (0.4–11.9)	1.9 (0.6–6.6)	0.0001
1 month	1.6 (0.4–6.9)	1.9 (0.6–5.3)	0.07	1.5 (0.6–6.5)	1.3 (0.5–2.6)	0.002
6 months	1.5 (0.6–9.2)	1.7 (0.8–4.8)	0.04	1.5 (0.3–10.5)	1.4 (0.5–2.8)	0.2
1 year	1.45 (0.6–10.7)	1.6 (0.9–5.4)	0.3	1.5 (0.3–9.7)	1.6 (0.5–2.8)	0.7
Glomerular filtration rate (mL/min/1.73 m²)						
At evaluation	71 (0.7–175)	73 (6–139)	0.9	82 (3–218)	72 (4–189)	0.4
3 months	39 (7–94)	34.5 (12–79)	0.5	48 (5.5–147)	41.5 (22–163)	0.2
1 year	55 (15–119)	47 (26–104)	0.06	55 (6–182)	50 (24–171)	0.7
2 years	52 (0–128)	58 (20–84)	0.9	53 (5–184)	55.5 (23–190)	0.9
5 years	57 (15–105)	50 (19–85)	0.4	52 (5–151)	54 (14–100)	0.3

*Data available in 88 patients only.

†One-month renal recovery data available in 39 patients only.

RRT indicates renal replacement therapy.

Overall, the incidence of fungal infections was significantly higher in the OKT3 group. Among the patients who had RRT, almost half of the patients in the OKT3 group were affected by fungal infections (47.6%). A similar pattern was observed among the patients who did not have RRT, where 43% of patients in the OKT3 group had fungal infections. Among the patients who had RRT, there was no difference in the bacterial, viral, and CMV infection rates between the control group and the OKT3 group. There was a higher incidence of bacterial infections in the OKT3 group among the patients who did not have RRT (62% vs. 41%, $P = 0.002$). In addition, there was no difference between the two groups in 1) viral and CMV infections, 2) de novo malignancies, 3) posttransplant lymphoproliferative disorders, and 4) death from hepatitis C recurrence.

Renal recovery and OKT3 doses

Table 5 illustrates the relationship between the rates of renal recovery and cumulative doses of OKT3 administered. In the first month, the highest rate of complete recovery was achieved

in the group of patients who received 45 to 50 mg of OKT3, and this correlated to 9 to 10 doses when given as 5 mg per day. After the first month, the highest rate of complete recovery was observed in the group of patients who received 35 to 40 mg of OKT3.

Immunosuppression in the first year

At the first-year mark, all the patients were on a CNI. Cyclosporine was more commonly used than tacrolimus in the control group (55% vs. 41%), whereas in the OKT3 group, tacrolimus was more commonly used (59% vs. 45%; $P = 0.004$).

Survival

Median follow-up was 85.5 months (range, 0.03–299 months). The overall long-term patient survival was higher in the control group than in the OKT3 treatment group ($P = 0.03$). As shown in Figure 2a, there was a significant difference in survival between control group patients who did not have RRT and OKT3 patients who did not have RRT, but there was

Figure 1. Renal recovery after liver transplant as illustrated by a change in serum creatinine in (a) the subgroups receiving renal replacement therapy and (b) the subgroups not on renal replacement therapy. There was a precipitous drop in the serum creatinine in the OKT3 group postoperatively. The control group patients who were on hemodialysis perioperatively had a similar pattern of renal recovery as the OKT3 group.

not a significant difference in survival between the two groups for those who had RRT.

Recovery from RRT was an important predictor of long-term survival, as illustrated in *Figure 2b*. In both the control and the OKT3 groups, the patients who recovered from RRT had a significantly better long-term survival than those who did not ($P < 0.0001$).

DISCUSSION

The acute renal failure rate of 65% in this study underscores the magnitude of this important problem. The patients who received OKT3 had more severe preoperative and postoperative renal failure and were more critically ill. This is consistent with the pattern of practice in our institution, in which the patients who are considered to have severe ARF are selected to have a CNI-free period with OKT3 as the backbone of their immunosuppression. In keeping with this, the OKT3 group had more risk factors for ARF: more severe preoperative renal failure, higher preoperative bilirubin, more blood products during the operation, longer intensive care unit stay, and higher rates of fungal and bacterial infections. In spite of this, a higher rate of complete renal recovery was achieved in this group. This regimen with OKT3 allows the patients to recover from their renal failure while avoiding additional nephrotoxicity from CNI.

Although the CNI nephrotoxicity from vasoconstriction of the glomerular arterioles can be reversed, it is more pronounced in the setting of other clinical parameters that predispose the patient to ARF (11). Conditions such as volume depletion, as well as aggressive diuretic therapy which is very common after liver transplant, may potentiate CNI nephrotoxicity (11). OKT3 allows total avoidance of such injury by CNI and results in an improvement of renal function in patients who need optimal conditions for their renal recovery. A similar pattern of improved renal function was observed with Thymoglobulin (12, 13), alemtuzumab (14), basiliximab (15), and a combination of daclizumab and mycophenolate mofetil (16).

A growing body of literature exists on perioperative renal failure in liver transplant, but there has been no study that focuses on renal recovery. Previously published studies focused on the risk factors for development of ARF after liver transplantation and identified preoperative Cr >1.2 mg/dL and baseline GFR <70 mL/min/1.73 m² as independent predictors of end-stage renal disease (17). In addition, a higher volume of blood transfused, liver allograft dysfunction (primary nonfunction), higher bilirubin levels, and bacterial infections were identified as risk factors for ARF and resulted in a higher mortality rate (2, 8, 18–22). In our study, a higher rate of complete renal recovery was achieved with an OKT3-based regimen in patients who were not on RRT. Once the patients had ARF severe enough to require RRT, there was no benefit in renal recovery with the OKT3 regimen. The fact that the factors contributing to renal recovery are multiple may be a possible explanation. Once the patient is already on RRT, the role nephrotoxic immunosuppression plays in ARF may be small relative to other factors. Although OKT3 did not result in improved renal recovery compared with the control group in patients who had RRT, it allowed the patients with higher MELD scores (median MELD 34) to achieve survival that was comparable to that of patients with lower MELD scores (median MELD 26).

If the patients were not on RRT, the CNI-free period with OKT3 coverage resulted in a significantly better complete renal recovery rate. This did not translate into an improvement in survival in this group of patients. The potential benefit in survival with the OKT3 group may have been negated by other factors in that group associated with worse survival. The OKT3 group had significantly higher MELD scores and rates of sepsis (bacterial and fungal).

Among the patients who were on RRT, recovery from RRT (i.e., independence of this modality) was the major determining factor in long-term survival. There was a dramatic difference between the patients who were off RRT compared with the patients who were not, as illustrated in *Figure 2b*. This underscores the importance of optimizing the conditions postoperatively to allow for renal recovery so as to avoid chronic renal failure and to achieve long-term survival.

Acute renal failure after liver transplantation in combination with other factors such as CNI use, preoperative diabetes, requirement for RRT, and Cr >1.7 mg/dL preoperatively have been associated with development of end-stage renal disease

Table 4. Acute cellular rejection, infection, and malignancy rates in the first year in patients with acute renal failure after liver transplantation who were treated with OKT3 vs low-dose calcineurin inhibitors (control)

	Patients on RRT			Patients not on RRT		
	Control (n = 94)	OKT3 (n = 42)	P value	Control (n = 1322)	OKT3 (n = 67)	P value
Acute cellular rejection	11 (11.7%)	2 (4.8%)	0.3	206 (16%)	6 (9%)	0.2
Bacterial infections	62 (66%)	25 (59%)	0.6	546 (41%)	41 (62%)	0.002
Viral infections	41 (43.6%)	13 (30.1%)	0.2	567 (43%)	22 (33%)	0.1
CMV infections	24 (25.5%)	6 (14.3%)	0.2	306 (23%)	12 (18%)	0.4
Fungal infections	25 (26.6%)	20 (47.6%)	0.02	183 (13.8%)	29 (43%)	<0.0001
PTLD	1 (1%)	1 (2.4%)	0.5	25 (2%)	3 (5%)	0.1
Death from HCV recurrence*	3 (23%)	1 (17%)	0.9	62 (25%)	4 (25%)	0.7
Malignancy	5 (5%)	2 (5%)	1	145 (11%)	8 (12%)	0.8

*Death from HCV recurrence calculated from number of deaths related to HCV recurrence occurring in each group (i.e., control group, 3/13 = 23%, OKT3 group, 1/6 = 17%; control group, 62/249 = 25%; OKT3 group, 4/14 = 25%).

RRT indicates renal replacement therapy; CMV, cytomegalovirus; PTLD, posttransplant lymphoproliferative disorder; HCV, hepatitis C virus.

Table 5. The relationship between renal recovery and the cumulative doses of OKT3 in liver transplant patients

Renal recovery	OKT3 dose (mg) (number of patients)					P value
	20–30 (n = 17)	35–40 (n = 21)	45–50 (n = 33)	55–60 (n = 20)	65–80 (n = 18)	
1 month						
Complete	80%	80%	93%	83%	81%	<0.0001
Partial	0%	20%	3%	0%	0%	
No recovery	20%	0%	3%	17%	19%	
6 month						
Complete	59%	86%	76%	60%	67%	<0.0001
Partial	31%	5%	3%	5%	0%	
No recovery	16%	9%	21%	35%	33%	
1 year						
Complete	65%	67%	66%	55%	56%	<0.0001
Partial	0%	5%	6%	5%	6%	
No recovery	35%	29%	28%	44%	39%	

(18, 23). Barri et al from our institution further characterized various degrees of ARF after liver transplantation and found that even mild acute kidney injury (a rise in serum Cr of >0.5 mg/dL) was associated with decreased patient and graft survival (7). The risk of end-stage renal disease was significantly increased with severe acute kidney injury (a rise in serum Cr of 50% above baseline to >2 mg/dL).

OKT3 was initially used in liver and kidney transplantation as an induction agent (24, 25). Millis et al had initially suggested its use for renal preservation after liver transplant (26). To our knowledge, ours is the only study outlining the long-term outcomes of OKT3 use for renal preservation. Because of the introduction of other immunosuppressive agents and the growing body of literature describing the association of OKT3

with recurrence of hepatitis C and posttransplant lymphoproliferative disorders, its popularity has declined. Also, the unfavorable side effect profile (cytokine release syndrome) has contributed to the decline in its popularity. Contrary to these concerns, in our study, there was no increase in the risk of posttransplant lymphoproliferative disorders, death from hepatitis C recurrence, and de novo malignancies with the use of OKT3.

Higher infection rates were present in the OKT3 group, but this was not solely related to the use of the agent. What is more likely is that the patients in the OKT3 group were more critically ill, as evidenced by their higher MELD scores, longer intensive care unit stay, and more severe renal failure. It appears that there was a dose-dependent response of renal recovery in patients who received OKT3. The dose of OKT3 that afforded the best renal recovery was 35 to 50 mg, as the 45 to 50 mg range resulted in the best renal recovery in the first month and the 35 to 40 mg range after the first month.

This study has several limitations. Although the data are from a prospective research database, the study's retrospective design and a difference in patient groups make it difficult to draw definite conclusions. In addition, although there were general guidelines for starting and stopping OKT3, there was not complete consistency in the pattern of practice of OKT3 use among different surgeons. These decisions were made at the discretion of the transplant surgeons, which may have introduced bias. These limitations reflect the challenges that the transplant team faces in management of the complex liver transplant patients with ARF.

In summary, this study has outlined the long-term results of the use of OKT3 in liver transplant patients for renal preservation. Although the patients in the OKT3 group had worse renal function preoperatively, they experienced impressive renal recovery. The use of OKT3 in patients who required RRT allowed more critically ill patients to achieve long-term survival

Figure 2. Survival of patients with acute renal failure after liver transplantation managed with or without the OKT3 renal-sparing protocol. **(a)** Comparison of the treatment and control groups, divided according to whether they received renal replacement therapy. **(b)** Comparison of the treatment and control groups who received renal replacement therapy, divided according to whether they came off hemodialysis.

comparable to that of patients who were less critically ill. This benefit was not evident in patients who did not require RRT. Among the patients who were on RRT after liver transplant, recovery from RRT was a major determining factor in achieving long-term survival. The use of OKT3 in this clinical setting was safe long term, in that it was not associated with any deleterious long-term effects on hepatitis C recurrence-related deaths or occurrence of posttransplant malignancies.

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In memoriam

BILLIE L. ARONOFF, MD

Department of Surgery, Baylor University Medical Center at Dallas

Dr. Billie L. Aronoff, a distinguished surgeon, died on May 28, 2011, his 97th birthday. He was born in Dallas and did his undergraduate premedical training at the University of Chicago and Southern Methodist University. He then graduated Alpha Omega Alpha from Baylor University College of Medicine in 1938. Subsequently, he completed his general surgery residency at Parkland Memorial Hospital and did postgraduate training at Memorial Hospital in New York, Lahey Clinic, and Ochsner Clinic before beginning the practice of surgical oncology at Baylor University Medical Center at Dallas (BUMC). Dr. Aronoff served in World War II and returned to BUMC in 1945. He married Valerie Rosenthal in 1942, and they spent 68 years together. Dr. Aronoff was active with the American Cancer Society: he was president of the Dallas County Unit, president of the Texas Division, on the national board of directors, and a recipient of its Volunteer of the Year Award. He also served on the Commission on Cancer of the American College of Surgeons and on the executive committee of the Society of Surgical Oncology. Dr. Aronoff was the first surgeon in Dallas to perform laser surgery in 1974. In 1981 he became president of the International Society for Laser Surgery. He published extensively regarding the use of the laser and managing the patient with malignancy. Dr. Aronoff was editor of *Lasers in Surgery and Medicine* and on the editorial board of *Oncology Times* and *Seminars in Surgical Oncology*. He lectured nationally and internationally. Dr. Aronoff is credited with keeping a major portion of head and neck surgery within the Department of Surgery. He retired in 1991 after 50 years of practice at BUMC and was able to devote his time to his four children, six grandchildren, and four great-grandchildren.

See the tributes to Dr. Aronoff on page 346 of this issue.

SHIELDS O. LIVINGSTON, MD

Department of Surgery, Baylor University Medical Center at Dallas

Dr. Shields Livingston, acting chairman of BUMC's surgery department from 1986 to 1987, died of a stroke on June

28, 2011, at the age of 91. Born in Morristown, Tennessee, Dr. Livingston served as a lieutenant commander in the Naval Air Force during World War II and then obtained his medical degree from Washington University School of Medicine in 1950. His residency was completed at the Veterans Administration Hospital in McKinney, Texas, in 1955, and he joined the attending staff at BUMC. Dr. Livingston was a member of the Texas Surgical Society, Western Surgical Association, and American College of Surgeons. He retired from active practice on June 30, 1990. Dr. Livingston was married to Harriette Lutz Livingston, an anesthesiologist, for 62 years, and they had three children, five grandchildren, and two great-grandchildren.

DMITRIY A. NIKITIN, MD

Past Fellow, Simmons Transplant Institute, Baylor University Medical Center at Dallas

Dmitriy A. Nikitin, MD, a transplant fellow at BUMC from 2006 to 2008, died tragically on May 26, 2011, in a shooting at a Florida hospital parking garage. He was 41 years old. Born in Russia, Dr. Nikitin received his medical degree from the Omsk Medical Institute in 1993 and completed a residency in anesthesia and intensive care medicine in Omsk. He immigrated to the United States in 1996, where he worked for several years as a senior manufacturing scientist at Hemagen Diagnostics in Waltham, Massachusetts. He then completed a general surgery residency at Drexel in Philadelphia. During his transplant fellowship at BUMC, he was awarded the Young Investigator Award from the International Liver Transplant Society. In 2008, he joined the Florida Hospital Transplant Center in Orlando, Florida, where he performed 168 transplant surgeries. Dr. Nikitin was a member of the American Society of Transplant Surgeons and the International Liver Transplant Society and was a fellow of the American College of Surgeons. He conducted clinical trials and wrote numerous articles and book chapters. He is survived by his wife, Lyubov, a 17-year-old daughter, Mariya, and three sons, Dmitriy, Andrey, and Maxim, aged 13, 6, and 3.