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A PROSPECTIVE RANDOMIZED TRIAL OF TACROLIMUS AND PREDNISONE VERSUS TACROLIMUS, PREDNISONE AND MYCOPHENOLATE MOFETIL IN PRIMARY ADULT LIVER TRANSPLANTATION: A SINGLE CENTER REPORT[1]

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Background. **Tacrolimus (TAC) and mycophenolate mofetil (MMF) are currently approved immunosuppressants for prevention of rejection in liver transplantation (LTx). They have different modes of action and toxicity profiles, but the efficacy and safety of MMF in primary liver transplantation with TAC has not been determined.**

Methods. **An Institutional Review Board–approved, open-label, single-center, prospective randomized trial was initiated to study the efficacy and toxicity of TAC and steroids (double-drug therapy (D)) versus TAC, steroids, and MMF (triple-drug therapy (T)) in primary adult LTx recipients. Both groups of patients were started on the same doses of TAC and steroids. Patients randomized to T also received 1 gm MMF twice a day.**

Results. **Between August 1995 and May 1998, 350 patients were enrolled at a single center–175 in the D and 175 in the T groups. All patients were followed until May 1998, with a mean follow-up of 33.8±9.1 months. Using an intention-to-treat analysis, the 1-, 2-, 3-, and 4-year patient survival was 85.1%, 81.6%, 78.6%, and 75.8%, respectively, for D and 87.4%, 85.4%, 81.3%, and 79.9%, respectively, for T. The 4-year graft survival was 70% for D and 72.1% for T. Although the rate of acute rejection in the first 3 months was significantly lower for T than for D (28% for triple vs. 38.9% for double, $P=0.03$), the overall rate of rejection for T at the end of 1 year was not significantly lower than for the D (38.9% triple vs. 45.2% double). The median time to the first episode of rejection was 14 days for D versus 24 days for T ($P=0.008$). During the study period, 38 of 175 patients in D received MMF to control ongoing acute rejection, nephrotoxicity, and/or neurotoxicity. On the other hand, 103 patients in the T discontinued MMF for infection, myelosuppression, and/or gastrointestinal disturbances. The need for corticosteroids was less after 6 months for T and the perioperative need for dialysis was lower with use of MMF.**

Conclusion. **This final report confirms similar patient survival and graft survival up to 4 years with a trend towards fewer episodes of rejection, lower need for steroids, and better perioperative renal function. However, the complex nature of LTx patients and their posttransplantation course prevents the routine application of MMF.**

INTRODUCTION

The FDA approved tacrolimus (TAC) in 1993 for liver transplantation (LTx), whereas the FDA approved mycophe-

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nolate mofetil (MMF) in 2000 for use in LTx. Approval for TAC was based upon randomized trials of TAC and steroids versus cyclosporine-based immunosuppression, in which TAC demonstrated significantly lower rates and severity of rejection (*1*, *2*). MMF approval for LTx was based on comparison with azathioprine (AZA) in conjunction with a cyclosporine (CsA)-based immunosuppressive regimen (*3*). Each drug has a different mode of action and different side effects. TAC acts to block the production of interleukin (IL)-2, which in turn prevents the proliferation of T helper lymphocytes, thus preventing allogeneic responses in the host (*4*). The main side effects of TAC were delineated in early clinical trials and include neurotoxicity and nephrotoxicity (*5*, *6*). MMF interferes with inosine monophosphate dehydrogenase, a key enzyme involved with de novo synthesis in lymphocytes (*7*). The main side effects of MMF are gastrointestinal and bone marrow suppression (*8*, *9*).

Until the initiation of the current study, no prospective trials combining these two agents as primary immunosuppression in LTx had been performed. The aim of the present study was to compare the combination of TAC and steroids (double-drug therapy (D) group), versus TAC, steroids, and MMF (triple-drug therapy (T) group) in primary adult (age >18 years) LTx recipients. The endpoint of the study included patient and graft survival, incidence and severity of rejection, incidence and nature of infection, and nature and severity of side effects. In November 1990, we published an interim report on the first 200 patients with a mean follow-up of 12.7±0.4 months (*10*). The current report represents the entire 350-patient enrollment. with long-term follow-up.

MATERIALS AND METHODS

The Institutional Review Board of the University of Pittsburgh approved the following protocol in August 1995. Patients were randomized in 1:1-ratio computerized sequential draw assignments using a variable block randomization procedure (*11*).

Patient Characteristics

The present report consists of the entire study population of 350 consenting adult patients enrolled between August 1995 and May 1998. All patients were followed until January 2000, with a mean follow-up of 33.8±9.1 months (range 20–53). The patient and donor characteristics for both Groups are shown in Table 1. The indications for LTx are shown in Table 2.

Immunosuppression Protocol

Patients in both groups received TAC at 0.03 to 0.05 mg/kg/day intravenously as a starting dose, commencing immediately after reperfusion of the liver allograft. Subsequent adjustments in the TAC dosage were made to achieve a whole blood TAC concentration of 15 to 20 ng/ml when on intravenous therapy and a trough level of 12 to 15 ng/ml when on oral TAC therapy during the first postoperative month. The target trough levels were 10 to 15 ng/ml beyond the second postoperative month. All patients also received 1 g methylprednisolone upon reperfusion of the liver and a 6-day methylprednisolone taper thereafter, starting at 200 mg/day and ending at a baseline dose of 20 mg/day. Subsequent adjustment in maintenance prednisone was dependent upon the patient's clinical course. Patients who experienced an acute rejection episode were initially treated with a single 1-g bolus of methylprednisolone and optimization of TAC levels. If the liver function tests did not improve within 24 hr after the steroid bolus, a gradual steroid taper was introduced, starting at 200 mg of methylprednisolone and tapering by 40 mg/day to 20 mg prednisone over the ensuing 5 days. Patients who failed augmented steroids were considered to have steroid-resistant rejection and were treated with 5 mg OKT3 (Ortho Biotech, Raritan, NJ) for 5 to 10 days. Patients who were randomized to TAC, steroids, and MMF (T) also received 1 g MMF orally twice a day through nasogastric tube from the day of transplantation and then orally. The protocol allowed reduction or discontinuation of MMF if there were any side effects ascribed to MMF or if the clinical course of the patient made it necessary to do so. In addition, patients randomized to D could receive MMF to control acute rejection or TAC-related toxicity. Criteria used for the pathologic diagnosis of acute hepatic rejection were as described in an international consensus document (*12*). All biopsy-proven or clinically suspected rejection episodes that required treatment were considered to be rejection for purposes of determining incidence of rejection. A small proportion of biopsies that were graded as borderline to mild and not considered as clinically signif-

TABLE 1. Patient characteristics

Group	Double	Triple
	n(%)	n(%)
Recipient		
Male	111 (63.4)	91 (52.0)
Female	64 (36.6)	84 (48.0)
Mean age (years)	52.4±10.8	52.3±11.9
Range	17.6–72	18.3–73
UNOS		
Home bound	60 (34.3)	66 (37.7)
Hospital bound	38 (21.7)	33 (18.9)
ICU bound	77 (44.0)	76 (43.4)
Donor		
Mean age (yrs)	39±17	40.2±19.3
Range (yrs)	7.8–75	6.9–75.6
Donor age<50	117 (66.9)	114 (65.1)
Donor age>50	58 (33.1)	61 (34.9)
CIT (hrs)	12±4	12±4
Blood group		
A	68 (38.9)	81 (46.3)
B	29 (16.6)	15 (8.6)
AB	16 (9.2)	15 (8.6)
O	62 (35.4)	69 (39.4)
CMV(+)(donor)/(−)(recip)	39 (22.3)	39 (22.3)
Cytotoxic crossmatch	16 (9.1)	20 (11.4)

TABLE 2. Indications for Liver Transplantation

Diagnosis	Group	
	Double n(%)	Triple n(%)
HCV	51 (29.1)	44 (25.1)
PNCE	35 (20.0)	35 (20.0)
Cryptogenic	30 (17.1)	20 (11.4)
PSC	17 (9.7)	14 (8.0)
PBC	10 (5.7)	20 (11.4)
Metabolic	8 (4.6)	11 (6.2)
(A1A)	6	7
(Wilson's disease)	1	3
(Hemochromotosis)	1	1
HBV	6 (3.4)	9 (5.1)
AIH	6 (3.4)	13 (7.4)
Benign tumour	4 (2.3)	
Primary liver malignancy	4 (2.3)	2 (1.2)
Fulminant failure	3 (1.7)	5 (2.9)
Other	1 (0.6)	2 (1.2)

HCV, hepatitis C virus; PNCE, Alcoholic cirrhosis; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; HBV, hepatitis B virus; AIH, Auto immune hepatitis; A1A, alpha 1 antitrypsin deficiency

icant (and thus not treated) was not considered to represent a rejection episode.

Statistical Analysis

Patient and graft survival rates were calculated using the Kaplan-Meier method and compared by the log-rank test. Differences between means were tested by the standard two-sample t-test, whereas differences in proportions were tested by the Pearson chi-square test. Analyses were performed by intention-to-treat analysis. A P-value <0.05, was considered statistically significant. Continuous data are presented as mean ± standard deviation (mean ± SD) and categorical data are presented as proportions.

RESULTS

Patient Survival

There were no differences in patient survival or graft survival between the two groups, as shown in Figure 1. The 1-year actual patient survival was 85.1% and actuarial survival for 2, 3, and 4 years was 81.6%, 78.6%, and 75.8%, respectively, for D, and 87.4%, 85.4%, 81.3%, and 79.9%, respectively, for T. The causes of death in both groups are shown in Table 3. As expected, infection remained the most common cause of death in both groups.

Retransplantation

Twenty patients (11.4%) in the double- and 21 (12%) in triple-drug regimen required retransplantation (Table 4). The most common cause of the need for retransplantation was primary nonfunction and hepatic artery thrombosis. The mean time to retransplantation was 6.4±10.3 months (range 0.03–26.8) from the first transplant in group D and 5.9±11.2 months (range 0.03–42.6) in group T. The overall graft survival for group D was 77%, 73.4%, 71.2%, and 70% for 1 to 4 years respectively and 82.3%, 78.2%, 75.1%, and 72.1%, respectively, for group T.

Cross-over

During the follow-up period, 38 patients (18.3%) who were randomized to the two-drug regimen received MMF to control ongoing rejection (n=23; 13.1%), nephrotoxicity (n=5; 2.8%), nephrotoxicity plus rejection (n=5; 2.8%), neurotoxicity (n=3; 1.7%), neurotoxicity plus rejection (n=1, 0.6%) and neurotoxicity plus nephrotoxicity plus rejection (n=1, 0.6%). The mean time to introduction of MMF from LTx was 46.4±72.1 days (median 17: range 1–385). One hundred three patients (58.9%) who were randomized to T discontinued MMF. Of these 103 patients, 47 (45.6%) discontinued within the first month, 76 (73.7%) by 6 months, and 92 (89.3%) by 1 year. The mean time to discontinuation of MMF was 68.7±87.7 days (median 34: range 1–434) from the time of transplantation. The various causes for discontinuation of MMF are shown in Table 5. MMF was not necessarily considered to be the direct cause of adverse events, but anticipation or realization of significant complications in the clinical course contributed to the discontinuation of MMF in

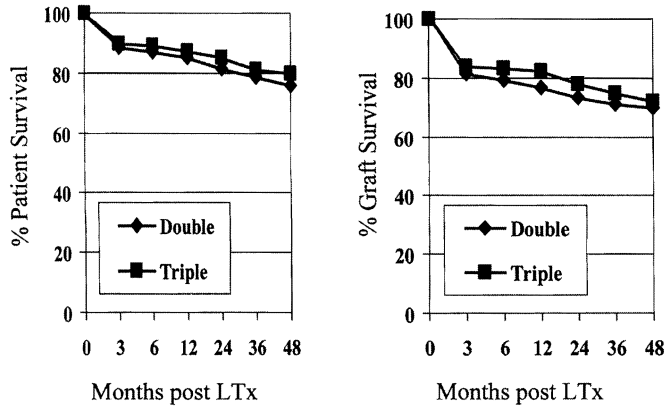

FIGURE 1. Overall patient survival (left) and graft survival (right) for both double and triple groups.

TABLE 3. Causes of death

Diagnosis	Group	
	Double [n(%)]	Triple [n(%)]
Sepsis & MSOF	19 (10.8)	16 (9.2)
Intracranial	4 (2.2)	4 (2.3)
Cardiopulmonary	3 (1.7)	3 (1.7)
Malignancy	5 (2.8)	4 (2.3)
Pulmonary embolism	2 (1.4)	0 (0)
Respiratory	1 (0.6)	2 (1.2)
Gastrointestinal	1 (0.6)	0 (0)
Recurrent HCV	1 (0.6)	0 (0)
PTLD	1 (0.6)	0 (0)
Portal vein thrombosis	1 (0.6)	0 (0)
Hepatic necrosis	0 (0)	1 (0.6)
Suicide	0 (0)	1 (0.6)
Anemia, hemorrhage (Jehova's witness)	0 (0)	1 (0.6)
Total	38 (21.7)	32 (18.3)

MSOF, Multisystem organ failure; PTLD, Post transplant lymphoproliferative disorder; HCV, hepatitis C virus

TABLE 4. Causes of retransplantation[a]

Causes	Group	
	Double [n(%)]	Triple [n(%)]
Primary nonfunction	10 (5.7)	12 (6.8)
Hepatic artery thrombosis	8 (4.5)	4 (2.2)
Hepatitis recurrence	1 (0.6)	3 (1.7)
Graft vs. host disease	1 (0.6)	0 (0)
Bile duct necrosis	0 (0)	1 (0.6)
Chronic rejection	0 (0)	1 (0.6)
Total	20 (11.4)	21 (12)

[a] First retransplantation only, two patients in each group received second retransplantation.

TABLE 5. Reason to discontinue MMF

Infection 36(20.6%)		Gastrointestinal 29(16.6%)	
Sepsis	17	Diarrhea	17
Cytomegaloviral infection	10	Nausea, vomiting, abdominal pain	8
Recurrent HCV	4	Failure to thrive	3
Fungal	3	Paralytic ileus	1
Herpes	1	Miscellaneous 7(4.0%)	
Cryptococcus	1	Primary nonfunction	2
Hematological 31(17.7%)		Postretransplantation	1
Leukopenia	15	Rash	1
Anemia	13	Neurological	1
Thrombocytopenia	3	Cardiac	1
Recurrent myeloma	1		
Total 103(58.9%)			

many of these discontinuations. The most common reason to discontinue MMF was infection in the face of normal liver function and absence of any rejection.

Rate of Rejection and Treatment of Rejection

The rate of rejection and the treatment used to control rejection were catalogued and then divided into time intervals of <3 months, >3 to <12 months, >12 to <24 months, and >24 months after LTx for all patients. Freedom from rejection is shown in Figure 2. As shown in Table 6, the overall rate of rejection was not different between the D (45.2%) and T (38.9%) groups (P=0.23). However, the rate of rejection in the first 3 months was significantly lower for the T group (28%) than the D group (38.9%) (P=0.03). Thus the rate of rejection for the T group was higher (9.1%) in the interval between 3 and 12 months than it was for the D group (5.1%), but this did not reach statistical significance (P=0.2). The median time to the first episode of rejection from liver transplantation was longer for the T group (24 days), than for the D group (14 days) (P=0.08). Of the 79 patients (45.2%) in the D group who experienced rejection, 16 had two episodes, 4 had three episodes, 6 had four episodes of rejection. Similarly, of the 68 patients (38.9%) in the triple group who had rejection, 15 had two episodes, 6 had three episodes, and 4 had four episodes.

The cumulative episodes of rejection were 121 (0.69 episodes per patient) in group D versus 108 (0.61 episodes per patient) in group T. One hundred eleven (91.7%) in the D group and 101 (94.3%) in the T group were biopsy-proven rejection and the rest were clinical rejections. Ten patients in the D group and five in the T group had borderline-to-mild rejections on liver biopsy but were not treated and therefore are not included in the overall rate of rejection.

Treatment of Rejection

Seven patients (4%) in the D group and three patients (2.8%) in the T group required OKT3 antibody. The other rejections were treated with 1 g methylprednisolone (n=51 for D, and n=40 for T) or 1 g methylprednisolone and 600 mg of steroid taper over the next 5 days (n=63 for D, n=62 for T). Two patients in the T group were treated with oral prednisone only (Table 6).

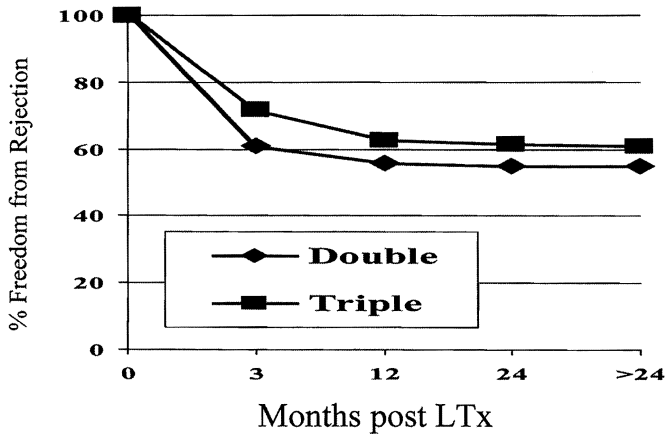

FIGURE 2. Rate of freedom from rejection in both groups.

Baseline Maintenance Immunosuppression

The baseline mean maintenance dose of TAC and trough TAC concentration were comparable in both groups (Table 7). The mean prednisone dose was 3.6% to 12% lower for the T group during the follow-up period. Freedom from prednisone was slightly higher in the T group (68.6%) at 2 years than in the D group (60.6%), but this did not reach statistical significance.

Rate of Infection

The rate of bacterial infection (positive blood culture) was 35.4% (n=62) in the D and 32% (n=56) in the T group. Similarly, 24% (n=42) of patients in the D group and 22.2% (n=39) in the T group received gancyclovir either to treat cytomegalovirus infection or as preemptive treatment based on pp65 surveillance (*13*, *14*). In addition, 12 patients (6.9%) in the D group and 6 (3.4%) in the T group had an invasive fungal infection (Table 8).

Renal Function

The mean serum creatinine and blood urea nitrogen at the time of LTx was 1.0±0.8 mg/dl and 19.7±12.8 mg/dl, respectively, in the D group and 1.1±0.9 mg/dl and 18±12 mg/dl, respectively, in the T group. The mean rise in serum creatinine and blood urea nitrogen after LTx was slightly lower in the T group than in the D group. Two patients in the group D and six patients in the T group were on hemodialysis prior to LTx. Thirty-nine patients (22.7%) in the D group who were not on dialysis before transplantation required dialysis after LTx, and 20 patients (11.4%) in the T group who were not on dialysis prior to transplantation required dialysis after LTx (P=0.007). At the last follow-up, 11 patients (6.2%) in the D group and 12 patients (6.8%) in the T group were on dialysis. One of the patients in the T group suffers from hyperoxalosis type I. The mean serum creatinine and blood urea nitrogen are shown in Table 9 for various time points post-LTx.

Liver Function

Liver biochemical function were the same in both groups; the mean values are shown in Table 9.

Hematology

The rate of anemia (hematocrit<25), leukopenia (white blood cell<4,000/ml), and thrombocytopenia (platelets<50,000/ml) before LTx and at various times after LTx are shown in Table 9. The incidence of anemia was 10.7% in group D and 10.1% in group T before LTx. Leukopenia was observed in 29.5% of patients in group D and 26.8% of patient in group T pre-LTx. Leukopenia improved in both groups post-LTx; however, the improvement was less notable in group T than in group D (17.8% in T vs. 9.9% in D) during the first 6 months. Interestingly, the white blood cell counts became comparable after 6 months, presumably because MMF was discontinued in nearly 45% of patients by this time. Thrombocytopenia existed pre-LTx in 32.2% of group D and 31.5% of group T (Table 9).

DISCUSSION

Several reports have been published on the utility of adding MMF to a CsA or TAC immunosuppressive regimen in

TABLE 6. Rate of rejection and treatment of rejection

Months post-LTx		<3	>3<12	>12<24	>24	Total
No. of rejection episodes	Group	n(%)	n	n	n	n(%)
0	D	107 (61.1)*	98	96	96	96 (54.8)***
	T	126 (72)*	110	108	107	107 (61.1)***
1	D	68 (38.9)*	9	2	0	79 (45.2)***
	T	49 (28)*	16	2	1	68 (38.9)***
2	D	14	10	1	1	26
	T	18	6	1	0	25
3	D	4	5	1	0	10
	T	1	9	0	0	10
4	D	2	2	2	0	6
	T	2	2	0	0	4
Total n (% of total rejection episodes)	D	88 (72.2)	26 (21.5)**	6 (5.0)	1 (0.8)	121
	T	70 (65.4)	33 (30.8)**	3 (2.8)	1 (0.8)	107
Mean rejection per patient	D	0.69		P=0.69		
	T	0.61				
Mean/median interval to first rejection episodes days	D	53±103/14		P=0.08		
	T	83±129/24				

* =p value 0.03, ** =p value 0.32, *** p value 0.23

TABLE 7. Immunosuppression

Months post-LTx		1	3	6	12	24	
Group							
Mean Tac Dose mg/d	D	8.6	8.3	7.2	4.9	3.4	
	T	8.2	8.3	7.2	5.6	4.6	
Mean Tac level ng/ml	D	12	11	10.1	7.1	8.1	
	T	11.2	10.3	9.8	8.7	9.2	
Mean Prednisone dose mg/d	D	10.1	7.9	5.6	3.7	2.5	
	T	9.1	7.5	5.4	3.5	2.2	
Percentage difference in Prednisone dose between D and T groups		9.9	5.1	3.6	5.4	12	
Percentage patients off steroid	D	1.8	12	20.2	36.9	60	
	T	1.2	12.7	30.5	47.5	68.6	

TABLE 8. Post-LTx infections

Infection	Group	
	Double [n(%)]	Triple [n(%)]
Bacterial	62 (35.4)	56 (32)
Cytomegalovirus[a]	42 (24)	39 (22.2)
Fungal	12 (6.8)	6 (3.4)
(Candidiasis)	3	1
(Toruloposis)	2	2
(Cryptococcosis)	2	1
(Aspergillosis)	3	1
(Histoplasmosis)	1	1
(Pseudoclescheriasis)	1	0

[a] treatment for cytomegalovirus disease or preemptive based on PP65 ref. 13, 14.

LTx, primarily in the setting of treatment for steroid-resistant rejection or to improve renal function by reducing the dose of calcineurin inhibitor (*15–20*). However, the utility and safety of MMF in conjunction with either CsA or TAC as primary immunosuppressive therapy in LTx has not been previously established. This is the largest reported prospective trial using TAC and MMF in LTx, with a mean follow-up of nearly 3 years.

There have been other prospective, randomized trials studying the use of MMF with TAC or CsA in primary LTx. Klupp et al reported a series of 120 cases (**randomized in three** groups) comparing Neoral, steroids + MMF (**groupI**) to TAC, steroids + MMF (**groupII**) to TAC and steroids alone (**groupIII**) (21). They did not find any benefit in terms of patient survival, graft survival or rate of rejection with use of MMF with TAC compared (**groupII**) to TAC alone (**groupIII**). However, when compared to a Neoral and MMF combination (**groupI**), patient survival in both TAC groups (**II and III**) were numerically greater and the graft survival was significantly higher with TAC (**groupII and III v/s group I**), while the corresponding rate of rejection was significantly lower (**groupII and III v/s group I**). The rate of discontinuation of MMF in either the TAC or CsA groups was 58%. In addition, there was a tendency to higher cytomegalovirus and fungal infections in both MMF groups. Therefore, they concluded that there was no added benefit of adding MMF to a TAC-based immunosuppressive regimen in primary LTx. In the pivotal randomized, multicenter trial (*3*), consisting of 565 patients, Neoral, steroids, plus AZA (n=287) was compared with Neoral, steroids, plus MMF (n=278) in primary LTx. MMF was given i.v. initially, and doses were adjusted to obtain a similar area under the curve as was obtained for renal recipients receiving MMF 1 g twice a day. The withdrawal rate of MMF was 45.3% and that of AZA was 44% in this trial. Rates of rejection were 38.1% and 47.7%, respectively ($P<0.02$); however, the follow-up was less than 1 year post-LTx.

TABLE 9. Biochemical and hematological values hematological function

Months Post LTx	Group	0	3	6	12	24
	Group					
Liver Function						
T. Bilirubi mg/dl	D	7.4±6.2	0.8±1.8	0.5±1.1	0.3±0.4	0.2±0.4
	T	7.1±5.3	0.7±1.8	0.5±1.5	0.6±2.8	0.1±0.3
AST u/l	D	1519±1687	33.4±41.2	24.3±35	21.6±41.4	17.2±37.9
	T	1311±1434	32±37.8	25±40	36.5±57.6	14.6±55
ALT u/l	D	673±807	49±72.2	38±64	28.4±55	20.5±45.1
	T	631±750	48±66.4	35.4±57.6	41.8±78	16.4±44
Alk PO4 u/l	D	74±105	80.2±204	39±106	22.1±55	22±67
	T	115±172	57±102.1	43±191.2	33.2±120	19.7±58
GGTP u/l	D	103±151	179±361.7	142.4±435	90.9±251	59±157
	T	101±230	157±407.5	114±284	88.7±203	31.6±94
Renal Function						
BUN	D	19.7±12.8	28±15.7	28.3±13.8	24.9±10.6	25±11
	T	18±12	25±11	26±11	24±11	24±11
Creat	D	1.0±0.8	1.3±0.6	1.3±0.6	1.3±0.3	1.6±1.5
	T	1.1±0.9	1.3±0.9	1.4±1.1	1.3±0.6	1.6±1.4
Hematology						
Hematocrit %	D	32±5	35±5	35±6	37±4	37±4
	T	32±5	34±5	35±4	36±5	35±5
Platelates k/dl	D	76±48	171±89	166±94	160±81	170±89
	T	81±63	170±102	159±62	151±70	155±84
Leukocyte k/dl	D	7.1±4	7±3	5.8±2.5	6±2.4	7.3±7.8
	T	7.0±4	6±4	5.8±2	5.6±2	5.6±2.4
Hematological disorders						
Leukopenia	D	29.5	9.9	18.8	18.1	17.6
(WBC<4.0k/ml)	T	26.8	17.8	15.3	19.3	21.2
Anemia	D	10.7	2.2	1.9	1.2	1.6
(HCT<25%)	T	10.1	4.2	0	1	2
Thrombocytopenia	D	32.2	2.2	1.9	2.5	5
(Platlets<50k/ml)	T	31.5	1.4	1.9	2	6.2

Our report noted similar patient survival and graft survival post-LTx regardless of whether MMF was included in the immunosuppressive regimen used. Although the initial rate of rejection was significantly lower in the group of patients randomized to MMF, this rate increased during the remainder of the year as MMF was discontinued. This limited the overall advantage of MMF from the rejection standpoint. The use of MMF appeared to be associated with an advantage in terms of reduced renal toxicity in the early post-LTx period. The need for new-onset dialysis post-LTx was 11.4% with MMF versus 22.7% in patients who did not receive MMF, although the renal function at 1 year was not different.

The addition of MMF did not appear to increase the risk of infectious complications, because the rate of bacterial, viral, or fungal infection was not higher with use of MMF than without MMF (*22*). However, the high withdrawal rate of MMF in this study reflects the inherently high incidence of infectious complications in LTx patients, regardless of their induction or baseline immunosuppressive regimen. The limitation of antiproliferative agents such as MMF is the preexisting leukopenia, thrombocytopenia, and hypersplenism in the majority of LTx candidates. Our study noted that, in almost half of the patients after primary LTx, the clinicians elected to discontinue MMF because of infectious events, depressed hematological counts, and gastrointestinal complaints. Similar findings have been reported in a European multicenter trial of TAC, steroids, plus AZA versus TAC and steroids (*23*). In this study, almost half of the patients randomized to the T group were taken off AZA by 1 year post-LTx. Although some of these interpretational issues would have been easily addressed by the addition of a placebo to the non-MMF group (thus blinding the clinicians involved in the management of these complex patients), this was not deemed to be of priority by the manufacturer of MMF. These factors that limit the ability to use MMF are not usually seen in kidney transplant patients and explain the differences in dropout rates. Fisher et al. reported in their randomized trial of MMF with Neoral versus TAC, that gastrointestinal toxicity and bone marrow suppression were not notable, although the study was limited to a 6-month follow-up, and target dose of MMF at 6 month was 1 g/day (*24*).

This study was not designed to evaluate steroid withdrawal after LTx, although there appeared to be a slightly higher number of patients in the MMF group that were steroid free. However, the mean dose of corticosteroids was 4% to 12% lower with use of MMF. Stegall et al. have (*15*) reported a greater ability to wean patients from corticosteroids at 14 days post-LTx with a modest rejection rate, approximately 40%. A kidney transplant trial designed to assess the ability of the addition of MMF to a Neoral and corticosteroid immunosuppressive regimen resulted in satisfactorily low rates of rejection-free maintenance but did not allow corticosteroid withdrawal without a significantly higher incidence of rejection (*25*).

Although this study, like others that have utilized MMF in LTx, has not clearly demonstrated a role of MMF as a primary immunosuppressant, MMF has a role in the treatment

of steroid-resistant rejection in patients experiencing nephrotoxicity or neurotoxicity due to calcineurin inhibitors or for its steroid-sparing effects following LTx. MMF treatment may also be useful for other immunosuppressive drug complications, such as new-onset insulin-dependant diabetes mellitus, hypertension, or osteoporosis. However, it remains to be defined which population of LTx patients and under which conditions will benefit from MMF (*26*).

CONCLUSIONS

The use of MMF in an immunosuppressive regimen for LTx patients is not associated with differences in patient or graft survival. There is less rejection, improved early renal function, and the need for less corticosteroids with the use of MMF in a TAC-based regimen; however, several factors inherent in the LTx procedure, leading MMF discontinuation in a significant proportion of patients, limit its general use and maximal potential. MMF may be best suited for selected patients who develop rejection, nephrotoxicity, and neurotoxicity or in whom aggressive steroid weaning is desirable after LTx.

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