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Prospective Randomized Trial of Tacrolimus and Prednisone Versus Tacrolimus, Prednisone, and Mycophenolate Mofetil: Complete Report on 350 Primary Adult Liver Transplantations

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TACROLIMUS (Tac) was approved by the FDA for clinical use in liver transplantation in 1993 and mycophenolate mofetil (MMF) was approved in 1995 for use in kidney transplantation with cyclosporine. The aim of the present study was to compare the combination of Tac and steroids (double therapy, group D) versus tacrolimus, steroids, and MMF (triple therapy, group T) in primary adult (age > 18 years) liver transplantation (LTx). An interim report was published on the first 200 patients with a mean follow-up of 12.7 ± 0.4 months.[1] The present report includes the entire study population of 350 consenting 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 to 53). Patient and donor characteristics were similar in both groups.

PROTOCOL

Patients in both arms of the study received Tac at 0.03 to 0.05 mg/kg per day intravenously as a starting dose. All patients also received 1 g of methylprednisolone on reperfusion of the liver and a 6-day methylprednisolone taper, starting at 200 mg/d and ending at a baseline dose of 20 mg/d. Patients randomized to Tac, steroids, and MMF (group T) received 1 g of MMF twice a day orally from the day of transplant. 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 deemed it necessary. In addition, patients randomized to double-drug therapy could receive MMF to control acute rejection or Tac-related toxicity. Acute rejection episodes were initially treated with steroid bolus. Steroid-resistant rejections were treated with 5 mg of OKT3. All rejection episodes, which required treatment (biopsy proven or clinically suspected) were included.

RESULTS

There were no differences in Kaplan–Meier patient survival and graft survival in the two groups as shown in Table 1. One-year actual patient survival was 85.1% and actuarial survival was 81.6%, 78.6%, and 75.8% for 2, 3, and 4 years, respectively, for group D, and that for group T was 87.4%, 85.4%, 81.3%, and 79.9%, respectively, at the same timepoints. Twenty patients (11.4%) in group D and 21 (12%) in group T required retransplantation. Overall graft survival for group D was 77%, 73.4%, 71.2%, and 70% for 1, 2, 3, and 4 years, respectively, and that for group T was 82.3, 78.2%, 75.1%, and 72.1% for the same timepoints.

Crossover

During the study period, 38 patients (18.3%) who were randomized to the two drug regimens received MMF to control ongoing rejection (n = 23; 13.1%), nephrotoxicity (n = 5; 2.8%), nephrotoxicity + rejection (n = 5; 2.8%), neurotoxicity (n = 3; 1.7%), neurotoxicity + rejection (n = 1, 0.6%), and neurotoxicity + nephrotoxicity + rejection (n = 1, 0.6%). Mean time to introduction of MMF was 46.4 ± 72.1 (median 17, range 1 to 385) days after LTx. On the other hand, 103 patients (58.9%) in group T discontinued MMF, including 36 (20.5%) for infection, 29 (16.6%) for gastrointestinal complications, 31 (17.7%) for hematologic reasons, and 7 (4.0%) for miscellaneous reasons. Mean time to discontinuation of the drug was 68.7 ± 87.7 (median 34, range 1 to 434) days from the time of transplantation.

Rate and Treatment of Rejection

The overall rate of rejection was not significantly different between group D (15.2%) and group T (38.9%), at P = .23. However, the rate of rejection in the first 3 months was significantly lower in group T (28%) than in group D (38.9%), at P = .03. The rate of rejection for group T was higher in the 3- to 12-month interval (23.5%) than in group D (11.3%); however, this did not reach statistical signifi-

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Table 1. Study Results

Survival						
Months Post-LTx		3	6	12	24	36
Patient survival	D	88.6	86.9	85.1	81.6	78.6
	T	89.7	89.1	87.4	85.1	81.3
Graft survival	D	81.6	79.3	77.0	73.4	71.2
	T	84.0	83.4	82.3	78.2	75.1
Rejection						
Months post-LTx		<3 n(%)	>3<12 (n%)	>12<24 n(%)	>24 n(%)	Total n(%)
No. of rejection episodes	D	107 (61.1)*	98	96	96	96 (54.8)†
0	T	126 (72%)*	110	108	107	
1	D	68 (38.9)*	9	2	0	79
	T	49 (28)*	16	2	1	68
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	4
4	D	2	2	2	0	6
	T	2	2	0	0	4
Total *n* (% of total rejection)	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 in	D	0.69‡				
	T			0.61‡		
Immunosuppression						
Months post-LTx		1	3	6	12	24
Mean Tacro 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 Tacro level ng/mL	D	12.0	11	10.1	7.1	8.1
	T	11.20	10.3	9.8	8.7	9.2
Mean Pred 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
% Difference in pred dose between D and		9.9	5.1	3.6	5.4	12.0
Patients % off steroid	D	1.8	12	20.2	36.9	60.0
	T	1.2	12.7	30.5	47.5	68.6
Hematology						
Months post-LTx		0	1	3	6	12
Leukopenia %	D	29.5	3.8	9.9	18.8	18.1
(WBC < 4.0 k/mL)	T	26.8	7.1	17.8	15.3	19.3
Anemia %	D	10.7	13.7	2.2	1.9	1.2
(HCT < 25%)	T	10.1	14.2	4.2	0.0	1.0
Thrombocytopenia %	D	32.2	7.6	2.2	1.9	2.5
(Platelets < 50 k/mL)	T	31.5	2.5	1.4	1.9	2.0
Renal Function						
Months post-LTx		0	3	6	12	24
Blood urea nitrogen mg/dl*	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
Creatinine mg/dl*	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

D, double group; t, triple group.
All values are mean ± SD.
*P = 0.03.
†P = .23.
‡P = .69.

cance ($P = .2$). The median time to the first episode of rejection from liver transplantation was delayed for group T (24.0 days) compared with group D (14 days) ($P = .08$). Cumulative episodes of rejection were 121 (0.69/patient) in group D versus 108 (0.61/patient) group T.

Treatment of Rejection

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

Baseline Maintenance Immunosuppression

The baseline mean maintenance dose of tacrolimus and trough tacrolimus concentration were comparable in both groups (Fig. 1). Also, mean prednisone dose was 3.6% to 12% lower in group T at most timepoints. Freedom from prednisone was slightly higher in group T (68.6%) at 2 years versus group D (60.6%), but his did not reach statistical significance.

Renal Function

The mean serum creatinine and blood urea nitrogen at the time of LTx was 1.0 ± 0.8 and 19.7 ± 12.8 in group D and 1.1 ± 0.9 and 18 ± 12 in group T, respectively. Subsequent changes are shown in Table 1. In group D, 39 patients (22.7%) required dialysis who were not on dialysis before transplantation, and 20 (11.4%) patients in group T required dialysis who were not on dialysis prior to transplantation.

Hematology

At pretransplant, 10.7% of the patients in group D were anemic (Hct < 25) before LTx, and 10.1% in group T. Leukopenia (total leukocyte count <4000/mL) was observed in 29.5% of patients in group D and 26.8% of patients in group T. Thrombocytopenia was detected in 32.2% in group D and 31.5% in group T (Fig. 1).

DISCUSSION

Several reports have been published on its use in liver transplantation with CsA and tacrolimus as primary treatment for steroid-resistant rejection, steroid-sparing effects, or to improve renal function by reducing the dose of calcineurin inhibitor and other immunosuppression-related complications. Klupp et al[2] reported a series of 120 cases comparing neoral + MMF and tacrolimus + MMF with tacrolimus alone. The rate of discontinuation of MMF was 58%. In multicenter trial[3] consisting of 565 patients randomized to CsA + steroid + azathioprine ($n = 287$), or CsA + steroid + MMF ($n = 278$), the withdrawal rate of MMF was 45.3% and that of azathioprine was 44%. Both studies found that, after primary LTx, almost half of the patients could not be continued on MMF. The rate of rejection was significantly lower at 3 months in the group of patients randomized to MMF in our protocol; however, this rate of rejection increased in the subsequent year as MMF was discontinued, and although the overall rate was lower the initial significant advantage was lost. The use of MMF did have some other advantages, however, including reduced renal toxicity.

In conclusion, no benefit in patient survival or graft survival was observed with use of MMF. Preexisting leukopenia and thrombocytopenia contributed to the need for discontinuation of MMF in a large percentage of patients. Trends toward lower incidence of rejection, lower rate of preioperative renal impairment, and slightly lower steroid requirement were observed. MMF may be more suitable for selected patients after LTx who have steroid-resistant rejection, nephrotoxicity, neurotoxicity, or a need for a steroid-weaning protocol.

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