A Prospective Randomized Trial of Mycophenolate Mofetil in Liver Transplant Recipients With Hepatitis C

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Hepatitis C is the most common indication for liver transplantation (LT) in the United States. Recurrence of hepatitis C virus (HCV) infection post-LT remains a problem for which there is no completely satisfactory treatment. The aim of the present study is to evaluate mycophenolate mofetil (MMF), which has both immunosuppressive and antiviral properties, to determine whether it is associated with a difference in the rate of HCV recurrence and also examine its impact on patient and graft survival. Between August 1995 and May 1998, a total of 106 patients who were HCV positive before LT were randomized to tacrolimus (TAC) and prednisone versus TAC, prednisone, and MMF therapy. The rate of recurrence of HCV, patient and graft survival, incidences of rejection, and histological findings were examined. Fifty six patients were randomized to TAC and steroid therapy (double [D] drug; group D), and 50 patients were randomized to TAC, steroid, and MMF therapy (triple [T] drug; group T). Liver biopsies were performed when liver function was abnormal; protocol liver biopsies were not performed. Mean follow-up was 4.3 ± 0.8 years. Actuarial patient survivals at 4 years were 72.6% in group D and 73.8% in group T (*P* = not significant). Actuarial graft survivals at 4 years were 65.6% in group D and 65.4% in group T. One patient in group D and 2 patients in group T underwent a second LT for recurrent HCV. One patient in each group died of recurrent HCV without re-LT. Twenty-six patients in group D (46.4%) and 23 patients in group T (46.0%) showed signs of recurrent HCV. Mean hepatitis activity index (HAI) scores were 7.4 ± 2.7 in group D and 7.0 ± 3.4 in group T, and mean fibrosis scores were 2.9 ± 1.7 in group D and 2.6 ± 1.1 in group T. The rate of rejection was 0.57/patient in each group for the entire follow-up period. None of these values reached statistical significance. Rates of HCV recurrence, graft loss or death from recurrent HCV, and 4-year actuarial patient and graft survival were not different between the groups. In liver transplant recipients with HCV, MMF has no impact on patient survival, graft survival, rejection, or rate of HCV recurrence based on biochemical changes and histological findings. In addition, there was no difference in HAI or fibrosis score between the two groups. Either MMF has no anti-HCV effect or its immunosuppressive properties overwhelm its antiviral effect in the clinical setting. (*Liver Transpl 2002;8:40-46.*)

At the present time, the most common indication for liver transplantation (LT) in adults in the United States is hepatitis C virus (HCV)-related end-stage liver disease.[1-5] However, hepatic replacement does not cure the disease, and the virus recurs in the transplanted liver.[2,6,7] The administration of immunosuppressive agents for the prevention and treatment of rejection results in acceleration of viral replication. Quantitative viral loads post-LT are much greater than they are pre-LT.[8] Reinfection of the transplanted liver allograft is almost uniform, leading to recurrent hepatitis in up to 75% of patients.[2,9-11] Progression of HCV disease in the general population to end-stage liver disease takes approximately 20 years.[10] In the post-LT population, the course can be much more aggressive, resulting in early graft loss, particularly if the transplant recipient experiences recurrent acute cellular rejection and requires augmented immunosuppression to control it.[10,12-15] It is conceivable that the use of an immunosuppressive agent with antiviral properties could have an advantage in this population. Mycophenolate mofetil (MMF) has proven antiviral activity both in vitro and in small animal models, apart from its proven immunosuppressive effect.[16-20]

The aim of the present study is to examine the impact of MMF therapy in HCV-positive liver transplant recipients administered tacrolimus (TAC)-based immunosuppression.

Patients and Methods

Between August 1995 and May 1998, a total of 350 liver transplant recipients were enrolled onto an open-label

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prospective randomized trial of TAC and prednisone (double [D] drug; group D) versus TAC, prednisone, and MMF (triple [T] drug; group T).[21,22] One hundred six patients on this trial underwent LT for end-stage liver disease secondary to HCV infection. The diagnosis of HCV was made on the basis of qualitative analysis of reverse-transcriptase polymerase chain reaction. Randomization was originally performed in variable blocks of 6 to 12 to keep numbers close to equal. Each block consisted of equal numbers of patients. The statisticians gave sealed envelopes to clinicians.[23] All patients were followed up until January 2001, with a mean follow-up of 4.3 ± 0.8 years.

Protocol

All adult patients older than 18 years undergoing primary LT were eligible for enrollment. The only exclusion criterion was pregnancy.

Immunosuppression

Patients in both groups were administered TAC, 0.03 to 0.05 mg/kg/d, intravenously as a starting dose immediately after reperfusion of the liver allograft. Subsequent adjustments in TAC dosage were made to achieve a whole-blood TAC concentration of 15 to 20 ng/mL on intravenous therapy and trough level of 12 to 15 ng/mL on TAC oral therapy during the first postoperative month. Target trough levels were 10 to 15 ng/mL after the second postoperative month. All patients also were administered 1 g of methylprednisolone on reperfusion of the liver and a 6-day methylprednisolone taper thereafter, starting at 200 mg/d and ending at a baseline dose of 20 mg/d. Subsequent adjustment in maintenance prednisone dosage was dependent on the clinical course of the patient.

Liver biopsies were performed when aspartate aminotransferase, alanine aminotransferase, or total bilirubin levels were twice the upper limit of normal in the absence of vascular or biliary abnormality on Doppler ultrasound. Protocol liver biopsies were not performed. Cholangiography and arteriography were performed when clinically indicated.

Patients who experienced an acute rejection episode were initially treated with a 1-g bolus of methylprednisolone and optimization of TAC levels. In the event that liver function test results did not improve within 24 hours after the steroid bolus, a gradual steroid taper was introduced, starting at 200 mg of methylprednisolone and tapering by 40 mg/d to 20 mg of prednisone over the ensuing 5 days. Patients in whom augmented steroid therapy failed were considered to have steroid-resistant rejection and were treated with muromonab-CD3 (OKT3; Ortho Biotech, Raritan, NJ), 5 mg/d, intravenously for 5 to 10 days. Patients randomized to TAC, steroid, and MMF therapy (group T) also were administered MMF, 1 g, orally or by nasogastric tube twice daily. The protocol allowed for reduction or discontinuation of MMF if there were side effects attributed to MMF or the clinical course of the patient deemed it necessary. In addition, patients randomized to double-drug therapy could be administered MMF to control acute rejection or TAC-related toxicity. Banff criteria for grading and staging of acute rejection[24] and hepatitis[25] and distinguishing hepatitis from rejection[26] are described elsewhere. Patients with biopsy-proven recurrent hepatitis C with elevated hepatic enzyme levels were treated until October 1997 with interferon (IFN), 3 million units, subcutaneously three times weekly, and ribavirin, 400 mg, orally twice daily was added for recurrence diagnosed after October 1997.

Table 1. Patient Characteristics

	Group D	Group T
Recipient		
Men	41 (73.2)	36 (64.2)
Women	15 (26.8)	14 (35.8)
Mean age (yr)	52 ± 9	51 ± 9
Range (yr)	31-68	28-78
Donor		
Men	32 (57.1)	27 (54)
Women	24 (42.9)	23 (46)
Mean age (yr)	39 ± 16	36 ± 16
Range (yr)	12-75	8-70
Blood group		
A	26	21
B	6	2
AB	2	7
O	22	20

NOTE. Values expressed as number (percent) or mean ± SD unless noted otherwise.

Study Population

Patient demographics are listed in Table 1. Fifty-six patients were randomized to TAC and steroid therapy (group D), and 50 patients were randomized to TAC, steroid, and MMF therapy (group T). Man-woman ratios were 41:15 in group D and 36:14 in group T.

Statistical Analysis

Patient and graft survival rates were calculated using the Kaplan-Meier method and compared by log-rank test. Patient death or need for re-LT was considered graft loss. Differences between means were tested by the standard two-sample *t*-test, whereas differences in proportions were tested by Pearson's Chi-squared test. Analyses were performed by intention-to-treat analysis. *P* less than .05 is considered statistically significant. Continuous data are presented as mean ± SD, and categorical data are presented as proportions.

Results

Patient Survival

Fifteen patients in each group died. Causes of death for both groups are listed in Table 2. Actuarial patient

Table 2. Causes of Death

Diagnosis	Group D	Group T
Sepsis & MSOF	8	4
Intracranial	3	1
Cardiopulmonary	2	2
Malignancy		1
Recurrent HCV	1	1
PTLD/GVHD		1
Portal vein thrombosis	1	
Liver failure (PNF)		1
Suicide		2
Chronic renal failure		2
Total	15	15

NOTE. Values expressed as number of patients.
Abbreviations: MSOF, multisystem organ failure; PTLD, posttransplant lymphoproliferative disorder; PNF, primary nonfunction; GVHD, graft-versus-host disease.

survivals at 4 years were 72.8% in group D and 73.8% in group T (P = not significant [NS]; Fig. 1).

Graft Survival

Four-year actuarial graft survivals were 65.6% in group D and 65.4% in group T (P = NS; Fig. 2).

Seven patients (12.5%) in group D and six patients (12%) in group T received a second transplant. Two patients in group D and one patient in group T received a third transplant. Indications for re-LT are listed in Table 3.

Rejection

Rejection was confirmed by biopsy in more than 95% of cases. Borderline to mild rejection was not treated (n = 8; 5 patients, group D; 3 patients, group T) and not included in analysis.

Thirty-five patients (62.5%) in group D and 35 patients (70%) in group T did not receive antirejection treatment. Twenty-one patients (37.5%) in group D and 15 patients (30%) in group T had at least one episode of rejection (P = NS), and 7 patients (12.5%) in group D and 10 patients (20%) in group T had a second episode of rejection. Three patients (5%) in group D and 2 patients (4%) in group T had three episodes of rejection, and 1 patient in each group had a fourth episode (Table 4). Thus, there were 32 episodes of rejections in group D (0.57/patient) and 28 episodes in group T (0.56/patient; P = NS).

Recurrent HCV

Three patients underwent re-LT for recurrent HCV; one patient (2%) in group D and two patients (4%) in group T. Two patients died with recurrent HCV without re-LT, one patient in each group, 10.2 and 29.8 months post-LT. Recurrence was diagnosed by liver biopsy in patients with abnormal liver function. Ninety-eight biopsies (1.75/patient) were performed in group D and 89 biopsies (1.78/patient) were performed in group T. Pathologists were blinded with regard to the treatment regimen. The same criteria were used in all cases to diagnose recurrent HCV: hepatitis activity index (HAI) and fibrosis score, described by Ishak et al.[27] Overall, 49 patients (46.2%) had recurrent HCV; 26 patients (46.4%) in group D and 23 patients (46%) in group T. Mean times to recurrence were 10.7 ± 9.5 months (median, 9.8 months; range, 1.1 to 20.9) in group D and 14.1 ± 14.6 months (median, 9.1 months; range, 1.8 to 43 months; P = NS) in group T. Mean HAI scores were 7.4 ± 2.7 (median, 7) in group D and 7.0 ± 3.4 (median, 6) in group T, and mean fibrosis scores were 2.9 ± 1.7 (median, 2) in group D and 2.6 ± 1.1 (median, 3) in group T. Mean times to recurrence were 612 ± 352 days in group D and 644 ± 441 days in group T. When a patient had undergone more than one liver biopsy, the highest score was used.

All recurrences were treated with a 20% to 40% decrease in baseline immunosuppression; in addition, 32 patients were administered IFN alfa, 3 million units, three times weekly subcutaneously, and 10 patients in group D and 9 patients in group T were administered ribavirin, 400 mg, orally twice daily. Nineteen patients (33.9%) in group D and 13 patients (26%) in group T were administered IFN. Recurrent HCV was established by biopsy. Prophylactic antiviral treatment was

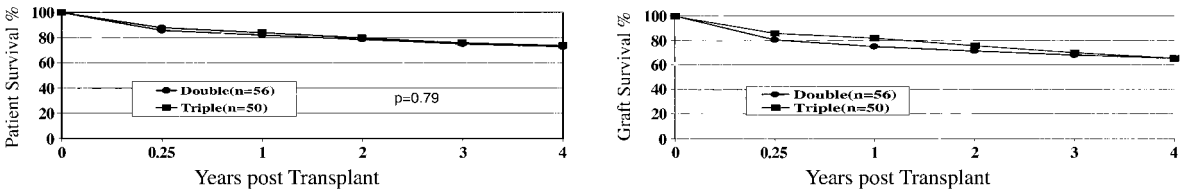

Figure 1. (Left) Patient and (right) graft survival over time in both groups.

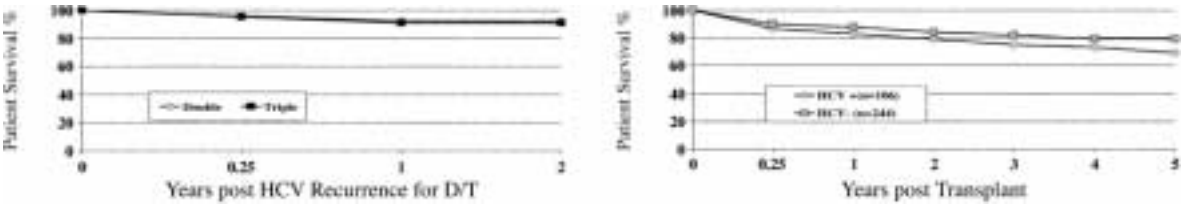

Figure 2. (Left) Patient survival after recurrent HCV for both groups and (right) for HCV-positive and HCV-negative patients.

not used. Liver function test results at the time of diagnosis of recurrent HCV and 3, 6, 12, and 24 months after diagnosis are listed in Table 5.

Rejection Before HCV Recurrence

The incidence of rejection was not different between patients who did or did not develop recurrent HCV. Of 49 patients who developed recurrence (26 patients, group D; 23 patients, group T), 32 patients (65%) were rejection free before the diagnosis of recurrent HCV. Seventeen patients (35%; 11 patients, group D; 6 patients, group T) had one or more episodes of rejection. Two patients in group D had two episodes of rejection, and one patient in group T had three episodes of rejections (Table 6). Of the 3 patients who required re-LT for recurrence, only 1 patient in group D had a single episode of mild acute rejection, whereas the other 2 patients in group T had no rejection.

Crossover

Nine patients (16%) in group D had MMF added to their maintenance immunosuppression therapy because of ongoing acute cellular rejection (n = 6) or nephrotoxicity (n = 3) a median of 7 days (mean, 81 ± 132 days; range, 2 to 385 days) after LT.

In group T, MMF therapy was discontinued in 30 patients (60%) because of infectious complications (n = 13; 26%), hematologic disorders (n = 8; 16%), gastrointestinal complications (n = 5; 10%), or other reasons (n = 4; 8%) a median of 35 days (mean, 80 ± 110 days; range, 2 to 434 days) post-LT.

Table 3. Causes of Re-LT

Causes	Group D	Group T
Primary nonfunction	3	1
Hepatic artery thrombosis	3	1
Hepatitis recurrence	1	2
Graft-versus-host disease		1
Biliary stricture (intrahepatic)		1
Total	7 (12.5)	6 (12)

NOTE. Only first re-LT is included; two patients in group D (for primary nonfunction and late chronic rejection) and one patient in group T (hepatic artery thrombosis) underwent a second re-LT. Values expressed as number (percent).

Discussion

Mycophenolic acid (the active component of MMF) has been shown to inhibit replication of yellow fever, parainfluenza, coxsackievirus B4, Epstein-Barr virus, and human immunodeficiency virus in vitro.[18-20,28] Neyts and De Clercq[18] reported the inhibitory effect of MMF and acyclovir on herpes virus in a murine model and in vitro. Birkeland et al[20] showed a reduced rate of primary or reactivation Epstein-Barr virus infection when MMF was administered with acyclovir to 208 kidney transplant recipients.

In the present report, there was no difference in patient or graft survival between the two groups. In

Table 4. Rate and Severity of Rejection for All Patients

	Group D	Group T	Total
No. of rejection episodes			
0	35 (62.5)	35 (70)	70 (66)
1	21	15	36
2	7	10	17
3	3	2	5
4	1	1	2
Total	32	28	60
Rejection/patient	0.57	0.56	0.57
Clinical without biopsy (included as mild)	2	1	3
Untreated borderline (not included)	5	3	8
Severity of rejection			
Borderline/mild	24 (75)	22 (79)	46 (77)
Moderate	6	5	11
Severe	2	1	3

NOTE. Values expressed as number (percent). N = 106.

Table 5. Biochemical Changes After Recurrent HCV and Histological Findings

	Treatment Group	At Time of Recurrence	Months Postrecurrence				
			1	3	6	12	24
Biochemical changes							
T Bili (mg/dL)	D	1.1	1.3	1.5	0.9	16	0.9
	T	1.3	1.1	4.1	1.3	1.4	0.9
AST (U/L)	D	131	147	81	78	83.7	84.2
	T	108	112	126	89	89	111
ALT (U/L)	D	180	159	102	96	80	99
	T	142	128	128	101	99	129
GGTP (U/L)	D	171	180	199	216	155	162
	T	170	165	184	210	143	132
ALKP (U/L)	D	146	141	144	195	138	133
	T	220	237	250	249	173	201

Histological Findings							
Treatment Group	HAI			Fibrosis Score			Mean Days to Recurrence
	Mean	Median	Range	Mean	Median	Range	
D	7.4 ± 2.7	7	1-12	2.9 ± 1.7	2	1-6	612 ± 352
T	7.0 ± 3.4	6	3-11	2.6 ± 1.1	3	1-5	644 ± 441

Abbreviations: T Bili, total bilirubin; AST, aspartate amino transferase; ALT, alanine amino transferase; ALKP, alkaline phosphatase; GGT, γ-glutamyl transferase; HAI, hepatitis activity index.

addition, rates of HCV recurrence were similar. Fasola et al[29] studied 37 patients and found no advantage of MMF at 1 or 2 years in terms of the incidence or severity of HCV recurrence. Similarly, Smallwood et al[30] failed to show a difference in rate of recurrence, time to recurrence, rate of response to IFN, HAI, or survival in 47 patients administered MMF. Platz et al[31] described 11 patients with HCV who were administered MMF and found a reduction in viral load and a biochemical response in 77% of patients, with 100% patient and graft survival. Weppler et al[32] reported on 11 patients administered MMF for recurrent HCV and initially reported 100% patient and graft survival; however, with additional follow-up to 29 months, a patient survival rate of 63% and graft survival rate of 54% were observed.

Table 6. Rate of Rejection in Patients With Recurrent HCV

No. of Rejections	Group D	Group T	Total
0	15 (58)	17 (74)	32 (65)
1	9 (35)	5 (21)	14 (30)
2	2 (8)	0 (0)	2 (4)
3	0 (0)	1 (4)	1 (2)
Total	11 (42.3)	6 (26.1)	17 (34.7)

NOTE. Values expressed as number (percent). N = 49.

In the present report, we failed to show a beneficial affect of MMF with TAC in the prevention of HCV recurrence based on biochemical changes and clinically indicated liver biopsies. It is conceivable that the anti-HCV effect of MMF is not potent enough to prevent recurrent HCV in patients administered TAC-based immunosuppression. In long-term survivors after LT in whom maintenance immunosuppression is lower, MMF may have antiviral effects, as observed by Platz et al.[31] It is possible that in the present study, patients were exposed to a greater level of immunosuppression, which allowed HCV replication at a faster rate. A future study with reduced dosages of steroids and calcineurin inhibitors at the time of introduction of MMF may be able to achieve similar immunosuppression and at the same time offer the antiviral advantages of MMF.

Kato et al reported a beneficial effect of an interleukin-2 (IL-2) receptor antagonist after recurrence of HCV in patients resistant to conventional treatment.[33] At the American Society of Transplantation meeting, two separate groups with contradictory findings presented the prospect of using IL-2 receptor blockade from the outset. In a randomized study of 28 patients with HCV, the Miami group showed a beneficial effect of IL-2 receptor blockade with steroids,[34] whereas the

Washington group showed aggressive and early recurrence of HCV with the use of IL-2 receptor blockade in 26 patients. However, in the latter experience, the antibody was used with steroids.[35] Future studies to examine genotype, serial viral loads, and protocol biopsies may be more useful. Liver biopsies alone at the time of biochemical changes may not be adequate to diagnose recurrent HCV in all cases.

The response to antiviral treatment of HCV in immunocompetent patients has not improved as much as it has in hepatitis B virus. Because of the lack of significant improvement in immune modulation for HCV, e.g., effective vaccination and passive immune prophylaxis, the prognosis for patients with HCV undergoing LT remains clouded. Thus, trials using new combinations of agents in this group of transplant recipients are warranted.

In conclusion, in liver transplant recipients with HCV, MMF with TAC and steroids was not found to be effective in prolonging patient or graft survival or reducing the incidence of rejection or recurrent HCV based on liver biopsies at the time of biochemical changes. In addition, there was no difference in HAI or fibrosis score with or without MMF. Future protocols consisting of lower doses of steroids and calcineurin inhibitors, perhaps with an IL-2 receptor antagonist and MMF, may be worth considering as part of a strategy to reduce the rate of recurrent HCV after LT.

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