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ORIGINAL ARTICLE

Potential Immunological Advantage of Intravenous Mycophenolate Mofetil with Tacrolimus and Steroids in Primary Deceased Donor Liver Transplantation and Live Donor Liver Transplantation Without Antibody Induction

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With the current immunosuppressive regimens, graft loss secondary to immunological reasons after successful liver transplantation is a rarity; acute rejections, however, do occur, with the majority of them being steroid-responsive. The aim of the present study is to examine the rate of acute rejection with tacrolimus, intravenous (IV) mycophenolate mofetil (MMF), and steroids in primary deceased donor liver transplant (DDLT) and live donor liver transplant (LDLT) recipients. During the year 2005, 130 patients (mean age: 54.9 ± 10.8, males: 84, females: 46, 112 DDLT and 18 LDLT) received primary liver transplantation. They were followed up for the incidence of acute rejection in the first 12 months. Liver biopsies were performed as clinically indicated; protocol liver biopsies were never performed. A total of 127 liver biopsies were performed. Thirty-two had a rejection activity index (RAI) score of ≥3, of which 24 biopsies in 20 patients were not treated with a steroid bolus. Eight (6.1%) patients (mean RAI score: 5.1 ± 1.4) received 750 to 1500 mg of methylprednisolone over 3 days. Out of these, 2 were noncompliant, 4 were off MMF, and 1 was on cyclosporine. All patients responded to steroid therapy. None of the patients required any antibody preparation. In conclusion, IV MMF with tacrolimus and steroids is useful and required antirejection therapy in 6.1% of liver transplant recipients. ***Liver Transpl 14:202–209, 2008.*** © **2008 AASLD.**

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The introduction of cyclosporine in the early 1980s almost doubled patient and graft survival after liver transplantation.[1-3] Steroid-resistant acute cellular rejection could be reversed with the use of monoclonal murine anti-CD3 (OKT3) preparation.[4] With the introduction of tacrolimus in the early 1990s, the hepatic graft loss from acute or chronic rejection became a rarity.[5,6] However, acute rejections after primary liver transplantation do occur, although with reduced incidence and severity.[7-10] Most of the acute rejections can be easily reversed with the use of steroids and/or conversion to tacrolimus from cyclosporine A.[11-14] Newer

Abbreviations: Alk PO4, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CsA, cyclosporine A; DDLT, deceased donor liver transplant; ETOH, alcohol-induced cirrhosis; GGTP, gamma glutamyl transpeptidase; HAI, hepatitis activity index; HBV, hepatitis B viral infection–related cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus, hepatitis C viral infection, or hepatitis C viral infection–related cirrhosis; IV, intravenous; LDLT, live donor liver transplant; LTx, liver transplant; MELD, Model for End-Stage Liver Disease; MMF, mycophenolate mofetil; MPA, mycophenolic acid; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; Pred, prednisolone; PSC, primary sclerosing cholangitis; RAI, rejection activity index; Tacro, tacrolimus; SD, standard deviation; TTP, thrombotic thrombocytopenic purpura.

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immunosuppressive medications, mycophenolate mofetil (MMF) and chimeric and humanized antibody against interleukin 2 receptor, have been successfully used with calcineurin inhibitor and steroids to reduce the rate of acute rejection even further.[15-17] Rapamune, a target of rapamycin inhibitor,[18] had also been used with tacrolimus, and the initial results were very promising.[19] Unfortunately, because of the increased rate of hepatic artery thrombosis[20] in primary liver transplantation, the Food and Drug Administration has prohibited its use for the first 30 days after liver transplantation.

MMF is an inosine monophosphate dehydrogenase inhibitor that prevents the *de novo* synthesis of purine in lymphocytes.[21,22] The drug was initially used with cyclosporine in kidney transplantation with significant reduction in the rate of acute rejection. Subsequently, the drug was used in liver transplantation.[23] It showed a further reduction in acute rejection with better preservation of the renal function. However, in more than 50% of the patients, the drug was discontinued for gastrointestinal, bone marrow suppression, and other reasons.[15,24] All the trials in kidney and liver transplantation were performed with an oral formulation of MMF. There are several reports to suggest a reduced rate of acute cellular rejection after primary liver transplantation with the use of oral MMF, tacrolimus, and steroids,[16,24,25] but the fact remains that rejection does occur.

Bioavailability of oral MMF in liver transplant (LTx) recipients is different compared to that in healthy volunteers and kidney transplant, heart transplant, and lung transplant recipients, for whom the absorption is more than 90%. In LTx patients, it was found that the trough concentration of mycophenolic acid (MPA; active metabolite of MMF) improved during the first 30 days post transplantation,[26] and bioavailability was almost double 4 weeks post LTx compared to 1 week post LTx.[27] At our institution, we have been using intravenous (IV) MMF in immediate post-LTx patients until the patients can take oral MMF. We initially reported a retrospective analysis of 28 live donor liver transplants (LDLTs) using IV MMF with a 10.5% rate of late acute rejections; in the majority of those patients, compliance was in question.[28] We subsequently performed a pharmacokinetic study in LTx recipients and found that the bioavailability of oral MMF and peak concentration of MPA were less than 50% in comparison with IV MMF.[29]

The aim of the present study is to examine the rate of acute rejection, severity of rejection, and response to antirejection therapy in primary deceased donor liver transplant (DDLT) and LDLT recipients.

PATIENTS AND METHODS

Between January 2005 and December 2005, 130 consecutive, nonrandomized patients with primary liver transplantation (112 DDLT and 18 LDLT) were examined according to an institute review board–approved protocol. There were 84 male and 46 female patients. The mean age of the recipients was 54.9 ± 10.8 years (DDLT, 55.3 ± 11.4; LDLT, 52.1 ± 5.9), and the mean donor age was 49.3 ±16.2 years (DDLT, 51.2 ± 16.2; LDLT, 37.7 ± 10.5). The overall mean Model for End-Stage Liver Disease score at the time of LTx was 20.4 ± 9.6 (DDLT, 21.6 ± 9.8; LDLT, 13.5 ± 4.6). The primary diagnosis of the patients is shown in Table 1. Post transplantation, the incidence and severity of rejection, treatment and response of rejection, and liver function for the first 12 months were examined. Biopsies were performed as clinically indicated. Protocol biopsies were never performed. All biopsies were reviewed by the same pathologist and scored for rejection activity index (RAI; per Banff's criteria[30]), hepatitis activity index, fibrosis, cholestasis, steatohepatitis, and ischemic injury. Immunosuppression at various time intervals from LTx for DDLT and LDLT is given in Table 2.

Immunosuppression Protocol

All patients were initiated on IV MMF at a dose of 1 g twice daily (constant 2-hour infusion) and then converted to oral MMF at a dose of 1 g twice daily when they would tolerate oral intake. In addition, study patients received oral tacrolimus, starting at a dose of 0.05 mg/kg twice daily. The dose of tacrolimus was adjusted according to the clinical conditions, and the target trough levels were normally maintained around 8-10 ng/mL in the first month and then gradually reduced to 6 ng/mL by 12 months. The patients also received 500 mg of methylprednisolone prior to reperfusion of the liver. A total dose of 200 mg/day of methylprednisolone was given over 5 days with 20 mg of prednisolone thereafter as maintenance.

RESULTS

Every patient was followed up for a period of 12 months to evaluate the rate of rejection. A total of 127 liver biopsies were performed as clinically indicated. Sixty-seven patients had 1 liver biopsy, 31 had 2 liver biopsies, 15 had 3 liver biopsies, 8 had 4 liver biopsies, and 6 had 5 liver biopsies.

Out of these, 71 biopsies were performed for patients with hepatitis C virus (HCV) infection (1.6 biopsies per patient), and 56 were performed for non-HCV patients (0.6 biopsies per patient). The distribution of RAI is given in Table 3. Out of 127 biopsies, 95 biopsies (74.8%) had an RAI score of ≤2 (0: 15, 1: 39, 2: 41), and the remaining 32 (25.2%) had an RAI score of ≥3. Out of 32 biopsies with an RAI score of ≥3, 24 biopsies in 20 patients were not treated with steroid bolus because of associated HCV infection (n = 12 patients), bile duct stricture (n = 3 patients), and other associated conditions (n = 5 patients; Table 4).

The remaining 8 patients (DDLT: 7, LDLT: 1, mean RAI score: 5.1 ± 1.4) received 750 to 1500 mg of methylprednisolone over 3 days. Details of these patients are summarized in Table 5. One patient had moderate cholestasis (#71) and ischemic injury, and another (#109) had moderate central cholestasis and 30% steatosis; however they both responded to steroid bolus. Three patients had subtherapeutic tacrolimus trough concentrations (<5.0 ng/mL). One patient (#113) was on a

TABLE 1. Characteristics of Patients: DDLT Versus LDLT

	DDLT	LDLT	Overall
Demographics			
Male	75	9	84
Female	37	9	46
Mean age recipients (years)	55.3 ± 11.4	52.1 ± 5.9	54.9 ± 10.8
Mean age donors (years)	51.2 ± 16.2	37.7 ± 10.5	49.3 ± 16.2
Mean MELD score	21.6 ± 9.8	13.5 ± 4.6	20.4 ± 9.6
Diagnosis			
HCV	37	8	45
ETOH	30	5	35
PBC	4	2	6
Autoimmune	6	0	6
PSC	3	0	3
NASH	3	0	3
Hemochromatosis	2	0	2
HBV	3	0	3
Sarcoidosis	2	0	2
Acute fulminant hepatic failure	1	0	1
Biliary atresia	1	0	1
Cryptogenic	19	3	22
HCC without cirrhosis	1	0	1
*Total	112	18	130

Abbreviations: DDLT, deceased donor liver transplant; ETOH, alcohol-induced cirrhosis; HBV, hepatitis B viral infection–related cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C viral infection–related cirrhosis; LDLT, live donor liver transplant; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.
*Twenty-three patients also had HCC.

microemulsion formulation of cyclosporine without MMF, and another 3 patients (#83, LDLT; #109 and #121, DDLT) were not on MMF at the time of rejection. The mean time to rejection was 74.0 ± 76.2 days post transplant. Two patients (#80 and #92) were noncompliant for taking immunosuppressive medication. Seven patients are currently alive with nearly normal liver function. All patients responded to steroid therapy. None of the patients received monoclonal antibodies for induction or as treatment for rejection.

DISCUSSION

Despite improvement in patient survival and graft survival with an extremely low rate of graft loss from acute or chronic rejection, acute rejection does occur with varying frequencies. The majority are steroid-responsive; steroid-resistant rejections, however, are also cited in up to 36% of cases (Table 6).

The rate of acute cellular rejection in the US multicenter trial[31] was 58.55% in the tacrolimus group and 65.03% in the cyclosporine group. Corticosteroid-resistant rejection occurred under the tacrolimus group and cyclosporine group in 16.34% and 30.82% of patients, and refractory rejection occurred in 2.28% and 12.03% of patients, respectively. In the European multicenter trial,[32] the rates of acute rejection were 40.5% for tacrolimus and 49.8% for cyclosporine. For refractory acute and chronic rejections, comparisons for tacrolimus versus cyclosporine were 0.8% versus 5.3% and 1.5% versus 5.3%, respectively. The highest rate of acute rejection of 83.2% was reported in the cyclosporine group in the Pittsburgh randomized trial.[9] In several other studies, rates varying from 26% to 76% have been reported.[7,8,16,33,34] The rate of acute rejection with tacrolimus and MMF in the Pittsburgh prospective randomized study[24] was 38.9% for triple versus 45.2% for double at 12 months. The lowest rate of acute rejection (10.7%) was reported for IV MMF with tacrolimus and steroids in LDLT with a mean follow-up of 17 months.[28]

In the present study, the overall rate of acute rejection that required antirejection therapy in the first year post transplant was 6.1%. All patients were steroid-responsive. Out of the 8 patients who required steroid bolus, 2 patients were noncompliant for taking immunosuppressive agents, 3 patients had a subtherapeutic tacrolimus concentration, and 4 patients were not on MMF. Higher rates of rejection have been reported in patients who were not on MMF maintenance therapy.[35] The main difference in the present study is that we used the IV formulation of MMF, whereas in other studies oral MMF was used (Table 6).

Oral MMF is reported to have a bioavailability of >90% in healthy volunteers, kidney transplant recipients, and heart transplant recipients.[28,36-38] In LTx patients, a progressive rise of the MPA trough concentration has been reported over the first month post transplant, which correlates with the rise in serum albumin.[26,39] Also, an increase in the area under the curve after oral MMF at 2 weeks post LTx and after 4

TABLE 2. Immunosuppression (Mean Values)

	Post LTx																	
	1 Month				3 Month				6 Month				9 Month				12 Months			
	Tacro Dose (mg/day)	Tacro Level (ng/mL)	MMF Dose (mg/day)*	Pred Dose (mg/day)*	Tacro Dose (mg/day)	Tacro Level (ng/mL)	MMF Dose (mg/day)*	Pred Dose (mg/day)*	Tacro Dose (mg/day)	Tacro Level (ng/mL)	MMF Dose (mg/day)*	Pred Dose (mg/day)*	Tacro Dose (mg/day)	Tacro Level (ng/mL)	MMF Dose (mg/day)*	Pred Dose (mg/day)*	Tacro Dose (mg/day)	Tacro Level (ng/mL)	MMF Dose (mg/day)*	Pred Dose (mg/day)*
Overall	6.0	10.2	1750	18.8	5.2	8.0	2201	14.1	4.7	6.9	1245	10.0	5.0	8.3	1118	9.9	4.8	7.7	1023	9.5
DDLT	6.0	10.3	1716	18.7	5.3	8.0	2318	14.0	4.8	6.8	1216	10.0	4.8	8.2	1071	9.9	4.7	7.8	972	9.4
LDLT	5.7	9.1	1929	19.4	4.9	8.2	1692	14.4	4.1	7.1	1333	10.3	5.9	8.9	1250	10.0	4.9	6.8	1200	10.0
Mean	5.9	9.9	1798	19.0	5.1	8.1	2070	14.2	4.5	6.9	1264	10.1	5.2	8.5	1146	9.9	4.8	7.4	1065	9.6
SD	0.2	0.7	114	0.4	0.2	0.1	332	0.2	0.4	0.1	61	0.2	0.6	0.4	92	0.1	0.1	0.5	119	0.3

Abbreviations: DDLT, deceased donor liver transplant; LTx, liver transplant; MMF, mycophenolate mofetil; LDLT, live donor liver transplant; Pred, prednisolone; SD, standard deviation; Tacro, tacrolimus.
*Mean daily dose for the patients who were on the drug.

TABLE 3. Distribution of RAI

	Biopsy 1	Biopsy 2	Biopsy 3	Biopsy 4	Biopsy 5	Total
RAI						
0	11	2	1	1	0	15
1	19	10	6	2	2	39
2	20	8	5	4	4	41
3	8	6	2	0	0	16
4	4	4	1	1	0	10
5	2	0	0	0	0	2
6	2	0	0	0	0	2
7	1	1	0	0	0	2
Total	67	31	15	8	6	127
HCV	34	20	10	4	3	71
Non-HCV	33	11	5	4	3	56
DDLT	56	27	15	8	6	112
LDLT	11	4	0	0	0	15

Abbreviations: DDLT, deceased donor liver transplant; HCV, hepatitis C viral infection; LDLT; live donor liver transplant; RAI, rejection activity index.

weeks post LTx compared to the first week was also described.[27] However, a formal kinetic study in the immediate postoperative period in LTx recipients was never done. It was presumed that it would be the same as that of healthy volunteers and kidney transplant and heart transplant patients. Our previous study has shown that oral absorption of MMF in the second week is less than 50% and may be even less in the first week in LTx recipients. Also, the peak concentration of MPA with IV MMF was more than twice that of oral MMF.[29] A higher peak concentration and higher area under the curve of MPA with tacrolimus and steroids allow the hepatic allograft to survive without significant risk of acute rejection.

It is true that over a period of time clinicians have learnt not to treat borderline acute rejection (RAI < 3). Also, borderline acute rejection could be hard to distinguish from recurrent HCV. Indication of LTx with HCV infection has increased. Avoidance of steroid bolus in the presence of HCV recurrence with borderline rejection is currently practiced more frequently than in the past. In the present study, 20 patients (24 biopsies) had an RAI score of ≥ 3 and were elected not to receive steroid bolus, whereas in some other studies, the same patients may have been treated. With 3 immunosuppressive agents as baseline maintenance, clinicians may feel more comfortable by adjusting the baseline maintenance doses of immunosuppressive agents rather than steroid bolus.

Despite this change in management of acute rejection, we feel that immediate postoperative administration of the IV formulation of MMF may have an advantage over oral MMF, for which bioavailability and peak concentration are less than 50% in LTx recipients.[29] Further immunological studies with qualitative differentiation of various lymphocytic populations using immunological markers and measurements of cytokine

TABLE 4. Rejection—No Treatment

					Liver Function					Biopsy Findings						Immunosuppression at the Time of Rejection			
Case No.	Age (years)	M/F	Primary Diagnosis	Days Post LTx Rejection	Bilirubin (mg/dL)	AST (u/L)	ALT (u/L)	Alk PO4 (u/L)	GGTP (u/L)	RAI	HAI	Fibrosis	Steatosis	Cholestasis	Ischemic Injury	Tacro Level (ng/mL)	MMF (mg/day)	Prednisone (mg/day)	Reason for No Treatment
DDLT																			
2	45.6	F	Hepatitis C	114	6.1	75.0	96.0	851.0	1194.0	3.0	1.0	1	None	None	None	3.9	0	0	Hepatitis C viral infection
9	55.8	M	Hepatitis C	115	3.3	382.0	391.0	635.0	2861.0	4.0	6.0	2	None	None	None	4.0	0	5	Hepatitis C viral infection
14	54.2	M	Hepatitis C	146	5.9	94.0	128.0	1634.0	3734.0	3.0	2.0	2	None	None	None	10.7	0	10	Hepatitis C viral infection
16*	52.8	M	Hepatitis C	41	1.9	107.0	174.0	290.0	443.0	3.5	3.0	1	Mild	None	None	11.6	2000	10	Hepatitis C viral infection
24	45.3	M	Hepatitis C	543	0.4	125.0	153.0	172.0	197.0	3.5	7.0	3	1	None	None	8.4	0	20	Hepatitis C viral infection
41	44.1	M	Hepatitis C	141	2.4	159.0	367.0	341.0	637.0	3.0	4.0	0	None	None	None	9.0	2000	20	Hepatitis C viral infection
42†	51.2	M	ETOH	29	5.6	57.0	72.0	605.0	—	3.5	0.0	0	5%	None	None	3.6	2000	40	Bile duct stricture
43	75.8	M	ETOH	37	1.5	446.0	580.0	1097.0	—	4.5	0.0	0	None	None	None	0.0	1000	15	Neurotoxicity‡
45	46.0	F	ETOH	6	22.1	77.0	119.0	86.0	45.0	3.5	0.0	0	None	Marked	None	0.0	0	0	Had TTP§
48	45.1	M	ETOH	180	0.5	303.0	374.0	570.0	1028.0	4.5	0.0	0	None	None	None	3.4	1000	5	Baseline medication changed‖
56	56.6	M	Hepatitis C	23	10.9	71.0	82.0	281.0	338.0	3.0	0.0	5	None	None	None	6.9	1000	10	Hepatitis C
60	44.5	F	ETOH	18	10.5	92.0	106.0	586.0	387.0	3.0	0.0	0	None	None	None	9.6	2000	20	Biliary abscess
70	40.5	M	Hepatitis C	13	2.7	10.0	64.0	101.0	—	4.0	0.0	0	None	None	None	5.2	2000	20	Hepatitis C viral infection + neurotoxicity
75	52.8	F	Autoimmune	166	0.6	99	179	208	85.0	3.0	0.0	0	None	None	None	8.5	0	5	Cellulitis with fever¶
113	32.7	M	Hepatitis C	149	8.6	115.0	240.0	795.0	682.0	3.0	2.0	0	None	None	None	—#	2000	20	Hepatitis C viral infection
115	47.9	M	Hepatitis C	296	0.7	101.0	162.0	122.0	—	3.0	5.0	0	None	None	None	11.0	0	5	Hepatitis C viral infection
116	53.1	M	Hepatitis C	248	0.7	19.0	35.0	286.0	—	3.5	2.0	0	None	None	None	5.9	0	20	Hepatitis C viral infection
119	60.6	F	PBC	223	0.5	85.0	138.0	367.0	767.0	3.0	0.0	0	Mild	None	None	8.2	1000	10	Bile duct stricture
LDLT																			
40	60.2	M	Hepatitis C	55	0.6	78.0	127.0	381.0	694.0	3.0	1.5	0	Mild	Mild	None	—**	2000	15	Hepatitis C viral infection
83	53.2	F	Cryptogenic	93	1.4	33.0	48.0	145.0	118.0	4.0	0.0	0	None	None	None	7.0	0	15	Baseline medication changed††

Abbreviations: Alk PO4, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DDLT, deceased donor liver transplant; ETOH, alcohol-induced cirrhosis; F, female; GGTP, gamma glutamyl transpeptidase; HAI, hepatitis activity index; LDLT, live donor liver transplant; LTx, liver transplant; M, male; MMF, mycophenolate mofetil; PBC, primary biliary cirrhosis; RAI, rejection activity index; Tacro, tacrolimus; TTP, thrombotic thrombocytopenic purpura.

*Case 16 had 2 biopsies.

†Case 42 had a total of 5 biopsies. The first biopsy was treated with steroids (Table 6); he had persistent bile duct stricture with recurrent cholangitis and did not receive steroid bolus.

‡For case 43, Tacro was put on hold, and he was switched to cyclosporine A.

§Case 45 had TTP. Tacro was put on hold, and he was given intravenous immunoglobulin.

‖For case 48, Tacro was increased from 2 to 3 mg twice daily, MMF was increased from 1000 to 2000 mg/day, and prednisolone was increased from 5 to 20 mg/day.

¶For case 75, the Tacro dose was increased from 4 to 5 mg twice daily.

#Case 113 had 2 biopsies; the first was treated (Table 6), and the second was not treated. The patient was on cyclosporine A at a level of 160 ng/mL.

**Case 40 was on cyclosporine A at a level of 159 ng/mL.

††For case 83 (Biopsy 1), the Tacro dose was increased from 3 to 5 mg/day, and labs spontaneously improved.

TABLE 5. Details of Acute Rejection and Management

					Liver Function					Biopsy Findings						Immunosuppression at the Time of Rejection			Treatment of		
Case No.	Age (Years)	M/F	Primary Diagnosis	Days Post LTx Rejection	Bilirubin (mg/dL)	AST (u/L)	ALT (u/L)	Alk PO4 (u/L)	GGTP (u/L)	RAI	HAI	Fibrosis	Steatosis	Cholestasis	Ischemic Injury	Tacro Level (ng/mL)	MMF (mg/day)	Prednisone (mg/day)	Rejection: Methyl Prednisone	Associated Risk Factors	Outcome
DDLT																					
42	51.2	M	Laennec's	10	9.3	40	78	106	136	6	0	0	7%	—	—	5.9	1000	5	750 mg over 3 days	Renal failure, Tacro dose reduced	Responded
71	45.7	M	HCV and ETOH	11	20.9	39	97	247	398	4	0	0	—	moderate	moderate	5.9	2000	20	750 mg over 3 days	None	Responded
80*	68.9	M	Hemochromatosis and ETOH	112	0.6	275	500	561	294	3	0	0	—	—	—	3.5	1000	0	750 mg over 3 days	Non-compliant for medications,	Responded
92†	57.0	M	HCV and ETOH	53	12.8	88	341	206	569	7.5	0	0	—	—	—	5.6	1000	10	1500 mg over 3 days	Non-compliant for medications and ETOH	Responded
109	49.4	M	HCV and ETOH	34	5.7	100	113	551	172	5	2	0	30%	moderate	—	4	0	10	750 mg over 3 days	Severe sepsis, bile duct stricture, severe cholangitis	Delayed response, 7 weeks
113	32.7	M	HCV	143	1.2	447	542	398	229	5	0	0	—	—‡	—	—§	0	0	1000 mg over 3 days	On CsA, not on MMF	Delayed response, 10 weeks
121	60.8	F	Cryptogenic	12	6.2	20	67	199	460	6	0	0	0	mod	—	4.3	0	10	1000 mg over 3 days	Not on MMF	Responded
LDLT																					
83	53.2	F	Cryptogenic	217	1.3	195	412	197	26	4	0	0	—	—	—	6.4	0	15	1500 mg over 3 days	Not on MMF	Responded
Mean	52.4			74.0	7.3	150.5	268.8	308.1	285.5	5.1	0.3	0.0		5.1	625.0	8.8					
SD	10.7			76.2	7.0	148.1	201.7	173.3	181.0	1.4	0.7	0.0		1.1	744	6.9					

Abbreviations: Alk PO4, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CsA, cyclosporine A; DDLT, deceased donor liver transplant; ETOH, alcohol-induced cirrhosis; F, female; GGTP, gamma glutamyl transpeptidase; HAI, hepatitis activity index; HCV, hepatitis C viral infection–related cirrhosis; LDLT, live donor liver transplant; LTx, liver transplant; M, male; MMF, mycophenolate mofetil; RAI, rejection activity index; SD, standard deviation; Tacro, tacrolimus.

*Case 80 was noncompliant for medications.

†Case 92 was noncompliant for medications and ETOH.

‡Case 113 had multiple microabscesses.

§Case 113 had a CsA level of 86 ng/mL.

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TABLE 6. Rate of Acute Rejection in Some Published Studies

Author	No. of Cases	Immunosuppression Protocol	Rate of Acute Rejection at 12 Months	Rate of Steroid-Resistant Rejection (%)
Jain et al.[28]	28	IV MMF + low-dose tacrolimus + steroids	10.7%*	Not given
Gonzalez et al.[7]	180	Dual therapy: tacrolimus + steroids; triple therapy: tacrolimus + steroids + azathioprine	40.7% (dual therapy); 24.4% (triple therapy)†	4.4% (dual therapy); 2.3% (triple therapy)
Fagiuali et al.[33]	3323	Variable	43.50%	19.10%
Boillot et al.[34]	245	Dual therapy: tacrolimus + steroids; triple therapy: tacrolimus + steroids + azathioprine	38.0% (dual therapy); 37.9% (triple therapy)	7% (dual therapy); 7.4% (triple therapy)
Jain et al.[24]	350	Dual therapy: tacrolimus + steroids; triple therapy: tacrolimus + steroids + oral MMF	45.2% (dual therapy); 38.9% (triple therapy)	4% (dual therapy); 2.8% (triple therapy)
Eckhoff et al.[16]	130	Study: tacrolimus + oral MMF + steroids; controls: tacrolimus + steroids	26% (study); 45% (control)	0% (study); 6.25% (control)
Wiesner et al.[8]	529	Cyclosporine + azathioprine + steroids; tacrolimus + steroids	76% (cyclosporine); 68% (tacrolimus)	36% (cyclosporine); 19% (tacrolimus)
Fung et al.[9]	154	Tacrolimus + steroids; cyclosporine + steroids	63.8% (tacrolimus); 83.2% (cyclosporine)	Not given
US Multicenter FK506 Liver Study Group[31]	529	Tacrolimus + steroids; cyclosporine + azathioprine + steroids	58.55% (tacrolimus); 65.03% (cyclosporine)	16.34% (tacrolimus); 30.82% (cyclosporine)
European Multicenter FK506 Liver Study Group[32]	545	Tacrolimus + steroids; cyclosporine + steroids	40.5% (tacrolimus); 49.8% (cyclosporine)	0.8% (tacrolimus); 5.3% (cyclosporine)

Abbreviations: IV, intravenous; MMF, mycophenolate mofetil.
*Mean follow-up of 17 months.
†Rate of rejection at 3 months.

and compliment levels may be useful for providing an effective rejection-free immunosuppression regime that is well tolerated in clinical practice without causing overimmunosuppression.

This is a single-center nonrandomized study; however, we do not believe that this precludes our observation of a low rate of rejection with IV MMF, tacrolimus, and steroids in post-LTx patients. Prospective randomized multicenter trials would, however, be useful to confirm our findings.

In conclusion, our observation suggests that IV use of MMF immediately after LTx, in combination with oral tacrolimus and steroids, may provide rejection-free status in a majority of LTx recipients. This may be related to the peak concentration and bioavailability of IV MMF being more than twice that of oral MMF in the immediate post-LTx period.

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