Long-Term Outcome of Adding Mycophenolate Mofetil to Tacrolimus for Nephrotoxicity Following Liver Transplantation

Ashokkumar Jain,[1,2,3,4] Raman Vekatramanan,[3] Bijan Eghtesad,[2] Mary Gadomski,[2] Ravi Mohanka,[1] Amadeo Marcos,[2] and John Fung, [2]

Mycophenolate mofetil (MMF) has no known nephrotoxicity. This report examines the outcome in patients who received MMF for renal impairment on tacrolimus-based immunosuppression. From 1995 to 1996, twelve liver transplantation (LTx) patients (mean age 54.6 years) with serum creatinine >1.8 mg/dl were included in the study. MMF was introduced and tacrolimus dose was reduced by 30–50%. Each patient was followed for 6 years. Renal function showed improvement in seven patients, deterioration in four, and no change in one patient. Overall mean serum creatinine decreased from 2.5 to 1.9 mg/dl at 6 months but increased to 2.2 mg/dl at 18 to 24 months. After that, renal function remained stable for 72 months. Iothalamate clearance showed 18.5% improvement at 1 year. Three patients developed renal failure. Six patients died in the follow-up period. Addition of MMF with reduced tacrolimus dose resulted in sustained improvement in renal function in 58% of patients.

Keywords: Liver transplantation, Nephrotoxicity, Tacrolimus, Mycophenolate mofetil.

(*Transplantation* 2005;80: 859–864)

Calcineurin inhibitors are potent immunosuppressive agents used in liver transplantation (LTx), but both cyclosporine and tacrolimus can cause nephrotoxicity (*1*,*2*). Mycophenolate mofetil (MMF) has been approved for clinical use for the last eight years. MMF has been used to reduce the nephrotoxicity of calcineurin-inhibitors by sparing or eliminating the use of these agents (*3*–*7*). Although MMF has been found to stabilize or reverse the nephrotoxicity in short term, the data with long-term follow-up is lacking.

The aim of the present study is to examine the long-term outcome of the patients who received MMF for tacrolimus-related nephrotoxicity in post-LTx patients.

PATIENTS AND METHODS

Consenting adult patients (age >18 years) were enrolled in the institutional review board (IRB) approved study. Pre-IRB approval committee had concerns about having a control group. Criteria included more than 6 months post-LTx, serum creatinine >1.8 mg/dl, and stable liver function. Pregnant women or women in childbearing age who refused double contraception were excluded. Before commencing MMF, glomerular filtration rate (GFR) was measured using iothalamate clearance analyzed by high-performance liquid chromatography (HPLC) (*8*). Ultrasound of the native kidneys was performed to rule out obstructive uropathy and measure the size of the kidneys. MMF was given orally 1 g twice a day and the dose of tacrolimus was reduced by 1 to 2 mg per dose (approximately 30–50%). The baseline dose of prednisone was held constant for 6 months. Each patient was followed for 6 years or until death, whichever was earlier. Liver function, tacrolimus level, and side effects of MMF were collected prospectively. Patients with decrease in serum creatinine and/or increase in GFR were considered as responders. Patients with increase in serum creatinine and/or decrease in GFR or commencement of dialysis were considered as failure and patients who maintained stable serum creatinine were considered as nonresponders.

Statistical Analysis

Values are given as mean and standard deviation. Parametric values are compared with Pearson chi-square. Changes in mean serum creatinine at various time points after MMF were compared with preMMF values using inde-

[1] Department of Surgery, Transplant Division, Strong Memorial Hospital, University of Rochester, Rochester, NY.
[2] Department of Surgery, Thomas E. Starzl Transplantation Institute, University of Pittsburgh, Pittsburgh, PA.
[3] Department of Pharmaceutical Sciences, University of Pittsburgh, Pittsburgh, PA.
[4] Address correspondence to: Ashokkumar Jain, M.D., University of Rochester Medical Center, Department of Surgery, Division of Transplantation, 601 Elmwood Ave., Box SURG, Rochester, NY 14642.
E-mail: ashok_jain@urmc.rochester.edu.
Initial data was presented at the 49th American Association for the Study of Liver Diseases. Chicago, IL, November 4–10, 1998 and the 9th Meeting of International Liver Transplantation, Barcelona, Spain, May 30 to June 4, 2003.
Received 7 February 2005. Revision requested 8 April 2005.
Accepted 23 May 2005.

ISSN 0041-1337/05/8006-859
DOI: 10.1097/01.TP.0000173994.63299.63

pendent *t* test. SPSS 12.0 for Windows, statistical package was used for analysis.

RESULTS

During the enrollment period, 12 patients entered the study. Mean age was 54.6±14.1 years (median 57.5, range 33–72), there were eight males and four females. Mean time to enter the study from liver transplantation was 57.25±32.37 months (median 46.35, range 21.4–127.9). The details of individual patient demographics with size of the native kidney are given in Table 1. Pre-MMF mean serum creatinine was 2.5±0.8 mg/dl (median 2.2, range 1.9–4.8)

Patient Survival and Renal Function

During the follow-up period, six patients died. Causes of death included cardiac arrest (n=2), head injury, cerebral anoxia, heart failure, and recurrent hepatocellular carcinoma (cases 1, 4, 5, 6, 8, 9, respectively). Three patients went into end-stage renal failure (case 4, 8, and 11), two of which received kidney transplantation (case 4 and 11). Blood urea nitrogen (BUN) and serum creatinine before MMF and 1, 3, 6, 12, 18, 24, 36, 48, 60, and 72 months after MMF are shown in Table 2. Mean serum creatinine decreased from 2.5±0.8 mg/dl to 1.9±2.0 mg/dl at 6 months (P=0.05), which increased to 2.2±2.1 mg/dl at 24 months (P=0.29). However, it remained stable until 72 months (mean serum creatinine 1.9±1.7; P=0.39) post-MMF in all responders, except in case 7 where it increased at 6 years (Table 3). In four patients (cases 4, 8, 9, 11), the serum creatinine deteriorated and three of them required dialysis. In one patient (case 7), the serum creatinine remained stable until 5 years and was considered as a nonresponder. GFR was available in only seven patients before and after starting MMF because one patient died in the first year, one patient underwent a kidney transplant and three patients refused to come for study at 1 year. The mean GFR was 59.6±17.7 ml/min (median 60.0, range 39.4–88.7) before MMF and 68.5±16.3 ml/min (median 68.6, range 39.4±90.1) 1-year post-MMF, an increase of 18.5%.

Immunosuppression

The preMMF mean tacrolimus dose was 4.3±2.1 mg/day (median 3.5, range 2–8). Mean detectable tacrolimus concentration was 8.6±1.5 (median 8.1 ng/ml), and 6 of the 12 patients had undetectable levels (<5 ng/ml). The mean tacrolimus dose was reduced to 2.8±1.1 mg/day (median 3, range, 2–4 mg/day) at 3 months postaddition of MMF. This tacrolimus dose remained unchanged for most part of the trial period. Details of individual patients immunosuppression at various time points is given in Table 3.

Liver Function

Three patients had rise in hepatic enzyme during the first year. The liver functions normalized in all three, after increasing the baseline immunosuppression. There were no further significant changes in hepatic enzyme beyond the first year after starting MMF. There were no retransplantations during study period for any reason.

Recipient Age Effect

There were six patients <60 years of age at the time of introduction of MMF and six were >60 years of age. Four out of six patients (66.7 %) <60 years of age were responders and two were failures (33.34 %). In patients >60 years, three (50%) were responders, two (33.3%) were failures, and one (16.6 %) was a nonresponder (P=0.565).

Sex Effect

Out of eight male patients, four (50%) responded, three were failures, and one was nonresponder. Out of four female patients, three (75%) were responders and one (25%) was failure (P=0.366).

Length of Tacrolimus Effect

At the time of enrollment, five patients were on tacrolimus for >5 years and seven were for on tacrolimus for <5 years. There were three responders (60%) and two failures (40%) for patients who spent >5 years tacrolimus, whereas four patients responded (57.1%), two failed (28.6%), and one was a nonresponder (14.31%) of those on tacrolimus for <5 years (P=0.659).

Size of Native Kidney Effect

The majority of the patients had smaller sized kidneys than expected for their age. The right kidney was of smaller size than left in all cases except in case 3. The mean size of right kidney was 9.5±0.6 cm and left kidney was 10.5±0.7 cm. The mean combined size of both kidneys was 20±1.3 cm. The combined size of both kidneys <20 cm was observed in seven cases and out of these, three patients (42.9%) responded, three (42.9%) failed to respond, and one (14.3%) was a nonresponder, whereas in five cases were combined renal size was >20 cm, four patients (80%) were responders and one (20%) failed to respond (P=0.659).

Renal Function before MMF

Three patients had serum creatinine >2.5 mg/dl (cases 3, 5, 11 had serum creatinine 3.0, 2.7, and 4.8 mg/dl, respectively; Table 2). Two patients (66.7%, cases 3 and 5) showed response, whereas one patient (case 11, serum creatinine 4.8 mg/dl) did not show any improvement and underwent subsequent kidney transplantation. Of the remaining nine patients with baseline serum creatinine <2.5 mg/dl, five patients (55.61%) were responders, three (33.3%) failed to respond and one (11.1%) was a nonresponder.

Side Effects of MMF

In five patients, MMF was discontinued (cases 2, 3, 6, 10, and 11) for leukopenia, diarrhea, gastrointestinal upset, aspergillus infection, and renal failure, respectively. In three cases (cases 2, 6, and 10), MMF was restarted 4–6 weeks later at a reduced dose (Tables 1 and 3). In two patients (cases 7 and 8), the dose of MMF was reduced for mild gastrointestinal disturbance.

DISCUSSION

Introduction of cyclosporine in the early 1980s resulted in significant improvement in patient survival after liver transplantation (*9*, *10*). OKT3 was used not only to control steroid resistant rejection (*11*), but also advocated as a means to avoid cyclosporine induction and subsequent early nephrotoxicity. Because tacrolimus has been used clinically, graft

TABLE 1. Patient characteristics

Patient	Age (years)	Sex	Diagnosis pre-LTx	Months from LTx to MMF	Kidney size (cm)			Clinical events post-MMF	Liver function at last follow-up				
					Right	Left	Total		Bilirubin (mg/dl)	AST u/l	ALT u/l	GGTP u/l	ALKPO4 u/l
1	44	Male	Primary sclerosing cholangitis	21.38	10.6	12.1	22.7	Died 10 months post-MMF cardiac arrest. No side effects from MMF	0.9	22	16	71	ND
2	61	Female	Ethanol-induced cirrhosis	52.40	9.8	10.4	20.2	MMF was stopped for 6 weeks due to leukopenia and restarted at reduced dose	0.8	31	41	101	ND
3	68	Male	Ethanol-induced cirrhosis	91.84	9.9	9.4	19.3	MMF stopped 6 weeks later due to diarrhea not restarted	1.2	30	22	129	73
4	41	Male	Ethanol-induced cirrhosis	61.35	10.1	11.3	21.4	Died 50 months post MMF from traumatic head injury, received KTx post-MMF	0.5	21	12	20	77
5	48	Female	Primary sclerosing cholangitis	88.65	9.5	10.3	19.8	Died 58 months after a valvular cardiac surgery from hypoxic brain injury	4.6	158	124	78	139
6	66	Male	Ethanol-induced cirrhosis	39.41	9.8	10.4	20.2	MMF discontinued after 18 weeks nausea and vomiting restarted 6 weeks later, died 55 months post-MMF cardiac arrest	0.5	42	56	311	ND
7	72	Male	Alpha-1 antitrypsin deficiency	40.30	8.8	10.4	19.2	MMF dose reduced for mild GI symptoms	1.9	40	39	186	ND
8	66	Female	Ethanol-induced cirrhosis	35.99	8.6	10.0	18.6	MMF dose reduced for mild GI symptoms; commenced hemodialysis 26 months post-MMF; died heart failure 4 months postdialysis	0.6	16	25	425	281
9	61	Male	Autoimmune hepatitis	28.06	9.6	10.2	19.8	Died 28 months post MMF due to recurrent HCC	0.6	20	14	76	181
10	54	Female	Primary biliary cirrhosis	27.43	8.9	10.3	19.2	MMF discontinued 8 months aspergillous infection, restarted after 10 month	0.1	12	12	20	86
11	33	Male	Motor vehicular accidental trauma	127.89	8.8	10.3	19.1	MMF stopped 9 weeks later by the patient, hemodialysis 15 weeks post-MMF and KTx 11 months post-MMF	1.9	139	194	1238	ND
12	37	Male	Cryptogenic cirrhosis	72.34	9.7	10.3	20.0	None	0.3	18	21	85	191
Mean	54.6			57.25	9.5	10.5	20.0						
SD	14.1			32.37	0.6	0.7	1.3						
Median	57.5			46.35	9.7	10.3	20.0						

AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGTP, gamma glutamyl transferase; ALKPO4, alkaline phosphatase; MMF, mycophenolate mofetil; ND, not done; KTx, kidney transplantation; GI, gastrointestinal.

TABLE 2. Renal function

	Pre-MMF		Months Post-MMF																					
			1		3		6		12		18		24		36		48		60		72		Iothalamate clearance pre-MMF	Iothalamate clearance post-MMF	Percent change in Iothalamate clearance post-MMF
Case	BUN	Cr	BUN	Cr	BUN	Cr	BUN	Cr	BUN	Cr	BUN	Cr	BUN	Cr	BUN	Cr	BUN	Cr	BUN	Cr	BUN	Cr			
1	34	2.2	22	1.6	21	1.7	19	1.5	Died 10 months post-MMF from cardiac arrest																
2	24	2.2	24	1.7	17	1.4	23	1.3	11	1.1	19	1.4	21	1.3	27	1.3	33	1.4	21	1.4	27	1.3	65.1	90.1	38
3	34	3.0	38	2.9	44	3.3	38	2.6	33	2.3	34	2.9	33	2.3	31	2.5	33	2.5	33	2.5	30	2.4	40	62.9	57
4	21	2.2	20	2.2	27	2.7	34	2.4	42	2.7	27	2.5	35	2.8	50	4.1	18	1.4	Died post kidney transplantation, head injury						
5	45	2.7	22	1.5	24	1.3	18	1.4	21	1.1	26	1.3	27	1.6	30	1.5	42	2.1	Died from postcardiac surgery, cerebral anoxia						
6	38	2.4	45	2.3	34	2.0	49	2.2	47	1.9	39	1.8	46	2.0	16	1.4	41	1.8	Died from cardiac arrest				52.1	65.4	26
7	27	1.9	27	1.9	19	1.6	28	1.7	31	1.9	26	1.9	29	1.9	30	1.8	32	2.0	31	1.7	63	2.7	39.4	39.4	0
8	41	2.1	34	1.8	54	2.0	38	2.0	47	2.1	77	2.5	62	2.9	Commenced hemodialysis 26 months post-MMF; died from heart failure 4 months postdialysis								88.7	68.6	-23
9	31	2.0	32	2.2	35	2.2	28	2.1	33	2.2	34	3.1	32	3.0	38	2.5	Died from recurrent HCC								
10	33	2.4	32	2.2	27	2.1	24	1.9	35	2.1	41	2.1	35	2.1	36	2.0	18	1.8	37	1.7	34	2.1	72.2	84.2	17
11	66	4.8	30	4.7	Received kidney transplantation																				
12	33	1.9	25	1.9	28	2.1	30	2.1	36	2.1	33	2.4	29	1.7	35	1.8	36	2.0	39	2.0	55	2.2	60	69	15
Mean	36	2.5	29.3	2.2	30	2.0	30	1.9	34	2.0	36	2.2	35	2.2	33	2.1	32	1.9	32	1.9	41.8	2.14	59.64	68.51	18.57
SD	12	0.8	7.4	0.9	11	0.6	9	0.4	11	0.5	16	0.6	12	0.6	9	0.9	9	0.4	7	0.4	16	0.5225	17.7	16.3	25.8
Median	34	2.2	28.5	2.1	27	2.0	28	2.0	34	2.1	34	2.3	33	2.1	31	1.8	33	1.9	33	1.7	34	2.2	60	68.6	17
P value								0.05		0.08				0.29				0.06		0.12		0.39			

TABLE 3. Immunosuppressive changes

	Pre-MMF		Months post-MMF: 1			3			6			12			18			24			36			48			60			72		
Case	Tac dose (mg/d)	Tac level (ng/ml)	Tac dose (mg/d)	Tac level (ng/ml)	MMF dose (mg/d)	Tac dose (mg/d)	Tac level (ng/ml)	MMF dose (mg/d)	Tac dose (mg/d)	Tac level (ng/ml)	MMF dose (mg/d)	Tac dose (mg/d)	Tac level (ng/ml)	MMF dose (mg/d)	Tac dose (mg/d)	Tac level (ng/ml)	MMF dose (mg/d)	Tac dose (mg/d)	Tac level (ng/ml)	MMF dose (mg/d)	Tac dose (mg/d)	Tac level (ng/ml)	MMF dose (mg/d)	Tac dose (mg/d)	Tac level (ng/ml)	MMF dose (mg/d)	Tac dose (mg/d)	Tac level (ng/ml)	MMF dose (mg/d)	Tac dose (mg/d)	Tac level (ng/ml)	MMF dose (mg/d)
1	8	11.4	6	7	2.5	3	15.8	2000	3	5	2000	Died 10 months post MMF cardiac arrest																				
2	6	8.4	4	7.2	2	4	8.3	2000	6	9.4	500	5	8.4	500	6	7.8	500	5	8.4	500	5	6.6	500	5	7.9	500	5	9.2	500	4	7.2	500
3	3	7.2	3	5	0.5	4		0	4	7.8		4		0	4	5.5		4	5.5	0			0			0			0	4	7.3	0
4	6	<5	4	NDA	2	4	NDA	2000	3	NDA	2000	2		2000	1.5	<2.5	2000	1.5	2.5	2000	3	<2.5	2000	18	12.9	2000	Died post kidney transplantation, head injury					
5	8	8.8	2	7.8	3	2	9	2000	2	6.3	2000	2	nda	1000	6		2000	6	4.1	1.5	4	5.5	2000	4	4.8	2000	Died post cardiac surgery, cerebral anoxia					
6	3	NDA	2	<5	2	1	NDA	2500	1	NDA	500	2	6.3	1000	2	<2.5	1000	2		1000	1	<2.5	1000	1	<2.5	1000	2	3.5	Died, cardiac arrest			
7	3	7.8	2	7	2	2	9	2000	2	5.6	1000	4	7.9	1000	2		1000	2	4.6	1000	2	5.9	1000	2	1.5	500	1	2.5	500	1	4.8	500
8	2	NDA	3	<5	1	3	NDA	1000	3		1000	2	2.9	1000	1		500	2	4.5	500	Commenced dialysis 26 months post-MMF, died from heart failure 4 months later											
9	4	7.7	3	<5	2.5	4	5.7	2500	3	9.8	500							2	5.8	1500	2	13.3	1500	Died from recurrent HCC								
10	3	NDA	2	NDA	1	2	NDA	500	2	7.6	500	1	9.2	0	3	4.9	0	4	8.2	500	2	3.6	500	2	2.7	500	2	5.1	500	2	4.7	500
11	4	NDA	2	5.6	2	Received kidney transplantation																										
12	2	NDA	2	1.3	2	2		2000	2		2000	2		2000	2		2000	2	2.5	2000	4	<2.5	2000	4	3.6	2000	4		2000	4	3.6	2000
Mean	4.3	8.6	2.9	5.8	1.9	2.8	9.6	1682	2.8	7.4	1200	2.7	6.9	944	3.1	6.1	1125	3.1	5.1	900	2.9	7.0	1167	5.1	5.6	1063	2.8	5.1	700	3.0	5.5	700
SD	2.1	1.5	1.2	2.2	0.7	1.1	3.7	815	1.3	1.8	715	1.3	2.5	726	1.9	1.5	791	1.6	2.1	738	1.4	3.7	750	5.8	4.2	821	1.6	3.0	758	1.4	1.6	758
Median	3.5	8.1	2.5	7.0	2.0	3.0	9.0	2000	3.0	7.6	1000	2.0	7.9	1000	2.0	5.5	1000	2.0	4.6	750	2.5	5.9	1000	4.0	4.2	750	2.0	4.3	500	4.0	4.8	500

MMF, mycophenolate mofetil; Tac, tacrolimus; NDA, nondetectable amount.

loss from acute or chronic rejection is rare (*12,13*). However, the concern for short and long-term nephrotoxicity still exists. Patients with serum creatinine >2.5 mg/dl at 1 year are shown to have an incidence of end-stage renal failure of 18.1% by 13 years (*14*). On the other hand, MMF is not associated with nephrotoxicity (*15,16*).

The short-term results of this study have been presented previously (*17,18*). In addition, several reports have suggested similar early benefits (*3–7*). However, none of these studies reported long-term follow up. This is the first report where long-term results have been analyzed. It is of interest to know that after 2 years of commencing MMF, the serum creatinine was relatively stable in almost all patients without any further significant deterioration. Although six patients died in the follow-up period, none of the deaths were attributed to MMF or hepatic dysfunction. Three patients experienced mild hepatic dysfunction and were quickly restored with adjustment in baseline immunosuppression. In five patients, MMF was discontinued for toxicity and in other two patients, the dose was reduced; however, in three patients, it could be restarted at lower dose without any side effects.

The size of the kidneys appeared to predict response to addition of MMF and reduction of tacrolimus. Combined size of native kidney <20 cm appeared to have a lower success rate compared to >20 cm, although this did not reach statistical significance in this study. The time interval from liver transplantation to MMF was not found to be a predicted indicator for overall improvement. Starting serum creatinine of >4.0 mg/dl may have poor outcome; however, there was only one patient in the series of serum creatinine of 4.7 mg/dl. All the other subjects had serum creatinine of ≤3.0 mg/dl. Female patients had a better response rate compared to male patients; however, this was not significant. This study only has a small sample size but the subjects were carefully studied prospectively. In the future, larger prospective studies with targeted mycophenolic acid concentration may help to further elucidate the utility of this approach to posttransplant nephrotoxicity (*7,19*).

CONCLUSION

MMF was found to be useful for tacrolimus-related nephrotoxicity in post liver transplant patients. In all, 58% of patients experienced sustained benefit for long follow-up period. Careful monitoring is necessary as mild reversible rejection can occur in 25% of patients after reduction of tacrolimus dose. Although not significant, smaller size of the native kidneys had relatively poor outcome and female subject responded better then male. More future prospective randomized trials on a larger population may be helpful to evaluate these factors.

ACKNOWLEDGMENTS

We thank Dr. Ann Olzinski for editing the manuscript.

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