Delayed Introduction of Tacrolimus Postliver Transplant With Intravenous Mycophenolate Mofetil Preserves Renal Function Without Incurring Rejection

In most liver recipients, tacrolimus is used as a primary immunosuppressive agent, which has both an acute and a chronic nephrotoxic effect. Renal dysfunction has a significant impact on survival outcome after liver transplantation (LTx). Mycophenolate mofetil (MMF) has no known nephrotoxicity. The absorption of oral formulation of MMF is reported to be more than 90% in healthy volunteers, kidney, heart, and lung transplant recipients (*1–3*). The absorption of oral MMF was not studied in immediate post-LTx until 2007 (*4*).

We have previously shown that after LTx, the trough concentration of mycophenolic acid rises with time (*5*). Furthermore, after LTx, we have shown an improvement in the bioavailability of oral MMF overtime (*5, 6*). Subsequently, we have demonstrated that oral absorption of MMF in the second week after LTx is only 48% (*4*), this potentially being even lower in the first week after LTx. In previously reported 130 patients, the rate of acute rejection was 6.1% with the use of intravenous (IV) MMF. Acute rejections were easily reversed with methyl prednisolone (*7*).

The aim of our study is to examine the number of days tacrolimus introduction could be delayed after LTx, to preserve the renal function while avoiding rejection, by using IV MMF. This is a retrospective study from a newly started, small volume LTx program, with close monitoring. From February 2009 to July 2012, 70 patients underwent LTx. There were 51 men and 19 women with a mean age of 54.5±9.5 years. Forty-eight (68.5%) patients were infected with hepatitis C virus (HCV), and 17 patients (24.2%) had ethanol induced cirrhosis. Twenty-eight of these (40%) had hepatocellular carcinoma (HCC).

Management of immunosuppression in pretransplant phase was identical for all patients. In the pretransplant phase; all patients received induction with single oral dose of tacrolimus 0.03 to 0.05 mg/kg given on call to surgery, IV MMF 1 g infused over 2 hr with the start of surgery and MP 500 mg IV in anhepatic phase. We preferred this approach based on the theory of tolerogenic immunosuppression for organ

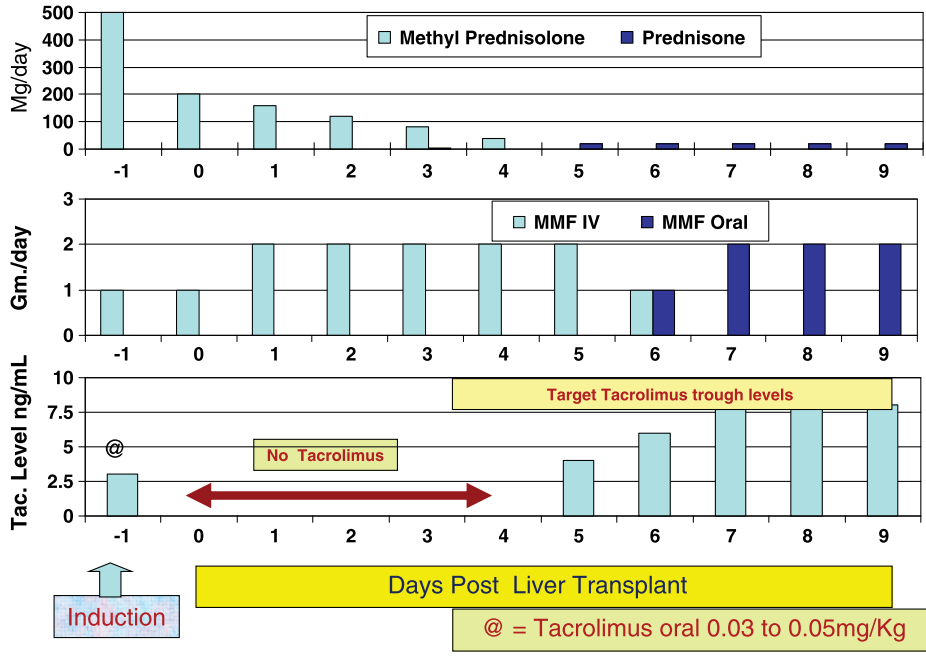

FIGURE 1. Immunosuppression protocol; induction dose of tacrolimus 0.03 to 0.05 mg/kg, 1 g. IV MMF and 500 mg MP before reperfusion of the liver. No further tacrolimus for 4 days and continue IV MMF 1 gm. twice a day until tacrolimus trough level ≥5 ng/mL, and steroid taper. IV, intravenous.

TABLE 1. Group I: Pretransplant on dialysis (n=9)

Age	Sex	Pre-LTx weeks on dialysis	Post-LTx dialysis sessions	Creatinine, mg/dL: days posttransplant −1	7	14	30	90	180	360
60	F	2	5	4.1	1.7	1.9	1.1	1	1	1.0
52	M	2	7	9.4	6.0	5.4	3.3	4.3	1.8	1.0
52	M	1	2	2.9	2.5	2.7	1.7	1.1	1.5	1.4
53	M	1	1	4.0	4.2	1.8	1.4	1.2	1.0	0.9
61	F	1	2	1.2	2.6	2.3	1.7	1.6	1.5	0.9
44	M	14	1	2.2	6.2	4.3	4.1	2.5	2.2	4.7
26	F	1	0	2.6	0.5	0.4	0.7	1.0	0.8	0.8
48	M	2	9	4.5	3.4	3.2	6.5	2.7	2.2	2.8
55	M	3	0	6.5	8.1	[a]				
		Mean Creatinine		4.16	3.91	2.44	2.56	1.94	1.49	1.68
		± SD		2.49	2.44	1.55	1.96	1.17	0.52	1.39

[a] Expired from myocardial infarction.

SD, standard deviation; LTx, liver transplantation.

transplantation where recipients pretreatment allows posttransplant minimal immunosuppression (*8*). In the posttransplant phase, subsequent introduction of tacrolimus was gradually delayed from 1 to 5 days after the LTx as the program matured with progression based on prior observations, renal function, hepatic function, and mental status. All patients received IV MMF 1 g infused over 2 hr twice per day for 4 to 7 days after LTx. Two days after whole blood tacrolimus trough concentrations were greater than 5 ng/mL, IV MMF rout was switched to oral. A standard total dose of 600 mg MP was tapered over 5 days (50 mg every 6 hr, four doses; then 40 mg every 6 hr, four doses; then 30 mg every 6 hr, four doses; then 20 mg every 6 hr, four doses; then 20 mg every 12 hr, two doses) (Fig. 1). On day 6, a daily maintenance oral dose of 20 mg prednisone was started and reduced to 15 mg by postoperative day 15. Subsequent reduction in the dosage of all three immunosuppressive agents were made as clinically indicated.

The introduction of tacrolimus after LTx was progressively delayed as our experience grew with this novel approach; for the first 16 cases (February 2009 to December 2009), in two patients (12.5%), tacrolimus introduction was delayed for 2 days after LTx. In the next 28 patients (January 2010 to July 2011), tacrolimus introduction was delayed in 26 of these patients (92.7%) for 1 to 5 days after transplantation. In the last 26 patients, tacrolimus introduction was delayed in all cases (100%) for 2 to 5 days. Thus, of the last 54 patients, tacrolimus introduction was delayed in 52 patients (96.3%) for 1 to 5 days after LTx. The goals for tacrolimus trough level were: > 5 ng/mL by postoperative day 6, and 6 to 8 ng/mL in the second week after LTx.

All patients were followed up for 1 year from the transplant. Patient survival, graft survival, causes of death, causes of graft loss, rate of rejection, and renal function were examined.

One year actual patient survival was 88.6%. Eight (11.4%) patients died from recurrent HCC (n=2), myocardial infarction (n=2), sepsis (n=2), one each from recurrent hepatitis C virus infection, and withdrawal of support with functioning allograft.

One year actual graft survival was 86.5%. Four (5.7%) patients required retransplantation, three for primary nonfunction and one for early fibrosing cholestatic hepatitis. Two of these four patients survived after retransplantation.

Thirty-three patients underwent 87 liver biopsies as clinically indicated. Protocol biopsies were not performed. Rejection was diagnosed only in two recipients. One patient (27-year-old woman)

TABLE 2. Pretransplant without dialysis

Group II: pretransplant serum creatinine> 3 mg/dL (n=11)

Case no	Serum creatinine mg/dL: days posttransplant −1	7	14	21	30	60	90	180	360	Days tacro dose delayed
11	3.3	3.1	2.1	1.9	2.1	2.7	1.7	[a]		0
18	3.1	1.9	1.5	0.8	0.5	0.4	0.8	0.9	1.71	4
30	3.3	1.2	1.7	1.8	2.8	1.6	0.9	[b]		2
32	3.7	1.1	0.7	0.8	0.7	0.8	0.8	0.7	1.0	3
36	3.2	1.2	1.3	1.1	0.8	2	0.9	0.9	1.3	3
40	5.1	0.9	1.1	1	1.1	1.2	1.5	1.6	1.4	4
45	3.3	2.4	2.2	1.1	1.3	1.4	1.9	2.1	1.8	3
49	5.4	1.8	1.4	1.8	1.9	1.7	1.5	1.8	1.5	4
51	4.2	4.5	4.3	3.3	3.5	3.1	3.2	2.7	5.1	2
61	4	1.2	1	1.2	0.8	0.7	0.9	1.0	1.7	3
68	4.4	2.9	1.9	1.6	1.8	1.4	1.4	1.4	1.3	4
Mean	3.91	2.02	1.75	1.49	1.57	1.54	1.40	1.44	1.86	2.9
± SD	0.79	1.11	0.97	0.72	0.95	0.82	0.71	0.66	1.24	1.2

Group III: pretransplant serum creatinine<3.0 mg/dL (n=50)

	Serum creatinine mg/dL: days posttransplant −1	7	14	21	30	60	90	120	180	360
Mean	1.10	1.14	1.22	1.14	1.08	1.09	1.05	1.11	1.32	1.32
± SD	0.51	0.58	0.67	0.52	0.41	0.42	0.30	0.53	1.12	1.13

[a] Required dialysis after 4 months and 12 days after retransplantation; support withdrawn by family.

[b] Died from metastatic HCC.

One patient (2%) required RRT for 1 week after retransplantation and intravenous contrast.

SD, standard deviation; RRT, renal replacement therapy; HCC, hepatocellular carcinoma.

experienced moderate to severe acute cellular rejection (ACR); rejection activity index was 6, 4 months after transplant. She was noncompliant for her medications and clinic visits. She had undetectable tacrolimus levels for several weeks before rejection. She responded to MP 1.5 g total dose spread over 4 days without antibody use. Another patient (37-year-old man) experienced severe ACR (rejection activity index=8) on postoperative day 8. The rejection was reversed with MP 2 g total dose spread over 5 days and antibody preparation was not required.

Renal function was examined in three groups of patients based on pre-LTx renal function. Group I patients were on renal replacement therapy (RRT), group II patients had severe renal dysfunction not on RRT (serum creatinine >3.0 mg/dL), and group III were the remaining patients (serum creatinine <3.0 mg/dL).

Group I patients (n=9, 12.8%) were on hemodialysis for 1 to 14 weeks before LTx. Of these patients, one died at home after discharge from myocardial infarction, whereas all remaining eight recipients were alive at 12 months after LTx without RRT. Dialysis regimen and serum creatinine in each patient are shown in Table 1. During the early part of the program in first four patients, introduction of tacrolimus was not delayed and RRT after LTx varied from 1 to 7 dialysis sessions. In last five patients, tacrolimus induction was delayed for 2 to 4 days, and dialysis requirement was zero to nine sessions. Incidentally, one patient who was on dialysis for 14 weeks before LTx required one dialysis session after LTx.

Group II patients (n=11, 15.7%) had severe renal dysfunction at the time of LTx without requiring RRT. Serum creatinine and the delay in tacrolimus introduction are shown in Table 2 (*top*). Mean serum creatinine before LTx was 3.91±0.79 mg/dL and 1.86±1.24 mg/dL at 12 months after LTx. None of the LTx recipients required dialysis, except one who was commenced on hemodialysis 4 months and 12 days after retransplantation. Unfortunately, after 6 weeks of hemodialysis, support was withdrawn by the family. Another patient died from metastatic recurrence of HCC.

Group III patients (remaining 50 cases) with normal to moderate renal dysfunction had mean serum creatinine 1.1±0.51 mg/dL before LTx which remained stable up to 3 months (1.05±0.3 mg/dL) and increased to 1.32±1.12 mg/dL at 12 months after LTx. Mean serum creatinine for group III at various time intervals before and after LTx is given in Table 2 (*bottom*). One patient, who received IV contrast for a pulmonary angiogram 2 days after retransplant, required RRT for 1 week.

All patients tolerated IV MMF. Discontinuation of IV MMF was not required in any patient for known side effects of diarrhea, gastrointestinal intolerance, or leukopenia.

In conclusion, use of pre-LTx induction with single dose of oral tacrolimus, 1 g IV MMF and 500 mg MP, followed by IV MMF posttransplant and 600 mg MP taper over 5 days provide adequate immunosuppression, without the risk of acute rejection. This allows a delay of up to 4 days in tacrolimus introduction after LTx. This regimen provides a beneficial effect on the recovery of renal function in patients with renal impairment or renal failure before LTx and after LTx, reducing the risk of renal dysfunction and new onset dialysis, without the use of any antibody preparation.

Because the completion of the present study, we have treated 17 more patients with IV MMF and 4 days delay in introduction of tacrolimus without ACR. This immunosuppressive strategy has become the standard of care at out LTx center.

Ashokkumar Jain[1]
Serban Constantinescu[2]
Manoj Maloo[1]
Amar Nath Mukerji[3]
Andreas Karachristos[1]
Kwan Lau[1]
Antonio Di Carlo[1]

[1] Department of Surgery
Temple University School of Medicine
Philadelphia, PA
[2] Department of Medicine
Temple University School of Medicine
Philadelphia, PA
[3] Department of Surgery
Bronx Lebanon Hospital
Bronx, NY

The authors declare no funding or conflicts of interest.

Address correspondence to: Ashokkumar B. Jain, M.D., F.A.C.S., Penn State Milton, Hershey Medical Center, Department of Surgery, Mail Code: H062, 500 University Drive, PO Box 850, Hershey, PA 17033.
E-mail: ajain1@hmc.psu.temple
E-mail: Ashokkumar.jain@tuhs.temple.edu

A.J. participated in research design, writing of the article, performance of research, analytic tool, and data analysis. S.C. participated in writing of the article, performance of research, analytic tool, and data analysis. M.M. participated in writing of the article, performance of research, analytic tool, and data analysis. A.N.M. participated in writing of the article, performance of research, analytic tool, and data analysis. A.K. participated in performance of research, analytic tool, and data analysis. K.L. participated in performance of research, analytic tool, and data analysis. A.D.C. participated in performance of research, analytic tool, and data analysis.
Data was presented at 19th annual ILTS Sydney June 12–15, 2013
Received 27 May 2014.
Accepted 24 June 2014.

ISSN: 0041-1337/14/9807-e68
DOI: 10.1097/TP.0000000000000371

REFERENCES

1. Armstrong VW, Tenderich G, Shipkova M, et al. Pharmacokinetics and bioavailability of mycophenolic acid after intravenous administration and oral administration of mycophenolate mofetil to heart transplant recipients. *Ther Drug Monit* 2005; 27: 315.
2. Bullingham R, Monroe S, Nicholls A, et al. Pharmacokinetics and bioavailability of mycophenolate mofetil in healthy subjects after single-dose oral and intravenous administration. *J Clin Pharmacol* 1996; 36: 315.
3. Ensom MH, Partovi N, Decarie D, et al. Mycophenolate pharmacokinetics in early period following lung or heart transplantation. *Ann Pharmacother* 2003; 37: 1761.
4. Jain A, Venkataramanan R, Kwong T, et al. Pharmacokinetics of mycophenolic acid in liver transplant patients after intravenous and oral administration of mycophenolate mofetil. *Liver Transplant* 2007; 13: 791.
5. Jain A, Venkataramanan R, Hamad IS, et al. Pharmacokinetics of mycophenolic acid after mycophenolate mofetil administration in liver transplant patients treated with tacrolimus. *J Clin Pharmacol* 2001; 41: 268.
6. Pisupati J, Jain A, Burckart G, et al. Intraindividual and interindividual variations in the pharmacokinetics of mycophenolic acid in liver transplant patients. *J Clin Pharmacol* 2005; 45: 34.
7. Jain A, Sharma R, Ryan C, et al. 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. *Liver Transplant* 2008; 14: 202.
8. Starzl TE, Zinkernagel RM. Transplantation tolerance from a historical perspective. *Nat Rev Immunol* 2001; 1: 233.