

Impact of Mycophenolic Acid Dose Modifications on Renal Function After Kidney Transplantation

Nassim Kamar,¹ Loubna Oufroukhi,¹ Federico Sallusto,² Olivier Cointault,¹
Laurence Lavayssière,¹ Marc Mouzin,² Joelle Guitard,¹ Dominique Durand,¹ Lionel Rostaing¹

Objective: Mycophenolic acid dose modifications after renal transplantation seem to adversely affect renal allograft outcome. The aim of this retrospective study was to examine the effect of mycophenolic acid dose modifications on renal function 1 year after transplantation and to determine the factors predictive of those dose modifications within the first year after renal transplantation.

Patients and Methods: All 130 patients at our institution who were treated de novo between January 2002 and April 2003 with either a mycophenolate mofetil-based or an enteric-coated mycophenolate sodium-based therapy and who had a functioning renal allograft 1 month after transplantation were included in this study.

Results: Fifty-seven patients (43.8%) underwent a dose modification during the first year after transplantation. One, 3, 6, and 12 months after transplantation, renal function was significantly improved in the patients who did not receive a dose modification. A mycophenolic acid dose that 1 year after transplantation was less than the initial dose received just after transplantation was an independent factor associated with deteriorating renal function. Sirolimus immunosuppression, Cytomegalovirus infection, and pretransplant lymphocyte counts were independent factors associated with mycophenolic acid dose modifications within the first year after kidney transplantation.

Conclusions: Modification of the mycophenolic

acid dose may adversely affect renal function 1 year after transplantation.

Key words: MPA Dose modification, Mycophenolate mofetil, Mycophenolate sodium, Predictive factors, Renal function

Because of its beneficial effects in the prevention of both acute rejection [1-3] and chronic renal allograft dysfunction [4-6], mycophenolate mofetil (MMF), the prodrug of mycophenolic acid (MPA), is used by most transplant centers worldwide after renal transplantation. However, enteric-coated mycophenolate sodium (EC-MPS), a new prodrug formulation of MPA, has recently been developed. EC-MPS has been found to be as effective and safe as MMF in the de novo treatment of renal transplant patients [7] and those receiving renal maintenance therapy [8]. However, MPA-related adverse effects might lead to discontinuation, dose interruption (DI), or a reduction in dosage. Such dose modifications (DMs) increase the risk of acute rejection [9, 10], compromise renal allograft survival [10, 11], and increase posttransplantation healthcare costs [11]. However, to our knowledge, the effect of MPA dose modifications on renal function has not yet been assessed. The aim of this retrospective study was to determine the effect of MPA DM on renal function 1 year after transplantation and to identify the factors predictive of MPA DM during the first year after renal transplantation.

Patients and Methods

Between January 2002 and April 2003, 159 patients received a kidney graft at our institution. Of those individuals, all patients treated with an MMF-based or an EC-MPS-based therapy and who had a functioning renal allograft 1 month after transplantation ($n = 130$) were included in this study. We excluded 8 patients who had a nonfunctioning graft 1 month after transplantation (6 from the MMF group and 2

¹Department of Nephrology, Dialysis and Multiorgan Transplantation, CHU Rangueil, Toulouse, France; ²Department of Urology, CHU Rangueil, Toulouse, France

Acknowledgement: We thank Roche France for its financial support for data collection.

Address reprint requests to: Nassim Kamar, MD, PhD, Department of Nephrology, Dialysis and Transplantation, CHU Rangueil, 1 Avenue Jean Poulhès, TSA 50032, 31059 Toulouse Cedex 9, France

Phone: 00 33 5 61 32 26 84 **Fax:** 00 33 5 61 32 28 64 **E-mail:** kamar.n@chu-toulouse.fr

from the EC-MPS group) and 21 patients who were not receiving MMF or EC-MPS 1 month after transplant surgery. The study group consisted of 77 men and 53 women (age range, 18-69 years; median age, 45.5 years). Immunosuppressive therapy data regarding the study subjects are presented in Table 1. Treatment was based on the administration of either a calcineurin inhibitor or sirolimus with MMF or EC-MPS, with or without steroids and with or without induction therapy. EC-MPS, which was administered only with cyclosporin A (CsA) at our center at that time, was given at a dose of 720 mg twice daily. The following MMF doses were administered: Five hundred milligrams twice daily with tacrolimus (FK 506), 750 mg twice daily with sirolimus, and 1 g twice daily with cyclosporin A. The target trough level of cyclosporin A at the 2-hour level was 1000 to 1300 ng/mL during the first 3 months, 800 to 1000 ng/mL between months 3 and 6, and 700 to 800 ng/mL thereafter. The target trough level of tacrolimus was 10 to 15 ng/mL from transplantation to posttransplant month 3 and from 8 to 12 ng/mL thereafter. The target trough level of sirolimus was

between 8 and 12 ng/mL. During the first 6 months after transplantation, all patients received sulfamethoxazole-trimethoprim therapy for prophylaxis against *Pneumocystis jiroveci*. With respect to prophylaxis against *Cytomegalovirus* (CMV) infection, only patients in the CMV seropositive donor / CMV seronegative recipient group received intravenous ganciclovir therapy at a dosage of 500 mg/d for the first 2 weeks after transplantation; that regimen was followed by valacyclovir 3000 mg/d for the next 90 days.

For each patient, we assessed the number of DMs (reduction, discontinuation, or interruption), the cause of the DM, the length of the interval between transplantation and DM, and the duration of the DM. We defined DM as the discontinuation (permanent withdrawal) of MPA, the interruption (temporary withdrawal) of MPA, or the reduction (a decrease in the dose) of the MPA dose for a duration of at least 2 days. The MPA dose was reduced in patients with a severe hematologic disorder (eg, a hemoglobin level of < 8 g/dL, a white blood cell count of < 3000/mm³, or a polymorphonuclear cell

Table 1. Clinical profile of the patients studied

Clinical Profile of Renal Donors and Recipients	Renal Transplant Patients Studied (n = 130)	Patients with Dose Modification (n = 57)	Patients with No Dose Modification (n = 73)
Recipients			
Age at transplantation (y)	44.2 ± 1.1	47.2 ± 1.8	42 ± 1.4
Sex (male/female)	77/53	34/23	43/30
Previous renal transplantations (no.)	0 (0-1)	0 (0-1)	0 (0-1)
Highest level of PRA (%)	0 (0-100)	0 (0-100)	0 (0-69)
PRA level at transplantation (%)	0 (0-100)	0 (0-85)	0 (0-100)
Donors			
Age (y)	42.4 ± 1.3	48 ± 1.5	37.9 ± 1.5
Sex (male/female)	69/61	26/31	43/30
Serum creatinine level (μmol/L)	99.3 ± 5.9	102 ± 9	97.2 ± 7.7
Creatinine clearance (mL/min)	92.6 ± 3.5	84 ± 4.5	99.8 ± 5
Cadaveric/living	117/13	54/3	65/8
Cold ischemia time (h)	18.9 ± 0.9	21.1 ± 1.34	17. ± 1.16
Warm ischemia time (min)	45.9 ± 1.2	48.4 ± 1.9	43.9 ± 1.5
Cytomegalovirus status (%)			
D+/R-	18.5	21	16.4
R+	58.5	61.4	56.2
D-/R-	23	17.6	27.4
Immunosuppressive therapy			
Induction therapy: yes/no	116/14	54/3	62/11
Polyclonal Ab/anti-CD25 mAb	54/62	33/21	21/41
Cyclosporine/tacrolimus/SRL	83 /36 /11	31 /16 /10	52/ 20/ 1
MMF/EC-MPS	93/37	48/9	45/28
Steroids	127	55	69

PRA, Panel reactive antibodies; D+, *Cytomegalovirus* - seropositive donor; D-, *Cytomegalovirus* - seronegative donor; R-, *Cytomegalovirus* - seronegative recipient; R+, *Cytomegalovirus* - seropositive recipient; Ab, antibodies; mAb, monoclonal antibodies; SRL, sirolimus; MMF, mycophenolate mofetil; EC-MPS, enteric-coated mycophenolate sodium.

count of $< 1500 / \text{mm}^3$) and in those with a persistent severe CMV infection despite comprehensive antiviral therapy, CMV disease, BK virus infection, a severe infection that required hospitalization, or a gastrointestinal disorder that was refractory to therapy. In the absence of improvement of those disorders after MPA dose reduction (DR), treatment with MPA was terminated and was reinitiated only after the disorder had resolved completely. Physicians could also decide to permanently terminate MPA therapy in patients with a severe complication such as a BK viral infection, nephropathy, or a hematologic disorder that was refractory to treatment. The dosages of the other immunosuppressive agents were not modified.

In addition, we assessed the following parameters for each patient: the donor's age and sex, the donor's serum creatinine level and creatinine clearance level (calculated according to the Cockcroft and Gault formula), the patient's age at transplantation, the number of previous renal transplantations, the level of panel reactive antibodies (PRA) (peak level and level at the time of renal transplantation), the length of cold and warm ischemia times, CMV status (donor and recipient), the patient's immunosuppression therapies, and the patient's trough levels of relevant immunosuppressive drugs 1, 3, 6, and 12 months after transplantation. Hematologic parameters (hemoglobin level and white blood cell, polymorphonuclear, lymphocyte, and platelet counts) and renal values (creatinine level and creatinine clearance calculated according to the Cockcroft and Gault formula) were assessed before transplantation, and 1, 3, 6, and 12 months after transplantation. In addition, biopsy-proven acute rejection episodes, CMV infection (defined as either a real-time PCR result that revealed CMV viremia [12] or established CMV disease that required anti-CMV therapy), and severe infection that was caused by an agent other than CMV and that required hospitalization of the patient were assessed.

Statistical analyses

Reported values represent either the mean $\pm$ SE or the median (range). Proportions were compared with the chi-square or the Fisher exact test. Quantitative variables were compared with the nonparametric Mann-Whitney *U* test, the Friedman test, and the Student *t* test. Independent factors associated with impaired renal function (a creatinine clearance value of $< 60 \text{ mL/min}$) and DM 12 months after transplantation were studied with a stepwise multivariate logistic regression model. A *P* value of $< .05$ was considered statistically significant.

Results

The patients' characteristics are summarized in Table 1.

MPA DMs

Fifty-seven (43.8%) of 130 patients underwent a DM of MPA during the first year after transplantation (Figure 1). Fifty-one (39.2%) of 130 patients underwent a DR of MPA. The median DR was 50% (range, 25%-75%). The mean time between transplantation and the first DR was 82 ± 11 days (median, 60 days; range, 15-290 days). The median number of DRs per patient was 1 (range, 1-3). The median duration of the DR within the first year was 216 days (range, 8-345 days). Sixteen of 130 patients (13%) underwent a DI (7 patients had 1 DI, 8 patients had 2, and 1 patient had 3 DIs). All but 1 of those individuals experienced a DR before DI. The DIs occurred 143 days (± 20 days) after transplantation (median, 120 days; range, 15-330 days). The median duration of the DIs was 30 days (range, 8-215 days). MPA was discontinued in 15 patients during the first post-transplant year. Of those individuals, 3 patients underwent a DR followed by a DI before MPA therapy was terminated, and 7 patients underwent a DR before the discontinuation of MPA treatment. MPA discontinuations were caused primarily by hematologic abnormalities and infections. MPA treatment was terminated after 135 days of treatment (± 19 days; median, 120 days; range, 20-300 days). The causes of the DMs are summarized in Table 2. Overall, the mean doses of MMF and MPS initiated after transplantation were, respectively, $1.6 (\pm 0.04) \text{ g/d}$ and 1.44 g/d . One year after transplantation, those doses

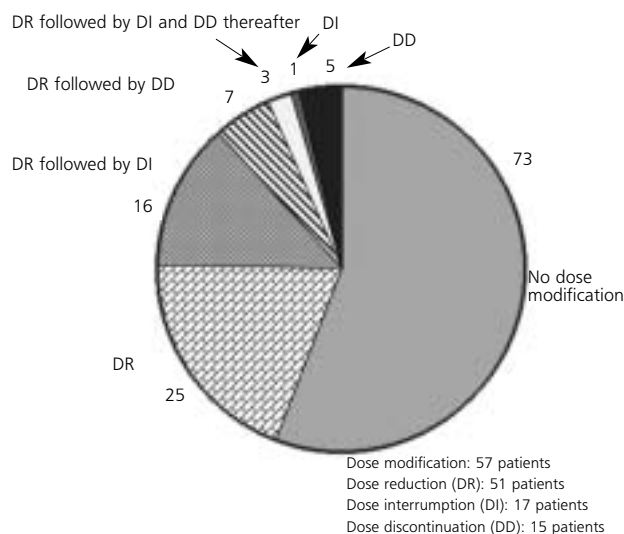


Figure 1. Mycophenolic acid dose modification within the first year after transplantation.

were 1.21 (± 0.06) g/d for MMF ($P < .0001$) and 1.047 (± 0.1) g/d for MPS ($P = .0004$). MPA DMs occurred at the same rate in 37.5% of patients who received CsA-based treatment and in 44% of those who received FK 506-based therapy. In contrast, DMs occurred at a significantly higher rate (91%) in patients who received sirolimus-based therapy than in those who received either CsA-based ($P = .0009$) or FK 506-based therapy ($P = .01$). During the first year after transplantation, sirolimus doses were reduced from 0.08 (± 0.008) mg/kg/d at 1 month, to 0.08 (± 0.01) mg/kg/d at 3 months, to 0.06 (± 0.009) mg/kg/d at 6 months, and to 0.06 (± 0.01) mg/kg/d at 12 months ($P = .1$). Sirolimus trough levels were 10 (± 1.24) ng/mL at 1 month after transplantation, 11 (± 3.4) ng/mL at 3 months, 8.5 (± 1.3) ng/mL at 6 months, and 5.5 (± 0.5) ng/mL at 12 months ($P = .1$). The recipients' body weight and body mass index did not have an effect on the MPA DM (data not shown).

Table 2. Causes of dose modifications in patients treated with mycophenolate mofetil

Variable	n (%)
Dose reduction (n = 51)	
Hematologic disorders*	27 (53)
Anemia	11
Leucopenia and/or neutropenia	12
Pancytopenia	4
Infections	18 (35)
Cytomegalovirus infection and/or positive viremia	14
Bacterial infection	2
Varicella zoster virus infection	1
BK virus infection	1
Diarrhea	6 (12)
Dose interruption (n = 17)	
Hematologic disorders*	9 (53)
Anemia	1
Leucopenia and/or neutropenia	5
Pancytopenia	3
Infections	8 (47)
Cytomegalovirus infection and/or positive viremia	3
Bacterial infection	3
Varicella zoster virus infection	1
BK virus infection	1
Dose discontinuation (n = 15)	
Hematologic disorders*	3 (20)
Anemia	1
Leucopenia and/or neutropenia	2
Infections	9 (60)
Cytomegalovirus infection and/or positive viremia	6
Varicella zoster virus infection	2
BK virus infection	1
Diarrhea	3 (20)

*Hematologic disorders were considered in the absence of *Cytomegalovirus* infection or the presence of *Cytomegalovirus*-related viremia.

Effects of MPA DM on renal allograft function

Only 3 of 57 patients (5.26%) who experienced a DM presented with acute rejection, which occurred 32, 68, and 105 days, respectively, after the MPA dose was modified. However, 1, 3, 6, and 12 months after transplantation, the serum creatinine level had improved to a significantly greater extent in patients who did not undergo a DM than in those who did experience a change in treatment during the first posttransplantation year (Figure 2A). Creatinine clearance, which was calculated according to the Cockcroft and Gault formula, also significantly improved in patients who did not undergo a DM (Figure 2B). To determine whether MPA DM had adversely affected the serum creatinine level 1 year after transplantation, we reviewed the factors that influence renal function at that postsurgical point. The median creatinine clearance 1 year after transplantation was 61.5 mL/min (range, 17-163 mL/min). We chose a creatinine clearance value of 60 mL/min 1 year after transplantation as the cutoff value. The results of univariate analysis showed that the following factors were associated with a creatinine clearance of < 60 mL/min after 1 year: the donor's age ($P < .0001$); the donor's serum creatinine level ($P = .045$); MPA DMs implemented during the first year after transplantation ($P = .0014$); MPA dose discontinuation ($P = .0016$); MPA DR ($P = .012$); an MMF or MPS dose 1 year after transplantation that was lower than the initial posttransplantation dose ($P = .0077$); creatinine clearance 1, 3, and 6 months after transplantation ($P < .0001$); and the hemoglobin level 1 ($P = .04$), 3 ($P = .0007$), and 6 months ($P < .0001$) after transplantation (Table 3). The donor's age and serum creatinine level, MPA DMs during the first year after transplantation, MPA dose discontinuation, MPA DR, or an MMF or MPS dose 1 year after transplantation that was lower than the initial posttransplantation dose (eg, MMF 2 g or MPS 1.44 g with cyclosporin A, MMF 1.5 g with sirolimus, or MMF 1 g with tacrolimus) were included in a multivariate logistic regression analysis model. Independent factors associated with a creatinine clearance of < 60 mL/min were the donor's age ($P < .0001$, OR = 0.91, 95% CI = 0.88-0.95), the donor's serum creatinine clearance ($P = .031$, OR = 1.01, 95% CI = 1.001-1.02), and an MMF or MPS dose that was less than the initial posttransplantation dose ($P = .034$, OR = 2.545, 95% CI = 1.07-6.05) (Table 4). Because the creatinine clearance decreased significantly as soon as 1 month after transplantation in the group of patients who underwent MPA DM to a greater degree than in those who experienced no modification in the MPA dose, it could be assumed that DMs

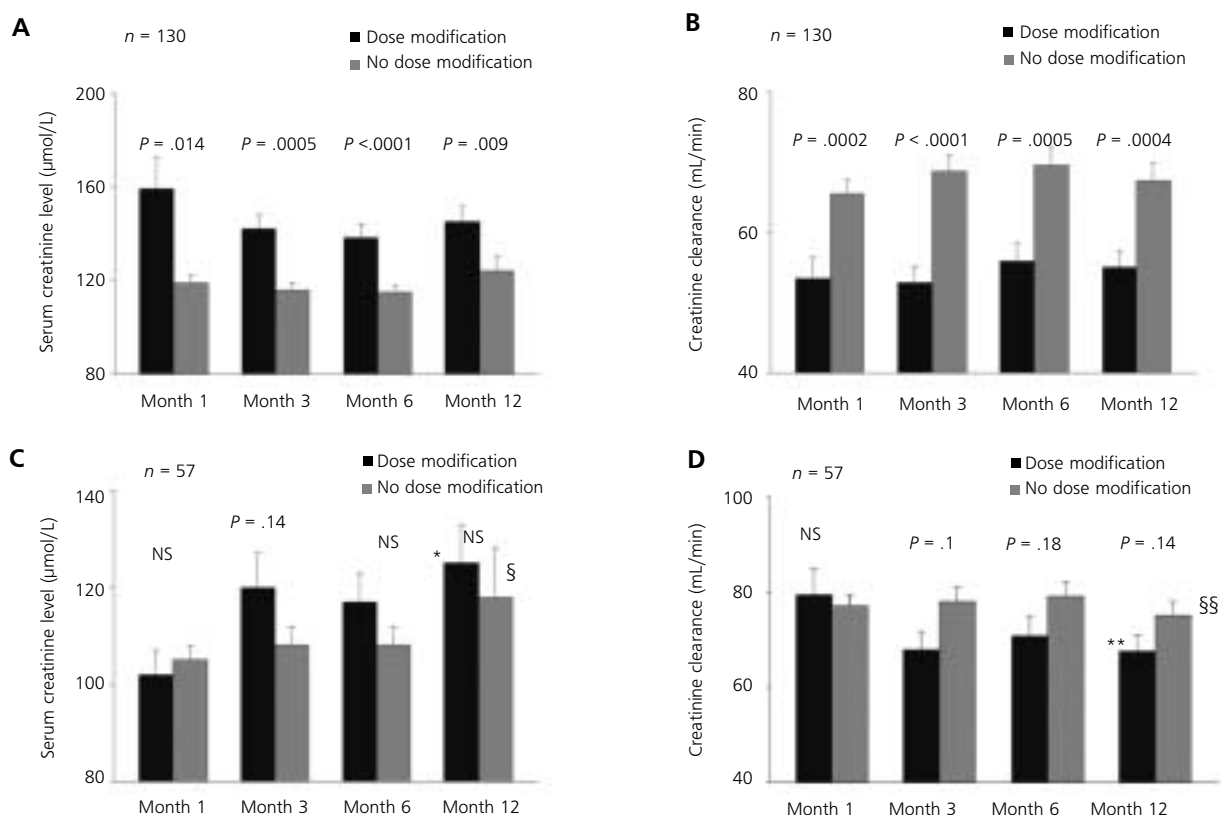


Figure 2, A-D. Renal function 1, 3, 6, and 12 months after kidney transplantation in patients who did or did not undergo mycophenolic acid dose modification. **(A and B)** All patients. **(C and D)** Patients with a creatinine clearance ≥ 60 mL/min 1 month after transplantation.

*Comparison via the Friedman test for repeated measurements of serum creatinine level during the first posttransplant year in patients with a creatinine clearance ≥ 60 mL/min 1 month after transplantation and who underwent mycophenolic acid dose modification; $P = .0003$.

†Comparison via the Friedman test for repeated measurements of the serum creatinine level during the first posttransplant year in patients with a creatinine clearance ≥ 60 mL/min at 1 month after transplantation and who did not undergo mycophenolic acid dose modification; $P = \text{ns}$.

‡Comparison via the Friedman test for repeated measurements of creatinine clearance during the first posttransplant year in patients with a creatinine clearance ≥ 60 mL/min 1 month after transplantation and who underwent a mycophenolic acid dose modification; $P = .02$.

§Comparison via the Friedman test for repeated measurements of the creatinine clearance during the first posttransplant year in patients with a creatinine clearance ≥ 60 mL/min 1 month after transplantation and who did not undergo mycophenolic acid dose modification; $P = \text{ns}$.

occurred more frequently in patients with initial renal function impairment. Therefore, we analyzed the evolution of renal function according to the presence or absence of DMs in the subgroup of patients with a creatinine clearance of ≥ 60 mL/min 1 month after transplantation. Among those 57 patients, 16 (28%) had undergone a DM during the first year after transplantation. One month after transplantation, the serum creatinine level and creatinine clearance were similar in the 2 groups of patients studied (ie, those who did and those who did not undergo an MPA DM). In contrast, during the first posttransplant year, the serum creatinine level increased significantly ($P = .0003$) and the creatinine clearance decreased significantly ($P = .02$) in those patients who had undergone a DM, but neither the serum creatinine level nor the creatinine clearance changed significantly in the patients whose MPA dose was not modified (Figure 2, C and

D). The incidence of acute rejection, CMV infection, and severe infection that required hospitalization and the immunosuppressive drug trough levels were similar in both groups (data not shown).

Predictive factors for MPA DM 1 year after transplantation

We identified, by means of univariate analysis, factors that were associated with MPA DMs 1 year after transplantation (Table 5). To identify independent factors associated with MPA DMs by means of multivariate analysis, we included the following factors in the logistic regression model: the recipient's age at transplantation; the highest level of PRA; the level of PRA at transplantation; the number of previous renal transplantations; the cold ischemia time; the pretransplant lymphocyte count; treatment with MMF, EC-MPS, or sirolimus; induction therapy with polyclonal antibodies or anti-CD25

Table 3. Factors influencing creatinine clearance 1 year after renal transplantation

Variables	Creatinine Clearance 1 Year After RT*		P Value
	≤ 60 mL/min (n = 61)	> 60 mL/min (n = 69)	
Donor age (y)	50.4 ± 1.4	35.3 ± 1.6	< .0001
Donor serum creatinine level (μmol/L)	85 ± 4.7	112 ± 10	.045
MPA dose modification (first year after RT) (Y/N)	36/25	21/48	.0014
MPA dose discontinuation (first year after RT) (Y/N)	13/48	2/67	.0016
MPA dose reduction (first year after RT) (Y/N)	31/30	20/49	.012
MPA dose 1 year after RT vs initial dose	33/28	21/48	.0077
Creatinine clearance 1 month after RT (mL/min)	49 ± 2	70 ± 2.4	< .0001
Creatinine clearance 3 months after RT (mL/min)	48 ± 2	73 ± 2	< .0001
Creatinine clearance 6 months after RT (mL/min)	50 ± 2	76 ± 2	< .0001
Hemoglobin 1 month after RT (g/dL)	11.35 ± 0.16	11.93 ± 0.17	.04
Hemoglobin 3 months after RT (g/dL)	12.28 ± 0.22	13.24 ± 0.18	.0007
Hemoglobin 6 months after RT (g/dL)	12.67 ± 0.21	13.8 ± 0.15	< .0001

RT, Renal transplantation; MPA, mycophenolic acid.

*Univariate analysis.

Table 4. Creatinine clearance* 1 year after renal transplantation

Variable	Odds Ratio	95% CI	P Value
Donor age (y)	0.91	0.88-0.95	< .0001
Serum creatinine level (donor)	1.01	1.001-1.02	.031
MPA dose modification	1.43	0.08-25.3	.8
MPA dose discontinuation	0.36	0.06-2.11	.25
MPA dose reduction	0.72	0.28-1.85	.5
MPA dose 1 year after RT	2.54	1.07-6.05	.034

MPA, Mycophenolic acid; RT, renal transplantation.

*Multivariate analysis.

monoclonal antibodies; the presence of viremia caused by CMV; and the creatinine level and creatinine clearance 1 month after transplantation. The independent factors associated with MPA DMs 1 year after transplantation were as follows: One-month creatinine clearance ($P = .0003$, OR = 0.955, 95% CI = 0.932-0.979), pretransplant lymphocyte count ($P = .0034$, OR = 0.999, 95% CI = 0.998-1.0), treatment with sirolimus ($P = .002$, OR = 163, 95% CI = 11-2407), and a positive test result for CMV viremia ($P = .0028$, OR = 3.79, 95% CI = 1.58-9.08).

Table 5. Mycophenolic acid dose modification* 1 year after renal transplantation

Variable	Dose Modification		P Value
	Yes (n = 57)	No (n = 73)	
Donor age (y)	48 ± 1.9	38 ± 1.5	< .0001
Donor creatinine clearance (mL/min)	83.4 ± 4.5	99.8 ± 5	.034
Recipient age at RT (y)	47 ± 1.8	41.8 ± 1.5	.014
Highest PRA level (%)	16.4 ± 4.4	3.5 ± 1.6	.004
PRA level at RT (%)	8.6 ± 2.9	2.9 ± 1.6	.016
Prior RTs (no.)	0 (0-1)	0 (0-1)	.017
Cold ischemia time (h)	21.2 ± 1.34	17 ± 1.16	.015
MMF/EC-MPS	48/9	45/28	.006
Polyclonal Ab/Anti-CD25 moAb	33/21	21/41	.005
Use of sirolimus (yes/no)	10/47	1/72	.001
Positive CMV viremia (yes/no)	29/28	23/50	.03
Pretransplant lymphocyte count (mm ³)	1452 ± 75	1777 ± 84	.005
Hemoglobin 1 month after RT (g/dL)	11.28 ± 0.19	11.96 ± 0.15	.008
WBCC 1 month after RT (mm ³)	7900 ± 539	9243 ± 377	.024
PMN cell count 1 month after RT (mm ³)	6091 ± 490	7100 ± 329	.022
Lymphocyte count 1 month after RT (mm ³)	910 ± 119	1788 ± 171	< .0001
Platelet count 1 month after RT (mm ³)	199,445 ± 10,793	245,602 ± 8662	.0015
Creatinine level 1 month after RT (μmol/L)	159 ± 13	119 ± 3	.014
Creatinine clearance 1 month after RT (mL/min)	53 ± 3	65 ± 2	.0002
Hemoglobin 3 months after RT (g/dL)	12.22 ± 0.22	13.25 ± 0.17	.0015
WBCC 3 months after RT (mm ³)	6862 ± 415	7903 ± 393	.034
Lymphocyte count 3 months after RT (mm ³)	1978 ± 106	1765 ± 138	< .0001
Hemoglobin 6 months after RT (g/dL)	12.99 ± 0.19	13.51 ± 0.19	.0155
Platelet count 6 months after RT (mm ³)	210,264 ± 9,843	238,197 ± 7198	.0203
WBCC 1 year after RT (mm ³)	6813 ± 389	7795 ± 275	.0034
PMN cell count 1 year after RT (mm ³)	4518 ± 303	5218 ± 234	.01

RT, Renal transplantation; PRA, panel reactive antibodies; MMF, mycophenolate mofetil; EC-MPS, enteric-coated mycophenolate sodium; Ab, antibodies; moAb, monoclonal antibodies; CMV, Cytomegalovirus; WBCC, white blood-cell count; PMN, polymorphonuclear.

*Univariate analysis.

Discussion

MMF, the first formulation of MPA, dramatically decreases the rate of acute rejection after renal transplantation [1,3,13] and has been found to have a beneficial effect on chronic allograft dysfunction [4-6]. However, the characteristic adverse effects produced by MMF, which include hematologic abnormalities, gastrointestinal disorders, and CMV infection, often result in DR during treatment. It has been shown that MPA DR after kidney transplantation increases the risk of acute rejection and decreases renal allograft survival. In a retrospective study, Knoll and colleagues showed that the risk of acute rejection is increased by 4% for every week that an MMF dose of < 2 g/d is given [9]. In another retrospective study, Pelletier and colleagues [10] found that the incidence of acute rejection was significantly higher in patients who underwent a DR in MMF than in those whose MMF regimen was not modified (23.3% vs 3.7%, respectively; $P < .0001$). This resulted in a reduced rate of graft survival by 3 years after transplantation (76.3% vs 88.3%; $P = .003$) [10]. More recently, Glander and colleagues have shown that MMF DR was an independent factor in acute rejection after kidney transplantation (OR = 4.64 [1.61-13.38]) [14]. In our study, only 3 episodes (5.6%) of acute rejection occurred after MMF DM. To our knowledge, our results are the first to show that patients who underwent a DM of MPA during the first year after transplantation exhibited a serum creatinine level that was significantly higher and a creatinine clearance that was significantly lower 1, 3, 6, and 12 months after transplantation than did those patients who received a fixed dose. After the exclusion of patients with a creatinine clearance of < 60 mL/min 1 month after transplantation, a significant impairment of renal function was observed in patients who experienced an MPA DM, a finding that eliminated the patients who were intolerant of MPA or had initial impaired renal function. By means of multivariate analysis, we found that, in addition to the donor's age and creatinine clearance, a lower dose of MPA 1 year after transplantation, when compared with the initial MPA dose after transplantation, was an independent factor for decreased renal function 1 year after transplantation. The decrease in the MPA dosage might be the cause of the subclinical or borderline acute rejection that occurred gradually after renal transplantation. Further studies involving protocol transplant biopsies are necessary to explain the negative impact of MPA DR on renal function.

In the literature, MMF DMs occurred in up to 70% of renal transplant patients [9-11,14], and about 32% of renal transplant patients treated with EC-MPS experienced a DM in their treatment with that agent [15, 16]. In our study, DM occurred in 43.8% of patients. According to previous reports, hematologic abnormalities are the primary cause of MPA DMs. Interestingly, posttransplant anemia, which is a rarely reported cause of MPA DM, was the reason for DM in 21.6% of the patients in our study. Infection, including that caused by CMV, was another reason for DM. In addition, in our study, MPA DM rates associated with gastrointestinal disorders were lower than those in earlier reports [9-11,14], perhaps because of our strategy in managing patients with gastrointestinal symptoms [17].

We identified a number of independent predictive factors for MPA DM during the first year after transplantation: the concomitant administration of immunosuppression therapies, pretransplant factors, and CMV infection. Of those, sirolimus therapy was the most powerful independent factor for MPA DM within the first posttransplant year. Like other investigators, we had previously demonstrated that sirolimus therapy is a prognostic factor for posttransplant anemia during the first posttransplant year [18, 19]. Because more than 20% of the MPA DMs in this study were made as a result of anemia in the patient, it is not surprising that sirolimus therapy is associated with MPA DM. Sirolimus also induces leucopenia and thrombocytopenia. Because of the increased risk of myelotoxicity in patients receiving both MPA and sirolimus and as a result of the pharmacokinetic interaction between those drugs, it has been suggested that lower doses of MMF might be used with sirolimus [20]. As has been recently described [21], our patients were already receiving 1.5 g/d of MMF in addition to sirolimus. Finally, to manage any adverse effects in the patients studied, we reduced the dose of sirolimus as well as that of MPA to lower the trough level of those drugs. Therefore, the pharmacokinetic and pharmacodynamic monitoring of both drugs might be extremely useful in preventing adverse effects in patients receiving that immunosuppressive drug combination.

CMV-positive viremia was also found to be predictive of MPA DM. A similar finding was reported in a large register study from the United States Renal Data System [11]. In patients with CMV-positive viremia, it seems logical to reduce the MMF dose because of reports that mildly symptomatic CMV infection can be managed effectively by MMF DR or withdrawal [22]. Hong and Kahan failed to find an association between pretransplant

demographic or laboratory data and the risk of posttransplant hematologic complications [23]. More recently, Glander and colleagues found that patients who required a reduction in the MMF dose during follow-up had significantly less pretransplant inosine monophosphate dehydrogenase activity than did those whose MMF dose was not reduced [14]. In our study, a low lymphocyte count was an independent factor associated with MPA DR 12 months after transplantation.

The main limitation of our retrospective study is the absence of MPA therapeutic drug monitoring. Indeed, the MPA AUC is significantly correlated with the incidence of acute rejection [24-26]. In contrast, the initial study by van Gelder and colleagues showed that the MMF dose, rather than the MPA trough level or the area under the curve, is significantly related to the development of adverse events that result in DR [24]. We concluded that MPA DM has a negative impact on renal allograft function 1 year after transplantation.

References

- [No authors listed] Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. European Mycophenolate Mofetil Cooperative Study Group. *Lancet* 1995; 345: 1321-1325
- Sollinger HW. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. U.S. Renal Transplant Mycophenolate Mofetil Study Group. *Transplantation* 1995; 60: 225-232
- [No authors listed] A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. The Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group. *Transplantation* 1996; 61: 1029-1037
- Meier-Kriesche HU, Steffen BJ, Hochberg AM, Gordon RD, Liebman MN, Morris JA, Kaplan B. Mycophenolate mofetil versus azathioprine therapy is associated with a significant protection against long-term renal allograft function deterioration. *Transplantation* 2003; 75: 1341-1346
- Merville P, Berge F, Deminiere C, Morel D, Chong G, Durand D, et al. Lower incidence of chronic allograft nephropathy at 1 year post-transplantation in patients treated with mycophenolate mofetil. *Am J Transplant* 2004; 4: 1769-1775
- Ojo AO, Meier-Kriesche HU, Hanson JA, Leichtman AB, Cibrik D, Magee JC, et al. Mycophenolate mofetil reduces late renal allograft loss independent of acute rejection. *Transplantation* 2000; 69: 2405-2409
- Salvadori M, Holzer H, de Mattos A, Sollinger H, Arns W, Oppenheimer F, et al. Enteric-coated mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in de novo renal transplant patients. *Am J Transplant* 2004; 4: 231-236
- Budde K, Curtis J, Knoll G, Chan L, Neumayer HH, Seifu Y, et al. Enteric-coated mycophenolate sodium can be safely administered in maintenance renal transplant patients: results of a 1-year study. *Am J Transplant* 2004; 4: 237-243
- Knoll GA, MacDonald I, Khan A, Van Walraven C. Mycophenolate mofetil DR and the risk of acute rejection after renal transplantation. *J Am Soc Nephrol* 2003; 14: 2381-2386
- Pelletier RP, Akin B, Henry ML, Bumgardner GL, Elkhammas EA, Rajab A, Ferguson RM. The impact of mycophenolate mofetil dosing patterns on clinical outcome after renal transplantation. *Clin Transplant* 2003; 17: 200-205
- Hardinger KL, Brennan DC, Lowell J, Schnitzler MA. Long-term outcome of gastrointestinal complications in renal transplant patients treated with mycophenolate mofetil. *Transpl Int* 2004; 17: 609-616
- Mengelle C, Pasquier C, Rostaing L, Sandres-Saune K, Puel J, Berges L, et al. Quantitation of human *cytomegalovirus* in recipients of solid organ transplants by real-time quantitative PCR and pp65 antigenemia. *J Med Virol* 2003; 69: 225-231
- [No authors listed] Mycophenolate mofetil in renal transplantation: 3-year results from the placebo-controlled trial. European Mycophenolate Mofetil Cooperative Study Group. *Transplantation* 1999; 68: 391-396
- Glander P, Hambach P, Braun KP, Fritsche L, Giessing M, Mai I, et al. Pre-transplant inosine monophosphate dehydrogenase activity is associated with clinical outcome after renal transplantation. *Am J Transplant* 2004; 4: 2045-2051
- Rostaing L, Mourad G, Legendre C. Sustainable tolerability effects of Myfortic in combination with Neoral and steroids at 12 months, in de novo kidney transplantation: a randomized, multicentre, open, prospective controlled study [abstract]. *Am J Transplant* 2005; 5: 190. Abstract 133
- Legendre C, Rostaing L, Kirchherr B. Tolerability of enteric coated mycophenolate sodium (EC-MPS) in combination with Neoral and steroids in de novo kidney transplant recipient: A 12 months prospective trial [abstract]. *Am J Transplant* 2005; 5: 464. Abstract 1209
- Kamar N, Oufroukhi L, Faure P, Ribes D, Cointault O, Lavyssiere L, et al. Questionnaire-based evaluation of gastrointestinal disorders in de novo renal-transplant patients receiving either mycophenolate mofetil or enteric-coated mycophenolate sodium. *Nephrol Dial Transplant* 2005; 20: 2231-2236
- Turkowski-Duhem A, Kamar N, Cointault O, Lavyssiere L, Ribes D, Esposito L, et al. Predictive factors of anemia within the first year post-renal transplant. *Transplantation* In press
- Augustine JJ, Knauss TC, Schulak JA, Bodziak KA, Siegel C, Hricik DE. Comparative effects of sirolimus and mycophenolate mofetil on erythropoiesis in kidney transplant patients. *Am J Transplant* 2004; 4: 2001-2006
- Cattaneo D, Merlini S, Pellegrino M, Carrara F, Zenoni S, Murgia S, et al. Therapeutic drug monitoring of sirolimus: effect of concomitant immunosuppressive therapy and optimization of drug dosing. *Am J Transplant* 2004; 4: 1345-1351
- El Haggan W, Ficheux M, Debruyne D, Rognant N, Lobbedez T, Allard C, et al. Pharmacokinetics of mycophenolic acid in kidney transplant patients receiving sirolimus versus cyclosporine. *Transplant Proc* 2005; 37: 864-866
- Anglicheau D, Lautrette A, Scieux C, Flamant M, Morinet F, Legendre C. Efficacy and safety of lowering immunosuppression to treat CMV infection in renal transplant recipients on valacyclovir prophylaxis: a pilot study. *Nephrol Dial Transplant* 2003; 18: 1654-1656
- Hong JC, Kahan BD. Sirolimus-induced thrombocytopenia and leukopenia in renal transplant recipients: risk factors, incidence, progression, and management. *Transplantation* 2000; 69: 2085-2090
- van Gelder T, Hilbrands LB, Vanrenterghem Y, Weimar W, de Fijter JW, Squifflet JP, et al. A randomized double-blind, multicenter plasma concentration controlled study of the safety and efficacy of oral mycophenolate mofetil for the prevention of acute rejection after kidney transplantation. *Transplantation* 1999; 68: 261-266
- Kiberd BA, Lawen J, Fraser AD, Keough-Ryan T, Belitsky P. Early adequate mycophenolic acid exposure is associated with less rejection in kidney transplantation. *Am J Transplant* 2004; 4: 1079-1083
- Le Meur Y, Buchler M, Lavaud S, Etienne I, Westeel PF, Thierry A, et al. Concentration controlled versus fixed dose of MMF in kidney transplant recipients: Preliminary results of a french multicenter randomized study [abstract]. *Am J Transplant* 2005; 5: 242