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Fixed- or Controlled-Dose Mycophenolate Mofetil with Standard- or Reduced-Dose Calcineurin Inhibitors: The Opticept Trial

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Mycophenolate mofetil (MMF) was developed with cyclosporine as a fixed-dose immunosuppressant. More recent data indicate a relationship between mycophenolic acid (MPA) exposure in individuals and clinical endpoints of rejection and toxicity. This 2-year, open-label, randomized, multicenter trial compared the efficacy and safety of concentration-controlled MMF (MMF_{CC}) dosing with a fixed-dose regimen in 720 kidney recipients. Patients received either (A) MMF_{CC} and reduced-level calcineurin inhibitor (MMF_{CC}/CNI_{RL}); (B) MMF_{CC} and standard-level CNI (MMF_{CC}/CNI_{SL}); or (C) fixed-dose MMF and CNI_{SL} (MMF_{FD}/CNI_{SL}). Antibody induction and steroid use were according to center practice. The primary endpoint was noninferiority ($\alpha = 0.05$) of group A versus group C for treatment failure (including biopsy-proven acute rejection [BPAR], graft loss and death) at 1 year. Although mean CNI trough levels in group A did not reach the prespecified targets, they were statistically lower than those in groups B and C ($p \leq 0.01$ for each comparison). BPAR rates (8.5%) were low across groups. Group A had 19% fewer treatment failures (23% vs. 28%, $p = 0.18$). MMF doses were highest ($p < 0.05$), with withdrawals for adverse events the fewest ($p = 0.02$), in group A. Of the 80% of subjects taking tacrolimus (Tac), those with higher MPA exposure had significantly less rejection ($p < 0.001$) and diarrhea correlated with Tac, but not with MPA levels. Thus, MMF_{CC} with low-dose CNI resulted in outcomes not inferior to those with standard CNI exposure and MMF_{FD}, indicating potential utility of MMF_{CC} in CNI-sparing regimens.

Key words: Calcineurin inhibitor, cyclosporine, mycophenolate mofetil, renal transplantation, tacrolimus

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Introduction

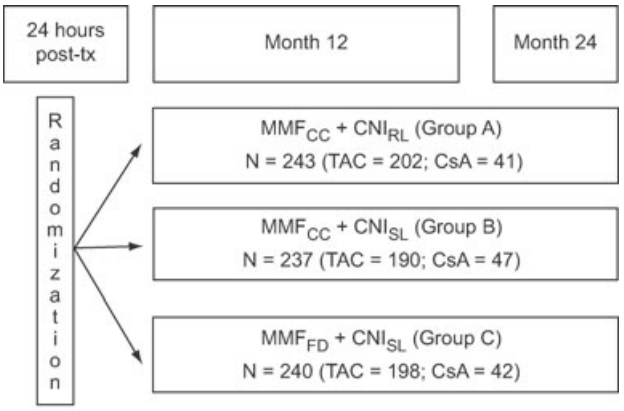
Although modern immunosuppression in kidney transplantation has led to significant reductions in allograft rejection, drug-specific complications (including new-onset diabetes mellitus, hyperlipidemia and hypertension) remain a serious concern (1). In addition, cyclosporine and tacrolimus, calcineurin inhibitors (CNI) on which most protocols are based, are nephrotoxic (2). Nankivell et al. (3) suggest that histopathologic changes characteristic of chronic allograft nephropathy are virtually universal in renal allografts after 10 years of CNI maintenance, although this viewpoint is not universally accepted.

Recent studies indicate immunosuppressive regimens that include mycophenolate mofetil (MMF) may attenuate CNI-associated histopathologic changes and decline in renal function (1,4,5). MMF as a maintenance immunosuppressant has not been associated with short- or long-term negative effects on renal function, lipid and carbohydrate levels or blood pressure, sequelae that can affect graft and/or patient survival (6). When used in combination with cyclosporine, MMF was associated with less chronic allograft nephropathy than azathioprine (7) and significantly improved renal function in patients with existing chronic allograft nephropathy (8). In a retrospective study of 66 774 renal allograft recipients receiving CNI maintenance, MMF (compared to azathioprine) decreased the relative risk of chronic allograft failure by 27% ($p = 0.001$) (9), an outcome consistent with the more recently published histologic findings of Nankivell and colleagues (10).

Fixed-dose administration of MMF, typically 2 g/day in adults, is the standard regimen employed in renal transplantation. This dosing regimen, established in cyclosporine-treated patients, was validated in several large clinical trials (11–13) and was shown in the recent Efficacy Limiting Toxicity Elimination (ELITE)-Symphony Study (14) to provide renal function and graft survival benefits over other regimens when combined with daclizumab induction and corticosteroid/low-dose tacrolimus maintenance. Mycophenolic acid (MPA) is the active metabolite of MMF; there are known to be wide ranges in MPA exposure between patients receiving identical doses of MMF (15). The physiological basis underlying these differences is not well established, although a variety of potential contributing factors (specific ethnic status, renal and liver function and concurrent medications) have been identified (16). This interpatient variability has fueled an increasing interest in evaluating the utility of MPA exposure monitoring in clinical transplantation. In several studies, MPA area under the concentration–time curve (AUC) has been inversely correlated with the risk of an acute rejection episode in both renal and cardiac transplant recipients (17–21) with overexposure thought to increase the risk of infection and malignancy (22,23). APOMYGRE (24) was a 12-month study in which kidney transplant recipients on cyclosporine were randomized to fixed-dose MMF or to a concentration-controlled dose based on MPA AUC. Subjects in the concentration-controlled group demonstrated significantly less treatment failure (29% vs. 48%; $p = 0.03$) and biopsy-proven acute rejection (BPAR) (8% vs. 25%; $p = 0.01$) than controls, but little difference in infectious complications. In contrast, another recently published multicenter study found no advantage associated with concentration-controlled dosing of MMF (25), noting an overlap of MPA exposure among treatment groups and reluctance of investigators to implement early MMF dose adjustments required to achieve target MPA AUC exposure. The effect of concentration-controlled dosing of MMF in conjunction with CNI minimization is unknown.

Although limited (abbreviated) MPA AUC sampling to estimate full interdose AUC has been found to be useful (6,26–28), it can be labor intensive and cumbersome. Predose (or trough) level monitoring of tacrolimus and cyclosporine is common in clinical practice; a similar approach to MPA monitoring could be easily implemented. However, while MPA trough levels have been reported to be good and practical surrogates for MPA AUC, their utility has not been tested in large trials. Existing studies have been limited to relatively small numbers of patients and usually in the setting of cyclosporine coadministration (6).

The Opticept® trial compared three different dosing regimens, including both fixed and monitored dosing of MMF, as well as standard and reduced levels of CNIs, to better define the utility of trough level-based concentration-controlled regimens of MMF in facilitating a CNI-sparing regimen in clinical kidney transplantation.



Time Frame	CNI_{RL}, ng/mL CsA	CNI_{RL}, ng/mL TAC	CNI_{SL}, ng/mL CsA	CNI_{SL}, ng/mL TAC
Days 1-30	250-325	8-12	250-325	8-12
Days 31-90	125-165	4-6	250-270	8-10
Day 91-2 years	95-145	3-5	190-220	6-8

Figure 1: Trial design and calcineurin inhibitor (CNI) dose adjustment by target trough level. MMF_{CC}/CNI_{RL} = controlled-concentration mycophenolate mofetil (MMF) with reduced-level CNI dosing; MMF_{CC}/CNI_{SL} = MMF_{CC} with standard concentrations of CNIs; and MMF_{FD}/CNI_{SL} = fixed-dose MMF with CNI_{SL}. CsA = cyclosporine; post-tx = posttransplant; TAC = tacrolimus.

Methods

Details of the methods are provided in Appendix S1.

Study design

This 2-year, open-label, prospective, randomized, controlled trial was conducted at 51 centers in the United States. Recipients of a single (first or second) renal allograft from living (related or unrelated) or deceased donors were eligible for enrollment. The study protocol was reviewed and approved by the institutional review board at each study site and was conducted in full conformance with the principles of the Declaration of Helsinki. All study participants provided signed informed consent prior to randomization. The study is listed on www.clinicaltrials.gov (NCT00087581).

Randomization and treatment

Patients entered the study within 24 h of transplantation. Eligible subjects were allocated sequentially in order of their enrollment to one of three treatment groups in a 1:1:1 ratio (Figure 1). Randomization was balanced within each center and stratified by CNI (tacrolimus or cyclosporine).

Each treatment group received one of the following regimens: group A, concentration-controlled MMF with reduced CNI levels (MMF_{CC}/CNI_{RL}); group B, concentration-controlled MMF with standard CNI administration levels (MMF_{CC}/CNI_{SL}); and group C, fixed-dose MMF with standard CNI administration levels (MMF_{FD}/CNI_{SL}). The target blood levels of tacrolimus or cyclosporine were as depicted in Figure 1. The initial dose of oral or intravenous MMF, to be administered within 24 h following transplantation, was at least 1 g twice daily for adults and 600 mg/m^2 twice daily for pediatric patients. For patients in the MMF_{CC} groups (groups A and B), the dose was adjusted to achieve whole blood MPA trough levels of $\geq$ 1.3 μg/mL if receiving cyclosporine and of $\geq$ 1.9 μg/mL if receiving tacrolimus (6), with the adjusted dose not exceeding 4 g/day regardless of trough level.

Table 1: Baseline demographics and clinical characteristics of patients and donors

Characteristic	MMF_{CC}/CNI_{RL} Group A (N = 243)	MMF_{CC}/CNI_{SL} Group B (N = 237)	MMF_{FD}/CNI_{SL} Group C (N = 240)
Gender, n (%)			
Male	163 (67.1)	159 (67)	163 (67.9)
Female	80 (32.9)	78 (32.9)	77 (32.1)
Age (years), mean (SD)	48.3 (12.8)	48.8 (13.6)	49.6 (13.2)
Race, N (%)			
Caucasian	160 (65.8)	168 (70.9)	167 (69.6)
African American	65 (26.7)	58 (24.5)	62 (25.8)
Other	18 (7.4)	11 (4.6)	11 (4.6)
Original kidney disease, N (%)			
Diabetes mellitus	64 (26.3)	64 (27.0)	54 (22.5)
Hypertension	56 (23.0)	51 (21.5)	64 (26.7)
Glomerulonephritis	51 (21.0)	55 (23.2)	58 (24.2)
IgA nephropathy	18 (7.4)	10 (4.2)	13 (5.4)
Focal glomerulosclerosis	18 (7.4)	21 (8.9)	21 (8.8)
Other or uncertain	36 (14.8)	36 (15.2)	30 (12.5)
Donor source, N (%)			
Deceased	119 (49.0)	118 (49.8)	124 (51.7)
Living related	73 (30.0)	72 (30.4)	61 (25.4)
Living unrelated	48 (19.8)	46 (19.4)	54 (22.5)
Panel reactive antibody levels ≥20%, N (%)	16 (6.6)	20 (8.4)	17 (7.1)
HLA mismatches, total, N (%)			
0	27 (11.1)	21 (8.9)	26 (10.8)
1–3	98 (40.3)	87 (36.7)	63 (26.3)
4–6	113 (46.5)	123 (51.9)	144 (60.0)
Unknown	0 (0.0)	2 (0.8)	1 (0.4)
Baseline eGFR (mL/min), mean (SD)	67.5 (19.6)	67.1 (18.4)	65.6 (19.3)
Patients receiving induction therapy, N (%)	182 (75)	178 (75)	181 (75)
Antithymocyte globulin	108 (44)	100 (42)	103 (43)
Basiliximab	50 (21)	55 (23)	52 (22)
Daclizumab	24 (10)	25 (11)	27 (11)
Patients receiving corticosteroids, N (%)			
Week 1	228 (93.8)	228 (96.2)	231 (96.3)
Patients receiving CMV prophylaxis, N (%)	111 (45.7)	120 (50.6)	107 (44.6)

CC = concentration controlled; CMV = cytomegalovirus; CNI = calcineurin inhibitor; eGFR = estimated glomerular filtration rate; FD = fixed dose; HLA = human leukocyte antigen; MMF = mycophenolate mofetil; N = number; RL = reduced level; SD = standard deviation; SL = standard level.

These levels were selected as an acceptable balance between underdosing and overdosing based on an exploratory reanalyses of prior MPA exposure data in renal transplant patients receiving cyclosporine (18) or tacrolimus (29). Essentially, the target trough level is higher when MMF is administered with tacrolimus because a greater proportion of the MPA exposure in tacrolimus-treated patients is in the latter part of the dosing interval due to greater enterohepatic recirculation (6). For patients experiencing leukopenia or gastrointestinal toxicity, MMF dose reductions were managed according to a defined protocol and were guided by the clinical severity and course of the adverse event. Induction therapy, corticosteroids and prophylaxis for opportunistic infections were administered according to center practice.

Study outcomes assessments and endpoints

Patients returned on days 3, 10 and 30 and at months 2, 3, 6, 9, 12 and 20–24 for routine clinical and laboratory evaluations, determination of MPA and CNI trough levels and reporting of adverse events. MMF doses were adjusted based on the trough levels although abbreviated AUCs were also determined during the trial. Abbreviated AUCs were determined by sampling at three time points over 2 h (0, 30 and 120 min) in fasted patients on days 3, 10 and 30 and months 3, 6 and 12, but were not made available to investigators.

The primary efficacy endpoint at 12 months posttransplant was the proportion of patients experiencing treatment failure, defined as any of the following: BPAR, graft loss, death, lost to follow-up or withdrawal of consent. The coprimary endpoint was the change in renal function from baseline assessed by estimated glomerular filtration rate (eGFR) at 12 months calculated using the Nankivell equation (30). The secondary endpoints included (for each treatment group) (i) the proportion of patients experiencing treatment failure within 24 months posttransplant; (ii) the proportion of patients experiencing BPAR; (iii) the proportion of patients treated for acute rejection (presumptive acute rejection) within 12–24 months posttransplant; (iv) the number of BPAR episodes per patient at 12 and 24 months posttransplant; (v) the time to first BPAR episode at 12 and 24 months posttransplant; (vi) the proportion of patients who died had a graft loss or discontinued MMF therapy within 12–24 months; and (vii) the time to treatment failure.

The diagnosis of BPAR was confirmed histologically using the Banff 97 classification criteria (31). Graft loss was defined as the initiation of chronic

Table 2: Mean daily dose of mycophenolate mofetil (MMF)

	MMF_{CC}/CNI_{RL} Group A		MMF_{CC}/CNI_{SL} Group B		MMF_{FD}/CNI_{SL} Group C	
MMF (mg)	Cyclosporine	Tacrolimus	Cyclosporine	Tacrolimus	Cyclosporine	Tacrolimus
1– 7 days						
Mean	1955.4	1987.8	2032.5	1995.2	1939.2	1958.3
SD	286.26	311.7	263.75	299.27	368.15	339.79
N	40	198	45	187	42	195
8–30 days						
Mean	2354.9[1]	2109.2[2]	2194.7	2078.4[3]	2093.8	1947.0
SD	527.45	498.78	463.04	436.24	307.98	367.31
N	37	191	45	185	40	189
31–90 days						
Mean	2465.0[2]	2063.7[2]	2318.8[3]	1972.4	2034.8	1862.3
SD	700.54	567.6	566.56	605.4	313.95	425.34
N	36	184	44	177	38	183
91–180 days						
Mean	2229.1[1]	1971.6[2,4]	2217.7[3]	1812.9	1872.4	1700.5
SD	977.97	629.57	772.57	670.2	379.5	503.51
N	33	175	42	162	37	168
181–365 days						
Mean	2024.4	1896.8[2,4]	1913.8	1723.5	1833.9	1662.7
SD	895.32	606.36	736.16	668.09	459.09	474.48
N	33	168	39	143	33	152

CC = concentration controlled; CNI = calcineurin inhibitor; FD = fixed dose; N = number; RL = reduced level; SD = standard deviation; SL = standard level.
[1]P <0.05 for group A versus group C.
[2]P <0.008 for group A versus group C.
[3]P <0.05 for group B versus group C.
[4]P<0.02 for group A versus group B.

dialysis (at least 6 consecutive weeks in duration), transplant nephrectomy, retransplantation or death with a functioning graft.

Safety endpoints included (i) all adverse events, defined as any medical occurrence whether related to treatment or not and including worsening of preexisting conditions; (ii) opportunistic infections; (iii) malignancies; (iv) abnormal laboratory findings; and (v) renal function as assessed by eGFR at 3, 6 and 24 months.

Results

Patient enrollment and baseline characteristics

The study was conducted between June 2004 and September 2007. A total of 720 patients were randomized (intent-to-treat population); the safety population included 709 patients. Approximately 80% of patients in each group received tacrolimus. Three quarters of participants in each treatment group received induction therapy; overall, antithymocyte globulin (43%) was used more frequently than basiliximab (22%) or daclizumab (11%) (Table 1).

Overall, 483/720 (67%) patients completed 12 months of treatment on protocol. Study withdrawal occurred less often among group A patients (63/243, 26%) compared with 87/237, 37% and 87/240, 36% in groups B and C, respectively ($p = 0.02$). Although the majority of discontinuations were unrelated to safety issues, there were also significantly fewer withdrawals due to adverse events in group A (18/243, 7.4%) versus group B (34/237, 14.3%) and group C (34/240, 14.2%; $p = 0.02$). After 12 months, 77% of patients in group A remained on MMF versus 66% of patients in group B and 68% in group C.

Immunosuppressant doses and exposure

After the first week posttransplant through day 180, the mean daily dose of MMF received by subjects in group A (MMF_{CC}/CNI_{RL}) was significantly higher than in those receiving MMF_{FD}/CNI_{SL} (group C) for either cyclosporine or tacrolimus (Table 2). For patients receiving tacrolimus (but not among those on cyclosporine), the MMF dose in the MMF_{CC}/CNI_{RL} treatment group was also significantly higher than in the MMF_{CC}/CNI_{SL} group after the first week of therapy.

A summary of MPA trough concentrations by CNI type is shown in Table 3. Mean MPA trough levels exceeded the target at and beyond day 10 for those receiving tacrolimus (but only after 2 months for cyclosporine-treated patients) and generally were maintained throughout the study. The mean abbreviated MPA AUC increased during the first 3 months of treatment and then stabilized with MPA exposure significantly greater in the tacrolimus-treated than in the cyclosporine-treated patients. By 6 months, MPA

Table 3: Summary of (A) mycophenolic acid (MPA) trough concentrations and (B) abbreviated MPA area under the concentration–time curve (AUC) by calcineurin inhibitor (CNI) type

	MMF_{CC}/CNI_{RL} Group A			MMF_{CC}/CNI_{SL} Group B			MMF_{FD}/CNI_{SL} Group C		
	CsA (N = 41)	TAC (N = 202)	p-Value	CsA (N = 47)	TAC (N = 190)	p-Value	CsA (N = 42)	TAC (N = 198)	p-Value[2]
(A) MPA trough concentrations by CNI type, μg/mL[1]									
Day 10			<0.0001			<0.0001			0.0022
Mean ± standard deviation	1.1 ± 0.8	2.1 ± 1.4		1.2 ± 0.7	2.1 ± 1.3		1.2 ± 1.1	2.0 ± 1.4	
Interval 25–75th percentile	0.6, 1.3	1.0, 2.9		0.7, 1.5	1.0, 2.8		0.6, 1.8	1.1, 2.7	
N	33	170		41	158		32	161	
Month 1			<0.0001			<0.0001			<0.0001
Mean ± standard deviation	1.1 ± 0.6	2.5 ± 1.2		1.2 ± 0.7	2.5 ± 1.4		1.4 ± 1.3	2.5 ± 1.3	
Interval 25–75th percentile	0.7, 1.4	1.6, 3.2		0.6, 1.6	1.6, 3.2		0.6, 1.7	1.5, 3.4	
N	32	165		40	156		31	153	
Month 3			0.002			0.002			<0.0001
Mean ± standard deviation	1.7 ± 0.9	2.6 ± 1.5		1.8 ± 1.3	2.7 ± 1.5		1.3 ± 0.8	2.6 ± 1.5	
Interval 25–75th percentile	1.0, 2.3	1.6, 3.5		0.9, 2.3	1.5, 3.6		0.7, 1.9	1.6, 3.4	
N	27	153		36	134		29	137	
Month 6			0.001			0.04			<0.0001
Mean ± standard deviation	1.6 ± 1.1	2.4 ± 1.3		1.9 ± 1.0	2.5 ± 1.5		1.0 ± 0.6	2.3 ± 1.5	
Interval 25–75th percentile	0.7, 2.2	1.4, 3.2		1.2, 2.2	1.4, 3.5		0.7, 1.2	1.3, 3.1	
N	30	147		29	112		24	120	
Month 12			0.001			0.67			0.001
Mean ± standard deviation	1.6 ± 1.1	2.6 ± 1.5		2.2 ± 1.5	2.4 ± 1.5		1.2 ± 0.7	2.5 ± 1.6	
Interval 25–75th percentile	1.0, 1.9	1.4, 3.6		1.0, 3.2	1.3, 3.1		0.8, 1.7	1.3, 3.0	
N	25	125		27	103		21	107	
(B) Abbreviated MPA AUC by CNI type, μg/h/mL									
Day 10			0.0177			0.0010			0.0069
Mean ± standard deviation	31.7 ± 14.7	38.9 ± 15.0		30.4 ± 12.3	38.5 ± 13.9		30.0 ± 11.3	38.2 ± 15.4	
Interval 25–75th percentile	19.6, 38.7	27.6, 49.2		22.6, 40.5	26.9, 47.9		23.7, 35.8	28.4, 44.5	
N	29	158		41	147		29	150	
Month 1			0.03			<0.0001			0.003
Mean ± standard deviation	39.2 ± 15.7	46.1 ± 16.0		32.3 ± 13.1	46.4 ± 17.0		36.3 ± 14.1	45.8 ± 15.5	
Interval 25–75th percentile	29.0, 48.3	35.2, 54.5		24.0, 41.3	35.5, 55.5		26.7, 45.6	33.9, 55.9	
N	30	159		39	146		29	143	

Continued.

Table 3: Continued

	MMF_{CC}/CNI_{RL} Group A			MMF_{CC}/CNI_{SL} Group B			MMF_{FD}/CNI_{SL} Group C		
	CsA (N = 41)	TAC (N = 202)	p-Value	CsA (N = 47)	TAC (N = 190)	p-Value	CsA (N = 42)	TAC (N = 198)	p-Value[2]
Month 3			0.046			0.02			0.001
Mean ± standard deviation	40.1 ± 19.7	48.3 ± 18.9		41.4 ± 16.9	49.4 ± 18.7		36.1 ± 11.3	49.2 ± 20.2	
Interval 25–75th percentile	29.6, 48.1	34.5, 59.4		27.1, 55.9	36.3, 60.6		28.2, 45.2	35.2, 61.4	
N	26	146		35	128		28	129	
Month 6			0.71			0.43			0.005
Mean ± standard deviation	48.8 ± 25.1	47.4 ± 17.2		43.9 ± 16.6	47.0 ± 19.5		34.6 ± 15.5	46.2 ± 17.7	
Interval 25–75th percentile	27.6, 61.6	36.3, 56.9		32.6, 53.5	30.6, 62.2		25.8, 41.9	33.0, 59.1	
N	30	139		29	107		22	110	
Month 12			0.62			0.86			0.04
Mean ± standard deviation	46.0 ± 14.1	47.9 ± 17.0		46.1 ± 19.2	45.3 ± 18.3		39.1 ± 14.3	48.8 ± 19.0	
Interval 25–75th percentile	34.5, 54.4	35.4, 59.8		33.3, 62.7	32.2, 55.4		27.6, 50.2	34.7, 61.5	
N	23	122		26	99		18	99	

CC = concentration controlled; FD = fixed dose; MMF = mycophenolate mofetil; N = number; RL = reduced level; SL = standard level.
[1]Tacrolimus (TAC): MPA target ≥ 1.9 μg/mL; and cyclosporine (CsA): MPA target ≥ 1.3 μg/mL.
[2]p-value comparing the CNI types was calculated using analysis of variance; records meeting the following criteria were excluded: MPA trough >7; MPA concentration at 30 min was greater than MPA trough by 112%; a switch to a different CNI type.

exposures equalized for the cyclosporine- and tacrolimus-treated patients in the two concentration-controlled groups but not in the fixed-dose group (Table 3). Trends in the dose-corrected MPA AUC values were similar. At 12 months, there was a positive correlation between abbreviated MPA AUC and trough concentrations overall, and the correlation was stronger for patients receiving tacrolimus (Figure 2A) than for those treated with cyclosporine (Figure 2B; $r^2 = 0.6864$; $p < 0.0001$ vs. $r^2 = 0.3288$; $p < 0.0001$, respectively).

As per protocol by month 3 and thereafter, the mean trough level of tacrolimus in the MMF_{CC}/CNI_{RL} group (group A), though not as low as originally targeted, was statistically lower ($p \leq 0.01$) than in the other two treatment groups (Figure 3). Although the trough levels of cyclosporine were also numerically lower in group A than in the other two treatment groups, the sample size was too small for statistical analysis.

Efficacy

The number and percentage of patients with treatment failure at 12 months posttransplant were 55/243 (22.6%) for the MMF_{CC}/CNI_{RL} group (group A), 67/237 (28.3%) for group B and 67/240 (27.9%) for group C (Table 4). Group A had a 5.3% lower rate of treatment failure (90% confidence interval [CI]: −11.8, 1.3; $p = 0.18$), a 19% reduction, confirming noninferiority of outcomes in this treatment group. There was also no significant difference in treatment failure among the groups stratified by CNI type (data not shown). Deaths were infrequent across the groups. Diabetes at baseline was significantly associated with time to death (risk ratio = 2.46; 95% CI: 1.0, 6.0; $p = 0.05$).

The baseline eGFR (30 days posttransplant) was similar across groups. At 12 months, patients in group A had a 12.3% increase in eGFR from baseline compared to a 5.4% increase in group B and an 8.2% increase in group C. When analyzed by CNI, the mean percentage increase in eGFR for those receiving cyclosporine in the MMF_{CC}/CNI_{RL} group (group A) was greater than in the MMF_{CC}/CNI_{SL} group ($p = 0.05$) (Figure 4), but similar to that in group C ($p = 0.11$).

The results of the secondary endpoints are provided in Table 5. A total of 61/720 (8.5%) participants had a BPAR episode during the 12 months of the study with a majority of rejection episodes occurring within the first 6 months posttransplant. Across groups, more patients receiving cyclosporine (16/130, 12.3%) experienced BPAR than those receiving tacrolimus (45/590, 7.6%). Although the percentage of patients with BPAR was somewhat lower in group A than in group C, the difference was not significant ($p = 0.17$). In the tacrolimus-treated group, dose-uncorrected MPA trough levels had a significant impact on the time to first BPAR at 6 and 12 months (risk ratio = 0.322 [$p < 0.0001$] and 0.390 [$p < 0.0001$], respectively), as did the abbreviated MPA AUC values (risk ratio = 0.933 [$p < 0.0002$]

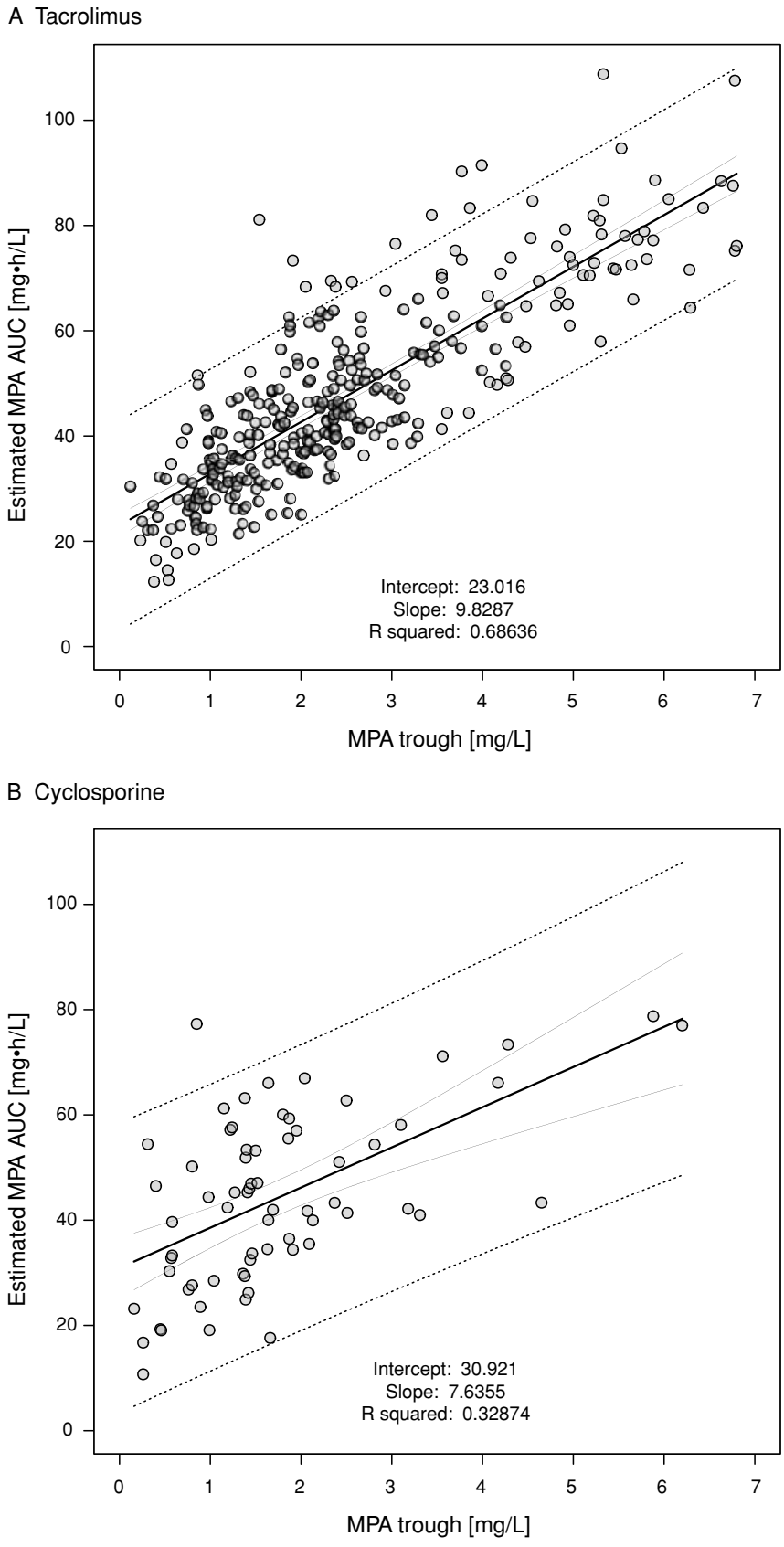


Figure 2: Linear regression analysis of the estimated mycophenolic acid (MPA) area under the concentration–time curve (AUC) versus trough in patients receiving (A) tacrolimus and (B) cyclosporine.

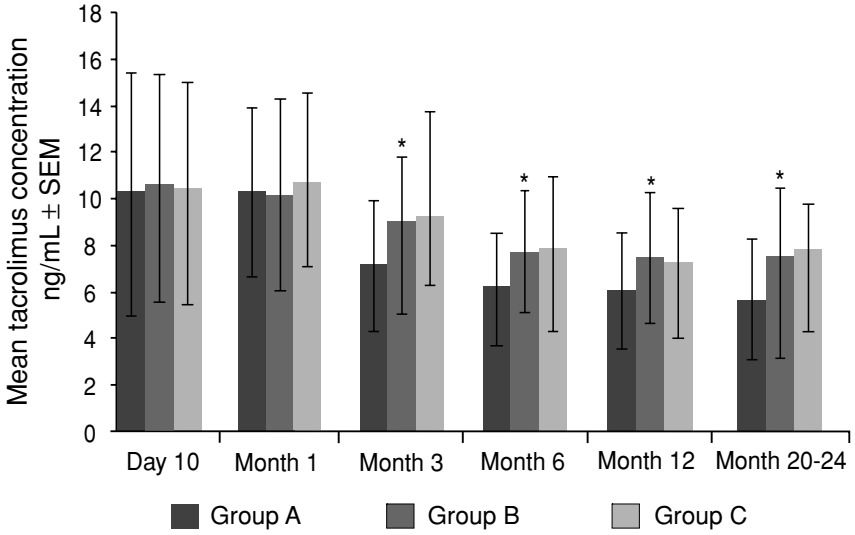


Figure 3: Tacrolimus trough levels. SEM = standard error of the mean. *p ≤ 0.0003 for group A versus group C; p ≤ 0.01 for group A versus group B.

and 0.926 [p < 0.0001], respectively). MPA trough concentrations ≥1.6 μg/mL were associated with a longer time to first BPAR episode in tacrolimus-treated patients from all three groups (Figure 5). For these tacrolimus patients, higher MPA trough concentrations or higher abbreviated MPA AUC values were associated with a lower risk of rejection. The number of cyclosporine-treated patients was too small for similar analyses. Similarly, the heterogeneity of antibody induction precluded meaningful analysis of its impact on the risk of rejection (data not shown).

Limited data analyses were conducted at 20–24 months, with approximately two-thirds of patients having final assessments. These data did not differ significantly from the 12-month data in terms of eGFR, BPAR or treatment failure. At 20–24 months, treatment failure had occurred in 30.5% (74/243), 40.5% (96/237) and 35.0% (84/240) of patients in groups A, B and C, respectively (p = 0.02 for the comparison between groups A and B). The proportion of patients with BPAR was 6.6% (16/243), 11.0% (26/237) and 10.0% (24/240) in groups A, B and C, respectively, with no significant differences among groups.

Table 4: Treatment failure within 12 months posttransplant by (A) treatment group and (B) calcineurin inhibitor (CNI) type, N (%)

	MMF_{CC}/CNI_{RL} Group A (N = 243)		MMF_{CC}/CNI_{SL} Group B (N = 237)		MMF_{FD}/CNI_{SL} Group C (N = 240)	
(A) Treatment failure within 12-months posttransplant by treatment group, N (%)						
Treatment failure[1]	55 (22.6)		67 (28.3)		67 (27.9)	
90% CI for treatment failure	17.5, 28.4		22.6, 34.5		22.3, 34.1	
Reason for treatment failure						
Biopsy-proven acute rejection	15 (6.2)		23 (9.7)		23 (9.6)	
Graft loss	5 (2.1)		4 (1.7)		4 (1.7)	
Death	4 (1.6)		2 (0.8)		6 (2.5)	
Lost to follow-up or discontinued	15 (6.2)		18 (7.6)		22 (9.2)	
Withdrew consent	16 (6.6)		20 (8.4)		12 (5.0)	
	CsA (N = 41)	TAC (N = 202)	CsA (N = 47)	TAC (N = 190)	CsA (N = 42)	TAC (N = 198)
(B) Treatment failure within 12 months posttransplant by CNI type, N (%)						
Treatment failure[2]	8 (19.5)	47 (23.3)	15 (31.9)	52 (27.4)	13 (31.0)	54 (27.3)
95% CI	8.8, 34.9	17.6, 29.7	19.1, 47.1	21.2, 34.3	17.6, 47.1	21.2, 34.0

CC = concentration controlled; CI = confidence interval; CsA = cyclosporine; FD = fixed dose; MMF = mycophenolate mofetil; N = number; RL = reduced level; SL = standard level; TAC = tacrolimus.

Events are mutually exclusive because only the first event was counted for each patient.

Ninety-five percent CI calculated using the exact method.

p-values are from the Cochran–Mantel–Haenszel test comparing the treatment groups and stratified by CNI type.

[1]p = 0.1825 for group A versus group C; 0.8683 for group B versus group C; and 0.1302 for group A versus group B.

[2]For cyclosporine, p = 0.23 for group A versus group C; 0.92 for group B versus group C; and 0.19 for group A versus group B; for tacrolimus p = 0.36 for group A versus group C; 0.98 for group B versus group C; and 0.35 for group A versus group B.

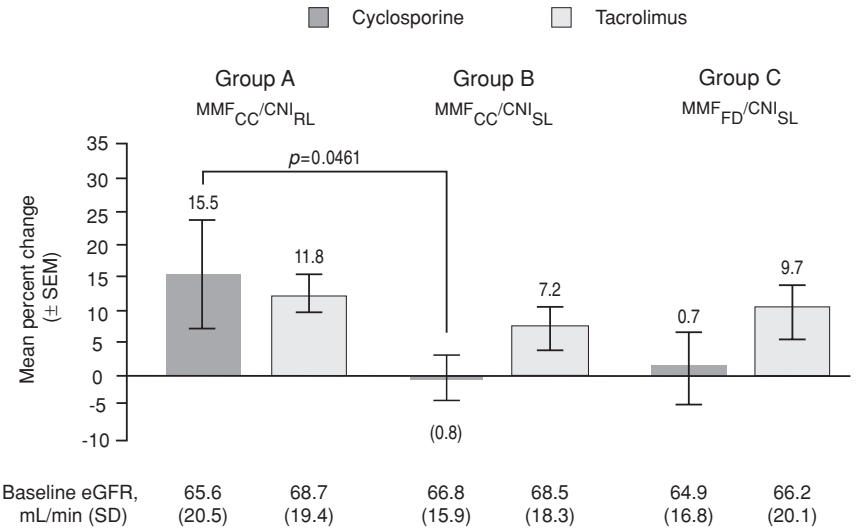


Figure 4: Mean change in estimated glomerular filtration rate (eGFR; Nankivell) stratified by calcineurin inhibitor (CNI) from baseline to 12 months. Cyclosporine: MMF$_{CC}$/CNI$_{RL}$ versus MMF$_{FD}$/CNI$_{SL}$, p = 0.11; and MMF$_{CC}$/CNI$_{RL}$ versus MMF$_{CC}$/CNI$_{SL}$, p < 0.05. Tacrolimus: MMF$_{CC}$/CNI$_{RL}$ versus MMF$_{FD}$/CNI$_{SL}$, p = 0.67; and MMF$_{CC}$/CNI$_{RL}$ versus MMF$_{CC}$/CNI$_{SL}$, p = 0.35. MMF$_{CC}$/CNI$_{RL}$ = controlled-concentration of mycophenolate mofetil (MMF) with reduced level of CNI dosing; MMF$_{CC}$/CNI$_{SL}$ = MMF$_{CC}$ with standard concentrations of CNIs; and MMF$_{FD}$/CNI$_{SL}$ = fixed dose MMF with CNI$_{SL}$; SD = standard deviation.

Safety outcomes

The occurrence of adverse events was similar across treatment groups. Common adverse events are listed by frequency in Table 6. Diarrhea was the most frequent, occurring in approximately 40% of participants in all treatment groups, but notably more common in patients receiving tacrolimus (269/582, 46%) than cyclosporine (27/127, 21%; p < 0.001). Within the first 90 days posttransplant, 243/720 (34%) of the total patients, 18/130 (14%) receiving cyclosporine and 225/590 (38%) receiving tacrolimus had diarrhea. Tacrolimus trough levels appeared to be higher in patients with diarrhea (N = 225) compared to patients without diarrhea (N = 365). A Cox proportional hazards model indicated that CNI type had a significant impact on the time to a first episode of diarrhea within 90 days posttransplant, with a risk ratio of 0.273 for cyclosporine versus tacrolimus (p < 0.0001). For patients taking tacrolimus, those with higher tacrolimus trough levels drawn prior to the occurrence of diarrhea were at a greater risk for experiencing diarrhea (risk ratio = 1.049; p = 0.004). Across all patients, MPA trough levels were not related to diarrhea (p = 0.5125). Overall, the incidence of new-onset diabetes mellitus was higher in those receiving tacrolimus compared to those receiving cyclosporine (73/582 [12.5%] vs. 5/127 [3.9%], respectively; p = 0.004).

At 12 months, 9–12% of patients in all three groups experienced one or more opportunistic infections, most commonly cytomegalovirus (CMV). Overall, 12/238 (5.0%), 14/233 (6.0%) and 18/238 (7.6%) patients had CMV infections, primarily viremia only, in groups A, B and C, respectively. BK virus infection occurred in 4/238 (1.7%), 7/233 (3.0%) and 8/238 (3.4%) and BK virus nephropathy in 0/238 (0%), 4/233 (1.7%) and 4/238 (1.7%) patients in groups A, B and C, respectively. No difference was seen between CNI types with regard to either CMV or BK virus infection,

Table 5: Secondary efficacy endpoints at 12 months

Endpoint	MMF$_{CC}$/CNI$_{RL}$ Group A (N = 243)	MMF$_{CC}$/CNI$_{SL}$ Group B (N = 237)	MMF$_{FD}$/CNI$_{SL}$ Group C (N = 240)	p-Value
Biopsy-proven acute rejection, N (%)	15 (6.2)	23 (9.7)	23 (9.6)	0.17[1]
Number of episodes of biopsy-proven acute rejection per patient				0.35[2]
0	228 (93.8)	214 (90.3)	217 (90.4)	
1	13 (5.3)	21 (8.9)	21 (8.8)	
2 or more	2 (0.8)	2 (0.8)	2 (0.8)	
Presumptive acute rejection, N (%)[3]	16 (6.6)	26 (11.0)	25 (10.4)	0.13[1]
95% CI	3.8, 10.5	7.3, 15.7	6.9, 15.0	
Unknown, N	36	42	39	
Time to treatment failure, mean days[4]	265.9	296.5	290.0	0.22[1]

CC = concentration controlled; CI = confidence interval; CNI = calcineurin inhibitor; FD = fixed dose; MMF = mycophenolate mofetil; N = number; RL = reduced level; SL = standard level.
[1]Comparison between MMF$_{CC}$/CNI$_{RL}$ and MMF$_{FD}$/CNI$_{SL}$.
[2]Overall treatment effect p-value from the Poisson regression model with treatment and CNI type as factors.
[3]Presumptive rejections include patients treated for rejections but no biopsy performed and all biopsy-proven acute rejections.
[4]Kaplan–Meier product limit estimates, mean days since first trial medication.

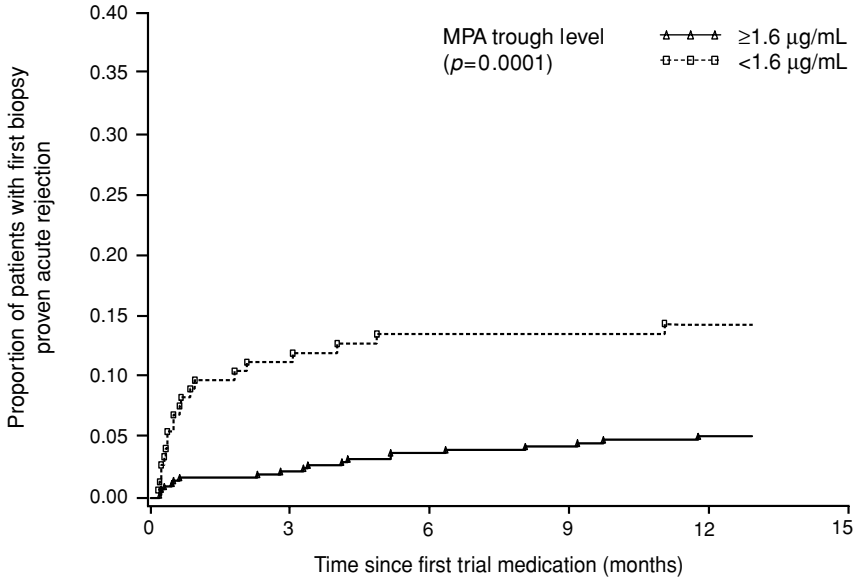


Figure 5: Mycophenolic acid (MPA) exposure and time to first biopsy-proven acute rejection (BPAR) episode. Cox proportional hazards model estimate with the abbreviated MPA area under the concentration–time curve, baseline hypertension/diabetes and treatment effect (groups A versus C, groups B versus C) as covariates. Cutoff point of ≥1.6 μg/mL was based on receiver operating characteristic analysis of the study data.

and no significant differences were observed in the risk of BK virus infection for those with MPA trough levels ≥ 1.6 μg/mL compared to those with levels < 1.6 μg/mL.

Discussion

The principal finding of this trial is that a maintenance immunosuppressive regimen employing concentration-controlled dosing of MMF in combination with a low-dose CNI was not inferior to a fixed-dose regimen of MMF with respect to treatment failure in renal transplant patients. In addition, these data confirm previously described differences in MPA exposure for patients receiving tacrolimus versus cyclosporine, with the former achieving target levels substantially earlier and more consistently after transplantation. Finally, as in previous trials, despite the absence of overall statistical differences among treatment groups, there was a strong statistical relationship between MPA exposure and the lower risk of rejection in tacrolimus-treated patients, as well as trends suggesting less rejection, better renal function and fewer adverse events in the low-dose CNI group with concentration-controlled MMF dosing.

The overall rates of BPAR were notably low across groups, especially when compared with other studies employing targeted dosing of MMF in combination with cyclosporine (the APOMYGRE study) (24) or standard-dose MMF in combination with low-dose tacrolimus (the ELITE-Symphony study) (14). The rate of BPAR in patients

Table 6: Selected adverse events reported postrandomization, N (%)[1]

	MMF_{CC}/CNI_{RL} Group A (N = 238)		MMF_{CC}/CNI_{SL} Group B (N = 233)		MMF_{FD}/CNI_{SL} Group C (N = 238)	
	CsA (N = 40)	TAC (N = 198)	CsA (N = 45)	TAC (N = 188)	CsA (N = 42)	TAC (N = 196)
Diarrhea[2]	5 (13)	93 (47)	16 (36)	86 (46)	6 (14)	90 (46)
Leukopenia	7 (18)	50 (25)	12 (27)	48 (26)	11 (26)	58 (30)
Hypertension	7 (18)	47 (24)	8 (18)	44 (23)	11 (26)	39 (20)
Hyperlipidemia	35 (85)	158 (78)	38 (81)	139 (73)	32 (76)	148 (75)
Opportunistic infections[3]	5 (13)	17 (9)	7 (16)	23 (12)	3 (7)	22 (11)
Diabetes mellitus[4]	2 (5)	32 (16)	2 (4)	23 (12)	1 (2)	18 (9)
Malignancies[5]	2 (5)	3 (2)	0 (0)	6 (3)	1 (2)	6 (3)

CC = concentration controlled; CNI = calcineurin inhibitor; CsA = cyclosporine; FD = fixed dose; MMF = mycophenolate mofetil; N = number; RL = reduced level; SL = standard level; TAC = tacrolimus.

[1]Safety population included patients who received ≥1 dose of the study medication.

[2]$p < 0.0001$ for TAC versus CsA stratified by treatment groups and the impact of TAC versus CsA on time to first episode within 90 days posttransplant.

[3]Patients with at least one opportunistic infection.

[4]$p < 0.05$ for TAC versus CsA stratified by treatment groups.

[5]Malignancies counting patients only.

receiving concentration-controlled MMF in this trial was approximately half that of subjects similarly treated in the ELITE-Symphony study (daclizumab induction, fixed-dose MMF and corticosteroids) (14) despite comparably low exposure to tacrolimus. The fact that antithymocyte globulin was used in >40% of patients in the present study could have contributed to the more positive outcomes. Still, in the present trial, the impact of induction therapy on BPAR appeared minimal in the patients receiving tacrolimus, particularly in the MMF concentration-controlled groups. Although BPAR rates tended to be higher in patients receiving cyclosporine, the number of patients receiving this CNI was too small for a meaningful comparison.

With a starting MMF dose of 2 g/day, MPA exposure was significantly (25–35%) greater in tacrolimus-treated than in cyclosporine-treated patients by day 10, and in the fixed-dose cohort this difference persisted throughout. This is thought to be due to the inhibition of the enterohepatic circulation of MPA by cyclosporine (32). Certainly, the increased early exposure to MPA that accompanies tacrolimus use may contribute to a lesser risk of rejection in patients so treated. In the concentration-controlled groups, MPA exposure did not vary by CNI after the third month posttransplant. The concentration-controlled groups received significantly higher doses of MMF regardless of CNI type; these differences in dose resulted in higher MPA AUC than in the fixed-dose MMF group receiving standard levels of cyclosporine, but comparable differences were not seen in those receiving tacrolimus.

The change from baseline in eGFR between the groups was numerically superior in the MMF_{CC}/CNI_{RL} group but was not statistically significant; however, the difference in eGFR from baseline for cyclosporine-treated patients in the reduced CNI level group was significant. Since most of the patients in the trial received tacrolimus, the presumed superiority of tacrolimus to cyclosporine in terms of renal function and immunosuppressive efficacy may have masked any additional benefits of tailoring MMF dosing in the group as a whole. Additionally, the failure to achieve CNI levels that differentiated treatment groups as distinctly as originally targeted may have contributed to the similarity in eGFR over time. It is also notable that MPA exposure in tacrolimus-treated patients was identical at all time points with or without monitored dosing. These findings, along with those of the APOMYGRE study (24), indicate that MPA monitoring and a CNI-reduction strategy may be particularly useful in cyclosporine-treated patients. However, as demonstrated by the relatively poor correlation of trough level with MPA AUC in the cyclosporine-treated patients, such an approach may require AUC rather than predose monitoring.

Mean CNI trough levels in group A were not as low as originally targeted but were still statistically significantly lower than levels in the other two treatment groups. However, these between-group differences did not appear to be clinically significant. Tacrolimus levels in group A were not low enough to result in a clinical difference between groups in eGFR. Similarly, reports of adverse events such as diarrhea, diabetes mellitus and opportunistic infections were comparable among groups A, B and C.

There are obvious limitations to this trial. First, as in the Fixed-Dose Concentration-Controlled Trial (25), what appeared to be a reluctance to adhere to target MPA trough levels resulted in a wide variability among doses, dose changes and exposure among subjects, with little differentiation among treatment groups in MPA exposure. Second, the attempt to facilitate broad enrollment by allowing investigators the choice of induction and CNI agents resulted in a great deal of heterogeneity among the three treatment groups, making interpretation difficult. This study emphasizes the ongoing challenge in designing clinical trials flexible enough to encourage enrollment yet rigorous enough to result in robust conclusions. Third, the failure to achieve and maintain target immunosuppressant levels, particularly in the reduced CNI group, may have contributed to the inability to detect significant differences among groups in several outcomes, illustrating the complexities of adherence to a study design in which blood-level targets are predetermined. Indeed, the benefits of MPA monitoring in the APOMYGRE study (24) emerged from a study with relatively homogenous CNI and induction therapies and specific MMF dose changes determined by an algorithm rather than by an investigator choice. Finally, it is possible that any advantage associated with concentration-controlled dosing of MMF is small enough that all of these factors make it easy to mask.

So, how is one to interpret Opticept? It is tempting to focus on data supporting the benefit of concentration-controlled MMF dosing: a strong correlation between MPA exposure and the risk of rejection, with trends to better renal function, fewer rejection episodes and fewer severe adverse effects. Indeed, if one presumes that lower CNI levels should result in more adverse immunological events, a finding of noninferiority in this study might be attributable to the strategy of concentration-controlled dosing. The truth is that most clinicians now use tacrolimus at doses and levels comparable to those used in group A, and the majority of tacrolimus-treated patients achieve therapeutic MPA exposure with empiric dosing (albeit perhaps not as quickly). In terms of safety, the ability to administer more MMF with fewer discontinuations for adverse events and the relative absence of serious BK disease in the MMF_{CC}/CNI_{RL} group is intriguing. Perhaps the benefit of tailoring MMF dosing to exposure, particularly in tacrolimus-treated patients, manifests in a relatively small number of recipients for whom maintaining appropriate exposure without overimmunosuppression is critical. Such an interpretation is consistent with the trends suggestive of a benefit but not discernable by analysis of broad group statistics.

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Appendix: The Opticept Study Group

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Appendix S1.

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