The CLEAR Study: A 5-day, 3-g Loading Dose of Mycophenolate Mofetil *versus* Standard 2-g Dosing in Renal Transplantation

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Background and objectives: Adequate early mycophenolic acid (MPA) exposure is associated with lower rates of acute rejection in renal transplantation. The aim of this randomized controlled trial was to determine if higher initial mycophenolate mofetil (MMF) doses increased the proportion of patients reaching therapeutic MPA levels (30 to 60 mg·h/L) by day 5.

Design, setting, participants, & measurements: *De novo* renal transplant patients were randomized to receive intensified dosing of MMF (1.5 g twice daily on days 1 to 5, then 1.0 g twice daily) or standard dosing (1.0 g twice daily). All recipients received tacrolimus and prednisone. Full MPA areas under the curve (AUCs) were completed on days 3 and 5, whereas a limited sampling strategy was utilized at four subsequent time points.

Results: At day 5, 47.5% of the MMF 3-g arm achieved the MPA therapeutic window *versus* 54.4% of the MMF 2-g arm. However, MPA AUC levels were significantly higher in the 3-g arm at day 3 and 5. This resulted in a trend for fewer treated acute rejections at 6 months. Significantly more acute rejections (treated, biopsy-proven including and excluding borderline) occurred in patients with MPA AUC levels <30 mg·h/L compared with those ≥30 mg·h/L at day 5. No significant differences were seen in common adverse events.

Conclusions: A limited intensified dose of MMF increased early MPA exposure and was well tolerated. Further studies are required to determine whether limited intensified MMF dosing can reduce acute rejection.

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Mycophenolate mofetil (MMF, CellCept®) is an effective immunosuppressant and a key component of the immunosuppression regimen in most renal allograft recipients (1,2). A recent review and preliminary meta-analysis showed that overall graft survival is better with MMF compared with azathioprine when administered with calcineurin inhibitors (3,4). Traditionally, MMF is administered as a fixed dose without therapeutic drug monitoring (TDM). It remains unclear what role TDM of MMF has in improving graft and patient outcomes.

There is a growing body of evidence supporting the utility of TDM. The drug has a large interpatient variability, with a 6-fold variation for a fixed daily dose (5). Van Gelder and his colleagues demonstrated a clear dose-effect relationship between acute rejection and 12-hour mycophenolic acid (MPA) area under the curve (AUC) exposures (6). MPA AUC values between 30 and 60 mg·h/L are proposed to be the target therapeutic window for patients treated with cyclosporine and prednisone (5). However, nearly 50% of cyclosporine-treated subjects are below the therapeutic target within the first week when administered the standard MMF dose of 2 g daily post-transplantation (7). More recently, a randomized controlled trial demonstrated that a concentration-controlled arm (dosed to achieve a mean exposure of 45 mg·h/L) resulted in significantly less rejection as compared with a standard-dosed arm (8).

However, TDM is problematic given the poor correlation with any convenient single point concentration and AUC (5). Furthermore, there is some evidence that early exposure is important, with day-3 values being better predictors of acute rejection as compared with later values (7,9). Accordingly, clinicians would need to monitor exposure early and aim to intensify treatment within the first 3 days. Nonsteady-state conditions and the requirement for rapid turnaround times

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make TDM problematic in the early posttransplantation period. Alternatively, higher initial doses could either be given during the early critical period or until TDM can be performed. However, the safety profile of this approach is unknown. In addition, tacrolimus is now the most commonly used calcineurin inhibitor in the United States and there is limited information on MMF exposure when used in combination with tacrolimus (2,10).

This study compared the ability of early, intensified, but limited-duration MMF dosing to increase the number of patients adequately exposed to MPA within the first week posttransplantation as compared with standard dosing in renal transplant recipients treated with tacrolimus.

Materials and Methods

Study Population

Adult renal transplant recipients, (age >18 years) who received a solitary renal transplant from a deceased or non-HLA identical living donor were eligible for the study. Patients were excluded for a cold ischemia time >30 hours, PRA evaluation >25% within 6 months, incompatible ABO type or positive donor cross-match, need for polyclonal anti-lymphocyte therapy, serum albumin <31 g/L, history of malignancy, and women who did not agree to use adequate contraception.

This trial was conducted in accordance with the current International Conference on Harmonization Tripartite Guideline on Good Clinical Practice and applicable Health Canada regulations. The research ethics boards at each center approved the study protocol and each patient provided written informed consent. The study is registered in ClinicalTrials.gov (NCT00788567). CLEAR is an acronym for "CellCept Loading Dose in Early Posttransplant Period in Renal Allograft Recipients."

Study Design and Procedures

This 6-month, open-label, prospective, randomized, controlled, multicenter study was conducted in nine centers across Canada. Randomization was performed centrally in a 1-to-1 ratio and in random permuted blocks of four patients.

The intervention arm received a loading dose of MMF (CellCept®) at 1.5 g twice daily until day 5, followed by 1.0 g twice daily thereafter. The control arm received a fixed dose of MMF 1 g twice daily. Both groups received 1 g MMF up to 6 hours before transplantation. The use of intravenous MMF was not permitted. Dose modifications of MMF on or between days 1 and 5 were not permitted unless there was MMF-related toxicity. Use of IL-2 receptor antibody was at the discretion of the individual center. All patients received tacrolimus with targeted dosing to achieve trough levels between 8 and 15 ng/ml. All patients received prednisone, according to center practice. Prophylaxis for cytomegalovirus and *Pneumocystis jirovicii* were administered according to center practice. Delayed graft function was defined as the need for dialysis in the first week posttransplantation.

In both arms, full 12-hour trapezoidal rule MPA AUC profiles were collected and analyzed on days 3 and 5 (time 0, 0.5, 1, 2, 3, 4, 6, 8, and 12 hours). A 3-point limited sampling strategy was utilized for MPA AUC assessments at the day of discharge and month 1, 3, and 6 (time 0, 0.5, and 2 hours) (11). Sampling was carried out in fasted patients (8 hours before and 1 hour after time 0). For diabetic patients, the fasting period was 2 hours before and 1 hour after time 0. MPA concentrations were measured using HPLC at a central laboratory that is registered with an international proficiency-testing scheme (Analytic Unit at St George's, University of London, United Kingdom).

The primary efficacy end point was the proportion of patients achieving the therapeutic window (30 to 60 mg·h/L) by day 5. Secondary efficacy end points included the proportion of patients achieving the therapeutic window at day 3, day of discharge, and months 1 and 3 and the proportion of patients experiencing acute rejection throughout the study. A core biopsy was performed for suspicion of acute rejection. Protocol biopsies were not performed. All biopsies were read by local pathologists and graded according to the Banff classification (12). Acute rejection episodes were analyzed in three ways: (*1*) biopsy-proven with Banff ≥grade 1, (*2*) biopsy-proven including borderline, and (*3*) all suspected and treated acute rejection episodes. Secondary safety end points included renal function (Cockcroft–Gault formula) (13), incidence of opportunistic infections, malignancies, and the occurrence of adverse events.

Statistical Analyses

Sample size was based on the expected proportion of patients achieving the primary end point, which was 80% in the 3-g loading dose arm and 60% in the 2-g standard-dose arm. Assuming a significance level of 5% and power of 80%, 164 patients had to be enrolled in the study. To account for a predicted 20% dropout rate, a total of 200 patients were required.

For the primary efficacy analysis, the modified intention-to-treat population was used, which included all randomized patients who received at least one dose of study medication and provided follow-up MPA AUC data at any time point on day 3. The safety analysis was based on all randomized patients who received at least one dose of MMF. Numerical data are presented as mean ± SD. The Cochran-Mantel-Haenszel test stratified by center was used to compare the proportion of patients between treatment groups who achieved the primary end point. Kaplan–Meier event-free curves were used to compare the time to first acute rejection between treatment groups. Significance was tested using the log-rank test. Differences in safety end points were evaluated by the χ^2 or Fisher's exact test.

Exploratory analyses were undertaken to further analyze acute rejection episodes stratified by MPA AUC levels. Kaplan–Meier curves were produced to compare the time to acute rejection for patients with MPA AUC levels <30 *versus* ≥30 mg·h/L at day 5. Univariate and multivariate logistic regression analyses was performed to determine risk factors for suspected and treated acute rejection and the factors associated with inadequate exposure (MPA AUC <30 mg·h/L) on day 5. A receiver-operator characteristic analysis was completed to determine the trough level threshold for predicting MPA AUC <30 mg·h/L. Lastly, adverse events were compared for patients with MPA AUC levels ≤60 as compared with >60 mg·h/L.

Statistical significance was tested at the 5% level. All statistical analyses were performed with SAS version 8.2.

Results

Study Population

One-hundred thirty-five renal transplant patients underwent randomization from nine centers across Canada ($n = 68$ in the 3-g arm; $n = 67$ in the 2-g arm). The two study groups were balanced with respect to baseline demographics (Table 1). A flowchart showing patient disposition is presented in Figure 1. For the purpose of the primary efficacy analysis (modified intention-to-treat population), 126 patients ($n = 65$ in the 3-g arm and $n = 61$ in the 2-g arm) had at least one dose of study medication and provided MPA AUC data on day 3. At days 3 and 5, 98.4% and 93.7% of patients, respectively, had complete

Table 1. Baseline characteristics for intensified (3-g) *versus* standard (2-g) arms

Characteristics	3-g MMF (n = 68)	2-g MMF (n = 67)
Age (years)	44.4 ± 12.4	47.5 ± 13.2
Race or ethnic group, *n* (%)		
Caucasian	56 (82.4)	53 (79.1)
black	0 (0.0)	0 (0.0)
Asian	5 (7.4)	4 (6.0)
native Canadian	3 (4.4)	4 (6.0)
other	4 (5.9)	6 (9.0)
Gender, *n* (%)		
male	47 (69.1)	45 (67.2)
Weight (kg)	77.2 ± 20.5	77.7 ± 19.4
Historical peak PRA (%)	1.9 ± 3.9	2.2 ± 4.6
Primary renal disease, *n* (%)		
GN	16 (23.5)	15 (22.4)
Diabetes mellitus	9 (13.2)	8 (11.9)
Polycystic kidney disease	9 (13.2)	8 (11.9)
Obstructive and/or reflux nephropathy	3 (4.4)	3 (4.5)
Unknown	1 (1.5)	3 (4.5)
Other	30 (44.1)	30 (44.8)
Donor type, *n* (%)		
deceased	38 (55.9)	42 (62.7)
living related	21 (30.9)	16 (23.9)
living unrelated	9 (13.2)	9 (13.4)
Delayed graft function, *n* (%)	16 (23.5)	13 (19.4)
Cold ischemia time (hours)		
deceased donors	15.9 ± 5.9	15.6 ± 6.2
living donors	4.2 ± 1.7	3.3 ± 1.0
Donor age (years)	45.3 ± 13.3	47.4 ± 15.4

All enrolled patients, intention-to-treat (ITT); P = NS for all; Mean ± SD. Percentages are based on the number of patients in each group.

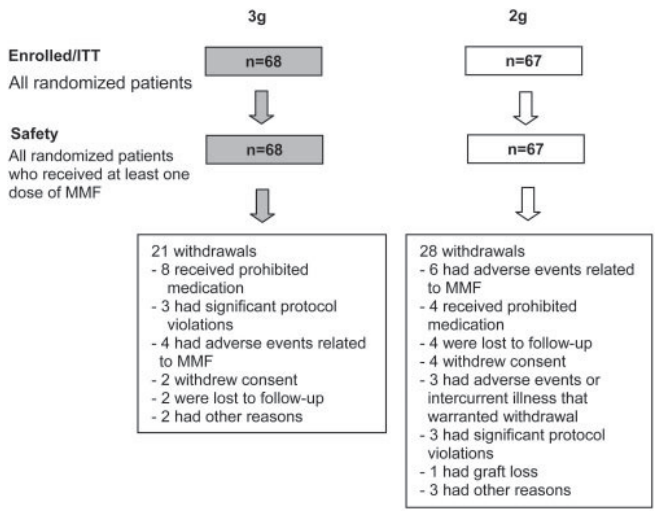

Figure 1. Flowchart of patient disposition. The modified ITT group included 65 and 61 patients in the 3- and 2-g arms, respectively. All randomized patients were included if they had received at least one dose of MMF and had MPA AUC data at any time point on day 3.

MPA data. All patients received steroids during the course of the study and a similar proportion of patients in both arms received IL-2 receptor antibody induction therapy (81.5% *versus* 88.5% in the 3-g *versus* 2-g arm, respectively, P = NS). Tacrolimus levels were not different between the groups over the study period. Mean tacrolimus levels in the 3- and 2-g groups were 11.6 ± 5.9 *versus* 12.0 ± 5.9 ng/ml and 10.3 ± 4.6 *versus* 9.8 ± 5.3 ng/ml at days 3 and 5, respectively (P = NS).

Sample Size Limitations

The recruitment target of 200 patients was not met despite an extension of the enrollment period and this was not due to any safety concerns. On the basis of the actual number of enrolled patients and the assumed proportion of patients achieving the therapeutic window, the study achieved a power of 72% to detect statistical significance in the primary end point.

AUC Levels

There was no significant difference between the study arms regarding the proportion of patients achieving the therapeutic window of 30 to 60 mg·h/L at day 5 (47.5% *versus* 54.4%, 3 g *versus* 2 g, respectively, P = NS). Although the target sample

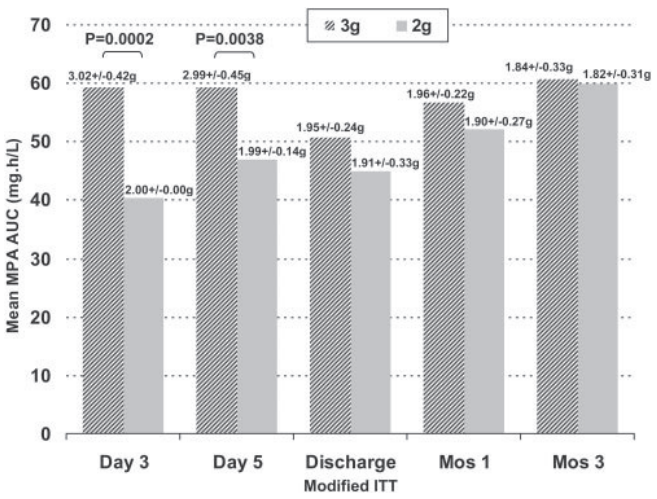

Figure 2. Mean MPA AUC levels for intensified (3-g) *versus* standard (2-g) arms. Complete MPA AUC levels were calculated using the trapezoidal rule for days 3 and 5. The limited sample formula was used to calculate abbreviated MPA AUC levels at day of discharge and months 1 and 3 (11). The day of discharge was on average 10.4 ± 5.8 days posttransplant.

size was not met for the primary end point, the mean AUC levels at day 3 (59.3 *versus* 40.3 mg·h/L, $P = 0.0002$) and day 5 (59.3 *versus* 46.8 mg·h/L, $P = 0.0038$) were significantly higher in the 3-g *versus* the 2-g group. After day 5, the MMF doses between the arms were similar as were their exposures at the day of discharge and months 1 and 3 (Figure 2).

At day 3, significantly fewer patients in the 3-g arm had AUC levels <30 mg·h/L (14.1% *versus* 33.3%, $P = 0.0113$), whereas more patients in the 3-g arm had AUC levels >60 mg·h/L (45.3% *versus* 16.7%, $P = 0.0006$). This resulted in a similar proportion of patients in both arms achieving MPA AUC levels within the therapeutic window of 30 to 60 mg·h/L (40.6% *versus* 50.0%, 3 g *versus* 2 g, respectively, P = NS).

At day 3, MPA AUC levels were in the range of 30 to 60 mg·h/L for 56 patients (both study arms combined). Out of the 54 patients who also had MPA levels available at day 5, 64.8% of patients remained in this therapeutic range and an additional 18.5% of patients had levels >60 mg·h/L. Similarly, of the 25 patients who had AUC levels <30 mg·h/L at day 3 (and had levels available at day 5), 44% of patients continued to have subtherapeutic MPA levels at day 5.

Acute Rejection

There was a trend for fewer suspected and treated acute rejections in the 3-g arm *versus* the 2-g arm at 6 months (11.8% *versus* 28.4%, $P = 0.0546$) (Table 2). This trend was also present when acute rejection was analyzed as biopsy-proven with and without the inclusion of borderline cases (Table 2). Biopsies indicated that most of the excess acute rejections in the 2-g arm were classified as borderline.

Figures 3A through 3C show that there were significantly more acute rejections (all definitions) in patients with MPA AUC levels <30 mg·h/L ($n = 16$) compared with those with levels ≥30 mg·h/L ($n = 84$) at day 5 (P values ranging from 0.0008 to <0.0001). In the group of patients with MPA AUC levels <30 mg·h/L at day 5, 50.0% (8 of 16) had a suspected and treated acute rejection episode. This compares to 15.5% (13 of 84) in those patients with MPA AUC ≥30 mg·h/L at day 5, $P = 0.0047$. Factors that significantly decreased the risk of acute rejection in the logistic regression analysis were treatment (3 g *versus* 2 g; $P = 0.0414$) and MPA AUC at day 5 ($P = 0.0138$) (Table 3). No other variables were associated with acute rejection.

Renal Function and Graft Survival

Overall renal function did not differ between groups at 6 months (53.9 ± 19.5 ml/min *versus* 55.2 ± 25.1 ml/min in the 3-g *versus* 2-g arms, $P = 0.7894$). There were no patient deaths in the study. There was a trend toward a higher rate of graft survival in the 3-g arm as compared with the 2-g arm (100% *versus* 94.0%, $P = 0.0579$). Four patients lost their graft in the 2-g treatment arm because of acute rejection (two patients), poor graft function, and technical complications.

Inadequate Exposure

Risk factors for inadequate exposure (MPA AUC <30 mg·h/L) were examined separately in the two arms given the

Table 2. Kaplan–Meier estimates of acute rejection at 6 months

	3-g MMF	2-g MMF	*P*
Suspected and treated	11.8%	28.4%	0.0546
Biopsy-proven (including borderline)[a]	10.2%	25.0%	0.0689
borderline changes	1	5	
mild acute rejection (grade 1)	1	4[b]	
moderate acute rejection (grade II)	4	3	
severe acute rejection (grade III)	–	1	
Biopsy-proven (excluding borderline)	8.7%	16.7%	0.3197

Modified ITT.

[a]Biopsy results were obtained from the initial report of the acute rejection episode. One patient in the 2-g MMF group had missing biopsy data.

[b]One patient did not have biopsy results reported in their initial report of the acute rejection episode. Therefore, biopsy results were obtained from a report at a later time point.

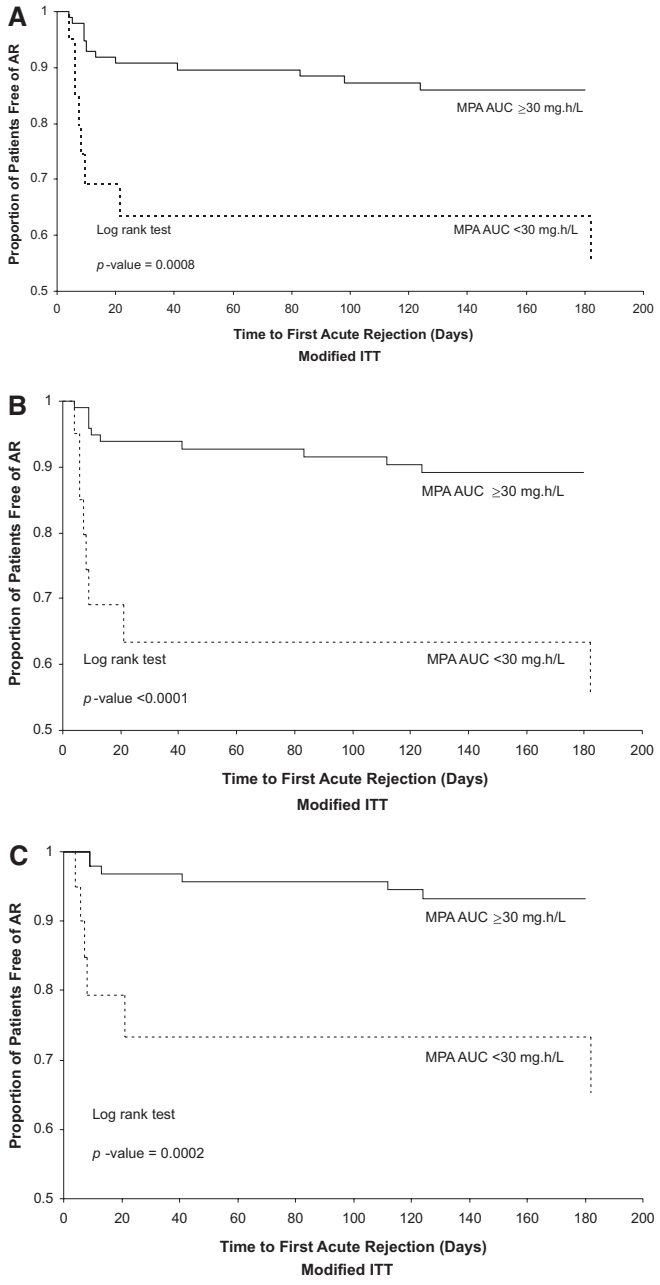

Figure 3. Time to (A) first suspected and treated acute rejection (B) first biopsy-proven acute rejection (including borderline patients), and (C) first biopsy-proven acute rejection (excluding borderline patients) by day 5 MPA AUC levels. (B and C) Biopsy results were obtained from the initial report of the acute rejection episode. One patient in the 2-g group had missing biopsy data. One patient did not have biopsy results reported in their initial report of the acute rejection episode. Therefore, biopsy results were obtained from a later time period.

differences in MMF dose. In the 2-g cohort, serum creatinine (sCr) (odds ratio [OR] 1.05 per 10 μmol/L, 95% confidence interval [CI] 1.01, 1.09; $P = 0.0121$) and albumin level (OR 0.76, 95% CI 0.61, 0.93; $P = 0.0009$) on day 5 were significant in a logistic regression analysis. In the 3-g cohort, only serum albumin (OR 0.76, 95% CI 0.62, 0.94; $P = 0.0124$) on day 5 was significantly associated with inadequate exposure; sCr was no longer associated (OR 1.01 per 10 μmol/L, 95% CI 0.99, 1.04; $P = 0.273$). The mean sCr on day 5 was similar in both cohorts (252 and 261 μmol/L for the 2- and 3-g arms, respectively). All other variables were NS. At days 3 and 5, an MPA trough level of ≤1.5 ng/ml predicted an MPA AUC <30 mg·h/L (day 3: $c = 0.772$, sensitivity = 0.72, specificity = 0.85, $P < 0.0001$; day 5: $c = 0.680$, sensitivity = 0.70, specificity = 0.81, $P = 0.0025$).

Safety

The safety evaluation showed no significant differences in the incidence of adverse events between the two treatment arms (Table 4). In a comparison of adverse events in patients with MPA AUC levels ≤60 mg·h/L *versus* >60 mg·h/L at day 5, only reported anemia was found to be significantly higher in patients with MPA AUC levels >60 mg·h/L (55.3% *versus* 35.0%, $P = 0.0369$) (Table 4). However, there were no significant differences in mean hemoglobin levels at any study time point and no differences in erythropoiesis-stimulating agent use after day 5 (31.3% *versus* 39.5%, $P = 0.3779$).

Discussion

The study shows that there was no increase in the proportion of renal transplant recipients within the MPA AUC therapeutic window on day 5 with the intensified MMF dose, because many were above the upper level (>60 mg·h/L) of this range. Although the *a priori* recruitment sample size was not met to detect a difference in the proportion within the window, recruiting more patients is not likely to change this observation. However, this study demonstrates that intensified MMF dosing will increase overall MPA exposure and reduce the proportion of patients that are underexposed to MPA within the first 5 days. Higher doses of MMF were well tolerated and MPA AUC exposures >30 mg·h/L on day 5 were associated with less acute rejection.

In the standard-dose arm, 33% of patients were below the AUC 30-mg·h/L threshold on day 3. This is numerically similar to the 24% reported in the Fixed-Dose Concentration Controlled (FDCC) trial (7). Any small differences might be explained by the analytical assay used and the limited sample formula utilized for the estimation of MPA AUC levels (7). Some of the samples in the FDCC trial were analyzed by the enzyme-multiplied immunoassay technique (EMIT), which also measures a metabolite and in general reads approximately 10% to 25% higher than the HPLC method (14). A limited sample strategy was also used, whereas our study performed full AUCs on days 3 and 5. Surprisingly, 14% of patients in the 3-g arm had an AUC <30 mg·h/L on day 3. Our preliminary data from a pilot trial suggested that this percentage should have been approximately 5% for the 3-g group and approximately 25% for the 2-g group (10). However, MPA AUC values in the pilot trial were determined using a limited sampling strategy and may not truly reflect a full 12-hour AUC. MPA exposure has been associated with kidney function, albumin levels, cyclosporine levels, and hemoglobin (15). Similarly, our analysis showed that inadequate exposure was associated with lower albumin levels and higher sCr. There is evidence from

Table 3. Risk factors for suspected and treated acute rejection

Factor	Univariate Analysis		
	OR	95% CI	*P*
Recipient age	0.98	(0.95, 1.02)	0.3373
Recipient gender (female *versus* male)	0.41	(0.13, 1.31)	0.1322
Recipient race (Caucasian *versus* all others)	0.86	(0.28, 2.70)	0.8005
Delayed graft function	0.61	(0.19, 1.96)	0.4065
Donor source (deceased *versus* living)	0.91	(0.35, 2.35)	0.8398
Historical peak panel reactive antibodies	0.96	(0.85, 1.09)	0.5222
HLA antigen mismatch	0.96	(0.69, 1.33)	0.7970
Cold ischemia time	0.95	(0.89, 1.03)	0.2036
Previous diabetes	1.22	(0.23, 6.50)	0.8185
Use of IL-2 receptor antibody as induction therapy	0.61	(0.19, 1.96)	0.4065
Treatment (3 g *versus* 2 g)	0.35	(0.13, 0.96)	0.0414
MPA AUC at day 3 (increments of 10 units)	0.87	(0.70, 1.08)	0.2047
MPA AUC at day 5 (increments of 10 units)	0.71	(0.54, 0.93)	0.0138
Tacrolimus trough level at day 3	1.03	(0.96, 1.11)	0.3587
Tacrolimus trough level at day 5	0.98	(0.88, 1.09)	0.7480

Modified ITT.

Table 4. Safety evaluation in the 3-g *versus* 2-g treatment arms

	3 g MMF (n = 68)	2 g MMF (n = 67)	*P*	MPA AUC ≤60 mg·h/L at Day 5 (n = 80)	MPA AUC >60 mg·h/L at Day 5 (n = 38)	*P*
Anemia	29 (42.6)	26 (38.8)	0.6497	28 (35.0)	21 (55.3)	0.0369
Leukopenia	10 (14.7)	15 (22.4)	0.2506	16 (20.0)	7 (18.4)	0.8397
Neutropenia	4 (5.9)	2 (3.0)	0.6804	4 (5.0)	2 (5.3)	1.0000
Thrombocytopenia	2 (2.9)	2 (3.0)	1.0000	3 (3.8)	1 (2.6)	1.0000
Constipation	24 (35.3)	20 (29.9)	0.5827	26 (32.5)	9 (23.7)	0.3273
Diarrhea	35 (51.5)	28 (41.8)	0.2597	41 (51.3)	17 (44.7)	0.5084
Dyspepsia	9 (13.2)	13 (19.4)	0.3320	16 (20.0)	5 (13.2)	0.3639
Nausea	34 (50.0)	33 (49.3)	0.9309	39 (48.8)	19 (50.0)	0.8990
Vomiting	15 (22.1)	19 (28.4)	0.3992	17 (21.3)	13 (34.2)	0.1308
Weight loss	1 (1.5)	1 (1.5)	1.0000	0 (0.0)	2 (5.3)	0.1018
Posttransplant *de novo* diabetes mellitus[a] and IGT	9 (13.2)	11 (16.4)	0.6027	16 (20.0)	2 (5.3)	0.0531
Tremor	21 (30.9)	25 (37.3)	0.4710	31 (38.8)	11 (29.0)	0.2987
CMV infection[b]	1 (1.5)	6 (9.0)	0.0623	6 (7.5)	0 (0.0)	0.1750
Herpes simplex[c]	7 (10.3)	6 (9.0)	0.7920	7 (8.8)	4 (10.5)	0.7444
Urinary tract infection	11 (16.2)	17 (25.4)	0.1876	17 (21.3)	7 (18.4)	0.7213

Safety population. The values are given as n (%). IGT, impaired glucose tolerance; CMV, cytomegalovirus.
[a]Includes patients that did not require insulin.
[b]Also includes CMV enteritis.
[c]Also includes herpes esophagitis.

the study presented here that 3-g MMF might overcome the low exposures seen with higher sCr levels, but a larger sample size is required to confirm this observation. The use of proton pump inhibitors (PPIs) has recently been associated with lower MPA exposures in heart transplant patients receiving pantoprazole (16). However, we did not observe this effect in the entire cohort (day 5 MPA AUC 51.3 ± 24.8 mg·h/L PPI (n = 67) *versus* 55.8 ± 24.9 mg·h/L no PPI (n = 51, P = 0.265) or in each of the individual arms (data not shown).

There was a strong trend toward a lower rate of acute rejection and graft loss in the 3-g group as compared with the 2-g arm. This is likely due to significantly higher mean MPA levels in the first 5 days after transplantation with the 3-g dose. Supportive of this construct is that acute rejection rates were

considerably more frequent in those with an AUC <30 mg·h/L at day 5 compared with those above this exposure level. Previous investigations have demonstrated that higher MPA exposures in recipients treated with tacrolimus and prednisone are associated with less rejection. In the study by Kuypers (17), there was a trend (NS) for less rejection with MPA AUC levels >45 mg·h/L. However, this was an analysis at day 7, which might be too late to discriminate between rejecters and nonrejecters. In a subanalysis of the recently published FDCC trial, there was less rejection in tacrolimus-treated patients with greater MPA exposure (7,18). However, the benefit of adequate exposure was experienced only by high-risk patients (those with delayed graft function, retransplant, panel reactive antibodies >15%, ≥4 HLA mismatches, or of African descent). Acute rejection (biopsy-proven excluding borderline) within the first month was significantly greater if the day-3 MPA AUC was <30 mg·h/L compared with ≥30 mg·h/L (23.9%, 16 of 67 *versus* 10.4%, 18 of 173; $P = 0.012$, respectively). In the FDCC trial, 265 of the 413 (64.2%) tacrolimus-treated patients were considered high risk (7,18). It was also concluded that because approximately 75% of patients administered MMF with tacrolimus were above the lower therapeutic threshold, higher initial doses of MMF were not required (7). However, the study presented here demonstrates that higher initial doses of MMF in combination with tacrolimus results in fewer patients being underexposed, eliminates the need for TDM in the immediate posttransplant time period, and is relatively inexpensive (<$50 per patient).

It is not known if efficacy outcomes could be further improved with (*1*) higher doses of MMF (>3 g) or (2) a longer duration of 3-g dosing (>5 days). As seen in Figure 2, average MPA exposures in both groups had a tendency to decrease by the day of discharge. These more intensified strategies would likely result in patients sustaining higher MPA levels for a longer period of time. TDM might be a useful approach at day 5 to identify those with excess exposure who might benefit from dose reductions. However, overall this study shows that short-term higher dosing does not cause any increase in adverse events compared with patients receiving a standard dose of MMF.

One criticism of this study was the seemingly high rate of acute rejection compared with more recent reports with an overall cohort Kaplan–Meier rate of 19.9% at 6 months. However, not all subjects received an IL-2 receptor blocker and acute rejection was analyzed to include suspected and treated episodes. Furthermore, local pathologists read all biopsies. This rate is numerically similar to the 17.2% rate of suspected and treated acute rejection reported at 12 months in the MMF+ low-dose tacrolimus arm of the Efficacy Limiting Toxicity Elimination (ELITE) Symphony trial (19). It is important to note that all patients in the ELITE-Symphony study received an IL-2 receptor blocker, which in a recent meta-analysis was shown to reduce acute rejection by 34% (95% CI 26%, 41%) (20).

In summary, a limited course of intensified dosing with 3 g MMF is an inexpensive, well tolerated strategy that resulted in increased early MPA exposure. Further studies are required to determine whether this strategy can reduce acute rejection in tacrolimus-treated renal transplant recipients.

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Disclosures

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