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Impact of Changing From Cyclosporine to Tacrolimus on Pharmacokinetics of Mycophenolic acid in Renal Transplant Recipients With Diabetes

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Abstract

The rate of mycophenolic acid (MPA) absorption after oral administration of mycophenolate mofetil (MMF) is delayed in patients with diabetes. Cyclosporine (CsA) decreases MPA exposure by inhibiting enterohepatic recirculation of MPA/MPA glucuronide, and tacrolimus (TRL) may alter the rate and extent of MPA absorption due to its prokinetic properties especially in patients with diabetic gastroparesis. This study evaluated the effect of changing from CsA to TRL on pharmacokinetics of MPA in stable renal transplant recipients with long-standing diabetes. Eight patients were switched from a stable dose of CsA to TRL while taking MMF 1 g twice daily. The 12-hour steady-state total plasma concentration–time profiles of MPA and MPA glucuronide were obtained after oral administration of MMF on 2 occasions: first while taking CsA and second after changing to TRL. Pharmacokinetic parameters of MPA were calculated by the noncompartmental method. Changing from CsA to TRL resulted in significantly increased MPA exposure (area under the concentration–time curve from 0 to 12 hours, AUC_{0-12}) by $46 \pm 32\%$ ($P = 0.012$) and MPA predose concentration (C_0) by $121 \pm 67\%$ ($P = 0.008$). The magnitude of change in MPA exposure did not correlate well with MPA- C_0 or CsA trough concentration. Switching to TRL had minimal impact on peak concentration of MPA (15.0 ± 6.9 mg/L with CsA versus 16.1 ± 9.7 mg/L with TRL, $P = 0.773$) and time to reach the peak concentration (1.0 ± 0.4 hours with CsA versus 1.2 ± 0.8 hours with TRL, $P = 0.461$). Highly variable and unpredictable changes in MPA exposure among renal transplant patients with diabetes do not support a strategy of preemptively adjusting MMF dose when switching calcineurin inhibitors in this population.

Keywords

mycophenolic acid; pharmacokinetics; diabetes; cyclosporine; tacrolimus

INTRODUCTION

Mycophenolate mofetil (MMF; CellCept; Roche Laboratories, Inc., Nutley, NJ) is a prodrug of mycophenolic acid (MPA), a selective and reversible inhibitor of inosine 5'-monophosphate dehydrogenase (IMPDH) that inhibits lymphocyte proliferation. It is commonly used in combination with a calcineurin inhibitor [CNI; cyclosporine (CsA) or tacrolimus (TRL)] and

corticosteroids to prevent rejection after solid organ transplantation. Many studies observed that the area under the concentration–time curve (AUC) and predose plasma concentration (C_0) of MPA were significantly lower in patients taking MMF with CsA than in those taking MMF with TRL or without CsA.^{1–5} This differential effect of CNIs is because CsA inhibits the biliary secretion of MPA glucuronide (MPAG) through multidrug resistance protein 2 (MRP2) transporter, resulting in decreased MPA reabsorption during enterohepatic recirculation.^{6–8}

Switching maintenance immunosuppression after transplant is very common⁹ and changing to an alternative CNI can alter MPA-AUC, potentially increasing the risk for rejection or the side effects from MMF. Although the general recommendation is to initiate MMF at a higher dose with CsA,^{10–12} no specific guidelines are available regarding MMF dose adjustment when CsA is switched to TRL in stable renal transplant patients. Because MPA pharmacokinetics exhibits considerable intersubject variability,^{10,13} the differential effect of CNIs on MPA exposure is difficult to quantify from published studies using cross-sectional or parallel-group comparisons.^{1–4} Results of a previously published crossover study were hampered by deterioration of renal function in the study participants, which may have altered MPA pharmacokinetics.⁵

Diabetes mellitus is the most common cause of end-stage renal disease in the United States, and gastroparesis is a frequent and clinically important complication in long-standing patients with diabetes, affecting 30%–50% of this patient population.^{14–16} A significant delay in oral absorption of MPA from MMF has been described in patients with and without diabetes with increased gastric emptying time.^{17–20} Because TRL is a macrolide that has intrinsic prokinetic properties, it has the potential to affect gastric emptying and to alter the pharmacokinetics of concomitant drugs.^{21,22} Therefore, switching patients from a CsA-based regimen to a TRL-based regimen may alter MPA pharmacokinetics by both eliminating the CsA-induced MRP2 inhibition and enhancing gastric emptying, especially in those patients with diabetic gastroparesis. The purpose of this study was to evaluate the MPA pharmacokinetics when CsA was changed to TRL in stable renal transplant recipients with long-standing diabetes.

MATERIALS AND METHODS

Our study was an open-label, sequential, 2-period crossover pharmacokinetic drug interaction study in stable renal transplant recipients with diabetes. The study was approved by the Institutional Review Board at the University of Michigan. After written informed consent was obtained, study participants were switched from CsA to TRL while maintaining the same dose of MMF. The 12-hour steady-state total plasma concentration–time profiles of MPA and MPAG were obtained after an oral morning dose of MMF on 2 separate occasions: (1) during coadministration with CsA (MMF-CsA) and (2) at the steady state after changing to TRL (MMF-TRL).

Study Subjects

Renal transplant recipients with diabetes, age 18 years or older, who were at least 6 months after transplant with calculated creatinine clearance >30 mL/min by Cockcroft–Gault equation²³ and receiving maintenance immunosuppressive therapy consisting of CsA (Neoral; Novartis Pharmaceuticals, East Hanover, NJ), MMF, and prednisone were eligible for study entry. Presence of diabetes mellitus was confirmed by patient medical history, laboratory studies documenting glucose intolerance, hemoglobin A1c, and the need for exogenous insulin therapy. Subjects who were pregnant, nursing, or smokers and those who had received extrarenal transplant were excluded. Drugs that were known to significantly affect gastrointestinal motility such as erythromycin, loperamide, metoclopramide, and tegaserod and those that might significantly alter CsA, TRL, or MMF pharmacokinetics such as bile acid

resins, inhibitors, and inducers of cytochrome P450 3A and P-glycoprotein were prohibited during the study period.

Changing of CNIs

All subjects enrolled in this study had been on a stable dose of CsA for at least 2 weeks before study entry with whole-blood CsA trough concentrations of 100–200 ng/mL by high-performance liquid chromatography (HPLC).^{24,25} After completing the MMF-CsA pharmacokinetic study, subjects were instructed to discontinue CsA and start TRL 0.05 mg/kg twice daily 24 hours from the last dose of CsA. After the CNI change, subjects underwent safety assessment consisting of physical examination, vital signs, clinical laboratory evaluation including TRL trough concentration, and adverse events weekly up to 3 months. TRL dose was titrated to target whole-blood TRL trough concentrations of 5–10 ng/mL by HPLC–tandem mass spectrometry according to the center practice.^{24,25} Once steady state was achieved (defined by having at least 2 consecutive TRL trough concentrations within the target range on a stable dose of TRL), the MMF-TRL pharmacokinetic study was conducted. Throughout the study period, all subjects remained on their stable dose of prednisone and MMF 1 g twice daily.

Pharmacokinetic Analysis

In the morning of each pharmacokinetic study, subjects were admitted to the General Clinical Research Center at the University of Michigan after an overnight fast. Subjects took their regular morning dose of MMF and CNI (CsA for the MMF-CsA study and TRL for the MMF-TRL study) simultaneously at 12 hours after their last evening dose. Standardized meals were provided at 1, 5, and 10 hours after dosing. Serial blood samples were collected before and at 0.5, 1, 2, 3, 4, 6, 8, and 12 hours after administration of MMF and CNI.

Blood samples were centrifuged immediately after collection, and plasma was separated and stored at -80°C until analysis for MPA and MPAG. Plasma concentrations of total MPA and MPAG were measured by a validated HPLC assay at the Mayo Medical Laboratories (Rochester, MN). After thawing, each plasma sample was divided into 2 tubes. One tube (A) was used for direct measurement of unconjugated MPA concentration, and the other tube (B) was used to measure total hydrolyzed MPA concentration after glucuronidase treatment. The difference between unconjugated and total hydrolyzed MPA results allowed calculation of MPAG concentration. To tube A, 200 μL of the standards, controls, and samples was added, and to tube B, 50 μL of sample and 150 μL of blank plasma were added. To only tube B, 100 μL of 1:10 glucuronidase in sodium acetate buffer at pH 6.0 was added and incubated for 10 minutes at 37°C . To both tubes, 100 μL of the internal standard (5 $\mu\text{g/mL}$ zomepirac in acetonitrile) was added. Excess sodium sulfate was added and centrifuged, and the supernatant was removed. The extract was dried under nitrogen at 30°C and reconstituted in 200 μL of the mobile phase. Using Class-VP LC system (Shimadzu Scientific Instruments, Columbia, MD), 30 μL of the reconstituted sample was injected onto a guard column (5 μm , 2 cm $\times$ 4.6 mm) and an analytical column (5 μm , 5 cm $\times$ 4.6 mm) (both Discovery C18; Supelco; Sigma–Aldrich, Bellefonte, PA) at room temperature. Chromatographic separation was achieved by delivering isocratic solvent with a mobile phase of 20% acetonitrile and 80% triethylamine phosphate buffer at pH 7.0 (final concentration of 25% triethylamine and 1.875 mmol/L potassium phosphate buffer), with a flow rate of 2.0 mL/min. Detection was achieved by monitoring the absorbance at 213 nm. MPA and the internal standard were eluted at 2.8 and 6.75 minutes, respectively. Concentrations were calculated by comparing peak–height ratios of the drug with those of the internal standard. The lower limit of quantification was 0.5 mg/L for MPA and 10 mg/L MPAG. The inter- and intra-assay coefficients of variation were $<10\%$.

Pharmacokinetic parameters for MPA and MPAG were calculated by the noncompartmental method. The area under the concentration–time curve from 0 to 12 hours (AUC_{0-12}) was calculated using the linear trapezoidal rule for ascending concentrations and the log trapezoidal rule for descending concentrations. The predose concentration (C_0), the maximum concentration (C_{max}), and the time to reach C_{max} (T_{max}) were determined visually from the concentration–time profiles. Apparent oral clearance of MPA ($CL/F = \text{dose}/AUC_{0-12}$) was calculated after normalizing MMF dose for the subject's body weight and by multiplying by the ratio of MPA molecular weight to MMF molecular weight.

Statistical Analysis

The impact of changing CNi on MPA AUC_{0-12} and C_0 was determined by calculating the mean and SD of the percentage difference between the MMF-CsA phase and the MMF-TRL phase. To test the differences in pharmacokinetic parameters of MPA and MPAG and the biochemical laboratory variables between the 2 phases, a 2-sided paired *t* test for normally distributed data and the Wilcoxon signed rank test for non-Gaussian distribution were used. A *P* value of <0.05 was considered statistically significant.

RESULTS

Eight renal transplant recipients with diabetes participated in this study. Table 1 summarizes their demographic and laboratory characteristics. All subjects had juvenile-onset diabetes mellitus for 35 ± 7 years and hemoglobin A1c of $7.6 \pm 1.8\%$ (range 6.1%–11.6%) at the time of study entry. We did not perform radiological diagnostic studies for gastroparesis due to cost and concern for radiation exposure to the study participants.

All subjects tolerated well the change from CsA to TRL without experiencing any rejection episodes, allograft loss, or patient death during the follow-up period (94 ± 5 days). Three patients experienced adverse events including worsening of hypertension requiring the addition of an antihypertensive agent in the second month, an episode of shingles in the first month, and diarrhea in the first week after the change. No new-onset or worsening hematological abnormality or hyperlipidemia was observed. Serum creatinine, albumin, hemoglobin, and weight remained stable during the study period. No significant change in hemoglobin A1c occurred during this short follow-up, although insulin requirements increased in 3 patients. Steady-state TRL target trough concentrations were achieved at 32 ± 3 days after change and the MMF-TRL study was conducted after having been on a stable TRL dose for at least 14 days. All other medications remained unchanged throughout the study period.

After oral administration of MMF in combination with either CsA or TRL, pharmacokinetic parameters of MPA and MPAG exhibited high intersubject variability, with MPA- C_0 having the greatest variability (Table 2). The MPA plasma concentration–time profiles in the MMF-TRL phase showed a prominent second peak between 6 and 12 hours after MMF dosing, which was not observed in 6 of the 8 subjects during the MMF-CsA phase (Fig. 1). MPAG exposure was higher in the MMF-CsA phase compared with the MMF-TRL phase (Fig. 1; Table 2). When CsA was switched to TRL, AUC_{0-12} and C_0 of MPA increased significantly by $46 \pm 32\%$ (range 8%–98%, $P = 0.012$) and $121 \pm 67\%$ (range 0%–211%, $P = 0.008$), respectively (Fig. 2; Table 2). The percent change in MPA- AUC_{0-12} did not correlate well with the magnitude of change in MPA- C_0 ($r^2 = 0.39$, $P = 0.10$). Neither CsA- AUC_{0-12} nor CsA- C_0 predicted the changes in MPA- AUC_{0-12} ($r^2 = 0.22$, $P = 0.24$ and $r^2 = 0.08$, $P = 0.50$, respectively). Apparent oral clearance of MPA was slightly lower in the MMF-TRL phase compared with the MMF-CsA phase, as expected from the increased reabsorption of MPA. No significant changes in C_{max} and T_{max} of MPA were observed after changing to TRL (Table 2).

DISCUSSION

Diabetes mellitus is known to alter absorption and disposition of drugs partly due to gastroparesis.²⁶ For MMF, diabetes seems to slow the rate of absorption of MPA without a significant effect on MPA exposure.^{17–19} Lower MPA- C_0 was also observed in patients with diabetes compared with those without diabetes, but in this particular study, other pharmacokinetic parameters of MPA were not characterized.²⁷ Because TRL has the potential to hasten gastric emptying, we hypothesized that coadministration of TRL and MMF could alter MPA absorption in patients with long-standing diabetes.

We observed a significant increase in MPA exposure when CsA was changed to TRL in stable renal transplant recipients with diabetes. In addition, we observed an even larger increase in MPA- C_0 when CsA was changed to TRL. The magnitude of this change in MPA exposure was widely variable among patients, and CsA trough concentrations did not seem to have any predictive value for the change. The change in MPA- C_0 did not have a strong correlation with MPA exposure. A similar discordant change in MPA-AUC_{0–12} and MPA- C_0 after CNi change has also been reported with enteric-coated mycophenolate sodium in renal transplant recipients without diabetes (a mean increase of 19% in MPA-AUC_{0–12} and a mean increase of 200% in MPA- C_0 from CsA to TRL).²⁸

In our study, neither MPA- $C_{\max}$ nor MPA- $T_{\max}$ was significantly changed when CsA was switched to TRL. Although all subjects enrolled in our study had long-standing juvenile-onset diabetes mellitus that was not well controlled, no clear association exists between the length of diabetes and gastroparesis. One weakness of our study was the inability to measure gastric emptying, and it is possible that our study participants did not have severely impaired gastric motility as their MPA- $T_{\max}$ was shorter than that reported in patients with diabetes but comparable to that observed in patients without diabetes from other studies.^{18,19}

Changes in renal function, plasma albumin level, and hemoglobin level can alter clearance and protein binding of MPA and MPAG, contributing to the intrasubject variability in MPA pharmacokinetics.²⁹ Because serum creatinine, plasma albumin, and hemoglobin remained stable within the subjects during our study, these parameters could not account for the increased MPA exposure with TRL in our study. In contrast to the parallel-group study design, our crossover study design accounted for the intersubject differences that may influence MPA pharmacokinetics such as *UGT1A9* T-275A and C-2152T and *MRP2* C-24T polymorphisms.^{30,31} Comparison of the MPA concentration–time profiles of the MMF-CsA and the MMF-TRL revealed that the difference in MPA exposure was attributed mainly to the reduced second peak between 6 and 12 hours after dose with CsA coadministration. Conversely, MPAG exposure was higher with CsA than with TRL. These findings support the proposed mechanism of CsA inhibition of MPA/MPAG enterohepatic recirculation.^{6,7}

Because of large pharmacokinetic and pharmacodynamic variability of MPA, an interest is increasing in individualized dosing of MMF based on MPA concentrations, IMPDH activity, or both.^{10,13,32} Considering the inverse correlation between MPA exposure and the likelihood of rejection,³³ a total MPA-AUC_{0–12} target of at least 30 mg·hr/L has been proposed to minimize the risk of rejection in a CsA-based regimen. Although more convenient than measuring AUC_{0–12}, single determinants of MPA concentrations including C_0 have limited correlation with total MPA exposure and clinical outcomes. Investigations to find simple and robust limited sampling strategies continue, and availability of data supporting their clinical benefits will determine wider acceptance of MPA therapeutic monitoring in patient care. Considerable intersubject variability also exists in baseline IMPDH activity, and clinical outcomes with MMF therapy seem to vary depending on the pretransplant IMPDH activity.^{34,35} A small cross-sectional study has reported lower IMPDH activity in stable renal transplant

recipients with diabetes compared with the cohort without diabetes despite similar MPA-AUC₀₋₁₂ in both groups.³⁶ Whether the lower IMPDH activity in patients with diabetes reflects reduced basal IMPDH activity or higher pharmacological response to MPA is unclear without longitudinal monitoring of IMPDH activity in proper comparison groups. Moreover, how such differences affect graft outcome in patients with diabetes remains uncertain at this point. However, it should be noted that diabetes mellitus contributes to significant intersubject variability of MPA pharmacokinetics and pharmacodynamics; therefore, an MMF monitoring or dosing strategy that is developed in patients without diabetes may require careful validation in patients with diabetes because of the complex nature of diabetes.

CONCLUSIONS

This present study reports that MPA exposure was higher when the standard dose of MMF was taken in a TRL-based regimen compared with a CsA-based regimen in renal transplant recipients with diabetes mellitus. However, switching CsA to TRL did not seem to have significant impact on the rate of absorption of MPA, as judged by MPA- T_{max} . The magnitude of change in MPA exposure was substantially variable among patients with diabetes and difficult to predict based on CsA trough concentrations and MPA- C_0 . In patients with diabetes whose CNI will be switched to the alternative, a strategy of preemptively adjusting MMF dose by a fixed amount in anticipation of altered MPA exposure may result in suboptimal MPA exposure and should be discouraged.

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FIGURE 1.

Mean plasma concentration–time profile for (A) mycophenolic acid (MPA) and (B) mycophenolic acid glucuronide (MPAG) after oral administration of MMF with CsA (open circle) and TRL (closed circle). Error bars represent SD of the mean (n = 8).

FIGURE 2. Changes in (A) AUC_{0-12} and (B) predose plasma concentration (C_0) of mycophenolic acid (MPA) after change of concomitant CNI from CsA to TRL (thin line: individual subject; thick line: mean; $n = 8$).

TABLE 1

Demographics and Biochemical Variables of Study Participants (n = 8)

	CsA	TRL
Age (yrs)	46 ± 9	—
Gender (male/female)	4/4	—
Race (White/Asian)	7/1	—
Living donor/deceased donor transplant	5/3	—
Time after transplant (mo)	20 ± 14	—
Serum creatinine (mg/dL)	1.15 ± 0.27	1.13 ± 0.27
Creatinine clearance (mL/min)*	98 ± 40	101 ± 40
Albumin (g/dL)	3.8 ± 0.3	3.8 ± 0.3
Hemoglobin (g/dL)	12.7 ± 1.0	12.3 ± 1.0
Hemoglobin A1c (%)	7.6 ± 1.8	7.6 ± 1.8
Weight (kg)	85.9 ± 20.7	86.9 ± 20.7
CsA daily dose (mg/kg)	3.24 ± 0.82	—
CsA trough concentration (ng/mL)	127 ± 31	—
TRL daily dose (mg/kg)	—	0.07 ± 0.02
TRL trough concentration (ng/mL)	—	8.5 ± 3.4
Prednisone daily dose (mg/kg)	0.11 ± 0.09	0.10 ± 0.09

Data are numbers or mean ± SD.

* Creatinine clearance calculated by Cockcroft–Gault equation¹⁹

TABLE 2

Pharmacokinetic Parameters of Mycophenolic Acid and Glucuronide Metabolite After MMF Administration in Combination With CsA or TRL (n = 8)

	CsA		TRL		P
	Mean ± SD (range)	CV%	Mean ± SD (range)	CV%	
MPA					
AUC ₀₋₁₂ (mg·hr/L)	45.2 ± 15.9 (20.8–68.4)	35	66.2 ± 29.2 (34.7–114.8)	44	0.012
C ₀ (mg/L)	2.3 ± 2.1 (0.6–6.7)	91	4.6 ± 3.7 (1.6–12.4)	81	0.008
C _{max} (mg/L)	15.0 ± 6.9 (8.0–28.7)	46	16.1 ± 9.7 (5.7–30.2)	60	0.773
T _{max} (h)	1.0 ± 0.4 (0.5–2.0)	41	1.2 ± 0.8 (0.5–3.0)	67	0.461
CL/F (L·h ⁻¹ ·kg ⁻¹)	0.21 ± 0.05 (0.15–0.31)	25	0.15 ± 0.05 (0.09–0.21)	30	0.004
MPAG					
AUC ₀₋₁₂ (mg·hr/L)	1180 ± 291 (878–1663)	25	913 ± 299 (695–1587)	33	0.009
C ₀ (mg/L)	77 ± 21 (56–109)	28	66 ± 29 (30–125)	43	0.096
C _{max} (mg/L)	144 ± 36 (92–199)	25	102 ± 35 (68–180)	34	0.019
T _{max} (h)	2.7 ± 1.0 (1.9–4.0)	35	2.1 ± 1.1 (1.0–4.0)	53	0.142

CV, coefficient of variation.