Published in final edited form as:

Clin Pharmacokinet. 2015 April ; 54(4): 423–434. doi:10.1007/s40262-014-0213-7.

Influence of Sex and Race on Mycophenolic Acid Pharmacokinetics in Stable African American and Caucasian Renal Transplant Recipients

Kathleen M. Tornatore^{1,3}, Calvin J. Meaney¹, Gregory E. Wilding², Shirley S. Chang³, Aijaz Gundroo³, Louise M. Cooper¹, Vanessa Gray³, Karen Shin¹, Gerald J. Fetterly⁴, Joshua Prey⁴, Kimberly Clark⁴, and Rocco C. Venuto³

¹Department of Pharmacy Practice, Immunosuppressive Pharmacology Research Program; Translational Pharmacology Research Core, New York State Center of Excellence in Bioinformatics and Life Sciences, University at Buffalo, Buffalo, NY 14214

²Department of Biostatistics, School of Public Health and Health Professions, School of Pharmacy and Pharmaceutical Sciences, School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY 14214

³Erie County Medical Center, Division of Nephrology; Department of Medicine, School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY 14214

⁴Pharmacokinetic/ Pharmacodynamics Laboratory, Roswell Park Cancer Institute, Buffalo, New York

Abstract

Background and Objectives—No evaluation of sex and race influences on MPA pharmacokinetics and adverse effects (AE) during enteric coated mycophenolate sodium (ECMPS) and tacrolimus immunosuppression are available. MPA and MPA glucuronide(MPAG) pharmacokinetics with gastrointestinal AE were investigated in 67 stable renal transplant recipients: 22 African American males(AAM); 13 AA females(AAF); 16 Caucasian males(CM) and 16 Caucasian females(CF) receiving ECMPS and tacrolimus.

Methods—Validated gastrointestinal AE rating included diarrhea, dyspepsia, vomiting and acid suppressive therapy was completed. Apparent clearance, clearance normalized to body mass index (BMI), area under concentration time curve 0-12 (AUC₀₋₁₂) and dose normalized AUC₀₋₁₂

Address correspondence to: Kathleen M. Tornatore, PharmD, FCCP Associate Professor of Pharmacy Research Associate Professor of Medicine Department of Pharmacy Practice School of Pharmacy and Pharmaceutical Sciences NYS Center of Excellence in Bioinformatics & Life Sciences 701 Ellicott Street University at Buffalo Buffalo, New York, United States, 14203 Fax: 716-645-2886 tornator@buffalo.edu.

Authors Contributions:

KMT designed the study and obtained funding. KMT, RCV, SC, AG and VG enrolled patients. KMT, RCV, SC, AG, LMC, VG conducted the studies with some assistance from CJM. KMT, LMC, KC, JP and GF conducted MPA and MPAG sample analysis and quality control review. KMT, CJM, LMC and KS completed pharmacokinetic analysis, data summaries and quality control review. Statistical analysis was completed by GW. KMT, CJM, RCV, and GW collaborated on manuscript preparation. All authors reviewed and approved the final manuscript.

Disclosures have been submitted.

Statement of Competing Financial Interests: The authors of this manuscript have no conflicts of interest or financial relationships to disclose during the time this study was ongoing.

(AUC*) were determined using a statistical model that incorporated gastrointestinal AE and clinical covariates.

Results—Males had more rapid apparent MPA clearance (CM: 13.8 ± 6.27 L/h vs. AAM: 10.2 ± 3.73 L/h) compared to females (CF: 8.70 ± 3.33 L/h and AAF: 9.71 ± 3.94 L/hr; $P=0.014$) with a race-sex interaction ($P=0.043$). Sex differences were observed in MPA clearance/BMI ($P=0.033$) and AUC* ($P=0.033$). MPA AUC₀₋₁₂ was greater than 60 mg•h/L in 57% of RTR with 71% of patients demonstrating gastrointestinal AE and a higher score noted in females. In all patients, females exhibited 1.40-fold increased gastrointestinal AE scores compared to males ($P=0.024$). Race ($P=0.044$) and sex ($P=0.005$) differences were evident with greater MPAG AUC₀₋₁₂ in AAF and CF.

Conclusion—Sex and race differences were evident with females having slower MPA clearance, higher MPAG AUC₀₋₁₂ and more severe gastrointestinal AE. These findings suggest consideration of sex and race during MPA immunosuppression.

1 Introduction

Mycophenolic acid (MPA) is the active moiety in enteric coated mycophenolate sodium (ECMPS) and mycophenolate mofetil (MMF) [1]. Both MPA formulations are prescribed with tacrolimus or cyclosporine for maintenance immunosuppression. [1-4] The ECMPS formulation provides similar efficacy to MMF and may have less gastrointestinal adverse effects [1, 2, 5-8]. MPA associated gastrointestinal adverse effects may reduce medication adherence, patient tolerability, and therapeutic MPA exposure resulting in decreased allograft survival [2, 7, 9-11].

MPA has complex metabolism and notable inter- and inpatient pharmacokinetic variability which is related to the inactive metabolite, MPA glucuronide (MPAG) [1, 12-14]. Clinical and demographic factors contribute to interpatient variability in MPA and MPAG pharmacokinetics and include renal function, race, sex, albumin, hemoglobin, hematocrit, age, calcineurin inhibitor therapy and time post-transplant [1, 15, 16]. Prior research has described race differences in MPA and MPAG pharmacokinetics with MMF or ECMPS in African American (AA) and Caucasian renal transplant recipients receiving cyclosporine with a suggested sex influence [16, 17]. These studies were unique due to inclusion of intensive pharmacokinetic sampling with statistical models including pertinent clinical covariates to assess variability. These data contrast with other MPA pharmacokinetics in recipients receiving cyclosporine where no race or sex differences were found [18, 19]. To emphasize the need for evaluation of patient sub-populations, the Food and Drug Administration has advocated for pharmacokinetic assessments of new formulations of approved medication that include race and sex studies [20-23]. This approach may prevent clinicians from assuming that different formulations yield similar pharmacologic profiles in patient sub-populations.

MPA and MPAG pharmacokinetics and immunosuppression in renal transplant recipients are affected by the choice of the calcineurin inhibitor in the regimen [1, 24-26]. More enterohepatic circulation of MPAG occurs with concurrent tacrolimus with increased amount of the active moiety, MPA through intestinal and hepatic transport via the multi-

drug resistance protein 2 (MRP 2) resulting in an increased MPA area under the concentration vs. time curve (AUC) [24-27]. In contrast, MPA exposure is reduced by cyclosporine due to inhibition of MPR2 function with less enterohepatic circulation [24]. The influence of race and sex on this complex calcineurin inhibitor interaction with MRP2 has not been assessed. Since MPA and tacrolimus regimen are the most common immunosuppressive therapy prescribed in the United States, studies of this combination in AA and Caucasian male and female recipients are warranted and timely [28].

The primary objective of this study was to investigate the influence of sex and race on MPA and MPAG pharmacokinetics in stable renal transplant recipients receiving ECMPS and tacrolimus immunosuppression using a statistical model incorporating pertinent clinical factors with enterohepatic circulation. The secondary objective was to evaluate MPA associated gastrointestinal adverse effects using a validated, standardized assessment scale and association to race, sex and MPA pharmacokinetics [29].

2 Methods

2.1 Study Population

Sixty-seven (35 AA and 32 Caucasian) stable male and female renal transplant recipients receiving maintenance immunosuppression of tacrolimus (*Prograf*®) and mycophenolic acid as ECMPS (*Myfortic*®) for at least 6 months were evaluated in a 12-hour pharmacology study. Patients were considered clinically stable by physical exam, comprehensive metabolic panel and complete blood count at enrollment and prior to the study. Tacrolimus doses were adjusted to target troughs from 3 to 7 ng/ml based upon time post-transplant and clinical response. MPA dosing adjustment was based upon clinical response and adverse effects without therapeutic drug monitoring. Medication adherence at enrollment and one week prior to study was documented. Ethnicity for two previous generations was verified.

The inclusion criteria were: 1) 6 months post-renal transplant; 2) age 25-70 years; 3) first or second time deceased-donor or living allograft recipient; 4) stabilized on same dose of immunosuppressive drugs for 7 days prior to study; 5) Serum creatinine 3.25 mg/dl with no change in serum creatinine 0.25 mg/dl during prior 2 visits; 6) leukocyte count 3000/mm³ and hemoglobin 8.0 g/dl. Exclusion criteria were: 1) significant gastrointestinal disease; 2) infection within 2 weeks prior to study; 3) acute rejection within 2 weeks of study; 4) drugs interfering with MPA absorption; 5) significant cardiovascular, hematologic, psychiatric, neurologic or oncologic disease that would limit participation.

2.2 Study Procedure

This was a cross-sectional, open-label pharmacokinetic study in stable male and female AA and Caucasian renal transplant recipients receiving chronic immunosuppression of tacrolimus (*Prograf*®) and mycophenolic acid as ECMPS (*Myfortic*®) for at least 6 months. A sample size of at least 13 stable transplant patients for each race-gender group addressed the primary study objective.

This study was conducted at the University at Buffalo (UB) Renal Research Center at the Erie County Medical Center. Prior to study initiation, the UB Health Sciences Institutional

Review Board approved the study (IRB# PHP0720608B) which was conducted in accordance with the Declaration of Helsinki. Upon enrollment, patients provided written consent after review of the study purpose, risks and benefits.

All patients were studied at steady-state conditions of ECMPS and tacrolimus with receipt of the same dose of immunosuppressive drugs for at least 7 days prior to study. Proton pump inhibitors, H₂ antagonists and antacids were discontinued at least 36 hours preceding study. Patients took the immunosuppressive medications between 5:30 to 6:30 PM with the evening meal at 8:00 to 8:30 PM preceding study. Patients fasted and abstained from caffeine and alcohol for 12 hours prior to study. At 6:00 AM, patients were admitted, with vital signs documented and an intravenous angiocatheter inserted. A 0 hour blood sample (~15 ml) was collected prior to immunosuppressive administration for MPA and tacrolimus trough concentrations and comprehensive metabolic profile with lipid panel and complete blood count. Study medications were administered by mouth from a single lot of ECMPS (*Myfortic*®) and tacrolimus (*Prograf*®) by 7:00 AM. Patients remained in an upright position throughout the study. Standardized low fat and sodium meals were provided after the first 4 hours and consistently timed for study duration. Anti-hypertensive drugs were administered after 1.5 hours while insulin, anti-lipidemic and other medications were administered 4 hours after the immunosuppressives. Blood samples (7 ml) were collected and placed on ice at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 hours after drug administration. Plasma samples were harvested within 1 hour and stored at -70° C until analysis. Clinical laboratory tests and tacrolimus troughs were analyzed in the Clinical Laboratory at the Erie County Medical Center.

2.3 Gastrointestinal Adverse Effect Evaluation

Common drug-related gastrointestinal AE (Table 1) were evaluated by trained nephrologists during the 12 hour study using validated criteria with assignment of severity (i.e. 0 = no adverse effect; 1+ = mild to 3+ = severe manifestations) [29]. Significant gastrointestinal disease was excluded prior to patient enrollment. Patients received a ranked score for each gastrointestinal AE during the physical examination. A gastrointestinal score was then determined as the sum of the rating for each individual AE to compare severity with the possible minimum score of zero and maximum score of 9. Due to limited sample size, each gastrointestinal adverse effect was reported dichotomized as present or absent and monitored from enrollment through study.

2.4 Assay Methodology

A liquid chromatography/mass spectrometry assay was used for the simultaneous analysis of plasma MPA and MPAG with 5, 5-diphenylhydantoin and flumethasone as internal standards, respectively [30]. Standard curve concentrations ranged from 0.145 µg/mL to 15.5 µg/mL for MPA and from 22.1 to 295.2 µg/mL for MPAG. The lowest limit of quantitation was 0.072 µg/mL for MPA and 11.1 µg/mL for MPAG. The relative standard deviation for intraday variation for MPA ranged from 1.6 to 2.7 % and 2.87 to 6.54 % for MPAG. The relative standard deviation of interday variation for MPA ranged from 2.3 to 4.5 % and 3.8 to 7.5 % for MPAG. Tacrolimus troughs were analyzed within 24 hours at ECMC Clinical Laboratory using the *ARCHITECT* Tacrolimus assay (Abbott, Abbott Park,

IL), a chemiluminescent microparticle immunoassay. The lower limit of detection was 1.5 ng/ml and intraday assay variability was less than 7%.

2.5 Pharmacokinetic Analysis

Pharmacokinetic parameters for MPA and MPAG included the area under the concentration versus time curve from 0 to 12 hour (AUC_{0-12}), dose normalized MPA AUC_{0-12} (AUC^*); 12 hour trough ($C_{12\text{ hr}}$) and peak concentrations (C_{max}) and time to peak (T_{max}). The dose equivalent MPA was utilized. Oral apparent clearance of MPA was calculated as the ratio of MPA dose equivalent to MPA AUC_{0-12} . MPA clearances were adjusted for body mass index (BMI) to assess the impact of standardized body weights. Clearance and AUC_{0-12} were determined by the linear trapezoidal rule using non-compartmental pharmacokinetic methods (*Phoenix WINNONLIN* Version 6.3. *Pharsight Corp, Mountain View, Calif*). Since patients were stabilized on different daily doses of MPA, MPA AUC_{0-12} was dose-normalized to 1 mg MPA dose equivalent due to drug linearity to generate $AUC^*[1, 31]$.

Patients were identified as having enterohepatic circulation using these criteria: a.) inspection of the MPA concentration vs. time profiles for appearance of a second peak occurring from 6 to 12 over the dosing interval ; b) an increase in MPA concentration greater than 25% compared to the previous time point during the elimination phase [16,17, 32].

2.6 Statistical Analysis

The sample size was determined based upon a power of 80% to detect a difference of 30% in the MPA oral clearance between AA and Caucasian male and female recipients with a coefficient of variation of 30%. This required at least 13 patients per race-sex group.

Descriptive statistics such as frequencies and relative frequencies were computed for all categorical variables. Numeric variables were summarized using simple descriptive statistics including means and standard deviations with graphical techniques utilized for displaying data. Analysis of variance (ANOVA) was used to compare groups defined by race and sex in the case of continuous parameters such as pharmacokinetic endpoints, demographics, and clinical factors. A secondary analysis was completed to evaluate the presence or absence of enterohepatic circulation as a binary dependent variable in relation to the groups using logistic regression. Enterohepatic circulation was used as a covariate in relation to MPA and MPAG pharmacokinetics and gastrointestinal AE score between groups. Pairwise comparisons utilized Tukey-Kramer correction for multiple testing. Diagnostic plots were used to assess model fit and identify the need for data transformations. All data were found to meet model assumptions and no data required transformation. The modeling of binary endpoints for adverse effects was done in a similar fashion using logistic regression techniques. Statistical outliers were defined as studentized residuals outside ± 3 . Our results had no outliers. In the case of gastrointestinal AE endpoints, groups were compared using the Wilcoxon test.

To further examine race-sex group differences in MPA and MPAG pharmacokinetics, in the presence of confounding patient factors such as: age, tacrolimus trough, estimated

glomerular filtration rate (eGFR) [33], albumin, hemoglobin, hematocrit, time post-transplant, presence of diabetes and enterohepatic circulation were included in the established linear statistical model and refit using each covariate (factor) as an independent variable in a separate model[1]. The partial coefficient of determination for each pair of dependent and independent variables was calculated to estimate the variability explained by the independent variable relative to the grouping variables. All tests were two-sided with nominal significance level of 0.05 utilized for all hypotheses testing with SAS statistical software (version 9.3, SAS Institute, Cary, NC).

3 Results

3.1 Patients

Sixty-seven renal transplant recipients (13 AA females, 16 Caucasian females, 22 AA males, and 16 Caucasian males) completed this study with no differences in ages and times post-transplant. Demographics and clinical characteristics are summarized in Table 2. Albumin, liver function tests and hematologic parameters were within normal range for all patients. Females had lower albumin, hemoglobin, eGFR, total and lean body weights. No differences in body mass index were found among groups. African Americans had higher serum creatinine values as expected. Mean tacrolimus trough concentrations and mycophenolic acid doses were similar among groups. Diabetes was present in 52% of AA and 48% of Caucasians. No data transformation was required for demographics or pharmacokinetic results.

3.2 Pharmacokinetics

Table 3 summarizes MPA and MPAG pharmacokinetic parameters. Figure 1 represents mean MPA and MPAG AUC₀₋₁₂ as concentration verses time profiles for each group. The MPA C_{12h}, C_{max} concentrations and time to maximum concentration (t_{max}) were comparable among groups. Using the C_{12h} trough of 1.9 mg/L established for MMF and tacrolimus, 81% of patients exceeded this target with 55% having troughs >3.0 mg/L as a result of empiric dosing [22]. A 6.5-fold range in apparent MPA clearance was present. A significant sex effect (p=0.014) and race-sex interaction (p=0.043) were found with the oral MPA clearance with Caucasian females exhibiting the slowest clearance compared to Caucasian males. MPA clearance normalized for BMI was most rapid in Caucasian males with a sex (p=0.033) difference and racial trend (p=0.080) noted.

Two MPA AUC₀₋₁₂ patterns were observed among these 4 race-gender groups (Figures 2 A-D). One concentration-time pattern was bimodal with an initial increase in MPA concentrations representing drug absorption followed by a second increase from 6 to 12 hours. This pattern has been attributed to enterohepatic circulation of MPAG to MPA [1]. Enterohepatic circulation was found in 86.4 % of AA males; 81.3% of Caucasian males; 61.5% of AA females; 75.0% of Caucasian females (p=0.400). Figure 2 depicts mean MPA concentration vs. time graphs of patients with enterohepatic circulation. The second MPA AUC₀₋₁₂ pattern demonstrated a prolonged MPA decline with no secondary increase as described in 38.5% of AA females; 25 % of Caucasian females; 13.6% of AA males and 18.8% of Caucasian males. No difference in MPA clearances (p=0.792), AUC_{0-12h}

($p=0.982$) and tacrolimus troughs ($p=0.157$) were observed between patients with and without enterohepatic circulation.

Although no sex or race differences were found for total MPA AUC_{0-12} , drug exposure comparisons were depicted in Figure 3 using the MPA AUC_{0-12} therapeutic range of 30 to 60 mg•h/L established for steady-state MMF and cyclosporine regimens [34, 22]. Using this MPA AUC range depicted in Figure 3, 6 patients (< 9%) [3 Caucasians; 3 AA] were less than 30 mg•h/L; 23 (34%) patients were between 30 to 60 mg•h/L [10 AA; 13 Caucasians] and 38 patients (57%) [22 AA; 16 Caucasians] were greater than 60 mg•h/L with empiric dosing [34, 22]. For patients with MPA $AUC_{0-12} > 60$ mg•h/L, 50% were females (10 AA; 9 Caucasian). Sex differences were found with MPA AUC^* ($p=0.033$) with the lowest AUC^* found in Caucasian males.

Sex and race influences were exhibited with MPAG pharmacokinetics (Table 2). Sex differences in MPAG C_{12h} ($P=0.014$) and C_{max} ($p=0.017$) concentrations were observed with the greatest exposures observed in AA females. For MPAG AUC_{0-12} , sex ($P=0.005$) and race ($p=0.044$) differences were found with AA females exhibiting almost twice the metabolite exposure compared to Caucasian males. Sex ($p=0.031$) difference with a racial trend ($p=0.053$) were noted in the ratio of MPAG AUC to MPA AUC (metabolite to active drug exposure) when adjusted for hemoglobin with AA females exhibiting the highest ratio.

Analyses pertaining to MPA and MPAG pharmacokinetic variability provided insight into the effect of clinical covariates and included renal function (eGFR), hemoglobin and tacrolimus troughs. Inverse associations between the eGFR and MPA C_{12h} trough ($p=0.009$), AUC_{0-12} ($p=0.021$) and MPAG AUC/MPA AUC ($p=0.066$) represented 5.3 to 11% variability attributed to these pharmacokinetic parameters with increased drug exposure as renal function declines. Tacrolimus C_{12h} had an inverse association with MPA C_{max} ($p=0.004$) and AUC^* ($p=0.069$) accounting for 5.2 to 12.5% of variability. Hemoglobin had inverse associations with MPA C_{12h} ($p<0.0001$), AUC_{0-12} ($p=0.009$) and MPAG AUC/MPA AUC ($p=0.0084$) contributing 5 to 22% toward MPA pharmacokinetic variability. Inverse associations of eGFR with MPAG C_{12h} ($p=0.0002$), C_{max} ($p=0.0005$), and AUC_{0-12} ($p<0.0001$) were detected representing 18 to 24% of the metabolite variability indicating reduced renal function was associated with increased MPAG exposure.

3.3 Gastrointestinal Adverse Effect Evaluation

The gastrointestinal adverse effects were assessed using standardized criteria by trained nephrologists and summarized in Table 4 using criteria in Table 1. Sex difference were present in the gastrointestinal AE score ($p=0.024$) after adjustment for renal function and AA females exhibited the highest score (3.23 ± 1.42). For patients with MPA $AUC_{0-12} > 60$ mg•h/L (figure 3) and gastrointestinal AE, combined females had a higher score (3.93 ± 1.71) compared to males (2.67 ± 1.30 ; $p=0.076$). No sex difference was observed in MPA AUC_{0-12} (females: 90.4 ± 28.9 mg•h/L versus males: 92.2 ± 22.5 mg•h/L; $p=0.608$) with the MPAG AUC 0-12 higher in females (1244 ± 536 mg•h/L) compared to males (913 ± 306 mg•h/L; $P=0.083$) for this sub-group analysis. For patients with MPA $AUC_{0-12} > 60$ mg•h/L, 97% (37/38) had a MPA trough greater than 1.9 mg/L as established for MMF and tacrolimus.[22] For all 67 patients, recipients with enterohepatic circulation had a lower

gastrointestinal AE score (2.23 ± 1.69) compared to the no recycling group (3.40 ± 1.81 ; $p=0.027$). No difference was found in the MPAG AUC/MPA AUC in patients with enterohepatic circulation (13.61 ± 6.00) compared to no recycling (15.64 ± 6.48 ; $p=0.25$).

No significant associations of gastrointestinal score with MPA or MPAG AUC_{0-12h} or C_{12h} troughs for the entire group were found. No group differences were found for individual GI symptoms dichotomized as present or absent.

4 Discussion

Demographics, clinical factors and concurrent medications influence interpatient variability in MPA and MPAG pharmacokinetics but are rarely evaluated in bioequivalence studies of new formulations [1, 20, 35]. Since the combination of MPA and tacrolimus is the most frequently prescribed immunosuppressive regimen in the US, we examined race and sex influences on the MPA and MPAG pharmacokinetics of the ECMPS formulation using intensive sampling approach [28]. Sex influences were observed with more rapid apparent MPA clearance, clearance/BMI and lower dose normalized MPA AUC* in Caucasian males compared to AA and Caucasian females. A sex and race association was described with MPAG AUC₀₋₁₂ with renal function (eGFR) identified as a covariate accounting for variability. Interestingly, a sex effect was also detected in the gastrointestinal AE score with the highest score in AA females. MPA is extensively bound to albumin and competes with MPAG for binding [1, 36]. With a decline in renal function, accumulation of urea and other uremic compounds compete for albumin binding sites with the concurrent reduction in renal clearance of MPA and MPAG [1, 37]. These pharmacokinetic changes, lead to increased unbound drug concentration, and when accompanied by reduced renal function in female patients may partially account for sex differences in MPA and MPAG [1]. However, no clinical MPA AUC guidelines have been developed that would individualize ECMPS or MMF dosing according to patient sub-populations and declining renal function [14].

In addition to a sex effect, a combined sex-race influence was observed with a more rapid MPA clearance in Caucasian males compared to Caucasian females with similar findings in AA females and males. A sex effect and racial trend were found in the MPAG AUC/MPA AUC with the lowest ratio found in Caucasian males suggesting more extensive deconjugation of the metabolite, MPAG by uridine diphosphate glucosyltransferase (UGT) to MPA in males. Sex differences in glucuronidation with males exhibiting a more rapid clearance have been reported; however generally, race influences remain to be investigated for most medications [38-40]. During a study that used therapeutic drug monitoring, MPAG/MPA trough ratios were higher in male renal transplant recipients than females suggesting gender differences in glucuronidation [40]. However, MPA clearance was not determined and the use of the trough plasma ratio may be influenced by renal allograft function and concurrent cyclosporine therapy. Therefore, studies that are limited to trough concentration comparisons require further investigation utilizing a study design that employs pharmacokinetic analysis with intensive sampling. Population pharmacokinetic studies have described gender influences on MPA and MPAG as confirmed in our current study [41, 42].

The calcineurin inhibitor combined with MPA may further contribute to interpatient variability in MPA and MPAG pharmacokinetics and the resulting differences in systemic drug exposure [43-45]. The MRP-2 efflux transporter in liver, kidney and gut epithelium apical cell membranes plays a central role in the enterohepatic circulation of MPAG [46]. MPAG is then converted to MPA through deconjugation and is detected as a second peak in the pharmacokinetic profile that is observed beyond 4 hours after drug administration [24, 47, 48]. Cyclosporine inhibits MRP-2, thus preventing enterohepatic circulation of MPAG and minimizing its contribution on MPA pharmacokinetics [24, 47]. However, tacrolimus does not interfere with MRP-2 and enterohepatic circulation of MPAG is present contributing to an increased MPA exposure as measured by a greater AUC_{0-12} , slower MPA clearance and reduced MPAG AUC_{0-12} compared to cyclosporine [47, 43, 48]. Enterohepatic circulation is rarely described in MPA and MPAG pharmacokinetic studies but remains an integral component to accurate drug exposure [4, 49]. Our group has described a disparity in enterohepatic circulation present in Caucasian and AA male recipients stabilized on either MMF or ECMPS with cyclosporine [17]. The incidence of enterohepatic circulation may also be influenced by a range of cyclosporine concentrations among patients in these reports [24]. The minimization of calcineurin inhibitors post-transplantation is likely to result in a range of drug exposures that lead to inter-individual differences in MRP-2 function and the presence or absence of enterohepatic circulation. Dosing adjustments to the immunosuppressive regimen may also be a factor that contributes to MPA pharmacokinetic variability and requires further evaluation in patient sub-populations [50]. Therefore, clinicians should consider monitoring MPA and MPAG concentrations in patients during cyclosporine or tacrolimus dose adjustments or switching between MPA formulations due to the resulting change in enterohepatic circulation that impacts MPA and MPAG pharmacokinetics and immunosuppression.

An interesting observation was that 57% of our subjects had an MPA $AUC_{0-12} > 60 \text{ mg} \cdot \text{h/L}$ (Figure 4), a value that is considered to be above the upper end of the therapeutic range for MMF and cyclosporine immunosuppression [14]. In spite of using an empiric dosing approach, less than 9% of these patients had MPA AUC_{0-12} less than $30 \text{ mg} \cdot \text{h/L}$. Conflicting results from large clinical trials have been reported comparing fixed dosing to concentration-controlled approaches using predicted MPA AUC for dose adjustment of MMF regimens administered with cyclosporine or tacrolimus [51-53]. These studies have provided guidance for development of MPA therapeutic ranges for ECMPS in tacrolimus-based immunosuppression in spite of the differing MMF pharmacokinetics [51-53].

The higher gastrointestinal AE score in AA females provides the first gender specific observation of MPA-associated adverse effects. The occurrence of gastrointestinal AE may reduce medication adherence and quality of life with potential influence on the maintenance of long-term therapeutic MPA exposure and health care costs associated with allograft complications [8-10, 12, 54]. The proposed mechanism(s) that lead to gastrointestinal adverse effects include gut epithelial UGT that produces MPAG; enterocyte villous atrophy with MPA effects, and enterocyte inosine monophosphate dehydrogenase [55]. Reducing gastrointestinal AE associated with MPA is important for overall allograft survival and patient quality of life [9, 55]. Although it is unclear if gastrointestinal AE associated with ECMPS are less than with MMF, it has been suggested that patient tolerance is improved

with different formulations [2, 54, 55]. The gastrointestinal AE assessment scale we utilized was a component of the comprehensive immunosuppressive AE assessment developed to compare inter- and inpatient AE severity [29]. Interestingly, patients with enterohepatic circulation had lower gastrointestinal AE score compared to recipients with no recycling and requires further investigation. The gastrointestinal AE score was not associated with MPA or MPAG pharmacokinetics, possibly a reflection of the sample size. However, these findings are consistent with gender specific observations for adverse drug effects in the general population [56, 57].

A limitation of our study is that we evaluated stable patients using a cross-sectional, observational design. Therefore, our findings should be verified in a prospective manner to confirm the gender association to adverse effects we identified.

5 Conclusion

This study is the first to report sex and race differences in MPA and MPAG pharmacokinetics and gastrointestinal AE in stable renal transplant recipients receiving ECMPS and tacrolimus. These findings may occur through modification of MRP-2 function, sex-related differences in deconjugation of MPAG to MPA, and altered protein binding to albumin of MPA and MPAG during renal dysfunction. These findings may have important clinical implications for ECMPS dose adjustments between sex and race, during dose adjustment of tacrolimus and between MPA formulations, and the potential use of therapeutic drug monitoring.

Acknowledgements

Dr. Meaney was an Immunosuppressive Pharmacology Fellow in the Immunosuppressive Pharmacology Research Program at the School of Pharmacy and Pharmaceutical Sciences and New York State Center of Excellence for Bioinformatics and Life Sciences. Dr. Chang was an ECRIP Transplant Fellow during this research study in the UB Department of Medicine, Nephrology Division. Dr. Shin was a Doctor of Pharmacy Student during this research project.

The assistance of the following individuals is greatly appreciated: Lisa Venuto, PA, Brenda Pawl, LPN and Ellen Kendricks, RN from Erie County Medical Center and Renal Division.

This study was supported by grants from NIDDK ARRA R21: DK077325-01A1 (KMT-PI) and an Investigator Initiated Research Grant (KMT-PI) from Novartis Pharmaceuticals.

REFERENCES

1. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of mycophenolate in solid organ transplant recipients. *Clinical pharmacokinetics*. 2007; 46(1):13–58. doi: 10.2165/00003088-200746010-00002.
2. Budde K, Durr M, Liefeldt L, Neumayer HH, Glander P. Enteric-coated mycophenolate sodium. Expert opinion on drug safety. 2010; 9(6):981–94. doi:10.1517/14740338.2010.513379.
3. Mycophenolate mofetil in renal transplantation: 3-year results from the placebo-controlled trial. European Mycophenolate Mofetil Cooperative Study Group. *Transplantation*. 1999; 68(3):391–6. [PubMed: 10459543]
4. Staatz CE, Tett SE. Pharmacology and toxicology of mycophenolate in organ transplant recipients: an update. *Archives of toxicology*. 2014; 88(7):1351–89. doi:10.1007/s00204-014-1247-1.
5. Budde K, Bauer S, Hambach P, Hahn U, Roblitz H, Mai I, et al. Pharmacokinetic and pharmacodynamic comparison of enteric-coated mycophenolate sodium and mycophenolate mofetil

- in maintenance renal transplant patients. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2007; 7(4): 888–98. doi:10.1111/j.1600-6143.2006.01693.x.
6. Budde K, Glander P, Kramer BK, Fischer W, Hoffmann U, Bauer S, et al. Conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in maintenance renal transplant recipients receiving tacrolimus: clinical, pharmacokinetic, and pharmacodynamic outcomes. *Transplantation*. 2007; 83(4):417–24. doi:10.1097/01.tp.0000251969.72691.ea.
 7. Cooper M SM, Budde K, Oppenheimer F, Sollinger H, Zeier M. Enteric coated Mycophenolate Sodium Immunosuppression in Renal Transplant Patients: Efficacy and Dosing. *Transplantation reviews*. 2012; 26:233–40.
 8. Ortega F, Sanchez-Fructuoso A, Cruzado JM, Gomez-Alamillo JC, Alarcon A, Pallardo L, et al. Gastrointestinal quality of life improvement of renal transplant recipients converted from mycophenolate mofetil to enteric-coated mycophenolate sodium drugs or agents: mycophenolate mofetil and enteric-coated mycophenolate sodium. *Transplantation*. 2011; 92(4):426–32. doi: 10.1097/TP.0b013e31822527ca. [PubMed: 21760569]
 9. Machnicki G, Ricci JF, Brennan DC, Schnitzler MA. Economic impact and long-term graft outcomes of mycophenolate mofetil dosage modifications following gastrointestinal complications in renal transplant recipients. *Pharmacoeconomics*. 2008; 26(11):951–67. [PubMed: 18850764]
 10. Langone A, Doria C, Greenstein S, Narayanan M, Ueda K, Sankari B, et al. Does reduction in mycophenolic acid dose compromise efficacy regardless of tacrolimus exposure level? An analysis of prospective data from the Mycophenolic Renal Transplant (MORE) Registry. *Clinical transplantation*. 2013; 27(1):15–24. doi:10.1111/j.1399-0012.2012.01694.x. [PubMed: 22861144]
 11. Borrows R, Chusney G, Loucaidou M, James A, Lee J, Tromp JV, et al. Mycophenolic acid 12-h trough level monitoring in renal transplantation: association with acute rejection and toxicity. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2006; 6(1):121–8. doi:10.1111/j.1600-6143.2005.01151.x.
 12. Tett SE, St Marcoux F, Staatz CE, Brunet M, Vinks AA, Miura M, Kuypers DR, van Gelder T, Cattaneo D. Mycophenolate, clinical pharmacokinetics, formulations and methods for assessing drug exposure. *Transplantation reviews*. 2011; 25:47–57. doi:10.1016. [PubMed: 21190834]
 13. van Hest RM, Mathot RA, Pescovitz MD, Gordon R, Mamelok RD, van Gelder T. Explaining variability in mycophenolic acid exposure to optimize mycophenolate mofetil dosing: a population pharmacokinetic meta-analysis of mycophenolic acid in renal transplant recipients. *Journal of the American Society of Nephrology : JASN*. 2006; 17(3):871–80. doi:10.1681/asn.2005101070. [PubMed: 16452491]
 14. Kuypers DRJ LY, Cantarovich M, Tredger MJ, Tett SE, Cattaneo D, Tonshoff B, Holt DW, Chapman J, van Gelder T. Consensus Report on Therapeutic Drug Monitoring of Mycophenolic Acid in Solid Organ Transplantation. *Clinical journal of the American Society of Nephrology : CJASN*. 2010; 5:341–58. doi:10.2215. [PubMed: 20056756]
 15. Shaw LM, Korecka M, Venkataramanan R, Goldberg L, Bloom R, Brayman KL. Mycophenolic acid pharmacodynamics and pharmacokinetics provide a basis for rational monitoring strategies. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2003; 3(5):534–42.
 16. Tornatore KM, Sudchada P, Dole K, DiFrancesco R, Leca N, Gundroo AC, et al. Mycophenolic acid pharmacokinetics during maintenance immunosuppression in African American and Caucasian renal transplant recipients. *Journal of clinical pharmacology*. 2011; 51(8):1213–22. doi: 10.1177/0091270010382909. [PubMed: 21209244]
 17. Tornatore KM, Sudchada P, Attwood K, Wilding GE, Gundroo AC, DiFrancesco R, et al. Race and drug formulation influence on mycophenolic acid pharmacokinetics in stable renal transplant recipients. *Journal of clinical pharmacology*. 2013; 53(3):285–93. doi: 10.1177/0091270012447814. [PubMed: 23444283]
 18. Shaw LM, Korecka M, Aradhye S, Grossman R, Bayer L, Innes C, et al. Mycophenolic acid area under the curve values in African American and Caucasian renal transplant patients are comparable. *Journal of clinical pharmacology*. 2000; 40(6):624–33. [PubMed: 10868313]

19. Pescovitz MD, Guasch A, Gaston R, Rajagopalan P, Tomlanovich S, Weinstein S, et al. Equivalent pharmacokinetics of mycophenolate mofetil in African-American and Caucasian male and female stable renal allograft recipients. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2003; 3(12):1581–6.
20. Huang SM, Temple R. Is this the drug or dose for you? Impact and consideration of ethnic factors in global drug development, regulatory review, and clinical practice. *Clinical pharmacology and therapeutics*. 2008; 84(3):287–94. doi:10.1038/clpt.2008.144. [PubMed: 18714314]
21. Chen ML. Ethnic or racial differences revisited: impact of dosage regimen and dosage form on pharmacokinetics and pharmacodynamics. *Clinical pharmacokinetics*. 2006; 45(10):957–64. doi: 10.2165/00003088-200645100-00001. [PubMed: 16984210]
22. Food and Drug Administration 21 CFR Parts 312 and 314. 1998. <http://www.gpo.gov/fdsys/pkg/FR-1998-02-11/html/98-3422.htm>
23. Coakley M, Fadiran EO, Parrish LJ, Griffith RA, Weiss E, Carter C. Dialogues on diversifying clinical trials: successful strategies for engaging women and minorities in clinical trials. *Journal of women's health (2002)*. 2012; 21(7):713–6. doi:10.1089/jwh.2012.3733.
24. Hesselink DA, van Hest RM, Mathot RA, Bonthuis F, Weimar W, de Bruin RW, et al. Cyclosporine interacts with mycophenolic acid by inhibiting the multidrug resistance-associated protein 2. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2005; 5(5):987–94. doi: 10.1046/j.1600-6143.2005.00779.x.
25. Grinyo JM, Ekberg H, Mamelok RD, Oppenheimer F, Sanchez-Plumed J, Gentil MA, et al. The pharmacokinetics of mycophenolate mofetil in renal transplant recipients receiving standard-dose or low-dose cyclosporine, low-dose tacrolimus or low-dose sirolimus: the Symphony pharmacokinetic substudy. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. 2009; 24(7):2269–76. doi:10.1093/ndt/gfp162.
26. Naesens M, Kuypers DR, Verbeke K, Vanrenterghem Y. Multidrug resistance protein 2 genetic polymorphisms influence mycophenolic acid exposure in renal allograft recipients. *Transplantation*. 2006; 82(8):1074–84. doi:10.1097/01.tp.0000235533.29300.e7. [PubMed: 17060857]
27. Zucker K TA, Olson L, Esquenazi V, Tzakis A, Miller J. Evidence that tacrolimus augments the bioavailability of mycophenolate mofetil through the inhibition of mycophenolic acid glucuronidation. *Ther Drug Monit*. 1999; 21(1):35–43. [PubMed: 10051052]
28. Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients 2010 data report. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2012; 12(Suppl 1):1–156. doi: 10.1111/j.1600-6143.2011.03886.x.
29. Meaney CJ, Arabi Z, Venuto RC, Consiglio JD, Wilding GE, Tornatore KM. Validity and reliability of a novel immunosuppressive adverse effects scoring system in renal transplant recipients. *BMC nephrology*. 2014; 15:88. doi:10.1186/1471-2369-15-88.
30. DiFrancesco R, Frerichs V, Donnelly J, Hagler C, Hochreiter J, Tornatore KM. Simultaneous determination of cortisol, dexamethasone, methylprednisolone, prednisone, prednisolone, mycophenolic acid and mycophenolic acid glucuronide in human plasma utilizing liquid chromatography-tandem mass spectrometry. *Journal of chromatography B, Analytical technologies in the biomedical and life sciences*. 2007; 859(1):42–51. doi:10.1016/j.jchromb.2007.09.003.
31. Sollinger HW, Deierhoi MH, Belzer FO, Diethelm AG, Kauffman RS. RS-61443--a phase I clinical trial and pilot rescue study. *Transplantation*. 1992; 53(2):428–32. [PubMed: 1346731]
32. Roberts MS, Magnusson BM, Burczynski FJ, Weiss M. Enterohepatic circulation: physiological, pharmacokinetic and clinical implications. *Clinical pharmacokinetics*. 2002; 41(10):751–90. doi: 10.2165/00003088-200241100-00005. [PubMed: 12162761]
33. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Annals of internal medicine*. 1999; 130(6):461–70.

34. Kuypers DR, Claes K, Evenepoel P, Maes B, Vanrenterghem Y. Clinical efficacy and toxicity profile of tacrolimus and mycophenolic acid in relation to combined long-term pharmacokinetics in de novo renal allograft recipients. *Clinical pharmacology and therapeutics*. 2004; 75(5):434–47. doi:10.1016/j.clpt.2003.12.009. [PubMed: 15116056]
35. de Jonge H, Naesens M, Kuypers DR. New insights into the pharmacokinetics and pharmacodynamics of the calcineurin inhibitors and mycophenolic acid: possible consequences for therapeutic drug monitoring in solid organ transplantation. *Therapeutic drug monitoring*. 2009; 31(4):416–35. doi:10.1097/FTD.0b013e3181aa36cd. [PubMed: 19536049]
36. Johnston A, He X, Holt DW. Bioequivalence of enteric-coated mycophenolate sodium and mycophenolate mofetil: a meta-analysis of three studies in stable renal transplant recipients. *Transplantation*. 2006; 82(11):1413–8. doi:10.1097/01.tp.0000242137.68863.89. [PubMed: 17164710]
37. Johnson HJ, Swan SK, Heim-Duthoy KL, Nicholls AJ, Tsina I, Tarnowski T. The pharmacokinetics of a single oral dose of mycophenolate mofetil in patients with varying degrees of renal function. *Clinical pharmacology and therapeutics*. 1998; 63(5):512–8. doi:10.1016/s0009-9236(98)90102-3. [PubMed: 9630824]
38. Schwartz JB. The influence of sex on pharmacokinetics. *Clinical pharmacokinetics*. 2003; 42(2): 107–21. doi:10.2165/00003088-200342020-00001. [PubMed: 12537512]
39. Mulder GJ. Sex differences in drug conjugation and their consequences for drug toxicity. Sulfation, glucuronidation and glutathione conjugation. *Chemico-biological interactions*. 1986; 57(1):1–15. [PubMed: 3081267]
40. Morissette P, Albert C, Busque S, St-Louis G, Vinet B. In vivo higher glucuronidation of mycophenolic acid in male than in female recipients of a cadaveric kidney allograft and under immunosuppressive therapy with mycophenolate mofetil. *Therapeutic drug monitoring*. 2001; 23(5):520–5. [PubMed: 11591897]
41. Staatz CE, Duffull SB, Kiberd B, Fraser AD, Tett SE. Population pharmacokinetics of mycophenolic acid during the first week after renal transplantation. *European journal of clinical pharmacology*. 2005; 61(7):507–16. doi:10.1007/s00228-005-0927-4. [PubMed: 16049701]
42. Le Guellec C, Bourgoin H, Buchler M, Le Meur Y, Lebranchu Y, Marquet P, et al. Population pharmacokinetics and Bayesian estimation of mycophenolic acid concentrations in stable renal transplant patients. *Clinical pharmacokinetics*. 2004; 43(4):253–66. doi: 10.2165/00003088-200443040-00004. [PubMed: 15005639]
43. Kobayashi M, Saitoh H, Tadano K, Takahashi Y, Hirano T. Cyclosporin A, but not tacrolimus, inhibits the biliary excretion of mycophenolic acid glucuronide possibly mediated by multidrug resistance-associated protein 2 in rats. *The Journal of pharmacology and experimental therapeutics*. 2004; 309(3):1029–35. doi:10.1124/jpet.103.063073. [PubMed: 14978191]
44. Cattaneo D, Merlini S, Zenoni S, Baldelli S, Gotti E, Remuzzi G, et al. Influence of co-medication with sirolimus or cyclosporine on mycophenolic acid pharmacokinetics in kidney transplantation. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2005; 5(12):2937–44. doi:10.1111/j.1600-6143.2005.01107.x.
45. Hohage H, Zeh M, Heck M, Gerhardt UW, Welling U, Suwelack BM. Differential effects of cyclosporine and tacrolimus on mycophenolate pharmacokinetics in patients with impaired kidney function. *Transplantation proceedings*. 2005; 37(4):1748–50. doi:10.1016/j.transproceed.2005.03.078. [PubMed: 15919453]
46. Hesselink DA, van Gelder T. Genetic and nongenetic determinants of between-patient variability in the pharmacokinetics of mycophenolic acid. *Clinical pharmacology and therapeutics*. 2005; 78(4):317–21. doi:10.1016/j.clpt.2005.06.008. [PubMed: 16198650]
47. Hoffmann U, Kroemer HK. The ABC transporters MDR1 and MRP2: multiple functions in disposition of xenobiotics and drug resistance. *Drug metabolism reviews*. 2004; 36(3-4):669–701. doi:10.1081/dmr-200033473. [PubMed: 15554242]
48. van Gelder T, Klupp J, Barten MJ, Christians U, Morris RE. Comparison of the effects of tacrolimus and cyclosporine on the pharmacokinetics of mycophenolic acid. *Therapeutic drug monitoring*. 2001; 23(2):119–28. [PubMed: 11294511]

49. Sherwin CM, Fukuda T, Brunner HI, Goebel J, Vinks AA. The evolution of population pharmacokinetic models to describe the enterohepatic recycling of mycophenolic acid in solid organ transplantation and autoimmune disease. *Clinical pharmacokinetics*. 2011; 50(1):1–24. doi: 10.2165/11536640-000000000-00000. [PubMed: 21142265]
50. Ekberg H, Tedesco-Silva H, Demirbas A, Vitko S, Nashan B, Gurkan A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. *The New England journal of medicine*. 2007; 357(25):2562–75. doi:10.1056/NEJMoa067411. [PubMed: 18094377]
51. Le Meur Y, Buchler M, Thierry A, Caillard S, Villemain F, Lavaud S, et al. Individualized mycophenolate mofetil dosing based on drug exposure significantly improves patient outcomes after renal transplantation. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2007; 7(11):2496–503. doi:10.1111/j.1600-6143.2007.01983.x.
52. Gaston RS, Kaplan B, Shah T, Cibrik D, Shaw LM, Angelis M, et al. Fixed- or controlled-dose mycophenolate mofetil with standard- or reduced-dose calcineurin inhibitors: the Opticcept trial. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2009; 9(7):1607–19. doi:10.1111/j.1600-6143.2009.02668.x.
53. van Gelder T, Silva HT, de Fijter JW, Budde K, Kuypers D, Tyden G, et al. Comparing mycophenolate mofetil regimens for de novo renal transplant recipients: the fixed-dose concentration-controlled trial. *Transplantation*. 2008; 86(8):1043–51. doi:10.1097/TP.0b013e318186f98a. [PubMed: 18946341]
54. Bunnapradist S, Ambuhl PM. Impact of gastrointestinal-related side effects on mycophenolate mofetil dosing and potential therapeutic strategies. *Clinical transplantation*. 2008; 22(6):815–21. doi:10.1111/j.1399-0012.2008.00892.x. [PubMed: 18798850]
55. Arns W. Noninfectious gastrointestinal (GI) complications of mycophenolic acid therapy: a consequence of local GI toxicity? *Transplantation proceedings*. 2007; 39(1):88–93. doi:10.1016/j.transproceed.2006.10.189. [PubMed: 17275481]
56. Franconi F CI, Occhioni S, Antonini P, Murphy MF. Sex and gender in adverse drug events, addiction, and placebo. *Handb. Exp. Pharmacol.* 2012:107–26. [PubMed: 23027448]
57. Drug Safety: Most Drugs Withdrawn in Recent Years Had Greater Health Risks for Women. U.S. Government Accountability Office; 2001. <http://www.gao.gov/assets/100/90642.pdf>

Key Findings

- This is the first report of sex and race differences in mycophenolic acid (MPA) and glucuronide metabolite, MPAG pharmacokinetics in stable African American (AA) and Caucasian renal transplant recipients receiving enteric coated mycophenolate sodium (ECMPS) and tacrolimus as maintenance immunosuppression.
- Sex and race differences in MPA and MPAG pharmacokinetics with gastrointestinal adverse effects were evident with females having slower apparent MPA clearance, body mass index normalized clearance, higher MPAG AUC₀₋₁₂ and more gastrointestinal adverse effects.
- These findings may have important clinical implications for ECMPS dose adjustments between sex and race, when converting between MPA formulations, and the potential role of therapeutic drug monitoring.

a. Caucasian females **b. African-American females** **c. Caucasian males** **d. African-American males**

Figures 1. Mean Mycophenolic Acid and Mycophenolic Acid Glucuronide Concentration vs. Time Profiles for each Race-Sex Groups

Panel A: Caucasian Females (n=16); Panel B: African-American Females (n=13); Panel C: Caucasian Males (n=16); Panel D: African-American Males (n=22). Note the delayed time to MPA peak (closed circles) concentration. A second MPA peak occurs between 6 to 12 hours representing enterohepatic circulation which is most pronounced in Caucasian females. Mean MPAG concentrations (open squares) are approximately 10 fold greater than MPA with sustained concentrations over the dosing interval. Upper error bars represent standard deviation. MPA=Mycophenolic acid; MPAG=Mycophenolic acid glucuronide .

Figure 2. Mean Mycophenolic Acid Concentration versus Time profiles for Renal Transplant Recipients with Enterohepatic Circulation

Enterohepatic circulation occurred in 12 (75.0%) Caucasian females (Panel A); 8 (61.5%) African-American females (Panel B); 13 (81.3%) Caucasian males (Panel C), and 19 (86.4%) African-American males (Panel D). Note the second peak occurs between 6 to 12 hours in each group. For the overall group, 78% (52 patients) exhibited enterohepatic circulation compared to 15 patients (8 African Americans; 7 Caucasians) with no recycling. Upper error bars represent standard deviation. MPA=Mycophenolic acid.

Figure 3. This graph represents MPA AUC₀₋₁₂ for each patient group

There were 57% of patients with MPA AUC₀₋₁₂ exceeding 60 mg • h/L. MPA Clearance was lowest (8.13 ± 2.79 L/h) for patients with AUC₀₋₁₂ >60 mg • h/L compared to patients in the therapeutic range (12.9 ± 4.04 L/h) and <30 mg • h/L (17.6 ± 5.92 mg • h/L; $p < 0.0001$).

NOTE: The dotted lines denote the therapeutic range for MPA AUC of 30-60 mg • h/L refers to the MMF formulation when administered with cyclosporine as defined by consensus guidelines (13, 31). The solid line represents the respective group mean.

AA=African American, AE=Adverse effect, AUC=Area under the concentration vs. time curve, C=Caucasian, F= Female; GI=Gastrointestinal, M=Male; MPA=Mycophenolic acid.

Table 1

The Gastrointestinal Adverse Effects Rating Completed for all Renal Transplant Recipients.

Vomiting	0:	None
	1+:	Minimal vomiting
	2+:	Excessive vomiting requiring symptomatic treatment.
Diarrhea	0:	None
	+1:	One loose bowel movement per day
	+2:	Two to five loose bowel movements per day
Dyspepsia	0:	None
	1+:	Episode of indigestion within one hour after taking immunosuppressive medication
	2+:	Indigestion for at least half the day
	3+:	Indigestion the majority of the day requiring symptomatic treatment
Use of Proton Pump Inhibitor/Histamine-2 Receptor Antagonist	0:	None
	1+:	Daily use of either Proton Pump Inhibitor/Histamine-2 Receptor Antagonist
	2+:	Daily use of both Proton Pump Inhibitor/Histamine-2 Receptor Antagonist

This table provides the validated standardized rating scale utilized by clinicians for assessment of gastrointestinal adverse effects in each renal transplant recipient. For each patient, the score for each adverse effect that quantitates the severity was used to generate a total gastrointestinal adverse effect score [29].

Table 2

Demographic and Laboratory Parameters for Race and Sex Groups

Demographic Parameter	Females ^a		Males ^a		Overall P values for Main Effects			Pairwise Comparison P Values ^b
	African American (n=13)	Caucasian (n=16)	African American (n=22)	Caucasian (n= 16)	Sex	Race	Sex × Race Interaction	
Age (years)	47.9 (9.88)	50.4 (13.6)	47.5 (12.1)	50.4 (10.3)	0.942	0.363	0.942	None
Time Post Transplant (years)	2.98 (2.2)	3.06 (2.89)	2.56 (1.65)	3.59 (3.39)	0.935	0.388	0.455	None
Total Weight (kg)	87.9 (24.2)	73.1 (16.0)	91.6(17.9)	94.8 (17.6)	0.008	0.221	0.058	C-M vs. C-F: 0.009 AA-M vs. C-F: 0.020
Lean Body Weight (kg)	49.5 (6.33)	46.6 (3.91)	64.7(7.37)	66.8 (8.46)	0.001	0.818	0.142	AA-F vs. C-M: <0.001 AA-F vs. AA-M: <0.001 C-M vs. C-F: <0.001 AA-M vs. C-F: <0.001
BMI (kg/m ²)	32.5 (7.87)	28.1 (6.00)	30.0 (5.79)	30.3 (4.19)	0.936	0.174	0.121	None
Albumin (g/dL)	4.02 (0.34)	4.04 (0.28)	4.24 (0.24)	4.17 (0.29)	0.017	0.705	0.556	None
Adjusted eGFR ^c (ml/min)	49.9 (17.7)	49.8 (11.5)	55.5 (14.5)	64.5 (16.2)	0.008	0.243	0.227	AA-F vs. C-M: 0.054 C-M vs. C-F: 0.035
Serum Creatinine (mg/dL)	1.52 (0.54)	1.22 (0.28)	1.72 (0.47)	1.26 (0.29)	0.223	<0.001	0.425	AA-M vs. C-M: 0.006 AA-M vs. C-F: 0.002
WBC (cells/mm ³)	5.64 (2.10)	4.93 (1.49)	4.84 (1.35)	5.93 (2.62)	0.830	0.688	0.060	None
Hemoglobin (g/dL)	11.2 (0.884)	11.6 (0.842)	12.6 (1.17)	13.4 (1.37)	<0.001	0.031	0.516	AA-F vs. AA-M: 0.002 AA-F vs. C-M: <0.001 C-M vs. C-F: <0.001 AA-M vs. C-F: 0.031
MPA Dose (mg/ 12 hour)	637 (158)	563 (159)	638 (213)	664 (108)	0.229	0.564	0.240	None
Tacrolimus C _{trough} (ng/mL)	7.12 (1.91)	7.13 (1.86)	7.52 (2.26)	6.89 (1.42)	0.866	0.519	0.508	None

AA: African Americans; AUC: Area under the concentration vs. time curve; BMI: Body mass index; C: Caucasian; C_{trough} trough concentration; eGFR Estimated Glomerular Filtration rate; F: Females; M: Males; MPA: Mycophenolic acid; WBC: White blood cells

^aValues are expressed as mean (SD)

^bPairwise Comparisons completed using Tukey- Kramer adjustment for multiple comparisons

^cAdjusted Estimated Glomerular Filtration Rate(ml/min) was determined by clinical laboratory using the MDRD definition [33].

Table 3

MPA and MPAG Pharmacokinetic parameters by Race and Sex

Pharmacokinetic Parameter	Females ^a		Males ^a		Overall P Values for Main Effects			Pairwise Comparison p-values ^a
	African American (n=13)	Caucasian (n=16)	African American (n=22)	Caucasian (n=16)	Sex	Race	Sex × Race Interaction	
MPA AUC ₀₋₁₂ (mg·h/L)	75.3 (31.2)	71.7 (32.1)	70.2 (32.2)	59.0 (28.1)	0.253	0.343 ⁺	0.621 ⁺	None
MPA AUC* (mg·h/L)/mg	0.122 (0.057)	0.132 (0.051)	0.113 (0.046)	0.089 (0.039)	0.033	0.534	0.154	C-M vs. C-F : 0.063
MPA CL _{ss} (L/hr)	9.71 (3.94)	8.70 (3.33)	10.2 (3.73)	13.8 (6.27)	0.014	0.256	0.043*	AA-F vs. C-M: 0.077 AA-M vs. C-M: 0.082 C-M vs. C-F: 0.010
BMI-adjusted MPA CL _{ss} (L/h)/(kg/m ²)	0.309 (0.141)	0.322 (0.146)	0.338 (0.098)	0.467 (0.238)	0.033	0.080	0.149	AA-F vs. C-M: 0.051 AA-M vs. C-M: 0.078 C-M vs. C-F: 0.061
MPA C _{12h} (mg/L)	4.06 (2.22)	3.60 (2.06)	4.04 (2.01)	3.03 (1.83)	0.556	0.147	0.589	None
MPA C _{max} (mg/L)	20.4 (9.89)	22.8 (11.4)	17.9 (8.17)	21.9 (14.2)	0.534	0.244	0.767	None
MPA t _{max} (hr)	3.66 (2.95)	2.76 (2.23)	3.20 (2.38)	2.43 (1.49)	0.492	0.149	0.906	None
MPAG AUC ₀₋₁₂ (mg·h/L)	1221 (650)	944 (453)	852 (353)	682 (293)	0.005	0.044	0.621	AA-F vs. C-M : 0.008 AA-F vs. AA-M: 0.085
MPAG C _{12h} (mg/L)	86.2 (50.1)	66.0 (40.2)	59.8 (31.3)	47.1 (21.6)	0.014	0.071	0.678	AA-F vs. C-M : 0.026
MPAG C _{max} (mg/L)	138 (70.7)	116 (49.7)	108 (52.7)	81.7 (36.0)	0.017	0.071	0.893	AA-F vs. C-M: 0.028
MPAG t _{max} (h)	4.32 (2.64)	3.16 (2.22)	3.64 (1.39)	4.23 (2.17)	0.705	0.575	0.093	None
MPAG AUC ^c MPA AUC	17.2 (8.33)	13.5 (5.23)	13.5 (5.57)	12.9 (5.25)	0.031	0.053	0.268	CM vs. AAF: 0.046 AAM vs. AAF: 0.090

^b Mean(SD): Mean(Standard Deviation)AA: African Americans; AUC: Area under the concentration vs. time curve; AUC*: AUC/dose; AUC₀₋₁₂ AUC from time zero to 12 hours; BMI: Body mass index; C: Caucasian; C_{trough}: trough concentration (at 12 hours); C_{max}: Maximum concentration; CL_{ss}: steady state clearance; F: Females; M: Males; MPA: Mycophenolic acid; MPAG: Mycophenolic acid glucuronide; t_{max}: Time to C_{max}^a Pairwise Comparisons completed using Tukey–Kramer adjustment for multiple comparisons^c Sex was significant in statistical analysis during covariate analysis with hemoglobin.

Table 4

Gastrointestinal Adverse Effects [n (%)] by Race and Sex [29]

Adverse Effect	Females		Males		p-Value ^a	
	African American (n=13)	Caucasian (n=16)	African American (n=22)	Caucasian (n=16)	Sex	Race
Vomiting	1 (7.69)	3 (18.8)	3 (13.6)	0 (0.0)	0.415	0.704)
Diarrhea	4 (30.8)	8 (50.0)	6 (27.3)	5 (31.3)	0.533	(0.526)
Dyspepsia	11 (84.6)	9 (56.3)	11 (50.0)	11 (68.8)	0.349	(0.879)
Proton Pump Inhibitor Treatment	6 (46.2)	3 (18.8)	5 (22.7)	5 (31.3)	0.613	(0.520)
Histamine-2 Receptor Antagonist treatment	7 (53.9)	5 (31.3)	7 (31.8)	5 (31.3)	0.350	(0.388)
Total GI Adverse Effect Score ^b Mean (SD)	3.23 (1.42)	2.86 (2.48)	2.00 (1.60)	2.38 (1.46)	0.024	(0.999)

Table 1 outlines the specific criteria used for objective GI adverse effect assessment.

Values are expressed as n (%) unless specified otherwise.

GI: Gastrointestinal

^a P-value generated from logistic regression model

^b Sex is significant during covariate analysis with estimated glomerular filtration rate. See Statistical Analysis.