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Influence of Calcineurin Inhibitor and Sex on Mycophenolic Acid Pharmacokinetics and Adverse Effects Post-renal Transplant

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Abstract

Tacrolimus or cyclosporine is prescribed with mycophenolic acid posttransplant and contributes to interpatient variability in mycophenolic acid pharmacokinetics and response. Cyclosporine inhibits enterohepatic circulation of the metabolite mycophenolic acid glucuronide, which is not described with tacrolimus. This study investigated mycophenolic acid pharmacokinetics and adverse effects in stable renal transplant recipients and the association with calcineurin inhibitors, sex, and race. Mycophenolic acid and mycophenolic acid glucuronide area under the concentration-time curve from 0 to 12 hours (AUC_{0-12h}) and apparent clearance were determined at steady state in 80 patients receiving cyclosporine with mycophenolate mofetil and 67 patients receiving tacrolimus with mycophenolate sodium. Gastrointestinal adverse effects and hematologic parameters were evaluated. Statistical models evaluated mycophenolic acid pharmacokinetics and adverse effects. Mycophenolic acid AUC_{0-12h} was 1.70-fold greater with tacrolimus (68.9 ± 30.9 mg·h/L) relative to cyclosporine (40.8 ± 17.6 mg·h/L); $P < .001$. Target mycophenolic acid AUC_{0-12h} of 30–60 mg·h/L was achieved in 56.3% on cyclosporine compared with 34.3% receiving tacrolimus ($P < .001$). Mycophenolic acid clearance was 48% slower with tacrolimus (10.6 ± 4.7 L/h) relative to cyclosporine (20.5 ± 10.0 L/h); $P < .001$. Enterohepatic circulation occurred less frequently with cyclosporine (45%) compared with tacrolimus (78%); $P < 0.001$; with a 2.9-fold greater

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Declaration of Conflicting Interests

The authors have no conflicts of interest or financial relationships to disclose during the time this study was ongoing.

Data Accessibility Statement

Data will not be able to be shared.

mycophenolic acid glucuronide AUC_{0-12h} to mycophenolic acid AUC_{0-12h} ratio ($P < .001$). Race did not affect mycophenolic acid pharmacokinetics. Gastrointestinal adverse effect scores were 2.2-fold higher with tacrolimus ($P < .001$) and more prominent in women ($P = .017$). Lymphopenia was more prevalent with tacrolimus (52.2%) than cyclosporine (22.5%); $P < 0.001$. Calcineurin inhibitors and sex contributed to interpatient variability in mycophenolic acid pharmacokinetics and adverse effects post-renal transplant, which could be attributed to differences in enterohepatic circulation.

Keywords

calcineurin inhibitor; enterohepatic circulation; mycophenolic acid; pharmacokinetics

Mycophenolic acid is the active immunosuppressive moiety in mycophenolate mofetil and enteric-coated mycophenolate sodium.^{1,2} Although the 2 formulations have similar efficacy, it is proposed that enteric-coated mycophenolate sodium has fewer gastrointestinal adverse effects than mycophenolate mofetil.²⁻⁵ Mycophenolic acid is commonly prescribed with tacrolimus or cyclosporine as maintenance immunosuppression post-renal transplant.^{6,7} The disposition of mycophenolic acid is complex, with significant intra- and interpatient pharmacokinetic variability.^{1,2,8} Mycophenolic acid pharmacokinetic variability is influenced by concurrent medications, sex, race, genetics, glomerular filtration rate, renal allograft function, time posttransplant, and gastrointestinal disease.^{1,2}

One major source of pharmacokinetic variability is the drug-drug interaction between calcineurin inhibitors and mycophenolic acid.² Cyclosporine interferes with the enterohepatic circulation of the inactive metabolite, mycophenolic acid glucuronide, through inhibition of hepatobiliary transporters such as multidrug resistance protein 2 and prevents deglucuronidation to the active moiety, mycophenolic acid.^{1,2} This inhibition eliminates the secondary mycophenolic acid peak between 6 and 12 hours postdose, with a reduction in the area under the concentration-time curve from 0 to 12 hours (AUC_{0-12h}).⁸⁻¹² Tacrolimus does not interfere with enterohepatic circulation, and a second peak is evident, causing an increase in overall mycophenolic acid exposure.^{13,14} Tacrolimus has no apparent drug-drug interaction with mycophenolic acid in healthy subjects or renal transplant recipients.^{15,16} Enterohepatic circulation is important to characterize because this process contributes 10%–60% to the mycophenolic acid AUC_{0-12h} .^{1,2} Interestingly, dosing recommendations for mycophenolate mofetil or enteric-coated mycophenolate sodium do not provide suggested adjustments based on the concurrent calcineurin inhibitor.^{9-12,17-19} There are conflicting data comparing mycophenolic acid pharmacokinetics when coadministered with tacrolimus or cyclosporine using different protocols.¹⁹⁻²¹ With the increased prescribing of minimization protocols for calcineurin inhibitors, investigation into mycophenolic acid pharmacokinetics with concurrent tacrolimus or cyclosporine in stable recipients is a clinical necessity to document adequate drug exposure.^{7,22-24}

Sex and race contribute to the interpatient variability of mycophenolic acid pharmacokinetics. African American recipients exhibit faster clearances, and females have slower clearances.^{13,14,25} To avoid health disparities in disease outcomes, the United States

Food and Drug Administration recommends pharmacologic evaluation of approved and new drugs in sex and race subpopulations.^{26–29} However, mycophenolic acid pharmacokinetics and adverse effects have not been examined comparing concurrent calcineurin inhibitors relative to sex and race.^{13,14,30}

Unpredictable manifestations of gastrointestinal and hematologic adverse effects further complicate clinical use of mycophenolic acid posttransplant.^{1,2} A target mycophenolic acid AUC_{0–12h} of 30 to 60 mg·h/L has been suggested in consensus reports to optimize efficacy.^{8,22–24,31,32} Mycophenolic acid exposure and adverse effect manifestations are not consistently correlated.^{1,2,33} The minimization of mycophenolic acid adverse effects remains an important clinical dilemma. These adverse drug manifestations have been associated with medication nonadherence and increased risk of posttransplant infections and may result in multiple dose adjustments that can complicate allograft survival.^{34–38} Therefore, it is critical to evaluate mycophenolic acid adverse effects using an integrated systematic approach concurrent with mycophenolic acid pharmacokinetics in transplant subpopulations.

The primary objective of this study was to investigate the influence of concurrent calcineurin inhibitor (ie, tacrolimus or cyclosporine), race, and sex on steady-state mycophenolic acid and mycophenolic acid glucuronide pharmacokinetics in stable renal transplant recipients receiving long-term maintenance immunosuppression. The secondary objective was to evaluate these factors in relation to gastrointestinal adverse effects and hematologic parameters in this patient population.

Methods

Study Population

The study was approved by the University at Buffalo institutional review board. Each patient provided written informed consent prior to participation. All research activities adhered to the principles of the Declaration of Helsinki and the United States Federal Policy for the Protection of Human Subjects. The clinical research reported was consistent with the Principles of the Declaration of Istanbul, as outlined in the *Declaration of Istanbul on Organ Trafficking and Transplant Tourism*. The study site was the Nephrology Division at the University at Buffalo and Erie County Medical Center in Buffalo, New York.

This study pooled data from three 12-hour pharmacokinetic studies conducted by the same principal investigator and physician coinvestigator.^{13,14,30} All studies used the same study design, patient inclusion/exclusion criteria, screening and enrollment processes, study procedures, adverse effects scoring, analytical drug assays, and clinical research site. Comparable quality control outcomes were reported in all studies for drug assays and adverse drug effect assessments as described below and previously published.^{13,14,30,39–41} Renal transplant recipients from the University at Buffalo Renal Transplant Clinic only were enrolled in prospective cross-sectional clinical pharmacology studies after a collaborating nephrologist confirmed the clinical stability of each patient after inclusion and exclusion criteria had been confirmed (see below). Each study evaluated the 12-hour pharmacokinetics of mycophenolic acid with standardized adverse effect evaluation.⁴¹ In all studies, a small group of collaborating nephrologists received pretraining and evaluation to verify consistent

patient assessment and adverse effect rating techniques compared with the primary rating physician with quality control outcomes maintained. All patients receiving maintenance calcineurin inhibitor and mycophenolic acid immunosuppression for greater than 3 months and receiving steady-state dosing regimens were enrolled using standardized eligibility criteria to verify clinical stability. Ethnicity for 2 previous generations was verified. For all patients, the inclusion criteria were: (1) age 25–70 years, (2) minimum 6 months post-renal transplantation, (3) immunosuppressive regimen of either cyclosporine with mycophenolate mofetil or tacrolimus with enteric-coated mycophenolate sodium for greater than 3 months, (4) no change in immunosuppressive doses for more than 7 days prior to study, and (5) stable serum creatinine with changes no greater than 0.25 mg/dL in the 2 prior clinic visits, (6) leukocyte count no less than 3000 cells/mm³ and hematocrit no less than 30% for 4 weeks prior to the study. Exclusion criteria were: (1) serum creatinine > 3.5 mg/dL; (2) active infection or acute rejection within 2 weeks; (3) significant diseases limiting participation including gastrointestinal, cardiovascular, hematologic, psychiatric, neurologic, or oncologic disease; (4) medication nonadherence; (5) drugs, herbal supplements, or drinks (eg, grapefruit juice) that are cytochrome P450 3A or P-glycoprotein inhibitors or inducers within 4 weeks; and (6) drugs that interfere with absorption of calcineurin inhibitor or mycophenolic acid. Physical exams including comprehensive metabolic panels and complete blood counts were completed after enrollment and repeated after overnight fast on the study morning. Medication history and adherence assessment were performed on enrollment and 7 days prior to the study. Routine therapeutic drug monitoring for calcineurin inhibitors was ongoing. Targeted trough concentrations were 5–10 ng/mL for tacrolimus and 90–150 ng/mL for cyclosporine. Mycophenolic acid dosing adjustments were based on clinical response, concurrent calcineurin inhibitor, and adverse effects without therapeutic drug monitoring. Estimated glomerular filtration rate was reported by the Clinical Laboratory Improvement Amendments-certified Erie County Medical Center clinical laboratory using the 4-factor Modification of Diet in Renal Disease equation.⁴²

Study Procedure

All patients were studied in steady-state conditions and received the same dose of brand-name immunosuppressive drugs for at least 7 days prior to the study. Patients were stabilized on either tacrolimus and enteric-coated mycophenolate sodium or cyclosporine with mycophenolate mofetil. Proton pump inhibitors, histamine₂ receptor antagonists, and antacids were discontinued at least 36 hours preceding the study. Patients took the immunosuppressive medications between 5:30 and 6:30 PM and had their evening meal at 8:00 to 8:30 PM on the evening preceding the study. Patients fasted and abstained from caffeine and alcohol for 12 hours prior to the study. At 6:00 AM on the study morning, patients were admitted to the research unit with vital signs documented and placement of an intravenous angiocatheter. The 0-hour samples (~15 mL) were collected prior to mycophenolic acid and calcineurin inhibitor administration to determine immunosuppressive trough concentrations, comprehensive metabolic profile, and complete blood count. After 0-hour blood collection at approximately 7 AM, the doses of tacrolimus (as Prograf; Astellas) and enteric-coated mycophenolate sodium (as Myfortic; Novartis) or cyclosporine (as Neoral; Novartis) with mycophenolate mofetil (as Cell-Sept; Roche) were administered orally from a single lot of each immunosuppressive. Patients remained in an upright position

throughout the study. Standardized low-fat and low-sodium meals were provided after the first 4 hours and consistently timed over the course of the study. Antihypertensive drugs were administered after 1.5 hours, whereas insulin, antilipidemic, and other medications were administered 4 hours after the immunosuppressives.

All blood samples collected from patients were immediately placed on ice and harvested within 60 minutes and then stored at -70°C until assayed as separate aliquots.³⁹ The intermediate sampling strategy included specimens collected at time 0 and at 2, 4, 7, 9, and 12 hours for 53 patients receiving a cyclosporine and mycophenolate mofetil regimen.¹⁴ Intensive sampling was employed including time 0 and every 30 minutes until 4 hours followed by 2-hour collections for the remaining 12 hours in 67 patients receiving tacrolimus and enteric-coated mycophenolate sodium and 27 patients treated with cyclosporine and mycophenolate mofetil.^{13,14,30,39} Clinical laboratory tests and tacrolimus or cyclosporine troughs were collected at time 0 and analyzed in the Clinical Laboratory Improvement Amendments-certified Clinical Laboratory at the Erie County Medical Center.

Adverse Effect Evaluation

Trained nephrologists used validated criteria to evaluate gastrointestinal adverse effects associated with mycophenolic acid therapy (Table 1) in each patient.⁴⁰ Significant gastrointestinal disease was excluded prior to patient enrollment. Patients received a ranked score for each gastrointestinal adverse effect during the physical examination (Table 1).⁴¹ To compare severity, a composite gastrointestinal adverse effect score was then determined as the sum of the rating for each individual adverse effect, with a minimum possible score of zero and a maximum score of 9. Individual gastrointestinal adverse effects were also reported as present or absent.

Hematologic status including hematocrit and hemoglobin with total leukocyte, neutrophil, lymphocyte, and platelet counts was determined in each patient using the 0-timed blood collection for the study day and evaluated on the basis of standard clinical laboratory ranges for the institution. Further evaluation of these hematologic tests and their relation to the immunosuppressive regimen was conducted using a subanalysis described in the Statistical Analysis section.

Drug Assay Methodology

A liquid chromatography/mass spectrometry assay was used for the simultaneous analysis of plasma mycophenolic acid and mycophenolic acid glucuronide, with 5,5-diphenylhydantoin and flumethasone, respectively, as internal standards.³⁹ Assay methodology and sample preparation adhered to previously validated procedures and included plasma acidification during sample preparation.³⁹ Standard curve concentrations ranged from 0.145 to 15.5 $\mu\text{g/mL}$ for mycophenolic acid and from 22.1 to 295.2 $\mu\text{g/mL}$ for mycophenolic acid glucuronide. The lowest limit of quantitation was 0.072 $\mu\text{g/mL}$ for mycophenolic acid and 11.1 $\mu\text{g/mL}$ for mycophenolic acid glucuronide. The relative standard deviation for intraday variation for mycophenolic acid ranged from 0.76% to 3.99% and for mycophenolic acid glucuronide ranged from 2.11% to 9.57%. The relative standard deviation of interday

variation for mycophenolic acid ranged from 2.3% to 6.36% and for mycophenolic acid glucuronide from 3.8% to 8.14%.

Cyclosporine whole-blood trough concentrations at time 0 hour ($C_{p[0h]}$) were determined using a TLX-2 high-turbulence liquid chromatography 2 channel system (Franklin, Massachusetts) with detection by mass spectrometry (Sciex API 3000) using the internal standard, cyclosporine D.⁴³ The cyclosporine whole-blood standard curve ranged from 11.6 to 1823 ng/mL. The relative standard deviation for cyclosporine low-, medium-, and high-quality controls for interday variation ranged from 2.47% to 5.63%, with intraday variation ranging from 1.70% to 4.11%. Tacrolimus whole-blood trough concentration $C_{p(0h)}$ was analyzed using the Architect (Abbott, Abbott Park, Illinois) assay, a chemiluminescent microparticle immunoassay with a standard curve ranging from 1 to 30 ng/mL. The lower limit of detection was 1.5 ng/mL. The intraday assay variability was less than 7%, and the interday coefficient of variability for tacrolimus low- and high-quality controls was less than 5%.⁴⁴

Pharmacokinetic Analysis

Pharmacokinetic parameters for mycophenolic acid and mycophenolic acid glucuronide included area under the concentration-versus-time curve from 0 to 12 hours (AUC_{0-12h}), dose-normalized AUC_{0-12h} , 12-hour trough concentration ($C_{p[12h]}$), maximum concentration (C_{max}), and time to maximum concentration (t_{max}). The mycophenolic acid dose equivalent was used (720 mg mycophenolic acid = 720 mg enteric-coated mycophenolate sodium = 1000 mg mycophenolate mofetil). Oral apparent mycophenolic acid clearance was calculated as mycophenolic acid dose equivalent divided by AUC_{0-12h} as determined by the linear trapezoidal rule using noncompartmental pharmacokinetic methods (Phoenix WinNonlin version 6.3; Pharsight Corp., Mountain View, California). Clearance was adjusted to body mass index (BMI) to assess the impact of standardized body weights. Because patients were stabilized on different mycophenolic acid doses, AUC_{0-12h} was normalized to 1-mg mycophenolic acid dose equivalent because of drug linearity to generate the dose-normalized AUC_{0-12h} .⁴⁵ The metabolic ratio of mycophenolic acid glucuronide AUC_{0-12h} to mycophenolic acid AUC_{0-12h} was calculated. This ratio reflects the relationship between primary metabolite and active drug and as a surrogate for enterohepatic circulation.

Enterohepatic circulation was defined as: (1) appearance of a secondary peak occurring between 6 and 12 hours postdose through visual inspection of the mycophenolic acid concentration-versus-time profiles and (2) an increase in mycophenolic acid concentration greater than 25% compared with the previous point during the elimination phase.^{13,14,30,46} The mycophenolic acid AUC from 6 to 12 hours postdose (AUC_{6-12h}) was used as an estimate of enterohepatic recirculation.^{47,48} The ratio of mycophenolic acid AUC_{6-12h} to mycophenolic acid AUC_{0-12h} reflects the relative contribution of enterohepatic circulation to overall mycophenolic acid exposure.

Statistical Analysis

Continuous data were reported using means and standard deviations and categorical data using frequencies and percentages. Group differences in demographic variables by sex, race, and immunosuppressive regimen were statistically assessed with the student *t*, analysis of variance (ANOVA), chi-square, or Fisher exact tests when appropriate. Diagnostic plots were used to assess model fit and identify the need for data transformations. Statistical outliers were defined as studentized residuals outside ± 3 .

A series of general linear models containing sex, race, and calcineurin inhibitor as separate main effects plus the interaction between sex and race were used to determine the association of these predictors with mycophenolic acid pharmacokinetic and continuous adverse effect parameters. Logistic regression models using the same set of predictor variables (sex, race, calcineurin inhibitors) were used to determine associations of these predictors with categorical adverse effect parameters. Groups defined by categorical predictors were compared in a pairwise fashion, with the associated presented *P* values computed using the standard Tukey-Kramer adjustment for multiple testing. Adjusted pairwise comparisons of potential interactions included the sex-calcineurin inhibitor, sex-race, and race-sexcalcineurin inhibitor groups. Model assumptions such as normality and linearity were assessed using diagnostic plots, and data transformations were applied as necessary. For the pharmacokinetic analysis, to examine the effect of the predictors independent of confounding variables, separate models were fitted incorporating single covariates including time posttransplant, cyclosporine trough, tacrolimus trough, serum creatinine, estimated glomerular filtration rate, hemoglobin, hematocrit, albumin, presence of diabetes mellitus, and use of prednisone. For the adverse effect analysis, similar models were fitted including covariates mycophenolic acid study dose, mycophenolic acid $C_{p(12h)}$, mycophenolic acid C_{max} , mycophenolic acid AUC_{0-12h} , mycophenolic acid dose-normalized AUC_{0-12h} , mycophenolic acid clearance, mycophenolic acid glucuronide $C_{p(12h)}$, mycophenolic acid glucuronide AUC_{0-12h} , mycophenolic acid glucuronide C_{max} , mycophenolic acid glucuronide AUC_{0-12h} to mycophenolic acid AUC_{0-12h} ratio, and presence of enterohepatic circulation. 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 2 sided, with a nominal significance level of 0.05 used for hypothesis testing with SAS statistical software (version 9.3; SAS Institute, Cary, North Carolina).

Results

This study included 147 clinically stable renal transplant recipients 4.0 ± 3.2 years posttransplant. Table 2 includes the demographics and clinical characteristics of the patients receiving the 2 immunosuppressive regimens. The cyclosporine group included more men and whites, and this group received low-dose prednisone more frequently.^{14,30} There was an equal distribution of race and sex in the tacrolimus group.¹³ Albumin and liver function tests were within the normal range for all patients. Blacks had an estimated glomerular filtration rate (53.9 ± 15.5 mL/min/1.72 m²) similar to whites (50.0 ± 18.4 mL/min/1.72 m²); *P* = .172.

Table 3 provides a summary of mycophenolic acid and mycophenolic acid glucuronide pharmacokinetic parameters. The mycophenolic acid $C_{p(12h)}$ ($P < .001$), C_{max} ($P < .001$), and t_{max} ($P = .006$) were higher in patients treated with tacrolimus. Patients in the tacrolimus group received lower mycophenolic acid doses based on empiric adjustment. These patients exhibited 48% slower apparent clearance ($P < .001$) and BMI-normalized clearance ($P < .001$). Patients on the tacrolimus regimen exhibited a 1.9-fold greater dose-normalized mycophenolic acid AUC_{0-12h} ($P < .001$). Significant pairwise comparisons of immunosuppressive regimen-sex groups are shown in the footnotes of Table 3. Using the mycophenolic acid therapeutic range of AUC_{0-12h} from 30 to 60 mg·h/L established for the mycophenolate mofetil and cyclosporine regimens,²²⁻²⁴ 56.3% of patients receiving cyclosporine achieved this target compared with 34.3% of the tacrolimus group (Figure 1). In patients on cyclosporine, 30% were below the 30 mg·h/L target. In the tacrolimus-based regimen, 38 patients (56.7%), 22 blacks and 16 whites, were above the AUC_{0-12h} target of 60 mg·h/L.

Table 3 summarizes the mycophenolic acid glucuronide pharmacokinetics. Higher mycophenolic acid glucuronide $C_{p(12h)}$ ($P < .001$), C_{max} ($P < .001$), and AUC_{0-12h} ($P < .001$) were observed with cyclosporine. The ratio of mycophenolic acid glucuronide AUC_{0-12h} to mycophenolic acid AUC_{0-12h} (metabolite to active drug exposure) was 2.9-fold greater for this regimen, suggesting less metabolite conversion and reduced enterohepatic circulation. More than 75% of patients receiving tacrolimus regimen exhibited enterohepatic circulation ($P < .001$) with greater mycophenolic acid AUC_{6-12h} to mycophenolic acid AUC_{0-12h} ratio ($P = .036$) and lower metabolite-to-active drug ratio (mycophenolic acid glucuronide AUC_{0-12h} to mycophenolic acid AUC_{0-12h} ; $P < .001$).

Women exhibited greater dose-normalized AUC_{0-12h} ($P = .038$) compared with men. No sex difference was found with mycophenolic acid clearance ($P = .052$). Pair-wise differences in mycophenolic acid clearance between sex and calcineurin inhibitor were observed for men on cyclosporine compared with women receiving tacrolimus ($P = .0077$) and women on cyclosporine compared with men on tacrolimus ($P = .0012$). Women exhibited 1.37-fold higher mycophenolic acid glucuronide AUC_{0-12h} ($P = .006$) than men in the tacrolimus group. When MPA clearances were adjusted for body mass index, no significant sex differences were found. There were no significant differences between race in mycophenolic acid and mycophenolic acid glucuronide pharmacokinetics.

The statistical model incorporated demographic and laboratory covariates on an individual basis, providing insight into sources of pharmacokinetic variability in these patients. Inverse associations between estimated glomerular filtration rate and mycophenolic acid $C_{p(12h)}$ ($P < .001$), mycophenolic acid glucuronide $C_{p(12h)}$ ($P < .001$), mycophenolic acid glucuronide AUC_{0-12} ($P < .001$), mycophenolic acid glucuronide C_{max} ($P < .001$), and mycophenolic acid glucuronide AUC_{0-12h} to mycophenolic acid AUC_{0-12h} ratio ($P < .001$) were reported. These inverse associations with estimated glomerular filtration rate accounted for 7.8%–34.7% of the variability of the pharmacokinetic parameters. Cyclosporine $C_{p(0h)}$ concentration had an inverse association with mycophenolic acid $C_{p(12h)}$ ($P = .021$) and mycophenolic acid dose-normalized AUC_{0-12h} ($P = .004$). Cyclosporine $C_{p(0h)}$ also had a direct association with mycophenolic acid clearance ($P = .019$) and clearance/BMI (P

= .021), which accounted for 6.8%–10.2% of the variability. Hemoglobin demonstrated an inverse relationship with mycophenolic acid $C_{p(12h)}$ ($P < .001$) accounting for 10.5% of the variability.

Gastrointestinal adverse effects are summarized in Table 4 and graphically depicted in Figures 2 and 3. Diarrhea was most prevalent in the tacrolimus group ($P = .002$) and positively associated with mycophenolic acid study dose ($P = .007$), mycophenolic acid glucuronide $C_{p(12h)}$ ($P = .037$), and mycophenolic acid glucuronide AUC_{0-12h} ($P = .014$). The gastrointestinal adverse effect score associated with tacrolimus immunosuppression was twice the cyclosporine group ($P < .001$; Figure 2) and more pronounced among women ($P = .017$). Figure 3 depicts the relationship of gastrointestinal adverse effects with mycophenolic acid AUC_{0-12h} .

Subanalysis of hematologic parameters revealed that patients receiving tacrolimus immunosuppression exhibited reduced circulating leukocytes and lymphocytes (Figure 4A–D). These parameters remained within acceptable inclusion criteria. Leukocytes exhibited an inverse association with mycophenolic acid dose ($P = .002$) and mycophenolic acid dose-normalized AUC_{0-12h} ($P = .018$). Figure 4A–D depicts the relationship between steady-state mycophenolic acid AUC_{0-12h} , leukocytes, and lymphocytes. Lymphopenia, defined as the total lymphocyte count of less than 1000 cells/mm³, was more pronounced with the tacrolimus regimen, with notable associations with the sex-race subgroups (Figure 4C,D). Sex ($P < .0001$) and race ($P = .018$) associations were observed with hemoglobin and hematocrit. African American women receiving tacrolimus exhibited the lowest hematocrit ($34.7\% \pm 3.0\%$) and the slowest mycophenolic acid clearance (9.7 ± 3.9 L/h).

Discussion

This report describes the influence of calcineurin inhibitor therapy and sex on the interpatient variability of mycophenolic acid and mycophenolic acid glucuronide pharmacokinetics in a stable cohort of black and white male and female renal transplant recipients receiving long-term immunosuppression. This investigation provides novel insight into the interpatient variability in mycophenolic acid pharmacokinetics and the interrelationship to targeted adverse drug effects using preestablished enrollment criteria. The pharmacokinetics of mycophenolic acid and mycophenolic acid glucuronide were influenced by the concurrent calcineurin inhibitor therapy. Despite reduced mycophenolic acid dosing, recipients receiving the tacrolimus-based regimen exhibited slower apparent clearance, higher AUC_{0-12h} , and reduced AUC_{0-12h} ratio of metabolite to active drug. These findings are consistent with the mycophenolic acid pharmacokinetic substudy comparing different calcineurin inhibitor dose regimens in a smaller cohort that did not evaluate race or sex influences.^{7,21} The characterization of enterohepatic circulation provides additional novelty to this report because this parameter is rarely included in mycophenolic acid pharmacokinetic studies. Enterohepatic circulation was reduced in patients receiving concurrent cyclosporine, as documented by increased mycophenolic acid glucuronide AUC_{0-12h} , increased ratio of metabolite to active drug, and reduced dose-normalized mycophenolic acid AUC_{0-12h} . This study also identified women receiving tacrolimus-based immunosuppression as a high-risk subpopulation because they exhibited increased dose-

normalized mycophenolic acid AUC_{0-12h} and more frequent or severe gastrointestinal adverse effects. In addition, men receiving the tacrolimus regimen demonstrated more lymphopenia than women.

The overall contribution of enterohepatic circulation to interpatient variability in mycophenolic acid pharmacokinetics is primarily impacted by concurrent calcineurin inhibitor.^{17,18,21,49-52} It is hypothesized that cyclosporine contributes to lower mycophenolic acid exposure by interfering with enterohepatic circulation of mycophenolic acid glucuronide to mycophenolic acid.^{9,10,53} This occurs through inhibition of multidrug resistance protein 2 efflux transporter found in the liver, kidney, and gut epithelium apical cell membranes.^{9,10,53} The inhibition of multidrug resistance protein 2 function and reduction in enterohepatic circulation of mycophenolic acid does not consistently occur with concurrent tacrolimus therapy. The precise mechanism of the interaction between mycophenolic acid and cyclosporine has been further investigated with additional drug transporters.^{11,12} For instance, the hepatic uptake transporter family solute carrier organic anions may be inhibited by cyclosporine and contribute to alterations in the enterohepatic circulation process.¹² Our report has generated pharmacokinetic parameters that objectively document enterohepatic circulation during mycophenolic acid and calcineurin inhibitor immunosuppression in a clinically stable renal transplant cohort. Interpatient pharmacokinetic variability of mycophenolic acid exists based on the presence or absence of enterohepatic circulation. Complete inhibition was neither achieved in all patients on cyclosporine nor described in all recipients on tacrolimus (Table 3). Enterohepatic circulation can also be affected by standard or minimization dosing regimens of calcineurin inhibitors. These regimens can result in varying drug exposures and may impact the extent of inhibition in multidrug resistance protein 2 function.^{7,21-23,54,55} Notably, calcineurin inhibitor treatments and trough concentrations in our recipients were similar to the “low-dose” tacrolimus regimen and the standard cyclosporine doses evaluated in the ELITE-SYMPHONY study.^{7,21} Enterohepatic circulation was present in most patients treated with tacrolimus with mycophenolic acid AUC_{0-12h} that exceeded the upper target of 60 mg·h/L despite lower doses (Figures 2 and 3). It is important to emphasize that no therapeutic drug monitoring of mycophenolic acid troughs was conducted prior to or during these studies. Although these patients were clinically stable, the increased mycophenolic acid AUC_{0-12h} during concurrent tacrolimus treatment may contribute to overimmunosuppression and increased risks of toxicities, adverse effects, infectious complications, and costs.²²⁻²⁴ In contrast, 30% of patients on cyclosporine were below the target mycophenolic acid AUC_{0-12h} and may have had increased risks of allograft rejection. These differences in mycophenolic acid pharmacokinetics between calcineurin inhibitors emphasize the need for individualized mycophenolic acid dosing regimens and therapeutic drug monitoring throughout maintenance immunosuppression, during calcineurin inhibitor conversion, and with minimization protocols.

Sex differences in mycophenolic acid pharmacokinetics were observed including increased dose-normalized mycophenolic acid AUC_{0-12h} and mycophenolic acid glucuronide AUC_{0-12h} in women irrespective of calcineurin inhibitor. Previous studies have suggested a sex difference because of increased hepatic glucuronidation in men or altered enterohepatic circulation of mycophenolic acid.⁵⁶⁻⁵⁸ Cyclosporine-treated men exhibited 2-fold more

rapid mycophenolic acid clearance and 42% greater mycophenolic acid glucuronide exposure than women treated with tacrolimus. However, similar differences were observed for mycophenolic acid clearance and mycophenolic acid glucuronide exposure between men treated with each calcineurin inhibitor (see pairwise comparisons in Table 3). These findings suggest that the effect of coadministered calcineurin inhibitor may be more pronounced than sex differences in mycophenolic acid pharmacokinetics.

The estimated glomerular filtration rate was identified as an important covariate that contributes to mycophenolic acid pharmacokinetic variability.² There were inverse relationships between estimated glomerular filtration rate and mycophenolic acid glucuronide $C_{p(12h)}$, AUC_{0-12h} , C_{max} , and metabolite to-active drug AUC_{0-12h} ratio. As renal function declines, accumulation of uremic toxins compete with albumin-binding sites, resulting in a reduction in renal clearance of mycophenolic acid and mycophenolic acid glucuronide.^{1,2} Because of these binding changes, an increase in unbound drug and metabolite concentrations may result.⁵⁹⁻⁶¹ Our findings further substantiate these mechanisms. Although the estimated glomerular filtration rate was similar among patient groups in this study, tacrolimus-based regimens have shown improved renal function compared with cyclosporine-based regimens.⁷ This finding may also contribute to the calcineurin inhibitor-mycophenolic acid interaction as renal function declines over time. With fluctuation in renal function posttransplant, it is imperative to monitor calcineurin inhibitor and mycophenolic acid troughs during dosing adjustments to minimize variation in immunosuppression.

Gastrointestinal adverse effects are commonly associated with mycophenolate mofetil or enteric-coated mycophenolate sodium. These adverse effects complicate medication adherence and impact patient quality of life posttransplant.^{34-37,62} Our findings corroborate previously described adverse effect patterns and provide novel severity scores, indicating ~2-fold higher severity of gastrointestinal adverse effects among tacrolimus-treated patients compared with cyclosporine (Table 4).⁴¹ Possible mechanisms for gastrointestinal adverse effects include local effects of mycophenolic acid or the glucuronide metabolites produced by epithelial cell uridine 5'-diphospho-glucuronosyltransferase enzymes, the antiproliferative effect through inosine monophosphate dehydrogenase inhibition (IMPDH), and enterocyte villous atrophy.^{33,63,64} These increased gastrointestinal adverse effects observed with tacrolimus and enteric-coated mycophenolate sodium, which may result from increased enterohepatic circulation with greater mycophenolic acid and mycophenolic acid glucuronide exposure to the enterocytes, slower mycophenolic acid apparent clearance, and enhanced systemic exposure. In addition, these gastrointestinal adverse effects may represent the additive impact of tacrolimus exposure because the macrolide structure can increase gastrointestinal motility.^{65,66} The majority of patients with more severe gastrointestinal adverse effects received concurrent tacrolimus and exhibited mycophenolic acid AUC_{0-12h} greater than the upper target of 60 mg·h/L (Figure 3). These findings suggest that the mycophenolic acid pharmacologic mechanisms may be the primary contributor to these adverse effects. Prior research into mycophenolic acid-associated gastrointestinal adverse effects has focused on the acute or 1-year posttransplant period with documentation of dichotomous adverse effect assessment. For instance, the ELITE-SYMPHONY study reported more diarrhea among tacrolimus- and mycophenolic acid-treated patients (25.3%)

compared with standard (15.6%) and low-dose (13.0%) cyclosporine.⁷ Our study observed diarrhea and dyspepsia more frequently in patients on tacrolimus and enteric-coated mycophenolate sodium (34.3%) compared with cyclosporine and mycophenolate mofetil (11.3%), with a higher gastrointestinal adverse effect score. Interestingly, our findings are not consistent with the perceived gastrointestinal adverse effects benefit associated with enteric-coated mycophenolate sodium compared with mycophenolate mofetil.³ Women had higher gastrointestinal adverse effect scores, which may have been the result of higher mycophenolic acid dose-normalized AUC_{0-12h} and greater mycophenolic acid glucuronide exposure compared with men. Generally, women appeared to display more frequent and severe adverse effect manifestations than men.⁶⁷ Sex-based differences in mycophenolic acid pharmacokinetics and adverse effect manifestations may also contribute to these findings.^{13,67} Routine clinical monitoring of gastrointestinal adverse effects combined with mycophenolic acid AUC_{0-12h} may reduce empiric dose regimen adjustments that can contribute to increased risks of rejection and improve patient tolerance of immunosuppression.

Abnormal hemoglobin and leukocytes posttransplant may increase the risk of cardiac and infectious complications.^{68,69} This study excluded patients with leukocytes less than 3000 cells/mm³ and hematocrit less than 30% in order to evaluate stable recipients. Thus, severe anemia and leukopenia were not observed. However, lower numbers of leukocytes and lymphocytes were observed in patients receiving concurrent tacrolimus. This finding may be explained by higher mycophenolic acid AUC_{0-12h} with enhanced antiproliferative activity.^{2,70} Lymphopenia was observed more frequently with tacrolimus and enteric-coated mycophenolate sodium in which the majority of patients exhibited mycophenolic acid AUC_{0-12h} greater than 60 mg·h/L (Figure 4). The interaction of sex-race was associated with reduced circulating lymphocytes in black and white men on tacrolimus. This finding may be attributed to increased mycophenolic acid exposure that contributed to preferential inhibition of IMPDH type II in B and T lymphocytes, resulting in decreased cell turnover and subsequent lymphopenia.^{2,71} These data have important clinical implications because lymphopenia may increase the risk of posttransplant viral infections that contribute to the increased morbidity and reduced allograft survival.^{72,73} Despite acceptable hematologic parameters in these recipients, routine laboratory monitoring is essential to avoid precipitous lymphocyte declines during dosing modifications of tacrolimus and mycophenolic acid regimens. Increased monitoring will also aid in identification of nonimmunosuppressive drug-drug interactions that can contribute to hematologic abnormalities.

Limitations are present in this study despite comparable methodology and systematic evaluation of extrarenal adverse effects. This study included 2 different mycophenolic acid formulations with the respective calcineurin inhibitor. However, all mycophenolic acid concentrations were adjusted to the equivalent active moiety that was used to generate the respective pharmacokinetic parameters. When used at equimolar doses, mycophenolate mofetil and enteric-coated mycophenolate sodium have equivalent mycophenolic acid AUC_{0-12h} and IMPDH inhibition.^{5,74} Therefore, these formulations are considered therapeutically equivalent.^{5,74} Another study limitation was based on the skewed sex distribution within the calcineurin inhibitor groups with more men than women receiving the cyclosporine and mycophenolate mofetil regimen, resulting in a sex imbalance. Therefore,

the findings of altered mycophenolic acid pharmacokinetics and adverse effects based on sex warrant further investigation in a larger transplant population with balanced enrollment stratification by race and sex. To extend the single 12-hour “snapshot” of the pharmacokinetics of mycophenolic acid with adverse effect evaluation in stable patients on long-term treatment, observational pharmacology studies at different times posttransplant may provide insightful assessment to individualize immunosuppression based on calcineurin inhibitor therapy and sex.

These findings have important clinical implications for the optimization of long-term mycophenolic acid-based immunosuppression post-renal transplant. Therapeutic drug monitoring of mycophenolic acid using an AUC_{0-12h} method is recommended by consensus groups.²²⁻²⁴ This approach has not consistently demonstrated improved outcomes compared with fixed mycophenolic acid dosing approaches.^{8,31,32} Our findings document the interpatient variability in mycophenolic acid pharmacokinetics in stable recipients receiving long-term immunosuppression. Using these findings, clinical monitoring of mycophenolic acid exposure may ensure efficacy and minimize adverse effects during extended therapy during critical posttransplant periods such as conversion between calcineurin inhibitors, during adverse effect assessment, or evaluation of long-term medication adherence. This report presents a novel integrated clinical pharmacology investigation of the effect of calcineurin inhibitors and sex on mycophenolic acid pharmacokinetics that includes the interrelationship with selected adverse effects. Our findings may be conservative when compared with the general transplant population because clinically stable recipients were evaluated.

Conclusions

The pharmacokinetics of mycophenolic acid and mycophenolic acid glucuronide and targeted adverse effects differ between tacrolimus and cyclosporine maintenance immunosuppression in stable renal transplant recipients. Limited systematic clinical pharmacologic investigations with statistical model development and covariate evaluation have been reported during maintenance therapy. This report provides a novel “real-time” perspective in this transplant population. Increased mycophenolic acid exposure that was quantitated by AUC_{0-12h} reflecting reduced clearance was reported during concurrent tacrolimus therapy compared with cyclosporine treatment. This finding could be attributed to the presence of enterohepatic circulation in the majority of recipients compared with the cyclosporine-based regimen. Gastrointestinal adverse effects and lymphopenia were increased in patients receiving the tacrolimus regimen. Sex influences on mycophenolic acid pharmacokinetics with increased gastrointestinal and hematologic adverse drug effects were also described. The clinical implications of this report reinforce the need for therapeutic drug monitoring of mycophenolic acid and mycophenolic acid glucuronide concentrations with gastrointestinal manifestations and hematologic parameters in stable recipients receiving long-term immunosuppression to maintain efficacy and minimize adverse drug effects.

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Figure 1.

Comparison of mycophenolic acid AUC_{0-12h} according to calcineurin inhibitor treatment and sex. Patients treated with tacrolimus and enteric-coated mycophenolate sodium exhibited 1.7-fold higher mycophenolic acid AUC_{0-12h} (mean $\pm$ standard deviation, 68.9 ± 30.9 mg·h/L) compared with cyclosporine-based regimen (mean $\pm$ standard deviation, 40.8 ± 17.6 mg·h/L; $P < .001$) despite an 18% lower mycophenolic acid dose in the tacrolimus group. In the cyclosporine and mycophenolate mofetil group, 56.3% of recipients achieved the target mycophenolic acid AUC_{0-12h} range of 30–60 mg·h/L, and 31.3% of patients were below 30 mg·h/L. During tacrolimus and enteric-coated mycophenolate sodium treatment, 34.3% of patients were within the target AUC_{0-12h} range, and 56.7% of recipients were above this range. Note: The dotted horizontal lines display the target mycophenolic acid AUC_{0-12h} of 30–60 mg·h/L suggested by consensus reports.^{22–24} AUC_{0-12h}, area under the concentration-time curve from 0 to 12 hours.

Figure 2.

Comparison of mycophenolic acid AUC_{0-12h} and gastrointestinal adverse effect responses between cyclosporine (A), tacrolimus (B), and sex. (A) Nine of the 14 women (64.3%) and 36 of the 66 men (54.5%) receiving cyclosporine and mycophenolate mofetil were within the target mycophenolic acid AUC_{0-12h} range of 30–60 mg h/L. The gastrointestinal adverse effects were generally mild, with women exhibiting a mean 18% higher score than men. (B) Nineteen of the 29 women (65.5%) and 19 of the 38 men (50%) receiving tacrolimus and enteric-coated mycophenolate sodium exceeded the target mycophenolic acid AUC_{0-12h} range of 30–60 mg h/L. The gastrointestinal adverse effect score was 2.2-fold higher than the comparative group, and women exhibited a 36% higher score than men. Forty patients on tacrolimus and enteric-coated mycophenolate sodium had a gastrointestinal adverse effect score above 2, of whom 20 (50%) were female. Note: The dotted horizontal lines display the

target mycophenolic acid AUC_{0-12h} of 30–60 mg h/L suggested by consensus reports.^{22–24}
 AUC_{0-12h} , area under the concentration-time curve from 0 to 12 hours.

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Figure 3.

Mycophenolic acid AUC_{0-12h} target range stratified by immunosuppressive regimen and gastrointestinal adverse effect score. (A) Patients with no gastrointestinal adverse effects. In this group, 62.2% (23 of 37) received cyclosporine and mycophenolate mofetil, of whom 87% (20 of 23) were within or below the mycophenolic acid AUC_{0-12h} target range of 30–60 mg·h/L. No gastrointestinal adverse effects were present in 14 recipients on tacrolimus and enteric-coated mycophenolate sodium despite 78.6% (11 of 14) above the target range. (B) Patients with mild gastrointestinal adverse effects (score of 1–2). Eighty percent (52 of 65) received cyclosporine, of whom 88.5% (46 of 52) were within or below the mycophenolic acid AUC_{0-12h} target range. Twenty percent (13 of 65) received tacrolimus, of whom 53.8% (7 of 13) were within or below the target range. (C) Patients exhibiting moderate to severe gastrointestinal adverse effects (score = 3). Of these patients, 88.9% (40 of 45) received tacrolimus and enteric-coated mycophenolate sodium, of whom 50% (20 of 40) exceeded the mycophenolic acid AUC_{0-12h} target range. In all patients with gastrointestinal adverse effects present (score > 0; B and C), there was a lower score of 1.7 ± 0.8 ($n = 22$) for mycophenolic acid $AUC_{0-12h} < 30$ mg·h/L compared with 2.2 ± 1.1 for patients within the target of 30–60 mg·h/L ($n = 54$) and 3.0 ± 1.7 for patients > 60 mg h/L ($n = 34$; $P < .001$). AUC_{0-12h} , area under the concentration-time curve from 0 to 12 hours.

Figure 4.

Comparison of mycophenolic acid AUC_{0-12h} and hematologic parameters between immunosuppressive regimens and sex groups. (A, B) Based on inclusion criteria at enrollment, all patients had a leukocyte count > 3000 cells/ mm^3 , values that are compared for cyclosporine and mycophenolate mofetil (A) with tacrolimus and enteric-coated mycophenolate sodium (B) in relation to mycophenolic acid AUC_{0-12h} . These findings were within the normal range. (C, D) No difference in total lymphocyte cellular distribution was found between treatment groups. However, lymphopenia, defined as total lymphocyte count < 1000 cells/ mm^3 , was present in 52.2% of patients treated with tacrolimus-based immunosuppression (D) compared with 22.5% of recipients on cyclosporine regimen (C; $P < .001$). In the lymphopenic patients receiving a tacrolimus-based regimen (D), 62.9% (22 of 35) had a mycophenolic acid $AUC_{0-12h} > 60$ mg·h/L. A sex-race interaction ($P = .040$) was noted with lower lymphocytes in African American and white men on tacrolimus with covariates of mycophenolic acid AUC_{0-12h} ($P = .074$) and mycophenolic acid apparent clearance ($P = .045$) associated with this hematologic finding. AUC_{0-12h} , area under the concentration-time curve from 0 to 12 hours.

Table 1.
Gastrointestinal Adverse Effect Scoring System⁴⁰

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 5 loose bowel movements per day
Dyspepsia	0 None
	1+ Episode of indigestion within 1 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 antacid therapy	0 None
	1+ Daily use of either proton pump inhibitor or histamine receptor antagonist
	2+ Daily use of both proton pump inhibitor and histamine receptor antagonist
Gastrointestinal adverse effect Score	Sum of each category: _____

This table provides the validated standardized rating scale used 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 gastrointestinal adverse effect score.^{13,40}

Table 2.

Demographic and Clinical Characteristics by Immunosuppressive Regimen and Sex

Parameter ^a	Cyclosporine and Mycophenolate Mofetil (n = 80)				Tacrolimus and Enteric-Coated Mycophenolate Sodium (n = 67)	
	Male (n = 66)	Female (n = 14)	Male (n = 38)	Female (n = 29)		<i>P</i> ^{b,c}
Age (years)	52.1 ± 10.0	54.6 ± 12.0	48.7 ± 11.3	49.3 ± 11.9		.649
Race						<.001
White	36 (54.6%)	14 (100%)	16 (42.1%)	16 (55.2%)		
Black	30 (45.5%)	0 (0%)	22 (57.9%)	13 (44.8%)		
Total body weight (kg)	94.7 ± 20.2	69.0 ± 15.9	93.0 ± 17.6	79.7 ± 21.1		.097
Body mass index (kg/m ²)	30.8 ± 6.2	26.1 ± 5.4	30.2 ± 5.1	30.1 ± 7.1		.049
Time posttransplant (years)	5.0 ± 3.7	3.6 ± 2.8	3.0 ± 2.6	3.0 ± 2.6		.346
Serum creatinine (mg/dL)	1.8 ± 0.6	1.5 ± 0.5	1.5 ± 0.5	1.4 ± 0.4		.708
Estimated glomerular filtration rate (mL/min/1.73 m ²)	50.4 ± 17.9	41.2 ± 16.8	59.3 ± 15.7	49.8 ± 14.3		.976
Albumin (g/dL)	4.0 ± 0.4	3.7 ± 0.4	4.2 ± 0.3	4.0 ± 0.3		.295
Leukocytes (× 10 ³ cells/mm ³)	6.11 ± 1.87	6.23 ± 2.11	5.30 ± 2.03	5.24 ± 1.79		.880
Neutrophils (× 10 ³ cells/mm ³)	3.76 ± 1.54	4.14 ± 1.88	3.60 ± 1.74	3.38 ± 1.42		.058
Lymphocytes (× 10 ³ cells/mm ³)	1.59 ± 0.64	1.43 ± 0.60	0.97 ± 0.43	1.18 ± 0.55		.099
Platelets (× 10 ³ cells/mm ³)	226 ± 57	249 ± 94	191 ± 51	212 ± 57		.965
Hemoglobin (g/dL)	12.8 ± 1.5	12.8 ± 1.4	13.0 ± 1.3	11.4 ± 0.9		.004
Hematocrit (%)	39.0 ± 4.1	39.0 ± 3.7	39.3 ± 3.3	36.0 ± 4.1		.010
Cyclosporine study dose (mg)	120.8 ± 52.7	82.1 ± 26.7	NA	NA		NA
Cyclosporine Cp(0h) (ng/mL)	130 ± 47	127 ± 46	NA	NA		NA
Tacrolimus Cp(0h) (ng/mL)	NA	NA	7.3 ± 2.0	7.1 ± 1.9		NA
Tacrolimus study dose (mg)	NA	NA	3.1 ± 1.5	3.7 ± 2.0		NA
Prednisone use	34 (51.5%)	5 (35.7%)	5 (13.2%)	9 (31.0%)		.001
Diabetes	30 (45.5%)	3 (21.4%)	16 (42.1%)	9 (31.0%)		.298

The significant *P*-values <0.05 are expressed in bold type.

Cp(0h), trough concentration at 0 hour; NA, not applicable.

^aData presented as mean ± standard deviation or n (%).

^bContinuous data were analyzed using ANOVA between treatment-sex groups with the overall *P*-value listed.

^cCategorical data were analyzed via chi-square or Fisher's exact test as appropriate.

Table 3.

Pharmacokinetics of Mycophenolic Acid and Mycophenolic Acid Glucuronide Stratified by Calcineurin Inhibitor and Sex

Parameter ^a	Cyclosporine and Mycophenolate Mofetil			Tacrolimus and Enteric-Coated Mycophenolate Sodium		Calcineurin Inhibitor P	Sex P
	Male (n = 66)	Female (n = 14)	Male (n = 38)	Female (n = 29)			
Mycophenolic acid study dose (mg)	715 ± 219	591 ± 165	587 ± 195	546 ± 156	.001	.184	
Mycophenolic acid C _{P(12h)} (mg/L) ^b	2.1 ± 1.5	2.2 ± 1.0	3.9 ± 2.2	4.3 ± 2.3	<.001	.433	
Mycophenolic acid AUC _{0-12h} (mg·h/L)	41.0 ± 18.4	40.1 ± 13.8	65.5 ± 30.6	73.4 ± 31.2	<.001	.264	
Mycophenolic acid dose-normalized AUC _{0-12h} (mg·h/L/mg)	0.058 ± 0.032	0.066 ± 0.015	0.103 ± 0.045	0.127 ± 0.053	<.001	.038 ^c	
Mycophenolic acid apparent clearance (L/h)	21.4 ± 10.6	16.1 ± 4.64	11.7 ± 5.19	9.15 ± 3.59	<.001	.052 ^d	
Mycophenolic acid clearance/BMI (L/h/kg/m ²)	0.714 ± 0.366	0.638 ± 0.218	0.392 ± 0.180	0.316 ± 0.141	<.001	.187	
Mycophenolic acid C _{max} (mg/L)	10.3 ± 6.5	6.49 ± 2.3	19.6 ± 11.2	21.7 ± 10.6	<.001	.845	
Mycophenolic acid t _{max} (h)	1.92 ± 1.20	2.07 ± 0.11	2.88 ± 2.06	3.16 ± 2.57	.006	.229	
Mycophenolic acid AUC _{6-12h} (mg·h/L)	12.6 ± 7.40	15.4 ± 5.51	23.8 ± 13.4	29.3 ± 24.0	<.001	.112	
Mycophenolic acid AUC _{6-12h} /Mycophenolic acid AUC _{0-12h}	0.297 ± 0.098	0.390 ± 0.068	0.356 ± 0.111	0.371 ± 0.144	.036	.087	
Mycophenolic acid glucuronide C _{P(12h)} (mg/L)	96.5 ± 56.7	99.3 ± 59.8	54.5 ± 28.0	75.1 ± 45.2	<.001	.062	
Mycophenolic acid glucuronide AUC _{0-12h} (mg·h/L)	1512 ± 727	1494 ± 684	780 ± 336	1068 ± 557	<.001	.006 ^e	
Mycophenolic acid glucuronide C _{max} (mg/L)	157 ± 66.1	154 ± 65.0	96.7 ± 47.7	126 ± 60.0	<.001	.065	
Mycophenolic acid glucuronide t _{max} (h)	2.80 ± 1.55	3.10 ± 1.47	3.89 ± 1.76	3.68 ± 2.45	.007	.640	
Mycophenolic acid glucuronide AUC _{0-12h} /Mycophenolic acid AUC _{0-12h}	41.6 ± 21.7	37.1 ± 11.9	13.3 ± 5.4	15.1 ± 6.9	<.001	.835 ^f	
Enterohepatic circulation, n (%)	29 (44%)	7 (50%)	32 (84%)	20 (69%)	<.001	.204 ^g	

The significant *P*-values <0.05 are expressed in bold type.

AUC_{0-12h}, area under the concentration-time curve from 0 to 12 hours; AUC_{6-12h}, area under the concentration-time curve from 6 to 12 hours; BMI, body mass index; C_P(12h), trough concentration 12 hours postdose; C_{max}, maximum concentration; t_{max}, time to maximum concentration.

Note: No significant differences were found relative to race.

^aData displayed as mean ± standard deviation or frequency (percentage). *P*-values generated using general linear models. *P*-values for pairwise comparisons were determined using Tukey-Kramer adjustment as listed in the footnotes below.

^b Consensus reports recommend a target mycophenolic acid trough concentration of at least 1.3 mg/L for cyclosporine coadministration and 1.9 mg/L for tacrolimus coadministration with a suggested upper limit of 3.5 mg/L.^{22–24}

^c Pairwise comparisons for mycophenolic acid dose-normalized AUC — cyclosporine male versus tacrolimus male: $P < .0001$; cyclosporine female versus tacrolimus female: $P < .0001$.

^d Pairwise comparisons for mycophenolic acid clearance — cyclosporine male versus tacrolimus male: $P < .0001$; cyclosporine male versus tacrolimus female: $P = .0077$; cyclosporine female versus tacrolimus male: $P = .0012$.

^e Pairwise comparisons for mycophenolic acid glucuronide AUC — cyclosporine male versus tacrolimus male: $P < .0001$; cyclosporine male versus tacrolimus female: $P < .0001$; cyclosporine female versus tacrolimus female: $P = .0002$.

^f Pairwise comparisons for mycophenolic acid glucuronide AUC with mycophenolic acid AUC ratio — cyclosporine male versus tacrolimus male: $P < .0001$; cyclosporine male versus tacrolimus female: $P < 0.0001$; cyclosporine female versus tacrolimus female: $P < .0001$.

^g P values determined using logistic regression.

Table 4.

Gastrointestinal Adverse Effects: Associations With Sex and Calcineurin Inhibitor The significant *P*-values <0.05 are expressed in bold type.

Parameter	Cyclosporine + Mycophenolate Mofetil				Tacrolimus + Enteric-Coated Mycophenolate Sodium		Sex <i>P</i>
	Male (n = 66)	Female (n = 14)	Male (n = 38)	Female (n = 29)	Calcineurin Inhibitor <i>P</i>		
Vomiting, n (%)	2 (3.1%)	1 (7.1%)	3 (7.9%)	4 (13.8%)	.200 ^a		.412 ^a
Diarrhea, n (%)	9 (14.1%)	0 (0.00)	11 (29.0%)	12 (41.4%)	.002^a		.946 ^a
Dyspepsia, n (%)	17 (26.6%)	7 (50.0%)	22 (57.9%)	20 (69.0%)	.003^a		.045^a
Proton pump inhibitor use, n (%)	22 (33.3%)	5 (35.7%)	10 (26.3%)	9 (31.0%)	.304 ^a		.351 ^a
Histamine 2 receptor antagonist use, n (%)	17 (25.8%)	3 (21.4%)	12 (31.6%)	12 (41.4%)	.459 ^a		.342 ^a
Gastrointestinal adverse effect score, mean ± SD	1.09 ± 0.99	1.29 ± 0.99	2.16 ± 1.53	2.93 ± 1.98	<.001^b		.017^b

The significant *P*-values <0.05 are expressed in bold type.

Data displayed as frequency (percentage) or mean ± standard deviation.

Note: no significant differences were found relative to race.

^a *P*-values from logistic regression.

^b *P*-values generated from general linear modeling.