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Population Pharmacokinetics of Mycophenolic Acid and Metabolites in Patients with Glomerulonephritis

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Abstract

Mycophenolic acid (MPA) is an inosine monophosphate dehydrogenase inhibitor used for glomerulonephritis treatment. The objective of the current study was to develop a population pharmacokinetic model for MPA and metabolites in glomerulonephritis in order to enable appropriate design of MPA regimens in these patients with alterations in kidney structure and function.

Thirty-nine patients with glomerulonephritis and receiving mycophenolate mofetil were recruited to participate in a 24-hour pharmacokinetic (PK) study. Blood was collected at times 0, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours and urine was collected over the intervals of 0-6, 6-12, and 12-24 hours. Plasma and urine samples were assayed for MPA and MPAG by high-performance liquid chromatography (HPLC), and for AcMPAG by liquid chromatography / mass spectrometry (LC/MS). Population PK analysis and covariate model building were evaluated using Non-linear Mixed Effect Modeling software (NONMEM, version 6.2.0, ICON Development Solutions, Ellicott City, MD).

The final model for MPA and its metabolites consisted of 9 discrete compartments; 1)depot gastrointestinal, 2)central MPA, 3)peripheral MPA, 4)gallbladder, 5)MPA urine, 6)MPAG central, 7)MPAG urine, 8)AcMPAG central, and 9)AcMPAG urine compartment. The MPA population mean estimates for apparent non-renal clearance (CL_{NR}/F) and apparent central volume of distribution were 14.3 L/hr and 21.1 L, respectively. The mean population estimate for apparent renal clearance (CL_R/F) was dependent on estimated creatinine clearances ($eClcr$); 0.0975 L/hr for $eClcr \leq 80$ mL/min and 0.157 L/hr for $eClcr > 80$ mL/min. Covariate analyses identified: $eClcr$ on $CL_{NR,MPA}/F$ ($P < 0.001$), $eClcr$ (with a cut-off value at 80 mL/min) on $CL_{R,MPA}/F$ ($P < 0.025$), serum albumin on $CL_{NR,MPA}/F$ ($P < 0.01$), $eClcr$ on $CL_{R,MPAG}/F$ ($P < 0.001$) and $eClcr$ on $CL_{R,AcMPAG}/F$ ($P < 0.001$). Evaluation of the final model by visual predictive check showed that most of the observed values were within the 95th percent prediction interval generated from 100 simulations of the final model.

The current population PK model demonstrated $eClcr$ and serum albumin influenced the renal and nonrenal components of Cl/F , suggesting patients with glomerulonephritis would have highly altered MPA exposures.

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Keywords

mycophenolic acid; mycophenolic acid glucuronide; pharmacokinetics; glomerulonephritis

Introduction

The pharmacokinetics of mycophenolic acid (MPA), the pharmacologically active component of mycophenolate mofetil (MMF) (Roche, Nutley, NJ) are well described in transplant recipients and population pharmacokinetic models are reported.¹⁻⁸ After oral intake, MMF is rapidly and completely absorbed, hydrolyzed into the active MPA, which is 98% bound to plasma proteins, including albumin. MPA is primarily metabolized by glucuronidation to form the 7-O-glucuronide conjugate (7-O-MPAG) which then undergoes elimination via the kidneys or enterohepatic recirculation back to MPA in the gastrointestinal tract. MPA is also metabolized to form a minor active acyl-glucuronide (AcMPAG). Besides its use in transplant patients, MPA is used off-label in induction and maintenance regimens for glomerulonephritis, including systemic lupus erythematosus (SLE)⁹⁻¹³ and small vessel vasculitis (SVV).¹⁴⁻¹⁶ The knowledge and applicability of MPA pharmacokinetics data from transplant populations to other kidney diseases are limited. This is because, unlike kidney transplant patients who receive a 3-4 drug immunosuppressive regimen, glomerulonephritis patients receive only 1-2 immunosuppressive drugs. Hence, glomerulonephritis patients have a smaller potential for pharmacokinetic drug-drug interactions, may exhibit different pharmacokinetics from transplant patients, and may require different exposure targets. In addition, results from noncompartmental pharmacokinetic analyses have suggested altered disposition of MPA in glomerulonephritis,^{17,18} a finding that is not surprising given urinary protein losses, serum protein reductions, kidney function declines, and inflammation. Compartmental pharmacokinetic modeling approaches¹⁹ and integrated pharmacokinetic models for MPA and its metabolites are currently lacking in patients with glomerulonephritis.

The aims of the current study was to develop a population pharmacokinetic model for MPA and its two metabolites [MPA glucuronide (MPAG) and acyl-MPA glucuronide in patients with glomerulonephritis using plasma and urine data (AcMPAG)] in order to characterize the disposition of MPA and its metabolites in this population, to determine the contribution of relevant covariates such as kidney function and structure abnormalities on MPA pharmacokinetics, and to develop Bayesian estimators which can accurately estimate MPA interdose AUC in glomerulonephritis patients.

Methods

Patients and Samples

Data were included from two pharmacokinetic studies in patients with glomerulonephritis from SLE or SVV and receiving MPA as MMF (Cellcept, Roche, New Jersey) for at least 2 weeks on a stable dose. All patients were recruited and assessed at one study center, both studies were approved by the institution's Biomedical Institutional Review Board, and patients provided written informed consent. Details of these studies and results from noncompartmental pharmacokinetics for MPA and MPAG were previously described.^{17,18}

Briefly, blood samples were collected at times 0, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours and urine was collected from 0-6, 6-12, and 12-24 hours after the initial dose. Plasma and urine samples were assayed for MPA and MPAG by a high-performance liquid chromatography (HPLC) with ultraviolet detection assay as previously described.²⁰ Plasma and urine standard curves for MPA were linear over the range of 0.2-200 µg/mL and 1-50 µg/mL, respectively. Plasma and urine standard curves for MPAG were linear over the range of 1-200 µg/mL and

5-1500 µg/mL, respectively. The AcMPAG metabolite was assayed in plasma and urine by liquid chromatography/mass spectrometry (LC/MS) developed in the laboratory. Tuning, operation, peak integration, and data analysis were performed in negative ion mode using multiple reaction monitoring (Analyst software v.1.4.1, Applied Biosystems) and azidothymidine served as the internal standard. Reverse phase separation (gradient elution using 0.1% acetic acid aqueous phase and 100% acetonitrile organic mobile phase) was accomplished using a Zorbax RX-C8 150×2.1mm column with a 5 micron particle size (Agilent Technologies, CA). Analysis required a 10 µL injection, solvent flow of 0.3 mL/min, and total run time of 15 minutes per injection. Plasma and urine standard curves for AcMPAG were linear over the range of 0.01-50 µg/mL and 1-500 µg/mL, respectively. MPAG and AcMPAG concentrations were represented in terms of MPA-equivalents by multiplying the MPAG and AcMPAG concentration by 0.646 (molecular mass of MPA to MPAG/AcMPAG) and reported in mcg/mL. The amount of MPA available from a dose of the prodrug (MMF) was estimated as 72% of the dose (molecular mass of MPA to MMF).

Population Pharmacokinetic Analysis

Pharmacokinetics of MPA, MPAG, and AcMPAG were evaluated using Non-linear Mixed Effect Modeling software (NONMEM Version 6.2.0, ICON Development Solutions, Ellicott City, MD). Initial visual inspection of semi-logarithmic plasma concentration-time plots for MPA, MPAG and AcMPAG demonstrated bi-exponential and mono-exponential decay patterns (Figure 1), consistent with a two-compartmental pharmacokinetic model for MPA and one-compartment pharmacokinetic models for MPAG and AcMPAG. Pharmacokinetic models were parameterized in terms of apparent clearances and volumes with the subroutines ADVAN6 TRANS1 and incorporated a gallbladder compartment to account for enterohepatic recycling of MPA via MPAG. The enterohepatic recycling process was modeled by introducing a rate constant describing the transfer from the MPAG central compartment to a gallbladder compartment. During gallbladder emptying, MPAG was transferred and converted back to the parent MPA in the depot compartment. Double precision and first-order conditional estimation (FOCE) were used. Inclusion of urine data allowed estimation of apparent renal clearance (CL_R/F) and apparent nonrenal clearance (CL_{NR}/F). Both MPAG and AcMPAG pharmacokinetics were modeled as a central metabolite compartment for plasma that was connected to the central MPA compartment. Each metabolite compartment had a non-reversible elimination pathway to a urine compartment, and an additional elimination pathway such as through enterohepatic recycling through the gallbladder compartment for MPAG.

Intersubject variability in structural model parameters was estimated by an exponential error model (Equation 1).

$$P_j = \theta \cdot e^{\eta_j} \quad (1)$$

Where P_j is the individual value for P in the j^{th} individual, θ is the population mean value of the pharmacokinetic parameter P (e.g. CL/F , V_c/F , etc), and η_j is a random error term (the difference between the typical value and individual value).

Residual variability $\varepsilon_{ij,k}$ ($k=1, 2, 3, 4, 5, 6$), which is the discrepancy between the individual observed ($C_{\text{obs},ij}$) i^{th} plasma or urine concentration measured in the j^{th} individual for the MPA, MPAG, and AcMPAG and the respective individual model-predicted plasma or urine concentrations ($C_{\text{pred},ij}$) in the natural logarithm domain and was modeled according to an additive error model (Equations 2-7).

$$\text{Ln} (C_{\text{obs}, ij}) = \text{Ln} (C_{\text{pred}, ij}) + \varepsilon_{ij,1} \text{ for MPA plasma} \quad (2)$$

$$\text{Ln} (C_{\text{obs}, ij}) = \text{Ln} (C_{\text{pred}, ij}) + \varepsilon_{ij,2} \text{ for MPAG plasma} \quad (3)$$

$$\text{Ln} (C_{\text{obs}, ij}) = \text{Ln} (C_{\text{pred}, ij}) + \varepsilon_{ij,3} \text{ for AcMPAG plasma} \quad (4)$$

$$\text{Ln} (C_{\text{obs}, ij}) = \text{Ln} (C_{\text{pred}, ij}) + \varepsilon_{ij,4} \text{ for MPA urine} \quad (5)$$

$$\text{Ln} (C_{\text{obs}, ij}) = \text{Ln} (C_{\text{pred}, ij}) + \varepsilon_{ij,5} \text{ for MPAG urine} \quad (6)$$

$$\text{Ln} (C_{\text{obs}, ij}) = \text{Ln} (C_{\text{pred}, ij}) + \varepsilon_{ij,6} \text{ for AcMPAG urine} \quad (7)$$

Random effect parameters η and ε were assumed to be symmetrically distributed with 0 mean and variances of ω^2 and σ^2 , respectively. Different pharmacokinetic models were tested and the best structural model was chosen based on goodness-of-fit criteria including diagnostic plots, minimum objective function value (MOFV) after accounting for the number of fitted parameters, akaike information criteria (AIC), equal to MOFV plus two times the number of parameters, precision, and physiological plausibility of parameter estimates.

Covariate Models

Covariate models were created to evaluate for the influence of patient demographics (age, weight, gender), clinical status (serum creatinine, eClcr, serum albumin, urinary protein to creatinine ratio), and genotypes for single nucleotide polymorphisms relevant for MPA metabolism or transport (uridine glucuronosyltransferase genes; *UGTs*, e.g. *UGT2B7 C802T*, *UGT1A7 T622C*, multidrug resistance gene; *MDR1*, e.g. *MDR1 C3435T*, and *MDR1 C1236T*) on the pharmacokinetic parameters. These data were abstracted from the medical record or research database, where applicable. Kidney function was assessed by estimated creatinine clearance (eClcr) calculated by the Cockcroft-Gault equation.²¹

For continuous covariates (age, weight, serum creatinine, eClcr, serum albumin, urinary protein to creatinine ratio) on the population parameter, P_{pop} , Equation 8 was used:

$$P_{\text{pop}} = \theta_p * (\text{COV} / \text{COV}_{\text{median}})^{\theta_{\text{cov}}} \quad (8)$$

where θ_p is the typical value of P_{pop} for a patient with the median covariate value in the population, $\text{COV}_{\text{median}}$ and θ_{cov} is the change in $\ln(P_{\text{pop}})$ per unit change in $\ln(\text{COV} / \text{COV}_{\text{median}})$. For some continuous covariates which influenced P_{pop} only below a critical cutoff value, the covariate model was modified as shown in Equations 9 and 10:

$$P_{\text{pop}} = \theta_{p1} * (\text{COV} / \text{COV}_{\text{median}})^{\theta_{\text{cov}}} \text{ for } \text{COV} \leq \text{cutoff value} \quad (9)$$

$$P_{\text{pop}} = \theta_{p2} \quad \text{for } \text{COV} > \text{cutoff value} \quad (10)$$

where θ_{p1} is the typical value of P_{pop} for a patient with $\text{COV}_{\text{median}}$ below or equal to the cutoff value, θ_{cov} is the estimated effect of the covariate on P_{pop} below or equal to the cutoff value, and θ_{p2} is the typical value of P_{pop} for a patient with a COV value above the cutoff value. The critical cutoff values were determined graphically from the plots of the posthoc pharmacokinetic parameter estimates versus covariates.

For categorical covariates (race, gender, genotypes) on P_{pop} was modeled according to Equations 11 and 12:

$$P_{\text{pop}} = \theta_p \text{ for reference COV} \quad (11)$$

$$P_{\text{pop}} = \theta_p * \theta_{\text{cov}} \text{ for investigated COV} \quad (12)$$

where θ_p is the typical value of P_{pop} (e.g. CL/F, V_c /F, etc) for reference COV, θ_{cov} is the estimated fractional change in θ_p for the investigated covariate. Likelihood ratio tests to compare hierarchical models were performed by comparing differences in MVOF between models to χ^2 distributions with degrees of freedom equal to the difference in the number of parameters. A reduction in MVOF of >3.84 (1 degree of freedom) from the base or previous model to the current model was designated as statistically significant at $p < 0.05$.

The incorporation of covariates in the final model was determined by stepwise forward addition followed by backward elimination. During forward addition, covariates at the $p < 0.05$ level were included in the model, and during backward elimination, covariates at the $p < 0.01$ level were retained in the model.

Model Validation

A visual predictive check was employed to evaluate the predictability of the model. One hundred data sets were simulated each for plasma and urine MPA, MPAG, and AcMPAG from the final model. The observed data were superimposed with the 2.5th, 50th, and 97.5th percentiles of the simulated data calculated at each time point. Binomial exact tests were performed to evaluate the percentage of observed concentrations that were out of the 95th% prediction intervals.

Bayesian estimation of inter-dose area-under-curve (AUC_{0-12})

Using the observed data and final model parameters, a combination of three plasma samples (from 0 to 6 hr postdose) and one urine sample (0-6 hr postdose collection) were used to estimate MPA AUC_{0-12} of the glomerulonephritis patients included in the analysis. Due to the limited number of patients in the study, data-splitting or circular permutation method was used to validate the Bayesian estimators. The full dataset was randomly divided into five groups, each containing 20% of the patients. Five different subsets of four groups containing 80% of the data were obtained. The population parameters estimated in the five “80% subsets” were used as priors to calculate the individual pharmacokinetic parameters of the patients in the

remaining subset using Bayesian estimation. Predicted MPA AUC_{0-12} were compared with the observed values and the predictive performance was evaluated by calculating mean relative prediction error (%MPE) as a measure of bias and root mean squared relative prediction error (%RMSE) as a measure of precision.²² Observed MPA AUC_{0-12} were determined by the linear trapezoidal method/

Results

The characteristics from the combined set of 39 lupus nephritis and ANCA-associated vasculitis patients are presented in Table 1. The patients were predominantly Caucasian (60%) and African-American (28%) race. A minimal to moderate level of kidney dysfunction was present; eClcr 91.3 ± 45.7 mL/min and urinary protein to creatinine ratio 0.8 ± 1.6 , with conserved serum albumin (4.2 ± 0.5 g/dL). Approximately 40% of patients were receiving double immunosuppressant therapy with glucocorticoids (31%) or cyclosporine (8%).

A full steady-state 12-hour plasma concentration vs time profile was generated for all 39 patients. The entire dataset produced a total of 444 MPA, 441 MPAG, and 363 AcMPAG plasma and a total of 130 MPA, 130 MPAG, and 71 AcMPAG urine concentrations. Figure 1 shows the observed steady state plasma concentration vs time profiles for MPA, MPAG, and AcMPAG after orally administered MMF and demonstrate secondary peaks between 4 and 12 hours consistent with enterohepatic recycling of MPA.

Introduction of enterohepatic recycling of MPAG in pharmacokinetic model decreased the AIC by 647 units relative to the model without enterohepatic recycling. Introduction of interconversion of AcMPAG back to MPA via the central compartment in the pharmacokinetic model decreased the AIC by 110 units relative to the model without this interconversion. While several patient plasma concentration time curves demonstrated an absorption lag time of MPA, its inclusion into models resulted in a reduction of the MVOF but with the cost of decreased precision of other data parameters and was therefore not incorporated. Duration of gallbladder emptying was fixed at 0.01 hours.^{4,8} Due to insufficient data collected around the secondary peak, the transfer rate constant of MPAG from the gallbladder to the depot compartments (k_{41}) was fixed at 67.5 hr^{-1} .⁸ The final model parameters are presented in Table 2. Figure 2 is a schematic representation of the final model employing plasma and urine concentration data for MPA, MPAG, and AcMPAG.

The covariates were examined to determine their relationship with eta values for apparent Clr/F, apparent Clnr/F, and the central compartment volume (V_c/F). Stepwise forward addition identified the following significant covariate effects: eClcr on $CL_{NR,MPA}/F$ ($\Delta MVOF = -19.6$, $P < 0.001$), eClcr (with a cut-off value at 80 mL/min/1.73m²) on $CL_{R,MPA}/F$ ($\Delta MVOF = -8.8$, $P < 0.025$), serum albumin on $CL_{NR,MPA}/F$ ($\Delta MOF = -6.6$, $P < 0.01$), eClcr on $CL_{R,MPAG}/F$ ($\Delta MVOF = -18.7$, $P < 0.001$) and eClcr on $CL_{R,AcMPAG}/F$ ($\Delta MVOF = -11.0$, $P < 0.001$). All these covariates remained significant ($p < 0.01$) during backward elimination.

Table 2 shows the population parameter estimates and covariate relationships for MPA, MPAG, and AcMPAG for the final model. In general, parameters were estimated with acceptable precision (7-53% relative standard error, %RSE). eClcr ≤ 80 mL/min had a covariate effect on $CL_{R,MPA}/F$ (Equation 13).

$$CL_{R,MPA \text{ creatinine clearance} \leq 80} / F \text{ L/hr} = 0.0975 \text{ L/hr} * (eClcr / 54.93)^{1.33} \quad (13)$$

For apparent CL_{NR}/F , eClcr had a positive effect, while serum albumin was found to have an inverse effect (Equation 14).

$$CL_{NR_MPA} \text{ L/hr} = 14.3 \text{ L/hr}^* (eClcr/88.54)^{0.831} (\text{albumin}/4.2)^{-1.35} \quad (14)$$

For MPAG and AcMPAG, increased eClcr resulted in increased apparent CL_R/F for each respective metabolite. (Equations 15 and 16).

$$CL_{R_MPAG} \text{ L/hr} = 1.77 \text{ L/hr}^* (eClcr/88.54)^{0.641} \quad (15)$$

$$CL_{R_AcMPAG} \text{ L/hr} = 1.75 \text{ L/hr}^* (eClcr/88.54)^{1.00} \quad (16)$$

None of the *UGT2B7*, *UGT1A7*, and *MDR1* genotypes were found to be significant in the final model.

Model diagnostic plots for plasma MPA, MPAG and AcMPAG data are shown in Figures 3, 4 and 5, respectively. Similar to the plasma data, the natural-logarithm transformed population predicted concentrations ($\ln(\text{PRED})$) and individual predicted concentrations ($\ln(\text{IPRED})$) for the urine MPA, MPAG and AcMPAG data (not shown) were in good general agreement with the natural-logarithm transformed observed concentrations ($\ln(\text{DV})$). Similar to the plasma data, no trends were associated with the weighted residuals (WRES) when plotted against increasing values of $\ln(\text{PRED})$ and time after dose for the urine MPA, MPAG and AcMPAG data (not shown). These plots showed that our comprehensive model adequately described the data.

The results of the visual predictive check evaluation for plasma and urine MPA, MPAG, and AcMPAG are presented in Figures 6 and 7, respectively. Results of binomial tests showed that 4.28% (95% C.I. 2.60-6.60%) of observed plasma MPA concentrations, 4.31% (95% C.I. 2.61-6.65%) of observed plasma MPAG concentrations and 3.86% (95% C.I. 2.12-6.39%) of observed plasma AcMPAG concentrations were out of the 95th% prediction intervals. Results of binomial tests showed that 1.54% (95% C.I. 0.187-5.45%) of observed urine MPA concentrations, 2.31% (95% C.I. 0.478-6.60%) of observed urine MPAG concentrations and 5.63% (95% C.I. 1.56-13.8%) of observed urine AcMPAG concentrations were out of the 95th% prediction intervals. Overall, the percentages of observations that were out of the 95th% prediction intervals were not statistically different from 5% as indicated by their 95% C.I. This analysis suggests that the final model provided an adequate fit to the data.

Figure 8 demonstrates the relationships of predicted population values for MPA CL/F , CL_R/F , CL_{NR}/F and area-under-curve in a dosing interval ($AUC_{0-\tau}$) after a 1000 mg MMF dose in a glomerulonephritis population exhibiting selected values for eClcr and serum albumin that are clinically relevant.

For the analysis of Bayesian estimation of inter-dose AUC_{0-12} , Table 3 shows the time-points with unbiased predictions of MPA AUC_{0-12} with measured MPA AUC_{0-12} as indicated by the %MPE. A %MPE not significantly different from zero was indicative of unbiased predictions. The predictions had %RMSE of less than 35%, indicating reasonable imprecision of the estimations.

Discussion

The current study reported a population pharmacokinetic analysis of MPA and its metabolites MPAG and AcMPAG, in a group of patients with glomerulonephritis secondary to SVV and

SLE. This study was necessary to investigate the influence of patient-level characteristics including kidney function (e.g. eClcr), kidney structure (urinary protein to creatinine ratio), and serum protein (serum albumin concentration) that are altered in glomerulonephritis on MPA pharmacokinetics. Additionally, demographic and genotype variables were investigated for their influence on MPA pharmacokinetics. The population approach enabled us to estimate mean pharmacokinetic parameters, inter-individual variability, and residual variability, as well as to evaluate for covariate effects on MPA pharmacokinetics. As opposed to kidney transplant recipients, little is known about pharmacokinetic variability of MPA in glomerulonephritis, despite being used off-label for this indication for almost a decade.

As compared to our previous study in kidney transplant patients, our glomerulonephritis population had higher population mean (%RSE) absorption rate constant (K_a) [1.16 hr^{-1} (15.2%) vs 0.67 hr^{-1} (24.8%)], higher apparent intercompartmental clearance (Q/F) [23.4 L/hr (16.4%) vs 8.11 L/hr (24.2%)], and lower V_C/F . [21.1 L (34.1%) vs 25.9 L (34.9%)].¹ However different dosage forms of MPA were used in each of these studies, which may have accounted for variability in K_a . Published MPA population models by others in the kidney transplant population have reported population mean K_a estimates that range from 2.27 hr^{-1} to 4.1 hr^{-1} ^{5,7,23}, which are also greater than the estimate in glomerulonephritis. Mean population estimates for V_C/F have ranged from 10.3 to 97.7 L ^{4,5,7,24}, a range encompassing the mean value found in the current study.¹ A strength of the current study was the collection of urine samples, which enabled estimation of the Cl_R/F component of apparent oral clearance (CL/F). The model resulted in two population mean Cl_R/F estimates for MPA based on eClcr levels of $\leq 80 \text{ mL/min}$ and $>80 \text{ mL/min}$. The Cl_R/F estimate was nearly 2-fold higher in patients with eClcr values of $>80 \text{ mL/min}$ (0.157 L/hr) versus $\leq 80 \text{ mL/min}$ (0.0975 L/hr). Apparent renal clearance estimates of MPAG and AcMPAG were an order of magnitude greater than MPA estimates.

As would be expected, the Cl_{NR}/F estimate (%RSE) for MPA was significantly greater [14.3 L/hr (8.04%)] than the Cl_R/F estimates [0.0975 L/hr (20.8%) and 0.157 L/hr (20.5%)] as MPA is primarily metabolized by the liver. These estimates were not available from previously published MPA pharmacokinetic models as urine concentrations were not measured. Previous studies have reported only ranges for MPA CL/F between 11.9 L/hr and 33 L/hr .^{4,5,7,24} A recent publication in 38 patients with glomerulonephritis receiving MMF reported higher mean (%RSE) V_C/F [52.4 L (17%)], higher K_a [6.2 hr^{-1} (22%)], lower V_P/F [262 L (5%)], and lower Q/F [16.2 L/hr (22%)] than our current study.¹⁹ However, the studies were comprised of different types of patients, with our study having a higher percentage of females, more diverse racial make-up, higher kidney function (eClcr), and a lower percentage of patients on concomitant glucocorticoids. The final structural model that fit the MPA pharmacokinetic data obtained from our glomerulonephritis patients consisted of nine compartments, a model slightly more complex than our previous model in kidney transplant recipients¹, and higher complexity than the previous glomerulonephritis model.¹⁹

Although the volumes of the central metabolite compartments are not uniquely identifiable in this analysis, if we use the central MPAG compartment apparent volume of 4.4 L from a previous study,⁸ the percentage of MPAG clearance that undergo recycling through the gallbladder in glomerulonephritis patients would be estimated as 17.9%. Previous reports of the percentage of MPA clearance that underwent recycling through gallbladder were 29.1% and 37%, respectively, in the two reported studies.^{8, 19} The current model shows that AcMPAG undergoes rapid reversible interconversion with the parent MPA in plasma. This is consistent with recent animal data from our laboratory which suggests that AcMPAG is actually cleaved to MPA by nonspecific esterases within the liver (data not shown), whereas MPAG is reportedly cleaved by β -glucuronidases in the intestine.²⁵

It is known that there is a large degree of interpatient variability in the pharmacokinetic parameters of MPA in kidney transplant patients.²⁶ Previous studies have reported CL/F interpatient variability in the range of 28% to 41%^{5,6}, and V_C/F interpatient variability in the range of 18% to 87.8%.^{1,3} In the current study, estimated interpatient variability for MPA pharmacokinetic parameters (%RSE) were: $CL_{R,MPA}/F$ [72.5% (30.9%)], $CL_{NR,MPA}/F$ [39.7% (19.1%)], and V_C/F [143% (50.7%)]. This variability and relationships between exposure and treatment-related outcomes in transplant patients supports the development of therapeutic drug monitoring strategies for MPA.²⁶⁻³³

Covariate modeling enabled the evaluation of disease-state variables on estimates of MPA renal and nonrenal clearance, and apparent oral clearance, for the purpose of simulating the influence of typical clinical alterations in albumin and kidney function (eClcr) found in patients with glomerulonephritis on clearance parameters and ultimately MPA exposures. Covariate modeling demonstrated that MPA CL_R/F is directly related to eClcr (covariate coefficient 1.33) in patients with eClcr values of ≤ 80 mL/min and MPA CL_{NR}/F is directly related to eClcr (covariate coefficient 0.831). A glomerulonephritis patient with eClcr of 60 mL/min would be predicted to have an approximately 3-fold higher MPA CL_R/F than a patient with an eClcr of 30 mL/min (0.11 L/hr vs 0.04 L/hr). Serum albumin concentrations were also found to influence CL_{NR}/F , with decreased serum albumin resulting in increased CL_{NR}/F (covariate coefficient -1.35). An increase in eClcr from 30 to 60 mL/min in the presence of a normal serum albumin (4.4 g/dL) would double the calculated CL_{NR}/F from 5.5 to 9.7 L/hr. For the same increase in eClcr, patients with reduced serum albumin to 2.5 g/dL would have a doubling of the calculated CL_{NR}/F , above that demonstrated at each level of eClcr in patients with normal serum albumin concentrations (from 11.7 to 21 L/hr). The clinical manifestations of glomerulonephritis are typically not solely a reduction in serum albumin or a reduction in eClcr, but some combination of these previous covariates. Hence, the influence of the combination of factors needs to be considered for their effects on MPA exposure. For a group of patients with normal serum albumin concentrations, the $AUC_{0-\tau}$ would be decreased when evaluating patients with increased eClcr values 30 to 120 mL/min (131 to 41.4 mg hr/L). When these same patients also have serum albumin values reduced from 4.4 to 2.5 g/dL, the $AUC_{0-\tau}$ is reduced another 2-fold at each level of eClcr (from 61.2 to 19.4 mg hr/L). While it is important to note that MPA $AUC_{0-\tau}$ clinical targets are not defined for glomerulonephritis, if one were to target the $AUC_{0-\tau}$ values suggested for renal transplant recipients (30 to 60 mg hr/L) as a starting point for therapy, the covariate effects would result in many patients either above or below the former targets. In particular, patients with low serum albumin and patients with low eClcr would be at highest risk. As unbound MPA $AUC_{0-\tau}$ may be more relevant to target in patients with these clinical manifestations, future assessments should address these unbound targets. However, the relative contribution of unbound levels to efficacy versus availability for elimination would dictate the relevance of unbound levels.

The CL_R/F of MPA's metabolites (MPAG and AcMPAG) were also found to positively influence kidney function, e.g. creatinine clearance. Glomerulonephritis patients with decreased eClcr would be expected to have at least transiently increased metabolite (AcMPAG and MPAG) concentrations prior to recycling and subsequently, at least transiently increased MPA concentrations. However, the relative influence of decreased eClcr on levels of MPA or its metabolites may be influenced by altered metabolism secondary to reductions in protein binding of MPA to serum albumin due to uremic competitors,⁵ or concomitant cyclosporine therapy.¹⁹ Decreased kidney function will lead to reduced renal clearance of MPAG and increased biliary excretion. As a result, more MPAG will undergo enterohepatic recirculation and conversion back to MPA. Our kidney disease model, e.g. glomerulonephritis, would be predicted to result in reductions in protein binding of MPA secondary to reductions in serum albumin due to kidney losses and also due to accumulation of metabolites (MPAG and AcMPAG) secondary to the loss of kidney function. Since we measured MPA and metabolites

in the urine, the Cl_R/F component could be estimated and the Cl_{NR}/F component could also be calculated. Our results suggest that the Cl_{NR}/F component of MPA Cl/F is influenced to a greater extent than Cl_R/F in patients with glomerulonephritis. Studies into the influences of the systemic diseases that result in glomerulonephritis on phase II drug metabolizing processes may elucidate the role of serum albumin versus alterations in *UGTs* on nonrenal clearance.

Finally, our data demonstrate a clear application of the model using a combination of three time points that accurately estimate the MPA exposure. Based on the final population pharmacokinetic model, accurate prediction of MAP AUC_{0-12} is feasible using bayesian estimation at nine different combinations of three time-points as shown in Table 3. This would facilitate the optimization of the exposure of MPA in glomerulonephritis patients.

Conclusions

This study reported a population pharmacokinetic model for MPA and its glucuronide metabolites in patients with glomerulonephritis secondary to SLE and SVV. Unlike previous models of MPA pharmacokinetics, our model was developed with extensive plasma and urine sample collections from a well-defined population of patients and allowed the estimation of both the renal and nonrenal components of apparent oral clearance. The resulting parameter estimates were considerably different than those obtained in many of the previous publications of kidney transplant patients receiving MPA. Two covariates, $eClcr$ and serum albumin, influenced the renal and nonrenal components of apparent clearance. The clinical relevance of the current study can be realized when using the population parameters to simulate $AUC_{0-\tau}$ values under scenarios of altered creatinine clearance and/or altered serum albumin. We demonstrated that patients with glomerulonephritis would have highly altered MPA exposures when one includes assessment of covariates on renal and nonrenal apparent clearance estimates. Additionally, our model can be applied clinically as demonstrated by the combination of three time points accurately estimating MPA exposure. Future work will elucidate unbound exposures and relevance to efficacy, toxicity, and metabolic pathways.

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Figure 1. Observed Plasma Concentration Versus Time After Dose. Figure shows observed plasma concentration versus time after dose for a). mycophenolic acid (MPA), b). mycophenolic acid glucuronide (MPAG), and c). acyl-mycophenolic acid glucuronide (AcMPAG).

Figure 2.

Final compartment model for mycophenolic acid (MPA), mycophenolic acid glucuronide (MPAG), and acylmycophenolic acid glucuronide (AcMPAG) plasma and urine data. Abbreviations: mycophenolic acid, MPA; mycophenolic acid glucuronide, MPAG; acylmycophenolic acid glucuronide, AcMPAG; absorption rate constant, k_a ; apparent renal clearance of MPA, $CL_{R, MPA/F}$; apparent non-renal clearance of MPA, $CL_{NR, MPA/F}$; compartment, CMT; apparent volume of central compartment, V_C/F ; apparent volume of peripheral compartment, V_P/F ; apparent renal clearance of MPAG, $CL_{R, MPAG/F}$; apparent renal clearance of AcMPAG, $CL_{R, AcMPAG/F}$; ratio of fraction of MPA metabolized to MPAG to volume of distribution of MPAG, $FM1^*$; ratio of fraction of MPA metabolized to AcMPAG to volume of distribution of AcMPAG, $FM2^*$; rate constant for the transfer of MPAG from central to gall bladder compartment, k_{84} ; rate constant for the transfer of AcMPAG from central to MPA central compartment, k_{102} ; rate constant for the transfer of MPAG from gallbladder to depot; k_{41} .

Figure 3. Mycophenolic Acid in Plasma Goodness-of-Fit Plots. (Upper left and right panels) Natural logarithmic-transformed population and individual predicted plasma mycophenolic acid (MPA) concentration vs natural logarithmic-transformed observed plasma MPA concentration. (Lower left and right panels) Natural logarithmic-transformed population predicted plasma MPA concentration and time after dose vs weighted residuals (WRES).

Figure 4. Mycophenolic Acid Glucuronide in Plasma Goodness-of-Fit Plots. (Upper left and right panels) Natural logarithmic-transformed population and individual predicted plasma mycophenolic acid glucuronide (MPAG) concentration vs natural logarithmic-transformed observed plasma MPAG concentration. (Lower left and right panels) Natural logarithmic-transformed population predicted plasma MPAG concentration and time after dose vs weighted residuals (WRES).

Figure 5. Acyl-Mycophenolic Acid Glucuronide in Plasma Goodness-of-Fit Plots. (Upper left and right panels) Natural logarithmic-transformed population and individual predicted plasma mycophenolic acid acyl glucuronide (AcMPAG) concentration vs natural logarithmic-transformed observed plasma AcMPAG concentration. (Lower left and right panels) Natural logarithmic-transformed population predicted plasma AcMPAG concentration and time after dose vs weighted residuals (WRES).

Figure 6. Visual predictive check for plasma A) MPA, B) MPAG and C) AcMPAG. Observed data (●) compared to the 97.5th (upper dotted line), 50th (middle solid line) and 2.5th (lower dotted line) percentiles of the simulated (100) data sets.

Figure 7. Visual predictive check for urine A) MPA, B) MPAG and C) AcMPAG. Observed data (●) compared to the 97.5th (upper dotted line), 50th (middle solid line) and 2.5th (lower dotted line) percentiles of the simulated (100) data sets.

Figure 8.

Three-dimensional surface plots showing the relationships between A) population predicted CL_{NR}/F of MPA, eCRCL and ALB; B) population predicted CL_R/F of MPA, eCRCL and ALB; C) population predicted CL/F (sum of CL_{NR}/F and CL_R/F) of MPA, eCRCL and ALB; D) $AUC_{0-\tau}$, eCRCL and ALB, in glomerulonephritis patients.

Table 1

Study Patient Characteristics (n=39)

	Mean $\pm$ standard deviation	Range (min-max)
Age (years)	46.9 $\pm$ 14.8	24-78
Weight (kg)	85.7 $\pm$ 20.9	47.4-128
Gender (male/female)	11/28	
Race n (%)		
Caucasian	23 (59)	
African-American	11 (28)	
American-Indian	2 (5)	
Asian	2 (5)	
Other	1 (3)	
Serum albumin (g/dL)	4.2 $\pm$ 0.5	2.9-5.2
Serum creatinine (mg/dL)	1.3 $\pm$ 0.7	0.6-3.4
Estimated Creatinine Clearance (mL/min) ^a	91.3 $\pm$ 45.7	25.1-239
Urinary protein to creatinine ratio	0.8 $\pm$ 1.6	0-7.90
Concomitant glucocorticoids (%)	12 (31)	
Concomitant cyclosporine (%)	3 (8)	
Mycophenolate mofetil dose (mg)	827 $\pm$ 325	250-1500

^a – estimated by Cockcroft and Gault equation 21

Table 2

Final parameter estimates of the population modeling

Model parameter (units)	Estimate (%RSE)	Interindividual variability, CV% (%RSE)
Mycophenolic Acid (MPA)		
Fixed effects		
k_a (hr^{-1})	1.16(15.2)	
$\text{CL}_{\text{R, MPA}}/\text{F}$ [$\text{eCLCR} \leq 80 \text{ mL/min}$] (L/hr)	0.0975 (20.8)	72.5 (30.9)
$\text{CL}_{\text{R, MPA}}/\text{F}$ [$\text{eCLCR} > 80 \text{ mL/min}$] (L/hr)	0.157(20.5)	72.5 (30.9)
$\text{CL}_{\text{NR, MPA}}/\text{F}$ (L/hr)	14.3(8.04)	39.7(19.1)
V_c/F (L)	21.1 (34.1)	143 (50.7)
V_p/F (L)	1240(23.4)	
Q/F (L/hr)	23.4 (16.4)	
Covariate coefficient		
Effect of creatinine clearance on $\text{CL}_{\text{R, MPA}}/\text{F}$ [$\text{eCLCR} \leq 80 \text{ mL/min}$], $\text{eCRCL}_{\text{R, MPA}}/\text{F}^a$	1.33(33.2)	
Effect of creatinine clearance on $\text{CL}_{\text{NR, MPA}}/\text{F}$, $\text{eCRCL}_{\text{NR, MPA}}/\text{F}^b$	0.831 (18.5)	
Effect of albumin on $\text{CL}_{\text{NR, MPA}}/\text{F}$, $\text{ALB}_{\text{NR, MPA}}/\text{F}^b$	-1.35(31.5)	
Residual error estimates (standard deviation)		
MPA, plasma ($\mu\text{g/mL}$)	1.81 (18.7)	
MPA, urine ($\mu\text{g/mL}$)	2.49 (16.6)	
Mycophenolic Acid Glucuronide (MPAG)		
Fixed effects		
$\text{CL}_{\text{R, MPAG}}/\text{F}$ (L/hr)	1.77(12.7)	71.8(25.4)
FM1*	0.271 (14.9)	72.7 (37.7)
k_{84} (hr^{-1})	0.0878 (53.2)	
Covariate coefficient		
Effect of creatinine clearance on $\text{CL}_{\text{R, MPAG}}/\text{F}$, $\text{eCRCL}_{\text{R, MPAG}}/\text{F}^c$	0.641 (37.0)	
Residual error estimates (standard deviation)		
MPAG, plasma ($\mu\text{g/mL}$)	1.50(7.54)	
MPAG, urine ($\mu\text{g/mL}$)	1.77(14.0)	
Acyl-mycophenolic acid glucuronide (AcMPAG)		
Fixed effects		
$\text{CL}_{\text{R, AcMPAG}}/\text{F}$ (L/hr)	1.75(18.2)	95.9 (29.5)
FM2*	0.0142 (24.4)	80.4 (25.9)
k_{102} (hr^{-1})	1.63 (40.3)	
Covariate coefficient		
Effect of creatinine clearance on $\text{CL}_{\text{R, AcMPAG}}/\text{F}$, $\text{eCRCL}_{\text{R, AcMPAG}}/\text{F}^d$	1.00 (31.4)	
Residual error estimates (standard deviation)		
AcMPAG, plasma ($\mu\text{g/mL}$)	1.54 (7.83)	

Model parameter (units)	Estimate (%RSE)	Interindividual variability, CV% (%RSE)
AcMPAG, urine (µg/mL)	1.31 (24.6)	

Abbreviations: coefficient of variation, CV; estimated creatinine clearance, eCLcr; percent relative standard error, % RSE; absorption rate constant, k_a ; apparent renal clearance of MPA, CL_R , MPA/F; apparent non-renal clearance of MPA, CL_{NR} , MPA/F; apparent volume of central compartment, V_C /F; apparent volume of peripheral compartment, V_p /F; apparent renal clearance of MPAG, CL_R , MPAG/F; apparent renal clearance of AcMPAG, CL_R , AcMPAG/F; ratio of fraction of MPA metabolized to MPAG to volume of distribution of MPAG, FM1*; ratio of fraction of MPA metabolized to AcMPAG to volume of distribution of AcMPAG, FM2*; rate constant for the transfer of MPAG from central to gall bladder compartment, k_{g4} ; rate constant for the transfer of AcMPAG from central to MPA central compartment, k_{102} ;

$$^a CL_R, \text{MPA/F individual} = CL_R, \text{MPA/F} [(eCRCL/54.93)^{CL_{CR_CLR,MPA}}] \times \exp(\eta_{CL_R, \text{MPA/F}});$$

$$^b CL_{NR}, \text{MPA/F individual} = CL_{NR}, \text{MPA/F} [(eCRCL/88.54)^{CL_{CR_CLNR,MPA}}] \times [(ALB/4.2)^{ALB_CLNR,MPA}] \times \exp(\eta_{CL_{nr}, \text{MPA/F}});$$

$$^c CL_R, \text{MPAG/F individual} = CL_R, \text{MPAG/F} [(eCLCR/88.54)^{CL_{CR_CLR,MPAG}}] \times \exp(\eta_{CL_R, \text{MPAG/F}});$$

$$^d CL_R, \text{AcMPAG/F individual} = CL_R, \text{AcMPAG/F} [(eCLCR/88.54)^{CL_{CR_CLR,AcMPAG}}] \times \exp(\eta_{CL_R, \text{AcMPAG/F}})$$

Table 3Predictive performance of the Bayesian estimators of MPA inter-dose area-under-curve (AUC_{0-12})

Time (hr)	% MPE (95% CI)	% RMSE
0, 1, 3	-8.26 (-18.1, 1.60)	31.7
0, 1, 4	-8.11 (-18.0, 1.83)	31.9
0, 2, 4	-7.41 (-18.0, 3.15)	33.6
0, 2, 3	-7.81 (-18.3, 2.71)	33.6
0, 3, 4	-5.77 (-16.7, 5.13)	34.3
0, 3, 6	-7.76 (-18.3, 2.74)	33.6
0, 1.5, 4	-7.53 (-18.3, 3.21)	33.6
0, 1.5, 6	-8.95 (-19.5, 1.58)	33.9
0, 4, 6	-7.93 (-18.4, 2.58)	33.6