

## INTRODUCTION

Mycophenolic acid (MPA) is an inhibitor of inosine monophosphate dehydrogenase (IMPDH) and is commonly used as an immunosuppressive agent following organ transplantation (1).

Enteric-coated mycophenolate sodium (Myfortic<sup>®</sup>, Novartis Pharmaceuticals) has been developed as a new oral formulation for delivery of MPA-mediated immunosuppression.

After absorption, MPA undergoes metabolism by uridine-diphosphate-glucuronyltransferase (UGT) isoenzymes (2).

The major metabolite of MPA is the pharmacologically inactive phenolic glucuronide (MPAG), which is excreted into the urine and the bile.

Biliary excreted MPAG undergoes enterohepatic recirculation (EHR), de-glucuronidated the parent MPA and is reabsorbed, generating a secondary peak in the MPA concentration-time profile (3).

Acyl-glucuronide of MPA (AcMPAG) is a minor metabolite that is pharmacologically inactive and is believed to have some toxic characteristics.

Little is known about the mechanism of excretion of AcMPAG.

## AIM

To develop an integrated "parent-metabolite" pharmacokinetic (PK) model for MPA, MPAG and AcMPAG using nonlinear mixed effects modeling (NONMEM) in stable kidney transplant recipients after oral administration with the enteric coated mycophenolate sodium.

## PATIENTS AND METHODS

Stable kidney transplant recipients (n=18) were recruited (Table 1).

Patients were on triple therapy with Myfortic<sup>™</sup>, prednisone, with either cyclosporine or tacrolimus.

Plasma samples were obtained at before and at 0.25, 0.5, 1, 1.5, 2, 3, 5, 7, 9, 10, 11 and 12 hours after the morning dose.

Concentrations of MPA, MPAG and AcMPAG were measured in plasma using a validated liquid chromatography method with ultraviolet detection (4).

Glomerular filtration rate (GFR) was measured using iohexol clearance method (5).

Population Pharmacokinetic modeling was carried out by the use of NONMEM (Version Globomax, MD) software using constant coefficient of variation inter- and intra-individual or models.

Individual AUCs of MPA, MPAG and AcMPAG were estimated using parameters of the model. The predictive performance of the model for the AUCs of MPA, MPAG and AcMPAG as compared with AUC values estimated from the noncompartmental analysis are assessed in terms of bias (mean prediction error, ME) and precision (root mean square prediction error, RMSE) and the associated 95% confidence intervals, CIs.

Continuous characteristics	Median	Range (min-max)
Age (years)	46	18-63
Body weight (kg)	85.7	57-133
Body surface area (m <sup>2</sup> )	2.03	1.59-2.46
Serum creatinine (mg/dL)	1.55	1.00-2.70
Serum albumin (g/dL)	4.30	3.60-4.80
Aspartate aminotransferase (U/L)	18.5	13.0-45.0
Alanine aminotransferase (U/L)	18.0	8.0-45.0
Glomerular filtration rate (mL/min/1.73 m <sup>2</sup> )	58.0	26-100
Dose of MPA (mg/day)	720	720-1440
Dose of calcineurin inhibitor		
Tacrolimus (mg)	5.0	4-14
Cyclosporine (mg)	90.0	25-125
Dose of prednisone (mg)	5.0	4-10
Number of samples per patient	13	12-13
Time post-transplant (days)	902	187-2744
Demographic characteristics	Number	%
Gender: Male	18	100
Concomitant medication		
Tacrolimus/Cyclosporine	10/8	56/44
Concomitant disease		
Diabetic/Non-diabetic	9/9	50/50
Ethnicity		
Caucasians	10	56
African American	5	28
Hispanics	3	16

Table 1. Patient demographic and biochemical characteristics and immunosuppressive agent doses.

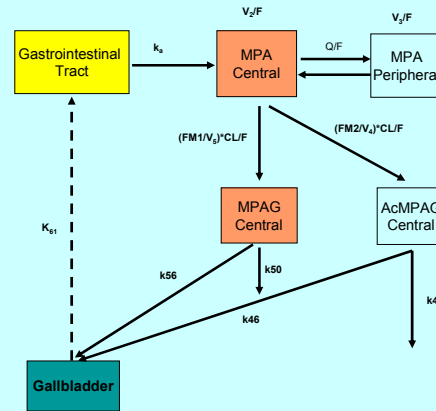


Figure 1. Proposed population pharmacokinetics model for MPA and its metabolites with EHR of MPA via both MPAG and AcMPAG.

### Abbreviations

<b>AcMPAG</b>	Mycophenolic acyl glucuronide
<b>CL/F</b>	Apparent clearance of MPA
<b>FM1*</b>	Fraction of MPA metabolized to MPAG to volume of distribution of MPAG
<b>FM2*</b>	Fraction of MPA metabolized to AcMPAG to volume of distribution of AcMPAG
<b>GFR</b>	Glomerular Filtration Rate
<b>k40</b>	Elimination rate constant of AcMPAG
<b>k46</b>	Rate constant for the transfer of AcMPAG from the central to the gall bladder compartment
<b>k50</b>	Elimination rate constant of MPAG
<b>k56</b>	Rate constant for the transfer of MPAG from the central to the gall bladder compartment
<b>k61</b>	Rate constant for the transfer of MPAG and AcMPAG from the gall bladder to the depot compartment
<b>ka</b>	Absorption rate constant
<b>MPA</b>	Mycophenolic acid
<b>MPAG</b>	Mycophenolic acid glucuronide
<b>Q/F</b>	Inter-compartmental clearance
<b>RSE%</b>	Percent relative standard error (SE/estimate*100)
<b>V2/F</b>	Apparent volume of central compartment
<b>V3/F</b>	Apparent volume of peripheral compartment

Parameter	Estimate (%RSE)	% Inter-individual variability (%RSE)	% Intra-individual variability (%RSE)
<b>MPA</b>			69.0 (15.7)
ka (hr <sup>-1</sup> )	0.998 (28.8)		
CL/F (L/hr)	11.1 (7.91)	15.7 (93.1)	
V <sub>2</sub> /F (L)	37.7 (17.9)	77.1 (46.0)	
Q/F (L/hr)	5.83 (42.9)		
V <sub>3</sub> /F (L)	153 (40.7)	3421 (140)	
<b>MPAG</b>			18.8 (32.1)
FM1* (L <sup>-1</sup> )	0.413 (19.0)	19.1 (249)	
k <sub>50</sub> (hr <sup>-1</sup> ) when GFR ≤ 70 mL/min/1.73 m <sup>2</sup>	0.178 (47.3)	55.2 (112)	
k <sub>50</sub> (hr <sup>-1</sup> ) when GFR > 70 mL/min/1.73 m <sup>2</sup>	0.357 (24.4)	55.2 (112)	
GFR effect on k <sub>50</sub> when ≤ 70 mL/min/1.73 m <sup>2</sup>	-0.321 (321)		
k <sub>56</sub> (hr <sup>-1</sup> )	0.152 (36.8)	60.2 (87.3)	
k <sub>61</sub> (hr <sup>-1</sup> )	0.0157 (48.7)		
<b>AcMPAG</b>			18.6 (25.1)
FM2* (L <sup>-1</sup> ) when GFR ≤ 60 mL/min/1.73 m <sup>2</sup>	0.0073 (25.3)	22.2 (86.0)	
FM2* (L <sup>-1</sup> ) when GFR > 60 mL/min/1.73 m <sup>2</sup>	0.0123 (13.3)	22.2 (86.0)	
GFR effect on FM2* when ≤ 60 mL/min/1.73 m <sup>2</sup>	-1.85 (14.2)		
k <sub>40</sub> (hr <sup>-1</sup> )	0.201 (13.4)	52.0 (62.2)	
k <sub>46</sub> (hr <sup>-1</sup> )	0.135 (31.3)		

Table 2. Parameter estimates of the final PK model.

## RESULTS

■ Schematic representation of the final PK model is shown in Figure 1. It comprises of a 6 compartment model for MPA and its metabolites and features an EHR model for MPA via biliary excreted MPAG.

■ Covariates screened included age, weight, body surface area, diabetes stats, concomitant medications cyclosporine or tacrolimus, GFR, albumin and glycated hemoglobin (HbA1c).

■ Parameters of the final PK model and diagnostic plots for the model are shown in Table 2 and Figures 2 and 3, respectively.

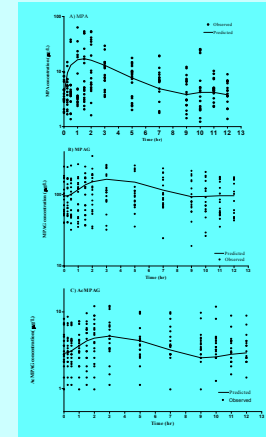


Figure 2. Semilog dose-normalized observed (dot) and population predicted (solid line) A) MPA, B) MPAG and C) AcMPAG plasma concentration vs. time profiles.

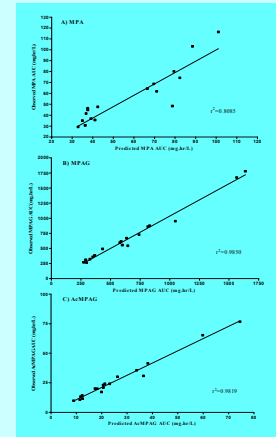


Figure 3. Correlation of observed and predicted A) MPA, B) MPAG and C) AcMPAG Area Under the Concentration-Time curves (solid line is the linear regression line).

## CONCLUSIONS

■ A population PK model for mycophenolic acid and its metabolites MPAG and Acyl-MPAG was developed in stable renal transplant recipients.

■ The model incorporates enterohepatic recirculation of MPA via both metabolite MPAG and Acyl-MPAG.

■ This model gives a good fit of the PK data as evidenced in the diagnostic plots (Figures 2 and 3).

■ Various sources of variability in the pharmacokinetics of MPA and its metabolites was identified.

■ Renal function (GFR less than 60 for MPAG and less than 70 for AcMPAG) is the most important predictor of the metabolite pharmacokinetics parameters.

■ This model can serve as the base model in which covariate effects on the PK parameters of MPA and its metabolites can be investigated so as to produce the final PK model.

■ The final PK model can be used to predict exposures of MPA and its metabolites at various doses of MPA and under different significant patient covariate values.

## REFERENCES

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