Cystatin C and myeloperoxidase based mycophenolic acid dosage optimization in pediatric anti-neutrophilic cytoplasmic antibody-associated nephritis

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June 17, 2021

Abstract

Aims Mycophenolic acid (MPA) is typically used for anti-neutrophilic cytoplasmic antibody associated nephritis (AAN) but with large individual variability of pharmacokinetics. This study aims to investigate clinical factors impacting MPA disposal so as to simulate dosage regimen in pediatric AAN. Methods We conducted a retrospective study in 25 children with AAN treated with MPA. A population pharmacokinetic model was developed to explore the effects of demographics and biochemical covariates on MPA. Monte Carlo simulations were performed to optimize dosage regimens. Results A total of 391 MPA concentrations from 25 patients were analyzed. MPA pharmacokinetics best fitted a two-compartment model with first-order absorption and linear elimination. The pharmacokinetic parameters for Ka, CL, Vc, Vp, and Q were 0.45 h-1, 9.86 L/h, 19.69 L, 408.32 L and 23.01 L/h, respectively. Dosage form significantly affected drug absorption. CL significantly decreased with increasing cystatin C, while with decreasing myeloperoxidase. Cystatin C was superior to serum creatinine in predicting CL of MPA. A dose of 650 mg/m2 was required to achieve the target exposure in children with normal renal function and no inflammation. Dose of MPA in patients with renal failure was almost 1/3 that of normal kidney function. The combined effects of myeloperoxidase and renal function resulted in a 6-fold range in MPA dose. Conclusions Myeloperoxidase was not only a biomarker of AAN, but also an inflammatory factor to impact drug CL. The influence of renal function and underlying diseases on drug metabolism should be fully considered in personalized medication for AAN children.

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Principal investigator statement: The authors confirm that the Principal Investigator for this paper is Zhiping Li and that she had direct clinical responsibility for patients.

Running head : PK of MPA in pediatric ANCA-nephritis

The abstract has a total of 249 words. The article has a total of 2985 words with 7 figures and 2 tables.

What is already known about this subject

- Mycophenolic acid (MPA) is widely used for ANCA associated nephritis (AAN) in children.
- High inter-individual variability of MPA exposure has been widely reported, leading to interest in population pharmacokinetic model to identify the sources of variability.
- Cystatin C outperformed serum creatinine in predicting drug clearance (CL).

What this study adds

- This was the first study to determined that Cystatin C, myeloperoxidase and dosage forms were important factors influencing MPA pharmacokinetics in pediatric AAN.
- Cystatin C had an advantage in predicting CL of MPA.
- The combined effects of myeloperoxidase and renal function resulted in a 6-fold range in MPA dose.

ABSTRACT

Aims Mycophenolic acid (MPA) is typically used for anti-neutrophilic cytoplasmic antibody associated nephritis (AAN) but with large individual variability of pharmacokinetics. This study aims to investigate clinical factors impacting MPA disposal so as to simulate dosage regimen in pediatric AAN.

Methods We conducted a retrospective study in 25 children with AAN treated with MPA. A population pharmacokinetic model was developed to explore the effects of demographics and biochemical covariates on MPA. Monte Carlo simulations were performed to optimize dosage regimens.

Results A total of 391 MPA concentrations from 25 patients were analyzed. MPA pharmacokinetics best fitted a two-compartment model with first-order absorption and linear elimination. The pharmacokinetic parameters for K_a, CL, V_c, V_p, and Q were 0.45 h^{-1}, 9.86 L/h, 19.69 L, 408.32 L and 23.01 L/h, respectively. Dosage form significantly affected drug absorption. CL significantly decreased with increasing cystatin C, while with decreasing myeloperoxidase. Cystatin C was superior to serum creatinine in predicting CL of MPA. A dose of 650 mg/m^2 was required to achieve the target exposure in children with normal renal function and no inflammation. Dose of MPA in patients with renal failure was almost 1/3 that of normal kidney function. The combined effects of myeloperoxidase and renal function resulted in a 6-fold range in MPA dose.

Conclusions Myeloperoxidase was not only a biomarker of AAN, but also an inflammatory factor to impact drug CL. The influence of renal function and underlying diseases on drug metabolism should be fully considered in personalized medication for AAN children.

KEYWORDS

mycophenolic acid, cystatin C, myeloperoxidase, pediatric, anti-neutrophilic cytoplasmic antibody associated nephritis, population pharmacokinetics

INTRODUCTION

Anti-neutrophilic cytoplasmic antibody (ANCA) associated vasculitis (AAV) is a rare autoimmune disease characterized by inflammatory necrosis of small blood vessels, including proteinase 3-ANCA and myeloperoxidase (MPO)-ANCA (1). Approximately 75%˜90% of patients with AAV have renal involvement, often progressed to end-stage renal disease at definitive diagnosis (1,2).

Although substantial advances have been in cyclophosphamide therapy for AAV, treatment-related complications have increased. Mycophenolate mofetil (MMF) is recommended as an alternative to cyclophosphamide

by EULAR/ERA-EDTA guidelines due to its good safety (3). Recently, the MYCYC trial has shown that MMF can be used as a first-line induction therapy for MPO-ANCA patients who have mild to moderate renal involvement without life-threatening extrarenal manifestations (4). ANCA-associated nephritis (AAN) with positive MPO may be a primary indication for administration of MMF (5).

Mycophenolic acid (MPA) is the active metabolite of MMF and mycophenolate sodium enteric-coated salt (EC-MPS). High inter-individual variability of MPA exposure has been widely reported in kidney transplant, stem cell transplant and autoimmune disease, leading to interest in population pharmacokinetic (PPK) model to identify the sources of variability (6). Unlike renal transplant recipients, patients with AAV had enhanced MPA clearance (CL), suggesting the need to comprehensively evaluate the role of disease factors on pharmacokinetics (7). Variability may be even more of a challenge in patients with AAV, who often have increased inflammatory markers, hypoalbuminemia and renal dysfunction, all of which can affect MPA levels (8,9).

To our knowledge, clinical trials on the variability of MPA in pediatric AAV are scarce, particularly the PPK of MPA for AAN children has not been described. This study aims to explore the factors contributing to pharmacokinetic variability of MPA and to optimize MMF dosage regimen in children with AAN.

METHODS

Study design and patients

We retrospectively recruited children diagnosed with AAN between November 2015 and November 2020 in the Department of Nephrology at Children's Hospital of Fudan University. Subjects were excluded if any of following were present: much missing data, severe liver damage or autoimmune diseases. All patients received a dose of MMF 10˜15 mg/kg twice daily as induction or maintenance therapy of their underlying disease, including dispersible tables (Huadong Medicine, Hangzhou, China), capsules (Roche, Basel, Switzerland) and EC-MPS (Novartis, Basel, Switzerland). Prednisolone was initiated at a daily dose of 1˜2 mg/kg/d. The protocol of dose adjustment varied according to patient's clinical status. This study was approved by the Research Ethics Committee from Children's Hospital of Fudan University (No. 2020-486) and was conducted in accordance with the Declaration of Helsinki. Informed consent was waived for this noninterventional retrospective study. The follow-up period was part of routine clinical care until death, loss and last inpatient visit.

Clinical and laboratory data

Data were compiled from the medical records that included demographics, type of clinical presentation, liver and renal function, immune status and co-medication. GFR were derived from $\text{Schwartz}_{\text{bed}}$equation = 0.413 × (Ht/serum creatinine) and $\text{Schwartz}_{\text{Cystatin C}}$ equation = $40.6 \times (1.8/\text{Cystatin C})^{0.93}$, respectively (10-12). MPA plasma concentrations were measured by ELISA using Siemens Viva-E Drug Testing System with Emit 2000 MMF Assay Test Kit (Siemens, Llanberis, UK). The quantitative linear range of MPA was 0.0˜15.0 mg/L. MPA exposure expressed by area under the curve (MPA-AUC) was a part of routine clinical care which is determined based on samples collected pre dose, at 20, 60, and 180 min after dose (13). MW·Pharm++ 1.6 was used to calculate $\text{MPA-AUC}_{\text{0-12h}}$. Data was entered and checked by second person verification.

Model development

MPA concentration-time profile was modeled by testing one and two-compartment models with first-order absorption and linear elimination without or with lag time. The first-order conditional estimate with extended least squares method was used in nonlinear mixed-effects model generated by Phoenix NLME 8.1. Fixed effects models were parameterized as K_a (absorption rate constants), CL and V_d (volume of distribution) for 1-compartment model as well as K_a, CL, Q (intercompartmental CL), V_c (central V_d), and V_p(peripheral V_d) for 2-compartment model. Additive, proportional and combination of additive with proportional error models were compared to evaluate residual variability. After the development of the base model, inter-individual

variability was described by an exponential model as follows:

$$\theta_i = \theta_{\text{pop}} \times exp\,(\eta_i)$$

where ϑ_{i} is the individual pharmacokinetic parameter, and ϑ_{pop} is typical value of parameter. The random variable η_{i} is normally distributed with mean zero and variance of ω^2, which is the deviation of $\eta_{\text{i}}$from ϑ_{pop}. The covariates were identified by a stepwise forward addition and backward elimination approach. A change in objective function value (OFV) of >3.84 ($P< 0.05$) was necessary for forward selection, and a strict threshold ΔOFV of >7.88 ($P < 0.01$) was used for backward elimination.

Evaluation and validation

Final model was evaluated by the minimum OFV and goodness-of-fit plots. A bootstrap with 1,000 replicates was performed to verify the accuracy and stability of the model, and the parameters were summarized as the median and 95% confidence interval (CI). Furthermore, visual predictive checks (VPC) with 1,000 simulations were performed to assess the predictive performance of model. The observed 5th, 50th, and 95th percentiles were plotted with their respective simulated 95% CI.

Dosage simulations

Monte Carlo simulations (n=1000) were performed based on covariate model to optimize dosage regimens in AAN children. Bayesian method was used to estimate the individual pharmacokinetic parameters. The target $AUC_{0–12h}$ was between 30˜60 mg/L·h. $AUC_{0–12h}$ is equal to dose divided by CL (14).

Statistical analyses

Continuous variables, if normally distributed, were compared using t-test, if not, were compared by Mann-Whitney U-test. Categorical variables were compared using chi-square test. Spearman rank correlation analysis was performed to determine the correlation between concentrations and $AUC_{0–12h}$. Sensitivity analysis was used to compare the influence of covariates on variation of MPA. A two-tailed P <0.05 was considered statistically significant. Statistics and graphs were performed using GraphPad Prism 8.0 and R 4.0.

RESULTS

Patient characteristics

A total of 391 samples were performed in 25 patients ranging from 1 to 17 years of age (Figure 1). Sixteen children were MPO-ANCA and the rest were negative. Patient characteristics were summarized in Table 1. MPA-$AUC_{0–12h}$ showed a large inter-individual variability, with a value of 45.11±30.26 mg/L·h. Trough level was 3.1±3.2 mg/L. There were significant correlations between MPA $AUC_{0–12h}$ and concentration at each time with C_{0h} (r =0.73, $P < 0.0001$), $C_{0.33h}$ (r =0.78, $P < 0.0001$), C_{1h} (r =0.84, $P < 0.0001$) and C_{3h} (r =0.85, $P < 0.0001$).

PPK model

The pharmacokinetics of MPA was best described by a two-compartment linear model with a first-order absorption rate. A mixed model of addition and proportion was used to describe residual variation. The population parameters for K_a, CL, V_c, V_p, and Q were 0.45 h^{-1}, 9.86 L/h, 19.69 L, 408.32 L and 23.01 L/h, respectively. In covariate model, dosage form had a significantly effect on K_a (Figure 2). Cystatin C (CysC) or serum creatinine (Scr) was negatively correlated with CL, while MPO was positively correlated with CL (Figure 3). In addition, MPA showed an extensive tissue distribution (408.32 L) and was significantly correlated with albumin. Simultaneous administration of prednisone statistically influenced on K_a, but did not facilitate an important refinement of model and were discarded during backward elimination. Overall, covariate model decreased inter-individual variability in K_a (from 164.2% to 107.0%), CL (from 101.9% to 74.3%) and V_p(from 112.9% to 70.0%) compared to base model. CysC and MPO provided an explanation of 26.4% and 10.0% of inter-individual variability for CL, respectively (Figure 4).

Comparison between CysC and Scr

The estimated PPK parameters between CysC-model and Scr-models were similar (Table 2). CysC significantly improved model fit (ΔOFV = -3.87,$P < 0.05$) compared with Scr and explained more inter-individual variability for CL (26.4% vs 23.3%), which suggested CysC had a better predictive performance for MPA CL. Furthermore, CKD staging graded by eGFR derived from CysC and Scr were divergent. The prevalence of eGFR of less than 60 mL/min/1.73 m^2 was higher with the CysC-eGFR than with the Scr-eGFR (61.1% vs 72.2%). A total of 52 patients were with eGFR>30 mL/min/1.73 m^2(CKD 1˜3 stages) when using $eGFR_{Scr}$, however, 31 of them were reclassified into a lower stage when using $eGFR_{CysC}$ (Figure 5).

Evaluation and validation

The addition of covariates greatly improved the stability of model, as a result, the OFV decreased from 1774.00 (base model) to 1673.89 (final model). The observation versus population and individual predictions (Figure 6A, B) were generally evenly distributed around the identity line, except for some positive bias at high concentrations, indicating a good model fitting. Of the conditional weighted residuals (CWRES) versus time after dose and population predictions (Figure 6C, D), the CWRES were symmetrically distributed around y=0 line and mostly within ±2 unit, confirming that the model has a good accuracy. The population typical value of final model closely agreed with mean estimated from bootstrap and is within 95% CI, which demonstrate that the model prediction is accurate and stability (Table 2). According to VPC (Figure 7), the major observations was distributed within 95% CI of simulated values, indicating a good predictive performance of final model.

Dosage simulation

Dosage regimens were simulated based on $eGFR_{CysC}$ and MPO stratification. AAV patients with elevated CysC should receive lower dose of MPA while patients with elevated MPO should receive higher dose of MPA (Supplemental Table 1). A dose of 750 mg (650 mg·m^{-2}) twice daily was needed to achieve the target $AUC_{0\text{-}12h}$ in AAV children with normal renal function and no inflammation. Impaired renal function ($eGFR_{CysC}$ =15 mL/min/1.73m^2) significantly impacted MPA CL, with almost a 2/3 dose reduction than normal renal function ($eGFR_{CysC}$=90 mL/min/1.73m^2). The combined effects of MPO and renal function resulted in a 6-fold range in MPA dose.

DISCUSSION

This was the first study to determined that CysC and MPO were important factors affecting the MPA individual variability and the Ka varied with dosage forms in childhood AAN. We also confirmed that CysC was superior to Scr for evaluation of renal function and developed dosage regimens based on different levels CysC and MPO.

Overview of PPK model

The MPA concentrations were well described by a two-compartment model parameterized as K_a (0.45 h^{-1}), CL (9.86 L/h), V_c (19.69 L), V_p (408.32 L), and Q (23.01 L/h). Previous reports in children supported this result where K_a ranged from 0.39 to 5.16 h^{-1}, CL ranged from 6.42 to 25.3 L/h, V_c ranged from 4.75 to 64.7 L, Q ranged from 3.74 to 25.6 L/h and V_p ranged from 16.8 to 411.0 L (15). The variability of Ka was 164.2%, where previous reports showed K_a were highly variable in pediatric patients ranging from 20.5% ˜ 308.4%. However, only age was identified as a significant covariate on absorption in current pediatric dataset. Our findings indicated that dosage forms significantly affected K_a, and its inclusion in final model resulted in a 57.2% reduction of inter-individual variation. The fastest absorption was dispersible formulation, followed by capsule, and then EC-MPS. Extremely variable and unpredictable pharmacokinetic curves were found in kidney transplant recipients who were given EC-MPS, whereas those who were treated with MMF had regular pharmacokinetic profiles (16). Therapeutic drug monitoring should be considered when switching between EC-MPS and MMF. When it comes to MPA metabolism, the CL was lower than that reported in AAV patients (17.28±9.24 L/h), because most of patients in our study had severe kidney damage (7). The CL in this study was similar to that reported in patients with idiopathic nephrotic syndrome (CL=9.7 L/h)

but lower than that conducted in systemic lupus erythematosus (CL=25.3 L/h),kidney and liver transplant (CL=12.7˜22.0 L/h), demonstrating the importance of underlying disease on drug metabolism (15). In addition, we did not find a significant effect of body weight on CL, perhaps because the use of a per kg for dose. Last but not least, a combination of glucocorticoids is inevitable in ANCA treatment. Our study revealed that glucocorticoids had a dose-dependent effect on absorption, but were not included in final model (Supplemental Figure 1). A significant increase on MPA CL has been reported in renal transplant and lupus nephritis patients with concomitant use of corticosteroids compared to those with a corticosteroid free (17-19).

CysC as a more sensitive biomarker of renal function

Scr does not significantly increase until at least 50% renal function is impaired leading to overestimation of GFR (20). As a second biomarker for GFR, CysC outperforms Scr in capturing earlier and more precise changes in renal function. In 2012, KDIGO proposed that CysC can improved accuracy of GFR estimation and CKD classification. CysC was strongly recommended when $eGFR_{Scr}$ not be reliable to confirm CKD in absence of other diagnostic evidence (21).

Abundant pharmacokinetic evidence shows that CysC has a better correlation with drug CL and trough levels compared with Scr, which is crucial for dose of renally excreted drugs (22,23). In this study, PPK model showed that CysC was superior to Scr in predicting CL of MPA (ΔOFV= -100.11 vs -96.24, $P<0.05$). It similar with the conclusions that CysC was superior to $Schwartz_{bed}$ in estimating CL and optimizing dosage for children with vancomycin (24,25). Tan et al. also demonstrated that $eGFR_{CysC}$improved prediction of ceftriaxone CL in elder with moderate or severe renal impairment compared with $eGFR_{Scr}$ (ΔOFV= -18.66 vs -15.83) (26). In addition, 60% of CKD 1-3 stages derived from $eGFR_{Scr}$ were reclassified to a lower region by $eGFR_{CysC}$, which was supported by 2012 KIDGO guideline that the prognostic advantage of CysC is most apparent among individuals with GFR >45 mL/min/1.73m^2 (21). A large multicenter European pediatric cohort study strongly suggested that CysC should replace Scr as the primary biomarker when estimating GFR in children with moderate to severe renal function decline (27).

MPO play an integral role in AAN

MPO, a marker of oxidative stress and inflammation, was associated with a 10% increased risk of CKD progression (28). More importantly, we found that MPO levels were associated with increased drug CL, suggesting that MPO may not only be a biomarker of AAN, but also an independent predictor of kidney function. MPO plays important role in mediating glomerular injury in AAV (29,30). An inflammatory trigger such as infection and drug, activate the neutrophil-mediated immune system, leading to release of MPO. Subsequently, MPO localized in glomeruli activated adaptive immune response, leading to release of inflammatory mediators and oxidants, thereby damaging glomerular capillaries. It has been reported that inflammation has significant effects on drug metabolism by changing the expression levels of drug metabolizing enzymes, which is of great significance to personalized medicine (31). We speculated that MPO, as an inflammatory factor for AAN, increased drug elimination through a similar mechanism.

Although the liver is quantitatively the most important site of glucuronidation, extrahepatic tissues, particularly kidney, may play a significant role in MPA metabolism (32). MPA is primarily conjugated by UDP-glucuronosyltransferase enzymes (UGTs). MPA-glucuronide (MPAG) is the most abundant metabolite primarily produced by UGT1A8 and UGT1A9, with minor part produced by UGT1A1, 1A7 and 1A10; another metabolite AcMPAG is produced mainly by isoform 2B7. UGT1A9 plays a predominant role in hepatic MPA metabolism. UGT1A8 and UGT1A10 are responsible for MPA metabolism in the gastrointestinal tract. MPA and its metabolites are mainly excreted through urine probably mediated by Mrp2 (33,34). In addition to its traditional role of excretion, human kidney possesses an extraordinary capacity for drug metabolism that in some instances surpasses that of liver. It has been reported the expression of UGTs in human kidneys, among which the most abundant UGT enzyme is UGT1A9, followed by UGT2B7 (35).

Inflammation-induced dysregulation patterns of UGTs are probably pathology-dependent, tissue-specific and isoform-heterogeneous. The direction and extent of change depend on the type of inflammation, cytokine

spectrum and time course (36,37). In rat colitis model, the expression and activity of hepatic UGTs were significantly down-regulated except for the up-regulation of UGT1A7, but those in small intestine were unaffected (36). Similarly, hepatic mRNA expression of UGT1A1, 1A9, and 2B5 were significantly down-regulated while renal UGT 1A9 and 2B5 were increased after LPS treatment (38). In arthritis rats, hepatic P-gp and Mrp2 significantly decreased, and those were up-regulated in kidney, but those were unchanged in small intestine (39). Interestingly, LPS-induced proinflammatory cytokines caused Mrp2 down-regulated in liver at 24 h post-treatment, but the Mrp2 rebounded at 48 h (40).

It has been reported that GFR failed to accurately predict 48% renal CL of the analyzed compounds, which may be confused by inflammation-mediated change of metabolic enzymes and transporters (41). Systemic inflammatory response to endotoxemia was associated with increased eGFR (42). In addition, augmented renal clearance is common in critically ill patients, which is also relevant to systemic inflammation (43). Consequently, we supposed that MPO was not only an important pathological marker of AAN, but also an inflammatory factor that can increase drug CL by regulating MPA-related metabolic enzymes and transporters.

Dosage optimization

The preliminary results supported CysC and MPO-tiered dosage regimen for individual medication, which can help prevent renal flares or the progress of glomerulonephritis. Dosage simulation indicated that a MMF dose of 750 mg (650 mg/m^2) twice daily was required to achieve the target $AUC_{0\text{-}12h}$ of 30 mg/L·h in ANCA children with normal renal function and no inflammation. An initial MMF dose of 600 mg/m^2 twice daily was suggested to reach target $AUC_{0\text{-}12}$ in pediatric liver transplant recipients (44). Similarly, a median MMF dose of 659.5 mg/m^{2}twice daily could reach target $AUC_{0\text{-}12h}$ in children after intestinal transplant (45). However, a higher dose of 900 mg/m^2 twice daily in conjunction with cyclosporine after renal transplantation has been suggested (46). Furthermore, patients with idiopathic nephrotic syndrome administered a standard initial dose of MMF 1200 mg/m^2/d, of which 40% decreased to a median dose of 940 mg/m^2/d and 60% increased to a median dose of 1400 mg/m^2/d (47).

There were some limitations in this study. First, this was a retrospective study so that we did not investigate all possible covariates, but we still found the valuable factors. Besides, this was a small study conducted in only 25 subjects over a period of 5 years because ANCA is a rare disease.

ACKNOWLEDGEMENTS

The authors thank Mr. Yong-chao Fu (Tri-I Biotech Ltd., Shanghai, China) and Mr. Wu Liang (Changsha VALS Technology Co.Ltd., Hunan, China) for their guidance in model building.

COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

Z.W.L. designed the study, developed the models and wrote the manuscript. Y.D.H were involved in patient data collection and acquisition. H.X and Z.P.L provided support for the research and reviewed the manuscript. All the authors read and approved the final manuscript.

FUNDING INFOAMATION

This work was supported by the National Natural Science Foundation [grant number 81874325]; Scientific Research Project of Science and Technology Commission of Shanghai Municipality [grant numbers 18DZ1910604, 19XD1400900, 19DZ1910703].

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author on reasonable request.

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48.

TABLES

Table 1. Baseline characteristics of study population

Characteristics	Data
Demographic data	
Gender (male/female)	25 (6/19)
Age (years)	11±3
Weight (kg)	35.0±13.0
Body surface area (kg/m^2)	1.15±0.28
Alanine aminotransferase (IU/L)	17±36
Aspartate aminotransferase (IU/L)	26±34

Characteristics	**Data**
Alkaline phosphatase (IU/L)	174±120
Total bilirubin (μmol/L)	7.0±2.7
Uric acid (μmol/L)	420±143
Serum creatinine (μmol/L)	452±412
Cystatin C	4.21±3.28
Albumin (g/L)	39.3±5.7
White blood cell (10^9/L)	7.82±3.21
Hemoglobin (g/L)	115.3±21.9
Neutrophils (%)	60.6±15.2
IgG	7.25±3.57
$CD3^+$	81.67±68.96
$CD4^+$	37.48±9.77
$CD19^+$	12.68±14.61
Myeloperoxidase $^+$	16 (64%)
Myeloperoxidase (RU/ml)	36.5±47.7
Pharmacokinetic data	
C_{0h} (ug/ml)	3.1±3.2
$C_{0.33h}$ (ug/ml)	6.2±6.7
C_{1h} (ug/ml)	7.3±8.2
C_{3h} (ug/ml)	4.3±3.6
$AUC_{0\text{-}12h}$ (mg/L·h)	45.11±30.26
Mycophenolate mofetil dosage (mg/d)	375 (125-1500)
Dosage forms (dispersible: capsule: Enteric-coated salt)	67:11:30
Concomitant prednisone (mg/d) 0: 0 ˜10: >10	29:46:32

Table 2. Pharmacokinetic population parameters in final model and bootstrap results (N=1000) of mycophenolate mofetil in patients with ANCA-associated nephritis

Parameter	
Structural parameters	
K_a (h^{-1})	
CL (L/h)	
Q (L/h)	
V_c (L)	
V_p (L)	
$\vartheta_{Dosage2}$	
$\vartheta_{Dosage3}$	
$\vartheta_{Cystatin\ C}$	
$\vartheta_{Serum\ creatinine}$	
$\vartheta_{myeloperoxidase}$	
$\vartheta_{Albumin}$	
Interindividual variability	
ω_K_a	
ω_CL	
ω_V_p	
Residual variability[a]	
Proportional	

Parameter
Additive
OFV
Cystatin C model: K_a (h^{-1}) = 0.45 · [1+(-0.449) · (if dosage=capsule preparations)] · [1+(-0.959) · (if dosage=enteric-coate

[a] Residual variability reported as standard deviation;[b] Simulation based on cystatin C model.

FIGURE LEGENDS

Figure 1. Plasma concentration-time profile of mycophenolic acid.

Figure 2. Comparison of K_a and its variability between base model (A) and covariate model (B). The random variable η is normally distributed with mean zero and variance of ω^2, which is the deviation of η_i from population value.

Figure 3. The variation of clearance rate before (A, B) and after addition of covariate (C, D). The random variable η is normally distributed with mean zero and variance of ω^2, which is the deviation of η_i from population value.

Figure 4. Covariate effects on pharmacokinetic parameters of mycophenolic acid. The X-axis is inter-individual variation (η_i) expressed by the mean±SD.

Figure 5. Distribution of estimated glomerular filtration rate (eGFR) calculated with the measurement of serum creatinine and cystatin C.

Figure 6. Goodness-of-fit plots of mycophenolic acid for population pharmacokinetic model. Observed concentration versus population (A) and individual (B) predictions, and conditional weighted residuals versus population predictions (C) and time from dose (D). y =±2 represents 95% confidence interval.

Figure 7. Visual predictive check for mycophenolic acid. The blank dots are actual observations. The redlines are 5^{th} (solid line), 50^{th} and 95^{th} (dash lines) quantiles from actual observations within their simulated 95% CIs (shaded areas).

SUPPORTING INFORMATION

Supplemental Figure1.The effect of prednisolone on absorption (P=0.017).

Supplemental Table 1. Dosage simulations of mycophenolate mofetil for ANCA-associated nephritis children (N=1000) based on different estimated glomerular filtration rates (eGFR) and myeloperoxidase