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RESEARCH ARTICLE

Early pharmacokinetics of low dosage mycophenolate exposure in Thai kidney transplant recipients

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Abstract

Background The effects of mycophenolic acid exposure in the early period after transplantation on clinical outcomes have been reported; however, mycophenolic acid exposure in the early period after transplantation in Asian kidney transplant recipients who receive 1.5 g/d mycophenolate mofetil has never been investigated. Objective To determine mycophenolic acid exposure on day 3 post-transplantation in kidney transplant recipiens who receive 1.5 g/d mycophenolate mofetil. The effects of the reduced renal function on mycophenolic acid area under the concentration–time curve (AUC) and the achievement of the target AUC on the incidence of biopsy proven acute rejection during the first month post-transplantation were also evaluated. *Setting* A university hospital *Method* Blood samples and 24-h urine were collected on day 3 post-transplantation. *Main outcome measures* The mycophenolic acid AUC was calculated by linear trapezoidal rule and compared with the target of 45 mg*h/L. Results Of 42 Thai kidney transplant recipiens, the mean mycophenolic acid AUC of 45.1 mg*h/L (SD 14.7) was comparable to the AUC target ($P=0.962$). Significant differences of the mycophenolic acid AUC were observed between patients with urine output of <2400 mL and those with urine output ≥ 2400 mL (35.3 ± 6.6 and 47.4 ± 15.2, respectively; $P=0.002$), and between patients with 24-h measured CrCl <25 mL/min and those with CrCl ≥ 25 mL/min (38.0 (29.0, 42.2) and 49.2 ± 14.0, respectively; $P=0.017$). Proportions of overall biopsy proven acute rejection among patients with mycophenolic acid AUC of <45 and ≥ 45 mg*h/L were comparable (20.0% and 23.5%, respectively; $P=1.000$). *Conclusions* After the starting dosage of 1.5 g/d mycophenolate mofetil, the mean mycophenolic acid AUC on day 3 post-kidney transplantation is comparable with the target of 45 mg*h/L. Severely reduced renal function significantly influences mycophenolic acid exposure.

Keywords Kidney transplantation · Mycophenolate mofetil · Mycophenolic acid · Pharmacokinetics · Renal function

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Impact on practice

- After a starting dose of 1.5 g/d mycophenolate mofetil, two-thirds of Asian kidney transplant recipiants have an AUC of between 30 and 60 mg*h/L mycophenolic acid and about one half had an AUC ≥ 45 mg*h/L on day 3 post-transplantation. Due to the large interpatient variability in dose-interval MPA AUC values, it may be necessary to monitor the full or abbreviated AUC to optimize mycophenolic acid exposure especially in high risk kidney transplant patients.
- An AUC of less than 45 mg*h/L mycophenolic acid can be expected among kidney transplant recipients with urine output <2400 mL on day 3 post-transplantation. To reduce unnecessary costs, there is no need to monitor

total mycophenolic acid exposure of these patients. Free MPA monitoring (if available) would be of value in this group of patients, especially for those with high risk.

Introduction

Mycophenolate mofetil (MMF), a non-nephrotoxic antiproliferative agent, has been commonly used in combination with a calcineurin inhibitor (CNI) to prevent allograft rejection in kidney transplantation (KT). A significant relationship between the area under the concentration–time curve from 0 to 12 h (AUC) of mycophenolic acid (MPA) on day 3 post-KT and the incidence of biopsy-proven acute rejection (BPAR) in the first month and in the first year post-KT has been reported [1]. The association between a higher MPA AUC of more than 45 mg*h/L and a lower risk of kidney allograft rejection have been shown, and the therapeutic range of 30–60 mg*h/L was proposed [2–4]. Most of the MPA AUC studies used the oral MMF dose of 2 g/d [5].

Large intra- and inter-patient variability and time dependent characteristics of MPA pharmacokinetics have been observed [5, 6]. Sources of pharmacokinetic variability of MPA include concomitant medications, hypoalbuminemia, low hemoglobin concentrations, and reduced renal function [7]. These factors are common during early period after kidney transplantation. The inter-patient variability of MPA is important since early MPA underexposure increased the risk of acute rejection in the early post-KT period [1].

Delayed recovery of allograft function is often seen after kidney transplantation. Titration of the dose of a CNI, a known nephrotoxic agent, is challenging in kidney transplant recipients (KTRs) with reduced renal function. The unmet therapeutic target of CNI is frequently observed during the early period after transplantation. Optimal MPA exposure is another important factor contributing to net state of immunosuppression of KTRs who receive CNI together with MMF therapy.

Studies in Asian patients showed higher MPA exposure at an equivalent MMF dosage as recommended for Caucasians. The higher MPA exposure in Asians has been associated with a high prevalence of adverse effects including nausea, vomiting, severe diarrhea, neutropenia, and opportunistic infection [8]. The difference in the effects of MPA exposure among Asians has resulted in a reduction of MMF dosage to 1–1.5 g/d. In stable Thai KTRs, adequacy of MPA exposure was reported in patients who received 1 g/d in combination with tacrolimus or cyclosporine and a steroid [8–10]. However, MPA exposure in the very early period after KT has not been investigated in Asians when administered with a MMF dose of 1.5 g/d. Of interest is the fact that during the first few days after kidney transplantation, urine output (UO) of less than 2400 mL/d is commonly observed in KTRs with delayed graft function. Furthermore, creatinine clearance (CrCl) of less than 25 mL/min has been reported to influence MPA pharmacokinetics [11]. The effect of these factors on MPA exposure during the very early period after KT have not been explored.

Aims of the study

The primary objective of the study was to compare the MPA AUC on day 3 post-transplantation with the target of 45 mg*h/L. The secondary objectives were to compare the MPA AUC between KTRs with UO of < 2400 mL and those with UO ≥ 2400 mL, and between KTRs with 24-h measured CrCl < 25 mL/min and those with CrCl ≥ 25 mL/min on day 3, and to compare the incidence of biopsy proven acute rejection (BPAR) during day 3 to day 30 after transplantation between KTRs whose MPA AUC were < 45 mg*h/L and those with MPA AUC of ≥ 45 mg*h/L on day 3 after transplantation.

Ethics approval

The study was approved by the ethics committee of the Faculty of Medicine, Chulalongkorn University, in Bangkok, Thailand. The IRB approval number is 718/59.

Method

Study patients

Adult KTRs (age ≥ 18 years) who underwent their first KT in King Chulalongkorn Memorial Hospital (KCMH), Bangkok, Thailand, from February, 2017 to January, 2018 and received MMF 1.5 g/d with tacrolimus, prednisolone, and basiliximab for prophylaxis of acute kidney allograft rejection were invited to participate in this study.

Patients with multiple organ transplants, positive cross match, ABO incompatible kidney transplants, panel reactive antibody (PRA) more than 50%, history of bowel or intestinal surgery, systemic infection, hypersensitivity to MMF, tacrolimus or prednisolone, liver dysfunction, and patients who had received medication with a significant degree of drug interaction to MMF (sevelamer, rifampicin, magnesium or aluminum-containing antacids, cholestyramine, norfloxacin, or metronidazole) [5] were excluded.

This prospective study was registered in the Thai Clinical Trials Registry (TCTR 20170206003) and was conducted in accordance with the Declaration of Helsinki and

its subsequent revisions. Written informed consent was obtained from all patients prior to enrollment. The datasets during this current study are available from the corresponding author on reasonable request.

Immunosuppressive medications and other regimens

All participants received an immunosuppressive regimen comprising tacrolimus (Prograf®; Astellas), MMF (Cellcept®; F Hoffmann-La Roche), corticosteroids and basiliximab (Simulect®; Novartis Pharma AG). All received 750 mg MMF every 12 h starting on day-1 or day 0 and continued at this dose until MPA concentrations were measured on day 3 post-transplantation. Thenceforward, adjustment of subsequent MMF dosages was allowed on the basis of the clinical evidence of efficacy and toxicity. The single tacrolimus loading dose of 0.1 mg/kg was preoperatively started, followed by 0.05 mg/kg every 12 h and adjusted to achieve the target trough concentration of 7–8 ng/mL during the first month after transplantation. A tapered corticosteroid regimen consisted of intravenous methylprednisolone (Solumedrol®; Pfizer Manufacturing Belgium MV) 1000 mg on day 0, 500 mg on days 1 and 2 after transplantation. On day 3, oral prednisolone (Prednisolone Patar®, Patar lab (2517)) was started at 1 mg/kg/d and tapered down 10 mg every 5–7 days. All patients received 20 mg of basiliximab preoperatively and on day 4 after transplantation. Intravenous (IV) furosemide and antimicrobial prophylaxis were prescribed according to KCMH protocol. All KTRs received IV ceftriaxone on days 0 and 1, oral sulfamethoxazole/trimethoprim double strength once daily and acyclovir 200 mg twice daily starting on day 1. IV pantoprazole 40 mg once daily was prescribed on days 0–6 then switched to oral omeprazole 20 mg once daily.

Following transplantation, fluid replacement was generally started with normal saline plus 5% dextrose in water on days 0 and 1, and adjusted based on serum electrolyte status and urine volume thereafter to maintain euvolemic status. An oral liquid diet was started on day 1, and from day 2 a standard soft diet was served.

MPA analysis

On day 3 post-transplantation, venous blood samples were drawn before (C0), and at 30 min, 1, 2, 3, 4, 6, 8, and 12 h after the MMF morning dose. The plasma MPA concentration was determined by the new enzymatic method (Roche Total MPA Assay, Hoffmann-La Roche), with the Cobas Integra® 400 plus system, with a limit of quantification of the assay of 0.3 mg/L [12].

Outcome measurements and statistical analysis

The MPA AUC was calculated by linear trapezoidal rule. Maximum plasma concentration of MPA (Cmax) and time to maximum MPA plasma concentration (Tmax) were obtained directly from concentration–time profiles. The kidney biopsy was done with surveillance protocol biopsy or if clinically indicated. A rejection episode was diagnosed according to Banff 2017 criteria [13] by the pathologist who was blinded to the study.

The distribution of continuous data was evaluated by Shapiro–Wilk test. Continuous data are presented as mean ± standard deviation (SD) when data are normally distributed or medians with interquartile ranges (IQR) when data are not normally distributed. Counts and percentages are expressed for categorical data. To compare the mean MPA AUC with the target of 45 mg*h/L, one sample *t*-test was conducted. In the case of an extreme outlier, such as one having a value that exceeds the first quartile (Q1) minus 3(IQR) or the third quartile (Q3) plus 3(IQR) of MPA AUC, data after exclusion of the outlier would also be tested and reported. To derive confidence intervals (CI) of the mean MPA AUC independent of any distribution assumption, bootstrapping was also performed. Five thousand bootstrap data sets were generated by repeated random sampling with replacement from the original observed data set to determine the reliable 95% confidence intervals of the population parameters [14]. Continuous data were compared between two groups by using the independent *t*-test or Mann–Whitney *U* test as appropriate. Proportions were compared by Chi-square test or Fisher's exact test. A linear correlation between two parameters was determined by either Pearson correlation coefficient test or Spearman rank correlation coefficient test as appropriate.

Power calculation was performed. The acceptable percentage of MPA AUC difference was set as 20% of 45 mg*h/L, with a power of 0.9, a significance level of 0.05, and an estimated dropout rate of 30%, a sample size of at least 42 persons was determined. All tests were performed using IBM SPSS statistics 22 (IBM, Bangkok, Thailand). A 2-sided *P*-value of less than 0.05 was considered statistically significant.

Results

Forty-two Thai adult KTRs participated in this study (Fig. 1). Demographic and clinical characteristics on day 3 after their transplantations are summarized in Table 1. The MPA AUC on day 3 ranged from 21.1 to 87.5 mg*h/L (Mean 45.1, SD 14.7). A bootstrap 95% CI for the mean, obtained from 5000 bootstrap data sets, was 40.8–49.7 mg*h/L.

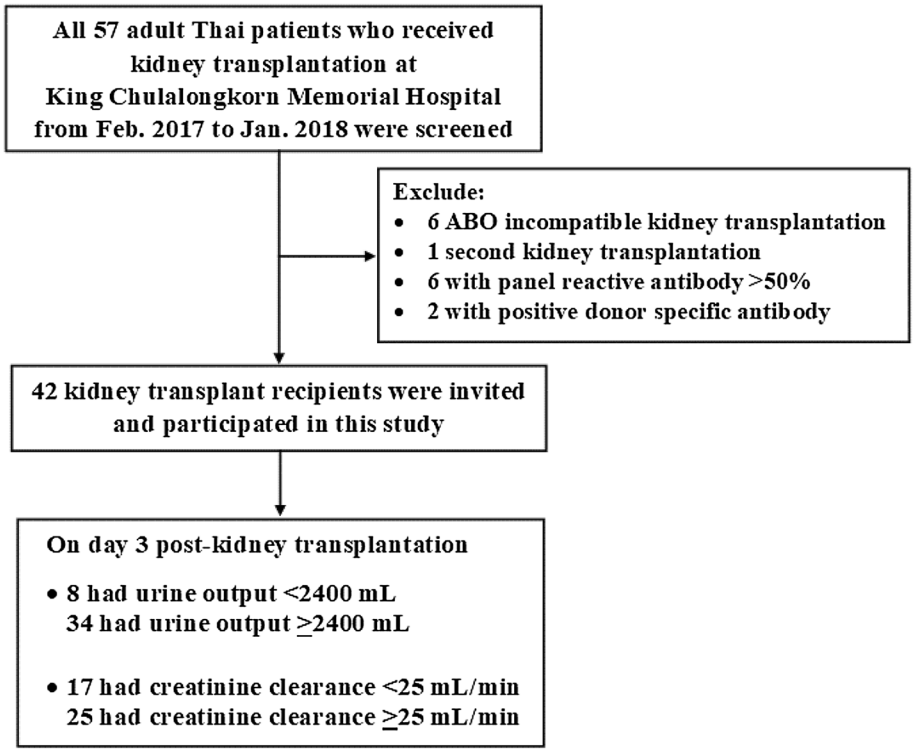

Fig. 1 Patients distribution

Table 1 Demographic and clinical characteristics on day 3 after kidney transplantation

Characteristics	Total ($n=42$)	24-h urine output		24-h measured CrCl	
		< 2400 mL ($n=8$)	≥ 2400 mL ($n=34$)	< 25 mL/min ($n=17$)	≥ 25 mL/min ($n=25$)
Male, *n* (%)	27 (64.3)	4 (50.0)	23 (67.6)	8 (47.1)	19 (76.0)
Body weight, kg	57.0 ± 10.1	62.3 ± 8.9	55.8 ± 10.1	59.5 ± 8.4	55.4 ± 11.0
Body mass index, kg/m^2	21.8 ± 3.3	24.1 ± 3.4	21.3 ± 3.1	23.3 ± 3.0	20.8 ± 3.1
Age at transplant date, years	44.8 ± 10.8	45.8 ± 5.3	44.6 ± 11.7	48.1 ± 9.2	42.6 ± 11.4
Dialysis duration before transplantation, years	4.1 (2.4, 6.5)	5.7 (4.2, 8.3)	4.0 (1.7, 6.5)	5.4 (4.0, 6.7)	3.1 (1.2, 5.9)
Deceased donor, *n* (%)	29 (69.0)	8 (100.0)	21 (61.8)	17 (100.0)	12 (48.0)
HLA mismatch, no.	3.0 ± 1.5	3.3 ± 1.7	2.9 ± 1.5	2.9 ± 1.3	3.0 ± 1.7
PRA > 10%, *n* (%)	2 (4.8)	0 (0.0)	2 (5.9)	1 (5.9)	1 (4.0)
Cold ischemic time, h[a]	17.4 ± 3.4	18.6 ± 3.3	17.0 ± 3.4	17.7 ± 3.8	17.1 ± 2.7
Delayed graft function, *n* (%)	8 (19.0)	8 (100.0)	0 (0.0)	8 (47.1)	0 (0.0)
Blood urea nitrogen, mg/dL	42.5 (26.0, 63.5)	69.6 ± 15.1	36.0 (21.8, 52.5)	70.8 ± 20.0	31.2 ± 12.3
Serum creatinine, mg/dL	3.73 (1.95, 7.86)	8.92 ± 1.84	2.39 (1.76, 6.78)	8.25 ± 1.94	2.24 (1.34, 2.64)
Urine output, mL/kg	66.8 ± 33.8	11.3 ± 9.9	79.9 ± 21.8	41.3 ± 32.1	84.1 ± 22.1
Serum albumin, g/dL	3.57 ± 0.42	3.26 ± 0.29	3.65 ± 0.42	3.45 ± 0.34	3.66 ± 0.46
Hemoglobin, g/dL	10.7 ± 1.7	9.7 ± 1.8	10.9 ± 1.6	10.2 ± 1.8	11.0 ± 1.6
AST, U/L	17.3 ± 6.4	23.4 ± 5.7	15.9 ± 5.7	20.9 ± 6.1	13.0 (11.0, 18.5)
ALT, U/L	14.5 (11.0, 20.5)	25.1 ± 14.6	13.5 (10.8, 17.8)	17.0 (10.5, 28.0)	13.0 (11.0, 16.5)
Total bilirubin, mg/dL	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 (0.3, 0.5)	0.4 ± 0.1
Direct bilirubin, mg/dL	0.2 (0.2, 0.2)	0.2 ± 0.0	0.2 ± 0.1	0.2 ± 0.0	0.2 ± 0.0

CrCl creatinine clearance, *HLA* human leukocyte antigen, *PRA* panel reactive antibody, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

[a]Cold ischemic time was that of deceased donor kidney transplant only

Table 2 Mycophenolate, tacrolimus, and steroid therapy on day 3 post-kidney transplantation

Immunosuppressive therapy	Total ($n=42$)	24-h urine output		*P* value	24-h measured CrCl		*P* value
		<2400 mL ($n=8$)	≥2400 mL ($n=34$)		<25 mL/min ($n=17$)	≥25 mL/min ($n=25$)	
MMF dose, mg/kg	13.16 (11.45, 15.21)	12.25 ± 1.69	13.91 ± 2.73	0.109[a]	12.85 ± 1.77	14.10 ± 3.01	0.098[a]
MPA AUC, mg*h/L	45.1 ± 14.7	35.3 ± 6.6	47.4 ± 15.2	0.002[a]	38.0 (29.0, 42.2)	49.2 ± 14.0	0.017[b]
MPA AUC/dose, mg*h/L per mg	0.060 ± 0.020	0.047 ± 0.009	0.063 ± 0.020	0.002[a]	0.051 (0.039, 0.056)	0.066 ± 0.019	0.017[b]
MPA dose/AUC, mg per mg*h/L	18.4 ± 5.8	22.0 ± 4.5	17.5 ± 5.9	0.051[a]	21.2 ± 6.5	16.4 ± 4.5	0.007[a]
MPA C0 concentration, mg/L	3.3 ± 1.9	2.2 ± 1.5	3.5 ± 1.9	0.093[a]	2.3 ± 1.4	3.9 ± 1.9	0.005[a]
MPA C0/dose, mg/L per mg	0.004 ± 0.003	0.003 ± 0.002	0.005 ± 0.003	0.093[a]	0.003 ± 0.002	0.005 ± 0.003	0.005[a]
Tacrolimus dose, mg/kg/d	0.10 (0.08, 0.11)	0.08 ± 0.02	0.10 (0.09, 0.11)	0.044[b]	0.09 (0.08, 0.10)	0.10 (0.09, 0.11)	0.025[b]
Tacrolimus C0 concentration, ng/mL	9.80 (8.08, 15.23)	11.79 ± 4.44	9.80 (7.85, 14.90)	0.718[b]	10.41 ± 3.94	12.10 ± 5.09	0.255[a]
Prednisolone, mg/kg/d	0.97 ± 0.11	0.93 ± 0.10	0.98 ± 0.11	0.228[a]	0.95 ± 0.08	0.99 ± 0.12	0.207[a]

AUC area under the concentration–time curve from 0–12 h after the morning dose of mycophenolate mofetil, *C0* trough concentration, *CrCl* creatinine clearance, *MPA* mycophenolic acid, *MMF* mycophenolate mofetil

[a]Comparison between two groups by Student *t*-test

[b]Comparison between two groups by Mann–Whitney *U* test

Seventeen KTRs (40.5%) achieved the target of MPA AUC of 45 mg*h/L. The mean ± SD of dose-normalized MPA AUC was 0.060 ± 0.020 mg*h/L per mg as presented in Table 2. A moderate positive relationship between MPA AUC and MPA trough concentration was observed (Pearson correlation coefficient, $r=0.577$; $P<0.001$). Tmax occurs 0.5–4 h after dose (Median 1.0, IQR 0.5–2.0) with the mean observed Cmax of 10.9 ± 4.4 mg/L.

The measured MPA AUC was normally distributed (Shapiro–Wilk test, $P=0.052$) and no extreme outlier was identified. The measured MPA AUC did not differ statistically from the target value of 45 mg*h/L (mean difference = 0.1, t = 0.048, df = 41, $P=0.962$). Significant differences of the MPA AUC were observed between KTRs with UO of < 2400 mL and those with UO ≥ 2400 mL (35.3 ± 6.6 and 47.4 ± 15.2 mg*h/L, respectively; *t*-test, $P=0.002$), and between KTRs with 24-h measured CrCl < 25 mL/min and those with CrCl ≥ 25 mL/min (38.0 (29.0, 42.2) and 49.2 ± 14.0 mg*h/L, respectively; Mann–Whitney *U* test, $P=0.017$) as presented in Fig. 2 and Table 3. Scatter plots that show the relationships between MPA AUC and UO and between MPA AUC and CrCl are displayed in Fig. 3 and 4.

Of 42 KTRs, 9 (21.4%) experienced BPAR (including borderline ACR cases) during the first month after transplantation. Of 8 patients whose rejections were identified on surveillance biopsy during days 7–12, two had borderline ACR and 6 had ABMR. Only one rejection, which was

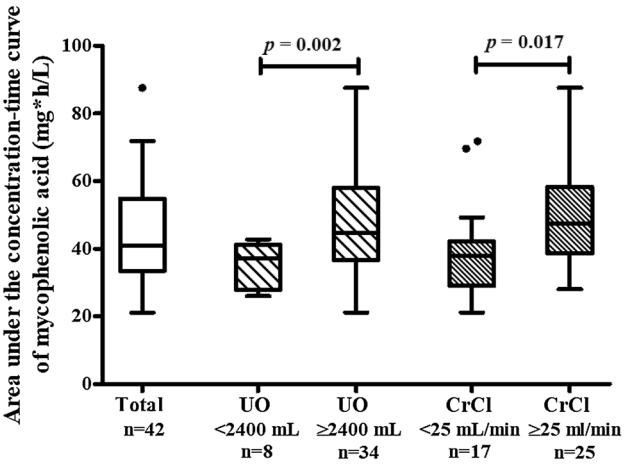

Fig. 2 Box plot of the mycophenolic acid area under the concentration–time curve distribution among groups (*UO* urine output, *CrCl* creatinine clearance)

ACR, was diagnosed on biopsy for cause at 1-month post-KT. Proportions of overall BPAR among patients with MPA AUC of < 45 and ≥ 45 mg*h/L were comparable (20.0% and 23.5%, respectively; Fisher's exact test, $P=1.000$). One (4.0%) of the patients with MPA AUC < 45 mg*h/L and 2 (11.8%) of those with MPA AUC ≥ 45 mg*h/L had ACR, and four (16.0%) with MPA AUC < 45 mg*h/L and 2 (11.8%) with MPA AUC ≥ 45 mg*h/L had ABMR. Tacrolimus trough

Table 3 Proportions of kidney transplant recipients who achieved the therapeutic target of mycophenolic acid area under the concentration–time curve on day 3 post-transplantation

MPA AUC (mg*h/L)	Total ($n=42$)	24-h urine output		*P* value	24-h measured CrCl		*P* value
		< 2400 mL ($n=8$)	≥ 2400 mL ($n=34$)		< 25 mL/min ($n=17$)	≥ 25 mL/min ($n=25$)	
< 45, *n* (%)	25 (59.5)	8 (100.0)	17 (50.0)	0.013[b]	14 (82.4)	11 (44.0)	0.013[a]
≥ 45, *n* (%)	17 (40.5)	0 (0.0)	17 (50.0)		3 (17.6)	14 (56.0)	
< 30, *n* (%)	6 (14.3)	2 (25.0)	4 (11.8)	0.288[a]	5 (29.4)	1 (4.0)	0.067[a]
30–60, *n* (%)	29 (69.0)	6 (75.0)	23 (67.6)		10 (58.8)	19 (76.0)	
> 60, *n* (%)	7 (16.7)	0 (0.0)	7 (20.6)		2 (11.8)	5 (20.0)	

MPA AUC mycophenolic acid area under the concentration–time curve, *CrCl* creatinine clearance

[a]Comparison between two groups by Pearson Chi-square tests

[b]Comparison between two groups by Fisher's exact test

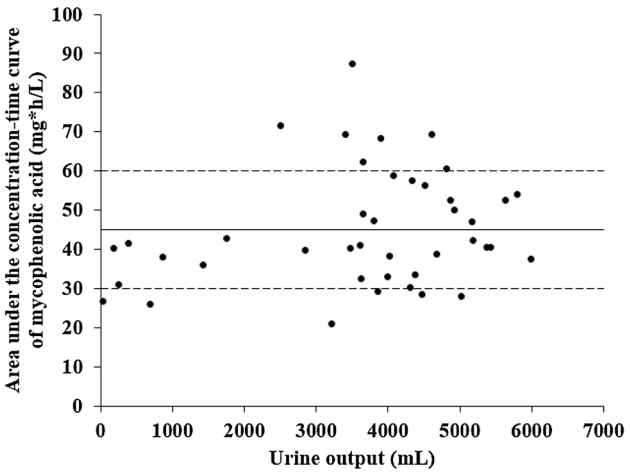

Fig. 3 Scatter plot of the mycophenolic acid area under the concentration–time curve versus urine output on day 3 post-transplantation

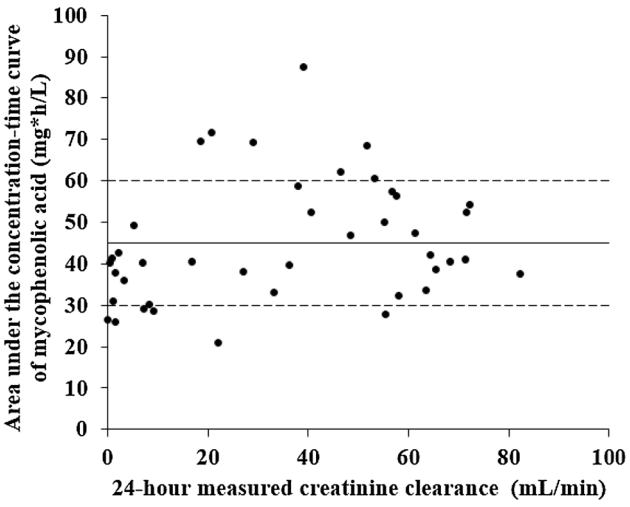

Fig. 4 Scatter plot of the mycophenolic acid area under the concentration–time curve versus creatinine clearance on day 3 post-transplantation

concentrations were comparable between rejecters and non-rejecters (12.2 ± 3.4 and 9.8 (7.1, 15.0) ng/mL, respectively; Mann–Whitney *U* test, $P=0.432$), and between recipients with MPA AUC < 45 versus ≥ 45 mg*h/L (11.1 ± 4.0 and 12.0 ± 5.6 ng/mL, respectively; *t*-test, $P=0.549$).

Discussion

In this study, the MPA exposure on day 3 after KT was evaluated in 42 adult Thai KTRs who received an immunosuppressive regimen consisting of tacrolimus, MMF, corticosteroid and basiliximab. Based on full 12-h pharmacokinetic profiles, the mean MPA AUC of 45.1 mg*h/L (SD 14.7) was found to be not statistically different from the target of 45 mg*h/L ($P=0.962$). The mean MPA AUC in KTRs in whom UO was < 2400 mL was lower than those who had UO ≥ 2400 mL on day 3 (35.3 ± 6.6 and 47.4 ± 15.2 mg*h/L, respectively; $P=0.002$). The MPA AUC was also significantly lower among KTRs with 24-h measured CrCl of less than 25 mL/min when compared with those with CrCl of ≥ 25 mL/min (median (IQR), 38.0 (29.0, 42.2) and mean ± SD, 49.2 ± 14.0, respectively; $P=0.017$). No significant difference in the incidence of BPAR during the first month post-KT was found between recipients whose MPA AUC reached or did not reach the target of 45 mg*h/L on day 3.

Our finding confirms the results of previous studies which demonstrated the higher dose-normalized MPA AUC during the very early period (days 3–7) after transplantation in Asian KTRs than in Caucasians [15]. The measured MPA AUC of 45.1 ± 14.7 mg*h/L observed in our studied patients was higher than those reported by Kiberd et al. [16] and Gourishankar et al. [17], which shown the mean MPA AUC on day 3 post-KT after a fixed dosage of 2 g/d MMF of 36.8 ± 11.1 and 40.3 mg*h/L, respectively. Pawinski et al. [18] and Barraclough et al. [19] also reported MPA AUC estimated by different

limited sampling strategies after the MMF dosage of 2 g/d of 28.6 ± 16.81 on day 7 and 29.8 (23.6, 40.8) mg*h/L on day 4 post-transplant, respectively. Meanwhile, with the same MMF dosage regimen of 1.5 g/d administered in our recipients, Chinese KTRs had comparable MPA AUC with ours (39.1 ± 14.4 mg*h/L on day 7 post-transplant) [20].

Pharmacokinetics of MPA is known to be time-dependent. In approximation, a lower mean MPA AUC of at least 30–50% was observed in the first few weeks when compared with during 1–6 months after transplantation [21–23]. Optimization of immunosuppressive therapy to avoid over- and under-immunosuppression is crucial during the very early days after transplantation, when the risk of acute allograft rejection and complications are usually the highest. In a prospective cohort of 100 KTRs who received MMF and tacrolimus therapy, a trend toward a higher BPAR incidence (26.3%) was observed in KTRs with MPA AUC < 45 mg*h/L and tacrolimus AUC < 150 ng*h/mL, in comparison with those in whom the targets MPA AUC of 45 mg*h/L and tacrolimus AUC of 150 ng*h/mL were achieved by day 7 (7.7%) [24]. In addition, a 2.5-fold increase in the incidence of acute rejection was reported from the FDCC trial when MPA AUC on day 3 post-kidney transplant was less than 30 mg*h/L [25]. Due to the limited number of patients in our study, it is possible that a concentration-effect relationship between MPA AUC and risk of rejection may have been missed.

High inter-patient variability of MPA exposure is also confirmed in our studied population. Only approximately 40% of our patients had MPA AUC ≥ 45 mg*h/L, higher MMF dose is needed in some KTRs, especially in those with high immunologic risk. In view of the poor correlation between MPA AUC and MPA trough concentration, it may be necessary to repetitively monitor full or abbreviated MPA AUC to optimize exposure to MPA in our patients.

We found that reduced renal function significantly influenced the pharmacokinetics of MPA. This finding is similar to the report by van Hest et al. [11] who showed that the MPA clearance is 34% higher in patients with CrCl below 25 mL/min when compared with those who had better renal function. The higher MPA clearance may lead to lower MPA AUC as shown in several studies where patients with low renal function had lower MPA AUC compared to others [26–28]. These effects can be explained by the binding of MPA to plasma proteins being influenced by the availability of serum albumin binding sites and competition for these sites by its major metabolite, 7-*O*-MPA-glucuronide (MPAG), and urea. Significant renal dysfunction and hypoalbuminemia can alter MPA and MPAG serum albumin binding, causing a higher free (unbound) fraction of MPA. Given that free MPA is available for metabolism and excretion, apparent clearance of total MPA would, therefore, increase.

To the best of our knowledge, this current study demonstrates for the first time the relationships between UO, a non-invasive bedside test for kidney function, and MPA AUC. In general, the urine volume is high within the first 24–48 h after kidney transplantation. An increase of urine volume represents the first sign of progressive recovery of kidney graft function, ahead of a decrease in serum creatinine [29]. Of interest is the fact that on day 3, all KTRs in whom UO < 2400 mL had MPA AUC of < 45 mg*h/L.

Also of note is that an alteration of the free fraction of MPA among KTRs with reduced renal function was demonstrated [26, 30–33] and the changes in total MPA concentration may not be associated with parallel changes in free MPA concentration [34]. Interpretation of total MPA exposure among patients with reduced renal function, therefore, should be done with caution. Free MPA monitoring would be of value for this group of patients, especially in those with high immunologic risk.

Our study has certain limitations. First, all of the patients who participated in this study received a combination of tacrolimus and MMF with corticosteroid. It was shown that dose-normalized MPA exposure was 30–40% lower in KTRs who received cyclosporine when compared with those who received tacrolimus or sirolimus [35]. Corticosteroids can also influence MPA exposure in KTRs due to possible enzyme induction effect. However, assessment of MPA pharmacokinetics in patients received combination therapy is based on a realistic situation. Second, all of our studied patients received proton pump inhibitor (PPI) injection during the first week post-transplantation. Possibly due to gastric acid secretion inhibitory effect, significant influence of PPIs on bioavailability of oral MMF have been reported [36–38]. MPA exposure could be different among those not receiving concomitant PPI. Third, this study was performed in patients not receiving any other interacting medications, this may result in an underestimation of MPA pharmacokinetic variability when the medications which may interact with MMF is concomitantly used. The impact of factors other than reduced renal function on MPA AUC was not explored in this study. In order to avoid some KTRs having a very low or high MPA exposure, further study to identify factors which may explain a variation of MPA pharmacokinetics after the fixed dosage of MMF is needed. A population pharmacokinetic study would be beneficial for better describing pharmacokinetics characteristics and explaining inter-patient variation and inter-occasion variation of this medication. Fourth, high performance liquid chromatography with mass-spectrometric detection, the gold standard method of MPA analysis, was not used in this study. However, cross-reactivity with acyl-MPAG was reported to be < 5% when

plasma MPA concentrations were determined by Roche Total MPA Assay [12]. Finally, the study did not have sufficient statistical power to detect any difference (if one existed) in the incidence of BPAR between the patients whose MPA AUC reached or did not reach the target of 45 mg*h/L on day 3.

Conclusion

After using an MMF starting dosage of 1.5 g/d, the mean MPA AUC on day 3 post-KT is comparable with the recommended target MPA AUC of 45 mg*h/L. Reduced renal function is found to significantly influence the MPA pharmacokinetics early after transplantation.

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