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Original Article

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Is a standard fixed dose of mycophenolate mofetil ideal for all patients?

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Abstract

Background. A standard fixed dose of 2 g/day of mycophenolate mofetil (MMF), irrespective of total body weight (TBW), is recommended when used in combination with cyclosporine and corticosteroids in renal transplantation.

Methods. To determine the optimal MMF dose in a population with wide variation in TBW, steady-state pharmacokinetics of mycophenolic acid (MPA) was performed in 53 Asian (Chinese, Malay, Indian, Eurasian) renal transplant recipients (RTX) receiving MMF [250–1000 mg twice daily (BD)] for at least 3 months. Blood samples were collected at 0, 0.5, 1, 1.5, 2 and 6 h after the MMF dose and total MPA quantified using HPLC.

Results. Drug exposure, as evaluated by $AUC_{ss,0-12}$, demonstrated a significant positive correlation with TBW-adjusted MMF dose (outliers omitted: $r^2 = 0.49$, $P < 0.0005$). An $AUC_{ss,0-12}$ of 45 mg h/l could be attained with an MMF dose of 12 mg/kg BD.

Conclusion. This study proposes that MMF should be dosed based on TBW rather than a fixed dose regimen in RTX.

Keywords: asian; cyclosporine; mycophenolic acid; pharmacokinetics; renal transplant; weight-adjusted dosing

Introduction

Mycophenolate mofetil (MMF, CellCept®, Roche Pharmaceuticals, Basel, Switzerland), the ester prodrug of mycophenolic acid (MPA), is a potent immunosuppressant that is approved for the prophylaxis of organ rejection in renal, cardiac and hepatic transplant recipients. MMF is an anti-metabolite, used in combination with a calcineurin inhibitor (cyclosporine (CsA) [1–3] or tacrolimus [4–7]) or mammalian target of rapamycin inhibitor (sirolimus) [8–12] and corticosteroids, for the prevention of rejection in various transplant populations. Three randomized, double blind, multi-centre clinical trials have demonstrated that MMF, administered in combination with CsA and corticosteroids, reduces the incidence of acute allograft rejection in renal transplantation [1–3].

In clinical practice, the dose of MMF prescribed currently is based on data from clinical trials carried out in America, Australia, Canada and Europe [1–3,13]. Although efficacy and toxicity of MMF are concentration dependent [14–22], a fixed dose of 2 g/day or 3 g/day of MMF, given in two divided doses, in combination with CsA and corticosteroids, is recommended for prophylaxis of rejection in adult Caucasian [1–3] or African-American [13] renal transplant recipients (RTX), respectively. On the other hand, MMF dosing based on body surface area (600 mg/m^2 twice daily, with concomitant CsA and corticosteroid) has been recommended for paediatric transplant recipients [23]. Therefore in practice, a fixed dose of MMF is prescribed for adults and doses are reduced to toxic side effects of MMF, including leucopenia, thrombocytopenia, infections or gastrointestinal side effects. However, such a dosing strategy does not address dosing in populations with wide variation in total body weight (TBW), in whom a disproportionately higher MMF dose per kg TBW may expose the patient to higher risk for immunosuppressive complications of the drug.

Indeed, a randomized controlled trial conducted in an Asian RTX population suggested the need for MMF dosage reduction in this population so as to minimize the adverse effect of leucopenia; leucopenic patients receiving the standard fixed dose of 2 g/day had received higher doses of MMF in terms of mg per kg TBW [24]. Other studies among Chinese RTX have also suggested that MMF dosed at 1.5 g/day was

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comparable in efficacy to standard dosing [25,26] and may have been associated with fewer adverse effects [25]. Lower doses of MMF have also been prescribed for Thai (0.5–2 g/day) [27,28], Korean (1–1.5 g/day) [29] and Japanese (0.25–2 g/day) [30–33] RTX so as to reduce side effects. The feasibility of using lower MMF doses in the Asian RTX to reduce the incidence of adverse effects and yet provide comparable efficacy as that of the Western counterpart receiving 2 g/day may be in part due to the typically lower TBW of Asians. The mean TBW among the Asians in these studies is ~58 kg [26,27,29–31,33] while that of the Western populations in Europe (mainly Caucasian) is ~69 kg [1] and in America is ~74 kg for non-African American (mainly Caucasian) and 79 kg for African-Americans [13].

In order to address the optimal dosing strategy for MMF in a RTX population with wide variations in TBW, we examined MPA pharmacokinetics (PK) in our RTX population. In this present study, the objectives were 2-fold: first, to characterize the PK of MPA in RTX at our institution, of whom, the majority were of Chinese, Malay or Indian origin. These RTX had wide variation in TBW and were receiving variable doses of MMF as maintenance therapy for at least 3 months, with concomitant CsA-corticosteroid immunosuppression. Secondly, the aim was to determine the optimal MMF dose, based on TBW, in RTX on concomitant CsA, based on the PK results attained in this study.

Subjects and methods

Patients

The study population included deceased and live-donor RTX who were on follow-up at the Department of Renal Medicine, Singapore General Hospital (SGH); all were receiving CsA-MMF-corticosteroid-based immunosuppression. Study subjects underwent CsA dose adjustments according to 2 h CsA levels and clinical circumstances, as previously described [34]. Doses of MMF were however not standard; some RTX had undergone MMF dose adjustments due to adverse effects at higher doses. Thus, patients were on maintenance twice daily (BD) MMF doses of 250, 500, 750 or 1000 mg.

The study was approved by the institutional review board at SGH and all patients were recruited after written and informed consent. Inclusion criteria were as follows: (i) immunosuppression with MMF, CsA and prednisolone for at least 3 months prior to recruitment into the study, (ii) maintenance on the same morning and night dose of MMF and (iii) maintenance on the same dosing regimen of MMF and CsA for at least one week before PK investigations. Patients were excluded from the study if they had (i) severe gastrointestinal disorders that interfered with their ability to receive or absorb oral medication, (ii) severe diarrhoea (more than five watery stools per day) and/or (iii) liver disease (seropositivity for hepatitis B surface antigen or anti-hepatitis C antibody or elevated alanine aminotransferase and/or aspartate aminotransferase levels more than three times normal).

Study design

This was a prospective, open-labelled, single-centre study carried out in an outpatient setting. On the day of PK investigations, venous blood samples (3 ml) were collected into ethylenediaminetetraacetic acid-containing Vacutainer® tubes over a 6 h period at the targeted time-points of 0 (pre-dose), 0.5, 1, 1.5, 2 and 6 h after administration of the steady-state morning dose of MMF under supervision. Food and fluid intake by the study subjects were allowed without special restriction, after collection of the 0 h blood sample and MMF administration. For each blood sampling time-point, ±10 min were allowed. The exact times of MMF administration and blood sampling were recorded. The blood samples were centrifuged at 3000 r.p.m. (1380 g) for 10 min at 25°C using a Universal 32R Benchtop Centrifuge (Hettich, Germany) to harvest plasma that was transferred to polypropylene tubes and stored at −20°C until analysis.

Sample analysis

Plasma samples were analysed for the concentrations of total MPA using a previously established and validated reversed-phase ion-pair high-performance liquid chromatographic (HPLC) assay [35].

Pharmacokinetic analysis

Based on the HPLC measurements of the plasma levels of MPA, 12 h PK profiles of MPA were constructed. The level of MPA at 12 h after drug administration was taken to be the same as the 0 h of the next dose. This assumption was made on the basis that steady state would have been reached as these patients had been on MMF for more than 3 months and maintained on the same dosing regimen for at least one week prior to sample collection. Moreover, their morning and evening doses of MMF were the same, so the trough levels (at 0 and 12 h after drug administration) of MPA would be theoretically the same.

The actual but not nominal sampling times were used for all PK calculations. The PK data for each of the patients were analysed by non-compartmental model using the WinNonlin Professional software (Version 5.0.1, Pharsight Corporation, Cary, NC, USA). The plasma concentration measured just before MMF administration (C_0), the maximum observed plasma concentration (C_{max}) and its corresponding sampling time (T_{max}), were obtained directly from the plasma concentration–time profiles. The area under the plasma concentration–time curve at steady state within the dosing interval ($AUC_{ss,0-12}$) was calculated from 0 to 12 h after MMF administration, using the linear trapezoidal method. The apparent oral clearance (CL_{oral}) of MPA was calculated as the ratio of the MMF dose (expressed as dose of MPA) to the corresponding $AUC_{ss,0-12}$.

Statistical analysis

Statistical analyses were performed using SPSS 13.0 (SPSS Inc., USA). The one-sample Kolmogorov–Smirnov test was

used to test for normality. As some demographic data were not normally distributed, patient demographics in Table 1 were all expressed as median (range). The PK parameters were normally distributed and hence, were expressed as mean ± standard deviation (SD). Linear regression was carried out to determine the relationships between TBW-adjusted MMF dose (mg/kg per dose) and MPA $AUC_{ss,0-12}$ or C_0. A *P*-value of less than 0.05 was considered statistically significant. Box plots were constructed for visual inspection of the relationships between MPA C_0 or $AUC_{ss,0-12}$ and TBW-adjusted MMF dose ranges. Outliers were defined as cases with values that were between 1.5 and 3 times the inter-quartile range away from the lower or upper quartile, while extreme outliers were defined as cases with values more than three times the inter-quartile range away from the lower or upper quartile.

Table 1. Characteristics of study population[a]

Characteristics	Data ($n = 53$)
Male, *n* (%)	35 (66.0%)
Ethnicity, *n* (%)	
Chinese	39 (73.5%)
Malay	9 (17.0%)
Indian	3 (5.7%)
Eurasian	2 (3.8%)
Donor source, *n* (%)	
Deceased	39 (73.5%)
Live-related	10 (18.9%)
Live non-related	4 (7.6%)
Twice daily dose of mycophenolate mofetil (MMF), *n* (%)	
250 mg	4 (7.6%)
500 mg	23 (43.4%)
750 mg	19 (35.8%)
1000 mg	7 (13.2%)
Age (years)	44.0 (26.0–58.0)
Total body weight (kg)	66.8 (33.1–108.1)
Body mass index (kg/m^2)	23.8 (15.5–36.2)
Interval post-transplant (months)	42.4 (3.4–184.0)
Serum creatinine (μmol/l)	163 (83.0–367.0)
Calculated creatinine clearance (ml/min)[b]	40.0 (12.4–78.3)
Total body weight-adjusted MMF dose (mg/kg per dose)	9.4 (3.6–19.0)
Cyclosporine dose (mg/day)	200.0 (80.0–320.0)
Prednisolone dose (mg/day)	10.0 (5.0–18.0)

[a]All data were expressed as median (range), unless specified otherwise.
[b]Creatinine clearance was calculated using the abbreviated Modification of Diet in Renal Disease formula [36].

Results

Patient characteristics

Fifty-three stable RTX patients on oral dosing of MMF (250–1000 mg BD) for at least 3 months and on follow-up at SGH were recruited into the study. These subjects were all stable patients in terms of their transplantation condition. The majority of the patients (86.8%, Table 1) were prescribed MMF doses of <1000 mg BD. The demographic characteristics of these study subjects are summarized in Table 1. Notably, the TBW in our study population was wide, ranging from 33 to 108 kg. Creatinine clearance was calculated based on serum creatinine, age, gender and race using the abbreviated Modification of Diet in Renal Disease (aMDRD) formula [36].

All RTX were also on CsA (80–320 mg/day) and prednisolone (5–18 mg/day) immunosuppression and oral sulphamethoxazole-trimethoprim for prophylaxis against *Pneumocystis jiroveci* infection. Other common oral medications administered by most of the patients included lipid-lowering agents, anti-hypertensives, calcium and iron supplements.

Pharmacokinetics of total MPA

The individual PK profiles of total MPA for the study subjects are depicted in Figure 1 and the mean PK data of total MPA are presented in Table 2. As stated earlier, the MMF doses in the study population were

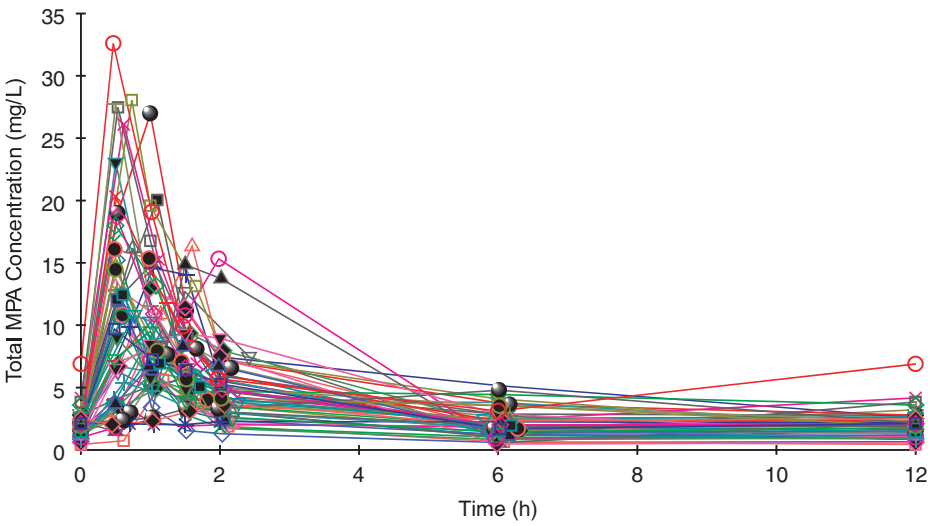

Fig. 1. Individual plasma concentration–time profiles of total mycophenolic acid (MPA) for 53 renal transplant patients on chronic dosing of mycophenolate mofetil with concomitant cyclosporine and corticosteroids.

not standard and TBW was varied in these study subjects; thus, C_0, C_{max} and $AUC_{ss,0-12}$ were normalized by MMF dose per kg TBW. The CL_{oral} was also adjusted to TBW.

A considerable inter-individual variability of all the PK data were observed, as shown by the large coefficients of variation (CV) (Table 2). The variability in C_0 and $AUC_{ss,0-12}$ and in CL_{oral} was slightly reduced by normalization according to MMF dose per kg TBW and TBW, respectively (Table 2); however these were not significantly reduced and the CV of the PK parameters, normalized to dose or weight remained large.

Table 2. Steady-state pharmacokinetic parameters of total mycophenolic acid (MPA) in 53 renal transplant patients receiving variable doses of mycophenolate mofetil (MMF) with concomitant cyclosporine and corticosteroids

	Mean ± SD	% CV[a]
Parameter		
C_0 (mg/l)	1.95 ± 1.06	54.7
C_{max} (mg/l)	13.4 ± 7.0	52.4
$AUC_{ss,0-12}$ (mg h/l)	41.4 ± 14.2	34.2
T_{max} (h)	1.02 ± 0.85	83.4
CL_{oral} (l/h)	12.3 ± 4.7	38.0
Parameter, normalized by total body weight (TBW)-adjusted MMF dose (mg/kg) or by TBW (kg)		
C_0 (mg/l), normalized by MMF dose (mg/kg)	0.207 ± 0.110	53.0
C_{max} (mg/l), normalized by MMF dose (mg/kg)	1.46 ± 0.82	56.3
$AUC_{ss,0-12}$ (mg h/l), normalized by MMF dose (mg/kg)	4.41 ± 1.46	33.1
TBW-adjusted CL_{oral} (l/h/kg)	0.185 ± 0.058	31.3

[a]Coefficient of variation did not improve significantly with normalization of pharmacokinetic parameters with TBW-adjusted MMF dose or TBW.

Correlation of TBW-adjusted MMF dose with total MPA $AUC_{ss,0-12}$ or total MPA C_0

Drug exposure of MPA, as evaluated by the total $AUC_{ss,0-12}$, demonstrated a weak but significant positive correlation with TBW-adjusted MMF dose ($r^2 = 0.30$, $P < 0.0005$; Figure 2A). The correlation ($r^2 = 0.49$, $P < 0.0005$) improved with the omission of outlying points (Figure 2B). On the other hand and in comparison to total MPA $AUC_{ss,0-12}$, total MPA C_0 demonstrated a much weaker though statistically significant positive correlation with TBW-adjusted MMF dose ($r^2 = 0.11$, $P = 0.017$; Figure 3A). The correlation ($r^2 = 0.20$, $P = 0.001$) improved only slightly with the omission of an extreme outlier (Figure 3B).

The box plots of total MPA C_0 against TBW-adjusted MMF BD dose showed that most patients would be able to attain the recommended target range of 1–3.5 mg/l for total MPA C_0 [37], with an MMF dose of at least 5 mg/kg BD (Figure 4A). Furthermore, as demonstrated by the box plots of total MPA $AUC_{ss,0-12}$ against TBW-adjusted MMF dose, an MMF dose of 5–15 mg/kg BD would achieve the recommended target range of 30–60 mg h/l for total MPA $AUC_{ss,0-12}$ [37] (Figure 4B).

Thus, TBW-adjusted MMF dose demonstrated a stronger correlation with the total MPA $AUC_{ss,0-12}$ than total MPA C_0. The TBW-adjusted MMF dose required to achieve any particular total MPA $AUC_{ss,0-12}$ could be estimated from the regression equations obtained (Table 3). In order to target a total MPA $AUC_{ss,0-12}$ of 30–60 mg h/l, it is estimated that MMF administered at doses between 5 and 17 mg/kg BD would be required. An $AUC_{ss,0-12}$ of 45 mg h/l, which is the mean of the recommended target therapeutic window of 30–60 mg h/l [37], could be attained with an average MMF dose of 11.5 mg/kg BD (Table 3).

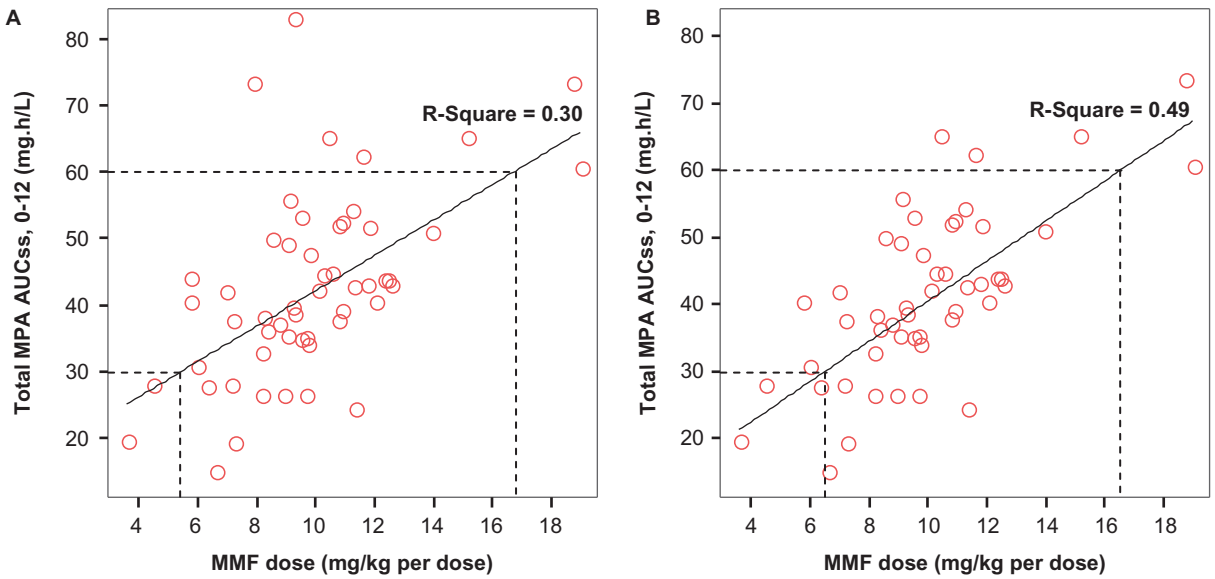

Fig. 2. Correlation of total mycophenolic acid (MPA) $AUC_{ss,0-12}$ with total body weight-adjusted mycophenolate mofetil (MMF) dose, (**A**) before and (**B**) after omission of outliers.

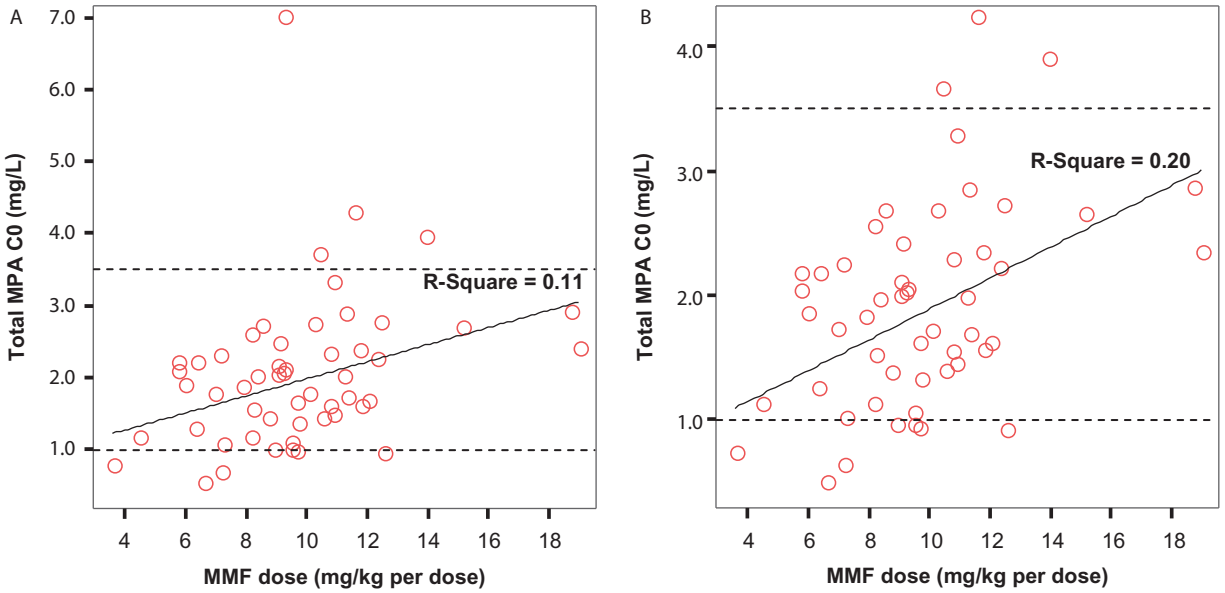

Fig. 3. Correlation of total mycophenolic acid (MPA) C_0 with total body weight adjusted mycophenolate mofetil (MMF) dose, (**A**) before and (**B**) after omission of outliers.

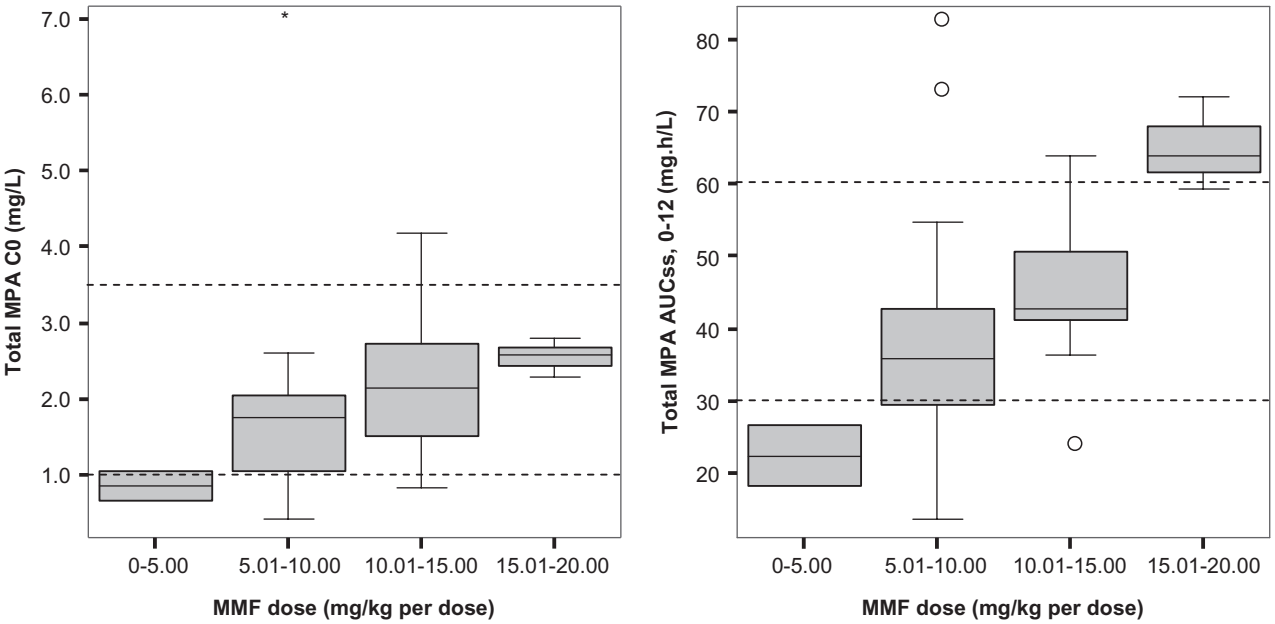

Fig. 4. Box plots of (**A**) total mycophenolic acid (MPA) C_0 and (**B**) total MPA $AUC_{ss,0–12}$ against total body weight adjusted mycophenolate mofetil (MMF) dose. The circles and asterisk denote the outliers and extreme outlier, respectively. The broken lines indicate recommended target ranges of 1–3.5 mg/l and 30–60 mg h/l for total MPA C_0 and $AUC_{ss,0–12}$, respectively.

This may be rounded off to 12 mg/kg BD for simplicity in calculation in the clinical setting. The body mass index failed to demonstrate a stronger correlation to PK parameters than TBW (not shown).

Discussion

Despite variations in body weight, MMF at a standard fixed dose of 1 g BD, irrespective of body weight, is recommended for prophylaxis of rejection in renal transplantation, when it is used in combination with CsA and corticosteroids. However, it is well established that MMF efficacy and toxicity are correlated with MPA concentrations. Based on the report of a roundtable discussion on therapeutic drug monitoring (TDM) of MPA, the proposed desirable target ranges are 30–60 mg h/l for total MPA $AUC_{ss,0–12}$, or 1–3.5 mg/l for total MPA C_0, when measured using HPLC technique [37].

Table 3. Estimated total body weight (TBW)-adjusted mycophenolate mofetil (MMF) doses based on the respective total mycophenolic acid (MPA) $AUC_{ss,0-12}$ (30, 45 or 60 mg h/l) according to the derived regression equations[a,b]

	Based on total MPA $AUC_{ss,0-12}$ of		
	30 mg h/l	45 mg h/l	60 mg h/l
Estimated TBW-adjusted MMF dose (mg/kg per dose):			
Before removing outlying points[a]	5.43	11.1	16.7
After removing outlying points[b]	6.52	11.5	16.5

[a]MMF BD dose per kg = (Total MPA $AUC_{ss,0-12} - 15.591$)/2.655.
[b]MMF BD dose per kg = (Total MPA $AUC_{ss,0-12} - 10.461$)/2.996.

Our study has clearly demonstrated that although 87% of the 53 subjects were on MMF doses below the recommended dose of 1000 mg BD, the mean total MPA C_0 (1.95 ± 1.06 mg/l) and $AUC_{ss,0-12}$ (41.4 ± 14.2 mg h/l) (Table 2) were nonetheless within the recommended therapeutic ranges. This was also demonstrated in similar studies among Thai RTX receiving maintenance MMF in combination with CsA and prednisolone for at least 3 months. The mean total MPA C_0 and $AUC_{ss,0-12}$ were 2.75 ± 0.07 mg/l and 37.54 ± 0.80 mg h/l, respectively, for 16 Thai RTX on MMF 500 mg BD [27]; the median total MPA C_0 and $AUC_{ss,0-12}$ were 1.46 mg/l and 34.3 mg h/l, respectively, in another 45 Thai patients receiving MMF doses of 0.5–2 g/day [28]. The lower doses used in our patients and those from other studies in Asian patients were likely adequate to achieve therapeutic levels of MPA because the average body weight of Asians is smaller than that of the Western population.

As MPA exposure and TBW-adjusted MMF dose are correlated (Figure 2), our study supports the use of TBW-adjusted dose of MMF for RTX, rather than a standard fixed dose of 1 g BD for all patients. From the regression results, in order to target an average total MPA $AUC_{ss,0-12}$ of 45 mg h/l in the maintenance period, MMF may be dosed based on TBW at ~12 mg/kg BD, rather than the standard fixed dose of 1 g BD. Indeed, a study carried out on Japanese RTX receiving MMF with tacrolimus and corticosteroids demonstrated that the MMF dose per kg TBW had an impact on the occurrence of acute rejection as the MMF dose per kg TBW was significantly lower in patients with acute rejection [31]. This provides evidence to support the use of TBW-adjusted MMF dosing to optimize clinical outcome.

On the market, MMF is available for oral administration as 250 mg capsule and 500 mg tablet and in some countries, also as 200 mg/ml oral suspension (supplied as powder to be constituted). From the practical viewpoint, the exact calculated dose based on 12 mg/kg BD would not be applicable precisely unless the oral suspension is available and accepted by the adult patient. Hence, doses prescribed according to the proposed recommendation of 12 mg/kg BD would have to be rounded off to the nearest 250 mg. This leveled dose would still be within the range of 5–17 mg/kg BD capable of achieving the desired therapeutic range of 30–60 mg h/l for total MPA $AUC_{ss,0-12}$ (Table 3).

Currently, there are two other studies that analysed the correlation of total MPA C_0 or $AUC_{ss,0-12}$ with TBW-adjusted MMF dose in patients receiving MMF with concomitant CsA immunosuppression [38,39]. The poor correlation between total MPA C_0 with TBW-adjusted MMF dose from the present study ($r^2 = 0.11$ before omission of outliers; Figure 3A) was similarly observed in the studies by Behrend *et al.* ($r = 0.09$) [39] and Brunet *et al.* [38] (no correlation reported). However, the weak correlation between total MPA $AUC_{ss,0-12}$ with TBW-adjusted MMF dose in the present study ($r^2 = 0.30$ before omission of outliers; Figure 2A) was not observed by Brunet *et al.* [38] (no correlation reported). Due to the lack of conclusive data in the literature, future prospective controlled studies based on MMF dosing at 12 mg/kg BD, as proposed by the present study, would thus be necessary to determine the reliability of this proposed MMF dosing strategy in achieving the desired total MPA $AUC_{ss,0-12}$ therapeutic range of 30–60 mg h/l for optimal clinical outcomes. Different ethnic populations could also be studied to investigate if this proposed dose could be extrapolated to all ethnic groups.

Although TBW-based MMF dosing may individualize initial strategy, the substantial inter-individual variability in the PK of MPA as reported herein and in the literature suggests that TDM of MPA may be necessary to further optimize efficacy and minimize toxicity.

In summary, the current recommended fixed dosing regimen of MMF may not be ideal for all patients. Although the TBW-adjusted MPA CL_{oral} tended to be lower than that reported from the Western population, whether there are ethnic differences in mycophenolate disposition in the Asian populations needs further investigation. Studies are currently underway to determine if genetic differences in the drug metabolizing enzymes of MPA could be a contributing factor underlying the difference in dose requirement between Asian and Western populations. Nevertheless, the observed correlation between drug exposure and TBW-adjusted MMF dose suggests that MMF may be dosed based on body weight, rather than the standard fixed dose. Based on our results, to attain an average total MPA $AUC_{ss,0-12}$ of 45 mg h/l, we propose that Asian patients on MMF with concomitant CsA may be initially dosed empirically at 12 mg/kg BD so as to reduce the potential complications of excessive immunosuppression, and doses subsequently adjusted based on TDM.

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Conflict of interest statement. None declared.

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