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 AUCss, 0–12, demonstrated a significant positive correlation with TBW-adjusted MMF dose (outliers omitted: \( r^2 = 0.49 \), \( P < 0.0005 \)). An AUCss, 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/m² 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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In this study, the optimal MMF dose, based on TBW, in RTX on nosuppression. Secondly, the aim was to determine 3 months, with concomitant CsA-corticosteroid immuno-
suppression. 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
that would be theoretically the same.

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 immuno-
suppression. 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).

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\textsubscript{ss,0–12} or C\textsubscript{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\textsubscript{0} or AUC\textsubscript{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.

**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

![Graph showing 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.](image-url)
not standard and TBW was varied in these study subjects; thus, $C_0$, $C_{\text{max}}$ and $\text{AUC}_{\text{ss},0-12}$ were normalized by MMF dose per kg TBW. The $\text{CL}_{\text{oral}}$ 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 $\text{AUC}_{\text{ss},0-12}$ and in $\text{CL}_{\text{oral}}$ 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>% CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_0$ (mg/l)</td>
<td>1.95 ± 1.06</td>
<td>54.7</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (mg/l)</td>
<td>13.4 ± 7.0</td>
<td>52.4</td>
</tr>
<tr>
<td>$\text{AUC}_{\text{ss},0-12}$ (mg h/l)</td>
<td>41.4 ± 14.2</td>
<td>34.2</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>1.02 ± 0.85</td>
<td>83.4</td>
</tr>
<tr>
<td>$\text{CL}_{\text{oral}}$ (l/h)</td>
<td>12.3 ± 4.7</td>
<td>38.0</td>
</tr>
</tbody>
</table>

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

$C_{\text{max}}$ (mg/l), normalized by MMF dose (mg/kg) 1.46 ± 0.82 56.3

$\text{AUC}_{\text{ss},0-12}$ (mg h/l), normalized by MMF dose (mg/kg) 4.41 ± 1.46 33.1

TBW-adjusted $\text{CL}_{\text{oral}}$ (l/h/kg) 0.185 ± 0.058 31.3

*aCoefficient 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 $\text{AUC}_{\text{ss},0-12}$ or total MPA $C_0$**

Drug exposure of MPA, as evaluated by the total $\text{AUC}_{\text{ss},0-12}$, 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 $\text{AUC}_{\text{ss},0-12}$, 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).

Thus, TBW-adjusted MMF dose demonstrated a stronger correlation with the total MPA $\text{AUC}_{\text{ss},0-12}$ than total MPA $C_0$. The TBW-adjusted MMF dose required to achieve any particular total MPA $\text{AUC}_{\text{ss},0-12}$ could be estimated from the regression equations obtained (Table 3). In order to target a total MPA $\text{AUC}_{\text{ss},0-12}$ of 30–60 mg h/l for total MPA $\text{AUC}_{\text{ss},0-12}$ [37] (Figure 4B). Furthermore, as demonstrated by the box plots of total MPA $C_0$ against TBW-adjusted MMF dose, an MMF dose of 5–15 mg/kg BD would achieve 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). As demonstrated by the box plots of total MPA $\text{AUC}_{\text{ss},0-12}$ 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 $\text{AUC}_{\text{ss},0-12}$[37] (Figure 4B). Thus, TBW-adjusted MMF dose demonstrated a stronger correlation with the total MPA $\text{AUC}_{\text{ss},0-12}$ than total MPA $C_0$. The TBW-adjusted MMF dose required to achieve any particular total MPA $\text{AUC}_{\text{ss},0-12}$ could be estimated from the regression equations obtained (Table 3). In order to target a total MPA $\text{AUC}_{\text{ss},0-12}$ 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 $\text{AUC}_{\text{ss},0-12}$ 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).
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 \( C_0 \) and AUC\( \text{ss,} \ 0–12 \) respectively. 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 \( C_0 \) and AUC\( \text{ss,} \ 0–12 \) respectively.
Table 3. Estimated total body weight (TBW)-adjusted mycophenolate mofetil (MMF) doses based on the respective total mycophenolic acid (MPA) AUC<sub>ss,0–12</sub> (30, 45 or 60 mg h/l) according to the derived regression equations<sup>a,b</sup>

<table>
<thead>
<tr>
<th>Based on total MPA AUC&lt;sub&gt;ss,0–12&lt;/sub&gt; of</th>
<th>30 mg h/l</th>
<th>45 mg h/l</th>
<th>60 mg h/l</th>
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<tr>
<td>Estimated TBW-adjusted MMF dose (mg/kg per dose):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before removing outlying points&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.43</td>
<td>11.1</td>
<td>16.7</td>
</tr>
<tr>
<td>After removing outlying points&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6.52</td>
<td>11.5</td>
<td>16.5</td>
</tr>
</tbody>
</table>

<sup>a</sup>MMF BD dose per kg = (Total MPA AUC<sub>ss,0–12</sub> - 15.591)/2.655.

<sup>b</sup>MMF BD dose per kg = (Total MPA AUC<sub>ss,0–12</sub> - 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<sub>0</sub> (1.95 ± 1.06 mg/l) and AUC<sub>ss,0–12</sub> (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<sub>0</sub> and AUC<sub>ss,0–12</sub> 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<sub>0</sub> and AUC<sub>ss,0–12</sub> 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<sub>ss,0–12</sub> 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<sub>ss,0–12</sub> (Table 3).

Currently, there are two other studies that analysed the correlation of total MPA C<sub>0</sub> or AUC<sub>ss,0–12</sub> with TBW-adjusted MMF dose in patients receiving MMF with concomitant CsA immunosuppression [38,39]. The poor correlation between total MPA C<sub>0</sub> with TBW-adjusted MMF dose from the present study (r<sup>2</sup> = 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<sub>ss,0–12</sub> with TBW-adjusted MMF dose in the present study (r<sup>2</sup> = 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<sub>ss,0–12</sub> 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<sub>oral</sub> 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<sub>ss,0–12</sub> 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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