Association between mycophenolic acid 12-h trough levels and clinical endpoints in patients with autoimmune disease on mycophenolate mofetil

Irmgard Neumann¹, Heinz Fuhrmann¹, I-Fei Fang², Adelheid Jaeger¹, Peter Bayer² and Josef Kovarik¹

¹6th Department of Internal Medicine, Nephrology and Dialysis and ²Laboratory Diagnostics, Wilhelminenspital, Vienna, Austria

Abstract

Introduction

Mycophenolate mofetil (MMF) is widely used in the transplantation setting for the prophylaxis of organ rejection. In combination with cyclosporine, the standard dosage is typically 1 or 1.5 g twice daily; if combined with tacrolimus lower doses of MMF are usually administered. Therapeutic drug monitoring (TDM) of mycophenolic acid (MPA), the active moiety of MMF, is not routinely done following transplantation but has recently been demanded to further improve the good clinical results that have already been obtained with MMF [1–3]. TDM appears particularly important in patient populations with a high intersubject variability in MPA pharmacokinetics (e.g. patients early after transplantation) [4]. When combined with cyclosporine, MPA levels between 1.0 and 3.5 mg/L (trough concentration) and 30–60 h mg/L (area under the curve [AUC]) have been suggested as target therapeutic ranges. For the combination with tacrolimus, the target ranges of 1.9–4.0 mg/L and 30–60 h mg/L for trough and AUC measurements, respectively, have been recommended for transplant recipients, whereas AUC monitoring should take preference over trough level monitoring [5]. In fact, weak correlations between MPA trough concentrations and MPA AUC have been reported in the majority of studies in which this relationship was assessed, suggesting that trough levels may not adequately reflect exposure to MPA in transplantation [6,7].

MMF has also been shown to be effective in patients with autoimmune diseases (AID) such as systemic lupus erythematosus (SLE), polymyositis, dermatomyositis and systemic sclerosis [8–12]. Moreover, promising data from pilot studies have suggested a therapeutic potential in the treatment of patients with antineutrophil cytoplasmic antibody (ANCA)-associated small vessel vasculitis [13–15]. Studies in AID patients used MMF dosages in the range of 1–3 g daily; and doses were adjusted according to response and tolerability [10,16]. No official dosing recommendations for MMF in non-transplant indications are available, and issues related to dosing have not been resolved yet [17]. Likewise, the usefulness of TDM in non-transplant indications is currently unclear; no target ranges
have been defined yet, neither for AUC nor for troughs. In a rather small study, we have previously shown that the pharmacokinetic characteristics of MPA in AID patients on MMF are different to transplant patients, most likely due to the use of different concomitant medications [18]. In contrast to transplant recipients, MPA trough concentrations at 12 h from AID patients provided a reasonable estimation of MPA exposure (AUC). We hypothesized that TDM for MPA based on troughs would be clinically practicable and may be useful for effective MMF dosing in patients with AID.

This was the impetus behind the present study which followed a two-step approach. First, we wanted to confirm our initial pharmacokinetic results [18] in a larger cohort of AID patients, and second, we performed an analysis of 12-h MPA trough levels collected from subjects with SLE or ANCA-associated small vessel vasculitis (AASV) receiving MMF for remission maintenance therapy, to elucidate possible associations with disease activity and MMF toxicity and to propose a possible therapeutic target range for MPA trough concentrations.

**Subjects and methods**

This was a two-part study consisting of a pharmacokinetic part and an explorative analysis of 12-h MPA levels; the latter part investigated possible associations between MPA trough levels and clinical endpoints.

**Pharmacokinetic study**

Thirty-eight patients with AID (18 women, 20 men; mean ± SD age, 52.4 ± 18.3 year) were consecutively enrolled in the open-label pharmacokinetic study. The group consisted of 26 patients with AASV (10 women, 16 men) and 12 patients suffering from SLE (10 women, 2 men) with a mean ± SD calculated creatinine clearance of 63.2 ± 27.8 mL/min. There was one patient with a creatinine clearance <30 mL/min. All enrolled patients granted written informed consent before the study commenced. The patients had been receiving MMF (1 g twice daily) for at least 10 weeks prior to the study. Subjects were allowed to receive low-dose steroids (usually ≤5 mg prednisolone/day) in addition to MMF. Drugs known to interfere with MPA pharmacokinetics were not permitted. Procedures for pharmacokinetic assessment followed the same protocol as previously described [18]. In brief, after a 12-h overnight fast, MMF was administered orally at a dose of 1 g. Venous blood samples for the determination of MPA in plasma were collected before the drug intake and then 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 12, 14 and 24 h thereafter. During the 24-h collection period no MMF dose was given. Concentrations of MPA in plasma were determined using the commercially available enzyme multiplied immunoassay technique assay (EMIT Mycophenolic Acid Assay System, Dade Behring, San Jose, CA, USA) according to the manufacturer's instructions as described previously [19,20]. The lower limit of quantification was 0.1 mg/L. Plasma MPA concentration-time profiles were analysed by standard non-compartmental methods using WinNonlin (version 1.5; Sci-entific Consulting Inc., NC, USA). The following pharmacokinetic parameters were determined: \( C_{\text{max}} \), \( T_{\text{max}} \) and MPA concentration after 12 (\( C_{12\ h} \)) and 24 h (\( C_{24\ h} \)). The MPA plasma concentration at 12 h (\( C_{12\ h} \)) reflects the concentration at the end of the dosing interval. AUCs from 0 to 12 h (\( \text{AUC}_{0-12\ h} \)) and from 0 to 24 h (\( \text{AUC}_{0-24\ h} \)) were calculated by the linear trapezoidal rule. The relationship between MPA level and \( \text{AUC}_{0-12\ h} \) was assessed by linear regression analysis, and the significance was judged by the \( r \) value (Spearman coefficients).

**Analyses of 12-h MPA trough levels**

In total, 39 consecutive patients (23 participated in the pharmacokinetic study) were followed up in our department of internal medicine and nephrology between 2000 and 2006 for AASV or SLE, all receiving MMF as remission maintenance therapy of their underlying disease. Only those patients were excluded who did not tolerate MFP within the first weeks of treatment (e.g. because of severe gastrointestinal complaints). From the patients, serial 12-h trough MPA levels were monitored at regular intervals during follow-up visits at the clinic (every 2–3 months); 26 patients had been diagnosed with AASV and 13 with SLE. No patient suffered from nephrotic syndrome and only one had a creatinine clearance <30 mL/min. Median follow-up time was 24 months (range, 2.5–53 months). One patient died of cancer after a follow-up of 6 months. Demographic and baseline characteristics of all enrolled patients are shown in Table 1.

If analysed by disease, SLE patients (12 women, 1 man) were younger and had better renal function and a longer follow-up when compared with AASV patients (15 women, 11 men): mean ± SD age, 39.6 ± 10.2 versus 57.5 ± 14.8 year, \( P < 0.001 \); mean creatinine clearance, 88 ± 19 versus 59 ± 30 mL/min, \( P < 0.01 \); median follow-up, 31.5 ± 11.9 versus 18.3 ± 12.8 months, \( P < 0.01 \).

ANCA serology identified cytoplasmic ANCA in 18 patients and perinuclear ANCA in 7 patients, all in the presence of their typical target antigen, either proteinase 3 or myeloperoxidase; one patient was ANCA negative. Thirteen patients were classified as having Wegener's granulomatosis; 12 with microscopic polyangiitis and 1 with renal limited disease [21]. At the time of diagnosis, all AASV patients had severe generalized active disease including renal and/or pulmonary disease and were initially

### Table 1. Demographic and clinical characteristics of patients from whom serial mycophenolic acid trough levels were collected

<table>
<thead>
<tr>
<th>Characteristic/parameter</th>
<th>( N = 39 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>51.2 ± 15.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.1 ± 24.7</td>
</tr>
<tr>
<td>Gender</td>
<td>27 females; 12 males</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>69.1 ± 34.9b</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>4.2 ± 0.3b</td>
</tr>
<tr>
<td>Hæmoglobin (g/dL)</td>
<td>12.8 ± 1.5</td>
</tr>
<tr>
<td>White blood cells, ×1000/mm³</td>
<td>6.5 ± 5.9</td>
</tr>
</tbody>
</table>

\( ^a \)Calculated using the Cockcroft–Gault equation [39].

\( ^b \)Based on 32 patients.
treated with steroids and cyclophosphamide for 6 months. Once remission was achieved, indicated by the complete absence of clinical disease activity using the Birmingham Vasculitis Activity Score (BVAS) [22], cyclophosphamide was replaced by MMF as remission maintenance therapy. SLE was diagnosed according to the criteria defined by the American College of Rheumatology [23]. Five patients had renal involvement earlier in the course of their disease (lupus nephritis Class III in two, Class IV in two and Class V in one); one further patient had pulmonary involvement (pleuritis and infiltrates). The main reasons for initiating MMF treatment included severe cutaneous manifestations (also with ulcers in four), arthritis/arthralgia, myalgia, malaise and weight loss refractory to low-dose corticosteroids and antimalarials.

At the study start, all subjects received MMF (CellCept®, Hoffmann-La Roche AG, Basel, Switzerland) as remission maintenance therapy, initially at 1 g twice daily. Dose adjustments for adverse events were performed from the beginning. After an observation period of ∼1 year, low MPA trough levels were observed, especially in patients experiencing recurrence of active disease. Thus, based on the results of the preceding observational pharmacokinetic study, an MPA trough level of ∼3 mg/L was targeted; MMF doses were modified accordingly and the trough level monitored at the subsequent visit. Decisions to change the MMF dose were also made on clinical grounds (e.g. because of leucopenia or gastrointestinal complaints). No drugs known to interfere with MPA pharmacokinetics were administered concomitantly.

A total of 294 MPA trough levels were collected (usually 8–10 samples/patient) 12 h following administration of the evening dose of MMF and were quantified using EMIT. For a given time period, patients with active disease had a comparable number of MPA determinations as patients in remission. Trough levels were categorized into 11 ranges and potential associations with clinical data were explored by manual allocation of clinical endpoints to MPA trough level ranges. Clinical endpoints included reoccurrence of active disease and experience of adverse events. For diagnosing disease recurrence, the BVAS and the British Isles Lupus Assessment Group (BILAG) index were consulted for AASV and SLE, respectively [22,24]. Patients were considered to have relapsed if the BVAS score reached one or more points (AASV patients) or if there was at least one episode of disease activity scoring newly an A or B in one or more of the eight systems recorded by the BILAG index (SLE patients).

Results

Pharmacokinetic findings

Mean pharmacokinetic parameters are given in Table 2. The results confirmed our initial findings in a study with a smaller sample size [18]. Intersubject variabilities (percent coefficient of variation [%CV]) in MPA pharmacokinetics were high (>30% for AUC values). When $C_{12\text{h}}$ values were subject to regression analysis, a significant association with $AUC_{0–12\text{h}}$ was observed ($r = 0.545$, $P < 0.001$). Data are mean ± SD [%CV]; $AUC_{0–12\text{h}}$, area under the concentration–time curve of MPA (0–12 h); $AUC_{0–24\text{h}}$, area under the concentration–time curve of MPA (0–24 h); $C_{12\text{h}}$, concentration of MPA 12 h after administration of MMF 1 g; $C_{24\text{h}}$, concentration of MPA 24 h after administration of MMF 1 g; %CV, intersubject coefficient of variation.

![Fig. 1. Relationship between mycophenolic acid (MPA) plasma concentration at 12 h ($C_{12\text{h}}$) and $AUC_{0–12\text{h}}$ for MMF following an oral dose of 1 g in patients with autoimmune disease.](https://academic.oup.com/ndt/article-abstract/23/11/3514/1940161)

The corresponding regression line is shown in Figure 1. If those patients were counted who achieved an MPA exposure within 40–75 h mg/L (i.e. close to the range of 30–60 h mg/L recommended for transplant recipients), then 24/38 patients (63.2%) met this AUC range, whereas 5 (13.1%) and 9 (23.7%) were below and above this target, respectively. The associated mean ± SD values for $C_{12\text{h}}$ were 3.3 ± 1.8 mg/L ($AUC \geq 40$ and <75 h mg/L), 1.5 ± 1.0 (<40) and 4.7 ± 2.6 (≥75). Hence, an MPA 12-h trough level of ∼3 mg/L was considered an appropriate surrogate for providing AID patients with an adequate MPA exposure and was chosen for monitoring immunosuppression in subsequent 12-h trough level studies. There was no discernible difference in MPA pharmacokinetics between the two cohorts of AASV and SLE patients.

Relationship between 12-h MPA trough levels and clinical endpoints

The association of MPA trough levels with reoccurrence of disease and MPA toxicity is displayed in Table 3. Seven of the 26 AASV patients (27%) developed at least one flare of their disease (range in BVAS scores: 1–4) out of which 3 were considered major [1 necrotizing crescentic glomerulonephritis (NCGN)], 1 NCGN and pulmonary infiltrates, 1 granulomatous inflammation and stenosis of the trachea). Minor activities included sinusitis, skin ulcer, single pulmonary granulomas, arthralgia/arthritis and scleritis. Of the 13 SLE patients, 8 (62%) experienced one or more flares;
Table 3. Relationship between mycophenolic acid (MPA) 12-h trough levels and clinical outcome in patients with autoimmune disease (N = 39)

<table>
<thead>
<tr>
<th>MPA trough range (mg/L)</th>
<th>n</th>
<th>Mean MMF dose (g/day)</th>
<th>Active disease, n (%)</th>
<th>Adverse event, n</th>
<th>Type of MPA-related adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>12</td>
<td>1.1 ± 0.4</td>
<td>6 (50)</td>
<td>1</td>
<td>GI complaint</td>
</tr>
<tr>
<td>1.0–&lt;1.5</td>
<td>25</td>
<td>1.5 ± 0.5</td>
<td>13 (52)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1.5–&lt;2.0</td>
<td>31</td>
<td>1.7 ± 0.6</td>
<td>9 (29)</td>
<td>1</td>
<td>Anaemia</td>
</tr>
<tr>
<td>2.0–&lt;2.5</td>
<td>42</td>
<td>1.9 ± 0.6</td>
<td>9 (21)</td>
<td>1</td>
<td>Herpes zoster</td>
</tr>
<tr>
<td>2.5–&lt;3.0</td>
<td>37</td>
<td>2.0 ± 0.7</td>
<td>6 (16)</td>
<td>2</td>
<td>Pneumonia, urogenital candida</td>
</tr>
<tr>
<td>3.0–&lt;3.5</td>
<td>41</td>
<td>1.9 ± 0.6</td>
<td>3 (7)</td>
<td>1</td>
<td>Leucopenia</td>
</tr>
<tr>
<td>3.5–&lt;4.0</td>
<td>25</td>
<td>2.0 ± 0.7</td>
<td>0</td>
<td>1</td>
<td>GI complaint</td>
</tr>
<tr>
<td>4.0–&lt;4.5</td>
<td>19</td>
<td>1.7 ± 0.4</td>
<td>0</td>
<td>1</td>
<td>GI complaint</td>
</tr>
<tr>
<td>4.5–&lt;5.0</td>
<td>17</td>
<td>1.8 ± 0.6</td>
<td>0</td>
<td>2</td>
<td>Anaemia (2)</td>
</tr>
<tr>
<td>5.0–&lt;6.0</td>
<td>22</td>
<td>1.7 ± 0.6</td>
<td>0</td>
<td>6</td>
<td>Anaemia, GI complaint, herpes zoster, myalgia (2), urogenital candida,</td>
</tr>
<tr>
<td>&gt;6.0</td>
<td>23</td>
<td>1.9 ± 0.3</td>
<td>0</td>
<td>3</td>
<td>Anaemia, GI complaint, pneumonia</td>
</tr>
</tbody>
</table>

aThe same adverse event may have occurred repeatedly in the same patient. 
bOne trough associated with severe disease. 
cTwo troughs associated with severe disease. 
GI, gastrointestinal; n = number of trough samples; N = number of patients.

Table 4. Relationship between mycophenolic acid (MPA) 12-h trough levels and clinical outcome in patients with SLE (N = 13) and AASV (N = 26)

<table>
<thead>
<tr>
<th>MPA trough range (mg/L)</th>
<th>SLE</th>
<th>AASV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Active disease, n (%)</td>
</tr>
<tr>
<td>&lt;1</td>
<td>8</td>
<td>4 (50)</td>
</tr>
<tr>
<td>1.0–&lt;1.5</td>
<td>13</td>
<td>7 (54)</td>
</tr>
<tr>
<td>1.5–&lt;2.0</td>
<td>20</td>
<td>6 (30)</td>
</tr>
<tr>
<td>2.0–&lt;2.5</td>
<td>25</td>
<td>7 (28)</td>
</tr>
<tr>
<td>2.5–&lt;3.0</td>
<td>22</td>
<td>4 (18)</td>
</tr>
<tr>
<td>3.0–&lt;3.5</td>
<td>24</td>
<td>2 (8)</td>
</tr>
<tr>
<td>3.5–&lt;4.0</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>4.0–&lt;4.5</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>4.5–&lt;5.0</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>5.0–&lt;6.0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>&gt;6.0</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

Adverse events may have occurred repeatedly in the same patient. 
AASV, ANCA-associated small vessel vasculitis; SLE, systemic lupus erythematosus; n = number of trough samples; N = number of patients.

Table 5. Relationship between mycophenolic acid (MPA) 12-h trough levels and MMF dose administered in patients with autoimmune disease (N = 39)

<table>
<thead>
<tr>
<th>MMF dosage (g/day)</th>
<th>n</th>
<th>Mean MPA 12-h trough concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>4</td>
<td>3.0 ± 2.4</td>
</tr>
<tr>
<td>1</td>
<td>59</td>
<td>2.6 ± 1.5</td>
</tr>
<tr>
<td>1.5</td>
<td>58</td>
<td>3.6 ± 2.2</td>
</tr>
<tr>
<td>2</td>
<td>125</td>
<td>3.7 ± 2.0</td>
</tr>
<tr>
<td>2.5</td>
<td>20</td>
<td>2.6 ± 0.9</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>3.3 ± 1.2</td>
</tr>
</tbody>
</table>

n = number of trough samples; N = number of patients.

all were of minor severity (new B score according to the BL-A score index comprising arthralgia/arthritis and/or myalgia and cutaneous manifestations (some with ulcers). Generally, lower MPA trough levels were associated with disease recurrence. In 28/68 samples (41%) with an MPA concentration <2 mg/L, reoccurrence of the underlying disease was present. An MPA level of 3 mg/L best discriminated between patients with and without flares. While at levels <3 mg/L 29% (43/147) of collected samples were from patients with active disease, this was only the case in 2% (3/147) of samples with an MPA concentration of 3 mg/L or greater. Remission persisted in all patients with 12-h MPA trough levels ≥3.5 mg/L. Twelve of the 39 patients (31%) have reported at least one suspected adverse experience upon MMF use during the observation period. The frequency of MMF-related adverse events was associated with higher MPA levels, mainly infections, anaemia and gastrointestinal complaints. Leucopenia of <3.0 × 1000/mm³ was noted in one patient only. Anaemia was classified as MMF-related adverse event if haemoglobin fell below 11 g/dL in the absence of infection or gastrointestinal bleeding and when reduction of MMF dose led to an increase in haemoglobin.

An MPA level of 4.5 mg/mL best discriminated between patients with and without adverse events. At MPA concentrations <4.5 mg/L, 7% (17/232) of samples were from
patients who reported adverse events, while this changed to 24% (15/62) of troughs when MPA concentrations ≥4.5 mg/L were investigated. Upon combined analysis of efficacy and safety data, most favourable results were obtained with MPA trough levels between 3.5 and 4.5 mg/L, providing protection from disease recurrence and minimizing the likelihood of treatment-related adverse events (incidence of 5% for that particular range). If analysed by disease (SLE versus AASV patients), results were comparable (Table 4).

There was no relationship apparent between MMF dose and clinical endpoints. Likewise, the amount of MMF necessary to achieve MPA levels close to the targeted trough (around 3 mg/L), showed a wide range as depicted in Table 5. The mean MMF dosage during follow-up was 1.8 ± 0.5 g/day which yielded an overall mean 12-h MPA trough concentration of 3.3 ± 1.8 mg/L. Most patients received MMF 2 g/day.

The overall intrasubject coefficient of variation of dose-normalized MPA 12-h trough levels was 38.6%. In an attempt to judge the clinical relevance of intrapatient variability of MPA trough levels, we calculated the rate of dose adjustments based on recorded MPA values only. There were 0.7 ± 0.6 dose adjustments per patient per year.

**Discussion**

This is the first study of serial 12-h trough MPA level monitoring in AID patients investigating possible associations between MPA trough levels and clinical endpoints. In the context of a two-step approach, a pharmacokinetic study was performed first, followed by the trough level analysis. The findings in patients with AID receiving MMF for remission maintenance therapy can be summarized as follows: (1) there is confirmation of a significant correlation between MPA $C_{12\text{h}}$ and MPA AUC$_{12\text{h}}$ values, (2) higher MPA 12-h trough levels are associated with better protection from recurrence of active disease, (3) best results for the maintenance of remission and prevention of adverse events are observed for MPA trough levels of 3.5–4.5 mg/L and (4) there is no discernable relationship between MMF dose and clinical endpoints.

The pharmacokinetic results from the first part of our study confirmed previous findings assessed in a smaller cohort of patients with SLE or AASV [18]. Most notably, the significant association between MPA $C_{12\text{h}}$ and AUC$_{12\text{h}}$ could be corroborated, thereby suggesting that trough levels of MPA are a relatively good estimation of MPA exposure although this correlation indicates that MPA trough does not always adequately reflect systemic exposure to MPA. A recent study in patients with progressive IgA nephritis reported a similar correlation between MPA $C_{12\text{h}}$ levels and AUC$_{12\text{h}}$ (coefficient of determination = 0.50; $P = 0.02$) for MMF [25]. In the latter study, the pharmacokinetics and pharmacodynamics of MPA after equivalent doses of enteric-coated mycophenolate sodium and MMF were compared in seven patients with progressive IgA nephritis and severe renal insufficiency (glomerular filtration rate 20–35 mL/min). However, no data were collected in patients with mild to moderate impairment of renal function.

Another study in 15 pediatric patients with vasculitis and connective tissue disease also described a significant correlation between the trough concentration and the MPA AUC$_{0-12\text{h}}$ ($r = 0.6234$; $P = 0.0005$) [26]. This is in contradiction to findings in renal transplants where the majority of pharmacokinetic studies showed a weak correlation between MPA trough levels (or $C_{12\text{h}}$ values) and MPA AUC [6,7]. Moreover, it has been reported that in transplantation the relationship between MPA trough and AUC depends on the type of calcineurin inhibitor used in combination with MMF [27]. Cyclosporine impairs the enterohepatic recirculation of MPA by inhibition of the multi-drug resistance protein-2 while tacrolimus does not, thereby producing different MPA plasma concentration-time profiles with different trough/AUC ratios [7,28,29]. Hence, the use of different concomitant medications in conjunction with distinctions in patient characteristics may explain the difference in pharmacokinetic features of MPA between AID and transplant patients.

We observed a large intersubject variability in pharmacokinetic parameters, which is in line with previous findings with MMF in organ transplant recipients [30] and patients with IgA nephritis [25]. Apart from clinical factors such as renal function or albumin levels that may explain some of the variability in MPA disposition [30], genetic factors have been reported as possible determinants for the high variability [31]. The large interpatient variability in MPA pharmacokinetics has been considered the main reason for performing TDM of MPA during MMF therapy [4]. With regard to the intrasubject variability of MPA trough concentrations, mean coefficients of variation of 36–62% have been reported in the transplantation setting [7]. In our study we observed an intrapatient variability at the lower end of this range. Thus, in contrast to renal transplants, intrapatient variability of MPA trough levels seems to be less in AID patients, leading to only few MPA-level triggered dose adjustments within a given patient. This is possibly due to fewer changes of concomitant therapy in the AID setting. Therefore, MMF dose management based on trough levels appears to be a worthwhile approach in AID patients.

Analyses of MPA 12-h trough concentrations showed that MPA levels were associated with both disease recurrence and side effects commonly seen in AID patients on MMF such as anaemia, leucopenia, gastrointestinal complaints, infections or myalgia [10,32]. We identified MPA trough concentrations predictive for disease recurrence and MMF toxicity; these were <3 and ≥4.5 mg/L, respectively. For transplant patients, slightly different thresholds have been defined. In the largest study of serial 12-h trough MPA levels performed to date in tacrolimus-based renal transplantation, an MPA level of 1.60 mg/L early post-transplantation best discriminated patients with and without rejection, and an MPA level of 2.75 mg/L best discriminated patients with and without toxicity later post-transplantation using also the EMIT immunoassay [33]. Others suggested a threshold trough level for toxicity of 3.0 mg/L in the same target population [34]. The disparity in threshold trough levels for MMF-related side effects between transplant and AID patients might be explained by differences in patient characteristics and the use of concomitant medications. Furthermore,
as MPA trough levels in transplant patients may not accurately reflect MPA exposure such a comparison might be inaccurate, but no previous data on the relationship between MPA trough levels and clinical outcome in non-transplant indications were available for comparison. In fact, the association between safety outcomes and MPA trough levels during MMF therapy for the prophylaxis of organ rejection has been inconsistently reported with the majority of studies showing no significant correlation [7,35]. It has also been suggested that the incidence of adverse events is related to dose rather than MPA concentrations in renal transplants on MMF [35–37]. This we have not seen in our analysis in AID patients where no such relationship was apparent.

In AID patients, MMF is usually administered at a fixed dose without serial measurements of plasma concentrations of MPA, and the contribution of TDM is currently unclear. Based on our study, we suggest a target range for MPA 12-h trough levels of 3.5–4.5 mg/L although this narrow range may be difficult to meet. In this context, it needs emphasis that this target range may not be applicable to patients with nephrotic syndrome or severe renal insufficiency. In these populations, there is a high clearance of non-protein bound MPA [38]. Dose increases in such patients may not lead to a substantial rise in MPA plasma concentrations. It has previously been shown that the pharmacokinetics of MPA is not affected by mild-to-moderate impairment of renal function [38]. Moreover, as all enrolled patients were in remission and on MMF for at least 10 weeks, the findings from this study may not apply to patients with active disease and those newly treated with MMF. Finally, it cannot be excluded with certainty that the different follow-up times with inconsistent numbers of MPA trough samples per patient had an influence on the study results. Nevertheless, the proposed target range may serve as an initial guidance for MPA monitoring in patients with AID if a TDM approach is pursued. In addition, it might be of help for the evaluation of MMF’s efficacy in the treatment of AID.

In conclusion, the data of this first study of serial 12-h trough MPA level monitoring in AID patients with a preceding pharmacokinetic trial suggest that trough levels provide a reasonable estimation of MPA exposure during treatment with MMF. MPA trough levels are associated with efficacy and safety outcomes rather than MMF dose. The drug is effective for remission maintenance therapy in AASV and SLE as long as adequate drug levels are achieved; too low troughs are associated with flares. Best results for maintenance of remission of the underlying disease and prevention of adverse events are observed for MPA trough levels between 3.5 and 4.5 mg/L. This target range proposed by this explorative study may prove to be useful for effective TDM and MMF dosing in patients with AID, but this needs further prospective controlled studies.

Acknowledgements. The authors would like to thank Petra Prudky and Sonja Hoffmann for their excellent collaboration and skilful assistance with blood sampling procedures.

Conflict of interest statement. None declared.

References

Received for publication: 28.3.08
Accepted in revised form: 3.6.08