Pharmacokinetics of Mycophenolate Mofetil in Patients with Autoimmune Diseases Compared Renal Transplant Recipients

IRMGARD NEUMANN,* MICHAEL HAIDINGER,* HEIDEMARIE JÄGER,† HANS GRÜTZMACHER,‡ ANDREA GRIESMACHER,§ MATHIAS M. MÜLLER,§ PETER M. BAYER,† and FRANZ THOMAS MEISL*  

Departments of *Nephrology, †Pharmacy, and ‡Laboratory Diagnostics, Wilhelminenspital, Vienna, Austria; and §Ludwig Boltzmann Institute for Cardiothoracic Research at the Department of Laboratory Diagnostics, Kaiser Franz Josef-Spital, Vienna, Austria.

Abstract. Mycophenolate mofetil (MMF), being effectively used as immunosuppressant in transplant medicine, has recently attracted interest as therapeutic agent for autoimmune diseases (AID). For these patients, no pharmacokinetic (PK) data are available. This study is an investigation of single-dose concentration-time profiles of 1 g off MMF in 16 patients with AID, including 10 patients with ANCA-associated vasculitis and 6 patients with systemic lupus erythematosus, and compares them with profiles of 16 renal transplant recipients (RTX). Mycophenolic acid (MPA) blood levels were measured by both HPLC and EMIT, and MPA-glucuronide was determined by HPLC. In AID, mean MPA concentrations at 12 h were significantly higher compared with RTX (4.1 ± 3.27 versus 1.8 ± 1.15 mg/L; P = 0.018), whereas peak concentrations were lower (P = 0.017). However, mean MPA-AUC at 12 h as well as at 24 h were comparable between both groups. In contrast to RTX, there was an association in AID between MPA trough levels at 12 h and at 24 h with AUC0-12 (P < 0.05 and P < 0.01). MPA trough concentrations at 24 h provided an estimation of AUC0-24 h in both patient groups (P < 0.001 and P < 0.01; AID and RTX, respectively). Compared with RTX, MPA-PK seems to be less affected in AID by renal function. Inter-individual variability of PK parameters was high in both groups. These data indicate that there are differences of MPA-PK between RTX and AID. The use of therapeutic drug monitoring in patients with AID appears to be clinically practicable and may be valuable to optimize individual immunosuppressive therapy.

The positive experience with mycophenolate mofetil (MMF) in the field of solid organ transplantation made this drug attractive for the treatment of several autoimmune diseases (1–4). Promising data derived from pilot studies suggests a therapeutic potential of MMF in the treatment of ANCA-associated small vessel vasculitis (ASVV) and systemic lupus erythematosus (SLE) (5,6). In a randomized trial from Hong Kong comparing MMF with cyclophosphamide in patients with diffuse proliferative lupus nephritis, remission and relapse rate were comparable in both groups, whereas MMF was better tolerated (7). Nevertheless, for these patients neither recommendations for optimal dosage of MMF nor data concerning drug exposure of MMF are available.

In kidney transplant recipients, several studies have shown a relationship between pharmacokinetic (PK) parameters with efficacy and toxicity. While patients with a low area under the concentration-time curve (AUC) of the active metabolite mycophenolic acid (MPA) appear to be at high risk for experiencing graft rejection (8), a relationship between MPA-PK and adverse effects has been found (9). Higher dosages like 3 g/d were associated with an increased occurrence of adverse effects; therefore, MMF is usually administered at a fixed daily dose of 2 g/d divided into two applications (10). However, the considerable individual variability and changes over time of PK parameters of MPA (10,11) as well as drug interactions (11,12) make the systemic drug exposure in the single patient unpredictable at a fixed-dose regimen. These observations argue in favor of tailoring the individual dosage by therapeutic drug monitoring. However, trough concentrations were not suitable for a precise estimation of MPA-AUC0-12 h, exhibiting a correlation coefficient of 0.232 in 20 adult kidney recipients (17), and no surrogate marker for systemic drug exposure has been established yet. The determination of a full AUC in each patient is impracticable in routine clinical practice. Attempts focused on abbreviated sampling strategies based on 3-point and 5-point MPA-AUC estimations (14,15,16) provided a better correlation with the respective full MPA-AUC in pediatric kidney recipients (r = 0.87) (17) but also in adults (r = 0.946) (13).

No PK-data are available for patients receiving MMF in a non-transplant setting. In contrast to RTX, these patients do not receive calcineurin inhibitors, which are known to affect MPA-AUC (11,12).

Our study was designed to elucidate possible differences of

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Correspondence to Dr. Irmgard Neumann, Wilhelminenspital, Department of Nephrology, Montleartstr. 37, A-1171 Vienna, Austria. Phone: 43-1-49150-2321; Fax: 43-1-49150-2329; E-mail: irmi_neumann@hotmail.com or irmgard.neumann@nep.wil.magwien.gv.at

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MMF-PK between the use of MMF in RTX and in the treatment of autoimmune diseases (AID), including ASVV and SLE, and to define a possible surrogate marker for drug exposure (AUC) in AID. We further addressed the impact of various degrees of renal function on MMF-PK. Since the enterohepatic influence on the course of the AUC-profiles is unknown in the non-transplant use of the drug and to exclude a possible interference of a late secondary MPA peak with the initial peak of the next dosing after 12 h, we decided to evaluate PK profiles over 24 h (10,18,19).

Materials and Methods

Patients

Thirty-two consecutive adult patients were included in this study. Sixteen stable renal transplant recipients (eight women, eight men; median age, 54 yr [range, 32 to 72 yr]) received MMF for prevention of rejection after their first renal transplantation (RTX group), and 16 patients were treated with MMF for AID (median age, 50 yr [range, 20 to 82 yr]). The latter group included ten patients with ASVV (seven women, three men) and six patients with SLE (all women). Informed consent of all patients enrolled in our study was obtained. All patients had been receiving the standard dosage of MMF (2 g/d in a twice daily schedule) for at least 10 wk. This 10-wk period was appointed because modifications of MMF-PK during the first 2 mo after transplantation have been reported (10). In all patients of the RTX group, MMF was given as part of a triple immunosuppressive regimen that included cyclosporine and steroids. Twelve patients of the AID group received prednisone in addition to MMF. Patients requiring drugs known to interfere with MMF metabolism other than cyclosporine in RTX were excluded from the study (11). Thus, none of the patients enrolled was taking cholestyramine, antacids, antibiotics, ganciclovir, or tacrolimus.

Pharmacokinetic Study Protocol

After a 12-h overnight fast, MMF was administered orally at a dose of 1 g. Blood samples were drawn immediately before the application of MMF and 20 min, 40 min, 1, 1.5, 2, 3, 4, 6, 8, 12, 14, and 24 h after administration. During this 24-h course, no further dose of MMF was given. This 24-h single-dose PK setting was chosen to avoid the possible interference of a late occurring secondary peak of MPA with the initial MPA peak of a following MMF dose. To avoid the influence of individual nutritional habits on primary absorption and enterohepatic cycling of MMF, three defined standard meals were served 1, 5, and 10 h after the first blood sample was drawn.

Pharmacokinetic Analyses

Samples were analyzed for MPA and MPAG by means of HPLC. The HPLC system consisted of a Beckman System Gold 118 Solvent Module delivery system (Beckman Instruments Inc., Fullerton, CA), a Jasco UV 970 UV/Vis Detector (Jasco Corporation, Tokyo, Japan), a Shimadzu autosampler, and a Shimadzu C-RSA integrator (Shimadzu Corporation, Kyoto, Japan). A Supelcosil LC-18 DB (reversed phase column: 25 cm × 4.65 μm particle size; Supelco Inc., Bellefonte, PA) was used. One hundred microliters of the samples was injected onto the column. The mobile phase consisted of equal volumes (50:50, vol/vol) of acetonitrile and α-phosphoric acid (50 mmol/L). A flow rate of 1 ml/min and a detection wavelength of 214 nm were used. In addition, MPA concentrations were also measured by the EMIT procedure (EMIT-MPA, Dade Behring).

The following PK parameters of MPA and MPAG were determined: maximum concentration (C max ), time to maximum concentration (T max ), concentration after 12 h (C 12 h) and 24 h (C 24 h), and area under the concentration-time curve from 0 to 12 h (AUC 0–12 h) and from 0 to 24 h (AUC 0–24 h). For MPA, 2nd peak concentration (C max2 ) and time to 2nd peak concentration (T max2 ) were also evaluated. At the time of the investigation in all patients, total blood count, renal function by 24-h creatinine clearance, and in RTX also cyclosporine 12 h trough concentrations, as measured by whole blood monoclonal fluorescence polarization immunoassay, were determined.

Statistical Analyses

 Plasma concentration versus time data for MPA and MPAG after administration of MMF were fitted to a non-compartmental model using WinNonlin V 1.5 (Scientific Consulting), where AUC represents the area under the concentration-time curve from 0 to 24 h using the linear trapezoidal rule. Results are expressed as mean ± SD. A t test was used to compare continuous variables. Spearman coefficients were used to test correlation.

Results

PK Parameters in AID and RTX

Mean PK parameters for both patient groups are given in Table 1. No significant difference was found between AID and RTX for mean MPA-AUC 0–12 h (70.6 ± 28.67 versus 76.6 ± 24.44 mg · h/L, NS). C 12 h MPA was significantly higher in AID compared with RTX (4.1 ± 3.27 versus 1.8 ± 1.15 mg/L, P = 0.018). MPA-AUC 0–24 h were comparable in both groups (99.6 ± 43.27 versus 100.6 ± 29.95 mg · h/L, NS). At 24 h, the concentration of MPA also did not differ between the AID and RTX (2.3 ± 1.73 versus 1.7 ± 1.34 mg/L, NS). C max MPA was significantly lower in the AID group compared with the RTX group (21.8 ± 14.09 versus 36.7 ± 18.02 mg/L, P = 0.017) and occurred somewhat later although this difference was NS (T max : 70.2 ± 48.86 versus 48.1 ± 29.4 min, NS). C max2 MPA and T max2 MPA were comparable in both groups; however, in four RTX and one AID, no second peak concentration of MPA was detected. MPAG-AUC 0–24 h values tend to be higher in RTX, but SD are high; this difference was NS. In RTX patients, cyclosporine trough levels (mean 159 ± 44 ng/ml) correlated with MPAG-AUC 0–24 h (r = 0.741, P < 0.05, data not shown). Generally, SD values were high, indicating a substantial inter-individual variability of MPA-PK as also observed by other authors (10,11,20).

Correlation of Single PK Parameters with AUC

In this study, the highest correlation between MPA-AUC and a single concentration was observed with MPA-AUC 0–24 h and C 24 h MPA, exhibiting a value of 0.779 (P < 0.001) for the whole cohort. This significance remained when calculated for AID (r = 0.846, P < 0.001) and RTX (r = 0.708, P < 0.01) separately as shown in Table 2. Significant correlations were observed additionally between C 12 h MPA and MPA-AUC 0–24 h for all patients (r = 0.606, P < 0.001) and for the both groups, being somewhat better for AID (Table 2). In contrast to RTX, a significant relationship in AID between C 12 h MPA and MPA-AUC 0–12 h was found (r = 0.578, P < 0.05). In these patients the correlation was even better.
Contrarily, only in RTX C\textsubscript{max} MPA could be related to MPA-AUC\textsubscript{0–24h}. Correlation of single PK parameters with AUC

Table 2. Correlation of single PK parameters with AUC

<table>
<thead>
<tr>
<th></th>
<th>AID</th>
<th>RTX</th>
<th>P</th>
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<tbody>
<tr>
<td>MPA-AUC\textsubscript{0–24h} (mg\cdot h/L)</td>
<td>99.5 ± 43.27</td>
<td>100.6 ± 29.95</td>
<td>NS</td>
</tr>
<tr>
<td>MPA-AUC\textsubscript{0–12h} (mg\cdot h/L)</td>
<td>70.6 ± 28.67</td>
<td>76.6 ± 24.44</td>
<td>NS</td>
</tr>
<tr>
<td>C\textsubscript{max} MPA (mg/L)</td>
<td>21.8 ± 14.09</td>
<td>36.8 ± 18.02</td>
<td>0.017</td>
</tr>
<tr>
<td>C\textsubscript{max2} MPA (mg/L)</td>
<td>6.1 ± 3.07</td>
<td>5.2 ± 3.01</td>
<td>NS</td>
</tr>
<tr>
<td>T\textsubscript{max} MPA (min)</td>
<td>70.2 ± 48.86</td>
<td>48.1 ± 29.41</td>
<td>NS</td>
</tr>
<tr>
<td>T\textsubscript{max2} MPA (min)</td>
<td>488.3 ± 183.13</td>
<td>545.2 ± 244.28</td>
<td>NS</td>
</tr>
<tr>
<td>C\textsubscript{12h} MPA (mg/L)</td>
<td>4.1 ± 3.27</td>
<td>1.8 ± 1.15</td>
<td>0.018</td>
</tr>
<tr>
<td>C\textsubscript{24h} MPA (mg/L)</td>
<td>2.3 ± 1.73</td>
<td>1.7 ± 1.34</td>
<td>NS</td>
</tr>
<tr>
<td>MPAG-AUC\textsubscript{0–24h} (mg\cdot h/L)</td>
<td>2017.2 ± 1123.77</td>
<td>3030.4 ± 1466.45</td>
<td>NS</td>
</tr>
</tbody>
</table>

\* Data are mean ± SD: MPA-AUC\textsubscript{0–24h}, area under the concentration-time curve of MPA (0 to 24 h); C\textsubscript{max} MPA, maximum concentration of MPA; C\textsubscript{max2} MPA, 2\textsuperscript{nd} maximum concentration of MPA; T\textsubscript{max} MPA, time to maximum concentration of MPA; T\textsubscript{max2} MPA, time to 2\textsuperscript{nd} maximum concentration of MPA; C\textsubscript{12h} MPA, concentration of MPA 12 h after administration of 1 g of MMF; C\textsubscript{24h} MPA, concentration of MPA 24 h after administration of 1 g of MMF; NS, not significant; AID, autoimmune disease; RTX, renal transplant recipients.

when C\textsubscript{24} MPA was related to MPA-AUC\textsubscript{0–12h} (r = 0.733, P < 0.01). In AID, a significant association of MPA-AUC\textsubscript{0–12h} with C\textsubscript{max2} MPA could also be demonstrated, which was higher when related to MPA-AUC\textsubscript{0–24h} (r = 0.725, P < 0.01). Contrarily, only in RTX C\textsubscript{max} MPA could be related to MPA-AUC\textsubscript{0–12} (r = 0.586, P < 0.05) (Table 2).

Comparison of HPLC and EMIT

Our study exhibited a high agreement between the two methods of MPA determination, HPLC and EMIT (n = 310, r = 0.922, P < 0.001). This tight correlation was also observed for each patient group separately, exhibiting a coefficient of 0.960 (P < 0.001) for AID and of 0.890 (P < 0.001) for RTX, data not shown. In agreement with previous reports, we found a bias between MPA values measured with HPLC and the immunoassay, the EMIT MPA-determination being 22% higher over the corresponding HPLC values (14,21).

Clinical Data and Relationship between PK and Renal Function

Patient characteristics are listed in Table 3. Renal function measured as creatinine clearance was comparable in AID and RTX (65.2 ± 29.37 \textit{versus} 60.6 ± 22.88 ml/min, NS). The higher proportion of women in the AID group may account for the difference in body weight. Nevertheless, gender analysis revealed no differences for creatinine clearance (61.2 ± 24.19 and 66.1 ± 29.98, NS, women and men, respectively) or for single PK parameters as shown in Table 4. Also, a further subanalysis for the AID group did not show any gender effects on single PK values (data not shown). Furthermore, neither for AID nor for RTX, any correlation was noted between MMF-dose when calculated by body weight and single PK-values (data not shown).

There was an overall inverse relationship between renal function and the AUC\textsubscript{0–24 h} values of the renal eliminated metabolite MPAG (r = −0.551, P < 0.01) (Figure 1.). This correlation was also significant when calculated for AID or RTX separately, as shown in Table 5.

An inverse correlation between creatinine clearance and MPA-PK values, including C\textsubscript{12}, C\textsubscript{24}, C\textsubscript{max} MPA, AUC\textsubscript{0–12h} and AUC\textsubscript{0–24h} was observed only in the RTX group. In AID, PK parameters of MPA were less affected by renal function (Table 5).
The influence of renal function on C12MPA is especially illustrated in Figure 2. Within the RTX group, C12MPA was significantly higher in patients with a creatinine clearance < 60 ml/min compared with a creatinine clearance > 60 ml/min (2.4 ± 1.26 versus 1.2 ± 0.76 mg/L, P = 0.032), whereas no significant difference in C12MPA was found in AID with respect to renal function (4.5 ± 4.49 versus 3.6 ± 2.46 mg/L, NS; < 60 ml/min and > 60 ml/min creatinine clearance, respectively). When compared with RTX, AID patients with a creatinine clearance > 60 ml/min exhibited a significantly higher C12MPA (3.6 ± 2.46 versus 1.2 ± 0.76 mg/L, P = 0.015; AID versus RTX, respectively), whereas the difference was NS between both patient groups at a creatinine clearance < 60 ml/min (Figure 2.).

In this study, no relationship between the obtained single-dose PK values and hematologic parameters, including hemoglobin, leukocytes, or platelets in peripheral blood, could be demonstrated (data not shown). Mean levels for hemoglobin, white blood cells, and platelets are given in Table 3. Non-hematologic side effects included diarrhea (n = 1) and infection (n = 3) and could not be attributed to alterations of single MPA-PK variables (data not shown).

### Discussion

Optimization of adequate immunosuppression in association with acceptable tolerability of the used drugs is a main goal in both transplant medicine and in the treatment of immune-mediated diseases, where undertreatment carries the risk of persistent disease activity and the occurrence of relapses (22). Furthermore, PK drug interactions of MPA, especially in the

### Table 3. Patient characteristics

<table>
<thead>
<tr>
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<th>AID</th>
<th>RTX</th>
<th>P value</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>50 ± 17.5</td>
<td>52 ± 14.2</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (female: male)</td>
<td>13:3</td>
<td>8:8</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.3 ± 13.01</td>
<td>73.9 ± 13.02</td>
<td>0.027</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>65.2 ± 29.37</td>
<td>60.6 ± 22.88</td>
<td>NS</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>4.3 ± 0.67</td>
<td>4.6 ± 0.34</td>
<td>NS</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12.7 ± 1.3</td>
<td>12.4 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>White blood cells (×1000/mm³)</td>
<td>7.9 ± 2.8</td>
<td>7.4 ± 2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Platelets (×1000/mm³)</td>
<td>240.7 ± 75.58</td>
<td>214.5 ± 37.57</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table 4. Gender analysis

<table>
<thead>
<tr>
<th></th>
<th>Male n = 11</th>
<th>Female n = 21</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>MPA-AUC0–24h (mg · h/L)</td>
<td>90.5 ± 29.56</td>
<td>105.1 ± 39.74</td>
<td>NS</td>
</tr>
<tr>
<td>Cmax MPA (mg/L)</td>
<td>28.8 ± 13.52</td>
<td>29.6 ± 19.72</td>
<td>NS</td>
</tr>
<tr>
<td>Cmax2 MPA (mg/L)</td>
<td>5.0 ± 2.55</td>
<td>6.0 ± 3.22</td>
<td>NS</td>
</tr>
<tr>
<td>Tmax MPA (min)</td>
<td>67.3 ± 46.73</td>
<td>54.8 ± 38.25</td>
<td>NS</td>
</tr>
<tr>
<td>Tmax2 MPA (min)</td>
<td>510.2 ± 230.43</td>
<td>514.7 ± 207.22</td>
<td>NS</td>
</tr>
<tr>
<td>C12h MPA (mg/L)</td>
<td>2.0 ± 1.16</td>
<td>3.4 ± 3.11</td>
<td>NS</td>
</tr>
<tr>
<td>C24h MPA (mg/L)</td>
<td>1.9 ± 1.66</td>
<td>2.0 ± 1.53</td>
<td>NS</td>
</tr>
<tr>
<td>MPAG-AUC0–24h (mg · h/L)</td>
<td>2981 ± 1725.1</td>
<td>2528 ± 1113.1</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>66.1 ± 29.98</td>
<td>61.2 ± 24.19</td>
<td>NS</td>
</tr>
</tbody>
</table>

*MMPA AUC0–24h, area under the concentration-time curve of MPA over 0 to 24 h; Cmax MPA, maximum concentration of MPA; Cmax2 MPA, 2nd maximum concentration of MPA; Tmax MPA, time to maximum concentration of MPA; Tmax2 MPA, time to 2nd maximum concentration of MPA; C12h MPA, concentration of MPA 12 h after administration of 1 g of MMF; C24h MPA, concentration of MPA 24 h after administration of 1 g of MMF; MPAG-AUC0–24h, area under the concentration-time curve of MPA-glucuronide over 0 to 24 h.*

The influence of renal function on C12MPA is especially illustrated in Figure 2. Within the RTX group, C12MPA was significantly higher in patients with a creatinine clearance < 60 ml/min compared with a creatinine clearance > 60 ml/min (2.4 ± 1.26 versus 1.2 ± 0.76 mg/L, P = 0.032), whereas no significant difference in C12MPA was found in AID with respect to renal function (4.5 ± 4.49 versus 3.6 ± 2.46 mg/L, NS; < 60 ml/min and > 60 ml/min creatinine clearance, respectively). When compared with RTX, AID patients with a creatinine clearance > 60 ml/min exhibited a significantly higher C12MPA (3.6 ± 2.46 versus 1.2 ± 0.76 mg/L, P = 0.015; AID versus RTX, respectively), whereas the difference was NS between both patient groups at a creatinine clearance < 60 ml/min (Figure 2.).

In this study, no relationship between the obtained single-dose PK values and hematologic parameters, including hemoglobin, leukocytes, or platelets in peripheral blood, could be demonstrated (data not shown). Mean levels for hemoglobin, white blood cells, and platelets are given in Table 3. Non-hematologic side effects included diarrhea (n = 1) and infection (n = 3) and could not be attributed to alterations of single MPA-PK variables (data not shown).
absence of calcineurin inhibitors, need to be taken into account in dosing MMF in AID (11,12,23).

This is the first study reporting on a systematic investigation of MPA-PK in a nontransplant setting, like in patients with ASVV and SLE. Our data clearly indicate that there are differences of PK between AID and RTX. Twelve hours after application of 1 g of MMF, trough levels of MPA were significantly higher in patients with AID compared with RTX. Lower MPA trough levels have been reported in kidney transplant recipients on triple immunosuppression with cyclosporine, MMF, and prednisone compared with patients on dual therapy with MMF and prednisone (24). Thus, it cannot be excluded that the absence of cyclosporine in the AID group may account for higher C_{12h} MPA levels in these patients. In addition, C_{max} MPA was lower in AID and occurred somewhat later. These alterations in the PK profiles did not result in a difference of MPA-AUC between AID and RTX.

The 12-h MPA trough levels correlated in AID significantly with MPA-AUC_{0–12h}, whereas, in agreement with other authors, the determination of C_{12h} MPA in the RTX group provided no accurate estimation of MPA-AUC_{0–12h} (13). In AID, the estimation of MPA-AUC_{0–12h} could further be improved when related to C_{24h} MPA. Thus, in contrast to RTX, trough levels may more adequately reflect drug exposure in AID.

We also found an association of MPA-AUC_{0–12h} with C_{max2} MPA, but not with C_{max} MPA, in AID. Contrarily, C_{max} MPA, but not C_{max2} MPA could be related to MPA-AUC_{0–12h} in RTX, suggesting that the enterohepatic recycling may play a crucial role for drug exposure in AID, whereas in RTX the initial peak seems to be the important.

The best surrogate marker in our study was C_{24h} MPA for MPA-AUC_{0–24h} in both patient groups. With respect to pharmacologic purposes, particularly the analysis of the enterohepatic impact of the drug, the estimation of 24-h PK profiles seems to be superior to 12-h profiles. Nevertheless, MPA-AUC_{0–12h} has the advantage of more adequately representing the clinical setting of the regular medication taking. Clearly, a single daily dose regimen cannot be recommended because the AUC_{12–24h} will be only 20 to 25% of the MPA-AUC_{0–12h}; thus, no adequate immunosuppression will be achieved over a 24-h period. Moreover, high MPA levels at 30 min have been shown to be associated with an increased risk of side effects, rather supporting a division of the daily oral dose in more of two divided doses to prevent toxicity (9). Therefore, with respect to our data, for AID the determination of MPA trough levels at 12 h may be suggested as a helpful marker for drug monitoring.

An inverse relationship between plasma MPA trough levels or MPA-AUC_{0–12h} and renal function has been reported in kidney transplant recipients (26). Our data confirm these results in the RTX group. In AID, however, MPA-PK seems to be less affected by renal function. Nevertheless, although NS,
the highest C_{12}MPA levels were observed in patients with AID and a creatinine clearance < 60 ml/min. Noteworthy in this subgroup, three adverse effects were observed (two infections, one diarrhea), whereas only one further side effect was noted in AID with a creatinine clearance < 60 ml/min. Severe side effects have also been reported in patients with underlying AID requiring hemodialysis (27). Although in renal recipients high levels of single MMF-PK variables like MPA trough levels, the free MPA fraction as well as the percentage of free MPA have been shown to be associated with hematologic side effects or infections (8,9,20,28,29), in this study no hematologic side effects were observed.

Neither for RTX nor for AID a relationship between MMF-dose per body weight and MPA-PK was found, suggesting that the initiation of MMF treatment in adults with a body weight-adapted dosage is not of advantage compared with a fixed standardized dose. According to observations in transplant recipients (25), MPAG-AUC increased in both patient groups as renal function diminished. A higher glucuronidation of MPA has been described in male than in female RTX patients (30). In our patients, no gender-related differences of MPA-PK were found, indicating that differences of PK between AID and RTX cannot be attributed to the predominance of female in the AID group.

Basically, in agreement with other authors, we found a tight correlation between the two methods, HPLC and EMIT, employed for the MPA-determination, which was similar in both patient groups (14,21). Compared with the HPLC analysis, MMF drug-monitoring by EMIT may have the advantage of a less time-consuming procedure. Moreover, it exhibits a cross-reactivity with the recently detected immunosuppressive active metabolite M2, an acyl glucuronide of MPA (31), which is not determined by HPLC. Although this seems to contribute to the systematic positive bias observed (14,21), the EMIT assay may thus more adequately reflect the whole immunosuppressive activity of MMF.

In conclusion, these data provide evidence that differences of MMF-PK between the nontransplant uses of this drug compared with the transplant setting exist. Concomitant therapy, enterohepatic recycling of MPA, as well as renal function, seem to influence PK differently in AID and RTX. Furthermore, there is a high degree of inter-individual variability of MPA-PK values. Thus, drug exposure at a fixed dose seems to be almost unpredictable in the individual patient, supporting the value of therapeutic drug monitoring. In AID, a single determination of C_{12}MPA may allow an estimation of drug exposure favoring the practicability of a tailored individual dosage. Although in RTX trough concentrations at 12 h do not truly reflect MPA-AUC_{0-12}, estimation of C_{24}MPA in these patient may contribute to a more adequate assessment. Generally, the determination of MPA blood levels by the commercially available EMIT assay provides an accurate and clinical practicable method for both AID and RTX. Larger MPA-PK trials will be mandatory to further standardize MMF-PK in nontransplant patients and to validate efficacy data on MMF for the treatment of AID.

References

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