Limited sampling strategies and Bayesian estimation for mycophenolic acid area under the concentration-time curve prediction in stable renal transplant recipients co-medicated with cyclosporine or sirolimus

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Background

Mycophenolate mofetil (MMF), an immunosuppressive agent used in combination with corticosteroids, calcineurin inhibitors or sirolimus for the prevention of acute rejection after solid organ transplantation, is the produg of mycophenolic acid (MPA), a reversible noncompetitive inhibitor of inosine monophosphate dehydrogenase, and blocks the de novo synthesis of guanosine nucleotide. Current manufacturer MMF dosing guidelines are standard for all patients within a transplant group: the pharmacokinetics (PK) of MPA, however, are characterized by a considerable inter- and intra-patient variability. In addition, MPA has a rather narrow therapeutic window. As a consequence, dose individualization and area under the MPA plasma concentration-time curve during one 12-hours-dosing interval (AUC0-12) rather than C0 based therapeutic drug monitoring (TDM) may improve the efficacy and tolerability of MMF.

Methods

Patients and samples: A total of 2372 samples drawn 12 hours postdose was analyzed for MPA and MPAG by HPLC-DAD at 7, 9 and 16 months after transplantation in 40 renal transplant patients under MMF and cyclosporine or sirolimus in a steroid regimen (methyl prednisolone).

Pharmacokinetic and statistical analyses: Full PK profiles were determined using the following sampling times: 0, 0.33, 1.25, 3, 4, 6, 8 and 12 hours after MMF administration. The AUC was estimated by using the linear trapezoidal method (Noncompartmental Analysis, WinNonlin® version 5.3.1, Pharsight, Mountainview, CA, USA).

Multiple linear regression (MLR) analysis using JMP Statistical Discovery™ version 6.0.0. (SAS, NC,USA) and population PK (PPK) modelling followed by Bayesian estimation using NONMEM version VI (Globomax, LLC, USA) were successively performed to predict MPA AUC from 2-3 concentrations-time points determined within 2 hours after dosing. For NONMEM analysis, MPA and MPAG concentrations were converted in equivalents and simultaneously used. Various structural models were tried. To explain PK variability, relationships were investigated between PK parameters and the following patient covariates: age, sex, race, weight, creatinine clearance calculated by Crockoft-Gault and Nank formulas, plasma albumin concentration, liver enzymes (GOT, GPT), total bilirubine and the use of either sirolimus or cyclosporin as co-medication drug.

Results

MLR models prediction equations and performance are shown in Table I. The best model was model 1 with sampling at 0, 0.66 and 2h.

Table I. Model performance

<table>
<thead>
<tr>
<th>Model</th>
<th>Sampling times</th>
<th>Prediction expression</th>
<th>r²</th>
<th>RMSE</th>
<th>MRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0, 0.66, 2</td>
<td>8.64+5.13t+0.62C14+1.86C2</td>
<td>0.79</td>
<td>7.22</td>
<td>0.93</td>
</tr>
<tr>
<td>2</td>
<td>0, 0.33, 2</td>
<td>10.69+4.90t+3.32C2</td>
<td>0.73</td>
<td>8.11</td>
<td>1.60</td>
</tr>
<tr>
<td>3</td>
<td>0, 1.25, 2</td>
<td>10.39+6.39C1+1.03C2+1.96C4</td>
<td>0.72</td>
<td>8.15</td>
<td>1.91</td>
</tr>
<tr>
<td>4</td>
<td>0, 0.66, 1.25</td>
<td>10.29+5.17C4+0.44C2+1.26C6</td>
<td>0.70</td>
<td>8.53</td>
<td>2.16</td>
</tr>
<tr>
<td>5</td>
<td>0, 0.33, 1.25</td>
<td>8.35+7.04C1+0.54C3+1.77C4</td>
<td>0.69</td>
<td>8.62</td>
<td>2.24</td>
</tr>
</tbody>
</table>

This model was additionally validated by 10 repeated cross validations and gave good performances (CV < 20%). PPK modelling results on 27 patients are summarized in Table II. A five compartment model with lag-time, first order absorption, inter-compartment transfer and elimination rates, best fitted the data. This model is schematised in Figure 1 and its important graphical analysis plots are shown in Figure 2. The GOT/GPT ratio significantly influenced MPA–MPAG biotransformation rate, whereas creatinine clearance calculated by Crockoft-Gault and Nank formulas positively and significantly influenced MPAG elimination constant. Only GOT/GPT ratio and Nank were retained in the final model. All parameters were well estimated. This model was validated by internal validation on 100 bootstraps and by external validation on the 13 remaining patients.

Conclusion

We have validated a series of limited sampling strategies (LSS) for fast MPA AUC TDM with only 2-3 blood samples drawn within 2 hours after drug intake. The population PK model allows faster and more accurate TDM of MPA as compared with the majority of previously reported LSS. None of the previously reported LSS using blood samples within 3 hours after dosing gave comparable results when applied to our sample set.

References


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