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 prodrug 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 (AUC_{0-12}) rather than C_0 based therapeutic drug monitoring (TDM) may improve the efficacy and tolerability of MMF.

Objectives

The objectives of the present study were:
1) to identify and model the effect of demographic and clinical factors on PK variability by using nonlinear mixed-effect modelling techniques;
2) to predict MPA AUC_{0-12} by using multiple linear regression models and MAP Bayesian estimation methods from a minimum of sampling time within 2 hours after drug intake.
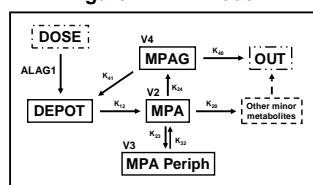
Methods

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, 0.66, 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 5.0.1, 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 drawn 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 Nankivell (Nank) formulas, plasma albumin concentration, liver enzymes (GOT, GPT), total bilirubine and the use of either sirolimus or cyclosporin as co-medication drug.

Figure 1. PPK model

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

Model	Sampling times	Prediction expression	r^2	RMSE	MRP
1	0, 0.66, 2	$8.64+5.13 \cdot C_0+0.62 \cdot C_{0.66}+2.88 \cdot C_2$	0.79	7.22	0.938
2	0, 0.33, 2	$10.69+4.90 \cdot C_0+0.58 \cdot C_{0.33}+3.33 \cdot C_2$	0.73	8.11	1.60
3	0, 1.25, 2	$10.09+6.39 \cdot C_0+1.03 \cdot C_{1.25}+1.96 \cdot C_2$	0.72	8.15	1.91
4	0, 0.66, 1.25	$10.29+5.17 \cdot C_0+0.44 \cdot C_{0.66}+1.26 \cdot C_2$	0.70	8.53	2.16
5	0, 0.33, 1.25	$8.35+7.04 \cdot C_0+0.54 \cdot C_{0.33}+1.71 \cdot C_2$	0.69	8.62	2.24

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.

Table II. PPK final model parameters

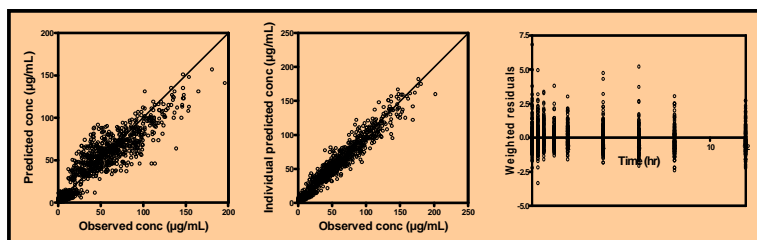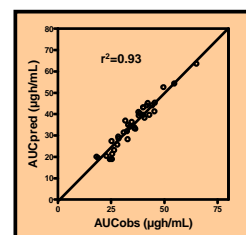| Parameter	Estimates	IIV (IOV**)
Alag1 (hr)	**0.24**	-
K_{12} (hr^{-1})	**1.94**	26.2 (15.6)
V_2(L)	**17**	10.34 (15.6)
V_3(L)	**118**	6.17
V_4(L)	**5.01**	7.19
K_{24} (hr^{-1})	**0.072**	7.18 (15.6)
Q (L/hr)	**26.5**	11
K_{25}(hr^{-1})	**0.01**	-
K40 (hr^{-1})	**0**	-
K_{41} (hr^{-1})	**0.0101**	-
Nank Vector on K_{40}	**0.144**	-
(GOT/GPT) vector on K_{24}	**-5**	-
Prop. Comp. of the res error on MPA conc	**0.281**	-
Prop. comp res error on MPAG conc	**0.0366**	-
Add. comp res error on MPA conc	**0.32**	-

Figure 2. Final model graphical plots

Figure 3. A patient's Bayesian predicted (–) and observed (-) PK profile
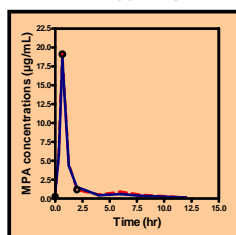
A Bayesian estimator was developed from the final model and samples drawn at 0, 1.25 and 2 hours after dosing; as compared to MLR models, the Bayesian estimator had better prediction performance (r^2 = 0.93, RMSE = 5.12, MRPE = 0.89).

Figure 4. MPA Bayesian predicted / observed AUC

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.

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