

PHARMACOKINETICS- GUIDED TARGETING OF MYCOPHENOLATE MOFETIL (MMF) IN COMBINATION RENAL TRANSPLANTATION TREATMENT LEADS TO IMPROVED AND REDUCED PATIENT DOSING

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Mycophenolate Mofetil (MMF) is used extensively, after transplantation (Tx) for immunosuppression in combination with calcineurin inhibitors (cyclosporin, tacrolimus), rapamycin (sirolimus) and corticosteroids. Administered orally, it is rapidly absorbed and hydrolyzed presystemically into the pharmacologically active mycophenolic acid (MPA). MPA is a selective noncompetitive but reversible inhibitor of inosine 5'-monophosphate dehydrogenase II (IMPDH), a key enzyme in the de novo pathway of guanine nucleotide biosynthesis. By inhibiting IMPDH, MPA blocks T and B lymphocyte proliferation, which have greater dependence on the de novo rather than the salvage pathway, thus also inhibiting T cell response and antibody formation.

MPA blood levels and lymphocyte function have been associated with allograft survival or rejection in vivo in the rat. In man, MMF is indicated as 1000 mg b.i.d. (2000 mg daily) in conjunction with cyclosporine. It is also being used in combination with tacrolimus, and increasingly, with rapamycin in calcineurin sparing protocols.

In renal Tx patients, there is, (A) no relationship between dose and the 12 h MPA area under the concentration-time curve (AUC_[0-12]) [1]; (B) a stronger relationship between AUC and acute rejection (AR) than with monitored concentration surrogates [2], and (C) the pharmacokinetics (PK) of MPA show larger interindividual and intraindividual variability than initially expected, with an overlap between the AUC's of patients with AR or successful therapy [3]. The putative target range of AUC appears to be 40 to 60 mg h/L [4] to avoid either AR or side effects such as diarrhea, leukopenia and anemia.

PURPOSE

A population PK model for MMF is developed in a stable renal transplant patient cohort in combination therapy, in order to explore the Bayes individual patient PK relation to the dosing regimen as well as the possible influence of patient covariates. Limited sampling combined with Bayes estimation to predict the CL, the AUC and next dose adjustment methods are tested with the relation $AUC_{ss} = \frac{Dose}{CL}$

METHODS

Adult "de novo" renal transplant recipients (n = 27; 19 male/ 8 female) who had MMF administered with methylprednisolone (Md) in combination with sirolimus (SRL – 6 patients), cyclosporine (CsA – 13 patients), tacrolimus (Tac – 4 patients), tacrolimus without Md (2 patients), or MMF with Md alone (2 patients) were included in the study. The study started several months post-Tx when patients were stable with serum creatinine (mean [range]) 1.9 (1.0 – 4.0) mg/dL, and albumin 4.2 (2 – 5) mg/dL. A total of 111 blood samples were analyzed from predose troughs (C₀), and 30 min (C₃₀) and 2 h (C₂) postdose, sampled from each patient, with 13 repeat occasions. A nonlinear mixed effects method (NONMEM) was used to build population pharmacokinetic (PK) priors for a two compartment oral absorption model with time lag, as patients entered the study, followed by Bayes estimation of individual patient PK parameters. Systemic clearance, CL, was used to titrate the dose for a putative target AUC (range) for MMF of 50 mg h/L (40 – 60 mg h/L). Demographic and biochemical variables were used for covariate modeling with the PK parameters.

Since the principal aim of this clinical study was to optimally target the therapy in patients using their individual PK characteristics, the Bayes estimates of the patient parameters (particularly CL via AUC = Dose/CL) were used for estimating the current AUC-related exposure to MPA and to make recommendations for the next dose. Thus, several methods of predicting the exposure and obtaining the AUC were tested, including the trapezoidal rule AUC from the observations, and Bayes approximations based on scenarios of sparse sampling (e.g. single concentration monitoring), hence the relation of C_{1/2}, C₂ and C₃₀ as predictors of AUC was also investigated.

RESULTS

The patients had, ages 41.5 (20 – 71) y and weights 68.8 (37 – 94) kg. Administered doses were 731.7 (250 – 1000) mg b.i.d., and AUC₀₋₁₂ of 63 (15.8 – 160.4) mg h/L. The bioavailability (F) - scaled NONMEM FOCE population PK parameters for MMF were (true value, interindividual coefficient of variation, CV%), for CL/F = 12.4 L/h (33%), central volume of distribution, V/F = 11.5 L (15%), intercompartmental clearance, Q = 20.2 L/h (45%), deep tissue volume of distribution, V₃ = 208 L (CV% not estimated), absorption rate constant, k_a = 2.27 h⁻¹ (CV% not estimated), and absorption time delay, Tlag = 0.35 h (CV% not estimated). Due to the unpredictability of the exposure or the therapeutic outcome by the dose, therapeutic drug monitoring (TDM) of MPA levels seems imperative. The C₂ appears a valid surrogate of the AUC through a linear relation, in agreement with other studies [1]. However, the Bayes method can be used even with the trough and provides better individualization for non typical patients or conditions.

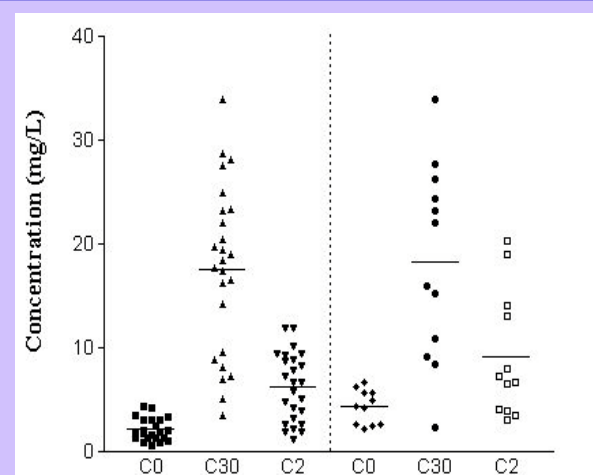


Figure 1. Observed concentration spread at the first, second and third sampling times (predose C₀ and postdose C₃₀ and C₂) after the first (left panel; n = 27) and later (right panel; n = 13) occasions in 27 renal transplant patients. The average levels are increased, although the dose is decreased. The change, although non significant in the mean, did improve individual patients therapy.

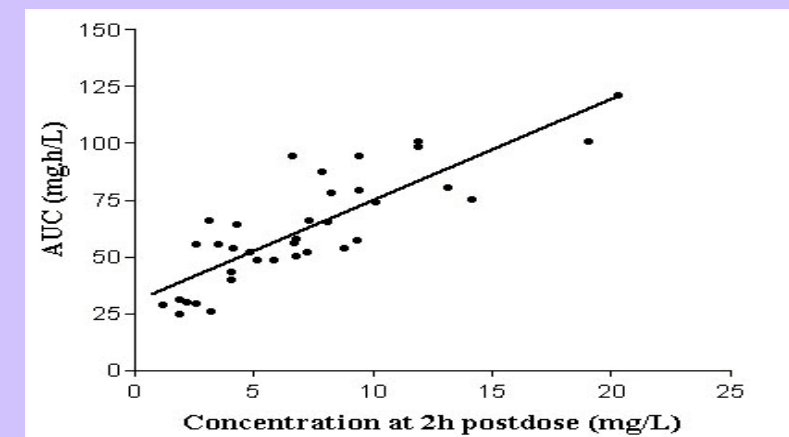


Figure 2. Relation of the three point Bayes estimated AUC_{0-∞} (area under the concentration versus time curve, AUC=Dose/CL) of MPA with the peak concentration (C₂), r₂ = 0.69. The straight line represents AUC = 31 + 4.4 * C₂.

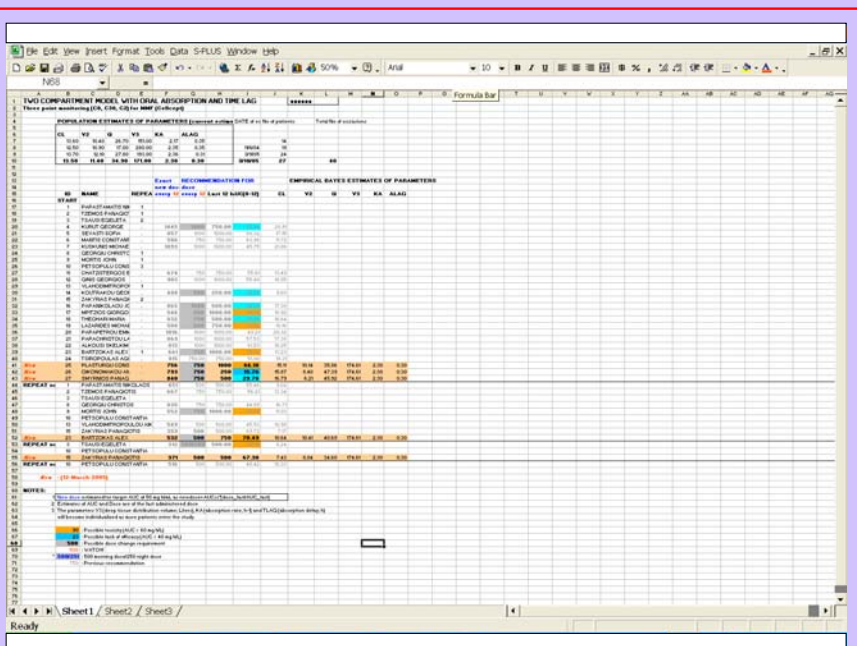


Figure 3. Example Excel report sheet to the clinic, with indication of low and high observed AUC's as well as recommendation for change in the dose

CONCLUSIONS

Prospective population two compartmental pharmacokinetic analysis of renal Tx patients and the estimation of Bayes posterior clearances and AUC's provided a rational means of MMF dose titration. The overall trend was for reduction with the recommended upper dose range limit located at the industry recommended mean.

TDM is necessary for MMF in combination immunosuppression. The C₂ appears a valid surrogate of the AUC, hence of AR avoidance, but optimally Bayes estimates of the AUC should be used. Future studies should include measurement of IMPDH activity in lymphocytes.

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