Population Pharmacokinetics of Mycophenolic Acid (MPA) and its Metabolites (MPAG and AcMPAG)

Helena Colom


Pharmacy and Technology Department, Biopharmaceutics and Pharmacokinetics Unit, University of Barcelona
Nephrology Service, Hospital Universitari de Bellvitge, Barcelona

Conferència de Recerca. Facultat de Farmàcia, 29 Novembre 2011
Outline

Background
- Population pharmacokinetics
  - Definition
  - Aim
  - Advantages and disadvantages
- MPA, MPAG, AcMPAG Pharmacokinetics

Population Pharmacokinetic study of MPA and its glucocojugated metabolites (MPAG and AcMPAG). The influence of MRP2 polymorphism: The Symphony study
- Background
- Methods
- Results
- Conclusions
Background

Definition

Population PK is the study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest.

Guidance for Industry. Population Pharmacokinetics
U.S. Department of Health and Human Services
Food and Drug Administration. Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
February 1999 CP 1
Background

Aims

♫ To describe the pharmacokinetics of a given drug in the target population
♫ ¿What is the mean population PK behaviour?

TVCL, TVV

Typical value

Concentration (mg/L)

Time (h)
Background

Aims

To describe the pharmacokinetics of a given drug in the target population

¿Which factors influence the mean population PK behaviour?

TVCL, TVV

Typical value

CLCR=90 mL/min

CLCR=60 mL/min

CLCR=30 mL/min
Background

Aims

♫ To describe the pharmacokinetics of a given drug in the target population
♫ ¿What is the uncertainty degree associated to the mean population PK behaviour?

TVCL, TVV
Typical value

CLCR=90 mL/min
TVCL1

CLCR=60 mL/min
TVCL2

CLCR=30 mL/min
TVCL3
Advantages

- **It allows:**
  - Simultaneous PK analysis of concentration-time data of parent compound and metabolites, plasmatic and urine concentrations, several doses, several administration routes
  - Sparse data (2/3 sampling time per subject / patient)
    - Observational data
    - Clinical studies phase II/III
    - Special populations (neonates, children, geriatrics…transplant, VIH)
    - Drugs to be monitored (ex. Antiepileptic drugs)
  - High number of patients with low restrictions concerning to inclusion and exclusion criteria
  - Non balanced studies; different number of samples per subject
  - Intensive sampling studies (rich data) and studies where subjects are characterized extensively.
Disadvantages

- Complexity and long running times sometimes!!!
Sparse vs rich data analysis

**Sparse**

**rich**

```
Time (h)          0  2  4  6  8  10  12
Concentration (mg/L) 2  4  6  8 10 12 14 16
```

```
Time (h)          0  2  4  6  8  10  12
Concentration (mg/L) 2  4  6  8 10 12 14 16
```
Applicability

♫ Preclinical and clinical development:

♫ Better Knowledge during the different steps of drug development:

♫ PK model (concentration-time profile)

♫ PD model (Response-concentration)

♫ PK/PD model (Response –time profile)

♫ Clinical practice (drugs of narrow therapeutic index) ↓

♫ Prediction of the PK behaviour of the drug in subpopulations (renal and hepatic impairment, aged populations, neonates): ¿Dose tailoring?

♫ Prediction of PK behaviour of the drug administered with other drugs (Interactions): ¿Dose tailoring?

♫ Simulation of new scenarios, dosage regimens, sampling designs, patient characteristics…, etc.
Outline

Background
  Population pharmacokinetics
    Definition
    Aim
    Advantages and disadvantages
  MPA, MPAG, AcMPAG Pharmacokinetics
MPA, MPAG Pharmacokinetics

Protein binding

Liver

MPA
MPAG

Portal vein
Systemic circulation

UGT1A
MRP2

Kidney

Enterocytes

Urine

Stomach

Duodenum

Jejunum
Ileum

Colon

MRP2 SNP

Cyclosporine: MRP2 inhibitor

Naessens, TDM, 2009
tMPA, Pharmacokinetics

Symphony study
MPA, MPAG, AcMPAG
Pharmacokinetics

Protein binding

Liver

MPA

MPAG

Portal vein

MPA

MPAG

Bile duct

Enterohepatic recirculation

MPA

MPAG

Systemic circulation

UGT1A

MRP2

Kidney

Enterocyte

Urine

Duodenum

Stomach

Jejunum

Ileum

Colon

MMF / EC-MPS

Cyclosporine: MRP2 inhibitor

MRP2 SNP

Naessens, TDM, 2009
MPA exposure variability?

- Changes in Albumin concentrations
- Changes in Renal function (CLCR)
- Immunosuppressive co-medication
- Genetic polymorphism, MRP2, UGT
MPA is widely used for maintenance immunosuppressive therapy and prevention of renal allograft rejection in renal transplant recipients. MPA inhibits inosine monophosphate dehydrogenase (IMPDH), an enzyme involved in the de novo synthesis of purine nucleotides, thus suppressing both T-cell and B-cell proliferation.

The pharmacodynamics depends on the free MPA concentrations and also the adverse events.
Outline

Background
  - Population pharmacokinetics
    - Definition
    - Aim
    - Advantages and disadvantages
  - MPA, MPAG, AcMPAG Pharmacokinetics

Population Pharmacokinetic study of MPA and its glucoconjugated metabolites (MPAG and AcMPAG). The influence of MRP2 polymorphism: The Symphony study
  - Background
  - Methods
  - Results
  - Conclusions
SYMPHONY: Comparison of 3 low-toxicity regimens with standard immunosuppression

POPULATION PHARMACOKINETICS OF MYCOPHENOLIC ACID AND ITS METABOLITES IN COMBINATION WITH FREE OR REDUCED DOSES OF CALCINEURIN INHIBITORS DURING THE RENAL POST-TRANSPLANT PERIOD: THE SYMPHONY STUDY.

\textsuperscript{8}COLOM H, \textsuperscript{1,9}LLOBERAS N, \textsuperscript{1}CALDÉS A, \textsuperscript{1}ANDREU F, \textsuperscript{2}OPPENHEIMER F, \textsuperscript{4}SÁNCHEZ PLUMED J, \textsuperscript{5}GENTIL M, \textsuperscript{6}KUYPERS D, \textsuperscript{2,3}BRUNET M, \textsuperscript{7}EKBERG H, \textsuperscript{1}GRINYÓ J.

\textsuperscript{1}Nephrology Service and Laboratory of Experimental Nephrology, Hospital Universitari de Bellvitge, Catalonia, Spain; \textsuperscript{2}Hospital Clinic i Provincial, Barcelona, Spain; \textsuperscript{3}Centre de Diagnostic Biomedic, Barcelona, Spain. \textsuperscript{4}Hospital La Fe, Valencia, Spain; \textsuperscript{5}Hospital Virgen del Rocío, Sevilla, Spain; \textsuperscript{6}Department of Nephrology and Transplantation University Hospital, Leuven, Belgium; \textsuperscript{7}Department of Nephrology and Transplantation University Hospital, Malmö, Swededen. \textsuperscript{8}Department of Pharmacy and pharmaceutical technology, School of Pharmacy, University of Barcelona, Barcelona, Spain; \textsuperscript{9}Pharmacogenetic group of the symphony study in Spain

Supported by funding from F. Hoffmann-La Roche
Background

SYMPHONY Pharmacokinetic (PK) Sub-Study

♫ Patients from 9 sites in Spain and 1 in Belgium

♫ PK sampling on Day 7 and 1, 3, 6 and 12 months post-transplant

♫ Sampling times: before dosing and at 20, 40, 75 min, 2, 3, 6, 8, 10 and 12 h post-dosing

♫ Patients were genotyped for C24T SNPs in MRP2 (CC, CT, TT)
Background

Grinyó et al, Nephrol Dial transplant, 2009

N Lloberas et al, Nephrol Dial transplant, 2011
Background

\[ t\text{MPA} = b\text{MPA} + f\text{MPA} \]

\[ C_{\text{BMPA}} = \frac{B_{\text{max}} \cdot C_{\text{fMPA}}}{K_D + C_{\text{fMPA}}} \]

\[ C_{\text{dMPA}} = K_{\text{PB}} \cdot C_{\text{fMPA}} \]

Fu vs time
Aim

To develop a population PK model in order to:

- Describe relationship among MMF doses and total MPA, free MPA, total MPAG and total acylMPAG exposures

- Identify potential predictive patients’ demographic and clinical characteristics for dose tailoring during the post-transplant immunosuppressive treatment.
Methods

Patients’ characteristics

<table>
<thead>
<tr>
<th></th>
<th>Units</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td></td>
<td>56</td>
</tr>
<tr>
<td>Standard Cyclosporine (A)</td>
<td>n</td>
<td>11</td>
</tr>
<tr>
<td>Low Cyclosporine (B)</td>
<td>n</td>
<td>17</td>
</tr>
<tr>
<td>Low Tacrolimus (C)</td>
<td>n</td>
<td>10</td>
</tr>
<tr>
<td>Low Sirolimus (D)</td>
<td>n</td>
<td>18</td>
</tr>
<tr>
<td>Creatinine clearance*</td>
<td>mL/min</td>
<td>59.51 (8.43 - 134.9)</td>
</tr>
<tr>
<td>Albumin</td>
<td>g/L</td>
<td>42.0 (28.0 - 67.0)</td>
</tr>
<tr>
<td>Patients with low graft function (y/n)</td>
<td>n</td>
<td>4/56</td>
</tr>
<tr>
<td>Cyclosporine Daily Doses</td>
<td>mg</td>
<td></td>
</tr>
<tr>
<td>Standard dose group (A)</td>
<td></td>
<td>150 (50 - 300)</td>
</tr>
<tr>
<td>Low dose group (B)</td>
<td></td>
<td>100 (40 - 225)</td>
</tr>
<tr>
<td>Cyclosporine trough concentrations ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard dose group (A)</td>
<td></td>
<td>175 (47 - 500)</td>
</tr>
<tr>
<td>Low dose group (B)</td>
<td></td>
<td>87 (26 - 480)</td>
</tr>
<tr>
<td>MRP2 Polymorphisms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C24T (CC/TT/CT)</td>
<td>n</td>
<td>36/1/19</td>
</tr>
</tbody>
</table>

* CL<sub>CR</sub> values estimated according to Cockroft-Gault

Patients with low graft function (y): CL<sub>CR</sub> < 25 mL/min
(n): CL<sub>CR</sub> > 25 mL/min

CC: non carrier, TT: homozygous T carrier, CT: heterozygous carrier
Methods: Population PK Pharmaco-statistical model

Inclusion of covariates

Base Model
- tMPA and tMPA (linear and non-linear protein binding)
- MPAG, EHC
- AcMPAG

Structural Model

Statistical Model
- BPV, exponential error model
- RE, proportional error model

Final Model

NONMEM VI ver 6.2

PK Model and error model (IIV and RE)
Base model + covariates

Albumin concentrations, MPAG concentrations, CLCR, low graft function (CLCR<25 mL/min), cyclosporine doses and trough concentrations, C24T SNP of MRP2…
Methods: Model evaluations

- Model evaluations
  - Non hierarchical models: AIC values
  - Hierarchical models ∆MOFV (7.879 units, p<0.005)
  - Parameter precision (RSE%)
  - Goodness-of-fit plots
  - Reduction of BPV
  - Covariate model backward elimination (10.8 units, p<0.001)

- Internal model validation
  - VPC, visual predictive check
  - PPC, posterior predictive check
Results: tMPA

N=2038 tMPA

Post-dosing time (h)

Concentration (mg/L)
Results: fMPA

Post-dosing time (h)

Concentration (mg/L)

N=2046 fMPA
Results: tMPAG

Concentration (mg/L) vs. Post-dosing time (h)

N=2054 MPAG
Results: tAcMPAG

Concentration (mg/L) vs. Post-dosing time (h)
**Results**
**Base PK model**

\[ C_{BMPA} = \frac{B_{max} \cdot C_{fMPA}}{K_D + C_{fMPA}} \]

\[ C_{bMPA} = K_{PB} \cdot C_{fMPA} \]

MPA free fraction, \( f_u = \frac{1}{1 + K_{PB}} \)

\[ CL_{MPA} = CL_{fMPAG} + CL_{fAcIMPAG} \]

\[ CL_{fAcIMPAG} = (1 - f_m) \cdot CL_{MPA} \]

**Equations**

\[ \text{Gut} \quad K_A \quad t_{lag} \]

\[ \text{MPA Peripheral Compartment} \quad V_{PMPA} \]

\[ \text{MPA Central Compartment} \quad V_{cMPA} \]

\[ \text{MPAG Central compartment} \quad V_{cCMPAG} \]

\[ \text{MPAG Peripheral compartment} \quad V_{pMPAG} \]

\[ \text{Bile Duct} \quad \text{EHC} \quad \text{ciclosporin} \]

\[ \text{Acyl-MPAG Central compartment} \quad V_{cAcMPAG} \]

\[ CL_{MPAG} \]

\[ CL_{AcMPAG} \]
Results
Covariate PK model

\[ C_{bMPA} = K_{PB} \cdot C_{fMPA} \]

\[ K_{PB} \left\{ \begin{array}{l}
\text{Albumin concentration} \\
\text{MPAG concentration}
\end{array} \right. \]

\[ CL_{MPAG} \left\{ \begin{array}{l}
\text{CL}_{CR}, \text{CsA trough concentrations} \\
\text{C24T SNPs MRP2}
\end{array} \right. \]

\[ CL_{AcylMPAG} \left\{ \begin{array}{l}
\text{CsA trough concentrations} \\
\text{C24T SNPs MRP2}
\end{array} \right. \]

\[ CL_{MPA} \left\{ \begin{array}{l}
\text{CsA trough concentrations} \\
\text{C24T SNPs MRP2}
\end{array} \right. \]
$\text{CL}_{\text{MPAG}}, \text{CL}_{\text{AcMPAG}}, \text{CL}_{\text{MPA}}$
## Results

### Covariate PK model

<table>
<thead>
<tr>
<th>Model</th>
<th>Ref. Model</th>
<th>Covariate relationships</th>
<th>ΔMOFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Base model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>+TVCL_MPAG_t+9 (CL_CR/59.51) _t+15</td>
<td>-1556.11</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>+TVCL_AcMPAG_t+12 (CL_CR/59.51) _t+16</td>
<td>-654.23</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>+TVCL_MPAG_t+9 (CL_CR/59.51) _t+15 (1-+17 _C_CSA)</td>
<td>-95.63</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>+TVCL_AcMPAG_t+12 (CL_CR/59.51) _t+16 (1+(1-_CSA) _t+21 _C_24T)</td>
<td>-28.11</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>+TVCL_MPAG_t+9 (CL_CR/59.51) _t+15 (1-_CSA _t+11 _C_CSA) _t+18 _C_24T)</td>
<td>-299.48</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>+TVCL_MPA_t+1 (1+_t+22 _CSA _t+CSA)</td>
<td>-45.61</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>+TVCL_MPA_t+1 (1+_t+22 _CSA _t+CSA) _t+23 (1-_CSA) _t+21 _C_24T)</td>
<td>-24.78</td>
</tr>
<tr>
<td>9</td>
<td>8</td>
<td>+TVCL_MPA_t+1 (1+_t+22 _CSA _t+CSA) _t+23 (1-_CSA) _t+21 _C_24T) _t+24 _COURSE)</td>
<td>-17.53</td>
</tr>
</tbody>
</table>

CsA=1, Std and low CsA  
CsA=0, Macrolides  
C24T=1, CT/TT carriers  
C24T=0, CC non carriers  
Course=1, Day7  
Course=0, months 1, 3, 6, 12
Results

Final PK Model

<table>
<thead>
<tr>
<th>Expression</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$+TVCL_{MPAG} = H_9 \cdot (CL_{CR}/59.51)^{H_5} \cdot (1-CSA \cdot H_7 \cdot C_{CSA}) \cdot (1+(1-CSA) \cdot H_8 \cdot C_{24T})$</td>
<td>Final model</td>
</tr>
<tr>
<td>$+TVCL_{AcMPAG} = H_2 \cdot (CL_{CR}/59.51)^{H_6} \cdot (1+(1-CSA) \cdot H_1 \cdot C_{24T})$</td>
<td></td>
</tr>
<tr>
<td>$+TVCL_{MPA} = H_1 \cdot (1+H_{22} \cdot CSA \cdot C_{CSA}) \cdot (1+H_{23} \cdot (1-CSA) \cdot C_{24T})$</td>
<td></td>
</tr>
</tbody>
</table>

CsA=1, Std and low CsA
CsA=0, Macrolides

AUC~ D/CL

C24T=1, CT/TT carriers
C24T=0, CC non carriers
## Results

### Final model Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Final model parameter estimate (RSE%)</th>
<th>BPV,% (RSE%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>fMPA</td>
<td></td>
<td>414 (9.3)\cdot (1+CSA\cdot 0.000966(69.1) \cdot C_{\text{csa}})(1+(1-\text{CSA})\cdot 0.158(88.0) \cdot \text{C24T})</td>
<td>28.9 (32.6)</td>
</tr>
<tr>
<td>CL\text{MPA}</td>
<td>L/h</td>
<td>1030 (7.3)</td>
<td>-</td>
</tr>
<tr>
<td>V\text{CMPA}</td>
<td>L</td>
<td>19800 (48.2)</td>
<td>-</td>
</tr>
<tr>
<td>f\text{m}</td>
<td></td>
<td>0.874 (fix)</td>
<td>-</td>
</tr>
<tr>
<td>K\text{PB}</td>
<td></td>
<td>44.7 (6.2)</td>
<td>28.2 (21.4)</td>
</tr>
<tr>
<td>K\text{A}</td>
<td>h\text{'}</td>
<td>1.26 (28.6)</td>
<td>-</td>
</tr>
<tr>
<td>LT</td>
<td>h</td>
<td>0.132 (24.1)</td>
<td>-</td>
</tr>
<tr>
<td>V\text{MPAG}</td>
<td>L</td>
<td>19800 (48.2)</td>
<td>-</td>
</tr>
<tr>
<td>f\text{AcMPAG}</td>
<td></td>
<td>71.9 (14.0)</td>
<td>-</td>
</tr>
<tr>
<td>t\text{MPA}</td>
<td></td>
<td>48.6 (13.9)</td>
<td>-</td>
</tr>
<tr>
<td>f\text{MPAG}</td>
<td></td>
<td>71.9 (14.0)</td>
<td>-</td>
</tr>
<tr>
<td>t\text{MPAG}</td>
<td></td>
<td>77.3 (19.9)</td>
<td>-</td>
</tr>
</tbody>
</table>

CsA: categorical covariate expressing cyclosporine administration or not. Patients treated with Cyclosporine CSA=1, Patients not treated with Cyclosporine CsA=0. C_{\text{csa}} = cyclosporine trough concentrations
C24T=1 for CT/TT carriers; =0, for CC non carriers
CLCR=creatinine clearance in mL/min, estimated according to Crookft-Gault
Goodness-of-fit plots

DV=Observed, PRED=population Predictions, IPRED=individual predictions

DV vs PRED

DV vs IPRED
Goodness-of-fit plots

WRES = (Obs - PRED) / W
IWRES = (Obs - IPRED) / W

Time series plots for fMPA, tMPA, MPAG, and AcMPAG.
Goodness-of-fit plots

Patient 54, tMPA, OBSERVED/IPRED/PRED

Concentration (mcmol/L) vs. Post-dosing time (h)

- Observed
- Individual predicted
- Population predicted

MMF+Tacrolimus
Visual predictive checks

Concentration (µmol/L) vs. Post-dosing time (h)

Macrolides CT/TT, CLCR= 65.8 mL/min
Macrolides CC, CLCR= 61.4 mL/min

OCC=2

Post-dosing time (h)
Protein binding plots

![Graph showing observed vs. individual predicted values for protein binding. The x-axis represents individual predicted values of $f_u$, ranging from 0.010 to 0.030. The y-axis represents observed values of $f_u$, ranging from 0.010 to 0.030. The data points are scattered with a trend line indicating a positive correlation.]
Posterior predictive check

Median (P5%-P95%)

\[ \text{tMPA} \]
\[ \begin{align*}
\text{Obs: } & 1.19 \ (0.52-2.50) \\
\text{Sim: } & 1.46 \ (0.58-3.32)
\end{align*} \]

\[ \text{tMPA} \]
\[ \begin{align*}
\text{Obs: } & 57.04 \ (24.24-110.80) \\
\text{Sim: } & 66.74 \ (23.41-170.66)
\end{align*} \]

\[ \text{AUC}_{0-12} \]

\[ \text{Obs: } 825.25 \ (585.69-3887.88) \\
\text{Sim: } 999.81 \ (386.20-2773.01) \]

\[ \text{AUC}_{0-12} \]
\[ \begin{align*}
\text{Obs: } & 10.46 \ (2.31-37.43) \\
\text{Sim: } & 11.35 \ (3.00-39.72)
\end{align*} \]

Median AUC simulated values are within the P5%-P95% interval of observed AUC values in all the cases.
Aplicability: Model simulations

AUC (mg/L)·h

fMPA

CC CT/TT CsA 100 CsA 300

0.0 0.5 1.0 1.5 2.0

CL<sub>CR</sub>=60

CL<sub>CR</sub>=25

CL<sub>CR</sub>=60

CL<sub>CR</sub>=120

MPAG

CL<sub>CR</sub>=60

AcMPAG

CL<sub>CR</sub>=25

CL<sub>CR</sub>=60

CL<sub>CR</sub>=120

1 g MMF
Conclusions

- An integrated population PK model to describe the relationships among MMF and fMPA, tMPA, MPAG, AcMPAG concentrations has been developed.
- EHC has not been described by the current model.
- The developed model did not allow to evaluate the impact of changes in albumin concentrations and renal function on tMPA and fMPA exposures.
- Renal function given by CL\textsubscript{CR} is a predictor of both CL\textsubscript{MPAG} and CL\textsubscript{AcMPAG}.
- Cyclosporine trough concentrations are predictors of CL\textsubscript{MPA}, and CL\textsubscript{MPAG} and C24T SNPs of MRP2 are predictors of CL\textsubscript{MPA}, and CL\textsubscript{MPAG} and CL\textsubscript{AcMPAG}.
- The developed model allows to predicts fMPA exposures from tMPA concentrations.
- According to this model and for patients belonging to the studied population, patients under macrolides and non carriers of the C24T SNP would require lower doses than those under cyclosporine or those under macrolides and CT/TT carriers of the C24T SNP.
- PK Differences between day 7 and the remaining occasions have to be explained in future analyses.
Centers participating in the Symphony PK substudy

♫ Spain:
♫ Dr. J.M. Grinyó. Hospital Universitari de Bellvitge, Barcelona.
♫ Dr. F. Oppenheimer. Hospital Clinic i Provincial de Barcelona, Barcelona.
♫ Dr. J. Sanchez-Plumed. Hospital Universitario La Fe, Valencia.
♫ Dr. M.A Gentil. Hospital Virgen del Rocio, Sevilla.
♫ Dr. D. Hernández. Hospital Universitario de Canarias, Tenerife.
♫ Dr. F. Valdés. Hospital Juan Canalejo, La Coruña.
♫ Dr. M. Gonzalez- Molina. Hospital Carlos Haya, Malaga.
♫ Dr. R. Lauzurica. Hospital Germans Trias i Pujol, Badalona.
♫ Dr. M. Arias. Hospital Universitario Marques de Valdecillas, Santander.

♫ Belgium:

Supported by funding from F. Hoffmann-La Roche
Thank you