Model-based dose adjustment in treatment personalization of immunosuppressive drugs

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Treatment personalization

« The right patient, the right drug, the right dose »

• TDM has been one of the first tools of treatment personalization
• Although routinely used for long, TDM is still progressing owing to scientific refinements
Background

Therapeutic Drug Monitoring (TDM) of immunosuppressants is either mandatory or consensually recommended.

Limitations:

1. Classic exposure indices (C0 or C2): not relevant in all situations.
2. Complex PK profiles: delayed absorption, flat or multiple concentration peaks.
3. Overall exposure: highly variable and hardly predictable.

Usefulness of TDM based on the AUC.

E.g., tacrolimus:

- \( C_0 = 8 \, \mu g/L \); \( AUC = 120 \, \mu g.h/L \)
- \( C_0 = 8.5 \, \mu g/L \); \( AUC = 180 \, \mu g.h/L \)
1. Data collection
   (concentrations + individual factors)

2. PK and PG/PK modeling → Bayesian estimators

3. Clinical validation of optimized individual dose adjustment of IS (comparative trials)

4. Models and Bayesian estimators made accessible to the transplant community

Translational strategy

- (PG)PK modeling
- Bayesian forecasting
- Proof of concept
- Sharing tools
- Multicenter observational clinical trials
PK modeling: methods

→ Aim: models compatible with different types of:
  → transplantation
  → co-administered IS (with DDI among them)
  → factors of variability
  → drug assays

Individual PK modeling (ABIS/ISBA®)
Iterative two-stage Bayesian approach + Bayesian forecasting

Non-linear, mixed-effect population modeling (NONMEM)
- Mixture models, Bayesian forecasting...
- Semi-parametric approach

Non-parametric population modeling (NPEM, NPAG, PMetrics)

FDA recommended validation procedures
(Bootstrap and/or simulation, External validation)
1. “Individual” PK methods

- Iterative two-stage Bayesian (IT2B) approach → requires full PK profiles from each patient
- Using commercial or home-made software
- At Limoges university, models developed for:
  - cyclosporine, tacrolimus, MMF, sirolimus, everolimus
  - In kidney, liver, heart and lung transplantation
  - CsA and MMF in bone marrow transplantation
  - MMF in auto-immune diseases (lupus, nephrotic syndrome …)
Absorption model for Csa

- CsA absorption is not well fitted by a zero- or first-order model

(Cyclosporine – renal transplant patient, Year 1)

[Debord et al., Clin Pharmacokinet 2001]
- CsA absorption is best fitted with an asymmetrical, S-shaped Gamma ($\Gamma$) distribution

![Graph showing CsA absorption profile]

- This $\Gamma$ absorption profile was convoluted with the classical bi-exponential elimination model, giving the general equation:

$$C(t) = FD \sum_{i=1}^{n} A_i \left( \frac{b}{b - \alpha_i} \right)^a P[a, (b - \alpha_i)t] \exp(-\alpha_i t)$$

[Debord et al., *Clin Pharmacokinet* 2001]
Γ model fitting of full CsA profiles

[Debord et al., Clin Pharmacokinet 2001]
• Bayesian estimation can provide estimates of all PK parameters for an individual (and complete $[C]_{\text{blood}} = f(t)$ curve) using only 1 to 3 time-concentration data.

\[ \Phi_2 = \sum_{i=1}^{n} \left( \frac{C_i - E_i}{S_i} \right)^2 + \sum_{k=1}^{m} \left( \frac{\theta_k - \mu_k}{\sigma_k} \right)^2 \]
Bayesian estimation of CsA (e.g., in adult renal transplant recipients)

Best sampling times: C0, C1h, C3h

Bayesian estimates vs. true AUC\(_{0-12h}\)

\[ r^2 = 0.934 \ (n = 24) \]

[Léger F et al., Clin Pharmacokinet 2002]
<table>
<thead>
<tr>
<th>Performance AUC_{BE}</th>
<th>W1 (n=24)</th>
<th>W2 (n=24)</th>
<th>M1 (n=24)</th>
<th>&gt; M3 (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( r^2 = )</td>
<td>0.91</td>
<td>0.90</td>
<td>0.93</td>
<td>0.96</td>
</tr>
<tr>
<td>Bias =</td>
<td>-4.5%</td>
<td>0.9%</td>
<td>0.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td>% poor estimation</td>
<td>8%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Mycophenolate mofetil (MMF)

- Once prescribed at standard dose (from 0.5 to 1 g bid, depending on the associated anticalcineurin), now TDM is recommended.
- AUC better than C0
- Complex PK, with enterohepatic cycling → two-stage absorption model
MPA PK modeling

Double gamma-absorption, one-compartment model

\[ V_{\text{abs}}(t) = FD \left[ \text{fast} \times f_1(t) + (1-\text{fast}) \times f_2(t) \right] \]

with \( f_1(t) = b_i^{a_i} t^{a_i-1} \exp(-b_i t) / \Gamma(a_i) \)

\[ C(t) = C_0 + FDA( \frac{b}{b - \lambda_1} )^a P[a, (b - \lambda_1) t] \exp(-\lambda_1 t) + FDB( \frac{b}{b - \lambda_2} )^a P[a, (b - \lambda_2) t] \exp(-\lambda_2 t) \]

[Prémaud et al., Clin Pharmacokinet 2005]
Model fitting of full MPA profiles
Bayesian estimation of MPA profiles and AUC after MMF administration

Best sampling strategy: 20min, 1h and 3h post-dose

[Prémaud et al., *Ther Drug Monit* 2005]
Tacrolimus (TAC, FK506)

• Immediate-release formulation (Prograf®) approved in 1995 in Europe

• New, prolonged-release formulation (Advagraf®) approved in 2009 in Europe

• TDM is recommended, generally C0 monitoring.

• AUC better than C0 for difficult cases

• PK Prograf® ≠ PK Advagraf® → need for specific models and Bayesian estimators
Mean 24-Hour Whole Blood Tacrolimus Levels

Conversion of Stable Kidney Transplant Recipients

Whole blood tacrolimus concentration (ng/mL) vs. Time (h)

- Day 1, Prograf
- Day 7, Prograf
- Day 14, Advagraf
- Day 21, Advagraf
Our experience with Advagraf® PK

ADVAGRAF® PK profiles
(45 renal transplant patients, stable post-transplant period)

Advagraf® PK modelling

Diversity of individual PK profiles

\[ V_{abs}(t) = FD \sum_{i=1}^{m} r_i f_i(t) \]
\[ f_i(t) = b_i^{a_i} t^{a_i-1} \exp(-b_i t) / \Gamma(a_i) \]
with \( i = 1 \) or 2

\[ C(t) = C_0 + FD A_{IV} \exp^{-kt} \sum_{i=1}^{m} r_i [b_i / (b_i - k)]^{a_i} P[a_i, (b_i - k)t] \]

1 compartment model; first-order elimination; **Gamma** absorption profile
Tacrolimus (Advagraf®) Bayesian estimation

Best sampling strategy: pre-dose, 1h and 3h post-dose

[Saint-Marcoux et al., *Ther Drug Monit* 2010]
2. Population Pharmacokinetics

- Population pharmacokinetic (popPK) analysis is:
  - a PK + statistical technique
  - capable of identifying the individual biometric, genetic or clinical covariates responsible for a part of the drug interindividual PK variability
  - a way to set up Bayesian estimators for large populations, encompassing different patient groups with different statuses or conditions (= covariate values)

[Rousseau et al. *ClinPK* 2004]
[Rousseau et al. *TDM* 2004]
[Saint-Marcoux et al. *ClinPK* 2006]
[Djebli et al. *ClinPK* 2006]
[Irtan et al. *TDM* 2007]

[Benkali et al. *ClinPK* 2010]
[De Winter et al. *ClinPK* 2012]
[Monchaud et al. *ClinPK* 2012]
**Example: parametric popPK of CsA (NONMEM)**

<table>
<thead>
<tr>
<th>Populations</th>
<th># of Patients</th>
<th>Post-transplant periods</th>
<th>Analytical technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>16</td>
<td>D3 – D7 – 1yr</td>
<td>FPIA</td>
</tr>
<tr>
<td>Lung non-CF</td>
<td>52</td>
<td>D15 to 4 yrs</td>
<td>EMIT</td>
</tr>
<tr>
<td>Lung CF</td>
<td>47</td>
<td>D15 to 4 yrs</td>
<td>EMIT</td>
</tr>
<tr>
<td>Kidney <em>de novo</em></td>
<td>24</td>
<td>D3 – D7 – M1</td>
<td>FPIA + LCMS</td>
</tr>
<tr>
<td>Kidney - stable</td>
<td>20</td>
<td>&gt; M3</td>
<td>FPIA + LCMS</td>
</tr>
<tr>
<td>Kidney – pediatrics</td>
<td>74</td>
<td>D6 to 1yr</td>
<td>EMIT</td>
</tr>
</tbody>
</table>

309 profiles - 3072 concentrations
Structural (PK) model: absorption best fitted by ERLANG distribution

\[ f(t) = \left\{ \begin{array}{ll} \frac{Ktr^a}{(a-1)!}.t^{a-1}.\exp(-Ktr.t) \\ \end{array} \right. \]

\[ \Gamma(a) = (a - 1)! \quad \text{(if } a \text{ is an integer)} \]

Linear chain of \( a \) compartments between the depot and the central compartments.
All connected by the same transfer constant \( Ktr \).

5 parameters:
- \( \text{CL/F (L/h), } Vc/F (L), Vp/F (L), Q/F (L/h) \)
- \( Ktr (h^{-1}) \)

[Rousseau et al., Ther Drug Monit. 2004]
Final popPK model

Parameters

Mean (estimation precision %)

Inter-individual variability (CI 95%)

Residual error

CsA absorption

Vc/F and Cl/F increase with body weight

Individual predicted concentrations (µg/L)

Observed concentrations (µg/L)

CsA absorption depends upon the graft type:
- kidney
- heart
- lung

Vc/F and Cl/F increase with body weight

Residual error

EMIT FPIA LCMS

Prop. (%) 10.7 11.2 10.8

Add. (µg/L) 47.5 28.2 37.4

[Saint-Marcoux et al., Clin Pharmacokinet 2006]
2nd example: popPK analysis of sirolimus in renal transplant patients

- Bi-compartimental model
- First-order elimination
- Absorption best described by the Erlang model with 3 «delay compartments» between the depot and the central compartments

[Djeblì et al., Clin Pharmacokinet. 2006]
CYP3A5*1/*3 genotype was the only significant covariate

<table>
<thead>
<tr>
<th>PK parameters</th>
<th>Mean pop values</th>
<th>Inter-individual variability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estim.</td>
<td>SD</td>
</tr>
<tr>
<td>Ktr (h⁻¹)</td>
<td>5.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Q/F (L.h⁻¹)</td>
<td>38.7</td>
<td>5.0</td>
</tr>
<tr>
<td>Vc/F (L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vp/F (L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL/F = ( \theta_1 + \theta_2 \times \text{CYP3A5} )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \theta_1 ) (L.h⁻¹)</td>
<td>14.1</td>
<td>1.0</td>
</tr>
<tr>
<td>( \theta_2 ) (L.h⁻¹)</td>
<td>14.2</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Non-exp. CYP3A5: CL/F = 14.1 L.h⁻¹
Expressors CYP3A5: CL/F = 28.3 L.h⁻¹

Residual error: proportional part = 5.9 % ; additive part = 3.1 µg/L

[Djebli et al., Clin Pharmacokinet. 2006]
Non-parametric popPK: CsA in bone marrow transplantation

• **Context:**
  – CsA is widely used in BMT
  – Very few PK information
  – No consensually recommended strategy for TDM of CsA in BMT
  – Limoges study: measurements of the AUC using multiple samples in the first weeks after BMT
• **Objectives:** to build a PK model and a MAP-BE to estimate CsA AUC on the basis of a limited sampling strategy

• **Patients:** 41 patients → 72 full-PK profiles (10 points per patients)

• **Modelling:** Non-parametric approach using PMETRICS

• **Strategy:**
  – 47 full profiles for model building
  – 25 full profiles for model validation
1 model file (.for)

1 data file (.csv)

1 instruction file (.inx)
Model development

R-squared = 0.462
Inter = 0.164 (95%CI 0.132 to 0.195)
Slope = 0.573 (95%CI 0.514 to 0.632)

R-squared = 0.972
Inter = 0.011 (95%CI 0.0033 to 0.0187)
Slope = 0.973 (95%CI 0.957 to 0.989)
Model validation: $\text{AUC}_{0-1-4h}$ vs. $\text{AUC}_{\text{trap}}$

- Mean bias (n=25): -1.29%  18.63%

ID 44183

Bias 10.65%

ID 44532

Bias 9.04%

ID 46930

Bias -2.99%

ID 47825

Bias 0.33%

ID 43289

Bias -29.54%

ID 44153

Bias 56.39%
Individualized Mycophenolate Mofetil Dosing Based on Drug Exposure Significantly Improves Patient Outcomes After Renal Transplantation

Y. Le Meur\textsuperscript{a,*}, M. Büchler\textsuperscript{b}, A. Thierry\textsuperscript{c}, S. Caillard\textsuperscript{d}, F. Villermain\textsuperscript{e}, S. Lavaud\textsuperscript{f}, I. Etienne\textsuperscript{g}, P.-F. Westeel\textsuperscript{h}, B. H. de Ligny\textsuperscript{i}, L. Rostaing\textsuperscript{j}, E. Thervet\textsuperscript{k}, J. C. Szela\textsuperscript{g}, J.-P. Rérolle\textsuperscript{a}, A. Rousseau\textsuperscript{i}, G. Touchard\textsuperscript{c} and P. Marquet\textsuperscript{m}

The APOMYGRE trial

• Randomized, multicentre clinical trial: 11 centres, 137 patients
Immunosuppressive regimen

MMF initial dose in the 2 groups: 2g/day (up to D7)

1. MMF concentration controlled group (CC):
   - Bayesian estimation of MPA AUC$_{0-12h}$ on D7, D14, M1, M3, M6, M12
   - Dose adjustment calculated by the computer programme (rounded up or down to the nearest possible dose)
   - Target AUC$_{0-12h} = 40$ mg.h/L

2. MMF fixed dose group (FD):
   - Modification of MMF dose on clinical decision
   - MPA AUC$_{0-12h}$ estimated but not reported to the physician
AUC$_{0-12h}$ obtained

[Le Meur et al., Am J Transplant 2007]
## MMF doses

<table>
<thead>
<tr>
<th></th>
<th>D 14</th>
<th>M 1</th>
<th>M3</th>
<th>M6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean dose (mg/day)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC group</td>
<td>2698*</td>
<td>2969*</td>
<td>2279*</td>
<td>1940</td>
</tr>
<tr>
<td>FD group</td>
<td>2000</td>
<td>1960</td>
<td>1852</td>
<td>1770</td>
</tr>
</tbody>
</table>

### Distribution of MMF daily dose in the CC group (%)

<table>
<thead>
<tr>
<th></th>
<th>M 1</th>
<th>M3</th>
<th>M6</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2g</td>
<td>8</td>
<td>6</td>
<td>26</td>
</tr>
<tr>
<td>2g</td>
<td>13</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>2.5 or 3g</td>
<td>79</td>
<td>42</td>
<td>36</td>
</tr>
<tr>
<td>3.5 or 4g</td>
<td>0</td>
<td>40</td>
<td>15</td>
</tr>
</tbody>
</table>
Efficacy: composite outcome called “treatment failures at M12”

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fixed dose</th>
<th>Concentration controlled</th>
<th>$p =$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure</td>
<td>31</td>
<td>19</td>
<td>0.03</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>1</td>
<td>ns</td>
</tr>
<tr>
<td>Graft loss</td>
<td>0</td>
<td>1</td>
<td>ns</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>20</td>
<td>8</td>
<td>0.01</td>
</tr>
<tr>
<td>MMF discontinuation</td>
<td>10</td>
<td>9</td>
<td>ns</td>
</tr>
</tbody>
</table>
Cumulative incidence of acute rejection

- FD
- CC

$p = 0.0137$

[Le Meur et al., Am J Transplant 2007]
The DICAM trial
DIminution of Cyclosporine in Association with Mycophenolate mofetil

Sponsor: University Hospital Rouen, FRANCE
Principal investigator: Dr. Isabelle ETIENNE

Collaborative “René Spiesser” group

[Etienne et al., Nephrol Dial Transplant. 2010]
Aim

• To try and prevent CsA nephrotoxicity in stable kidney transplant recipients with CsA and MMF, without corticosteroids

• By reducing exposure to CsA using refined TDM tools (Bayesian estimation $AUC_{0-12h}$)
The DICAM trial design

• Multi-centre, prospective, randomized trial

Day 0

CsA+MMF

Corticoids withdrawal (Month 4-6)

Month 12-24

Standard-CsA

target CsA AUC=4.3 (3.5-4.8) µg.h/L

Low-CsA

target CsA AUC=2.2 (2.0-2.6) µg.h/L

• Estimation of CsA and MMF AUC\textsubscript{0-12h}
  o 3-point limited sampling strategy
  o Bayesian estimators (1,2)

• 2-year follow-up
  o Visits every 2 months

1. Léger et al., ClinPK 2002
2. Prémaud et al., TDM 2005
Patients’ exposure to CsA and MMF

<table>
<thead>
<tr>
<th></th>
<th>M24</th>
<th>standard-CsA</th>
<th>low-CsA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CsA</td>
<td>n = 102</td>
<td>n = 106</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CsA dose mg/kg/d</td>
<td>3.1±0.8</td>
<td>2.1±0.6</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>CsA AUC µg.h/L</td>
<td>4.2±0.8</td>
<td>2.4±0.5</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>CsA C0 ng/ml</td>
<td>146.3±51.3</td>
<td>75.0±22.3</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>MMF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMF dose mg/d</td>
<td>1930.7±33.8</td>
<td>1886.8±35.6</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>MPA AUC mg.h/L</td>
<td>42.7±15.6</td>
<td>48.2±18.7</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

* p<0.0001
Primary endpoint

<table>
<thead>
<tr>
<th>M24</th>
<th>standard-CsA</th>
<th>low-CsA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure primary endpoint</td>
<td>34(35%)</td>
<td>19(18%)</td>
<td>0.006</td>
</tr>
<tr>
<td>1. SCr&gt;20% anytime during the study period with either acute rejection (AR) or CsA toxicity</td>
<td>12(12%)</td>
<td>11(10%)</td>
<td>0.67</td>
</tr>
<tr>
<td>biopsy proven acute rejection</td>
<td>3(3%)</td>
<td>6(6%)</td>
<td>0.50</td>
</tr>
<tr>
<td>biopsy proven nephrotoxicity</td>
<td>9(9%)</td>
<td>5(5%)</td>
<td>0.21</td>
</tr>
<tr>
<td>2. Increase in SCr&gt;15% at 2 years</td>
<td>21(22%)</td>
<td>11(10%)</td>
<td>0.004</td>
</tr>
<tr>
<td>3. graft loss</td>
<td>1(1%)</td>
<td>0(0%)</td>
<td>1</td>
</tr>
</tbody>
</table>

1 death in the standard-dose CsA group
Routine **IS Bayesian dose Adjustment:** the **ISBA** website
(Limoges, France)
(https://pharmaco.chu-limoges.fr)

63 Bayesian estimators for MMF
21 Bayesian estimators for CsA
32 Bayesian estimators for TAC
Access portal to the websites of routine and clinical trials of the Limoges University Hospital laboratory of Pharmacology

Access | TDM - Modalities | Available tools | ISBA Newsletters | Publications

Please identify yourself

Login: 
Password: 

You lost your identifier and/or your password

Delete Enter the Websites

Registration on ISBA website
<table>
<thead>
<tr>
<th>Ctr</th>
<th>Nº</th>
<th>Request Status</th>
<th>Type</th>
<th>Id-N</th>
<th>Id-FN</th>
<th>Transplantation</th>
<th>Assay</th>
<th>Transplant Date</th>
<th>Date of sampling</th>
<th>Request date</th>
<th>Applicant’s Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>175</td>
<td>41973</td>
<td>Submitted</td>
<td>CICLO</td>
<td>01</td>
<td>01</td>
<td>Liver</td>
<td>FPIA</td>
<td>18/05/2011</td>
<td>11/07/2011</td>
<td>02/06/2011</td>
<td><a href="mailto:mviola@cas.aula.edu.ar">mviola@cas.aula.edu.ar</a></td>
</tr>
<tr>
<td>11</td>
<td>43425</td>
<td>Underway</td>
<td>MMF</td>
<td>ZEB</td>
<td>PA</td>
<td>Greffe rénale</td>
<td>H.P.L.C</td>
<td>08/03/2010</td>
<td>29/09/2011</td>
<td>29/05/2011</td>
<td><a href="mailto:laurent.massias@bch.acp.fr">laurent.massias@bch.acp.fr</a></td>
</tr>
<tr>
<td>36</td>
<td>43158</td>
<td>On hold</td>
<td>TACRO</td>
<td>BUD</td>
<td>SU</td>
<td>Greffe pulmonaire</td>
<td>MMF</td>
<td>AUTRE-&gt; précisez</td>
<td>21/09/2011</td>
<td>21/09/2011</td>
<td><a href="mailto:edebroyn@ulb.ac.be">edebroyn@ulb.ac.be</a></td>
</tr>
<tr>
<td>19</td>
<td>43413</td>
<td>Result</td>
<td>MMF</td>
<td>BOC</td>
<td>SY</td>
<td>Greffe rénale</td>
<td>H.P.L.C</td>
<td>22/05/2011</td>
<td>26/09/2011</td>
<td>29/05/2011</td>
<td><a href="mailto:pascal.querard@chu-limoges.fr">pascal.querard@chu-limoges.fr</a></td>
</tr>
<tr>
<td>19</td>
<td>43412</td>
<td>Result</td>
<td>MMF</td>
<td>MAR</td>
<td>CH</td>
<td>Greffe rénale</td>
<td>H.P.L.C</td>
<td>24/05/2005</td>
<td>27/09/2011</td>
<td>29/05/2011</td>
<td><a href="mailto:pascal.querard@chu-limoges.fr">pascal.querard@chu-limoges.fr</a></td>
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<td>25</td>
<td>43410</td>
<td>Result</td>
<td>MMF</td>
<td>S</td>
<td>B</td>
<td>Lupus Pediatrique</td>
<td>H.P.L.C</td>
<td>08/07/2011</td>
<td>15/09/2011</td>
<td>29/05/2011</td>
<td><a href="mailto:brigitte.bader-meunier@ncl.ac.uk">brigitte.bader-meunier@ncl.ac.uk</a></td>
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<td>17</td>
<td>43408</td>
<td>Result</td>
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<td>LAL</td>
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<td>Greffe rénale</td>
<td>H.P.L.C</td>
<td>28/05/2008</td>
<td>28/09/2011</td>
<td>29/05/2011</td>
<td><a href="mailto:pharmacometique@chu-rouen.fr">pharmacometique@chu-rouen.fr</a></td>
</tr>
</tbody>
</table>
### Therapeutic Drug Monitoring of Mycophenolate-mofetil

#### Identification
- **Identification code:**
- **Renal transplantation (Adult)**
- **Cyclosporine**
- **HPLC**
- **Transplant Date:** 07/06/2008
- **Date of sampling:** 21/08/2008

#### Context of the request
- **Non-diabetic patient**

#### Concentration data
- **Dose before sampling in the morning (mg):** 1000
- **Number of doses per day:** 2
- **Time of sampling n°1 (min):** 20
- **Concentration n°1:** 5.81 mg/L
- **Time of sampling n°2 (min):** 50
- **Concentration n°2:** 13.21 mg/L
- **Time of sampling n°3 (min):** 180
- **Concentration n°3:** 4.71 mg/L
- **Time of sampling n°4 (min):**

#### Results interpreted by Dr. J. Delord
- **Delay between graft and dosage:** 14 days
- **Trough estimated by Bayesian method:** 0.95 mg/L
- **C max estimated by Bayesian method:** 16.73 mg/L

---

**AUC (0-12h) estimated by Bayesian method**: 37.32 h.mg/L

**Dose estimated for AUC = 45 h.mg/L**: 1250 mg

- **Current dosage (by dose):** 1000 mg
- **Dose estimated for AUC = 30 h.mg/L**: 750 mg
- **Dose estimated for AUC = 60 h.mg/L**: 1500 mg
- **Number of doses per day:** 2
- **AUC estimated par multilinear regression:** 41.17 h.mg/L
Bayesian modelling of metoclopramide concentration data, measured in patient [Graph showing C(mg/L) vs. t(h)]

Review of the estimated AUC values in patient [Graph showing AUC in h·mg/L over time]

The review is limited to the last 6 estimated AUC values over a period of 2 years
### Log des calculs pour la demande n°42335

**Forçage via calcul automatique par J.B. Woillard**

<table>
<thead>
<tr>
<th>Request</th>
<th>T0</th>
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<th>T180</th>
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<td>Err=0</td>
<td>AIC= 24.31</td>
<td>BIC= 17.09</td>
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<tr>
<td>mirth3p3</td>
<td>BEST!</td>
<td>AIC= 24.31</td>
<td>BIC= 17.09</td>
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</tbody>
</table>

**Log du calcul automatique**

<table>
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<tr>
<th>Request</th>
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<th>T180</th>
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<tr>
<td>mirth3_lbc</td>
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<td>BIC= 18.03</td>
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<tr>
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<td>BEST!</td>
<td>AIC= 23.14</td>
<td>BIC= 15.03</td>
</tr>
</tbody>
</table>
Ability of bayesian dose adjustment to achieve target AUC in patients with ≥ 2 dose adjustments

<table>
<thead>
<tr>
<th></th>
<th>After one dose recommendation (n=904)</th>
<th>After two dose recommendations (n=904)</th>
<th>After &gt;2 dose recommendations (n=971)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Dose recommended applied</td>
<td>61%</td>
<td>69%</td>
<td>73%</td>
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<tr>
<td>% AUC in the target range</td>
<td>72%</td>
<td>74%</td>
<td>80%</td>
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<tr>
<td>% AUC &lt; 30</td>
<td>17%</td>
<td>16%</td>
<td>12%</td>
</tr>
<tr>
<td>% AUC &gt; 60</td>
<td>11%</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>% Dose recommended not applied</td>
<td>39%</td>
<td>31%</td>
<td>27%</td>
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<td>% AUC in the target range</td>
<td>47%</td>
<td>43%</td>
<td>49%</td>
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<tr>
<td>% AUC &lt; 30</td>
<td>45%</td>
<td>46%</td>
<td>38%</td>
</tr>
<tr>
<td>% AUC &gt; 60</td>
<td>8%</td>
<td>11%</td>
<td>13%</td>
</tr>
</tbody>
</table>

[Saint-Marcoux et al., Ther Drug Monit 2011]
Conclusion

• Routine application of model-based treatment personalization helps physicians to improve patient care.

• Sophisticated tools for the management of organ transplant patients (as well as patients with autoimmune diseases) are available online.

• Our research now aims at integrating in such models:
  – Pharmacogenetic and/or pharmacodynamic biomarkers
  – Disease progression models
  – Biomarkers of graft injuries