Therapeutic Drug Monitoring in Transplant Patients

Eberhard Wieland, Medical Director Synlab Medical Center (MVZ), Leinfelden, Germany
Outline

- Introduction: TDM in solid organ transplantation
- IATDMCT recommendations on analytical performance of assays to measure immunosuppressive drugs
- IATDMCT consensus document on TDM of everolimus
- IATDMCT consensus document on TDM of tacrolimus: An update
- Barcelona consensus on biomarker-based immunosuppressive drugs management in solid organ transplantation
Defintion TDM

- TDM = Therapeutic **Drug Monitoring** = pharmacokinetic monitoring (PK)
- TDM = Therapeutic **Drug Management** >PK monitoring (e.g. pharmacodynamic monitoring (PD), pharmacogenetics (PG), demographics)
Immunosuppressive drugs

Halloran NEJM 2005; 351 (26):2715
Particularly calcineurin inhibitors and mTOR inhibitors require therapeutic drug monitoring because of their narrow therapeutic index, significant inter-individual variability in blood concentrations, and the potential of drug-drug interactions.

The aim is to avoiding under-exposure with an increased risk of rejection or over-exposure with an increased risk of toxicity.
# Current Practice of PK TDM

<table>
<thead>
<tr>
<th>Drug</th>
<th>Immunoassays</th>
<th>LC-MS/MS</th>
<th>HPLC-UV</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine (CsA)</td>
<td>53%</td>
<td>47%</td>
<td>0%</td>
<td>76</td>
</tr>
<tr>
<td>Tacrolimus (Tac)</td>
<td>47%</td>
<td>53%</td>
<td>0%</td>
<td>72</td>
</tr>
<tr>
<td>Sirolimus (Sir)</td>
<td>29%</td>
<td>70%</td>
<td>1%</td>
<td>66</td>
</tr>
<tr>
<td>Everolimus (Evr)</td>
<td>23%</td>
<td>75%</td>
<td>2%</td>
<td>51</td>
</tr>
<tr>
<td>Mycophenol. Acid (MPA)</td>
<td>26%</td>
<td>37%</td>
<td>37%</td>
<td>52</td>
</tr>
</tbody>
</table>

**LC-MS/MS: 59% LDT, 41% kits. 75% multianalyte (CsA, Tac, Sir, Evr)**

(Christians et al. The impact of laboratory practices on inter-laboratory variability in therapeutic drug monitoring of immunosuppressive drugs. Ther Drug Monit 2015;37:718–724)
<table>
<thead>
<tr>
<th>Year</th>
<th>Title</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>Analytic requirements for immunosuppressive drugs in clinical trials Ther Drug Monit. 1995 Dec;17(6):577-89</td>
<td>ISDs IATDMCT SC</td>
</tr>
<tr>
<td>2002</td>
<td>International Federation of Clinical Chemistry/International Association of Therapeutic Drug Monitoring and Clinical Toxicology working group on immunosuppressive drug monitoring Ther Drug Monit. 2002 Feb;24(1):59-67</td>
<td>ISDs IATDMCT SC</td>
</tr>
<tr>
<td>2004</td>
<td>Analytic aspects of cyclosporine monitoring, on behalf of the IFCC/IATDMCT Joint Working Group Ther Drug Monit. 2004 Apr;26(2):227-30</td>
<td>ISDs IATDMCT und IFCC</td>
</tr>
<tr>
<td>2009</td>
<td>Opportunities to optimize tacrolimus therapy in solid organ transplantation: report of the European consensus conference Ther Drug Monit. 2009 Apr;31(2):139-52</td>
<td>ISDs IATDMCT SC</td>
</tr>
<tr>
<td>2016</td>
<td>Therapeutic drug monitoring of overulumus: A consensus report Ther Drug Monit. 2016 Apr;38(2):143-69</td>
<td>ISDs IATDMCT SC</td>
</tr>
<tr>
<td>2016</td>
<td>Assuring the Proper Analytical Performance of Measurement Procedures for Immunosuppressive Drug Concentrations in Clinical Practice: Recommendations of the International Association of Therapeutic Drug Monitoring and Clinical Toxicology Immunosuppressive Drug Scientific Committee Ther Drug Monit. 2016 Apr;38(2):170-89</td>
<td>ISDs IATDMCT SC</td>
</tr>
<tr>
<td>2016</td>
<td>Barcelona Consensus on Biomarker-Based Immunosuppressive Drugs Management in Solid Organ Transplantation Ther Drug Monit.: Volume 38, Number 25, April 2016</td>
<td>ISDs IATDMCT SC</td>
</tr>
</tbody>
</table>
Assuring the Proper Analytical Performance of Measurement Procedures for Immunosuppressive Drug Concentrations in Clinical Practice: Recommendations of the International Association of Therapeutic Drug Monitoring and Clinical Toxicology Immunosuppressive Drug Scientific Committee

Christoph Seger, PhD,* Maria Shipkova, MD,† Uwe Christians, MD, PhD,‡
Elaine M. Billaud, PharmD, PhD,§ Ping Wang, PhD,¶ David W. Holt, DSc (Med),‖
Mercè Brunet, PhD,** Paweł K. Kunicki, PhD,†† Thomasz Pawiński, PhD,‡‡
Loralie J. Langman, PhD, §§ Pierre Marquet, MD, PhD, §§§ Michael Oellerich, MD, §§||
Eberhard Wieland, MD,† and Pierre Wallemacq, PhD***
Aims of the Document

- To provide recommendations for the establishment and maintenance of appropriate laboratory practices, to adequately reflect current clinical needs for TDM of ISDs;

- To addresses all phases of the analytical procedure life cycle, including method design, method validation and performance verification; the definition of appropriate acceptance criteria for analytical performance; risk assessment; and method life cycle management;

- To provide a proposal on how to adapt the recognized guidelines published by international scientific societies and governmental agencies, for the analysis of ISDs;

- To cover analytical specifics related to both LDT and commercial tests.

*Ther Drug Monit* • Volume 38, Number 2, April 2016
### TABLE 1. Drug Specific Considerations to Support Assay Development for Immunosuppressive Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Distribution in Blood</th>
<th>TDM Sample Matrix</th>
<th>Monitored PK Parameter</th>
<th>Typical Concentrations in ISD-TDM Samples</th>
<th>Major Metabolites</th>
<th>Bioactivity (% of Parent Drug)</th>
<th>Concentration Relative to Parent Drug (% at 0)</th>
<th>Stability in Sample Matrix*</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>≥41%–58% in erythrocytes</td>
<td>Whole blood</td>
<td>C0</td>
<td>50–350 mcg/L</td>
<td>AMI (1-Hydroxy)</td>
<td>10–20</td>
<td>89–159</td>
<td>AT: 7 d</td>
<td>8,25-31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AM 9 (9-γ-hydroxy)</td>
<td>5–10</td>
<td>50–75</td>
<td>2–8°C: 7 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AM 4N (4-N-desmethyl)</td>
<td>3–5</td>
<td>5–25</td>
<td>–20°C: 3 yrs</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>≥85% in erythrocytes</td>
<td>Whole blood</td>
<td>C0</td>
<td>3–15 mcg/L</td>
<td>M I (13-O-desmethyl)</td>
<td>6</td>
<td>6.4</td>
<td>AT (22°C): 14 d</td>
<td>9,11,27,30,32–35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M II (31-O-desmethyl)</td>
<td>100</td>
<td>ND</td>
<td>2–8°C: 14 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M III (15-O-desmethyl)</td>
<td>0</td>
<td>5.3</td>
<td>–70°C: 1 yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M IV (12-hydroxy)</td>
<td>3.5</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M V (15, 31-O-didesmethyl)</td>
<td>0</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M VII (13, 5-O-didesmethyl)</td>
<td>0</td>
<td>1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sirolimus</td>
<td>≥95% in erythrocytes</td>
<td>Whole blood</td>
<td>C0</td>
<td>3–20 mcg/L</td>
<td>39-O-desmethyl</td>
<td>10</td>
<td>5</td>
<td>AT (30°C): 8 d</td>
<td>6,14,30,36–38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12-hydroxy</td>
<td>7</td>
<td>11</td>
<td>4°C: 30 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>27, 39-O-desmethyl</td>
<td>ND</td>
<td>31</td>
<td>–40°C: 2 mo</td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>≥75% in erythrocytes</td>
<td>Whole blood</td>
<td>C0</td>
<td>3–15 mcg/L</td>
<td>46-hydroxy</td>
<td>ND</td>
<td>44</td>
<td>AT (30°C): 7 d</td>
<td>30,39-41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24-hydroxy</td>
<td>ND</td>
<td>4</td>
<td>2–4°C: 7 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25-hydroxy</td>
<td>ND</td>
<td>14.4</td>
<td>–80°C: 2 yrs</td>
<td></td>
</tr>
<tr>
<td>Mycophenolic</td>
<td>≥99.9% in plasma</td>
<td>Plasma (preferentially EDTA plasma)</td>
<td>C0</td>
<td>1–4 mcg/L</td>
<td>Mycophenolic acid</td>
<td>No bioactivity</td>
<td>20–100 fold higher</td>
<td>AT: 8 h</td>
<td>10,13,42,43</td>
</tr>
<tr>
<td>acid†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mycophenolic acid acyl glazeronide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*As reported in the literature, no extreme ambient temperatures evaluated. Transport and storage of whole blood clinical and clinical trial samples at ambient temperature for more than 3 days is discouraged due to the increasing risk of matrix degradation. Refrigeration at +4°C within 1 day of collection and freezing after 1 week is recommended.

†Native moiety of mycophenolic acid and mycophenolic sodium.

AT, ambient temperature; AUC, area under the concentration–time curve; C0, predose (trough) concentration; C2, concentration 2 hours after drug intake; Cmax, maximum concentration; EDTA, Ethylenediaminetetraacetic acid; ISD, immunosuppressive drug; LSS, limited sampling strategy; ND, not determined; PK, pharmacokinetic; 0, predose sampling time; TDM, therapeutic drug monitoring.
Specific Recommendations

GENERAL RECOMMENDATIONS FOR THE ESTABLISHMENT OF METHODS TO MEASURE IMMUNOSUPPRESSIVE DRUGS (ISDs)

- Sample Handling, Shipping, and Storage
- Method Design
- Method Validation
- Method Verification
- Method Crossvalidation
- Validation Reports

METHOD PERFORMANCE CHARACTERISTICS TO BE INCLUDED IN THE VALIDATION AND ACCEPTANCE CRITERIA

- Method Specificity for the Parent Drug (the target ranges currently specified by TDM of ISDs are for the parent drug)
- Assay-Measurement Range (covers the full concentration range expected for each single ISD in patient samples)
- Assay Precision (In general, for ISD methods, a CV of ≤10% or even ≤6% to meet current narrow therapeutic ranges)
- Assay Accuracy (the allowable analytical bias \( B_A \) must be lower than 5.8% if a \( TE_A \) goal of 15% is assumed to be feasible)

METHOD LIFE-CYCLE MANAGEMENT
Consensus Document on TDM of Everolimus: Aim

Therapeutic Drug Monitoring of Everolimus: A Consensus Report

- To address the evidence and provide recommendations for optimal use of Everolimus (EVL) in the clinical setting considering drug characteristics, specific clinical situations and methodological issues.

- Rather than providing guidance on the indications to select an EVL comprising therapy in a particular clinical situation the document focuses on the best practice for its monitoring.
Consensus Document EVR: Outline

I. Brief introduction

II. EVL formulations

III. Chemistry and mechanism of action

IV. General safety

V. Pharmacokinetic monitoring
   1. Pharmacokinetics of EVL
   2. Drug-drug and drug-food interactions
   3. Compatibility of EVL characteristics with the prerequisites for TDM and TDM strategy

VI. Evidence-based TDM for EVL in specific clinical situations
   1. Kidney-, Liver-, Heart- and Lung transplantation
   2. Oncology
   3. Tuberous sclerosis complex
   4. Pulmonary arterial hypertension

VII. Pharmacogenetic monitoring

VIII. Pharmacodynamic monitoring

IX. Measurement of EVL concentrations
   1. Sample stability
   2. Analytical methods
   3. Analytical requirements
   4. Method calibration and proficiency testing
**Recommendations:**

- **Pre-dose $C_0$ in whole blood** provides a simple and reliable index for TDM.

- Sampling should be standardized to occur **within 1 hour before** the next dose, which should be taken **at the same time every day** and **preferably without food**. If the latter is not possible for practical or medical reasons, EVR should be dosed consistently with food to reduce fluctuations.

- **EVR steady-state concentrations** should be monitored **4–6 days**
  - after the first or a change in the dose,
  - a change in co-therapy with CYP3A4 or ABCB1 inhibitors/inducers.
  - at changes: disease coincidence, poor adherence and dosing errors
<table>
<thead>
<tr>
<th>Organ</th>
<th>CNI minimisation</th>
<th>CNI elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kidney</strong></td>
<td>with reduced-dose CsA</td>
<td>3–8 ng/mL (starting D: 1.5 mg/d)</td>
</tr>
<tr>
<td></td>
<td>with reduced-dose TAC</td>
<td>3–8 ng/mL (starting D: 3 mg/d?)</td>
</tr>
<tr>
<td></td>
<td><strong>CNI elimination</strong></td>
<td>≥6 – 10 ng/mL</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td><strong>CNI minimisation</strong></td>
<td>3–8 ng/mL (introduction ≥ 1 month post transplantation)</td>
</tr>
<tr>
<td></td>
<td>with reduced-dose TAC</td>
<td></td>
</tr>
<tr>
<td><strong>Heart</strong></td>
<td><strong>CNI minimisation</strong></td>
<td>3–8 ng/mL</td>
</tr>
<tr>
<td></td>
<td>with reduced-dose CsA</td>
<td>insufficient data</td>
</tr>
<tr>
<td></td>
<td>with reduced-dose TAC</td>
<td>5–10 ng/mL</td>
</tr>
<tr>
<td><strong>Lung</strong></td>
<td><strong>CNI minimisation</strong></td>
<td>3–8 ng/mL (introduction ≥ 3 month post transplantation)</td>
</tr>
<tr>
<td></td>
<td>with reduced-dose CsA</td>
<td>insufficient data</td>
</tr>
<tr>
<td></td>
<td>with reduced-dose TAC</td>
<td>insufficient data</td>
</tr>
<tr>
<td></td>
<td><strong>CNI elimination</strong></td>
<td></td>
</tr>
</tbody>
</table>
PK TDM EVR: Preanalytical Issues

- The high uptake of EVL into erythrocytes results in the same recommendation as for CNIs, i.e. to measure its concentration in **whole blood**.

- **Ethylene-diamine-tetra-acetic acid** (EDTA) is the preferred anticoagulant because it minimizes problems with clotting and its use allows quantification of multiple immunosuppressive drugs in parallel.

- **Transportation** to the laboratory without refrigeration is acceptable, within ≤1 week at temperatures ≤ 30°C or 3 days at temperatures ≤ 37°C. Cooling of samples is advisable at higher temperatures. For **prolonged storage** times, specimens should be stored at −20°C or below.
Chromatographic methods:

LC-MS/MS

High sensitivity: LLOQ ≤ 1 ng/mL,
High specificity: no interferences reported
High intra-lab precision: < 10%

However, almost all developed in-house procedures: → broad inter-laboratory variability

Recommendation: A fully validated LC-MS/MS assay is the preferred method for the measurement of EVR concentrations. Improvements in LC-MS/MS method standardisation are needed.
The LC-MS/MS and immunoassay techniques are not interchangeable

**Recommendations***:

- Participation in an external QC programme that includes the use of **both spiked and pooled patient samples is highly recommended** for all laboratories that perform measurements of EVL. For sites using the immunoassay it is also advisable **to compare immunoassay measurements using a chromatographic reference method and real (non-pooled) samples** when implementing the QMS assay for patient samples.

- When using immunoassay, **laboratories should inform the clinician** that values obtained with different methods cannot be used interchangeably, due to differences in methods, method calibration and cross-reactivity with metabolites.

* The ECLIA EVL method has been approved and launched after the publication of in the Everolimus Consensus Document v.2016
TDM of Tacrolimus Updated: Introducing a new IATDMCT Consensus Document
Why an Update?

- New drug formulations & generics: Advagraf, Envarsus, generic TAC..
- New drug co-therapies
- Further reduction of targeted drug concentrations in blood
- New analytical methods available
- Improved availability of LC-MS/MS
- Commercial kits
- LC-MS/MS enables monitoring of drug concentrations in alternative matrices
- Technical progress fosters PG and PD monitoring

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Therapeutic Drug Monitoring of Tacrolimus - Personalized Therapy: Consensus Report 2018

Coordinators: M. Brunet (Spain) and S. Bergan (Norway)

Contributors:

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- DJAR Moes (The Netherlands)
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- NT Vethe (Norway)
- O Millán (Spain)
- O Noceti (Uruguay)
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- R van Schaik (The Netherlands)
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- T Pawinski (Poland)
- T van Gelder (The Netherlands)
- U Christians (USA)
- V Haufler (Belgium)
TACROLIMUS PHARMACOLOGY

- Chemistry & mechanism of action;
- Pharmacokinetics (PK)
- Pharmacodynamics (PD)
- Pharmacogenetics (PG)
- Galenic formulations (Envarsus) & generics

Coordinator: T. van Gelder
PHARMACOKINETIC MONITORING: Evidence-based TDM for tacrolimus in specific clinical situations

- Kidney transplantation
- Liver transplantation
- Heart transplantation, lung transplantation
- Bone marrow transplantation
- Other clinical applications

Coordinators: P. Marquet & S. Vinks

RATIONALE AND INDICATIONS (including Off-Label) FOR TACROLIMUS TDM
PHARMACOKINETIC MONITORING: Measurement of tacrolimus concentrations

- Sample stability
- Analytical methods for tacrolimus
  - Chromatographic methods
  - Immunoassays
  - Consistency of results between methods and between laboratories
  - Method calibrations and proficiency testing
- Standardization of tacrolimus TDM**

Coordinators: M. Shipkova, L. Langman & C. Seger
PHARMACOKINETIC MONITORING: New TDM approaches

- Microsample based tacrolimus concentrations monitoring (DBS and other)
  - Rationale
  - Preanalytical and analytical requirements/pitfalls
  - Future developments and clinical perspective

- Intracellular and tissue Tacrolimus concentrations monitoring
  - Rationale
  - Preanalytical and analytical requirements/pitfalls
  - Relationship with whole blood concentrations
  - Clinical evidences and future perspectives

Coordinators: P. Wallemacq & F. Lemaitre
PHARMACODYNAMIC MONITORING

- Principles of PD TDM
- Specific PD biomarkers of tacrolimus
  - NFAT
  - Calcineurin phosphatase
- Nonspecific PD Monitoring of tacrolimus *, **
  - Intracellular cytokines, chemokines
  - T-Cell activation (e.g. surface markers)
  - Gene expression
  - GfcDNA

Coordinators: E. Wieland & U. Christians
PHARMACOGENETICS

- PG/PK relationship (CYP3A5*3, CYP3A4*22, POR*28, ABCB1, PPAR-α..)
- PG/PD relationship

Coordinators: D.A. Hesselink & V. Haufroid
POP PK MODELING, PK/PG MODELING AND PK/PD MODELING FOR TACROLIMUS

Coordinators: J.B. Woillard & A. Åsberg
There is an urgent need of more sophisticated biomarkers to complement current clinical practices and achieve:

- Better personalization of immunosuppressive therapy
- Avoidance of over- and under-immunosuppression
- Identification of operational tolerant patients who would benefit from drug weaning

Sawitzki et al. Transplantation 2009, 87:1595-1601
Biomarkers Supporting Management of Immunosuppression in Transplantation

In „Personalized Immunosuppression in Transplantation: Role of Biomarker Monitoring and Therapeutic Drug Monitoring”
Barcelona Consensus on Biomarker-Based Immunosuppressive Drugs Management in Solid Organ Transplantation

Mercè Brunet, PhD,* Maria Shipkova, MD,† Teun van Gelder, MD, PhD,‡ Eberhard Wieland, MD,† Claudia Sommerer, MD,§ Klemens Budde, MD, PhD,¶ Vincent Hauflroid, PharmD, PhD,||
Uwe Christians, MD, PhD,** Marcos López-Hoyos, MD, PhD,†† Markus J. Barten, MD,†‡ Stein Bergan, PhD, §§ Nicolas Picard, PharmD, PhD, §§§ Olga Millán López, PhD,* Pierre Marquet, MD, PhD, ¶¶ Dennis A. Hesselink, MD, PhD, |||| Ofelia Noceti, PharmD, PhD, ¶¶¶***
Tomasz Pawinski, MD, ††† Pierre Wallemacq, PharmD, PhD, || and Michael Oellerich, MD † † †
# Barcelona Consensus

## TABLE 1. Grading System for Recommendations and Evidence Level Used in the Consensus Document

<table>
<thead>
<tr>
<th>Category, Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strength of recommendation</strong></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Good evidence to support a recommendation for biomarker monitoring</td>
</tr>
<tr>
<td>B</td>
<td>Moderate evidence to support a recommendation for biomarker monitoring</td>
</tr>
<tr>
<td>C1</td>
<td>Recommendation for biomarker monitoring regardless of poor evidence</td>
</tr>
<tr>
<td>C2</td>
<td>Poor evidence to support a recommendation for marker monitoring</td>
</tr>
<tr>
<td><strong>Quality of evidence</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Evidence from $\geq 1$ properly randomized, controlled multicenter clinical trial using validated methodology</td>
</tr>
<tr>
<td>II</td>
<td>Evidence from $\geq 1$ well-designed cohort or case-controlled, nonrandomized clinical trial, multiple time series, standardized methodologies</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports from expert committees</td>
</tr>
</tbody>
</table>
1. Predictive:
   - CYP3A5 genotype for tacrolimus dosing (A, I).

2. Diagnostic:
   - Chemokines (CXCL-9 and CXCL-10) in urine to indicate raft inflammation and rejection (A, II).
   - Circulating graft derived cell free DNA (GcfDNA) in blood to indicate graft damage (A, II).

3. Prognostic:
   - Interferon y (T cell activation) rejection and graft function (B, II).
   - sCD30 in serum to assess the risk of graft failure (B, II).
   - NFAT-regulated gene expression and clinical outcome of (B, II).
Optimization of Initial Tacrolimus Dose Using Pharmacogenetic Testing

E Thervet¹², MA Loriot⁴, S Barbier⁵, M Buchler⁶, M Ficheux⁷, G Choukroun⁷, O Toupance⁸, G Touchard⁹, C Alberti¹⁰, P Le Pogamp¹¹, B Moulin¹², Y Le Meur¹³, AE Heng¹⁴, JF Subra¹⁵, P Beaune³ and C Legendre¹²

CYP3A5 expressors (CYP3A5*1/*1) 0.30 tacrolimus mg/kg/day, CYP3A5 non-expressors (CYP3A5*3/*3) 0.15 mg/kg/day

fixed dose 0.2 mg/kg/day

Clin Pharmacol Ther. 2010;87:721–726
# CXCL-10 and Rejection

**Urinary C-X-C Motif Chemokine 10 Independently Improves the Noninvasive Diagnosis of Antibody-Mediated Kidney Allograft Rejection**

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### Table: ROC-Based Discrimination Measures

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>AUC (95% CI)^</th>
<th>AUC P Value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure ABMR</td>
<td></td>
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<tr>
<td>CXCL10</td>
<td>70.2 (61.5 to 79.0)</td>
<td>&lt;0.001</td>
<td>73.0</td>
<td>61.6</td>
<td>25.7</td>
<td>92.6</td>
</tr>
<tr>
<td>CXCL10:Cr</td>
<td>70.2 (61.4 to 79.0)</td>
<td>&lt;0.001</td>
<td>67.6</td>
<td>62.1</td>
<td>24.5</td>
<td>91.3</td>
</tr>
<tr>
<td>CXCL9</td>
<td>62.1 (53.0 to 71.2)</td>
<td>0.002</td>
<td>50.0</td>
<td>74.0</td>
<td>25.7</td>
<td>89.2</td>
</tr>
<tr>
<td>CXCL9:Cr</td>
<td>60.1 (49.1 to 71.1)</td>
<td>0.03</td>
<td>50.0</td>
<td>78.0</td>
<td>29.0</td>
<td>89.7</td>
</tr>
</tbody>
</table>

Combination DSA and CXCL-10

Donor-Derived Cell-Free DNA Is a Novel Universal Biomarker for Allograft Rejection in Solid Organ Transplantation


Donor-Derived Cell-Free DNA Is a Novel Universal Biomarker for Allograft Rejection in Solid Organ Transplantation

Deceased Donors
Living Donors

Days after KTx

ACR

GcfDNA (%)
GcfDNA (cp/mL)
Interferon y (ELISPOT) and Graft Function

Crespo et al. PLOS ONE, February 17, 2015
Interferon y ELISPOT and Rejection

Molecular and Functional Noninvasive Immune Monitoring in the ESCAPE Study for Prediction of Subclinical Renal Allograft Rejection

Elena Crespo, MS; Silke Roedder, PhD; Tara Sigdel, PhD; Szu-Chuan Hsieh, MS; Sergio Luque, MS; Josep Maria Cruzado, MD, PhD; Tim Q. Tran, MS; Josep Maria Grinyó, MD, PhD; Minnie M. Sarwal, MD, PhD, and Oriol Bestard, MD, PhD

75 patients: Sub-Clinical Acute rejection PrEdiction (ESCAPE) Study

kSORT: 17 genes qPCR

ELISPOT: living-donor PBMCs

6-month protocol biopsies.

ELISPOT + kSORT

Subclinical Acute Rejection

Transplantation ■ June 2017 ■ Volume 101 ■ Number 6
Influence of posttransplant sCD30 on kidney graft survival to 3 years in patients with a functioning graft on posttransplant day 30
Transplantation 2011;91: 1364–1369

Pretransplantation Soluble CD30 Level As a Predictor of Acute Rejection in Kidney Transplantation: A Meta-Analysis

Yile Chen, Qiang Tai, Shaodong Hong, Yuan Kong, Yushu Shang, Wenhua Liang, Zhiyong Guo, and Xianshun He

Transplantation 2012;94: 911Y918
NFAT Gene Expression and Rejection/Infection

Individualized Monitoring of Nuclear Factor of Activated T Cells-Regulated Gene Expression in FK506-Treated Kidney Transplant Recipients

Claudia Sommerer, Martin Zeier, Stefan Meuer, and Thomas Giese

Rejection

Infection

Transplantation 2010;89: 1417–142
Summary

- TDM (PK, PD, PG) needed to individualize immunosuppression in transplant patients
- IATDMCT is the leading scientific association in publishing consensus documents for TDM of immunosuppressants
- Very specific recommendations with respect to the performance of assays to measure immunosuppressants
- Interdisciplinary consensus on the TDM of everolimus (clinicians, pharmacologists, pharmacists, laboratory professionals)
- Comprehensive updated consensus document on TDM of tacrolimus in the near future
- Specific recommendations and critical evaluation of biomarkers to complement PK TDM in solid organ transplanatation (update scheduled for 2019)
Thank you for your Attention!