**THERAPEUTIC DRUG MONITORING OF TACROLIMUS AND MYCOPHENOLIC ACID IN RENAL TRANSPLANT RECIPIENTS USING A VOLUMETRIC DRIED BLOOD SPOT SAMPLING DEVICE**

**Objectives**
- To develop an LC-MS/MS assay to quantify tacrolimus and mycophenolic acid in dried blood spots (DBS)
- To clinically validate the method for tacrolimus and mycophenolic acid therapeutic drug monitoring (TDM) using a volumetric DBS sampling device

**Main findings**
- DBS sampled abbreviated AUC monitoring of tacrolimus and mycophenolic acid is feasible and comparable to conventional whole blood TDM
- Patient training and guidance on the DBS sampling procedure is essential to ensure clinical feasibility
- Single sample DBS based tacrolimus trough concentration monitoring shows no sufficient accuracy for clinical application yet

**Introduction**
- Renal transplant recipients require immunosuppression therapy to prevent graft rejection, typically including tacrolimus and mycophenolic acid
- Tacrolimus and mycophenolic acid dosing is individualized through TDM, because of their extensive inter- and intrapatient pharmacokinetic variability
- Conventional TDM, based on EDTA WB samples at the clinic is suboptimal as patients need to visit the clinic
- Home-based, DBS sampled TDM has great potential to replace conventional TDM but still is no common practice

**Methods**
- Clinical validation was performed by direct comparison of paired DBS and WB concentrations and abbreviated AUCs
- DBS samples were obtained by finger prick and collected through the HemaXis™ DBS device
- Participants were kidney (pancreas) graft recipients >1 year post-transplantation, with an eGFR >25 ml min⁻¹ 1.73 m⁻², on once daily tacrolimus (Advagraf®) and mycophenolic acid mofetil (Cellcept®)
- Each patient provided 4 paired DBS and WB samples, taken pre-dose and 1, 2 and 3 hours post-dose
- Tacrolimus and mycophenolic acid WB and DBS concentrations were determined on two LC-MS/MS systems
- Abbreviated AUCs were calculated in MW/Pharm, using maximum a posteriori Bayesian estimation and limited sampling population models for tacrolimus and mycophenolic acid (C₀, Cᵳ, Cᵱ, Cᵳ
- Method agreement was evaluated with Passing-Bablok regression and Bland-Altman analysis, for individual concentrations and AUCs. Dosing recommendation differences were assessed to investigate clinical impact

**Sample characteristics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>Mean</th>
<th>95%CI</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus WB concentration (µg l⁻¹)</td>
<td>200</td>
<td>9.05</td>
<td>8.39–9.71</td>
<td>1.26–22.56</td>
</tr>
<tr>
<td>Tacrolimus DBS concentration (µg l⁻¹)</td>
<td>200</td>
<td>8.35</td>
<td>7.71–9.00</td>
<td>1.15–23.54</td>
</tr>
<tr>
<td>Tacrolimus WB AUC₀₋₂₄ (µg h l⁻¹)</td>
<td>63</td>
<td>165.3</td>
<td>151.0–179.6</td>
<td>44–336</td>
</tr>
<tr>
<td>Tacrolimus DBS AUC₀₋₂₄ (µg h l⁻¹)</td>
<td>63</td>
<td>152.7</td>
<td>139.1–168.3</td>
<td>43–339</td>
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<tr>
<td>Mycophenolic acid WB concentration (mg l⁻¹)</td>
<td>192</td>
<td>5.47</td>
<td>4.74–6.20</td>
<td>0.38–34.84</td>
</tr>
<tr>
<td>Mycophenolic acid DBS, concentration (mg l⁻¹)</td>
<td>192</td>
<td>5.08</td>
<td>4.40–5.76</td>
<td>0.35–29.47</td>
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<tr>
<td>Mycophenolic acid WB AUC₀₋₂₄ (mg h l⁻¹)</td>
<td>43</td>
<td>42.8</td>
<td>37.5–48.1</td>
<td>6–90</td>
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<tr>
<td>Mycophenolic acid DBS, AUC₀₋₂₄ (mg h l⁻¹)</td>
<td>43</td>
<td>41.2</td>
<td>35.9–46.6</td>
<td>5–101</td>
</tr>
</tbody>
</table>

**Clinical validation of tacrolimus monitoring**

**Clinical validation of mycophenolic acid monitoring**

**References**

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