Clinical validation of intracellular pharmacodynamic (PD$_i$) based modelling for the prediction of fluoroquinolone activity against TB

Ghaith Aljayyoussi, PhD

Research Centre for Drugs and Diagnostics
Liverpool School of Tropical Medicine
Liverpool, UK
Extracellular *in-vitro* screens for anti-TB drugs: A predictive tool for clinical outcome?
PK/PD Modelling for prediction of clinical outcome

Rifampicin Ingested

Gut

Drug concentration in Systemic Circulation [conc.]

Clearance

ELF exposure

*Defined in-vitro*

\[
\frac{dN}{dt} = K_{g\text{max}} \cdot N - \frac{E_{max} \cdot [\text{conc.}]}{C_{50} + [\text{conc.}]} \cdot N
\]
The model predicts that most patients will need no more than 4 weeks of treatment with anti-TB drugs to achieve cure.
Clinically, elimination of bacillary load is slow and biphasic.
Would intracellular dynamics explain the discrepancy between *in-vitro* dynamics and clinical outcomes?
Inoculate macrophages with H37Rv-GFP/mCherry for 24h (MOI 1:5)

Drug treatment 7 days

Read every 24hr on Varioskan and/OR fixation & staining for Operetta

Image acquisition on Operetta

Image & Data analysis (Harmony)

Multi-parameter analysis of \textit{Mtb} populations in response to drugs & evaluation against clinical settings

Assay:
Our decision to move away from non-physiological assays

Aljayyoussi, G & Donnellan, S. 2017
Intracellular dynamics are quite different from extracellular

<table>
<thead>
<tr>
<th></th>
<th>Growth Rate (hr⁻¹)</th>
<th>Kill Rate (hr⁻¹)</th>
<th>C₅₀ (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracellular</td>
<td>0.033</td>
<td>0.055</td>
<td>18.4</td>
</tr>
<tr>
<td>Extracellular</td>
<td>0.078</td>
<td>0.18</td>
<td>5.6</td>
</tr>
</tbody>
</table>
Pharmacokinetic-Pharmacodynamic modelling of intracellular Mycobacterium tuberculosis growth and kill rates is predictive of clinical treatment duration

Ghaith Aljayyoussi, Victoria A. Jenkins, Raman Sharma, Alison Ardrey, Samantha Donnellan, Stephen A. Ward & Giancarlo A. Biagini
Can Intracellular modelling also predict activity of fluoroquinolones against TB?

- 4-Month MXF containing regimen achieves similar culture conversion rates as 6-month standard regimen.
- Relapse rates with MXF regimen were unfortunately worse.
MXF

SPX

OFX

CIP

LEX

NOX

Normalised Fluorescence Units

Time (h)

0 24 48 72 96 120 144 168

Control

RIF(25 mg/mL)

0.5 mg/mL

0.1 mg/mL

0.01 mg/mL

0.05 mg/mL

0.01 mg/mL

0.05 mg/mL

0.1 mg/mL

0.5 mg/mL

1.0 mg/mL

5.0 mg/mL

25.0 mg/mL

100.0 mg/mL

0.01 mg/mL

0.05 mg/mL

0.1 mg/mL

0.5 mg/mL

1.0 mg/mL

5.0 mg/mL

25.0 mg/mL

100.0 mg/mL

RIF(25 mg/mL)
Ranking Fluoroquinolones

<table>
<thead>
<tr>
<th>Drug</th>
<th>EC$_{50}$ (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin</td>
<td>MXF</td>
</tr>
<tr>
<td></td>
<td>0.24 (0.12-0.60)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>CIP</td>
</tr>
<tr>
<td></td>
<td>0.26 (0.16–0.41)</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>SPX</td>
</tr>
<tr>
<td></td>
<td>0.051 (N/A)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>LEX</td>
</tr>
<tr>
<td></td>
<td>0.38 (0.09-1.5)</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>OFX</td>
</tr>
<tr>
<td></td>
<td>1.41 (1.79-1.1)</td>
</tr>
<tr>
<td>Norofloxacin</td>
<td>NOX</td>
</tr>
<tr>
<td></td>
<td>1.71 (0.23-9.5)</td>
</tr>
</tbody>
</table>

Drug concentration (µg/mL) vs. Normalised Kill Rate.
Accurate Prediction of Culture Conversion for MXF Regimens

We observe the probability of culture positivity over time since treatment initiation. The solid line represents the observed data (Gillespie et al. 2014), while the dashed line represents the predicted probability of culture positivity using the PD1 index (Gillespie et al. 2014). The graph shows that the observed probability decreases over time, with the predicted probability following a similar trend.

The odds ratios (with 95% confidence intervals) for various studies are as follows:

- Burman (2006)
- Rustomjee (2008)
- Conde (2009)
- Wang (2010)
- Dorman (2009)
- Jawahar (2013)
- Velayutham (2014)
- Gillespie (2014)

Overall, the literature suggests that the PD1 prediction model accurately predicts culture conversion for MXF regimens.
How about Relapse Rates?

Our hypothesis:

- A ‘hidden’ TB population that requires further treatment after culture conversion is achieved.
- We estimate this ‘hidden’ population to require ~80 days of treatment AFTER culture conversion is achieved.
Thank you!

Thanks to

• Dr. Samantha Donnellan
• Professor Giancarlo Biagini
• Professor Steve Ward
• Dr Gerry Davis
• LSTM Directors Catalyst Fund