Translating TB Therapy Response:

Application of Mechanistic PKPD Modelling and Pharmacometrics

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Motivation (Tools)

- Apply state of the art tools to choose most promising regimens to be moved to late stage clinical development

- Provide toolbox:
  - to aid in seamless transition for all phases of drug development
  - to optimally combine drugs in the regimen
  - to optimally choose dosing regimen (dose, frequency and duration)
  - to allow for examination of other relevant science for potential impact on clinical trial outcomes
    - Host directed therapies
    - Lung TB pathology
Motivation (Pharmacology and PKPD)

- Murine model in TB is excellent model for studying TB
- Pharmacological principles are translatable
  - Small (and large) molecule pharmacokinetics
  - Drug combinations optimization (solid experience from other diseases)
  - Drug Related Bacterial Kill is the same
  - Preclinical/Clinical Endpoints are similar
Cases where Relapsing Mouse Model underperformed

- Combining Rifamycins with Fluoroquinolones (ReMOX, Rifaquin)
- Replacement of Rifampin and Rifapentine (Study 29/29X)
Measuring the treatment-shortening effect of a test regimen relative to a control regimen in mice

Colored symbols represent the proportion of mice relapsing after receiving the indicated regimen for various durations (error bars represent the 95% CI).
Treatment-shortening effect of substituting moxifloxacin for isoniazid in the 1st-line regimen in BALB/c mice

A 1 to 1.5-month treatment shortening effect is observed in our standard model.

Data from 5 experiments (4 JHU, 1 CSU)

Moxifloxacin (PMZ) Outperforms Isoniazid (PHZ) in Murine Models

A durable cure without relapse was achieved significantly earlier with M-containing regimens than H-containing regimens.

7 Response after dosing mice PMZ vs PHZ QD or BID 5/7 days, Rosenthal, M. I. et al. AJRCCM 2008:178(9)
Substitution of H with M in Clinical Trial Failed

ReMOX

RIFAQUIN Trial


Jindani, A. et al. NEJM 2014:371(17)
Case 2: Rifapentine (PHZ) Outperforms Rifampin (RHZ) in Murine Models

A durable cure without relapse was achieved significantly earlier with P-containing regimens than R-containing regimens.

Response after dosing mice RHZ vs PHZ QD 5/7 days

Data: study Rosenthal AAC 2012
Substitution of P for R in Correspondent Clinical Trial Failed

- Open label randomization: RHZE vs PHZE, both at 10 mg/kg QD 5/7 days for 8 weeks
- Comparison of probability of conversion on solid media (P=0.50)
  - 83.3% R (of 174 patients) vs 86.4% P (of 198 patients)
- Comparison of probability of conversion on liquid media (P=0.65)
  - 65.1% R (of 206 patients) vs 67.9% P (of 183 patients)

**Conclusion:** The P regimen was not significantly more active than a standard R regimen at the end of intensive phase by the surrogate endpoint of culture status.

Dorman, E.S. et al. JID 2012:206
Host

- Host Immune System
- Bacteria-related Death
- Formation of Disease Pathology
- Nude vs Balb C vs Kramnik
- Impact of Host on PK

Regimen

- Pharmacokinetics
- Drug—Drug Interactions
- Combinatorial Regimen
- Dose
- Frequency
- Penetration & PK in lesions
- PKPD Monotherapy and Combinational therapy
- Additive/Synergistic/
- Competitive effect

Bug

- Bacterial Growth
- Infection Model
- Formation of Disease Pathology
- Initial Bacterial Burden
- Cure Boundary
Systems Pharmacology Model

Lesion formation

Macrophage activation

k\text{\_growth} \rightarrow k\text{\_mutation} \rightarrow \text{Elimination}

Gut

Plasma

Lymph

Macrophage

Lesion

Lung

iDC

mDC

Naive T-cells

Precursor T-cells

Helper T-cells
Minimal Systems Model Limited by Available Measurements in the Murine Model
Mechanistic PKPD Model
Minimal Mechanistic TB Response Model informed by measurable data

- **Bacterial growth** (Incubation period)
- **Immune System Response** (Nude vs BalbC mouse)
- **Drug Pharmacokinetics** (PK)
- **Pharmacokinetics-Pharmacodynamics** (PKPD, longitudinal CFU)
- **Disease Pathology** (Lesion penetration)
- **Definition of Cure Boundary** (Cure = no bacteria)
Goals & Data

1. **To develop the Tool** (mechanistic PKPD model for regimens of interest)
   - Various combinations of rifamycins with moxifloxacin with backbone of ZH or ZE, or ZHE
   - Includes PK on drugs of interest (R,P,M)
   - PKPD of dose ranging R and P monotherapy and in combo with other drugs
   - Not full combinatorial design

2. **To utilize the Tool to perform Clinical Trial Simulations**
   - Assumptions
Baseline Model for Bacterial Growth

Raw PD Data without Treatment in Balb/c & Nude Mice

Gompertz Model

\[
\frac{dB}{dt} = K_g \times \left(1 - \frac{B}{B_{max}}\right) \times B - K_d \times B
\]

- **B**: bacterial number
- **Bmax**: maximal bacterial number
- **t**: time of bacterial growth, day
- **K_g**: bacterial growth rate, day\(^{-1}\)
- **K_d**: bacterial death rate, day\(^{-1}\)
Bacterial Baseline Model with Immune Function

BALBc = immune competent mice (ImmC)
Nude = immune deficient mice (ImmD)

Assumption: Immune response can be estimated using the difference in CFU counts between the immunocompetent and immunodeficient mice.
Raw PD Data with and without Treatment in Balb/c & Nude Mice

Immune competent, no treatment
Immune compromised, no treatment
Immune competent, RHZE
Immune compromised, RHZE

\[
\frac{dB}{dt} = K_g \times \left( 1 - \frac{B}{B_{max}} \right) \times B - K_{IND} \times B - (E_{drug} + K_{DOI} + K_d) \times B
\]

- B: bacterial number
- B_{max}: maximal bacterial number
- t: time of bacterial growth, day
- K_g: bacterial growth rate, day^{-1}
- K_d: bacterial death rate, day^{-1}
- E_{drug}: drug effect
- K_{DOI}: immune effect when drug is on board
- K_{IND}: 0, when drug is on board
Inclusion of Immune Effect With & Without Drug Treatment

\[ dB \, dt = K_g \times \left(1 - \frac{B}{B_{max}}\right) \times B - K_{IND} \times B - (E_{drug} + K_{DOI} + K_d) \times B \]

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Immune Effect (day-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0.4</td>
</tr>
<tr>
<td>10</td>
<td>0.6</td>
</tr>
<tr>
<td>15</td>
<td>0.7</td>
</tr>
<tr>
<td>20</td>
<td>0.8</td>
</tr>
</tbody>
</table>

No Drug

Immune killing (In CFU/day)

| No Drug   | 0.61     |
| With Drug | 0.048    |

Difference

12.7 times

Implications: Infection Model

- No Drug
- With Drug

Parameters

- KIND
- KDOI
Infection Model & Immune System

Nude Mice
BalbC Mice
# PK Models in Mice for R, P & M

<table>
<thead>
<tr>
<th>Drug</th>
<th>PK Data</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifapentine (P)</td>
<td>PK after 3 weeks (5/7) of daily doses ranging from 5 to 20 mg/kg</td>
<td>1 Compartment Model</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-Linear Clearance</td>
</tr>
<tr>
<td>Rifampin (R)</td>
<td>PK after 3 weeks (5/7) of daily doses ranging from 10 to 40 mg/kg</td>
<td>2 Compartment Model</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-Linear Absorption</td>
</tr>
<tr>
<td>Moxifloxacin (M)</td>
<td>PK of single dose with dose ranging from 100 to 400 mg/kg</td>
<td>2 Compartment Model</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Linear Clearance</td>
</tr>
</tbody>
</table>

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![Graphs showing PK models for Rifapentine, Rifampin, and Moxifloxacin](image)
TB Drug Effect Model in Mice

• Drug Effect on Bacterial Growth

\[
\frac{dB}{dt} = K_g \times \left(1 - \frac{B}{B_{\text{max}}}\right) \times B \times (1 - E_{\text{drug}}) - K_d \times B - K_{\text{DOI}} \times B
\]

Bacterial Growth  Bacterial Death  Immune Killing

• Drug Effect on Bacterial Death

\[
\frac{dB}{dt} = K_g \times \left(1 - \frac{B}{B_{\text{max}}}\right) \times B - (E_{\text{drug}} + 1) \times K_d \times B - K_{\text{DOI}} \times B
\]

Bacterial Growth  Bacterial Death  Immune Killing

Drug Effect Model

Linear Model: \( \text{EFF} = \text{LIN}_{\text{EFF}} \times \text{Conc} + \text{EFF}_0 \)

Non-Linear Model: \( \text{EFF} = \frac{\text{Conc}^y}{\text{EC}_{50}^y + \text{Conc}^y} \)

Emax Model: \( \text{EFF} = \frac{E_{\text{max}} \times \text{Conc}^y}{\text{EC}_{50}^y \times \text{Conc}^y} \)
Concentration & Response Relationship for R & P alone and wi HZ(E)

Composite Drug Effect of Combination Treatment

Extra Efficacy Term for the Additional Drugs: $E_0$

$$E_{drug} = E_0 + \left( \frac{E_0 + E_{max}}{EC_{50}^\gamma + C^\gamma} \right)$$

<table>
<thead>
<tr>
<th>Structural Model</th>
<th>Estimate</th>
<th>RSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIF alone $EC_{50}$ (mg/L)</td>
<td>1.79</td>
<td>26%</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.23</td>
<td>18%</td>
</tr>
<tr>
<td>Emax</td>
<td>1.64</td>
<td></td>
</tr>
<tr>
<td>RHZ $E_{HZ}$</td>
<td>0.018</td>
<td>56%</td>
</tr>
<tr>
<td>RHZE $E_{HZE}$</td>
<td>0.036</td>
<td>68%</td>
</tr>
<tr>
<td>RPT alone $EC_{50}$ (mg/L)</td>
<td>0.50</td>
<td>46%</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.86</td>
<td>19%</td>
</tr>
<tr>
<td>Emax</td>
<td>1.00</td>
<td>fixed</td>
</tr>
<tr>
<td>PHZ $E_{HZ}$</td>
<td>-0.015</td>
<td>53%</td>
</tr>
</tbody>
</table>
**Composite Drug Effect of Combination Treatment**

Extra Efficacy Term for the Additional Drugs: $E_0$

$$E_{\text{drug}} = E_0 + \left( \frac{E_0 + E_{\text{max}}}{EC_{s0}^\gamma + C^\gamma} \right)$$

$$E_{0, \text{moxifloxacin}} = E \times C_{\text{moxifloxacin}}$$

<table>
<thead>
<tr>
<th>Moxifloxacin effect with HZ*(E)</th>
<th>estimate</th>
<th>RSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\theta_{\text{conc}}$ (g/L, linear)</td>
<td>3.2797</td>
<td>6%</td>
</tr>
<tr>
<td>additional effect (d$^{-1}$)</td>
<td>0.0344</td>
<td>30%</td>
</tr>
</tbody>
</table>

*The effect of moxifloxacin on bacterial death was studied in combination with isoniazid and pyrazinamide (and ethambutol).*
Translational PK/PD Platform for TB Drugs

Mouse model

Dose mice mg/kg R, P, M

Plasma PK models

Volume plasma 2

K23

K32

absorption (non/linear)

elimination ((non)linear)

Volume plasma 1

CFU counts at inoculation

PD model

$K_s \times \left(1 - \frac{B}{B_{\text{max}}}\right)$

TB compartment

Dosing schedule HIGHRIF2, 29, 29x, ReMox, Rifapatin, TBTC study 31

Human translation model

absorption transit, food

Plasma PK models

Volume plasma 2

K23

K32

Drug drug interactions

elimination (linear)

Volume plasma 1

CFU counts at start treatment

PD model

$\frac{F_{\text{rat}}}{F_{\text{human}}} \times \left(1 - \frac{B}{B_{\text{max}}}\right)$

TB compartment

$\left(K_{\text{human}} + K_d\right) \times B$

Disease pathology
## Clinical Trial Summary

<table>
<thead>
<tr>
<th>Trial</th>
<th>Objective</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGHRIF2 (Phase II)</td>
<td>To optimize the dose of R-containing regimen for two months (10, 15 and 20 mg/kg)</td>
<td>Higher doses are needed for evaluation</td>
</tr>
<tr>
<td>Study 29X (Phase IIb)</td>
<td>To compare the potency of P-containing regimen vs the standard 6-month regimen containing R</td>
<td>The P-containing regimen was not significantly more active than the standard R-containing regimen.</td>
</tr>
<tr>
<td>REMox-TB (Phase III)</td>
<td>To test the noninferiority of two M-containing regimens (4-month) as compared with the standard 6-month regimen</td>
<td>Noninferiority for the two M-containing regimens was not shown as 4-month treatment</td>
</tr>
<tr>
<td>RIFAQUIN (Phase III)</td>
<td>To test the noninferiority of two M-containing regimens (4-month and 6-month) as compared with the standard 6-month regimen</td>
<td>The 6-month regimen was as effective as the control regimen. The 4-month regimen was not noninferior to the control regimen.</td>
</tr>
<tr>
<td>PanACEA MAMS (Phase IIb)</td>
<td>To find an optimal dose level of R for the standard 6-month regimen</td>
<td>A dose of 35 mg/kg rifampin was safe and reduced the time to culture conversion in liquid media.</td>
</tr>
<tr>
<td>Study 31 (Phase III)</td>
<td>To determine whether two P-containing 4-month regimens are as effective as the standard 6-month regimen</td>
<td>Pending (ongoing trial)</td>
</tr>
</tbody>
</table>
Can we use the translational model to predict long term efficacy?
Can we predict PK/PD relationships (exposure response) in patients in order to select the optimal dose of drugs in a regimen?
Extended Retention of R in Lung Cavities

The association between sterilizing activity and drug distribution into tuberculosis lesions


Prideaux B. et al. Nat. Med. 2015 Oct. 21
A 4-fold higher EC\textsubscript{50} for P in the cavity compartment was predicted compared to that in plasma.

In the cavities, the drug mediated-killing effect may be much weaker.
Summary

- Mechanistic PKPD model is solid tool for TB regimen optimization
- It incorporates bacterial dynamics, immune response, multidrug PKPD and lung pathology
- Clinical efficacy of R/P + M regimens are well described/predicted with this tool from CFU mouse data (not sterilizing mouse model)
- For successful prediction, info on lung penetration, accurate immune response & human PK is necessary
- This tool needs to be further evaluated with new regimens (PaMZ, JPaMZ, PaJL)
- Need for PKPD factorial design and experiments at not so common doses & schedules to enable full learning
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