Model-based rationale for drug combinations in tuberculosis

Morris Muliaditan
Oscar Della Pasqua

Clinical Pharmacology and Therapeutics Group, UCL, London, UK
Clinical Pharmacology Modelling & Simulation, GlaxoSmithKline, Uxbridge, UK

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Tuberculosis remains a major burden

Current first-line treatment:

Rifampicin, isoniazid, pyrazinamide and ethambutol (2 months) + rifampicin and isoniazid (4 months)

Long, complicated and toxic

Need to replace with shorter regimens
Recent Phase 3 trials in TB

All shorter regimens were inferior to the standard of care regimen

Jawahar et al, 2013
Merle et al, 2014
Jindani et al, 2014
Gillespie et al, 2014
Recent Phase 3 trials in TB

Global Phase 3 “STAND” Trial Launched to Test New Tuberculosis Drug Regimen PaMZ to Shorten, Improve Treatment

Pretomanid-Moxifloxacin-Pyrazinamide

Clinical Trial of BPaMZ Regimen Will Replace Phase 3 STAND Trial

Bedaquiline + Pretomanid-Moxifloxacin-Pyrazinamide

STAND trial will not re-open patient enrollment

December 16, 2016
Situation
Development of novel drug combinations in tuberculosis remains challenging.

Target
More effective use of preclinical data to inform selection of dose and drug combinations prior to clinical development.

Proposal
PKPD modelling for integration of preclinical data arising from different experimental protocols.
1. Demonstrate how NLME approach can be used to integrate \textit{in vivo} PKPD data arising from different experimental protocols.

2. Develop a parametric approach to describe the effect of combination treatments on the parameters of interest.

How were novel combinations assessed?

**Preclinical stage**
- Infection
- Serial lung CFU count
- Drug combinations with “standard” dosages
- 2-6 months

**Clinical stage (Phase 2)**
- Select combination with the highest in vivo efficacy
- Use currently approved dosages
- Serial sputum CFU count
- Phase 2a (2 wks)
- Phase 2b (8 wks)

**Empirical**
*Individual drug contribution to overall treatment effect unclear*
*Little emphasis on dose optimization based on underlying PKPD relationships*
Next challenge: systematic data evaluation

Factorial design to assess drug combinations?

Problems:
1. Large datasets
2. Complex to analyse
3. Results may still not be necessarily translatable to human
How to separate the good from the bad?
Approach: integrated PKPD modelling

Mean generation rate (k_{net})
Carrying capacity (B_{MAX})

Disease

Predict

Potency (IC_{50})
Maximum killing rate (E_{max})

Drug interactions in each combination

External validation

Predict

Predict

Disease

PKPD (backbone drug)

PKPD (drug combinations)

PKPD (backbone drug)

PKPD (drug combinations)
Key assumptions in analysis

In vivo

*Literature meta-analysis (CFU only)*
Simulations (VPCs) performed without inter-individual variability
PK assumed to be constant across experiments

Human

*Individual patient data available (demographics and CFU only)*
Published PK models used to simulate exposure in patient population
PK variability assumed to be constant between studies
Approach: integrated PKPD modelling

Disease

PKPD (backbone drug)

PKPD (drug combinations)

Disease

PKPD (backbone drug)

PKPD (drug combinations)
Disease progression in tuberculosis

Infection

Macrophages

Intracellular

Extracellular

Caseum

Granuloma
Extracellular and intracellular *M.tuberculosis* were treated as two different populations.

Evidence from preclinical experiments that each population display a different growth rate (fast and slow-growing).\(^1,2\)

A disease model was subsequently developed aiming to describe the equilibration of both populations over time.

1) *Beste et al*, 2009; 2) *Aljayyoussi et al*, 2017
Data for in vivo disease model

Zhang 2012

![Graph showing CFU count in untreated BALB/c mice over time post infection (days).]

Swanson 2016

![Graph showing CFU regrowth in BALB/c mice after 2 months of treatment.]
In vivo disease model

\[ DADT[F] = GROWTH_F \cdot F - k_{FS} \cdot F + k_{SF} \cdot S \]

\[ DADT[S] = GROWTH_S \cdot S + k_{FS} \cdot F - k_{SF} \cdot S \]

\[ k_{netF} = rF - dF \]
\[ k_{netS} = rS - dS \]

\[ GROWTH_F = k_{netF} \cdot \left(1 - \frac{(F + S)}{BMA\text{X}}\right) \]
\[ GROWTH_S = k_{netS} \cdot \left(1 - \frac{(F + S)}{BMA\text{X}}\right) \]

\[ k_{FS} = \frac{k_{netF} \cdot (F + S)}{BMA\text{X}} \]
\[ k_{SF} = \frac{k_{netS} \cdot (F + S)}{BMA\text{X}} \]
VPC of in vivo disease model

**Zhang 2012**

![Graph showing CFU count over time in untreated BALB/c mice](image1.png)

- **CFU count in untreated BALB/c mice**

**Swanson 2016**

![Graph showing CFU regrowth over time in treated BALB/c mice](image2.png)

- **CFU regrowth in BALB/c mice after 2 months of treatment**
Predicted in vivo disease progression

Predicted fraction from total population

Population
- Red: Fast growing
- Blue: Slow growing

Predicted fraction from total population

Log10 CFU/lung

Time post infection (days)
Approach: integrated PKPD modelling
Parameterization of in vivo rifampicin effect

Rifampicin dose → Depot

V/F

Assumed to be active against both populations

$DADT[F] = \left( GROWTH_F - \frac{E_{\text{max}} \cdot C_{ss,av}}{IC50_F + C_{ss,av}} \right) \cdot F - k_{FS} \cdot F + k_S \cdot S$

$DADT[S] = \left( GROWTH_S - \frac{E_{\text{max}} \cdot C_{ss,av}}{IC50_S + C_{ss,av}} \right) \cdot S + k_{FS} \cdot F - k_{SF} \cdot S$

$C_{ss,av} = \frac{AUC_{0-24}}{24}$
Model diagnostics and validation

Hu et al 2015

<table>
<thead>
<tr>
<th>Infection route</th>
<th>IC50, F (mg/L)</th>
<th>IC50, S (mg/L)</th>
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<tbody>
<tr>
<td>Intravenous (IV)</td>
<td>4.87 (reference)</td>
<td>60.2 (reference)</td>
</tr>
<tr>
<td>High-dose aerosol (HDA)</td>
<td>3.26</td>
<td>40.3</td>
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<tr>
<td>Low-dose aerosol (LDA)</td>
<td>4.97</td>
<td>61.4</td>
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</tbody>
</table>

**Model building**

- R0
- R10
- R15
- R20
- R30
- R50

**External validation**

- Almeida 2009 R10
- Hu 2016 R10
- Rosenthal 2012 R10
- Rosenthal 2012 R20
- Rosenthal 2012 R40
- Tasneen 2008 R10
Rifampicin IC50 was different between fast and slow-growing Mtb.

Longitudinal model to describe growth of fast and slow-growing Mtb.

Which companion drug(s) for rifampicin?
**Question:** how can we capture the contribution of additional drugs to the overall bacterial clearance, despite **limited** experimental data?

**Proposal:** treat additional drugs as **discrete covariates** of the potency (IC50) of the backbone drug (rifampicin)
How were drug combinations assessed?

Drug 1 (backbone)
Drug 1 + 2 (√)
Drug 1 + 2 + 3 (√)
Drug 1 + 2 + 4 (×)
Results with rifampicin as backbone drug

- Highest increase in potency with Z
- No effect on potency when E added
- Reduction in potency if H added

Regimen #1 = RZ

R = rifampicin
H = isoniazid
E = ethambutol
Z = pyrazinamide
Validation of RZ model

![Graph showing validation of RZ model](image.png)

<table>
<thead>
<tr>
<th></th>
<th>External validation dataset</th>
<th>Model building dataset</th>
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<tr>
<td>Almeida 2009 (exp 1)</td>
<td><img src="image.png" alt="Graph" /></td>
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<tr>
<td>Almeida 2009 (exp 2)</td>
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<td>De Groote 2012</td>
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<td>Grosset 2011</td>
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<td>Tasneen 2006</td>
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</table>
Our approach allowed parameterization of drug combination(s) as discrete covariates.
Scaling from animal to human

**SCALING OF PK**

PK model (clearance, volume of distribution, protein binding)

PK model (clearance, volume of distribution, protein binding)

**SCALING OF DISEASE**

Disease model (CFU levels)

Disease model (CFU levels)

CFU levels and ratio F:S at onset treatment
PKPD model of rifampicin in human

Smythe 2012
Predicted EBA of rifampicin in TB patients

Can we predict EBA following combination treatments too?

EBA = early bactericidal activity
Predicted EBA of combination treatments

EBA = early bactericidal activity

Jindani et al 1980 (2)
Dawson et al 2015 (3)
Diacon et al 2012 (4)
Diacon et al 2010 (5)
A longitudinal model describing bacterial growth over time provides insight into the dose rationale for the evaluation of drug combinations.

The proposed parameterization of drug combinations as discrete covariates offers a practical solution for the screening of novel compounds.

Accurate predictions of treatment response in humans require scaling of pharmacokinetics and disease characteristics, which often differ across experimental protocols.
The research leading to these results has received funding from the Innovative Medicines Initiative Joint Undertaking under grant agreement n°115337, resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.
Appendix
VPC of in vivo rifampicin PK model

<table>
<thead>
<tr>
<th>Serum concentration (mg/L)</th>
<th>R10</th>
<th>R20</th>
<th>R40</th>
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<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>10</td>
<td></td>
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<td></td>
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<tr>
<td>100</td>
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AUC$_{0-24}$ = 140.4
AUC$_{0-24}$ = 280.9
AUC$_{0-24}$ = 557.4