Development of a novel multi-compartment granuloma model to predict local drug distribution and its impact on pharmacodynamics and disease progression in tuberculosis

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Introduction

One of the hallmarks of pulmonary tuberculosis (TB) is the formation of granulomas, heterogeneous lesions composed of a macrophage and neutrophil rich cellular rim surrounding a necrotic core, in the lungs of the infected host. Anti-TB drugs must penetrate these lesions to exert their effects. A better understanding of the local distribution and pharmacodynamic effect of anti-TB drugs may aid the development and optimisation of treatment regimens (Dartois 2014).

Objectives

This work aimed to extend a permeability-limited lung model (Gaohua et al., 2015) to describe drug disposition within a tuberculosis granuloma and to incorporate a disease progression model that describes the growth of the granuloma and the pharmacodynamic (PD) effect of locally-acting drugs on bacteria located within different regions of the granuloma.

Method

Lung and granuloma PBPK model

- A multi-compartment PBPK model of the lung has been implemented within the Simcyp Simulator V15 R1 and used to predict disposition of 8 anti-TB drugs into lung tissue and epithelial lining fluid (ELF) following systemic administration (Gaohua *et al.*, 2015).
- The lung model has been extended to include 5 additional compartments that represent granulomas formed in the lung of patients with TB (Figure 1).
- The granuloma distribution model has separate compartments for vascular rim (including capillary blood, interstitial fluid (ISF) and macrophage) and necrotic caseum core (inner caseum and outer caseum).

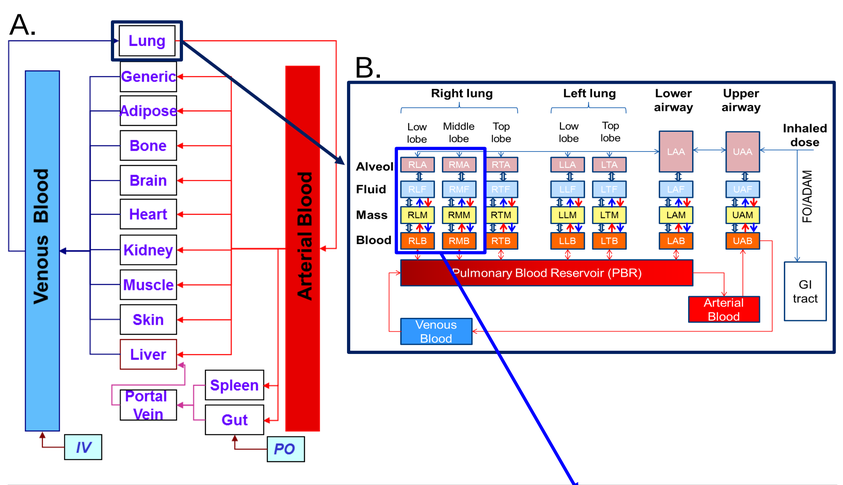

Figure 1. Distribution is modelled using the full PBPK model (A) extended to include a multi-compartment permeability limited lung model (B) linked to an integrated 5-compartment granuloma distribution, pharmacodynamic effect and tuberculosis disease progression model (C).

Pharmacodynamic and disease progression model

- The granuloma is described by a dynamic model consisting of the following components and their immunological crosstalk (Sud et al., 2006).
  - Intracellular bacteria within infected macrophages (B_I) and extracellular bacteria in the rim-ISF (B_E) and caseum (B_N) compartments
  - Cytokines (IL-4, IL-10, IL-12, TNF_α and IFN_γ)
  - T-cells (T_0, T_1, T_2, $T_{8,}$ T_{80}, and T_c)
  - Macrophages (resting, activated and infected)
- The granuloma disease progression and pharmacodynamic effect models and the granuloma distribution model are mutually linked (Figure 1C) such that the PD effect (bacterial killing) of anti-TB drugs are driven by local anti-TB drug concentrations in rim-mass (predominantly macrophages) or rim-ISF compartments and the total macrophage number from the disease progression model determines the rim-mass volume.
- The model has been implemented in Simcyp V16, with the disease progression model implemented via a Lua script (Figure 1C) to allow the user the flexibility to customise the PD and disease progression models.

Simulation design

Simulations were conducted for the four compounds used in the first line treatment of drug susceptible TB: rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E). Parameters for the full PBPK and multi-compartment lung model were as described by Gaohua *et al.* (2015). Parameters describing drug distribution to the granuloma and the PD effect were collated from the literature (Table 1). The built in Sim-NEurCaucasian population was used for all simulations.

The disease progression model was run for 200 days following infection with 20 bacteria prior to initiation of drug treatment. Simulated drug treatment regimens are as described in the figure legends.

Table 1. Input values used for the granuloma model for rifampicin, isoniazid, pyrazinamide and ethambutol.

Parameter	Rifampicin	Isoniazid	Pyrazinamide	Ethambutol	Reference
fu_{ISF}	1	1	1	1	Assumed
$fu_{macrophage}$	0.058	1	1	0.45	Assumed equal to fu_{lung}, Gaohua *et al.* (2015)
fu_{caseum}	0.019	0.69	1	0.349	Prideaux *et al.* 2015
$P_{lung\ mass\text{-}ISF}$ ($x10^{-4}$ cm/s)	35000	0.21	0.138	0.475	Assumed equal to apparent permeability in the lung, Gaohua *et al.* 2015. *Calibrated to data from Prideaux *et al.* 2015
$P_{blood\text{-}ISF}$ ($x10^{-4}$ cm/s)	35000	0.21	0.138	0.475	
$P_{rim\text{-}mass\text{-}ISF}$ ($x10^{-4}$ cm/s)	35000	0.21	0.138	0.475	
$P_{outer\ caseum\text{-}ISF}$ ($x10^{-4}$ cm/s)	350*	0.21	0.138	0.475	
$P_{inner\ caseum\text{-}outer\ caseum}$ ($x10^{-4}$ cm/s)	350*	0.21	0.138	0.475	
$K_{kmax,BE}$ (1/h)	0.576	0.096	0.0096	0.021	Cho et al. (2007), Goutelle *et al.* (2011), Gumbo *et al.* (2007a,b, 2009), Lalande *et al.* (2016), Musuka *et al.* (2013), Srivastava *et al.* (2010), de Steenwinkel *et al.* (2010), Zhang *et al.* (2002)
$EC_{50,BE}$ (µM)	9.3	0.15	2530	2.5	
α_{BE}	1	1	2	1	
$K_{kmax,BI}$ (1/h)	0.504	0.0085	0.0096	0.0096	
$EC_{50,BI}$ (µM)	9.3	0.15	51.2	2.5	
α_{BI}	1	1	2	1	
$K_{kmax,BN}$ (1/h)	0.576	0	0.0096	0.021	
$EC_{50,BN}$ (µM)	93	0.0085	12700	1000	
α_{BN}	1	1	2	1	

P – effective passive permeability of the unbound, unionised drug; fu – unbound fraction; K_{kmax}- maximal kill rate; EC_{50} – concentration resulting in 50% maximal kill rate; α - hill slope.

Results

Predicted distribution and pharmacodynamic effect of rifampicin

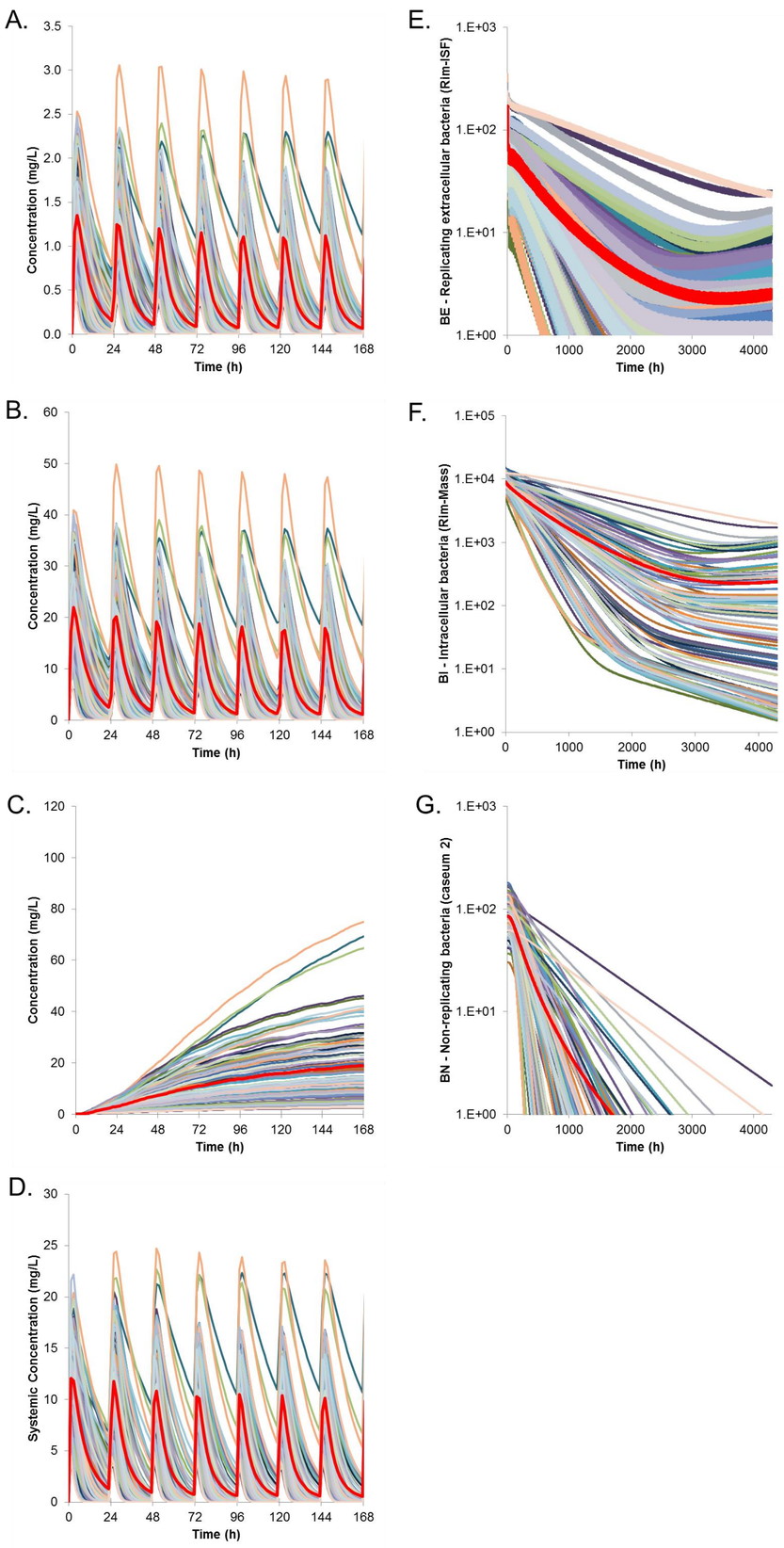

Figure 2. Predicted rifampicin concentration in the granuloma rim-ISF (A), rim-mass (B) and inner caseum (C) compartments and plasma (D) following daily dosing 600 mg rifampicin for 7 days. Predicted number of extracellular bacteria in the rim-ISF (E), intracellular bacteria within infected macrophages (F) and non-replicating extracellular bacteria in the inner caseum (G) following treatment with 600 mg rifampicin daily for 180 days. Result show the profiles for 100 simulated individuals and the population mean (red).

- A gradual accumulation of rifampicin in the caseum was accounted for by assuming a reduced passive permeability (Table 1). The predicted mean inner caseum: rim-mass ratio was 0.60 11.5 h the first dose and 4.0 after steady state compared to observed values of 0.7 (n = 4) and 9.8 (n=1), respectively (Prideaux *et al.* 2015).
- Considering uptake driven by passive permeability only, the simulation predicted a rifampicin mean rim-mass:rim-ISF and rim-mass:plasma concentration ratios of approximately 2.5 and 17, respectively, consistent with evidence of accumulation of rifampicin in alveolar macrophages (Ziglam *et al.* 2002, Hand *et al.,* 1984).
- Simulations predicted that rifampicin monotherapy (600 mg rifampicin daily for 180 days) was insufficient to clear all intracellular bacteria in all simulated individuals.

Predicted response to the standard HRZE regimen

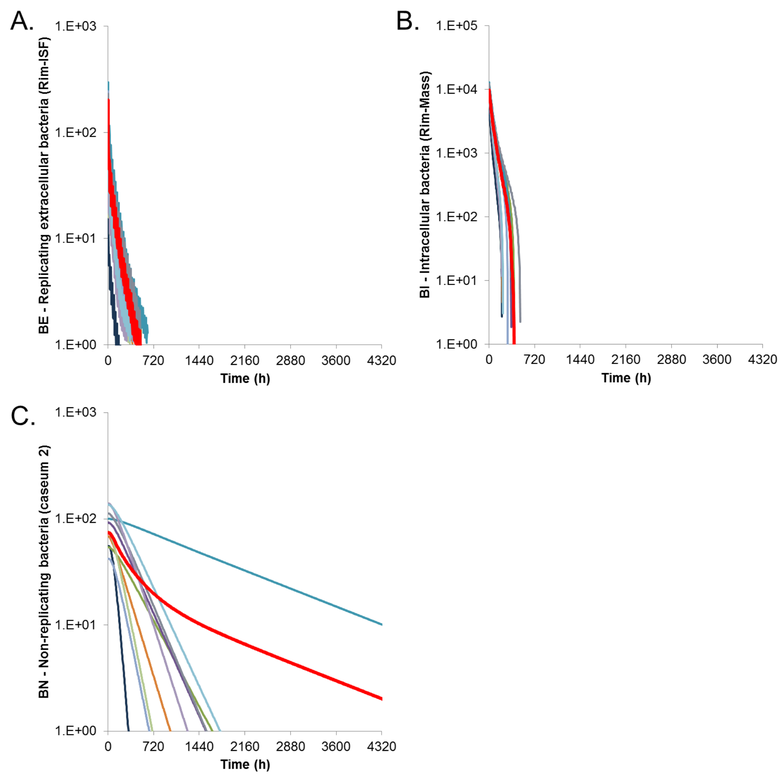

Figure 3. Predicted number of extracellular bacteria in the Rim-ISF (A), intracellular bacteria within infected macrophages (B) and non-replicating extracellular bacteria in the inner caseum (C) following treatment with the standard HRZE regimen of 600 mg rifampicin and 300 mg isoniazid daily for 180 days (4320 h) plus 25 mg/kg pyrazinamide and 15 mg/kg ethambutol daily for the first 60 days (1440 h) therapy. Results show the profiles for 10 simulated individuals and the population mean (red).

- Preliminary simulations were performed to predict response to the standard HRZE treatment regimen in 10 individuals with active TB.
- The model predicted clearance of all extracellular replicating and intracellular bacteria (B_E and B_I) within the treatment period.
- For 9/10 simulated individuals, non-replicating bacteria were completely cleared from the caseum within the treatment period, while for 1 individual there were bacteria remaining in the caseum at the end of the treatment period.

Conclusion

- A multi-compartment granuloma distribution and disease progression model for pulmonary TB was developed and integrated with the PBPK models in the Simcyp Simulator (V16).
- The granuloma model provides a framework for investigating the impact of inter-individual variability in drug pharmacokinetics and local drug concentration on the killing of *M. tuberculosis* sub-populations.
- Using pharmacodynamic parameters derived from *in vitro* experiments, the model predicted that rifampicin monotherapy is insufficient to clear TB infection from the granuloma, while the HRZE regimen eliminated infection from the majority of individuals.
- The inability to completely eradicate non-replicating TB from the granuloma caseum in 1/10 simulated individuals suggests the potential for relapse of TB following the standard HRZE regimen in some individuals.
- Ongoing work aims to further verify the model predictions for various anti-TB drugs and treatment regimens.

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