Pharmacokinetics of TB drugs at the site of disease in children with pulmonary TB

Elisa López Varela
Desmond Tutu TB Centre,
Department of Paediatrics and Child Health, Stellenbosch University
Barcelona Institute for Global Health
24 June 2021
The burden of paediatric TB

- 12% of global case burden
- 16% of mortality
- Excellent treatment outcomes
- ≈1.2m annual incident cases\(^1\)
- Half remain untreated

1. Global WHO TB Report, 2020,
2. Dodd Lancet Global Health 2017

Mortality rate paediatric TB (<5 years) in 2015\(^1\)
Need for better TB treatment

- Shorter duration, safe, tolerable
- Optimization of dosing and regimens
- Adults -> Suboptimal concentration (lung) → Treatment failure
- Sanctuaries - site of disease (TBM)
- Specificities of certain populations: children

Paed TB treatment → extrapolated from adult efficacy data

Limited consideration to spectrum of disease or PK variability
TB incidence and disease spectrum: a function of age

**FIGURE 1** | Conceptual framework to demonstrate the pattern of change in tuberculosis incidence with age. This represents a composite of risk of infection and risk of subsequent disease progression. The presentation of disease is demonstrated by a representative X-ray in a box colored according to the disease phenotype legend.
PK: children are not small adults

- PK variability
  - Relatively faster drug metabolism
  - Maturation of organs and absorption
- Lower plasma concentrations for same mg/kg
- Paediatric doses derived from extrapolating adult data -> underdosing
- Even with new WHO doses -> low plasma exposure
Rifampicin and children

- Higher RIF doses accelerate treatment response → enable shortening of TB therapy in adults \(^1,^2,^3\)
- Low exposure to RIF → possibly associated with worse treatment outcomes in children\(^4\)

The OPTIRIF Study\(^5\)

Rifampin doses needed for children to obtain exposures similar to adults on 35 mg/kg (AUC\(_{0-24h}\) 235 mg/L*h) ?

Doses of 60-75 mg/kg are needed for children to reach comparable exposures to adults getting a 35 mg/kg dose

Shortening TB treatment

Study 31

SHINE Trial

4m rifapentine, isoniazid, pyrazinamide and moxifloxacin is NON INFERIOR to standard 6m treatment

Dorman NEJM 2021

Turkova, under review
Site of Disease (SOD)

- Complex pathway of anti-TB drugs from blood → *M. tb* cells
- Most TB drugs were introduced without considering properties influencing drug distribution
- Plasma concentrations not predictive of SOD concentrations
Site of Disease (SOD)

Understanding factors that drive drug distribution at SOD could enable more effective use, design new regimens

- Few studies
- None in children

- Host
  - Tissue structure
  - Cell type
  - Vascularization

- Pockets of local/temporal monotherapy

- Aerobic/anaerobic
  - Phagolysosome

- Pathogen

- Drug
  - Size
  - Solubility
  - Protein binding
  - Pro-drug
SOD PK-PD methods

LC/MS/MS
Extract
Homogenize
MALDI MS imaging
100%
0%

Caseum

Laser capture microdissection

Drug activity in caseum

PD

PK

Laser capture microdissection

LC/MS/MS
Quantify

Cellular rim

Caseum

2mm

Courtesy of V Dartois, Center for Discovery and Innovation, Hackensak, NJ
Suboptimal concentrations: Acquisition of Resistance

Drug-Penetration Gradients Associated with Acquired Drug Resistance in Patients with Tuberculosis


American Journal of Respiratory and Critical Care Medicine Volume 198 Number 9 | November 1 2018

Genomic analyses of Mycobacterium tuberculosis from human lung resections reveal a high frequency of polyclonal infections


NATURE COMMUNICATIONS | (2020) 12:2796 | https://doi.org/10.1038/s41467-020-19705-9 | www.nature.com/naturecommunications
Suboptimal concentrations:

Ability to Sterilize

Rif most impacted natural variability in plasma PK
Wide spread of treatment outcomes (38-180 days to sterilization)
Lymph node: neglected battlefield

- Sites for antigen presentation and immune activation contain \textit{M. tb}
- \textit{M. tb} disrupts and replaces normal architecture LN
- Sites for mycobacterial persistence

Sharie Keanne C. GanchuaID. PLoS Pathog. 2020
Site of disease PK in children with complicated intrathoracic tuberculosis

SOD Study

IMPAACT Annual Meeting 2021
Objective

Proof of concept study:
Characterize antituberculosis drug concentration in children with complicated severe intra-thoracic TB at the site of disease and to compare to those in plasma.
Design

Tygerberg Hospital, Cape Town. Nov 2018-March 2019
Single site. Large collaboration

INCLUSION CRITERIA

- Intrathoracic complicated TB disease
- RIF containing TB treatment regimen 14 days
- Admitted and scheduled to undergo EITHER

PROCEDURES

BRONCHOSCOPY

- TB drug DOSING (HRZE-)
- PLASMA PK SAMPLING (0, +2, +4, +6h)
- SOD PK SAMPLE (1 TIME-POINT)

SURGICAL DECOMPRESSION

- BAL, LN TISSUE RANDOMIZED 2,4,6H
- LN TISSUE ALL AT 2H

ANALYTICAL

- LC/MS-MS: plasma and BAL
- Tissue homogenizing PLUS LC-MS/MS for LN TISSUE (1)
- Laser capture microdissection (LCM) coupled to LC/MS-MS for LN TISSUE (2)

MODELLING

- Plasma and SOD PK modelling
- Penetration coefficient: RATIO drug concentration SOD/PLASMA

H (10-15 mg/kg), R (10-20 mg/kg), Z (30-40 mg/kg), E (15-25 mg/kg)
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (N=8)</th>
<th>Group 2 (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (males/females)</strong></td>
<td>3/5</td>
<td>4/3</td>
</tr>
<tr>
<td><strong>Age (months)</strong></td>
<td>17.6 (6.3-41.0)</td>
<td>6.9 (3.4-17.2)</td>
</tr>
<tr>
<td><strong>Weight (Kg)</strong></td>
<td>9.9 (8.2-12.4)</td>
<td>7.1 (4.1-8.3)</td>
</tr>
<tr>
<td><strong>HIV positive</strong></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>PTB</strong></td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td><strong>PTB+EPTB</strong></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Previous bronchoscopy</strong></td>
<td>4 (50.0)</td>
<td>7 (100.0)</td>
</tr>
<tr>
<td><strong>Days on TB treatment</strong></td>
<td>64 (60-73)</td>
<td>34 (28-74)</td>
</tr>
<tr>
<td><strong>Dose (mg/kg) PK day</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td>12.8 (12.1-16.0)</td>
<td>12.3 (11.1-15.0)</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>12.8 (11.4-14.8)</td>
<td>12.2 (11.1-12.7)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>28.5 (23.8-30.9)</td>
<td>30.5 (25.3-34.2)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>20.2 (18.6-22.8)</td>
<td>20.8 (20.2-24.1)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>6 (75.0)</td>
<td>7 (100.0)</td>
</tr>
</tbody>
</table>

*2 patients recruited twice
Chest Radiology

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consolidation</td>
<td>7 (87.5)</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Collapse</td>
<td>3 (37.5)</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Cavity</td>
<td>1 (12.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Paratracheal LN</td>
<td>3 (37.5)</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Hilar LN</td>
<td>6 (75.0)</td>
<td>5 (71.4)</td>
</tr>
<tr>
<td>Subcarinal LN</td>
<td>7 (87.5)</td>
<td>6 (85.7)</td>
</tr>
<tr>
<td>Airway Compresion</td>
<td>6 (75.0)</td>
<td>6 (85.7)</td>
</tr>
</tbody>
</table>

Bilat mediastinal necrotic hilari LN and compression of LMB and BI (90%) and collapse consolidation of RU/RML with multiple scattered nodeules- (endobronchial spread)
Sample characteristics

**BRONCHOSCOPY**

**BAL (8/8)**
- 50% urea <BLQ
- All culture negative

**LN (3/8) endobronchial biopsy**
- Paratracheal (2-upper; 4-lower paratracheal)
- Hiliar (10, 11)
- Subcarinal (7, 9)

**SURGICAL DECOMPRESSION**

**LN (7/7)**
- Necrotizing granulomatous inflammation
- Little residual normal LN tissue
- 4/7 ZN +++
- 4/7 culture positive
Laser capture microdissection (LCM)

Hematoxylin and eosin stained lymph node containing two lesions

Corresponding serial sections taken for LCM-Regions 1-3 represent the areas dissected for drug quantitation by LC-MS/MS.

Histology of the different areas dissected

1. Caseum
2. Cellular layer
3. Lymphocyte rich region
### Raw PK data

<table>
<thead>
<tr>
<th></th>
<th>Plasma</th>
<th>BAL</th>
<th>Homogenized LN</th>
<th>Cellular</th>
<th>Necrotic</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>12(53)</td>
<td>3(4)</td>
<td>4(7)</td>
<td>3(6)</td>
<td>3(5)</td>
<td>5(18)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>INH</th>
<th>Rif</th>
<th>PZA</th>
<th>EMB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>13(61)</td>
<td>3(4)</td>
<td>4(7)</td>
<td>3(5)</td>
</tr>
<tr>
<td></td>
<td>11(50)</td>
<td>1(2)</td>
<td>3(6)</td>
<td>4(12)</td>
</tr>
<tr>
<td></td>
<td>8(38)</td>
<td>1(2)</td>
<td>3(6)</td>
<td>3(9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2(4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4(16)</td>
</tr>
</tbody>
</table>
Model structure

SOD Mechanistic population PK model (nonlinear mixed effect methodology)

Strydom et al., 2019
Penetration coefficients (ratio)

- EMB: Cellular: 6.1, Necrotic: 1.1

Adult data: Strydom et al., 2019
Despite similar penetration coefficients compared to adults, overall low plasma exposures led to low site of disease exposures for all drugs except for isoniazid.
Conclusion and implications
Conclusions

- Proof of concept study → first data on paediatric SOD PK in PTB
- Feasible, but high technical expertise required
- Penetration coefficient better than in adults (good lesión penetration)
- Suboptimal plasma PK exposures leading to low SOD concentrations
- Possibility of achieving target concentration at SOD with dosage?
Limitations

- Highly selected group of patients-severe PTB disease
- Impact of con-med and iv fluids (drug-drug interactions?)
- BAL- dilution factor
- Sparse sampling and SOD time-points
Next steps

- Optimization of doses/regimens should rely on SOD PK/PD and plasma based indices
- Methods: Less invasive methods? BAL, sputum?
- Correlate lesion PK, lesion PD and efficacy
- Immunology and microbiology
- Modeling- nesting within studies (disease spectrum, 2nd line drugs)
Acknowledgments

Desmond Tutu TB Centre, Stellenbosch University South Africa

Anneke C Hesseling
Anne-Marie Demers
Anthony J. Garcia-Prats
Aneen Van Deventer
Corne Bosch
Rory Dunbar
James Seddon

Pathology, paediatric pulmonology, clinical pharmacology

Ahmed Abulfathi
Abrie Van Wyk
Eric Decloedt
Hanes van der Merwe
Jacques Janson
Julie Morrison
Helmuth Reuter
Pierre Goussard
Rob Warren

Veronique Dartois
Matthew Zimmerman
Claire Carter

Rada Savic, Natasha Strydom

Elin M. Svensson
Thank you!

Elisa.lopez@isglobal.org
PK/PD

Caseum *M. tb* is highly drug tolerant to most drugs- only RFM sterilizing

Sarathy et al (2018) AAC.
Testing

- Optimization of doses and regimes should rely on SODPK/PD plus plasma based indices.
- Measure the concentrations of all TB drugs in cellular and necrotic lesion compartments.
- Measure the activity of all TB drugs against Mtb populations residing in each compartment.
- Correlate lesion PK, lesion PD and efficacy.

1. How much drug reaches each compartment?
2. How much drug does it take to kill the resident bugs?
3. How does that translate into lesion sterilization in an in vivo model?
Lesion PK-PD methods

- Homogenize
- Extract
- LC/MS/MS Quantify

Drug activity in caseum

MALDI MS imaging

Laser capture microdissection

PK

PD

V Dartois
Site of disease exposures

Dynamic imaging in patients with TB reveals heterogeneous drug exposures in pulmonary lesions.

Ordonez et al. Nat Med. 2020 April
Paediatric TB: spectrum of disease

- Paucibacillary
- Predominantly a disease of mediastinal lymph nodes in young children
- Spectrum of disease: extremely diverse and age-dependent

IMPAACT Annual Meeting 2021