New dosing recommendations for anti-tuberculosis therapy in Indian children

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PAGE meeting - Montreux
May 31st 2018
Tuberculosis in children
Worldwide in 2016

- 718,000 New cases
- 253,000 Deaths
- 10-60% HIV coinfection

30% in India

## Pediatric tuberculosis treatment in India

### Tuberculosis Treatment

<table>
<thead>
<tr>
<th>Phase</th>
<th>Previous RNTCP (pre-2012)</th>
<th>New RNTCP (Initiated Nov 2017)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regimen</strong></td>
<td>Thrice-weekly</td>
<td>Once-daily</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>10 mg/kg</td>
<td>10 mg/kg</td>
</tr>
<tr>
<td>Rifampin</td>
<td>10 mg/kg</td>
<td>15 mg/kg</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>33 mg/kg</td>
<td>35 mg/kg</td>
</tr>
<tr>
<td>Formulation</td>
<td>Single drug formulation</td>
<td>Fixed dose combination</td>
</tr>
<tr>
<td><strong>Intensive phase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Continuation phase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 months</td>
<td>4 months</td>
</tr>
</tbody>
</table>
Clinical data
Study design

Covariate Screening
Upon treatment initiation
- Demographic
  - weight, age, z-scores, ...
- Physiologic
  - acetylator status
- Co-medications
  - Anti-retroviral treatment

PK study
After 2 weeks
- Thrice-weekly dosing
  - 4 weight bands
    - 6-10, 11-17, 18-25 and 26-30 kg
- Sampling times
  - 0, 2, 4, 6, 8h

Treatment Outcome
After 6 months
- Favorable
  - Cured
  - Treatment completion
- Unfavorable
  - Death
  - Treatment failure

TB monoinfection
84 children (1-12y)

TB-HIV coinfection
77 children (1-15y)
Aims

1. To characterize the pharmacokinetics of isoniazid, rifampin and pyrazinamide in Indian children undergoing thrice-weekly dosing

2. To establish the relationship between drug exposure and the probability of unfavorable treatment outcome

3. To evaluate the previous and new Indian dosing recommendations and suggest dose revisions
Step 1
Characterize the pharmacokinetics of isoniazid, rifampin and pyrazinamide in Indian children undergoing thrice-weekly dosing
Clinical data
Pharmacokinetic profiles

mean ± standard error of the mean
HIV coinfection had a strong effect on the PK of isoniazid and rifampin

Dose ($F_{REL}$) → Gut → Central comp. → Periph. comp. → $CL$

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Isoniazid</th>
<th>Rifampin</th>
<th>Pyrazinamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>$CL$, $V$ (allometry) $F_{REL}$ (power)</td>
<td>$CL$, $V$ (allometry) $F_{REL}$ (power)</td>
<td>$CL$, $V$ (allometry) $F_{REL}$ (power)</td>
</tr>
<tr>
<td>HIV coinfection</td>
<td>↓ $F_{REL}$ (-20%)</td>
<td>↑ $CL$ (+32%)</td>
<td>–</td>
</tr>
</tbody>
</table>

$CL$, $V$: apparent clearance and volume $F_{REL}$: relative bioavailability
The PK models were predictive of $\text{AUC}_{\text{last}}$.
Step 2
Establish the relationship between drug exposure and the probability of unfavorable treatment outcome
The PK/PD modeling approach

• Treatment outcome evaluated at 6 months
  – 109 favorable (cured/treatment completion)
  – 33 unfavorable (death/treatment failure)
  – 19 unknown

• Probability of unfavorable treatment outcome \( (P_{\text{unfavorable}}) \) modeled using a logistic regression model

• Drug exposure (i.e. weekly AUC) and covariates were tested as predictors of the treatment outcome
Rifampin exposure was the only predictor of treatment outcome

Observed treatment outcome:
- Favorable (n = 109)
- Unfavorable (n = 33)
The PK/PD model was predictive of treatment outcome.
Step 3
Evaluate the previous and new Indian dosing recommendations and suggest dose revisions
Small and HIV coinfected children are at high risk.

![Graph showing the relationship between weight bands and P unfavorable for TB monoinfection and TB-HIV coinfection under three different dosing regimens: thrice-weekly, once-daily, and optimized once-daily. The graph includes weight bands for different age groups and shows the distribution of P unfavorable values for each group.](image)
First definition of a target exposure in children

Observed treatment outcome: 
- Favorable (n = 109)
- Unfavorable (n = 33)

Target weekly AUC (184 μg.h/mL)

\[ P_{\text{unfavorable}} = 5\% \]
Daily doses were optimized via a model-based approach.

**Optimized rifampin doses**

<table>
<thead>
<tr>
<th>Weight band kg</th>
<th>TB monoinfection mg/kg</th>
<th>TB-HIV coinfection mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>4–7</td>
<td>19.9</td>
<td>43.4</td>
</tr>
<tr>
<td>8–11</td>
<td>13.3</td>
<td>28.9</td>
</tr>
<tr>
<td>12–15</td>
<td>10.3</td>
<td>23.0</td>
</tr>
<tr>
<td>16–24</td>
<td>7.7</td>
<td>17.3</td>
</tr>
<tr>
<td>25–29</td>
<td>6.2</td>
<td>14.2</td>
</tr>
<tr>
<td>30–39</td>
<td>5.2</td>
<td>11.7</td>
</tr>
</tbody>
</table>

*Currently used dose: 15 mg/kg
The rifampin auto induction

Dose of 9.8 mg/kg in an HIV-children of 14kg

W. Smythe et al. (2012)
Conclusions

- **Rifampin exposure** was the **lowest** in children with **low body weight** or **HIV coinfection**

- **Low rifampin exposures** were linked to an **increased** probability of **unfavorable treatment outcome**

- **Optimized rifampin doses** were proposed based on a weekly target exposure

- The proposed PK/PD model could be used to **support** the use of **higher rifampin doses in children**
Acknowledgements

• Sneha Gupta
• Robin Svensson
• Elin Svensson
• Martin Bergstrand
• Paolo Denti