PKPD analysis of rifapentine in patients during intensive phase treatment for tuberculosis from Tuberculosis Trial Consortium Studies 29 and 29X


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Background

- Higher doses of rifamycins demonstrate promising preclinical activity to shorten duration of tuberculosis (TB) treatment.

- Two Phase 2B Trials of high dose rifapentine (RPT) were performed to assess treatment duration shortening potential
  - **TBTC Study 29**: 10 mg/kg RPT vs standard of care (RHZE)
  - **TBTC Study 29X**: Dose ranging RPT (10-20 mg/kg) vs standard of care
Aims:

- To guide design of Phase 3 trial
- To understand at which dose/exposure we will have the highest chance for treatment duration shortening (PKPD analysis)
- To understand how to dose patients to achieve the target exposure (mg/kg vs flat dose) (PK analysis)
- To identify covariates contributing/explaining between-subject variability in rifapentine PKPD (Treatment individualization)
PK data base (in context of study 29 & 29X)

**STUDY 29 (162 patients)**
base model for parent and metabolite
- Relationships between covariates and PK parameters

**STUDY 29X (233 patients)**
base model for parent and metabolite
- Relationship between dose and F
- Relationships between covariates and PK parameters

Join the two in the common base model (395 patients)
- More confidence in the relationship between dose and F for lower dose levels (450mg and 600mg)
- Auto-induction characterization

**Full covariate analysis on the full data base (395 patients)**
- More confidence in any relationship seen in study 29X or 29 on its own
- More confidence in lack of relationship with WT
Do we need mg/kg dosing?

- Study 29X has dosing per kilogram of body weight
- The reason for RPT being dosed per kilogram of body weight is that it is believed that clearance of drug is increasing with body weight
  - Therefore in order to maintain the same exposure, we need to give larger dose to heavier patients
  - If we got it right, then everybody, independent of the body size, shall have similar exposure in the same study arm

\[ AUC = DOSE \times \frac{F}{CL} \]
AUC distribution in all arms
# S29X AUC results

<table>
<thead>
<tr>
<th>Arm</th>
<th>10 mg/kg</th>
<th>15 mg/kg</th>
<th>20 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>99</td>
<td>77</td>
<td>75</td>
</tr>
<tr>
<td>450 mg: 49</td>
<td>600 mg: 50</td>
<td>600 mg:36</td>
<td>900 mg: 43</td>
</tr>
<tr>
<td>600 mg: 322</td>
<td>900 mg: 38</td>
<td>1200 mg: 3</td>
<td>1200 mg: 28</td>
</tr>
<tr>
<td>900 mg: 512</td>
<td>1200 mg: 642</td>
<td>1500 mg: 4</td>
<td>1500 mg: 659</td>
</tr>
<tr>
<td>AUC (mcg*h/L), median</td>
<td>313</td>
<td>406</td>
<td>582</td>
</tr>
<tr>
<td>450 mg: 272</td>
<td>600 mg: 301</td>
<td>900 mg: 524</td>
<td>900 mg: 512</td>
</tr>
<tr>
<td>600 mg: 322</td>
<td>900 mg: 524</td>
<td>1200 mg: 642</td>
<td>1200 mg: 584</td>
</tr>
<tr>
<td>99 - 668</td>
<td>171 - 1044</td>
<td>231 - 1431</td>
<td>Large variability</td>
</tr>
<tr>
<td>AUC (mcg*h/L) (Ranges)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Effect of Weight on CL

1. Graphically inspect the trend

2. Statistically assess the significance
   \[ p \approx 0.02 - 0.06 \]

3. Quantify effect of WT on CL
   For each increase of 10kg in WT, CL will increase 4.8%

Clinically meaningful effect of covariate should be > 20%
Effect of DOSE on Bioavailability

1. Graphically inspect the trend

2. Statistically assess the significance
   \[ p \approx 0.01 - 0.05 \]

3. Quantify effect of DOSE on F
   1200 mg dose has 20-30% less F than 450mg dose
PK take home messages

- CL is not dependent on weight, at least in our population
- Bioavailability is decreasing with dose
  - Doubling the dose (e.g. 450 or 600 to 900-1200 mg), the exposure will increase less than double (around 50%)
  - Bioavailability is variable
    - better bioavailability in Asians and women (?)
    - decreased in HIV+ patients

Decisions for future study:

- Flat dose
- Increasing the dose, we get less than proportional increase in exposure (50%)
PD clinical endpoints

- **Common PD endpoint:**
  1. Time to first negative results on solid medium
  2. Time to stable negative results on solid medium
  3. Time to first negative results on liquid medium
  4. Time to stable negative results on liquid medium

- **Elaborate PD endpoint (longitudinal)**
  - Longitudinal measurements of culture conversion on solid medium (graded)
  - Longitudinal measurements of culture conversion on liquid medium
  - Longitudinal measurements of MGIT data
  - ....
Methodology

- Time-to-event analysis (censoring taken into account)

**Modelling Steps:**

1. Baseline model (rifampin arm)
   - **Data:** Rifampin arm from 29 (73 subjects) and 29X (207 subjects)

2. Treatment effect
   - **Data:** RPT arms (203 subjects)

3. Covariates effect
Visual predictive check, baseline model, rifampin,
Time varying hazard
Introducing drug effect

- Effect can be estimated as:

1. Treatment on investigational drug vs comparative efficacy arm
   (RPT vs RIF)
2. Treatment arms vs comparative efficacy arm
   (RPT 10 mg/kg, RPT 15 mg/kg and RPT 20 mg/kg vs RIF)
3. Dose levels vs comparative efficacy arm
   (RPT 450mg, 600mg, 900mg, 1200mg vs RIF)
4. Exposure –response model (linear, Emax, sigmoidal Emax)
   - Exposure: RPT exposure
     RPT Cmax
     PKPD parameters (Time>MIC, AUC>MIC...)
# The power of exposure-response model

<table>
<thead>
<tr>
<th>PD outcome Description</th>
<th>P-value Arm effect</th>
<th>P-value Dose effect</th>
<th>P-value, exposure response</th>
</tr>
</thead>
<tbody>
<tr>
<td>First solid</td>
<td>0.36</td>
<td>0.04</td>
<td>0.0007</td>
</tr>
<tr>
<td>Stable solid</td>
<td>0.6</td>
<td>0.17</td>
<td>0.0002</td>
</tr>
<tr>
<td>First liquid</td>
<td>0.95</td>
<td>0.55</td>
<td>1*10^-5</td>
</tr>
<tr>
<td>Stable liquid</td>
<td>0.36</td>
<td>0.17</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Arm effect:** Is arm 20m/kg better than 15 mg/kg better than 10 mg/kg?

**Dose effect:** Is 1200mg dose better than 900mg, better than 600mg better than 450mg?

**Exposure-response effect:** Is exposure truly driving the effect?
Concept of maximal achievable effect

Median time: 38 days *(5.5 weeks)*
Time to conversion for 95% patients:
81 days *(12 weeks)*

Median time: 26 days *(3.5 weeks)*
Time to conversion for 95% patients:
57 days *(8 weeks)*
PKPD is a steep Emax curve

Maximal effect = 4 weeks shortening for culture conversion results

50% effect = 2 weeks shortening for culture conversion results

Legend:
Median exposure in 600 mg group
Median exposure in 900 mg group
Median exposure in 1200 mg group
900 mg vs 1200 mg?

Legend:
900 mg group
1200 mg group
Covariate analysis

- First negative on solid media: **Cavitary status on AUC50**
  - patients without cavities are clearing infection rapidly and they need much less drug

- Stable negative on solid media: **Women lower AUC50**

- First negative on liquid media: **Lighter people higher AUC50**

- Stable liquid: **RACE/CNT on Maximal effect**
  - High dose RPT may work better in certain population

- No consistent covariate effect
Covariate analysis (cavities)

- Presence of cavities increase AUC50 3 times
- Significant (p<0.008)
- Steepness is even greater
- Yes/No effect

![Diagram showing effect on AUC (mcg*h/L) for no cavities and with cavities]
Clincial Trial Simulations

Rifampin:
- 12 weeks
- 600 mg RPT: 11 weeks
- 900 mg RPT: 8.5 weeks
- 1200 mg RPT: 8.2 weeks

Probability distribution of time to conversion for 95% population (days)
Take home messages

- **Target RPT AUC** for treatment duration shortening is established
- **Flat dose** is better option than mg/kg
- 1200mg little additional benefit compared to the 900 mg, however
- Is 4 weeks shortening of culture conversion results enough for treatment duration shortening (down to 4 months?)
- Large variability
- **Exposure-response** is more powerful than dose-effect
- Phase 3 regimens evaluated in **clinical trial simulations**
## Overview of Emax, gamma and AUC50 for all other endpoints

<table>
<thead>
<tr>
<th>PD outcome Description</th>
<th>AUC50 (mcg*h/L)</th>
<th>Gamma</th>
<th>Emax</th>
</tr>
</thead>
<tbody>
<tr>
<td>First solid</td>
<td>340</td>
<td>&gt;5</td>
<td>-1</td>
</tr>
<tr>
<td>Stable solid</td>
<td>290</td>
<td>&gt;5</td>
<td>-1.02</td>
</tr>
<tr>
<td>First liquid</td>
<td>309</td>
<td>&gt;5</td>
<td>-1.08</td>
</tr>
<tr>
<td>Stable liquid</td>
<td>284</td>
<td>&gt;5</td>
<td>-0.57</td>
</tr>
</tbody>
</table>
Is F dependent on dose or is CL dependent on WT?

Facts:
- With oral data we can only estimate CL/F (ratio)
- Higher dose is given to the heavier patients
- Higher dose may have lower F

Dose proportional PK:
- When we give the higher dose, we expect higher exposure

Rifapentine PK
- Exposure is lower than expected (not dose-proportional)
- Either F is decreased with the higher dose
- Or CL is truly dependent on WT, therefore heavier patients who receive higher dose, have less exposure

\[
AUC = \text{DOSE} \times \frac{F}{CL}
\]

Decreasing with higher dose
Increasing with higher WT, e.g. higher dose