Optimization of the rifampicin dosage to improve therapeutic efficacy in tuberculosis treatment, using a murine model

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Background

The currently used dosage of rifampicin (RIF) (10 mg/kg/day) in treatment of tuberculosis (TB) is based on several trials in the 1970s and 1980s.

The aim of those studies was to investigate how little RIF was needed in addition to a base regimen of isoniazid (INH) and pyrazinamide (PZA), to enable a short-course (6-months) regimen.

The RIF dosage of 10 mg/kg/day appears to be at the lower end of the dose-response curve.

Objectives of the present study

- Determination of the optimal RIF dosage in mice with TB, resulting in a maximum therapeutic effect without adverse effects, including prevention of relapse of infection and emergence of resistance.

- Assessment of pharmacokinetic parameters of increased RIF dosages in mice.
Methods

Different RIF dosages were used to estimate:

- In mice with TB caused by the Beijing-1585 genotype strain\(^2\):
  - the Maximum Tolerated Dosage
  - the dose-dependent effect of RIF, administered as single-drug for 3 weeks
  - the therapeutic efficacy of increasing RIF dosage in combination therapy with INH and PZA administered for 2 months

- In non-infected mice:
  - the pharmacokinetic parameters

\(^2\) de Steenwinkel et al. Antimicrob Agents Chemother. 2012 Sep;56(9):4937-44
Results
Maximum Tolerated Dose (MTD)

In murine TB:

- Increasing RIF dosage from 10 mg/kg/day up to 320 mg/kg/day did not result in impaired kidney function (Creat/Bun).

- RIF dosage of 320 mg/kg/day resulted in:
  - impaired liver function (ALAT/ASAT), below five-times the upper limit of normal according to criteria
  - a strong impact on animal behavior (hyperactivity).

→ MTD of RIF in our mice was defined as 160 mg/kg/day.
Dose-dependent effect of RIF administered as single-drug treatment for 3 weeks

log CFU/organ

<table>
<thead>
<tr>
<th>Treatment (3 wks)</th>
<th>2</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>8/8</td>
<td>4/4</td>
</tr>
<tr>
<td>10 mg/kg RIF</td>
<td>4/4</td>
<td>4/4</td>
</tr>
<tr>
<td>20 mg/kg RIF</td>
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<td>4/4</td>
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<td>40 mg/kg RIF</td>
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</tr>
<tr>
<td>80 mg/kg RIF</td>
<td>4/4</td>
<td>4/4</td>
</tr>
<tr>
<td>160 mg/kg RIF</td>
<td>4/4</td>
<td>4/4</td>
</tr>
</tbody>
</table>

de Steenwinkel et al. submitted
Conclusions

- In murine TB a significantly dose-dependent killing activity was observed for RIF after 3 weeks of single-drug treatment ($p=0.0001$ one-way ANOVA).

Next question:

Will increasing the RIF dosage in the combination therapy (INH-RIF-PZA) improve the therapeutic efficacy?
Therapeutic efficacy of increasing RIF dosage administered in combination with INH and PZA

Therapy-duration: 2 months

Lung

- Untreated
- HR(10)Z
- HR(40)Z
- HR(80)Z
- HR(160)Z

de Steenwinkel et al. submitted
Conclusions

In murine TB:

- A significantly dose-dependent killing activity was observed for RIF at single-drug treatment after 3 weeks

- An 8-fold increase in RIF dosage up to 80 mg/kg/day was well tolerated and allowed reduction of therapy duration from 6 to 2 months
Pharmacokinetic parameters of RIF

<table>
<thead>
<tr>
<th>Dose (mg/kg/day)</th>
<th>$fAUC_{0-24h}$ (mg/L*h)</th>
<th>$C_{\text{max}}$ (mg/L)</th>
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</thead>
<tbody>
<tr>
<td>RIF as single drug</td>
<td>10</td>
<td>4.0</td>
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<tr>
<td>160*</td>
<td>59.4</td>
<td>142.1</td>
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</tbody>
</table>

* MTD

de Steenwinkel *et al.* submitted
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<td></td>
<td>160*</td>
<td>59.4</td>
</tr>
<tr>
<td>RIF in combination</td>
<td>10</td>
<td>4.2</td>
</tr>
<tr>
<td>RIF-INH-PZA</td>
<td>160*</td>
<td>57.0</td>
</tr>
</tbody>
</table>

* MTD

de Steenwinkel et al. submitted
Conclusions

In murine TB:

- A significantly dose-dependent killing activity was observed for RIF at single-drug treatment after 3 weeks.

- An 8-fold increase in RIF dosage up to 80 mg/kg/day was well tolerated and allowed reduction of therapy duration from 6 to 2 months.

- Increase of RIF dosage resulted in a similar increase of $f_{AUC}$ and almost similar increase of $C_{\text{max}}$. 
Summarizing conclusions

In murine TB:

- A significantly dose-dependent killing activity was observed for RIF at single-drug treatment after 3 weeks.

- An 8-fold increase in RIF dosage up to 80 mg/kg/day was well tolerated and allowed reduction of therapy duration from 6 to 2 months.

- Increase of RIF dosage resulted in a similar increase of \( fAUC \) and almost similar increase of \( C_{\text{max}} \).

- This study is a proof of concept for the clinical studies on tolerability and efficacy of increased RIF dosages in TB patients.
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