High dose rifampicin for the treatment of TB meningitis: a dose finding study

TB meningitis

• Most severe form of TB
• Treatment follows the model for pulmonary TB
• Standard 4-drug regimen

• Rifampicin: low penetration into CSF
• Donald P, Tuberculosis 2010:
  ‘18 papers, only 7 with individual or mean conc. >1 mg/L in CSF’
TB meningitis

- Most severe form of TB
- Treatment follows the model for pulmonary TB
- Standard 4-drug regimen

- Rifampicin: low penetration into CSF
- Donald P, Tuberculosis 2010:
  ‘18 papers, only 7 with individual or mean conc. >1 mg/L in CSF’

-> higher doses of rifampicin are needed
The concept of higher doses of rifampicin

in vitro (□), in infected macrophage monolayers (•), in vivo (●)

Jayaram et al, Antimicrob Agents Chemother 2003
Development of high dose rifampicin for TBM

• First study: open-label, randomized, phase II clinical trial:
  N=60, 14 days of intervention, 13 mg/kg intravenously  Rulsami te al, LID 2013
First study: open-label, randomized, phase 2 clinical trial

Survival:

- 50% died within 6 months
- 22 (73%) in the first month
- Mortality was much lower in the high dose rifampicin group
  
  adjusted HR 0.42
  (95% CI 0.2-0.87), p=0.0193

First study: open-label, randomized, phase II clinical trial:

N=60, 14 days of intervention, 13 mg/kg intravenously  
Ruslami te al, LID 2013
Development of high dose rifampicin for TBM

• First study: *open*-label, randomized, phase II clinical trial:
  N=60, *14 days of intervention*, 13 mg/kg *intravenously*  
  Rulsami te al, LID 2013

• PK-PD analysis of first study: conc. effect relationship,
  *highest desirable exposures not reached*,
  target values: AUC0-24h = 116 h*mg/L, Cmax = 22 mg/L  
  Te Brake et al, IJAA 2015
Development of high dose rifampicin for TBM

• First study: open-label, randomized, phase II clinical trial:
  N=60, 14 days of intervention, 13 mg/kg intravenously  Rulsami te al, LID 2013

• PK-PD analysis of first study: conc. effect relationship,
  highest desirable exposures not reached,
  target values: AUC0-24h = 116 h*mg/L, Cmax = 22 mg/L  Te Brake et al, IJAA 2015

• Second study: open-label, randomized, phase II trial
  N=30, 14 days, 17/20 mg/kg orally vs 13 mg/kg iv  Yunivita et al, IJAA 2016
Development of high dose rifampicin for TBM

- First study: *open*-label, randomized, phase II clinical trial:
  \[N=60, \text{14 days of intervention, 13 mg/kg intravenously}\]  
  Ruslami et al, LID 2013

- PK-PD analysis of first study: conc. effect relationship,
  *highest desirable exposures not reached*,
  target values: \(AUC_{0-24h} = 112 \, \text{h*mg/L}, \ C_{\text{max}} = 22 \, \text{mg/L}\)  
  Te Brake et al, IJAA 2015

- Second study: open-label, randomized, phase II trial
  \[N=30, \text{14 days, 17/20 mg/kg orally vs 13 mg/kg iv}\]  
  Yunivita et al, IJAA 2016

- Third study: *double-blinded*, randomized, placebo-controlled phase II trial
  \[N=60, \text{30 days, 10 vs 20 vs 30 mg/kg orally}\]
Aims, objectives and study design

• Overall aim: to find the dose of rifampicin to be evaluated in a phase III trial
• Primary objective: to describe the PK of high dose rifampicin in patients with TBM
  Secondary objectives: to evaluate safety/tolerability & to explore efficacy
Aims, objectives and study design

- Overall aim: to find the dose of rifampicin to be evaluated in a phase III trial
- Primary objective: to describe the PK of high dose rifampicin in patients with TBM
- Secondary objectives: to evaluate safety and tolerability & to explore efficacy
Inclusion criteria:

- Age > 14 years
- Clinically suspected meningitis
- CSF/blood glucose ratio less than 0.5
- No history of TB treatment within the last 3 days
- Signed informed consent

Exclusion criteria:

- ALT > 5 times the ULN
- Kidney dysfunction (eGFR <50 ml/min)
- Pregnancy, lactation
- Rapid clinical deterioration at time of presentation (e.g. signs of sepsis, decreasing consciousness or signs of cerebral oedema, or herniation)
- Hypersensitivity or intolerance to rifampicin.
- No CSF data to enable a diagnosis of definite TBM
- Potential non-compliant subjects as judged by the investigators
- Evidence of bacterial or cryptococcal meningitis
Drugs
• Three tablets: 1, 2 or 3 tablets of rifampicin 450 mg with matching placebo tablets
• Administration of drugs on an empty stomach
• Unconscious patients: drug delivery through a nasogastric tube
• Adherence: facility-based DOT, community-based DOT, pill count, diary

PK study
• PK sampling: day 2 (±1) and day 10 (±1)
• Sampling times: plasma: 0, 1, 2, 4, 8 and 12 h, CSF: one sample at 3-9 hours
• Bio-analysis using a validated UPLC-UV method & NC PK methods

Adverse effects
• Clinical assessment, blood count, ALT and creatinine at days 1,3,7,10,14,30,45,60
• AEs: those likely to be related to TBM treatment (hepatotoxicity, hypersensitivity, haematological changes)

Efficacy: mortality, GCS, brain MRI
Results – recruitment of patients

264 Suspected Meningitis

TBM (n=157)

60 randomly assigned
after stratification according to Medical Research Council (MRC)
Definite TBM (n=43) Probable TBM (n=17)

107 not TB meningitis
72 not meningitis
18 no lumbar puncture
13 Cryptococcal meningitis
4 Bacterial meningitis

70 with exclusion criteria
5 declined to signed ICF
22 rapid clinical deterioration

20 in group A
14 definite; 6 probable; HIV=1

20 in group B
14 definite; 6 probable; HIV=1

20 in group C
15 definite; 5 probable; HIV=4
<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n=60)</th>
<th>Group A (450 mg) (n=20)</th>
<th>Group B (900 mg) (n=20)</th>
<th>Group C (1350 mg) (n=20)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male (%)</td>
<td>32 (53.3)</td>
<td>12 (60)</td>
<td>8 (40)</td>
<td>12 (60)</td>
<td>0.343</td>
</tr>
<tr>
<td>Age (median [IQR])</td>
<td>29.5 [23-38.8]</td>
<td>28 [22.3-45.8]</td>
<td>29 [21.3-38.3]</td>
<td>33 [24.3-37.3]</td>
<td>0.976</td>
</tr>
<tr>
<td>Body weight (median [IQR])</td>
<td>45 [40.1-50]</td>
<td>45 [40-47.3]</td>
<td>45 [38.5-50.5]</td>
<td>48.4 [41.6-54.7]</td>
<td>0.491</td>
</tr>
<tr>
<td>Temperature (median [IQR])</td>
<td>37.7 [37-38.3]</td>
<td>37.2 [36.5-38.2]</td>
<td>38 [37.2-38.2]</td>
<td>37.6 [37-38]</td>
<td>0.162</td>
</tr>
<tr>
<td>Chief complaint, lowered</td>
<td><strong>51 (85%)</strong></td>
<td>17 (85)</td>
<td>16 (80%)</td>
<td>18 (90)</td>
<td>0.594</td>
</tr>
<tr>
<td>consciousness (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBM grade (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.663</td>
</tr>
<tr>
<td>1</td>
<td>1 (1.7)</td>
<td>0 (0.0)</td>
<td>1 (5.0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><strong>54 (90)</strong></td>
<td>18 (90.0)</td>
<td>18 (90.0)</td>
<td>18 (90)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5 (8.3)</td>
<td>2 (10.0)</td>
<td>1 (5.0)</td>
<td>2 (10)</td>
<td></td>
</tr>
<tr>
<td>HIV, positive (%)</td>
<td><strong>6 (10)</strong></td>
<td>1 (5.0)</td>
<td>1 (5.0)</td>
<td>4 (20)</td>
<td>0.261</td>
</tr>
<tr>
<td>Chest X Ray, TB (%)</td>
<td><strong>37 (62)</strong></td>
<td>13 (86.7)</td>
<td>12 (85.7)</td>
<td>12 (85.7)</td>
<td>0.752</td>
</tr>
<tr>
<td>Bacteriologically confirmed (%)</td>
<td><strong>43 (71.7)</strong></td>
<td>14 (70)</td>
<td>14 (70)</td>
<td>15 (75)</td>
<td>0.921</td>
</tr>
<tr>
<td>Using NGT on PK 1</td>
<td>35 (61.4)</td>
<td>10/16 (62.5)</td>
<td>12/17 (70.0)</td>
<td>13/20 (65)</td>
<td>0.917</td>
</tr>
</tbody>
</table>
## Results – pharmacokinetics at day 2 (±1)

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=15)</th>
<th>Group B (n=18)</th>
<th>Group C (n=19)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</td>
<td>7.2 [2.18-14.12]</td>
<td>18.13 [2-43.61]</td>
<td>25.54 [11.88-55.49]</td>
<td>0.000</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h), (Median [range])</td>
<td>3.63 [1.00-9.00]</td>
<td>3.94 [0.90-12.00]</td>
<td>3.86 [1.00-12.00]</td>
<td>0.385</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>4.88 [2.12-20]</td>
<td>6.29 [3.69-10.64]</td>
<td>8.76 [3.74-25.62]</td>
<td>0.022</td>
</tr>
<tr>
<td>Cl/F (L/h)</td>
<td>8.42 [3.86-33.61]</td>
<td>5.28 [2.39-34.11]</td>
<td>4.6 [2.53-7.10]</td>
<td>0.020</td>
</tr>
<tr>
<td>Vd/F (L)</td>
<td>59.19 [26.01-217.13]</td>
<td>47.87 [22.42-516.28]</td>
<td>58.13 [24.75-146.28]</td>
<td>0.644</td>
</tr>
<tr>
<td>CSF conc.</td>
<td>0.28 [0.13-0.48]</td>
<td>0.59 [0.13-1.69]</td>
<td>0.74 [0.24-1.19]</td>
<td>0.000</td>
</tr>
</tbody>
</table>
Results - Pharmacokinetics

$AUC_{0-24}$ decreased by 26%, 16% and 36% after 10 days of treatment for group A, B and C.
## Results - Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=15)</th>
<th>Group B (n=18)</th>
<th>Group C (n=19)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</td>
<td>7.2 [2.18-14.12]</td>
<td>18.13 [2-43.61]</td>
<td>25.54 [11.88-55.49]</td>
<td>0.000</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h), (Median [range])</td>
<td>3.63 [1.00-9.00]</td>
<td>3.94 [0.90-12.00]</td>
<td>3.86 [1.00-12.00]</td>
<td>0.385</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>4.88 [2.12-20]</td>
<td>6.29 [3.69-10.64]</td>
<td>8.76 [3.74-25.62]</td>
<td>0.022</td>
</tr>
<tr>
<td>Cl/F (L/h)</td>
<td>8.42 [3.86-33.61]</td>
<td>5.28 [2.39-34.11]</td>
<td>4.6 [2.53-7.10]</td>
<td>0.020</td>
</tr>
<tr>
<td>Vd/F (L)</td>
<td>59.19 [26.01-217.13]</td>
<td>47.87 [22.42-516.28]</td>
<td>58.13 [24.75-146.28]</td>
<td>0.644</td>
</tr>
<tr>
<td>CSF conc.</td>
<td>0.28 [0.13-0.48]</td>
<td>0.59 [0.13-1.69]</td>
<td>0.74 [0.24-1.19]</td>
<td>0.000</td>
</tr>
</tbody>
</table>

**PK target attainment (te Brake, IJAA 2015)**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; &gt;22 mg/L</td>
<td>0</td>
<td>7/18 (39%)</td>
<td>15/19 (79%)</td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-24&lt;/sub&gt; &gt;116 mg*h/L</td>
<td>1/15 (6%)</td>
<td>13/18 (72%)</td>
<td>17/19 (90%)</td>
<td></td>
</tr>
<tr>
<td>CSF conc. &gt;MIC (0.5 mg/L)</td>
<td>0/10</td>
<td>4/10</td>
<td>8/11</td>
<td></td>
</tr>
</tbody>
</table>

Data showed as Gmean (range), unless otherwise stated
Results – Safety/tolerability

- All AEs during 60 days: 51/60 patients (85%)
- All AEs, distribution over arms: 85% vs 80% vs 90% (p=0.7)
- 14 grade 3 AEs – all resolved without drug discontinuation
- 1 grade 4 AE (hepatotoxicity) – resolved after drug discontinuation

<table>
<thead>
<tr>
<th>Grade</th>
<th>AE</th>
<th>Group</th>
<th>Group</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A (n=20)</td>
<td>B (n=20)</td>
<td>C (n=20)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Hepatotoxicity</td>
<td>3</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Hepatotoxicity</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>total</td>
<td></td>
<td>3 (15%)</td>
<td>8 (40%)</td>
<td>4 (20%)</td>
</tr>
</tbody>
</table>
# Results – Efficacy

<table>
<thead>
<tr>
<th></th>
<th>All (n=60)</th>
<th>A (n=20)</th>
<th>B (n=20)</th>
<th>C (n=20)</th>
<th>A (n=14)</th>
<th>B (n=14)</th>
<th>C (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality until discharge</td>
<td>13 (78.3%)</td>
<td>5 (25%)</td>
<td>5 (25%)</td>
<td>3 (15%)</td>
<td>3 (21.4%)</td>
<td>4 (28.6%)</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Mortality until 30 days</td>
<td>14 (23.3%)</td>
<td>5 (25%)</td>
<td>6 (30%)</td>
<td>3 (15%)</td>
<td>3 (21.4%)</td>
<td>4 (28.6%)</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Mortality until 45 days</td>
<td>15 (25%)</td>
<td>5 (25%)</td>
<td>7 (35%)</td>
<td>3 (15%)</td>
<td>3 (21.4%)</td>
<td>5 (35.7%)</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Mortality until 60 days</td>
<td>15 (25%)</td>
<td>5 (25%)</td>
<td>7 (35%)</td>
<td>3 (15%)</td>
<td>3 (21.4%)</td>
<td>5 (35.7%)</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Mortality until 180 days</td>
<td>19 (31.7%)</td>
<td>7 (35%)</td>
<td>9 (45%)</td>
<td>3 (15%)</td>
<td>5 (35.7%)</td>
<td>6 (42.9%)</td>
<td>1 (6.7%)</td>
</tr>
</tbody>
</table>
### Results – Efficacy

<table>
<thead>
<tr>
<th></th>
<th>All (n=60)</th>
<th>A (n=20)</th>
<th>B (n=20)</th>
<th>C (n=20)</th>
<th>A (n=14)</th>
<th>B (n=14)</th>
<th>C (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality until discharge</td>
<td>13 (78.3)</td>
<td>5 (25)</td>
<td>5 (25)</td>
<td>3 (15)</td>
<td>3 (21.4)</td>
<td>4 (28.6)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Mortality until 30 days</td>
<td>14 (23.3)</td>
<td>5 (25)</td>
<td>6 (30)</td>
<td>3 (15)</td>
<td>3 (21.4)</td>
<td>4 (28.6)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Mortality until 45 days</td>
<td>15 (25)</td>
<td>5 (25)</td>
<td>7 (35)</td>
<td>3 (15)</td>
<td>3 (21.4)</td>
<td>5 (35.7)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Mortality until 60 days</td>
<td>15 (25)</td>
<td>5 (25)</td>
<td>7 (35)</td>
<td>3 (15)</td>
<td>3 (21.4)</td>
<td>5 (35.7)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Mortality until 180 days</td>
<td>19 (31.7)</td>
<td>7 (35)</td>
<td>9 (45)</td>
<td>3 (15)</td>
<td>5 (35.7)</td>
<td>6 (42.9)</td>
<td>1 (6.7)</td>
</tr>
</tbody>
</table>
Results – Efficacy

<table>
<thead>
<tr>
<th></th>
<th>All pts</th>
<th>Bacteriologically confirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n=60) A (n=20) B (n=20) C (n=20)</td>
<td>A (n=14) B (n=14) C (n=15)</td>
</tr>
<tr>
<td>Mortality until discharge</td>
<td>13 (78.3) 5 (25) 5 (25) 3 (15)</td>
<td>3 (21.4) 4 (28.6) 1 (6.7)</td>
</tr>
<tr>
<td>Mortality until 30 days</td>
<td>14 (23.3) 5 (25) 6 (30) 3 (15)</td>
<td>3 (21.4) 4 (28.6) 1 (6.7)</td>
</tr>
<tr>
<td>Mortality until 45 days</td>
<td>15 (25) 5 (25) 7 (35) 3 (15)</td>
<td>3 (21.4) 5 (35.7) 1 (6.7)</td>
</tr>
<tr>
<td>Mortality until 60 days</td>
<td>15 (25) 5 (25) 7 (35) 3 (15)</td>
<td>3 (21.4) 5 (35.7) 1 (6.7)</td>
</tr>
<tr>
<td>Mortality until 180 days</td>
<td>19 (31.7) 7 (35) 9 (45) 3 (15)</td>
<td>5 (35.7) 6 (42.9) 1 (6.7)</td>
</tr>
</tbody>
</table>
Results – Efficacy

Survival at 180 days: 30 vs 10 mg/kg RIF

HR: 0.38 (95% CI 0.09-1.46, p=0.16) – in all patients
HR: 0.16 (95% CI 0.02-1.34, p=0.09) – in confirmed TBM patients
Conclusions

• Increasing the dose of rifampicin from 10 to 30 mg/kg results in a more than proportional increase in AUC0-24h in plasma, an increase in Cmax and an increase in exposure in CSF

• Large interindividual variability in rifampicin PK at 10, 20 and 30 mg/kg

• One grade 4 AE; grade 3 AEs resolved without discontinuation of rifampicin

• Increased PK target attainment

• A possible trend for improved efficacy
Stage I 
(2010 – 2011)
Pharmacokinetic study of 600mg iv Rifampicin + Moxi
Lancet Infectious Disease 2013

Stage II 
(2013)
Explorative PK study higher oral dose Rifampicin (REMOVER Study)
IJAA 2016

Heemskerk et al
No added value of RIF 15 mg/kg + levoflox

Heemskerk et al
Improved survival in INH-R TBM of RIF 15 mg/kg + levoflox
Clin Infect Dis 2017

Stage III 
(2014-17)
Drug-dose finding (ReDEFINe study)

Stage IV 
(2018 – 2022)
phase 3, multicenter, clinical trial
......

Ultimate goal:
Implementation findings ➔
new guidelines for TB-Meningitis

Radboudumc
Acknowledgements

• PEER Health / NIH

• Colleagues of Tuberculosis Research Group Bandung, Indonesia

• Colleagues at Radboudumc, The Netherlands