Pharmacokinetics of and safety of high dose of rifampicin and moxifloxacin for tuberculosis meningitis: preliminary data from a RCT in Indonesia

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Presented at the 4th International Workshop on Clinical Pharmacology of TB Drugs, 16 September 2011, Chicago, IL, USA
Background
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Tuberculosis meningitis (TBM):

- The most lethal form of tuberculosis (TB)
- High mortality (30-60% died in the 1\textsuperscript{st} month after diagnosis)
- With HIV $\rightarrow$ TBM is increased
- TBM patients often come at the late stage
  - Organ dysfunction, incl. for drugs abs
  - Other co-morbidities
Background

• **TBM treatment:**
  - Bad outcome ≈ sub optimal therapy??
  - Follows the model of pulmonary TB
  - Based on limited data (trials)
    - Different patophysiology
    - Characteristics of TB drugs related to BBB
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• TBM treatment:
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  o Based on limited data (trials)
    • Different patophysiology
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• Characteristics of TB drugs
  o INH: main drug and could pass the BBB
  o RIF: main drug, but <<< pass the BBB
  o PZA: good penetration into the CSF, but effect???
  o EMB: no effect
Background

• **Strategy (Cape Town, 2009)**
  - Using high dose of RIF and/or
  - Using moxifloxacin/MXF  
    (good penetration to the BBB)

→ MAY INCREASE THE EFFICACY OF THESE DRUGS
→ INCREASE THEIR EXPOSURE IN CSF
Background

• Strategy (Cape Town, 2009)
  o Using high dose of RIF and/or
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• Aim of the study:
  to evaluate the PK and safety/tolerability of an intensified regimen for TBM (using higher dose of RIF and MXF)
Methods

• Open-label, randomized, two-arm (factorial design), phase II clinical trial
  o Adult newly diagnosed TBM patients
  o Hospitalized in referral hospital, Bandung, Indonesia

Excluded if:
  o Has taken TB drugs ≥ 7 days
  o ALT>5 ULN
  o Abnormal ECG inc. prolong QTc or other heart block
  o Known hypersensitivity to RIF or MXF
  o Pregnant /lactation
  o No informed consent
Methods

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Methods

- all subjects receive INH 300 mg and PZA 1500 mg
- 14 day of intensified regimen → back to standard regimen
- 10 patients/group

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Methods

• Drug administration:
  o Unconscious pts: via NGT (empty stomach)
  o RIF iv: 600 mg in 250 ml NaCl 0.9% - 90 min

• PK assessment:
  o Plasma: 0, 1, 2, 4, 6 and 24h after drug administration
  o CSF: 3-6h (I) and 6-9h (II) in 2 different days

• Safety/tolerablity assessment:
  o Daily close clinical monitoring
  o CBC, ECG and ALT 2x/week
Results
Patients’ characteristics

• 25 patients were recruited for this report
  o 44% male
  o median age (range): 32 (20 – 60) yrs
  o No DM; 3 (12%) HIV positive

• Clinical pictures when admission:
  o TBM criteria: definite (48%), probable (36%), possible (16%)
  o GCS baseline: 12 (8 – 15)
  o Chief complain: unconsciousness (80%), headache (16%), fever
  o CXR: 48% with pulmonary TB
  o BW: 49.2 (4.7) kg and BMI: 19.3 (2.4) kg/m²
Patients’ characteristics

- Median ALT: 19 (5 – 192)
- Hb baseline: 11.3 (2.1) gr/dl
- QTc baseline: normal (0.39 F, 0.41 M)

**Drug dose (mg/kg)**

<table>
<thead>
<tr>
<th></th>
<th>all</th>
<th>SD</th>
<th>HD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIF</td>
<td>10.6</td>
<td>9.2</td>
<td>12.3</td>
<td>0.000</td>
</tr>
<tr>
<td>MXF</td>
<td>11.8</td>
<td>8.1</td>
<td>16.7</td>
<td>0.000</td>
</tr>
<tr>
<td>INH</td>
<td>6.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PZA</td>
<td>30.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMB</td>
<td>15.6</td>
<td></td>
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</tbody>
</table>
 Patients’ distribution

MTB

RIF 450 mg p.o.
No MXF (EMB 750 mg p.o.)
MXF 400 mg p.o.
MXF 800 mg p.o.

RIF 600 mg i.v.
No MXF (EMB 750 mg p.o.)
MXF 400 mg p.o.
MXF 800 mg p.o.

A  B  C  D  E  F
4  4  5  4  5  3
Table. PK parameters of RIF in 23 TBM patients

<table>
<thead>
<tr>
<th>Rifampicin b</th>
<th>Value for group a</th>
<th>Ratio of RIF 450 mg vs. 600 mg value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RIF 450 mg (n=12)</td>
<td>RIF 600 mg (n=11)</td>
<td></td>
</tr>
<tr>
<td>C max (mg/L)</td>
<td>7.5 (5.3 – 10.5)</td>
<td>21.1 (17.5 – 25.6)</td>
<td>0.35 (0.24 – 0.52)</td>
</tr>
<tr>
<td>T max (h) Median (range)</td>
<td>2 (1 – 6)</td>
<td>2 (1 – 2)</td>
<td></td>
</tr>
<tr>
<td>AUC0–24 (mg.h/L)</td>
<td>72.5 (50.9 – 103.3)</td>
<td>130.4 (109.2 – 155.7)</td>
<td>0.56 (0.40 – 0.77)</td>
</tr>
<tr>
<td>AUC0–6 (mg.h/L)</td>
<td>31.1 (21.1 – 1.66)</td>
<td>79.7 (67.4 – 94.3)</td>
<td>0.39 (0.26 – 0.59)</td>
</tr>
</tbody>
</table>

a Data are presented as geometric means (95% confidence intervals) unless stated otherwise.

b Given within the first three days of drug intake

c By an independent t test on log transformation data

d By Wilcoxon rank-sum test
Table. PK parameters of MXF in 17 TBM patients

<table>
<thead>
<tr>
<th>Moxifloxacin&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Value for group&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Ratio of MXF 400 mg vs. 800 mg value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MXF 400 mg (n=9)</td>
<td>MXF 800 mg (n=8)</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</td>
<td>3.4 (2.4 – 4.8)</td>
<td>9.3 (7.6 – 11.4)</td>
<td>0.36 (0.24 – 0.54)</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h) Median (range)</td>
<td>2 (1 – 6)</td>
<td>2 (1 – 4)</td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-24&lt;/sub&gt; (mg.h/L)</td>
<td>28.0 (21.1 – 37.3)</td>
<td>97.7</td>
<td>0.29 (0.15 – 0.54)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-6&lt;/sub&gt; (mg.h/L)</td>
<td>13.8 (10.3 – 18.6)</td>
<td>41.7 (34.5 – 50.6)</td>
<td>0.33 (0.23 – 0.46)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data are presented as geometric means (95% confidence intervals) unless stated otherwise.

<sup>b</sup> Given within the first three day of drug intake

<sup>c</sup> By an independent t test on log transformation data

<sup>d</sup> By Wilcoxon rank-sum test
RIF and MXF concentrations in CSF

Patient group

RIF (n=19): 0.37 vs. 0.5 mg/L
RIF and MXF concentrations in CSF

RIF (n=19): 0.37 vs. 0.5 mg/L
MXF (n=11): 1.17 vs. 3.9 mg/L
Safety/Tolerability data

• Grade 3 and 4 toxicity
  - Hepatotoxicity: 5 (20%)
    - No death related to the serious adverse event

<table>
<thead>
<tr>
<th></th>
<th>RIF 450 mg</th>
<th>RIF 600 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>dose/kg BW (mg/kg)</td>
<td>8.6</td>
<td>12.5</td>
</tr>
<tr>
<td>C_{max} (mg/L)</td>
<td>8.9</td>
<td>17.9</td>
</tr>
<tr>
<td>AUC_{0-24} (mg*h/L)</td>
<td>74.4</td>
<td>131.3</td>
</tr>
</tbody>
</table>

• Cardiotoxicity (-)
• Hematologic reaction (-)
Mortality data

• Overall: 9 (36%) dead within 1 month
  o 6 in the 1\textsuperscript{st} week of treatment (2 before PK day)
  o 3 in the 3\textsuperscript{rd} week

• Cause of death:

<table>
<thead>
<tr>
<th></th>
<th>RIF 450 mg</th>
<th>RIF 600 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No MXF</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>MXF 400 mg</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>MXF 800 mg</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

• None was caused by drug-toxicity
Conclusions
Conclusions

• Increasing the dose of RIF and MXF is associated with
  o a significant increase in exposure to this drugs both in the plasma and CSF → might be related to the efficacy of the treatment.
  o Without affecting the incidence of SAE and mortality

• Intensified regimen using high dose of RIF and MXF might be promising for optimization of TBM treatment.
Conclusions

• Limitations:
  o More time-points needed for PK MXF
  o Full PK in CSF are not available (technical problem in the field)

• More data will follow:
  o Complete data from all subjects
  o Protein-unbound (free) RIF and MXF in plasma & CSF
  o PD data (incl. MIC)
Acknowledgement

- Neurology Dept., Hasan Sadikin Hospital, Bandung
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- Andalan, UNPAD