Evaluation of co-trimoxazole in treatment of multidrug-resistant tuberculosis

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Background

• Co-trimoxazole (SXT):\textsuperscript{1-2}
  – Sulfamethoxazole (SMX) and Trimethoprim (TMP) (ratio 1:5)
  – Old, inexpensive, well tolerated, not registered for TB
    • ie. urinary tract infections, otitis media, chronic bronchitis
  – Time-dependent killing, AUC/MIC

• SMX
  – \textit{In vitro} activity against \textit{M. tuberculosis}\textsuperscript{3-5}
  – Lack of PK / PD and safety profile in TB patients\textsuperscript{3,4}

\textsuperscript{1}DeAngelis \textit{et al}; TDM 1990, \textsuperscript{2}Nightingale \textit{et al}; Marcel Dekker Inc 2003, \textsuperscript{3}Forgacs \textit{et al}; AAC 2009, \textsuperscript{4}Huang \textit{et al}; JAC 2012, \textsuperscript{5}Ong \textit{et al}; AAC 2010
Study design

• Retrospective study

• 1\textsuperscript{st} January 2006 – 1\textsuperscript{st} July 2012
  – MDR-TB patients
    (1) Drug susceptibility testing (DST) for SXT
    (2) SXT as part of their TB regimen
  – Tuberculosis Center Beatrixoord, Haren, The Netherlands

• To explore SXT use as part of MDR-TB regimen
  – PK / PD parameters
  – Safety
Data collection

• Demographic data:
  – age, sex, weight, length, ethnicity,

• Medical data:
  – co-morbidity, type of diagnosis, localisation of TB, resistance pattern, medical history, dose and duration of TB co-medication
  – SXT:
    • Dose and duration of treatment
    • MIC for SMX (MIC of SXT, TMP: SMX ratio 1:19)
    • SXT-induced adverse effects
    • Pharmacokinetic data
Methods: PK / PD

• Pharmacokinetics
  – Blood samples at steady state
    • T = 0, 1, 2, 3, 4 and 8 h
    • SMX concentrations analyzed by LC-MS/MS
  – Calculation of PK parameters (AUC, $V_d$, Cl, $t_{1/2}$)
    • AUC: non compartmental method (KINFIT, MWPharm)
    • $f_{AUC} = AUC \times 0.23$ (unbound fraction )
  – One compartment POPPK model
    • SMX concentrations and patient characteristics (KINPOP, MWPharm)

• AUC/MIC and $f_{AUC}$/MIC
Methods: safety

- **GI tract**\(^1\)\(^-\)\(^2\)
  - Nausea, vomiting, diarrhea
- **Hepatic injury (grade 3 CTC)**
- **Anemia**\(^3\) (normal Hb: 7.5 – 9.9 (f); 8.7 – 10.6 (m))
- **Blood count abnormalities**
  - Leukocytes (normal: 4*10\(^9\)/L)
  - Plateletes (normal: 150 – 350*10\(^9\)/L)

- **Causality between adverse effect and SXT treatment**\(^4\)
  - Naranjo algorithm,
  - 0 to 9 points, 9 represents the highest likelihood

Results: patients

- DST for SXT 17 MDR isolates
  - 4/17: resistant
  - 3/17: “standard” second-line TB regimen

- MDR-TB patients (10/17)
  - 480 mg SXT once daily
  - Median dose of 6.5 (IQR, 6.1 – 6.8) mg/kg
  - Median period of 381 (IQR, 129 – 465) days
  - 2/10 patients: ↑ 960 mg once daily
Results: patients (2)

• **MDR tuberculosis**
  – Pulmonary TB 8/10 patients

• **Characteristics**
  – Median age 29 (IQR, 24 – 31) years
  – Median BMI 21.1 (IQR, 19.1 – 23.6) kg/m²
Results: PK of SMX

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Plasma (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{0-24}$ (mg*h/L)</td>
<td>372 (360 – 575)</td>
</tr>
<tr>
<td>$Cl$ (Liter/h)</td>
<td>0.9 (0.5 – 1)</td>
</tr>
<tr>
<td>$V$ (Liter)</td>
<td>11.5 (9.2 – 14.9)</td>
</tr>
<tr>
<td>$T_{1/2}$ (h)</td>
<td>10.1 (8.7 – 10.8)</td>
</tr>
</tbody>
</table>

Data is presented as median (IQR)
## Results: POPPK model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl (L.h/1.85 m²)</td>
<td>1.14 ± 0.43</td>
</tr>
<tr>
<td>Vd (L.Kg⁻¹ LbMc)</td>
<td>0.24 ± 0.05</td>
</tr>
<tr>
<td>Ka (h⁻¹)</td>
<td>0.43 ± 0.17</td>
</tr>
<tr>
<td>F (fixed)</td>
<td>1</td>
</tr>
</tbody>
</table>

Data is presented as geometric mean ± sd

- Cross validated population model
- Median AUC underestimation: **0.7** (range, -6.2 – 2.8) %
Results: PK / PD of SMX

- Median MIC for SMX
  - 9.5 (IQR, 4.8 – 25) mg/L

- Geometric mean AUC/MIC
  - 48.4 (IQR, 34.8 – 71.3)

- Geometric mean $fAUC/MIC$
  - 11.1 (IQR, 8 – 16.4)
Results: safety / tolerability

- Well tolerated
- GI tract
  - 1/10 patients: diarrhea and vomiting (naranjo 4)
- No hepatic injury (grade 3 CTC)
- Anemia
  - No clinical relevant decrease in HB
- Blood count abnormalities (naranjo 3)
  - 1/10: leucocytopenia
  - 1/10: mild thrombocytopenia
Discussion: optimal dose?

- **Target: personalized optimal dose**
  - $fAUC_{0-24h}/MIC > 25$, meliodiosis$^1$
    - 1/8 patients $fAUC/MIC > 25$
    - 1dd 480 mg -> 1dd 960 mg?
  - $fAUC/MIC < 25$, SMX no efficient TB agent?
    - Variance within-species$^2$
    - Multiple drug treatment$^3$

$^1$Cheng *et al*; AAC 2009, $^2$Neurmonberger *et al*; EJCMID 2004, $^3$Balasubramanian *et al*; AAC 2012
Conclusions

• SXT treatment was well tolerated
• Consistent PK profile in MDR-TB patients

• Further investigation:
  • Target-finding, *in vitro* PK / PD infection model
  • Dose-finding of SXT in TB, prospective clinical trial