Pharmacokinetics of Levofloxacin in M(X)-DR tuberculosis patients.

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- 5,000 TB patients diagnosed each year
- 3,000 bacteriological confirmed diagnosis.
- Survey nov.’09- dec.’10, Minsk, population of 1.8 mln:
  - New treated TB - 35.3% MDR-TB and 2.0% XDR-TB.
  - Previously treated TB - 76.5% MDR-TB and 19.4% XDR-TB[8].
- OFX resistance:
  - 14.5% (new MDR-TB).
  - 46.2% (previously treated MDR-TB).

[8] Skrahina et al. ERJ 2012
Why LFX

- Later-generation of FQs and WHO group 3 drug
- Affordable drug, comparing with MFX or GFX.
- Available drug in local market.
- Equivalent efficacy with MXF for treating MDR-TB (similar treatment success rate, sputum conversion, rate of adverse reactions) \(^6\)\(^7\).

\(^6\)Koh AJRCCM 2013, \(^7\)Giang IJAA 2013
Activity of LFX

- High *in vitro* en *in vivo* bactericidal activity \cite{1,2}

- Efficacy has been shown to be predicted by the AUC/MIC ratio \cite{3}

PK of LFX:

- >95% oral absorption.
- Good penetration into lung tissue, cerebrospinal fluid and bone [4,5].
- 24% to 38% is bound to plasma proteins, independent of serum drug concentration.

Plasma concentrations of levofloxacin versus time after dosing in 10 adults with pulmonary tuberculosis.*

Objective

• To determine PK LFX M(X)DR-TB patients.

• To determine MIC values in M(X)DR-TB patients.

• To assess pharmacokinetic variability and potential consequence for AUC/MIC ratio.
Materials and Methods

- Pulmonary M(X)DR-TB
- Dose 15 mg/kg per os daily, rounded to 750-1000 mg.
- Samples taken at T= 0, 1, 2, 3, 4, 7, 12 hr at steady state.
- Sample analysis using LC/MS-MS analysis.
- Resistance:
  - Breakpoint testing using BACTEC MGIT960, 2 mg/L.
  - MIC testing 0.25-2.0 mg/L (7H10 and BACTEC MGIT960).
- Non-compartmental analysis (MW/Pharm®, version 3.82)
- Clinical data.
Results

Patients characteristics at baseline (n=20)

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<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Female</strong></td>
<td>8 (40)</td>
<td><strong>Pulmonary tuberculosis:</strong></td>
<td>13 (65)</td>
<td>7 (35)</td>
</tr>
<tr>
<td><strong>Age yrs</strong></td>
<td>31 (27-35)</td>
<td><strong>Cavitary</strong></td>
<td>13 (65)</td>
<td>7 (35)</td>
</tr>
<tr>
<td><strong>Weight kg</strong></td>
<td>63.4 (55.3-77)</td>
<td><strong>Non-cavitary</strong></td>
<td>7 (35)</td>
<td></td>
</tr>
<tr>
<td><strong>Length cm</strong></td>
<td>174 (167-182)</td>
<td><strong>Sputum:</strong></td>
<td>10 (50)</td>
<td>20 (100)</td>
</tr>
<tr>
<td><strong>LBM</strong></td>
<td>22.87 (11.1-37.2)</td>
<td><strong>Smear-positive</strong></td>
<td>10 (50)</td>
<td>20 (100)</td>
</tr>
<tr>
<td><strong>BMI kg·m⁻²</strong></td>
<td>20.1 (18.9-23.4)</td>
<td><strong>Culture-positive</strong></td>
<td>20 (100)</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis:</strong></td>
<td></td>
<td><strong>Resistance pattern:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New</td>
<td>12 (60)</td>
<td><strong>MDR</strong></td>
<td>15 (75)</td>
<td></td>
</tr>
<tr>
<td>Previous treated</td>
<td>8 (40)</td>
<td><strong>XDR</strong></td>
<td>5 (25)</td>
<td></td>
</tr>
<tr>
<td><strong>Comorbidity:</strong></td>
<td></td>
<td><strong>Alcohol abuse</strong></td>
<td>2 (10)</td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td></td>
<td><strong>Smoking</strong></td>
<td>11 (55)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td><strong>Renal insufficiency</strong></td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td></td>
<td><strong>HIV</strong></td>
<td>none</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as n (%) or median (interquartile range)
Results

Steady-state pharmacokinetics of LFX.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Levofloxacin (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0–24h (mg*h/liter)</td>
<td>98.8 (84.8 – 159.6)</td>
</tr>
<tr>
<td>Cmax (mg/liter)</td>
<td>10.1 (8.4 – 16.2)</td>
</tr>
<tr>
<td>Cmin (mg/liter)</td>
<td>1,2 (0.9 – 4)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1 (1-7)</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>6.7 (6 -16.3)</td>
</tr>
<tr>
<td>CL (liter/h)</td>
<td>8.3 (6.7 – 31.2)</td>
</tr>
<tr>
<td>Vd (liters)</td>
<td>88.2 (69.6 – 196.5)</td>
</tr>
</tbody>
</table>

Data are presented in median values (IQR)
Results

Plasma concentration time curve of LFX.

Peloquin et al, AAC 2008

Authors
Target attainment (%) for MIC values based on individual PK-PD results (n=17)

MIC 0.5 mg/L (IQR 0.25-2.0 mg/L).

\( fAUC0-24/MIC 109.5 \text{(IQR 89.39-399.36)} \)
Target attainment (%) for varying MIC values based on individual PK results.
Discussion

- Identification of new susceptibility breakpoints.
- Dose exceeding 15mg/kg.
- PK variability of LFX is less than MFX.
Conclusion

- Large variability in AUC, Cmax and MIC

- Targets $fAUC_{0-24}/MIC$ of $\geq 100$ were only observed in case MIC values 0.25-0.5 mg/L.

- Prospective evaluation high-dose LFX is needed.