Levofloxacin target attainment analysis in MDR-TB patients: time is ripe for proactive TDM

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Disclaimer

- No conflicts of interest to declare
- I’m not Samiksha Ghimire
Background

• Current doses of anti-TB drugs are based on mínimo effective concentration
  – Underdosing and lack of adherence -> amplification of resistance
  – Inter-individual pharmacokinetic variabilities and differences in MIC -> further complicates the treatment

• For concentration dependent antibiotics (rifampicin, fluoroquinolones) -> máximum tolerated dose seem critical in achieving excellent bactericidal and sterilizing activities
<table>
<thead>
<tr>
<th>Group</th>
<th>Anti-TB drugs</th>
<th>Weight-based daily dose</th>
<th>Usual daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Levofloxacin OR Moxifloxacin</td>
<td>➢ 10-15 mg/kg ➢ 7.5-10 mg/kg</td>
<td>➢ 750-1000 mg/ 400-800 mg ➢ 400 mg ➢ 600-1200 mg</td>
</tr>
<tr>
<td></td>
<td>• Bedaquiline</td>
<td>➢ --</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Linezolid</td>
<td>➢ --</td>
<td></td>
</tr>
<tr>
<td><strong>Group B</strong></td>
<td>• Clofazimine</td>
<td>➢ --</td>
<td>➢ 100 mg ➢ 1000 mg</td>
</tr>
<tr>
<td></td>
<td>• Cycloserine or terizidone</td>
<td>➢ 10-15 mg/kg</td>
<td></td>
</tr>
<tr>
<td><strong>Group C</strong></td>
<td>• Ethambutol, Delamanid, Imipenem–cilastatin OR meropenem, Amikacin (OR streptomycin) Ethionamide OR prothionamide, P-aminosalicylic acid</td>
<td>➢ 15-25 mg/kg, --, ➢ 15-20 mg/kg ➢ 15-20 mg/kg (OR 12-18 mg/kg) ➢ 15-20 mg/kg ➢ 8-12 g/day</td>
<td>➢ 1200 mg, 200 mg ➢ 2 vials (1g + 1g) bd ➢ Upto 1000 mg ➢ Upto 1000 mg ➢ 500-1000 mg ➢ Upto 12000 mg</td>
</tr>
</tbody>
</table>
Levofloxacin

- Levofloxacin is a 3rd generation FQ
- Works by inhibiting bacterial DNA gyrase and highly active against *M. tuberculosis*
- Currently prescribed at 750-1000 mg once daily dose
- Bactericidal and sterilizing activities (*in vitro* and *in vivo* models)
  - HFM suggest AUC/MIC >146 as a PK/PD target
- Widely used in the developing country, and is generally well tolerated

1. WHO Global Tuberculosis Report 2018
2. Deshpande *et al.* Clin Infect Dis 2018
Levofloxacain plasma concentration versus time curves at first and second months of treatment (n=23 and 18).

CV inter % (min, max)
19.13% , 67.29%
Levofloxacain probability of target attainment

A. Probability of target attainment vs minimum inhibitory concentration in patients with assumed MIC of 0.5 mg/L and 1 mg/L; B. AUC$_{0-24}$/MIC ratios of Lfx versus actual MIC of 0.5 and 1 mg/L; Dashed horizontal line- AUC$_{0-24}$/MIC 146

Ghimire et al. Eur Respir J 2019
Dose ranging trial: Opti-Q trial
Levofloxacin 750, 1000, 1250 and 1500 mg once daily dosing
Aims

• To estimate the levofloxacin probability of target attainment in MDR-TB patients on standardized regimen
• To assess proportion of patients that would benefit from TDM on higher simulated levofloxacin doses (1250 mg and 1500 mg)
Study design

- Prospective pharmacokinetic data from 23 MDR-TB patients\(^1\); utilized to evaluate the probability of target attainment
- Subset of large retrospective cohort study, \(n=98\)
- Patients enrolled at GENETUP Clinic, Kathmandu, Nepal
- Concentrations quantified with LC-MS/MS
Eligibility

• Inclusion:
  - ≥18 yo
  - Newly diagnosed or previously treated
  - MDR-TB (genotypic + culture)
  - Lfx as part of regimen

• Exclusion:
  - Neurologic / severe extrapulmonary TB
  - <35kg
  - Renal disorders / pregnant / breast feeding / drug-drug IA
## Study Design

<table>
<thead>
<tr>
<th>Prospective PK Study (n=23)</th>
<th>Retrospective Chart Review (n=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steady state blood samples (0,1,2,4,8h)</td>
<td>Medical Chart Review</td>
</tr>
<tr>
<td>May 2016- October 2017</td>
<td>April 2014- December 2016</td>
</tr>
<tr>
<td>Concentrations quantified by LC-MS/MS</td>
<td>Based on PK data from prospective PK study, doses were simulated for this cohort</td>
</tr>
<tr>
<td>AUC by one-compartmental kinetics</td>
<td></td>
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<tr>
<td>Individual MICs in Lowenstein Jensen Media</td>
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</table>
Dose simulation: Pharmacokinetic model

- One-compartment model with lag time
Figure 1: Flow chart of the study population

Total available records of MDR-TB patients (2014-2016) (n=113)

Excluded (n=15)
- 6 had pre-XDR TB
- 2 had missing information
- 6 had infection caused by NTM
- 1 patient treatment was cancelled

Total patients record included (n=98)
# Demographics: Retrospective Study

April 2014-December 2016, Nepal

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<table>
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<tbody>
<tr>
<td>98 MDR-TB patients</td>
<td></td>
</tr>
<tr>
<td>29 years (22-40 IQR)</td>
<td></td>
</tr>
<tr>
<td>48 kg (44-58 IQR)</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>56</td>
</tr>
</tbody>
</table>

**Co-morbidity**

- Diabetes: 6 (6.9%)
- HIV: 6 (6.9%)
- Seizure disorder: 4 (4.6%)
Demographics: treatment regimen in Nepal

20-24 months (8-12 Intensive + 12 Continuation):
- Ethionamide 500-750mg
- Pyrazinamide 20-30 mg/kg/day
- Cycloserin 500-750mg
- Kanamycin IM 500-1000mg
- Levofloxacin (Lfx)

Actual dose Lfx: **750-1000 mg**
Median mg/kg dose: 15.6 (13.5-17.0)

Simulated dose: **1250 mg and 1500 mg**
### Results

#### Primary Treatment Outcome

<table>
<thead>
<tr>
<th></th>
<th>60 days (60-90 IQR)</th>
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<tbody>
<tr>
<td>Sputum smear conversion</td>
<td></td>
</tr>
<tr>
<td>Culture conversion</td>
<td>90 days (60-90 IQR)</td>
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</table>

#### Secondary Treatment Outcome

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<tbody>
<tr>
<td><strong>Cured</strong></td>
<td>73 (74.5%)</td>
</tr>
<tr>
<td><strong>Treatment completion</strong></td>
<td>12 (12.2%)</td>
</tr>
<tr>
<td><strong>Lost to follow up</strong></td>
<td>3 (3.1%)</td>
</tr>
<tr>
<td><strong>Transferred out</strong></td>
<td>4 (4.1%)</td>
</tr>
<tr>
<td><strong>Death and failure</strong></td>
<td>5 (5.1%) and 1 (1%)</td>
</tr>
</tbody>
</table>
• N=98
• Actual received dose: 750-1000 mg
• Simulated doses: 1250 mg once daily 1500 mg once daily
ADDED BENEFITS OF TDM

PTA: additional 39%

PTA: additional 48%

PTA: additional 87%

MIC = 1 mg/L

1500 mg

1250 mg

750-1000 mg

ADDED BENEFITS OF TDM (n=98)
What next?

• Need for increased dosages
• Even on higher dosages, concentration of anti-TB drugs will vary between individuals -> scope for TDM
• Quantitative drug susceptibility testing
• AUC/MIC associated with clinical cure
Conclusions

• Timely TDM will enable adequate target attainment
• An equal platter of proactive TDM and quantitative drug susceptibility testing is needed for TB treatment individualization
  – Also in higher Lfx dosages
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THANK YOU FOR YOUR ATTENTION