Clofazimine pharmacokinetics in drug-resistant TB

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Inconsistent activity against Mtb in animal models
Weird PK
Toxicity
Other more potent drugs

1957
Discovery

1997
“Clofazimine has no place in the treatment of MDR-TB” – WHO

2006 – 2011
No recommended for routine use
Treatment with Group 5 drugs is recommended only if additional drugs are needed to bring the total to four.

2010
Bangladesh
Other observational data

2015
Small RCT
STREAM-1

< 10 years

Everywhere

Lepromatous leprosy

Early 2000’s
Small observational studies for MDR-TB
Part of multidrug regimen

50 years
## Rapid Communication:

**Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB)**

<table>
<thead>
<tr>
<th>GROUP</th>
<th>MEDICINE</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A:</strong> Include all three medicines (unless they cannot be used)</td>
<td>Levofloxacin OR Moxifloxacin &amp; Bedaquiline &amp; Linezolid</td>
<td>Lfx Mfx Bdq Lzd</td>
</tr>
<tr>
<td><strong>Group B:</strong> Add both medicines (unless they cannot be used)</td>
<td>Clofazimine &amp; Cycloserine OR Terizidone</td>
<td>Cfz Cs Trd</td>
</tr>
<tr>
<td><strong>Group C:</strong> Add to complete the regimen and when medicines from Groups A and B cannot be used</td>
<td>Ethambutol OR Delamanid &amp; Pyrazinamide &amp; Imipenem-cilastatin OR Meropenem &amp; Amikacin (OR Streptomycin) &amp; Ethionamide OR Prothionamide &amp; p-aminosalicylic acid</td>
<td>E Dlm Z Ipm-Cln Mpm Am (S) Eto Pto PAS</td>
</tr>
</tbody>
</table>
Activity

- Riminophenazine pigment derived from lichen
- Likely membrane-destabilizing agent
- *In vitro* activity against Mtb
  - MIC ≤ 0.25 µg/mL
  - More potent against slow-growing Mtb
- Anti-inflammatory effects
No observed EBA in DS-PTB patients

- Is the delay related to the need for depletion of energy stores?
- Does it reflect dominant activity on slow persister phenotypes?
- Limitations of EBA to predict sterilizing ability
Treatment shortening potential and potent sterilizing ability in BALB/c mice

With first line therapy

With second line therapy

No additive effect in first week, regardless of dose or concentration

Tyagi PNAS 2015
Grosset Am J Respir Crit Care Med 2013
Unusual PK

- Massive intracellular accumulation in organs (CLDIs)
- Extremely long half-life

The data of Tables 3 and 4 show that less than 1% of the body’s content of B663 is excreted per day. Therefore, the $t_{\frac{1}{2}}$ of B663 in man is greater than 69 days. At this rate of excretion, one may readily calculate that the patient receiving 100 mg B663 daily will accumulate 10 gm of the drug if this dosage is administered indefinitely. The $t_{\frac{1}{2}}$ of B663 for man is probably considerably longer than the minimal estimate of 69 days, and the quantity accumulated proportionately greater than 10 g for a 100-mg daily regimen.
Accumulates in macrophages

Penetration into macrophages but not caseum

Very low plasma concentrations
Accumulates in macrophages
Efficacy could be related to serum concentrations

Sustained antimicrobial activity associated with time serum concentration remained $\geq$ MIC (0.24 $\mu$g/mL)

Serum clofazimine levels appear critical to antimicrobial activity
Adverse events: skin changes and potent QT effects

Most frequent AE (universal)
- Can occur within 2 weeks
- Suicides reported as a result of skin changes

How are these related to drug exposures (PK variability)?

QT prolongation
- Clinical implications?
- Are there PK/PD interactions with other TB drugs?
High PK variability in healthy volunteers

Bioavailability influenced by food
Very low plasma concentrations
PK data from patients with drug-resistant TB
Importance of understanding clofazimine PK

• PK variability of antituberculosis agents associated with adverse treatment outcomes and emergent resistance
• Exposures may be different in our population
  • HIV
  • Genetics
  • Clinical factors
  • DDIs
• Estimating probability of achieving PK/PD targets may inform dose optimization
Aims of non-compartmental analysis

1. Describe the pharmacokinetics of clofazimine in a population of patients with drug-resistant TB in SA
2. Explore effect of key covariates on exposures
Methods

Open-label prospective PK study nested in observational cohort:

**PROBeX – James Brust**

Safety, PK, and resistance to bedaquiline in pre-XDR, XDR-TB and HIV
Age > 18, DR-TB, HIV and pregnancy included
220 participants, followed for 24 months

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![Diagram](image)
Methods

Single intensive PK visit at after observed dose and standardized meal

Non-compartmental analysis
• PK parameters
• Linear regression to determine associations with AUC$_{0-24}$
## Patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>n = 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>29 (25 – 44)</td>
</tr>
<tr>
<td>Male sex</td>
<td>11 (50)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>55.2 (48.0 – 64.8)</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>42.0 (38.4 – 47.9)</td>
</tr>
<tr>
<td>Percentage fat, %</td>
<td>22.9 (12.4 – 37.2)</td>
</tr>
<tr>
<td><strong>BMI, kg/m(^2)</strong></td>
<td><strong>19.1 (17.5 – 24.5)</strong></td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>38 (35 – 40)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>6 (27)</td>
</tr>
<tr>
<td>Mixed</td>
<td>16 (73)</td>
</tr>
<tr>
<td>HIV positive</td>
<td>9 (41)</td>
</tr>
<tr>
<td>Current ART</td>
<td>9 (100)</td>
</tr>
<tr>
<td>Current LPV/r</td>
<td>4 (44)</td>
</tr>
<tr>
<td>Creatinine, µmol/L</td>
<td>58 (52 – 71)</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
<td>115 (100 – 138)</td>
</tr>
<tr>
<td><strong>Duration on clofazimine, days</strong></td>
<td><strong>71 (62 – 80), range (18 – 97)</strong></td>
</tr>
<tr>
<td>Dose, mg/kg</td>
<td>1.8 (1.5 – 2.1)</td>
</tr>
</tbody>
</table>

Body fat significantly higher in women: 37.1% vs 12.8% in men  
\(p < 0.0001\)
Concentration-time profiles
# PK parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC(_{0-24}) (µg.h/mL)(^\wedge)</th>
<th>AUC(_{0-\infty}) (µg.h/mL)*</th>
<th>C(_{\text{max}}) µg/mL</th>
<th>T(_{\text{max}}) (h)</th>
<th>T(_{1/2}) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>22</td>
<td>17#</td>
<td>22</td>
<td>22</td>
<td>17#</td>
</tr>
<tr>
<td>Median</td>
<td>7.673</td>
<td>28.659</td>
<td>0.401</td>
<td>4</td>
<td>53.5</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>6.015 – 10.858</td>
<td>17.605 – 36.801</td>
<td>0.337 – 0.548</td>
<td>3 - 5</td>
<td>31.2 – 75.4</td>
</tr>
<tr>
<td>%CV</td>
<td>41.7</td>
<td>171.2</td>
<td>39.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^\wedge\) AUC calculated by trapezoidal method;
*Calculated using an exponential extension from the last point of AUC\(_{0-24}\);

* Not calculated for patients in whom the clofazimine concentration was either increasing or not decreasing at the last sampling time point

Higher exposures but similar C\(_{\text{max}}\) to healthy volunteers

**Similar absorption but lower weight in TB patients?**

Higher exposures compared to EBA study

**Longer duration of therapy**
## Predictors of $AUC_{0-24}$: not significant

<table>
<thead>
<tr>
<th>Predictor</th>
<th>$AUC_{0-24}$ change % (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[e^{(\beta)} - 1] \times 100$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>$-12.0$ (-26.5 to 5.3)</td>
<td>0.152</td>
</tr>
<tr>
<td>Black African</td>
<td>$-18.3$ (-48.1 to 28.7)</td>
<td>0.365</td>
</tr>
<tr>
<td>HIV positive</td>
<td>$-14.4$ (-43.5 to 29.4)</td>
<td>0.441</td>
</tr>
<tr>
<td>Current LPV/r</td>
<td>$14.3$ (-32.9 to 94.6)</td>
<td>0.607</td>
</tr>
<tr>
<td>Creatinine, µmol/L</td>
<td>$-0.7$ (-2.2 to 0.8)</td>
<td>0.336</td>
</tr>
<tr>
<td>Duration on clofazimine Per 30 days</td>
<td>$5.8$ (-26.9 to 53.0)</td>
<td>0.754</td>
</tr>
</tbody>
</table>
## Predictors of \( AUC_{0-24} \): significant

<table>
<thead>
<tr>
<th>Predictor</th>
<th>( e^{(\beta)} - 1 ) *100</th>
<th>( AUC_{0-24} ) change % (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>65.5 (17.8 to 132.6)</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>-16.2 (-28.6 to -1.8)</td>
<td>0.031</td>
<td></td>
</tr>
<tr>
<td>Per 10 kg increase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage body fat</td>
<td>-19.4 (-28.8 to -8.7)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Per 10% increase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>-4.9 (-7.9 to -1.7)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>-3.9 (-7.9 to 0.4)</td>
<td>0.071</td>
<td></td>
</tr>
<tr>
<td>Dose, mg/kg</td>
<td>66.2 (-3.0 to 184.9)</td>
<td>0.063</td>
<td></td>
</tr>
</tbody>
</table>
### Predictors of AUC\textsubscript{0-24}

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariable</th>
<th>P value</th>
<th>Multivariable</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>([e^\beta - 1] \times 100) AUC\textsubscript{0-24} change % (95% CI)</td>
<td>P value</td>
<td></td>
<td>AUC\textsubscript{0-24} change % (95% CI)</td>
<td>P value</td>
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<td>Age</td>
<td>-12.0 (-26.5 to 5.3)</td>
<td>0.152</td>
<td>-11.4 (-22.3 to 1.1)</td>
<td>0.069</td>
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<td>0.002</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>-3.9 (-7.9 to 0.4)</td>
<td>0.071</td>
<td>-3.3 (-6.5 to 0.03)</td>
<td>0.048</td>
</tr>
<tr>
<td>HIV positive</td>
<td>-14.4 (-43.5 to 29.4)</td>
<td>0.441</td>
<td></td>
<td></td>
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<tr>
<td>Current LPV/r</td>
<td>14.3 (-32.9 to 94.6)</td>
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<tr>
<td>Creatinine, (\mu)mol/L</td>
<td>-0.7 (-2.2 to 0.8)</td>
<td>0.336</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration on clofazimine</td>
<td>5.8 (-26.9 to 53.0)</td>
<td>0.754</td>
<td>23.0 (-5.2 to 59.7)</td>
<td>0.112</td>
</tr>
</tbody>
</table>

Similar findings for \(C_{\text{max}}\)
Limitations

• Sampling not designed around clofazimine PK
• Single sampling occasion – cannot determine intra-individual variability
• Varying durations on therapy
• Not at steady state (would be around 6 months)
• No observed dosing at 24 hours – uncertain trough concentrations
Conclusions and research priorities

• First PK study of clofazimine in patients with drug-resistant TB and HIV
• High PK variability
• Exposure not influenced by HIV, strongly influenced by body fat
• Plasma exposures of some patients below WT MIC and all below CC: what are the implications?

Next steps
• Integrate sparse PK data into a population PK model
• Explore exposure-response relationships (efficacy and toxicity)
• Understand toxicity better: quantify skin changes, independent effect on QT
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