Influence of Bacterial Growth Rate on Dose Optimization of Linezolid for Treatment of Tuberculosis

Kristina Bigelow
Johns Hopkins University School of Medicine
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Linezolid

• Recently added to WHO's 2nd line approved anti-TB agents
• Demonstrated efficacy as a salvage agent (Lee et. al, NEJM, 2012)
  • XDR-TB: LZD 300-600mg added to failing regimen
    • 87% sputum conversion after 6 months of LZD
    • 31 out of 38 patients had severe adverse events
      • Myelosuppression, peripheral neuropathy

• Component of novel “pan-TB” regimen (Conradie et al, CROI, 2017)
  • Pretomanid 200mg + Bedaquiline 200mg + LZD 1200mg x 6 months
    • Of first 34 pts completing treatment, 74% culture-negative at 8 wks (all negative at 16 wks)
    • Of first 20 pts completing 6 months of follow-up after treatment, only 1 relapse reported
    • 24 out of 33 had severe adverse events
      • Myelosuppression, peripheral neuropathy
LZD dose optimization

What PD parameter correlates best with LZD bactericidal effect?
- *In vitro* hollow fiber system, normal media (LZD, SZD) $T_{>\text{MIC}}^1$
- *In vitro* hollow fiber system, acidified media (LZD) $\text{AUC}/\text{MIC}^2$
- Mouse model (LZD, SZD, AZD) $\text{AUC}/\text{MIC}^{3,4}$

What TD parameter correlates best with LZD mitochondrial toxicity?
- *In vitro* hollow fiber system (LZD) $C_{\text{min}}^1$
- Clinic (LZD) $C_{\text{min}}^{5-8}$

5. Cattaneo et al, IJAA 2013; 41:586
6. Pea et al, JAC 2012; 67:2034
7. Matsumoto et al, IJAA 2014;44:242
8. Song et al, EBiomed 2015; 2:1627
Hypothesis

Under certain conditions less frequent administration of the same total dose will maximize bactericidal effects while minimizing toxicity.

If this is true then:

Dosing LZD at 1200 mg q48 hr will preserve efficacy (while reducing toxicity) compared to 600 mg q24 hr and 300 mg q12 hr.
Questions to be answered

• What is the effect of different linezolid dosing schedules on bacterial killing and selection of drug-resistant mutants?

• Does the PK/PD parameter that best correlates with efficacy differ against different “growth states” of *Mtb*?

<table>
<thead>
<tr>
<th></th>
<th>Log phase growth</th>
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<th>No net growth (induced by companion drug)</th>
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*Constraints in the in vitro system are imposed by achieving the stationary phase of culture. Constraints in the in vivo system are imposed by the onset of adaptive immune response.*
I. *In-vitro* Pharmacodynamics/Pharmacokinetics (IVPD) system
Linezolid PK/PD Parameters in IVPDS expts.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Cmax (µg/mL)</th>
<th>AUC (µg*h/ml)</th>
<th>%Time/MIC</th>
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<tbody>
<tr>
<td>300mg q12hr</td>
<td>7.95</td>
<td>180</td>
<td>92</td>
</tr>
<tr>
<td>600mg q24hr</td>
<td>13.71</td>
<td>173</td>
<td>67</td>
</tr>
<tr>
<td>1200mg q48hr</td>
<td>27.42</td>
<td>176</td>
<td>29</td>
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</table>
Effect of linezolid dose fractionation against log phase growth in the IVPD system

Effect of linezolid dose fractionation against log phase growth in the IVPD system

- Untreated
- 300mg q12hr
- 600mg q24hr
- 1200mg q48hr

Log cfu/mL Day 0
- Control = 6.68 ± 0.64

Δ log cfu/mL (Day 0 → Day 14)
- 1200mg q48hr = -2.09 ± 1.14
- 600mg q24hr = -2.62 ± 0.85
- 300mg q12hr = -3.58 ± 0.49
Effect of linezolid dose fractionation against a no-growth state imposed by companion drugs in the IVPD system

Log cfu/mL Day 0
- Control = 7.78

Difference log cfu/mL Day 14
- 1200mg q48hr = 4.72 ± 0.33
- 600mg q24hr = 4.74 ± 0.36
- 300mg q12hr = 5.05 ± 0.1
Questions to be answered

- What is the effect of different linezolid dosing schedules on bacterial killing and selection of drug-resistant mutants?
- Does the PK/PD parameter that best correlates with efficacy differ against different “growth states” of *Mtb*?

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<td>Time above MIC</td>
<td>AUC/MIC</td>
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II. *In-vivo* Mouse Studies
Effect of linezolid dose fractionation in a log phase growth TB infection model in BALB/c mice

Dosing frequency and # of weekly doses
- 3 doses/week
- 5 doses/week
- 10 doses/week
- 14 doses/week
- No treatment

Total dose per week
- 100 mg/kg
- 300 mg/kg
- 1000 mg/kg

Log_{10} CFU/lung

Day 0
Effect of linezolid dose fractionation in a no net growth TB infection model in BALB/c mice

Dosing frequency and # of weekly doses
- 3 doses/week
- 5 doses/week
- 7 doses/week
- 14 doses/week
- No treatment

Log₁₀ CFU/lung

Total dose per week
- No Treatment
- 100 mg/kg
- 300 mg/kg
- 1000 mg/kg

Day 0

INH (Control)
Rifampin (Control)
LZD (Control)
Rifampin + Ethambutol
Questions to be answered

• What is the effect of different linezolid dosing schedules on bacterial killing and selection of drug-resistant mutants?

• Does the PK/PD parameter that best correlates with efficacy differ against different “growth states” of *Mtb*?

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*Constraints in the in vivo system are imposed by the onset of adaptive immune response*
Effect of linezolid dose fractionation in a slow growth TB infection model induced by pretomanid (Pa) 12.5 mpk/day
Effect of linezolid dose fractionation in a no net growth TB infection model induced by Pa 50 mpk/day

- **3 doses/week**
- **5 doses/week**
- **7 doses/week**
- **14 doses/week**

**Dosing frequency and # of weekly doses**
- 3 doses/week
- 5 doses/week
- 7 doses/week
- 14 doses/week
- No treatment

**Log$_{10}$ CFU/lung**

- **No Treatment**
- **Control**
- **Total dose per week**

**PA**
- 100 mg/kg
- 300 mg/kg
- 1000 mg/kg

**INH (Control)**

**Rifampin (Control)**

**LZD (Control)**
Comparison of dose fractionation studies in mice

Dosing frequency and 
# of weekly doses
- 3 doses/week
- 5 doses/week
- 7 doses/week
- 14 doses/week
- No treatment

No treatment

Log phase growth

Slow growth

No growth due to companion agent

No net growth
Questions to be answered

• What is the effect of different linezolid dosing schedules on bacterial killing and selection of drug-resistant mutants?

• Does the PK/PD parameter that best correlates with efficacy differ against different “growth states” of *Mtb*?

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*Constraints in the in vivo system are imposed by the onset of adaptive immune response*
Effect of linezolid dose fractionation on **selective amplification of resistance** during log phase growth in the IVPD system.
### Interim Conclusions

- Under net growth conditions, efficacy driver is likely Time above MIC.
- Under no net growth conditions, efficacy driver is likely AUC/MIC.
- $C_{\text{max}}$ appears to drive LZD resistance suppression.
- Taken together, these data suggest that:
  - When Mtb is actively replicating (e.g., early in treatment, with weak companion drugs), more frequent dosing to maintain adequate T>MIC may be beneficial.
  - When growth is restrained (e.g., with active companion drugs), the same total dosage delivered in higher, less frequent doses (e.g., q48 hrs) should achieve similar anti-TB effect while minimizing risk of trough-driven toxicity and selection of LZD resistance.

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Future Aims

• Replicate IVPDS experiments, using higher and lower drug exposures to account for population-level PK variability

• Perform PK/PD analyses to confirm target parameters for dose optimization

• Adopt toxicodynamic model using K562 cells to study mitochondrial toxicity in IVPD system

• Extend studies to novel TB-focused oxazolidinones in development with reduced MPS inhibition potential
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