Pharmacokinetics and pharmacodynamics of TB drugs: Prospects for improving TB therapy

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What’s wrong with TB therapy?

• 6 months is not “short-course”
• Only a minority of pts completes TB therapy in 6 mos
  – < 90% complete in 12 months
• Adverse drug reactions cause morbidity & mortality
• Drug-drug interactions
• Resistance happens

Better understanding and application of PK/PD science can help

Basic concepts

• Pharmacokinetics (PK): the study of what a body does with a dose of a drug
  – Absorption, Distribution, Metabolism, Excretion
  – Endpoints: AUC, Cmax, Tmax, half-life, Cmin, Cl, Vd

• Pharmacodynamics (PD): the study of what a drug does to the body
  – Endpoints: measures of efficacy (eg, CFU) or toxicity
PK/PD modeling
Examining the correlation between PK and drug effect (PK/PD)

Utility of PK/PD modeling
- Identify PK/PD parameter best linked to efficacy
- Identify target drug exposures for desired efficacy
- Estimate therapeutic window and/or identify strategies to divorce efficacious doses from toxic doses
- Select most effective dose for population
- Identify breakpoint for drug susceptibility testing

Which PK/PD parameter is linked to efficacy?
The dose fractionation paradigm
- **Principle:** for a given daily dose, the *shape* of the conc-time curve may determine the effect
- **Goal:** determine which PK/PD parameter(s) correlate best with efficacy
- **Challenge:** since PK/PD parameters are co-linear with dose, dose escalation alone will not suffice
- **Solution:** fractionation of doses
Which PK/PD parameter is linked to efficacy?
the dose fractionation paradigm

- **Principle:** for a given daily dose, the *shape* of the conc-time curve may determine the effect
- **Goal:** determine which PK/PD parameter(s) correlate best with efficacy
- **Challenge:** since PK/PD parameters are co-linear with dose, dose escalation alone will not suffice
- **Solution:** fractionation of doses

Identifying the PD-linked parameter:
the dose fractionation paradigm

- **Procedure:**
  - Estimate time-course of drug exposure (PK)
  - Examine correlation between time-course of drug exposure (PK) and drug effect (PD)
- **Purpose:**
  - Estimate therapeutic window (dose-response)
  - Select most effective dose(s)
  - Identify breakpoints for drug susceptibility testing

A classic example

*Time above MIC has best correlation with bactericidal effect for all β-lactams*

Concept of “portability”

Established PK/PD relationships should be translatable from:
- Pre-clinical models to humans
- One site of infection to another
- One member of the same drug class to another
- One bacterial strain to another strain or mutant with differing drug susceptibility

What PK/PD parameter best correlates with INH activity?

AUC/MIC has best correlation with bactericidal effect

Jayaram et al, AAC 2004; 48:2951

“Portability” of INH PK/PD relationships across TB models

<table>
<thead>
<tr>
<th>Model</th>
<th>EC50 for efficacy of INH (AUC/MIC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hollow fiber system (HFS)</td>
<td>62</td>
</tr>
<tr>
<td>Mouse</td>
<td>63</td>
</tr>
<tr>
<td>Human</td>
<td>40*</td>
</tr>
</tbody>
</table>

*assumes MIC of 0.03 ug/ml, as for H37Rv

Adapted from Gumbo et al, AAC, 2007
Pharmacodynamics of INH activity in mouse and man

Jayaram et al, AAC 2004
Donald et al, AJRCCM 1997

Target attainment and PK/PD-derived breakpoints for INH DST

Gumbo, AAC 2010; 54:1484

Estimating target attainment for optimal dose selection

- Monte Carlo simulations based on HFS-TB data indicated fast acetylators of INH will not achieve max EBA at 5 mpk dose
- Increasing INH dose from 5 to 10 mg/kg would increase the % of fast acetylators achieving EC90 from 33% to 100%

Gumbo et al, AAC 2007/51:2329
Population PK variability (INH)

- INH PK variability is largely (≥88%) determined by NAT status
- Rapid acetylators (RA) more likely to:
  - miss plasma AUC target for max EBA
  - fail therapy (esp. intermittent therapy)
  - acquire DR-TB
  - relapse (non-significant)
- Slow acetylators (SA) more likely to:
  - develop neuropathy
  - develop hepatotoxicity
- A rapid POC NAT test could enable optimized dosing


Pharmacogenetics-guided INH dosing

- Open-label, blinded endpoint RCT of STD vs. PG-guided dosing in Japan
- PG-guided dosing according to INH acetylator genotype:
  - Slow (SA): 150 mg
  - Intermediate: 300 mg
  - Rapid (RA): 450 mg
- Among SA genotypes, PG-guided grp had:
  - Less DILI (0 vs. 78%; p=0.003)
  - Less neuropathy (0 vs. 2 cases)
  - Less 8wk Crx+ (0 vs. 22%; p=NS)
- Among RA genotypes, PG-guided grp had:
  - Low DILI (4%), like STD arm
  - Less 8wk Crx+ (15% vs. 39%; p=0.013)


Current use of rifampin and the case for PK/PD-based optimization

Dose-response in humans

RIF dose  | log CFU/mg/day
---------|----------------
200 mg   | 3.096
300 mg   | 1.567
600 mg   | 0.19

In combination therapy with INH:
- RIF doses <9 mg/kg assoc w/ sputum Crx+ at 8, 16 and 20 wks
- 19% of pts administered 600 mg received <9 mg/kg

Jayaram et al, AAC (2003); 47:2118
Exposure-response curve for a TB drug

Inferiority of intermittent regimens
Reduced efficacy due to reduced rifamycin exposure

- Systematic review of clinical trials of short-course regimens

<table>
<thead>
<tr>
<th>Frequency of Initial Phase Therapy</th>
<th>Freq. of Continuation Phase Therapy</th>
<th>Odds of Relapse vs. Daily Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td>Daily</td>
<td>1.0</td>
</tr>
<tr>
<td>Daily</td>
<td>3x/wk</td>
<td>1.6 (0.6 - 4.1)</td>
</tr>
<tr>
<td>Daily</td>
<td>2x/wk</td>
<td>2.8 (1.3 - 6.1)</td>
</tr>
<tr>
<td>3x/wk</td>
<td>3x/wk</td>
<td>2.9 (1.4 - 6.1)</td>
</tr>
</tbody>
</table>

Chang et al, AJRCCM (2006); 174:1153

Population PK variability (RIF)

- Determinants
  - Genetic differences in drug transporter enzymes
  - Patient-specific characteristics
  - Large body mass
  - Diabetes mellitus
  - HIV infection
  - Food effect and other causes of dose-to-dose variability
  - Non-dose-proportional PK

[References]
Drug (2002) 62:2169
Rifamycin exposure-response in humans

**RIF dose-response**

Boeree et al., Am J Respir Crit Care Med (2015); 191:1058

**RPT exposure-response**

Heinrich et al., Lancet Infect Dis (2017); 17:39

Therapeutic drug monitoring (TDM) to ensure adequate RIF conc. among diabetic (DM+) pts in Va

- DM previously associated\(^1\) with:
  - slow response to TB Rx
  - lower RIF \(C_{\text{in}}\)
- 2013 intervention\(^2\):
  - All pts with DM (A1c \(\geq 6.5\)) have RIF \(C_{\text{in}}\) determined after 2 wks of treatment
  - If [RIF] < 6-24 μg/ml, increase dose to 900 mg
- Results\(^3\) after matching for basic demographics, cavitation, smear:
  - DM+ converted faster post-intervention vs. pre-intervention (42 vs. 62 days; \(p=0.01\))
  - and were less likely to be Cav+ at 8 wks (20% vs. 50%; \(p=0.04\))
  - post-intervention DM+ pts converted faster than DM- pts (42 vs. 57 days; \(p=0.08\))

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Low INH exposures assoc. with acquired rifamycin resistance (TBTC Study 22)

- Among HIV+ pts receiving once-weekly HP:
  - Relapse in 5/30 (17%)
  - 4 of 5 with acquired rifamycin monoresistance (ARR)
  - 3 of 4 had CD4 ct \(< 25\)
- One HIV-neg pt in RH\(2/7\) arm developed ARR
- Both ARR patients with PK sampling performed had low INH exposures

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\(^1\) Emerg Infect Dis (2010); 16:1546
\(^3\) BMC Infect Dis (2017); 17:125
Low INH, RBT exposures linked to failure, ARR (TBTC Study 23)

- Among HIV+ pts receiving twice-weekly RBT-based Rx:
  - Failure/relapse in 5.3%
  - 8 of 9 with acquired rifamycin resistance (ARR)
- Low RBT and INH exposures were associated with ARR


PK variability and acquired drug resistance

- RIF exposure associated with lack of kill (risk of AHR) in HFS-TB
  - AUC < 13.1 mg-h/L
- Monte Carlo simulation of 10,000 S. African pts receiving standard therapy
  - 0.68% would develop AHR, followed by MDR-TB

Srivastava et al, J Infect Dis (2011); 204:1981

Please Note:
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**PK variability and acquired drug resistance**

- RIF exposure associated with lack of kill (risk of AHR) in HFS-TB
  - AUC < 13.1 mg/h/L.
- Monte Carlo simulation of 10,000 S. African pts receiving standard therapy
  - 0.88% would develop AHR, followed by MDR-TB.
- Later study of 142 S. African pts w/DS-TB
  - One-third had RIF AUC < 13 mg/L.
  - 0.7% developed ADR (each with low RIF exposures).

Table 4: Pharmacokinetic Parameters in Patients Who Developed Acquired Drug Resistance

<table>
<thead>
<tr>
<th>Patient</th>
<th>Effect</th>
<th>AUC (mg/L)</th>
<th>Dose (mg/L)</th>
<th>Treatment Period</th>
<th>When RIF Detected</th>
<th>Type of ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>First 2 mo</td>
<td>0.98</td>
<td>25.96</td>
<td>First 2 mo</td>
<td>intermittent</td>
<td>intermittent</td>
</tr>
<tr>
<td>2</td>
<td>3 mo</td>
<td>7.61</td>
<td>8.86</td>
<td>30.96</td>
<td>3 mo</td>
<td>intermittent</td>
</tr>
<tr>
<td>3</td>
<td>3 mo</td>
<td>7.34</td>
<td>8.86</td>
<td>30.96</td>
<td>3 mo</td>
<td>intermittent</td>
</tr>
</tbody>
</table>

Srivastava et al, J Infect Dis (2011); 204:1921
Pasipanodya et al, J Infect Dis (2013); 208:1454

**Caseous necrosis and cavitation in C3HeB/FeJ mice**

- Caseating granuloma
- Cavity

Please Note:
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Conclusions re: INH and RIF

• Although activity of both drugs is driven by AUC/MIC, the approach to dose optimization is different
  – Optimal INH exposures could be safely obtained in the vast majority (rather than the minority) of pts if the acetylation genotype is known or TDM is performed
  – Optimal RIF exposures are not obtained in any patient at current doses, but it is possible to avoid sub-therapeutic exposures through dose escalation or targeted TDM

• The failure to optimize INH and RIF dosing is likely responsible for:
  – the current 6-month (and often longer) duration of TB treatment
  – the need to continue treatment beyond 6 months for many pts
  – the emergence of MDR/XDR-TB

Pyrazinamide (Z)
A unique sterilizing drug

Activity is pH-dependent in vitro, requiring acidic conditions for anti-TB activity at concentrations achievable in patients

EBA_{0,20} but EBA_{2,14d} = 0.03-0.11 logCFU/ml/d

Shortens treatment duration in the 1st-line regimen, but exerts all of its effect in the first 2 months

**Implication:**

Z exerts its greatest sterilizing activity against specific sub-population(s) of persisting bacteria of finite size residing in an acidic milieu which are not as susceptible to other anti-TB drugs.

PZA activity is a function of pH

<table>
<thead>
<tr>
<th>Median pH</th>
<th>PZA</th>
<th>IPDA (%)</th>
<th>Theoretical PZA MIC (mg/L)</th>
<th>Actual PZA MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5</td>
<td>30.4</td>
<td>2.5</td>
<td>5</td>
<td>NT</td>
</tr>
<tr>
<td>4.0</td>
<td>79.4</td>
<td>1.36</td>
<td>15</td>
<td>NT</td>
</tr>
<tr>
<td>5.0</td>
<td>123.0</td>
<td>0.8</td>
<td>16</td>
<td>NT</td>
</tr>
<tr>
<td>5.5</td>
<td>508.1</td>
<td>0.35</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>5.8</td>
<td>794.3</td>
<td>0.13</td>
<td>130</td>
<td>100</td>
</tr>
<tr>
<td>6.0</td>
<td>1250.0</td>
<td>0.08</td>
<td>156</td>
<td>200</td>
</tr>
<tr>
<td>6.8</td>
<td>794.3</td>
<td>0.033</td>
<td>992</td>
<td>1099</td>
</tr>
<tr>
<td>7.0</td>
<td>1250.0</td>
<td>0.008</td>
<td>1563</td>
<td>&gt;1000</td>
</tr>
</tbody>
</table>

Zhang et al, J Med Microbiol 2002
PZA PK/PD in non-clinical models

- AUC/MIC correlates best with activity\(^1\)
- Increasing current dose by 2-4x increases kill rate\(^1,2\)
- AUC associated with a -0.11 CFU/day reduction:
  - Hollow fiber system = 1500 µg-h/ml\(^1\)
  - BALB/c mouse = 323 µg-h/ml\(^2\)
- More potent effect of PZA in mice is likely due to lower pH (≤ 5) inside mature phagosomes of activated macrophages\(^1\) vs. that in the HFS-TB (5.8)

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Dichotomous activity of PZA in C3HeB/FeJ mice

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Differential drug distribution into TB lesions

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\(^1\) Gumbo et al. AAC (2009); 53:3197
\(^2\) Lanoix et al. AAC (2016); 60:735
\(^3\) Vandal et al. Nat Med 2008; 14:689
Neutral pH of liquefied caseum

- 13 liquefied lesions tested with needle probe:
  - pH = 7.39 ± 0.096 (range [7.19 - 7.54])

Lanoix et al, AAC (2016); 60:735

pH of caseum in other species

### Rabbits

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>pH</th>
<th>Lesion Type</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagram</td>
<td>6.1</td>
<td>Diagram</td>
<td>7.4</td>
</tr>
<tr>
<td>Diagram</td>
<td>≥ 6.8</td>
<td>Diagram</td>
<td>≤ 7.4</td>
</tr>
</tbody>
</table>

### Humans

1. In resected cavity tissue homogenates, the pH ranged from 6.1 to 7.4. However, it was ≥ 6.8 in 15 of 17 lesions
2. In resected cavity tissue from 9 refractory MDR-TB pts, the pH was < 5.5 in 7 lesions and > 7.0 in 2 lesions (the only 2 Cx+ specimens)

Weiss et al, Arch Pathol 1954; 57:179
Weiser and Dye, 1956
Kempker et al, Antimicrob Agent Chemother 2017; epublished

PZA (Z) is relatively ineffective in immunocompromised mice

Almeida et al, Mycobact Dis 2014; 4:145
Conclusions re: PZA

- PZA activity is driven by AUC/MIC, but the MIC depends on the local pH
- Thus, despite its free diffusion into caseous lesions, PZA activity may vary by lesion type, location in lesion and immune status
- PZA exerts its greatest sterilizing activity inside macrophages, where pH may be 4.5-5.5, and not in acellular caseum, which is not sufficiently acidic to enable full PZA activity, even at high drug exposures
- The compartmentalized sterilizing effect of PZA means that it may have reduced sterilizing activity in advanced HIV and limited ability to prevent selection of mutants resistant to companion agents
- Nevertheless, returning to PZA doses of 35 mg/kg would be expected to increase sterilizing effect

Linezolid for MDR/XDR-TB

Lee et al, NEJM (2012); 367:16

Efficacy
Toxicity
Resistance selection
**LZD dose-response in TB models**

- **Human EBA<sub>0-14d</sub>**
  - Brown et al, mBio 2015; 6:e01741

- **Hollow fiber model**
  - Brown et al, mBio 2015; 6:e01741

**Targets for LZD dose optimization**

- **Bactericidal effect**
  - What PD parameter correlates best w/LZD bactericidal effect?
    - In vitro hollow fiber system, normal media (LZD, SZD) T < MIC, AUC/MIC<sup>3, 4</sup>
    - In vitro hollow fiber system, acidified media (LZD) AUC/MIC<sup>4</sup>
    - Mouse model (LZD, SZD, AZD) T > MIC, AUC/MIC<sup>5, 6</sup>

- What AUC/MIC target is associated w/LZD bactericidal effect?
  - In vitro hollow fiber system, normal media fAUC/MIC of 80-100<sup>2, 3, 7</sup>
  - In vitro hollow fiber system, acidified media fAUC/MIC of 52<sup>4</sup>
  - Chronic mouse model fAUC/MIC of 85-170<sup>5, 6, 8</sup>

### Targets for LZD dose optimization

**Bactericidal effect**

- What PD parameter correlates best w/LZD bactericidal effect?
  - In vitro hollow fiber system, normal media (LZD, SZD) \( T_{\text{MIC}} \times \text{AUC/MIC}^{1,8} \)
  - In vitro hollow fiber system, acidified media (LZD) \( \text{AUC/MIC}^{2} \)
  - Mouse model (LZD, SZD, AZD) \( T_{\text{MIC}} \times \text{AUC/MIC}^{3,4} \)

- What AUC/MIC target is associated w/LZD bactericidal effect?
  - In vitro hollow fiber system, normal media \( f\text{AUC/MIC} \) of 80–100\(^{2,3,7}\)
  - In vitro hollow fiber system, acidified media \( f\text{AUC/MIC} \) of 52\(^{4}\)
  - Mouse model (LZD, SZD, AZD) \( T_{\text{MIC}} \times \text{AUC/MIC} \) of 85–170\(^{5,6,8}\)


### LZD target attainment by dose

- Assuming target is free drug AUC/MIC of 80–100\(^{1-4}\)
  - this target may be achieved by some TB pts on 300 mg/d, most pts on 600 mg/d & virtually all pts on 900–1200 mg/d (Table)\(^{1-8}\)

<table>
<thead>
<tr>
<th>LZD dose</th>
<th>( C_{\text{max}} ) (range)</th>
<th>( C_{\text{min}} ) (range)</th>
<th>AUC(_{0-24\text{h}} ) (range)</th>
<th>( f\text{AUC/MIC} ) (IQR or SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg qd</td>
<td>11.4 (7.2-18.0)</td>
<td>2.1 (0.9-3.4)</td>
<td>116 (76-194)</td>
<td>2.1 (0.8-3.4)</td>
</tr>
<tr>
<td>300 mg bid</td>
<td>9.5 (7.7-10.1)</td>
<td>1.9 (0.6-2.2)</td>
<td>116 (76-194)</td>
<td>2.1 (0.8-3.4)</td>
</tr>
<tr>
<td>600 mg qd</td>
<td>15.1 (11.9-21.3)</td>
<td>9.7 (6.1-14.6)</td>
<td>160 (91-231)</td>
<td>2.1 (0.9-3.4)</td>
</tr>
<tr>
<td>600 mg bid</td>
<td>20.4 (18.3-21.9)</td>
<td>9.6 (7.7-13.8)</td>
<td>233 (180-322)</td>
<td>2.1 (0.9-3.4)</td>
</tr>
<tr>
<td>1200 mg qd</td>
<td>18.6 (17.7-24.4)</td>
<td>9.6 (7.7-13.8)</td>
<td>233 (180-322)</td>
<td>2.1 (0.9-3.4)</td>
</tr>
</tbody>
</table>


### LZD mitochondrial toxicity correlates with \( C_{\text{min}} \)

- Systematic review of LZD in DR-TB: 8/c/d for AEs in 29% if doses ≤600 mg vs. 63% if >600 mg\(^{1}\)
- Thrombocytopenia associated with \( C_{\text{min}} >8-10 \text{ ug/ml}^{1,2}\)
- Korean XDR-TB trial: mitochondrial dysfunction & AEs associated with \( C_{\text{min}}^{5}\)
  - occurrence of mitochondrial AE was 100% if \( C_{\text{min}} >2 \text{ ng/ml} \) vs. <50% if \( C_{\text{min}} <2 \text{ ng/ml} \)
- In vitro HFM: mitochondrial tox more associated with \( C_{\text{min}} \) than AUC\(^6\)

2. Callahan et al, UAA 2015; 41:586
4. Matsumoto et al, UAA 2014;44:242
5. Song et al, ElBennah, 2016, in press
Conclusions re: LZD

- Although effect on actively multiplying bacteria is driven by $T_{\text{MIC}}$, activity in immune competent mice (like EBA) correlates highly with AUC/MIC
- Resistance suppression is associated with $C_{\text{max}}$/MIC
- Since mitochondrial toxicity is associated with $C_{\text{min}}$ and is duration-dependent:
  - Once daily dosing is preferred to twice daily dosing, but may not be the optimal strategy for the entire duration of treatment
- Strategies to better divorce toxicity from efficacy include:
  - Divide same total dosage into higher, more intermittent doses (eg, 1200 mg q48h or 3/7)
  - Front-load with higher daily doses (eg, 900-1200 mg qd x 2-4 months, then 1200 mg 3/7)
  - Limit overall treatment duration whenever able

Take-home points

- PK/PD science provides a rational basis for dose optimization to maximize efficacy and minimize toxicity
- Its importance for TB drug development is evidenced by ongoing efforts to optimize dosing of 1st and 2nd-line drugs
- PK/PD-supported opportunities to improve TB therapy include:
  - Supervised therapy to avoid non-adherence
  - Daily therapy, esp. for high-risk pts
  - Use of highest well-tolerated rifamycin and PZA doses
  - NAT-2 genotyping (or TDM) to personalize INH dosing
  - TDM to personalize RIF dosing (vs. empirical dose escalation?)
    - Slow responders (sputum Cx+ at 8 weeks)
    - Co-morbidities affecting drug exposure/outcomes (eg, diabetes, HIV+)
  - Baseline risk factors for poor outcome (eg, cavitary TB and/or 3-4+ smear)
  - TB meningitis
- MICs would be useful to modulate dose if toxicity is a concern

Acknowledgements

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  - Members of the Nuermberger lab
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