Optimizing existing drugs for the treatment of MDR-TB

Kelly Dooley, MD, PhD
4th International Workshop on TB Drugs
16 September 2011, Chicago, IL
MDR- and XDR-TB

• WHO estimates 440,000 cases of MDR-TB emerged in 2008
• 150,000 deaths from MDR-TB yearly
• In some settings 15-25% of new TB cases are MDR
• About 5% of MDR-TB cases have been found to have XDR-TB
• STOP-TB estimates that between 2010 and 2015, 1.3 million MDR-TB cases will require treatment in the 27 high burden countries
Current MDR-TB treatment

Principles
– >4 drugs to which the organism is likely to be sensitive
– At least 18-24 months
– Injectable for ≥6 months

Issues
– Toxicity
– Poor efficacy
– Cost

Example: KOZEtCs (can we do better?)
The case for optimizing existing drugs

• To **treat existing patients** in the most efficient and effective way
• To design an evidence-based **optimized background regimen (OBR)** to use in clinical trials of new compounds
• To **protect new drugs** against resistance
• Pipeline still limited
# 2016 DHHS/WHO Guidelines for Treatment of MDR-TB

<table>
<thead>
<tr>
<th>Column I</th>
<th>Column II</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Topoisomerase/Gyrase inhibitors</td>
<td>F. ATP synthase inhibitors</td>
</tr>
<tr>
<td>Moxifloxacin, levofloxacin</td>
<td>Bedaquiline (TMC207)</td>
</tr>
<tr>
<td>B. Mycolic acid synthesis inhibitors</td>
<td>G. Nitric oxide producers/electron transport suppressors</td>
</tr>
<tr>
<td>High-dose isoniazid, ethionamide, prothionamide</td>
<td>PA-824, delamanid (OPC67683)</td>
</tr>
<tr>
<td>C. Cell wall inhibitor</td>
<td>H. Clofazimine</td>
</tr>
<tr>
<td>Amoxicillin/clavulanic acid</td>
<td></td>
</tr>
<tr>
<td>D. Protein synthesis inhibitors</td>
<td>I. Inhibitors of trans-translation</td>
</tr>
<tr>
<td>Amikacin, Capreomycin, Kanamycin Linezolid</td>
<td>Pyrazinamide</td>
</tr>
<tr>
<td>E. New potent bactericidal agent with specific activity against mycobacteria</td>
<td>J. New potent sterilizing agent with low potential for drug interactions</td>
</tr>
</tbody>
</table>

**Preferred**

<table>
<thead>
<tr>
<th>Six-month regimen:</th>
<th>A+E+F+J</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nine-month regimen:</td>
<td>A+B+D+H+I</td>
</tr>
</tbody>
</table>

**Alternative**

<table>
<thead>
<tr>
<th></th>
<th>A+B+F+G+I</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>A+D+F+H+I</td>
</tr>
</tbody>
</table>

*Modified from a slide from Dick Chaisson*

Presented at the 4th International Workshop on Clinical Pharmacology of TB Drugs, 16 September 2011, Chicago, IL, USA
Research Themes/Questions

• Translation of preclinical findings to clinical settings
  – What are human equivalent doses for studies in animal models?

• Use of PK/PD relationships to optimize dosing
  – PK/PD targets
  – Toxicodynamics

• Enhanced use of genotypic and phenotypic testing to inform drug choices
  – Use of rapid resistant tests to identify people who will benefit from a drug
  – Correlation between phenotypic resistance and clinical resistance

• Designing optimized background regimen of existing drugs
  – What is the activity of this drug in humans?
  – Optimal duration?
  – Which to choose among drugs in same class/group?
Acknowledgements

RESIST-TB Drug Evaluation Working Group

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Group 1: Pyrazinamide

- Key **sterilizing and treatment-shortening** agent active in acidic milieu
- Pro-drug activated by mycobacterial amidase encoded by *pncA* (*mutations cause resistance*)
- Mechanism of action involves binding to ribosomal protein S1 (*RpsA*), involved in translation (Zhang, 2011)
- **AUC/MIC** is PD parameter that correlates best with activity *in vitro* (Gumbo, 2009)
Pyrazinamide - preclinical

Equivalent to standard human dose of 25-30 mg/kg

Dose-dependence in the mouse model (Ahmad, 2011)

Synergy with new drugs in clinical development for TB, for example TMC207 (J) (Ibrahim, 2007)

Pyrazinamide shows dose-dependent activity and synergy with new drugs in development and is most active against non-multiplying cultures (persisters) – when and how can we use it for the treatment of MDR-TB?
Pyrazinamide: areas for research

• Determination of patterns and **frequency of PZA resistance** using population-based studies

• Evaluation of **clinical impact of phenotypic PZA resistance** on activity of multidrug regimens (including investigational agents)

• **Rapid diagnostics** to identify genotypic PZA resistance (despite diverse group of resistance-conferring mutations)

• Clinical **toxicodynamics** of PZA – can we go higher?

• Optimal **timing and duration** of PZA use in DR-TB regimens
High-dose isoniazid (INH) – really Group 5?

- Activated by KatG
- Mutations in *katG* confer high-level resistance to INH (MIC 2-16 mcg/mL)

- Binds InhA, inhibiting mycolic acid synthesis
- Mutations in *inhA* confer lower-level resistance to INH (MIC 0.2-1 mcg/mL) and cross-resistance to ethionamide

Can we overcome INH “resistance” simply by increasing the dose? In which patients might this be possible? Vilcheze, 2007; Abate, 2001; Schaaf, 2009; Abe, 2008
Isoniazid pharmacodynamics

- In preclinical models, **AUC/MIC of 100-200 mcg*h/mL** achieves maximum INH activity, and ~60 achieves 50% of maximal effect.

- In **humans** an **AUC > 10.5 mcg*h/mL** is associated with 90% maximal EBA for DS-TB.

- In **slow acetylators**, this is achieved with a dose of 3 mg/kg; in **fast acetylators**, 6 mg/kg.

- For bactericidal activity against “drug-resistant” strains (MIC<0.5), dose of 300 mg in slow acetylators and 600 mg in fast acetylators likely needed.

How well can genotypic tests that detect **inhA** and **katG** mutations in *M. tuberculosis* isolates help us predict that patients that would benefit from higher-dose INH?

Jayaram, 2004; Donald, 1997; Donald, 2007
Can “resistance” be overcome with higher doses of INH?

United States

China

TABLE 4
INFLUENCE OF ACETYLATOR GENOTYPE ON EARLY BACTERICIDAL ACTIVITY

<table>
<thead>
<tr>
<th>Isoniazid Dose (mg)</th>
<th>EBA in Acetylator Genotypes</th>
<th>Between Genotypes</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rapid-Rapid</td>
<td>Rapid-Slow</td>
<td>Slow-Slow</td>
</tr>
<tr>
<td>600</td>
<td>0.166</td>
<td>0.591</td>
<td>0.682</td>
</tr>
<tr>
<td></td>
<td>0.313</td>
<td>0.633</td>
<td>0.651</td>
</tr>
<tr>
<td></td>
<td>0.350</td>
<td>0.651</td>
<td>0.732</td>
</tr>
<tr>
<td></td>
<td>0.437</td>
<td>0.878</td>
<td>0.878</td>
</tr>
<tr>
<td>Mean</td>
<td>0.352</td>
<td>0.697</td>
<td>0.682</td>
</tr>
<tr>
<td>9</td>
<td>−0.718</td>
<td>−0.373</td>
<td>−0.189</td>
</tr>
<tr>
<td></td>
<td>−0.448</td>
<td>−0.127</td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td>−0.054</td>
<td>−0.019</td>
<td>0.278</td>
</tr>
<tr>
<td>Mean</td>
<td>−0.583</td>
<td>−0.066</td>
<td>0.045</td>
</tr>
</tbody>
</table>

Definition of abbreviation: EBA = early bactericidal activity.

Donald 1997 & 2007; Gumbo 2007

Presented at the 4th International Workshop on Clinical Pharmacology of TB Drugs, 16 September 2011, Chicago, IL, USA
High-dose INH for MDR-TB: clinical evidence

- RCT for MDR-TB: OBR plus high-dose INH (16-18 mg/kg), standard INH (5 mg/kg), or placebo:
  - 6 mo culture conversion rate 74% vs. 45% vs. 49%
  - TTC conversion 3.4 months vs. 6.4 months vs. 6.6 months (Katiyar, 2007)
- Successful (87%) 9-month regimen in observational study in Bangladesh included high-dose INH (10-12 mg/kg) (Van Deun, 2009), similar results in recent study in four countries in Africa (IUATLD)

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Areas for research: INH

• Determination of **INH MIC distribution** among MDR-TB isolates with *inhA* or *katG* mutations

• EBA study to confirm relationship between INH AUC/MIC and effect among patients with MDR-TB (*pharmacodynamics and target AUC/MIC*)

• Rapid diagnostics for determining acetylator status

• **Optimal dose, by M. tuberculosis genotypic resistance pattern**
Group 2: Injectable agents

- *In vitro*, poor activity of KM and AMK against slowly-multiplying *M. tuberculosis* (Filippini, 2010)

- In mice, **AMK is weakly bactericidal at a dose of 200 mg/kg**, and **KM is bacteriostatic at the same dose** (Lounis, 1997)

- The human-equivalent dose, though, is likely ~24-45 mg/kg (Yuan, 2010; Mathe, 2007)

- PD parameter that correlates best with treatment response $C_{\text{max}}/\text{MIC}$ for other bacteria, unknown for *M. tuberculosis*
AMK and KM - clinical

- AMK has **minimal EBA and no dose-response** effect with doses 5-15 mg/kg daily
- **No clinical trials** evaluating the contribution of KM or AMK to multidrug therapy for MDR-TB
- Cohort studies show that **patients with pre-XDR (R to injectables) do worse** than patients with MDR-TB
- **Ototoxicity and vestibulotoxicity** (often irreversible) related to cumulative dose

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Mean EBA (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin 5 mg/kg</td>
<td>0.0405 (0.1004)</td>
</tr>
<tr>
<td>Amikacin 10 mg/kg</td>
<td>0.0453 (0.1441)</td>
</tr>
<tr>
<td>Amikacin 15 mg/kg</td>
<td>0.0518 (0.0962)</td>
</tr>
<tr>
<td>Isoniazid 6 mg/kg</td>
<td>0.5147 (0.1729)</td>
</tr>
<tr>
<td>No drug</td>
<td>0.0406 (0.113)</td>
</tr>
</tbody>
</table>

Donald, 2001; Donald, 2001; Kim, 2010; Chan, 2009; de Jager, 2002 Peloquin, 2004
AMK and KM – research agenda

• What, exactly, do these drugs do?
  – Preclinical studies to determine mouse:human PK correlates
  – Hollow fiber and mouse studies to determine contribution to multidrug therapy and target PK/PD parameters
  – Clinical trials to determine necessity and optimal duration of their use (not EBA), if concentrations needed to provide measurable effect can be safely achieved
Capreomycin – the other injectable

- In one *in vitro* experiment, CM was the only drug with *activity against nonreplicating MTB* (Heifets, 2005)
- In mice, less effective than AGs but testing limited by *narrow therapeutic margin* and human-equivalent dose not defined (LeConte, 1994; Grumbach, 1969)
- *M. tuberculosis* resistant to CM (*tlyA*) may not be resistant to AMK or KM, converse (*rrs*) less commonly true (Jugheli, 2009)
- Last clinical trial involving CM was in 1966

Limited ability to evaluate in mice; injectable drug with similar toxicities to AMK and KM; no trials evidence to support current dose and duration; comparative efficacy trials would take years → it is worth trying to optimize this drug?
Group 3: Fluoroquinolones

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pharmacokinetics</th>
<th>Pharmacodynamics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose (mg)</td>
<td>$C_{\text{max}}$ (µg/ml)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>500 (8.3)</td>
<td>2.4</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400 (6.6)</td>
<td>3</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 (8.3)</td>
<td>6.2</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>200 (3.3)</td>
<td>1.1</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>400 (6.6)</td>
<td>3.4</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 (6.6)</td>
<td>4.3</td>
</tr>
</tbody>
</table>

Nuermberger & Grosset, 2004 (adapted from Lubasch, 2000)

- Arguably **most important agent** in MDR-TB regimens
- **AUC/MIC** is parameter that correlates best with activity in other bacterial infections
- **AUC/MPC** (mutant prevention concentration) may also be important (Gumbo, 2004)
- In *in vitro persister* models, MOX > LEVO at same concentration (Hu, 2003)
Fluoroquinolones – *in vivo*

<table>
<thead>
<tr>
<th>Drug regimen</th>
<th>Method of estimation</th>
<th>Proportion of mice harboring mutant strains on day:</th>
<th>14</th>
<th>28</th>
<th>42</th>
<th>56</th>
<th>56 + 8 wk&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25% MXF</td>
<td>Direct</td>
<td>0/3</td>
<td>1/3</td>
<td>1/2</td>
<td>1/19</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indirect</td>
<td>0/3</td>
<td>1/3</td>
<td>NA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3/19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5% MXF</td>
<td>Direct</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/7</td>
<td>0/20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indirect</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/7</td>
<td>0/20</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Mice sacrificed after being kept without treatment for an additional 8 weeks.

<sup>b</sup> Not available due to overgrowth of contaminants.

In mice, keeping MXF concentrations > MPC can suppress emergence of FQ resistance (not clinically achievable) (Almeida, 2007)

Levofloxacin 1000 mg once daily
Moxifloxacin 400 mg once daily
Gatifloxacin 400 mg once daily

(Johnson, 2006)

No prospective comparative clinical trials of quinolones for treatment of MDR-TB
Fluoroquinolones – areas of research

Role of FQs in MDR-TB regimen may be bactericidal activity + protection against emergence of resistance

• Multidrug studies in preclinical models to determine FQ exposures needed to prevent resistance

• Prospective studies evaluating acceleration of resistance with different FQs, doses

• Comparative MDR-TB RCT of moxifloxacin vs. high-dose levofloxacin + OBR, follow for resistance and relapse
Group 4: Ethionamide

- Prodrug requiring enzymatic activation by EthA (not KatG), inhibits InhA (like INH)
- **Concentration-dependent** activity in mice, much less potent than INH (Rist, 1959)
- Bactericidal against established infection in mouse model
- Dose in mice needed to produce **human-equivalent** PK unknown
Ethionamide

• **Gastrointestinal intolerance** mandates gradual dose increase to MTD

• **Divided dosing** may improve tolerability but produces \( C_{\text{max}} \) below the MIC (Zhu, 2002)

• **About 50% cross-resistance with INH**, largely related to \( inhA \) promoter mutations (Schaaf, 2009; Abe, 2008; Warren, 2009)
As the only second-line agent with potentially bactericidal activity, ETA merits further evaluation:

- PK/PD studies in *in vitro* and animal models to identify PK/PD correlates and establish human-equivalent dose in mice
- Evaluate population PK and toxicodynamics to determine clinical MED
- Explore use of rapid genotyping of isolates to determine those with *inhA* mutations unlikely to benefit (and give them high-dose INH instead)
Group 5: worthy of further study?

- Clofazimine
- Beta-lactams
- Linezolid
- Clarithromycin
- Thioacetazone
Clofazimine

- **Potent *in vitro* activity** against hypoxic, non-replicating *M. tuberculosis* (Cho, 2007)
- Preclinical **activity** depends on the animal model
- In mice, bactericidal, but **onset of effect is slow** (Jaggarath, 1995)
- Estimation of sterilizing activity is complicated by **carryover effect** seen with pronounced tissue accumulation (Ji, 1994)
Clofazimine - clinical

• **Prolonged lag time** for absorption; high variability; $t_{1/2}$ **70 days**; **extensive tissue distribution** (Schaad-Lanyi, 1987; Nix, 2004)

• INH may reduce tissue accumulation and increase serum concentrations of CFZ (Vankatesan, 2007; McEvoy, 1990)

• **Observational studies show clinical efficacy of CFZ-containing regimens**
  – MDR-TB cured in >80% patients receiving gatifloxacin, high-dose INH, and CFZ-containing regimen (van Deun, 2009)
  – XDR-TB cured in >60% patients, most received CFZ (Mitnick, 2008)

• **Red-black skin discoloration**
Clofazimine – research directions

• Careful studies of **CFZ in combination regimens** with attention to carry-over and lag in activity in > 1 animal model

• **Clinical trials of CFZ-containing regimens** warranted, but slow time to steady state and delayed onset of effect complicate clinical evaluation

• **Water-soluble analogs** in development
Beta-lactams

• Inhibit peptidoglycan cross-linking needed for cell wall synthesis -- carbapenems may inhibit transpeptidases key to survival of persisters (Gupta, 2010)

• *M. tuberculosis* produces BlaC, a beta-lactamase
  – clavulanate is irreversible inhibitor of BlaC (Hugonnet, 2007)
  – Carbapenems are hydrolyzed more slowly than amoxicillin (Hugonnet, 2009)

• Pharmacodynamics against *M. tuberculosis* in mice unknown, but:
  – IMI 100 mg/kg **twice-daily** -> bactericidal (Chambers, 2005)
  – IMI 100 mg/kg + CLV **once-daily** → permits bacterial growth (Veziris, 2011)
EBA studies suggest **time-dependence** of bactericidal activity of beta-lactams against *M. tuberculosis*.

**EBA** 0.2 for AMX/CLV **3000/750 once-daily** (Donald, 2001)

**EBA** 0.2 for AMX/CLV **1000/250 thrice-daily** = 0.34 (+/- 0.03) (Chambers, 1998)
Beta-lactams – research directions

• Dose-fractionation studies in mice plus experiments in hollow fiber model to:
  – Determine dose/frequency with optimal kill and target T>MIC
  – Explore sterilizing activity of carbapenems

• Clinical trials of optimized dose/frequency derived from preclinical testing, but:
  – Only AMX/CLV is available as oral formulation
  – Divided dosing likely needed to capitalize on time-dependence of activity
  – CLV not commercially available by itself to pair with carbapenems
Summary points

• Optimization of existing drugs is essential to treat current and future patients with drug-resistant TB

• Research priorities:
  – **HIGH**: FQs, injectables, high-dose INH, PZA
  – **MEDIUM**: beta-lactams, clofazimine, ethionamide, linezolid, ethambutol
  – **LOW**: PAS, CS, RBT, thiacetazone, clarithromycin

• Can we fashion an effective 6-9 month regimen out of existing drugs?