TB Drug Pipeline and New Treatment Combinations for MDR-TB

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Outline

- Background
- Repurposable drugs for MDR-TB
- New drugs for MDR-TB
- Ongoing clinical trials of MDR-TB disease
- Designing the optimal MDR/XDR-TB regimen
MDR-TB - Background

- Estimated 450,000 new cases last year
- Less than 25% treated
- Recommended treatment takes 18-24 months, cures only ~65%, 15+% mortality
- No systematic study of currently recommended regimens
- Second-line drugs are associated with substantial toxicity
- Emergence of additional resistance in 9-15%
Goals of a New Regimen for MDR-TB

- Shorten duration of treatment from 20-24 months
- Improve on 60% cure proportion
- Improve tolerability
- Prevent the emergence of further resistance
REPURPOSING OLD DRUGS FOR MDR-TB
T tolerability of 3rd-generation fluoroquinolones

Class-specific:
- Peripheral neuropathy
- Tendon rupture
- Hepatotoxicity
- *C. difficile* superinfection

Moxifloxacin:
- QT-prolongation
Potential “Repurposable” Drugs

- PZA (WHO Group 1)
- Moxifloxacin (WHO Group 3)
- Levofloxacin (WHO Group 3)
- Linezolid (WHO Group 4)
- Clofazimine (WHO Group 5)
- Amoxicillin/Clavulinate (WHO Group 5)
- Imipenem/Cilastin (WHO Group 5)
- Clarithromycin (WHO Group 5)
Tolerability of Clofazimine

- Skin discoloration (75-100%)
- Gastrointestinal intolerance (40-50%)
- Eosinophilic enteritis
- Interstitial nephritis
- Rash, dry skin, ichthyosis
- QT prolongation
A 9-month regimen for MDR-TB in Bangladesh

- Kanamycin
- Prothionamide
- Isoniazid
- Gatifloxacin
- Ethambutol
- Pyrazinamide
- Clofazimine

*4-month intensive phase prolonged if still smear-positive after 4 months*

*Fixed 5-month continuation phase*

AJRCCM 2010:182:684-92
Bangladesh Regimen: Efficacy

206 patients

- 170 Cures (84.2%)
- 11 Completions (5.3%)
- 11 Deaths (5.3%)
- 12 Defaults (5.8%)
- 1 Failure (0.5%)
- 1 Relapse (0.5%)

AJRCCM 2010:182:684-92
Bangladesh Regimen: Tolerability

- 206 patients
  - 44 Vomiting (21.4%)
  - 13 Hearing Difficulties (6.3%)
  - 8 Dysglycemia (3.9%)
  - 8 Ataxia (3.9%)
  - 2 Arthralgia (1%)
  - 1 “Mental” (0.5%)
Tolerability of Linezolid in 72 Patients with MDR-TB*

- Peripheral neuropathy (40%)
- Anemia (25%)
- Optic Neuritis (10%)
- Thrombocytopenia (10%)
- GI disorders (8%)
- Neutropenia (2%)

*Dose ≤ 600mg/day
Prospective Study of Linezolid in XDR-TB Treatment

- 40 patients with XDR-TB in Korea
- Randomized to 300mg qd or 600mg qd
- Further randomized to immediate versus 2 month delayed linezolid (both with OBR)
- 36/40 converted sputum cultures (mean 90 days)
- 4 failures were all resistant to linezolid
Linezolid in the Treatment of XDR-TB
Tolerability of Linezolid in XDR-TB Treatment Trial

22 Patients treated with 600 mg/day
- Peripheral neuropathy (60%)
- Myelosuppression (20%)
- Optic Neuropathy (10%)

16 Patients on 600 mg then 300 mg after 2 months
- Peripheral neuropathy (50%)
- Myelosuppression (not seen)
- Optic Neuropathy (17%)

NEJM 2013;367 (on-line supplement)
NEW DRUGS FOR MDR-TB
Global TB Drug Pipeline

**Chemical classes:** fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

1 Details for projects listed can be found at [http://www.newtbdrugs.org/pipeline.php](http://www.newtbdrugs.org/pipeline.php) and ongoing projects without a lead compound series identified can be viewed at [http://www.newtbdrugs.org/pipeline-discovery.php](http://www.newtbdrugs.org/pipeline-discovery.php).

2 Combination regimens: NC-001-(J-M-Pa-Z), phase 2a, NCT01215851; NC-002-(M-Pa-Z), phase 2b, NCT01498419; NC-003-(C-J-Pa-Z), phase 2a, NCT01691534; PanACEA-MAMS-TB-01-(H-R-Z-E-Q-M), phase 2b, NCT01785186.
# New MDR-TB Drugs in Clinical Development, 2014

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Company</th>
<th>Status</th>
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<tbody>
<tr>
<td>Bedaquiline</td>
<td>Diarylquinolone</td>
<td>Tibotec</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Delamanid</td>
<td>Imidazooxazole</td>
<td>Otsuka</td>
<td>Phase 3</td>
</tr>
<tr>
<td>PA-824</td>
<td>Imidazooxazine</td>
<td>GATB</td>
<td>Phase 2</td>
</tr>
<tr>
<td>SQ-109</td>
<td>Ethylene Diamine</td>
<td>Sequella</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Sutezolid</td>
<td>Oxazolidinone</td>
<td>Sequella</td>
<td>Phase 2</td>
</tr>
<tr>
<td>AZD-5847</td>
<td>Oxazolidinone</td>
<td>AstraZenica</td>
<td>Phase 2</td>
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</tbody>
</table>
Bedaquiline Study C208 (Phase 2)

- **Description:** Addition of Bedaquiline to OBT for 6 months, followed by OBT for 18 months
- **Regimens:** OBT+Bedaquiline
  
  OBT+Placebo
- **Sponsor:** Janssen
- **Target population:** newly-diagnosed, smear+ MDR-TB, adults, CD4>300 if HIV+
- **Outcome:** Time to sputum culture conversion
- **Size:** 200 patients
Bedaquiline Phase 2 MDR-TB Study
Time to sputum culture conversion (MITT analysis)

Time to 50% culture conversion: 12 weeks
Time to 50% culture conversion: 18 weeks

Diacon, IUATLD 2013.
# Bedaquiline Study C208
## Final results

<table>
<thead>
<tr>
<th></th>
<th>Bedaquiline+OBT</th>
<th>Placebo+OBT</th>
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<tbody>
<tr>
<td>Number</td>
<td>79 patients</td>
<td>81 patients</td>
</tr>
<tr>
<td>Median Conversion</td>
<td>12 weeks</td>
<td>18 Weeks*</td>
</tr>
<tr>
<td>Cure at week 120</td>
<td>58%</td>
<td>32%**</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>23%</td>
<td>19%</td>
</tr>
<tr>
<td>Deaths</td>
<td>13%</td>
<td>2.5%**</td>
</tr>
</tbody>
</table>

*p=0.01  
**p=0.01

Diacon, IUATLD Nov 2013
Tolerability of Bedaquiline

- Nausea (~22%)
- Increased hepatic enzymes (?)
- QT prolongation
Delamanid Study 204 (Phase 2)

- Description: Addition of Delamanid (D) to OBT
- Regimens: OBT+D 100 mg bid
  OBT+D 200mg bid
  OBT+Placebo
- Target population: Adults with pulmonary MDR-TB, CD4>350 if HIV+
- Outcome: Sputum conversion at 8 weeks
- Size: 430 patients
Figure 2. Proportion of Patients with Sputum-Culture Conversion by Day 57.
Tolerability of Delamanid

- QT prolongation

NEJM 2012;366:2157
MDR-TB Clinical Trials in Progress

- AZD-5847 Phase 2
- NC-002 (PA-824)
- STREAM
- Delamanid Phase 3
- Opti-Q Phase 4
PA-824 (NC-002 Trial)

- Description: 8 week trial of PA-824 in combination with moxifloxacin and PZA
- Regimens: $PA_{100}$-M-Z for DS-TB
  $PA_{200}$-M-Z for DS-TB
  $PA_{200}$-M-Z for MDR-TB (FQ and Z susceptible)
  HRZE for DS-TB
- Sponsors: GATB
- Target population: smear+ MDR-TB, adults
- Outcome: quantitative sputum cultures
- Size: 230 patients – 100% enrolled
- Sites: Tanzania and South Africa
- Expected results: 2014
Description: Modified Bangladesh regimen (with moxifloxacin in place of gatifloxacin) compared to “standard” MDR-TB regimen

Regimens: 7-drug regimen (9 months)
4-5 drugs (18-24 months)

Sponsors: IUATLD, USAID

Target population: smear+ MDR-TB, adults

Outcome: Failure, relapse, default or death

Size: 400 patients – 50% enrolled

Sites: Ethiopia, Vietnam, South Africa

Expected completion: 2016
Delamanid Confirmatory Trial (Phase 3)

- Description: Addition of D to OBT
- Regimens: OBT+D 100 mg (D 6 months/OBT 18 months)  
  OBT+D 50 mg (D 6 months/OBT 18 months)  
  OBT+Placebo (24 months)
- Sponsor: Otsuka Pharmaceutical Development
- Target population: Adults with pulmonary MDR-TB,  
  CD4>350 if HIV+
- Outcome: Time to sputum conversion through 6 months
- Size: 430 patients
- Duration: 2015
- Status: 100% enrolled
Constructing a new MDR-TB Regimen: Principles

- At least 3 new drug classes
- Avoid overlapping toxicities
- Strive for all-oral regimen
- Estimate duration based on 2 month sputum culture conversion
MDR-TB Drug Menu

**Class**

*Diarylquinolone:* bedaquiline

*Nitroimidazole:* delamanid, PA-824

*Oxazolidinone:* linezolid, sutezolid, AZD-5847, others?

*Fluoroquinolone:* levofloxacin, moxifloxacin, (gatifloxacin)

*Riminophenazaine:* clofazimine

*Other:* PZA
MDR-TB Clinical Trials in Preparation

- Bedaquiline Phase 3
- MARVEL (ACTG A5319)
- Bedaquiline/Delamanid DDI
- PA-M-Z
- NiX-TB (for XDR-TB)
Conclusions - I

- New TB drug classes may increase treatment response rates, shorten treatment duration and decrease mortality
- Tolerability of a number of the new agents remains to be defined, especially when used in combination
- Combination studies are needed to assure that DDI with other TB drugs and ART will not preclude their concurrent use
Conclusions - II

- Trials currently in progress and under consideration will hopefully clarify DDI and overlapping toxicity issues
- A major challenge will be preventing the emergence of resistance to the new drugs
- Increased capacity for MDR-TB clinical trials will also be needed