Developing Novel TB Regimens: a proposed clinical development path

Ann M. Ginsberg, MD, PhD
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## Current TB Therapy and Unmet Needs

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Current Therapy</th>
<th>Unmet Needs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-Susceptible DS-TB</td>
<td>4 drugs; ≥6 month therapy (2RHZE + 4RH)</td>
<td>Shorter, simpler therapy</td>
</tr>
<tr>
<td>Drug-Resistant M(X)DR-TB</td>
<td>Few drugs (including injectables); ≥18 months; toxicities</td>
<td>Totally oral, shorter, more efficacious and safer therapy</td>
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<tr>
<td>TB/HIV Co-Infection</td>
<td>Drug-drug interactions (DDI) with ARVs</td>
<td>No or low DDI, co-administration with ARVs</td>
</tr>
<tr>
<td>Latent TB Infection</td>
<td>6-9 months H</td>
<td>Shorter, safer therapy</td>
</tr>
</tbody>
</table>

* Rifampin (R), Isoniazid (H), Pyrazinamide (Z), Ethambutol (E)

- Need shorter, simpler therapies against both DS and DR-TB
- To accomplish, will need to replace all or most current drugs
TB Alliance Vision

Success will require novel multi-drug combinations
For the first time in history, the opportunity exists to develop truly novel regimens, containing multiple new chemical entities with novel mechanisms of action.

TB treatment of ≤ 3 months
New Regimen: Optimal Target Profile

- Shorten and simplify treatment
  - Active against drug-persistent *Mtb* populations
- Equally effective against M(X)DR-TB
  - Novel mechanisms of action
- Easy, safe, co-administration with ARVs
  - No P450 mediated drug-drug interactions
- Excellent safety/tolerability
- Oral, < once daily dosing
- Low cost of goods
Approach to New Regimen Development

- Use animal model(s) to identify most promising combinations
- Conduct full preclinical, Phase I and Phase IIa evaluations of each drug singly
- Explore drug-drug interactions, and preclinical toxicology and safety pharmacology of the combination, as appropriate
- Take *combination* into clinical development (Phase I, II, III)

Approach now being taken for new drugs in development: for example, PA-824, TMC207, moxifloxacin
Bactericidal Activity of Different Treatment Regimens in the Mouse

Log$_{10}$ CFU in Lungs vs. Weeks

- Untreated
- RHZ
- PaMZ
- PaM
- PaZ
- MZ

R = rifampin
H = isoniazid
Z = pyrazinamide
Pa = PA-824
M = moxifloxacin
Proposed Clinical Development Path for Completely Novel Regimen

- **if new regimen contains only drugs suitable for both DS- and MDR-TB**

**MOUSE MODELS**
- Single drug dose-ranging in acute mouse model
- Only combos in relapse model

**PHASE 1** (SD, MD, ADME, DDIs, etc.)
- Single drugs

**14-DAY SINGLE DRUG EBA(S)**
- Acute (singles) and Relapse (combos)

**14-DAY COMBO EBA**
- All final combos tested

**COMBO 8-WEEK SSCC**
- >50 PTS^ PER ARM

**COMBO PHASE 3**
- Combo statistically better than HRZE for DS-TB and better than O2R for MDR-TB

Preclinical
- Phase 1
- Phase 2
- Phase 3

Regulatory Approval

**EBA:** Early Bactericidal Activity; **O2R:** optimized 2nd-line regimen

**SSCC:** Serial Sputum Colony Counts

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT
Proposed Clinical Development Path for Completely Novel Regimen
– if new regimen contains only drugs suitable for DS- and MDR-TB

PRECLINICAL and PHASE 1

PHASE 1 (SD, MD, ADME, DDIs, etc.)

SINGLE DRUGS

MOUSE MODELS

• ACUTE (singles)
  and
• RELAPSE (combos)

• Single drug dose-ranging in acute mouse model
• Only combos in relapse model

EBA: Early Bactericidal Activity
SSCC: Serial Sputum Colony Counts
Proposed Clinical Development Path for Completely Novel Regimen
– *if new regimen contains only drugs suitable for DS- and MDR-TB*

**PHASE 2**

14-DAY SINGLE DRUG EBA(S) → DOSE-RANGING → 14-DAY COMBO EBA → ALL FINAL COMBOS TESTED → COMBO 8-WEEK SCC → ≥50 PATIENTS PER ARM

- Combos better than HRZE for DS-TB
- Combo statistically better than HRZE for DS-TB and better than O2R for MDR-TB

EBA: Early Bactericidal Activity; O2R: optimized 2nd-line regimen
SSCC: Serial Sputum Colony Counts
Proposed Clinical Development Path for Completely Novel Regimen

- if new regimen contains only drugs suitable for DS- and MDR-TB

**PHASE 3**

**COMBO PHASE 3**

Treatment-shortening

**RA**

Regulatory Approval

- Combo statistically better than HRZE for DS-TB and better than O2R for MDR-TB
Proposed Clinical Development Path for Completely Novel Regimen

- if new regimen contains only drugs suitable for both DS- and MDR-TB

- Single drug dose-ranging in acute mouse model
- Only combos in relapse model

Preclinical
Phase 1
Phase 2
Phase 3

Regulatory Approval

EBA: Early Bactericidal Activity; O2R: optimized 2nd-line regimen
SSCC: Serial Sputum Colony Counts
Key Challenges For Regimen Development

- Resource mobilization
- Sponsor Partnering
  - Commitment from Sponsors
  - Antitrust issues
- Clinical trial capacity
  - Mycobacteriology labs
  - Clinical sites
- Ensuring adequate discovery pipeline globally
- Realistic regulatory guidance and harmonization
Thank you
Proposed Clinical Development Path for Drug-sensitive TB – if regimen contains H and/or R

MOUSE MODELS

• Single drug dose-ranging in acute mouse model
• Only combos in relapse model

PHASE 1 (SD, MD, ADME, DDIs, etc.)

SINGLE DRUGS

14-DAY MONORX EBA(S) DOSE-RANGING

14-DAY COMBO EBA

ALL FINAL COMBOS TESTED

COMBO 8-WEEK SSCC 50 PTS PER ARM

COMBO PHASE 3 500 PTS PER ARM; rx-shortening

Combo better than HRZE

Combo statistically better than HRZE

Preclinical
Phase 1
Phase 2
Phase 3

Regulatory approval

EBA: Early Bactericidal Activity
SSCC: Serial Sputum Colony Counts
A Clinical Development Path for MDR-TB – *single, novel drug*

MOUSE MODELS

- ACUTE
- RELAPSE

Phase 1 (SD, MD, ADME, DDIs, etc.)

SINGLE DRUG

14-DAY SINGLE DRUG EBA(S)

DOSE-RANGING

COMBO 8-WEEK SS CC

>25 TS PER ARM

PHASE 3 6-MONTH SPUTUM CONVERSION

>75 PTS PER ARM

New drug in O2R statistically better than O2R

Novel drug *substituted into* optimized 2nd-line regimen (e.g., replace cycloserine, ethionamide or PAS)

Subpart H registration

PHASE 3 TREATMENT-SHORTENING

SUBPART H POST-MARKETING COMMITMENT

Regulatory approval

O2R: optimized 2nd-line regimen

*new drug has novel mechanism of action and no cross-resistance to standard, first-line TB drugs*
Potential Novel Regimen for DS- and MDR-TB

Example: PA-824+moxifloxacin+PZA

<table>
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<tr>
<th>Treatment</th>
<th>Proportion (%) of mice cured after treatment for:</th>
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<tbody>
<tr>
<td></td>
<td>4 mos</td>
</tr>
<tr>
<td>1. 2 mos of RIF-INH-PZA plus 4 mos of RIF-INH</td>
<td>10 of 20 (50)</td>
</tr>
<tr>
<td>2. 2 mos of RIF-MXF-PZA plus 3 mos of RIF-MXF</td>
<td>19 of 20 (95)(^b)</td>
</tr>
<tr>
<td>3. 2 mos of Pa-MXF-PZA plus 4 mos of Pa-MXF</td>
<td>20 of 20 (100)(^b)</td>
</tr>
</tbody>
</table>

\(^b\) P = 0.01 versus regimen 1.

TB Regimen Development Path

- Acute
- Relapse

MOUSE MODEL

- Acute
- Relapse

14-DAY MONORX EBA(S)

Dose-ranging

14-DAY COMBO EBA

All final combos tested

8-WEEK SSCC

50 pts per arm

PHASE 3

500 pts per arm

Dose-ranging in acute model

Only combos in relapse model

Ph 1 SD, MD, ADME, DDIs, etc., as appropriate

Combos better than HRZE

Combos statistically better than HRZE