Treatment of MDR-TB…where are we headed?

C. Robert Horsburgh, Jr.
Boston University

Outline

- New and repurposed drugs for MDR-TB treatment
- Ongoing Phase 2 MDR-TB trials
- Treatment regimens currently in Phase 3 trials
- MDR-TB Trials of the future

2018 Global New TB Drug Pipeline [1]

Early Stage

- Caprazene nucleoside CPZEN-45*
- Spectinamide 1810*
- Gyrase inhibitor SPR-720 (pVXc-486)*
- Pyrazolopyridine carboxamide TB-47*
- Fluoroquinolone DC-159a

GMP/ GLP Tox.

- BTZ-043*
- TBAJ-587
- TBI-223
- GSK-286*

Phase 1

- TBI-166
- Macozinone* (PBTZ-169)
- OPC-167832*
- Q203*
- GSK-656* (070)
- TBA-7371*
- Contezolid (MRX-4/MRX-1)

Phase 2

- Delpazolid (LCB01-0371)
- Sutezolid (PNU100480)
- SQ-109*
- Macozinone* (PBTZ-169)

Phase 3

- Bedaquiline* (TMC-207)
- Delamanid* (OPC-67683)
- Pretomanid* (PA-824)

Underline = new to Phase since October 2017

New chemical class* Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline/discovery

WORKING GROUP ON NEW TB DRUGS
www.newtbdrugs.org

Updated: March 2018

Phase 2 Trials to optimize dosing and Minimize DDI and Adverse Effects

- Otsuka 232: Pediatric PK of DLM (2018)
- ACTG 5312: High dose INH for inhA mutations (2019)
- Opti-Q: Optimization of levofloxacin dosing (2019)
- ACTG 5343: BDQ and DLM QT interactions (2019)
- Janssen C211 Study: Pediatric PK of BDQ (2019)+
- Otsuka 233: Pediatric 6-month open label DLM (2020)
- ZeNiX: Optimization of linezolid dosing (2020)
- ACTG 5356: Optimization of linezolid dosing (2021)*
- IMPAACT P1108 Trial: Pediatric PK of BDQ (2020)+

*not yet started

+partial results being presented at Union Meeting

Phase 3 Clinical Trials for MDR-TB

Trials to replace injectable

- NEXT Trial – Phase 3 (2019)
- MDR-END Trial– Phase 2/3 (2021)
- STREAM Stage 2 Trial– Phase 3 (2021)
- endTB Trial – Phase 3 (2022)

NeXT Trial (Phase 3)

- Description: 6-9 month trial of bedaquiline in combination with other oral agents (duration dependent on culture conversion)
- Regimens: BDQ+LZD+LFX+ETA/INHH+PZA (6-9 Mo)
  MXF+ETH+TER+KM+PZA (21-24 Mo)
- Sponsors: MCC
- Target population: MDR-TB, adults
- Outcome: “favorable outcome” at 24 months
- Size: 300 patients; 108 enrolled (on hold)
- Sites: South Africa
- Expected results: 2019

MDR-END Trial (Phase 2/3)

- Description: Injectable-free DLM-based regimen vs SOC
- Regimens:

  SOC (WHO 20-24 months)

  DLM+LZD+LFX+PZA for 9-12 months
- Sponsor: Korean government
- Target population: smear+ MDR-TB, adults 18+
- Outcome: Failure, relapse, default or death
- Size: 204 Patients; 75% enrolled
- Sites: Korea
- Expected results: 2021

STREAM Trial, Stage 2 (Phase 3)

- Description: Addition of two new arms to STREAM
- Regimens:

  SOC (continues both WHO and Bangladesh)

  BDQ+CFZ+EMB+LFX+PZA+4(INH_H+PTO) – 9 mos
- Sponsor: USAID, others
- Target population: smear+ MDR-TB, adults
- Outcome: Failure, relapse, default or death
- Size: 550 patients; 330 enrolled
- Sites: Ethiopia, Vietnam, South Africa, Mongolia
- Expected results: 2021

endTB Trial (Phase 3)

- Description: Combination regimens, adaptive randomization
- Regimens:WHO SOC (20-24 months)
  BDQ+LZD+MXF+PZA for 9 months
  BDQ+CF+LZD+LFX+PZA for 9 months
  BDQ+DEL+LZD+LFX+PZA for 9 months
  DEL+CF+LZD+LFX+PZA for 9 months
  DEL+CF+MFX+PZA for 9 months
- Sponsor: MSF/UNITAID
- Target population: smear+ MDR-TB, adults 15+
- Outcome: Failure, relapse, default or death
- Size: 750 patients; 159 enrolled
- Sites: India, Pakistan, Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru
- Expected results: 2022

Trials to shorten duration

- NiX-TB Trial (2018)
- TB-PRACTECAL Trial (2022)
- SimpliciTB (2022)

NiX-TB (Phase 2/3)

- Description: 6 month trial of Pretomanid in combination with Bedaquiline and Linezolid
- Regimen: BDQ+PTM+LZD (Single Arm)
- Sponsor: GATB
- Target population: XDR-TB, adults
- Outcome: relapse-free cure
- Size: 100 patients; completed November 2017
- Sites: South Africa
- Expected results: This Thursday, OA03-213-25, 14:00 in KWA Plenary Hall

Status of Participants in Nix-TB

- 109 participants enrolled as of end enrollment November 15, 2017
  - 80 have completed treatment
  - 56 have reached their primary endpoint (6 months after end of treatment; NDA cutoff)
  - 10 patients have completed the study (Month 30)
- Overall relapse-free cure of TB disease among the first 30 followed to primary endpoint 6 months after end of therapy:
  - 26 / 30 = 87% (vs. historical up to 85% failure rate)
- Enrollment ended November 15, 2017
  - Transition to ZeNix

TB-PRACTECAL Trial (Phase 2/3)

- Description: Staged trial of BDQ/PTM/LZD regimens:
  - SOC (WHO 20-24 month regimen)
  - BDQ+PTM+LZD+MFX for 6 months
  - BDQ+PTM+LZD+CF for 6 months
  - BDQ+PTM+LZD for 6 months
- Sponsor: MSF
- Target population: smear/Xpert+ MDR-TB, adults 18+
- Outcome: Failure, relapse, default or death
- Size: 630 Patients; 115 enrolled
- Sites: Uzbekistan, Swaziland, Belarus
- Expected results: 2022

SimpliciTB Trial (Phase 3)

- Description: Staged trial of BDQ/PTM/LZD regimens:
  - BDQ+PTM+MFX+PZA for 4 months (DS)
  - BDQ+PTM+MFX+PZA for 6 months (MDR)
  - HRZE for 6 months
- Sponsor: GATB
- Target population: DS (randomized) and MDR (not randomized)
- Outcome: Failure, relapse, default or death
- Size: 300 DS, 150 MDR; 15 enrolled
- Sites: Georgia
- Expected results: late 2022

Phase 3 MDR-TB trial in preparation: endTB-Q

- Population: FQ-resistant MDR-TB
- Regimen: BDQ+DEL+LZD+CF
- Durations: 24 or 39 weeks
- Sites: India, Pakistan, Kazakhstan, Kyrgyzstan, Lesotho, Peru, South Africa
- To Start: 2019

Phase 3 MDR-TB trial in preparation: BEAT-TB

- Population: MDR-TB
- Regimen of BDQ, DEL, LFX, LZD and CF
- Duration: 6 months
- Site: South Africa
- To start 2019

A Universal Regimen?

If all the regimens currently under study are effective, we will have:

- 3 regimens for BDQ-resistant TB
- 6 regimens for PZA-resistant TB
- 2 regimens for oxazolidinone-resistant TB
- 4 regimens for FQ-resistant TB
- 8 regimens for CF-resistant TB
- 5 regimens for imidazo-resistant TB

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Prediction of Susceptibility to First-Line Tuberculosis Drugs by DNA Sequencing

The CRyPTIC Consortium and the 100,000 Genomes Project

ABSTRACT

BACKGROUND

The World Health Organization recommends drug-susceptibility testing of *Mycobacterium tuberculosis* complex for all patients with tuberculosis to guide treatment decisions and improve outcomes. Whether DNA sequencing can be used to accurately predict profiles of susceptibility to first-line antituberculosis drugs has not been clear.

METHODS

We obtained whole-genome sequences and associated phenotypes of resistance or susceptibility to the first-line antituberculosis drugs isoniazid, rifampin, ethambutol, and pyrazinamide for isolates from 16 countries across six continents. For each isolate, mutations associated with drug resistance and drug susceptibility were identified across nine genes, and individual phenotypes were predicted unless mutations of unknown association were also present. To identify how whole-genome sequencing

The members of the writing group (Timothy M. Walker, D.Phil., A. Sarah Walker, Ph.D., and Tim E.A. Peto, D.Phil.) assume responsibility for the overall content and integrity of this article. The authors' full names and academic degrees are listed in the Appendix. The authors' affiliations are listed in the Supplementary Appendix, available at NEJM.org. Address reprint requests to Dr. Timothy Walker at the Department of Microbiology, Level 7, John Radcliffe Hospital, Headley Way, Headington, Oxford, OX3 9DU, United Kingdom, or at timothy.walker@ndm.ox.ac.uk.

MDR-TB Trials of the future

- New Oxazolidinones
  - Sutezolid, Tedazolid, Delpazolid, Contazolid
- Benzothiazinones:
  - BTZ 043, Macozinone (PBTZ 169)
- Telacebec (Q203)
- Additional regimen shortening?
- Prevention of emergence of drug resistance?

Conclusions

- The pipeline for new TB drugs has been productive since 2000
- Six new drugs (4 new classes) are now in Phase 2 & 3 clinical trials
- Six additional new drugs (3 additional new classes) have recently entered Phase 1 trials
- Emergence of resistance to the new agents is already being seen
- The optimal way to use the new and repurposed drugs is still unknown

To follow developments in MDR-TB diagnosis and treatment:

RESIST-TB Clinical Trials Progress Report

www.resisttb.org/?page_id=1602