Progress in the fight against Drug-Resistant Tuberculosis – Update, March, 2023

The past few years have presented numerous challenges to progress in the fight against drug-resistant tuberculosis (DR-TB). Despite this, important steps forward (plus a few steps back) were made in the fight to bring better treatment to people with DR-TB in the past year. This World TB Day Report for 2023 inaugurates a new RESIS-TB feature, and annual summary of progress towards shorter and less toxic treatment for *all* persons with MDR-TB. These include advances in clinical trials, roll out of new drugs and regimens, regulatory approvals of new drugs, improved access to susceptibility testing for the new agents and lower diagnosis and treatment costs. We summarize these for the past year below:

Published Clinical Trials of DR-TB

Six major clinical trials with important implications for DR-TB were completed and published in the past year, the MDR-END trial, the NeXT trial, the TREAT-TB (India) trial, the ZeNiX trial, the TB-PRACTECAL trial and the STREAM Stage 2 trial.

MDR-END in South Korea evaluated a regimen containing delamanid, linezolid, levofloxacin, and pyrazinamide for 9-12 months for treatment of fluoroquinolone-sensitive multidrug tuberculosis compared to a 20-month conventional regimen with second-line drugs including injectables for 20-24 months, the WHO's recommended SOC in 2014 [1]. At 24 months, 75% in the shorter-regimen group had treatment success compared to 70.6% in the control arm.

The NeXT trial, a 6 to 9-month all oral regimen for FQ-S MDR-TB based on bedaquiline, linezolid and levofloxacin was compared to the 9-month injectable-based WHO-approved MDR-TB regimen. Participants in the experimental arm had 51% favorable outcomes while those in the control arm had 23% favorable outcomes. Thus, while both groups experienced substantial toxicity, the all-oral regimen performed significantly better.[2]

BEAT-TB in India evaluated a 6–9-month Bedaquiline, Delamanid, Linezolid, and Clofazimine – an entirely oral, short-course regimen for MDR-TB with additional resistance to fluoroquinolones (MDR-TBFQ+) or second-line injectable (MDR-TBSLI+) [3]. After 24-36 weeks of treatment, this regimen resulted in 91% favorable outcomes in pulmonary MDR-TB patients with additional drug resistance. While this result is encouraging, there was no control arm and study participants were not followed for relapse, so long-term favorable outcomes are likely somewhat less. Cardiotoxicity was minimal, and myelosuppression, while common, was detected early and treated successfully [3].

The ZeNix trial tested a 6-month bedaquiline, pretomanid and linezolid regimen with lower and/or shorter durations of linezolid to investigate the potential for decreasing toxicity of the NiX-TB regimen while retaining its efficacy [4]. Linezolid dosing was 1200 mg daily for 2 months or 6 months or 600 mg daily for 2 months or 6 months [4]. The overall risk-benefit ratio favored linezolid at a dose of 600mg for 26 weeks in combination with bedaquiline and pretomanid. With this regimen, 91% of participants had a favorable outcome, while peripheral neuropathy occurred in 24%, myelosuppression occurred in 2%, and modification of the linezolid dose occurred in 13% of regimen participants. Thus, while this reduced linezolid dosing reduced the toxicity seen with the NiX-TB regimen, there was still substantial toxicity. TB PRACTECAL was a phase II/III clinical trial evaluating the efficacy of three 24-week, all oral regimens for rifampin-resistant tuberculosis [5]. A regimen of bedaquiline, pretomanid, linezolid and moxifloxacin ("BPaLM") was compared to the local WHO-approved standard of care. BPaLM was shown to be superior to the standard of care, with favorable outcomes in 89%, compared to 52% favorable outcomes in the standard of care group, largely driven by early discontinuation of treatment because of adverse effects. The STREAM Stage II Trial compared a 9-month bedaquiline-based regimen, a six-month bedaquiline and injectable-based regimen (with the injectable for only an 8-week induction period) to

concurrent standard of care control arms [6]. The all-oral 9-month regimen had 83% favorable outcomes compared to 73% on the control regimen; the 6-month regimen had 91% favorable outcomes compared to 51% among the concurrent controls. Thus, both regimens had superior efficacy to the control arms. Tolerability of the regimens was similar, although hearing loss was more frequent in the control arm.

Clinical Trials of DR-TB Presented as Abstracts

BEAT-Tuberculosis was a phase III, multi-center trial aiming to compare the efficacy and safety of a 6-month regimen consisting of bedaquiline, delamanid, linezolid, levofloxacin, and clofazimine, modified by dropping either levofloxacin or clofazimine based on the results of fluoroquinolone susceptibility testing, compared to the South African standard of care (9-month all oral bedaquiline-based regimen). [7]. The investigational strategy was non-inferior to the standard arm [7].

SimpliciTB was a trial examining a pan-TB 4-month regimen of bedaquiline, pretomanid, moxifloxacin and pyrazinamide comared to HRZE with an additional arm of persons with FQ-S MDR-TB. The regimen did not achieve non-inferiority compared to the control arm, largely due to approximately 10% of participants on the investigational arm discontinuing the regimen due to side effects [8]. The SODUCU trial studied sutezolid added to a background regimen of bedaquiline, delamanid and moxifloxacin, given for 12 weeks. The regimen was well tolerated and modestly improved the treatment efficacy of the regimen [9].

Other Important Publications

The 8th edition of MSF Drugs Under the Microscope was released in 2022, noting a continued need for child-friendly formulations of DR-TB medicines. They also report that bedaquiline and delamanid are still patented medicines, contributing to the high costs of DR-TB treatment [10].

This year's TAG TB Pipeline Report provides an excellent summary of recent developments and works in progress in TB diagnosis, treatment, and prevention [11]. The TB Treatment report is a strong tool for clinicians to stay updated on current TB clinical trials.

In 2022, a campaign called 1/4/6 x 24 led by an international network of TB survivors, researchers, clinicians, and activists. The campaign name comes from its main goal: to demand action for implementation of shortest available regimens – one month or once-weekly for TB prevention, four months for drug-sensitive TB, and six months for drug-resistance TB by the end of 2024 [12]. They will continue to advocate for shorter regimens and equitable access to TB care in the following years.

New WHO Guidelines in the past year

This year, the WHO released updated module 4 of its consolidated guidelines on tuberculosis: Drug-resistant tuberculosis treatment. In Module 4 confirmed the earlier Rapid WHO Communication of May 2022 endorsing 9-month all-oral bedaquiline-containing regimens for patients with MDR/RR-TB and added a recommendation for the 6-month BPaLM regimen in patients with MDR-TB, rifampicin resistant TB, or pre-XDR TB [13]. An additional new regimen, 6 months of rifampicin, ethambutol, pyrazinamide and levofloxacin, is now recommended for patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis.

This year also saw release of an updated Module 5: Management of tuberculosis in children and adolescents. This update includes the following recommendations related to treatment of DR-TB (or suspected DR-TB) in children:

1. In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used
2. In children with MDR/RR-TB aged below 3 years delamanid may be used as part of longer regimens.

Around the corner…stay tuned!

Additional new developments are anticipated in the coming year that could bring us closer to better diagnosis, shorter and less toxic treatment, and even preventive regimens for DR-TB. These include the the V-QUIN trial, the TB-CHAMP trial, the endTB trial, and DECODE, all expected to report out in 2023. To hear the latest news, watch the RESIST-TB website (www.resisttb.org) and/or visit the website and subscribe to our monthly e-newsletter!

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