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Treatments of Multidrug-Resistant Tuberculosis: Light at the End of the Tunnel

Tuberculosis is the leading cause of bacterial infectious diseases death worldwide (1). Over the past decade, the number of patients identified with rifampicin-resistant tuberculosis (RR-TB) or multidrug-resistant tuberculosis (MDR-TB; RR-TB plus isoniazid-resistant tuberculosis) has increased by approximately 20% annually (2). MDR/RR-TB is related to long treatment duration, incurs high treatment costs, and generally leads to poor treatment outcomes (3).

After decades of neglect, the field of antituberculosis drug development is fortunately now observing explosive growth. A substantial number of novel compounds are entering the clinical stages of drug development, and repurposed drugs are being clinically evaluated for efficacy, safety, and tolerability in the treatment of MDR/RR-TB.

Repurposing of antibiotics that were developed for indications other than tuberculosis is an inexpensive strategy to bridge the time until novel drugs become available. This approach worked with moxifloxacin, linezolid, and clofazimine successfully, three of the five best available drugs for the treatment of MDR/RR-TB. β-lactams are another class of antibiotics under evaluation for this purpose. In this issue of the *Journal*, De Jager and colleagues (pp. 1228–1235) report on the early bactericidal activity of different concentrations of meropenem plus clavulanate (4). Unfortunately, the effect was only modest, and the treatment was poorly tolerated. Moreover, the intravenous route of administration of meropenem is operationally not feasible in most countries where MDR/RR-TB is prevalent.

The first clinical trial for a regimen to treat MDR-TB based on a novel antituberculosis medicine was initiated in 2007 (5), and we now find ourselves in the enviable position of having a World Health Organization–endorsed 9-month oral regimen for MDR-TB and a 6-month oral regimen for extensively drug-resistant TB (6) (i.e., at the time of World Health Organization endorsement defined as MDR-TB plus resistance to a fluoroquinolone and/or amikacin, capreomycin, or kanamycin; since then, extensively drug-resistant TB has been redefined as MDR-TB plus resistance to any fluoroquinolone plus bedaquiline and/or linezolid) (7) with 3 new regimens recently reported, plus 10 regimens currently under study (Table 1). Despite this, for many regions, including Europe, the majority of patients with MDR/RR-TB still require an individualized

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Table 1. Clinical Trials for the Evaluation of Novel Multidrug-resistant Tuberculosis/Rifampicin-Resistant Tuberculosis Treatment Regimens

Name	Regimen	Location	Status 2/2002	Clinical Trials Number
TRUST	Levofloxacin, linezolid, cycloserine, and pyrazinamide (or clofazimine if resistant to pyrazinamide)	China	Recruiting	NCT03867136
MDR-END	Delamanid, linezolid, levofloxacin, and pyrazinamide	Korea	Fully enrolled; in follow-up	NCT02619994
STREAM Stage 2	Bedaquiline, clofazimine, ethambutol, levofloxacin, pyrazinamide, isoniazid, and prothionamide	Ethiopia, Georgia, India, Moldova, Mongolia, South Africa, and Uganda	Fully enrolled; in follow-up	NCT02409290
InDEX	Gene-derived individualized DR-TB regimen	South Africa	Recruiting	NCT03237182
endTB	Bedaquiline, moxifloxacin, linezolid, and pyrazinamide; or bedaquiline, clofazimine, levofloxacin, linezolid, and pyrazinamide; or bedaquiline, delamanid, levofloxacin, linezolid, and pyrazinamide; or delamanid, clofazimine, levofloxacin, linezolid, and pyrazinamide; or delamanid, clofazimine, moxifloxacin, and pyrazinamide	Georgia, India, Kazakhstan, Lesotho, Pakistan, Peru, and South Africa	Fully enrolled; in follow-up	NCT02754765
SimpliciTB	Bedaquiline, pretomanid, moxifloxacin, and pyrazinamide	Africa, Asia, Europe, and South America	Fully enrolled; in follow-up	NCT03338621
BEAT-Tuberculosis	Bedaquiline, delamanid, and linezolid plus levofloxacin or clofazimine	South Africa	Recruiting	NCT04062201
GRACE-TB	Individualized regimen guided by rapid molecular drug susceptibility tests	China	Not yet recruiting	NCT03604848
DRAMATIC	Levofloxacin, bedaquiline, linezolid, delamanid, and clofazimine	Vietnam, The Philippines	Recruiting	NCT03828201
BEAT-TB	Bedaquiline, delamanid, linezolid, and clofazimine	India	Fully enrolled	CTRI/2019/01/017310

Definition of abbreviation: DR-TB = drug-resistant TB.
Adapted from Reference 16.

long-term treatment regimen of at least 18 months' duration owing to complex drug-resistance patterns of the causative bacteria (8).

The three new regimens recently reported include the NExT trial published by Esmail and colleagues in this edition of the *Journal* (pp. 1214–1227) (9), the ZeNiX trial, and the TB-PRACTECAL trial, the latter two as yet only reported in abstract form (10, 11). These trials build on the 6-month "NiX-TB" regimen (12), an all-oral 6-month treatment regimen with bedaquiline, pretomanid, and high-dose linezolid, which achieved a 90% cure rate in a cohort of patients with an advanced spectrum of drug-resistant TB. However, 81% of patients in the NiX trial experienced peripheral neuropathy, and 48% experienced myelosuppression, toxicities attributed to the high dose of the oxazolidinone linezolid used in the trial, 1,200 mg daily, given for a full 6 months. The NExT trial reduced the linezolid dose to 600 mg daily, and ZeNiX studied that dose plus two regimens in which linezolid was given for only the first 2 months at either 1,200 or 600 mg per day, and TB-PRACTECAL gave linezolid at 600 mg for 4 months followed by 2 months at 300 mg daily (9, 11, 12). All of these dose reductions decreased toxicity substantially. Although the protocol-defined favorable outcome proportion with the NExT regimen was only 51%, this was largely attributable to the discontinuation of linezolid; overall positive outcomes ("patient-centered") at 24 months were 75%. In the ZeNiX and TB-PRACTECAL trials, where discontinuation of linezolid was not an unfavorable outcome, cure proportions were 89–93%. Thus, we appear to be on the verge of having reasonably well-tolerated, effective 6-month treatment regimens for MDR/RR-TB with existing medicines.

Until entirely novel regimens become available, two important challenges remain: First, linezolid, and many of the newer oxazolidinones, were purposefully made to be broad spectrum, and the demand for spectrum enhances inhibition of mitochondrial translation, leading to the unfortunate toxicity observed in these reports. The toxicity of lower doses of linezolid still means that 15–25% of patients will require dose reduction or discontinuation of the drug (10). This challenge is being addressed in the TB Drug Accelerator program funded by the Bill and Melinda Gates Foundation to design a TB-selective, nontoxic oxazolidinone. By focusing on inhibiting only the *Mycobacterium tuberculosis* ribosome, a selective and nontoxic molecule has been developed by teams at Merck and the National Institute of Allergy and Infectious Diseases of the NIH (13). As a result of this effort, a novel potent oxazolidinone is now entering phase I trials this year to be evaluated for safety and tolerability.

The second challenge is that all of the 6-month MDR-TB regimens are built on a bedaquiline backbone. A recent report from South Africa, the first country to roll out bedaquiline-based regimens

for MDR/RR-TB nationwide, revealed baseline bedaquiline resistance in 3.8% of patients associated with previous exposure to bedaquiline or clofazimine (14). These findings are supported by a recent survey from Moldova, a high-burden country for MDR-TB, documenting >15% of acquired bedaquiline resistance under MDR/RR-TB therapy in a smaller cohort (15). Thus, identifying options for the treatment of bedaquiline-resistant TB needs to be addressed immediately. Unfortunately, of the 10 ongoing MDR-TB trials, only 3 are studying bedaquiline-free regimens (16). Moreover, none of the existing antimycobacterial agents appear to provide as much antimycobactericidal activity as bedaquiline.

It becomes evident that not single drugs but novel regimens consisting only of new drugs will be needed to combat the emergence of *M. tuberculosis* drug resistance. Presently, 7 new compounds are in clinical phase I, and an additional 10 compounds are in clinical phase II of drug development (17). In industry and academia partnerships, funded by UNITE4TB (the European Commission) and Project to Accelerate New Treatments for Tuberculosis (PAN-TB collaboration) (the Bill and Melinda Gates Foundation), these compounds are now being clinically evaluated around the globe to provide treatment regimens with entirely new antituberculosis medicines in the coming decade.

We have realistic hope for effective, short, and tolerable treatments becoming available for all patients with tuberculosis, irrespectively of current classifications of drug resistance, in the coming years. ■

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