A review of tuberculosis: Focus on bedaquiline

BONNIE CHAN, TINA M. KHADEM, AND JACK BROWN

Purpose. The history and prevalence of tuberculosis and the role of bedaquiline in multidrug-resistant (MDR) tuberculosis are reviewed.

Summary. Tuberculosis continues to cause significant morbidity and mortality worldwide. Increasing rates of drug-resistant tuberculosis are a significant concern and pose serious implications for current and future treatment of the disease. In December 2012, the Food and Drug Administration approved bedaquiline as part of the treatment regimen for pulmonary MDR tuberculosis. Bedaquiline's unique mechanism of action presents an alternative approach to current antimycobacterial killing. By directly inhibiting adenosine triphosphate (ATP) synthase, bedaquiline is effective against both replicating and dormant mycobacteria. Pulmonary cavitary lesions can contain heterogeneous populations. This potential mix of semireplicating and hypometabolic mycobacteria is more difficult to eliminate with conventional antitubercular drugs, thus increasing the risk of resistance. No in vitro cross-resistance between bedaquiline and currently available antitubercular agents has been observed thus far. Because bedaquiline targets a completely different enzyme, cross-resistance with other conventional agents remains unlikely. Enhanced sterilizing capacity via synergistic depletion of ATP further exhibits the promising potential of bedaquiline with pyrazinamide. A course of bedaquiline requires 24 weeks of therapy in combination with other antitubercular drugs.

Conclusion. The approval of bedaquiline represents a major milestone in MDR tuberculosis therapy. Bedaquiline should be considered in patients who have not responded to a regimen containing four second-line drugs and pyrazinamide and patients with documented evidence of MDR tuberculosis resistant to fluoroquinolones. The exact role of bedaquiline cannot be determined until further efficacy and safety data are obtained through ongoing Phase III trials.

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Before the mid-19th century, tuberculosis remained an ancient disease about which much was hypothesized but little was definitively known. Speculations of its origins date back nearly 15,000 to 20,000 years ago.[1,2] Tuberculosis paleopathological changes have been found in human remains from predynastic Egypt (3500–2650 BC), Neolithic Sweden (3200–2300 BC), and Neolithic Italy (fourth millennium BC).[2-4] The earliest human cases of tuberculosis thus far were confirmed in bone lesions from a 9,000-year-old Neolithic infant and woman in the eastern Mediterranean.[5] It was not until 1720 that English physician Benjamin Marten first proposed the transmission of small living organisms as the culprit for pulmonary tuberculosis, referred to then as "consumption." In 1882, German physician Robert Koch successfully visualized and identified this causative microbe as *Mycobacterium tuberculosis*. Koch went on to earn the Nobel Prize in Physiology or Medicine in 1905 for his tuberculin skin test.[2,6]

Modern era of tuberculosis

Tuberculosis continues to cause significant morbidity and mortality worldwide. Approximately 2 billion people—one third of the world's population—are thought to be infected with tuberculosis.[7] The highest rates for tuberculosis are among

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developing countries, where societal factors, such as rapid urbanization and migration, pose special challenges in tuberculosis prevention and control.[7,8] Urbanization, migration, and poverty remain invariably linked to tuberculosis transmission. Lower socioeconomic groups are at increased risk due to higher exposure in overcrowded living and working conditions, malnutrition, poor health awareness, and limited access to quality health care.[7] These circumstances, along with human immunodeficiency virus (HIV) and drug resistance, remain major contributors to global tuberculosis rates.

In 1993, the World Health Organization (WHO) declared tuberculosis a global public health emergency.[9] National and international efforts to treat and control tuberculosis were reinvigorated with strategies such as DOTS (Directly Observed Treatment, Short-Course) and Stop TB.[9] Introduced in the mid-1990s, DOTS was an international strategy focusing on five key elements of action, which were further expanded in the Stop TB strategy (appendix). The implementation of DOTS programs in 182 countries was met with positive results as countries were able to improve national tuberculosis control programs. By 2004, more than 20 million tuberculosis cases were treated through DOTS programs, and more than 16 million of these cases were cured.[9,10] The Stop TB strategy was launched by WHO in 2006 as an evidenced-based approach to reducing the burden of tuberculosis. Targets set by the STOP TB Partnership endeavor toward a 2015 goal to reduce tuberculosis prevalence and related mortality rates by 50% compared with the rates in 1990. The ultimate goal is to eliminate tuberculosis as a public health problem by 2050.[10] According to the 2012 WHO Global Tuberculosis Report, progress toward attaining the 2015 goal is being made. From 2010 to 2011, new cases of tuberculosis decreased by 2.2%. Tuberculosis-related mortality rates dropped 41% between 1990 and 2011.[9]

Burden of tuberculosis and multidrug-resistant tuberculosis

In 2011, tuberculosis ranked as the second leading worldwide cause of death among infectious diseases. An estimated 8.7 million new tuberculosis cases (125 cases per 100,000 persons) and 1.4 million tuberculosis-related deaths occurred in 2011.[9] In the United States, the number of reported tuberculosis cases declines each year. People infected with HIV as well as people who have come from countries with endemic tuberculosis represent a significant number of tuberculosis cases in the United States. Across all age groups, 6% of people with tuberculosis have reported being infected with HIV, a percentage that has remained unchanged since 2008.[9]

Although global tuberculosis rates are on the decline, concerns regarding multidrug-resistant (MDR) tuberculosis and extensively drug-resistant (XDR) tuberculosis are growing. MDR tuberculosis, defined as tuberculosis resistant to both isoniazid and rifampin, emerged during the 1970s. Of the 12 million cases of tuberculosis, approximately 630,000 are estimated to be MDR tuberculosis.[9] Tuberculosis surveillance programs were notified of nearly 60,000 cases of MDR tuberculosis globally in 2011.[11] More than half of these cases occurred in patients living in India, China, the Russian Federation, and South Africa. Approximately 4% of new cases (primary drug resistance) and 20% of previously treated cases (acquired drug resistance) qualified as MDR tuberculosis.[9] Of these MDR tuberculosis cases, approximately 9% are thought to be XDR tuberculosis. XDR tuberculosis is defined as tuberculosis resistant to isoniazid, rifampin, fluoroquinolones, and at least one of three injectable second-line drugs (amikacin, kanamycin, or capreomycin).[9] The incidence of drug-resistant tuberculosis may further rise as accessibility to antimicrobial susceptibility testing for isoniazid and rifampicin increases.

Tuberculosis microbiology and drug resistance

M. tuberculosis is inherently resistant to many antimicrobials. Classified as acid-fast bacilli, the virulence and slow growth of *M. tuberculosis* have been attributed to its unique cell wall structure.[12] Covalently linked to underlying arabinogalactan and peptidoglycan macromolecules, mycolic acids and free lipids create a tight, closely packed hydrophobic barrier. This barrier is approximately 1000-fold less permeable to hydrophilic molecules, such as water-soluble antibiotics, than the cell wall of *Escherichia coli*.[13] The inner saccharide layer further inhibits lipophilic substances from entering, making the cell wall remarkably difficult to penetrate. Besides being covalently attached to the cell wall, mycolic acids form trehalose 6,6´-dimycolate (TDM), a toxic glycolipid found in the cell envelope. TDM has been implicated in the intracellular survival of *M. tuberculosis*. By preventing phagosome–lysosome fusion and thus arresting the biogenesis of mature phagolysosomes, TDM allows *M. tuberculosis* to remain latent in host macrophages for years.[14]

The resistance of *M. tuberculosis* to antitubercular drugs is likely the result of a spontaneous genetic event; at worst, it is a "man-made amplification of the natural phenomenon."[15] The likelihood of spontaneous mutations to isoniazid and rifampin are 3.5×10^{-6} and 3.1×10^{-8}, respectively.[16,17] Given that pulmonary cavities often contain high bacterial loads (10^7–10^9 organisms), concern regarding spontaneous dual mutations has been noted.[18] However, as the chromosomal loci responsible for resistance are not linked, the risk of dual spontaneous mutations to

both isoniazid and rifampin is quite low (9×10^{-14}).[16] MDR tuberculosis isolates may arise via sequential accumulations of mutations in target genes for specific antibiotics due to subtherapeutic drug levels, such as from treatment errors or poor adherence. Resistance to first-line agents has been linked to mutations in at least 10 genes.[18-20] The transfer of these resistant mutations from one agent to another has been demonstrated through the evolution of two closely related subclones of MDR tuberculosis, W and W1, responsible for widespread disease in New York City and elsewhere.[21]

Drug-susceptibility testing for resistant tuberculosis

The lack of laboratory diagnostic capacity has been identified as a critical barrier in preventing early and appropriate identification of and subsequent therapy for MDR tuberculosis. According to WHO, the documented cases of MDR tuberculosis in 2011 represented 19% of the estimated 310,000 cases of MDR tuberculosis in patients with pulmonary tuberculosis for that same year.[9] Overall, the numbers of MDR tuberculosis cases diagnosed and subsequently treated with second-line agents remain below the Global Plan to Stop TB targets, which established that by 2015 (1) over 50% of estimated MDR tuberculosis cases will be detected and notified, (2) 100% of patients with confirmed MDR tuberculosis will receive treatment, and (3) over 75% of MDR tuberculosis cases will be successfully treated.[10]

In response to this growing crisis, WHO has published guidelines for the programmatic management of drug-resistant tuberculosis. The 2011 update provided further focus on the detection and treatment of drug-resistant tuberculosis in resource-limited settings. Specifically, rapid drug-susceptibility testing of isoniazid and rifampin or of rifampin alone is recommended over conventional testing or no testing at the time of diagnosis.[22] Rifampin resistance is a marker for MDR tuberculosis in over 90% of cases.[23] The results of conventional testing of cultured mycobacteria and drug-susceptibility testing may not become available for months. Studies have found that rapid drug-susceptibility testing with molecular techniques allows for a shorter time to diagnosis and earlier treatment of MDR tuberculosis.[22,24] Depending on the molecular test (line probe assays versus Xpert MTB/RIF [Cepheid, Sunnyvale, CA]) the *M. tuberculosis* complex as well as mutations in the *rpoB* (rifampin resistance) or *katG* (high-level isoniazid resistance) gene regions may be simultaneously detected.[25] However, conventional culture and drug-susceptibility testing still should be used to rule out resistance to second-line agents, which cannot be detected by molecular tests.

Current treatment for MDR tuberculosis

Lengthy therapy with multiple antitubercular drugs is necessary due to the intracellular location and slow growth of *M. tuberculosis* and the decreased likelihood of a resistant mutation to persist during combination therapy.[26,27] At least four antitubercular drugs are to be used in combination for MDR tuberculosis. As a conditional recommendation by WHO, treatment regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or protionamide), and cycloserine (or *p*-aminosalicylic acid if cycloserine cannot be used). These second-line agents are not as effective as isoniazid and rifampin, and there have been no randomized trials to help optimize their use against MDR tuberculosis.[28] Consequently, the choice of drug primarily depends on drug-susceptibility testing of the isolated resistant strain, prior tuberculosis treatment, and the frequency of the drug's use or documented background of resistance in the setting.[22,29,30]

Antitubercular drugs for the treatment for MDR tuberculosis have been grouped by WHO according to efficacy, experience of use, and drug class (Table 1).[31,32] Group 1 drugs are considered the most potent and best tolerated agents. Drugs in groups 2–5, apart from streptomycin, are considered second-line or reserve drugs for treating MDR tuberculosis. Treatment of MDR tuberculosis with more than one injectable agent is unnecessary.[31] Fluoroquinolones are used extensively in the treatment of MDR tuberculosis. Like the injectable agents, only one fluoroquinolone should be used per regimen, as they all share the same genetic target, *gyrA*. Newer-generation fluoroquinolones are recommended over earlier-generation fluoroquinolones. Given the cost and toxicity profiles of each agent, high-dose levofloxacin (1000 mg daily) and moxifloxacin are considered the fluoroquinolones of choice. Ciprofloxacin is no longer recommended to treat drug-susceptible or drug-resistant tuberculosis due to the rapid development of resistance.[22,33]

Among the oral bacteriostatic agents, thioamides followed by cycloserine and then *p*-aminosalicylic acid are recommended in the following order based on efficacy, adverse events, and cost. Thioamides, specifically ethionamide, are associated with higher cure rates than cycloserine and *p*-aminosalicylic acid.[22] Ethionamide inhibits the activity of the *inhA* gene product, enoyl–acyl carrier protein reductase. This is the same enzyme by which activated isoniazid inhibits mycolic acid biosynthesis and may account for cross-resistance between isoniazid-resistant isolates and ethionamide. When two oral bacteriostatic agents are warranted, cycloserine, which inhibits the incorporation of D-alanine into mycobacterial cell wall synthesis, may be added. Cycloserine is associ-

Table 1.
Antitubercular Agents for the Treatment of Multidrug-Resistant Tuberculosis[27,31,32]

Drug(s)	Adult Daily Dose	Major Adverse Effects
First-line oral agents[a]		
Pyrazinamide	20–30 mg/kg	Nausea, vomiting, hepatotoxicity
Ethambutol	15–25 mg/kg	Neuropathy (optic neuritis)
Rifabutin	5 mg/kg	Rash, discoloration of body fluids, neutropenia
Injectable agents		
Kanamycin	15–20 mg/kg	Renal, auditory, and vestibular toxicities
Amikacin	15–20 mg/kg	Renal, auditory, and vestibular toxicities
Capreomycin	15–20 mg/kg	Renal, auditory, and vestibular toxicities
Streptomycin	15–20 mg/kg	Vestibular, renal, and auditory toxicities
Fluoroquinolones		
Levofloxacin	1000 mg	Gastrointestinal symptoms, insomnia, dizziness, Q-T interval prolongation, tendon rupture
Moxifloxacin	400 mg	Gastrointestinal symptoms, insomnia, dizziness, Q-T interval prolongation, tendon rupture
Ofloxacin	800 mg	Gastrointestinal symptoms, insomnia, dizziness, Q-T interval prolongation, tendon rupture
Oral, bacteriostatic second-line agents		
p-aminosalicylic acid	150 mg/kg	Gastrointestinal intolerance
Cycloserine	15–20 mg/kg	Peripheral neuropathy, central nervous system dysfunction
Terizidone[b]	15–20 mg/kg	Neurologic and psychiatric disturbances
Ethionamide	15–20 mg/kg	Gastrointestinal intolerance, peripheral neuropathy, psychiatric disturbances
Protionamide[b]	15–20 mg/kg	Gastrointestinal intolerance, peripheral neuropathy, psychiatric disturbances
Agents with unclear role in treatment of drug-resistant tuberculosis		
Clofazimine[b]	100 mg	Gastrointestinal intolerance, skin pigmentation
Linezolid	600 mg	Myelosuppression, peripheral neuropathy
Amoxicillin/clavulanate	875 mg/125 mg every 12 hr	Diarrhea, rash
Thiacetazone[b]	150 mg	Cutaneous hypersensitivity
Imipenem/cilastatin	500–1000 mg every 6 hr	Seizures
High-dose isoniazid	16–20 mg/kg	Hepatotoxicity, peripheral neuropathy
Clarithromycin	500 mg every 12 hr	Gastrointestinal intolerance, Q-T interval prolongation

[a]Isoniazid and rifampin are not included as first-line oral agents for multidrug-resistant tuberculosis due to resistance.
[b]Not available in the United States.

ated with a high rate of neuropsychiatric symptoms, ranging from somnolence to severe psychosis and suicidal ideation. Greater than 50% of patients who receive cycloserine 1 g daily may experience these adverse effects. Finally, *p*-aminosalicylic acid remains a last-line agent because of its low effectiveness, poor tolerability in the gastrointestinal tract, and high cost.[34]

Group 5 agents are not recommended for routine use in drug-resistant tuberculosis treatment regimens. Inconclusive clinical evidence due to confounding results makes it difficult to provide definitive recommendations for these agents.[31] For the most part, these agents are used in difficult-to-treat drug-resistant tuberculosis against which agents from groups 1–4 are inadequate.

Focus on bedaquiline

The emergence and rise of drug-resistant tuberculosis are direct consequences of the shortcomings of current tuberculosis management strategies. The need for early and accurate diagnosis, supported by appropriate and supervised treatment, and a strong commitment to tuberculosis control and research have been heavily emphasized in the fight against resistance. However, many resource-limited countries may lack adequate laboratories and tools to detect and resources to treat MDR tuberculosis. The treatment of MDR tuberculosis presents serious challenges. Treatment of MDR tuberculosis is lengthy, costly, and associated with high rates of serious drug-related toxicity. Protracted therapy with complex regimens is

a significant barrier to adherence. Costs associated with these regimens further complicate an already difficult situation. A standard course of antitubercular drugs may cost about $20, while drugs to treat MDR tuberculosis may cost as much as $5000, depending on the agents used and the duration of therapy.[35] Costs from additional diagnostic tests, laboratory tests, and office visits may further augment expenses in an already prolonged and extensive treatment regimen.

The need for new drugs to combat MDR tuberculosis is critical. Current therapies primarily consist of older second-line agents that have been repurposed for the treatment of MDR tuberculosis.[36] The available evidence to guide the dosing and combination of these agents remains limited and of low quality. Without new drugs, the dilemma of treating progressively more-resistant tuberculosis with potentially nonsusceptible or less-effective regimens will escalate. Moreover, there is a profound need for newer agents that may shorten or simplify current treatment regimens for drug-sensitive, MDR, and XDR tuberculosis. To date, the target treatment success rate of at least 75% for MDR tuberculosis was achieved by only 30 of 107 countries that reported treatment outcomes.[9]

For over 40 years, no new agents for the treatment of tuberculosis had been approved. In light of resistance and cross-resistance among antitubercular agents, bedaquiline represents a much-needed treatment strategy when all other routes have been exhausted. Bedaquiline is the first novel antitubercular drug to be approved since rifampin in 1970.[37] New chemical entities, such as bedaquiline, account for a minority of compounds in the antitubercular drug pipeline. Furthermore, bedaquiline's novel mechanism of action sets it apart from analogs of known antitubercular drugs and existing antibiotics under investigation.

In December 2012, the Food and Drug Administration (FDA) approved bedaquiline as part of the treatment regimen for pulmonary MDR tuberculosis. Specifically, the use of bedaquiline should be reserved for patients for whom effective treatment regimens cannot otherwise be provided.[38] This constraint stemmed from FDA's accelerated approval program in which bedaquiline was granted approval based on efficacy and safety data from Phase II studies.[39] Below, the available data for and clinical implications of bedaquiline are discussed.

Drug discovery. The development of bedaquiline is an important advance against tuberculosis and involved the screening of over 70,000 compounds for inhibition against *Mycobacterium smegmatis*, a rapidly growing, nonpathogenic mycobacterium used as a model for tuberculosis.[40,41] From these prototypes, Andries et al.[42] identified bedaquiline (initially known as R207910, then TMC207) as the lead compound among a series of diarylquinolines. Bedaquiline was the most active among three compounds with in vivo antimycobacterial activity. Their results, which were seven years in the making, were first described at the 2004 Interscience Conference on Antimicrobial Agents and Chemotherapy meeting.[43]

Chemistry. Diarylquinolines contain a quinolinic central heterocyclic nucleus with side chains of tertiary alcohol and tertiary amine groups.[44] A pure enantiomer with two chiral centers, bedaquiline was isolated from a mixture of four isomers. Using high-performance liquid chromatography (HPLC), Andries et al.[42] purified and separated two diastereoisomers with an A:B ratio of 40:60. The active diastereoisomer was further separated by chiral HPLC; bedaquiline was the active *R,S*-isomer. The chemical name of bedaquiline is 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol, and the molecular formula is $C_{32}H_{31}BrN_2O_2$. Bedaquiline has a molecular weight of 555.51 daltons.[42]

Target and mechanism of action. Although derived from quinolones, bedaquiline exhibits no inhibitory effects on DNA gyrase. Instead, bedaquiline inhibits mycobacterial adenosine triphosphate (ATP) synthase, an essential enzyme in the generation of energy for *M. tuberculosis*.[42,45] Bedaquiline binds to the oligomeric and proteolipic subunit c of the proton pump of mycobacterial ATP synthase and is assumed to mimic a conserved basic residue in the proton transfer chain, arginine 186. Subsequently, conformational changes occur in mycobacterial ATP synthase by blocking the rotary movement of subunit c, which is necessary for proton flow.[45] Although bedaquiline is highly active against both replicating and dormant mycobacteria, *M. tuberculosis* in a dormant state may be especially sensitive to ATP depletion. Thus, for an organism that already exists in "low-energy" states, further depletion of low ATP stores results in an effective method of antimycobacterial killing.

The novel mechanism of action of diarylquinolines was initially identified in an analysis of mutant strains resistant to bedaquiline. Point mutations in the genome sequences of *M. tuberculosis* and *M. smegmatis* target the *atpE* gene responsible for encoding subunit c of ATP synthase. Further findings indicate bedaquiline's highly selective inhibition of *M. tuberculosis* ATP synthase.[42] Haagsma et al.[46] observed a 20,000-fold lower sensitivity for bedaquiline by human mitochondrial ATP synthase compared with mycobacterial ATP synthase. In their study, mitochondria from human cells, murine liver, and bovine heart all showed very low sensitivity for bedaquiline, indicating unlikely target-based toxicity in mammalian cells.

Antimicrobial spectra. Bedaquiline has demonstrated potent antimycobacterial activity against replicating bacilli both in vitro and in vivo. The activity of bedaquiline seems to be limited to mycobacteria. For in vitro antimycobacterial activity, the median minimum inhibitory concentrations (MICs) of bedaquiline against *M. tuberculosis* H37Rv and six susceptible isolates of *M. tuberculosis* were 0.03 and 0.06 μg/mL, respectively. The median MIC of bedaquiline against *M. tuberculosis* strains resistant to both isoniazid and rifampin was 0.03 μg/mL. Overall, these MICs were much lower than the MICs of gram-positive and gram-negative bacteria. MICs exceeding 32 μg/mL were observed for *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae*, and *E. coli*.[42]

No cross-resistance between bedaquiline and other antitubercular drugs has been detected. Bedaquiline demonstrated similar in vitro activity against *M. tuberculosis* clinical isolates resistant to isoniazid, rifampin, streptomycin, ethambutol, pyrazinamide, and moxifloxacin.[42] For susceptibility testing, Andries et al.[42] included a total of 50 strains of *M. tuberculosis*, of which 30 clinical isolates were MDR tuberculosis. Strains were subcultured on Löwenstein–Jensen media at 37 °C. The radiometric BACTEC 460 method (BD, Franklin Lakes, NJ) was used to determine the susceptibility of bedaquiline and other conventional tuberculosis agents at their standard breakpoint concentrations (rifampin 2.0 μg/mL, isoniazid 0.2 μg/mL, streptomycin 4.0 μg/mL, and ethambutol 5.0 μg/mL). All MDR tuberculosis isolates tested were susceptible to bedaquiline at 0.1 μg/mL with 57% of these isolates (17 of 30) susceptible at 0.01 μg/mL.[42]

Susceptibility testing. Current recommendations for susceptibility testing do not include the Löwenstein–Jensen medium, since the results from cultures using this medium are finalized within four to five weeks.[47] Instead, recommended susceptibility-testing methods include the Middlebrook 7H10/7H11 Agar method and the resazurin microtiter assay (REMA).[48,49] Both methods assess a range of concentrations from 0.008 to 1.0 μg/mL. With the Middlebrook 7H10/7H11 Agar method, the MIC is determined as the lowest concentration of bedaquiline with 99% inhibition of growth. The MIC for the REMA is determined by the lowest concentration of bedaquiline that prevents a visible change of resazurin color from blue to pink.[38]

Pharmacokinetics and pharmacodynamics. Pharmacokinetic studies in healthy male volunteers showed a linear relationship between bedaquiline doses and the maximum plasma concentration (C_{max}) and area under the concentration–time curve (AUC). In both single and multiple ascending-dose studies, C_{max} and AUC increased proportionally up to the highest doses tested—a single dose of 700 mg and multiple daily doses reaching 400 mg. After administration of a single dose, bedaquiline concentrations peaked at 5 hours and declined triexponentially once the C_{max} was reached. An "effective half-life" of approximately 24 hours was deduced from a twofold increase in the AUC from administration to 24 hours later.[42]

Comparable pharmacokinetic parameters were observed in Phase II studies. In an early bactericidal activity study of 75 treatment-naive patients with smear-positive pulmonary tuberculosis, a regimen of 400 mg daily for seven days resulted in a C_{max} of 5.5 μg/mL, an AUC of 64.75 μg·hr/mL, and a time to maximum concentration of four hours.[50] Mean plasma concentration–time profiles were described by Diacon et al.[51] in a study of 47 patients with pulmonary MDR tuberculosis. A treatment regimen of 400 mg daily for two weeks followed by 200 mg three times a week for six weeks correlated with mean peak and steady-state concentrations of 1.659 and 0.902 ng/mL at week 8, respectively. Steady-state plasma concentrations for most patients remained above the target level of 0.6 μg/mL throughout the eight-week study period.[51] A terminal elimination half-life of approximately 5.5 months was observed with bedaquiline and its major metabolite, *N*-monodesmethyl (M2). In fact, plasma concentrations of bedaquiline and M2 were still quantifiable at week 96.[52]

Long half-lives and prolonged effects of single-dose administrations in mice provided the initial rationale for less-frequent administration. In murine models, bedaquiline exhibited half-lives ranging up to 64 and 92 hours in plasma and tissue, respectively.[42] Diacon et al.[52] attributed prolonged half-lives in their study patients with the slow distribution of bedaquiline and M2 from tissues. Both compounds have cationic amphiphilic characteristics, which may cause intracellular accumulation of phospholipids and lead to drug accumulation. Excess accumulation of phospholipids in tissues is reversible on drug termination and subsequent elimination.

These prolonged effects from a single dose supported the potential for less-frequent dosing regimens. Once-weekly doses of 12.5 mg/kg for four weeks resulted in significantly lower bacterial loads per organ (spleen and lung) ($p < 0.0014$). This regimen demonstrated comparable efficacy to the minimum effective dosage of 6.5 mg/kg administered five times per week for four weeks. The minimum effective dosage was defined as the minimum dosage necessary to prevent mortality, spleen enlargement, and gross lung lesions in the mice. Dosages of 12.5 and 25 mg/kg further resulted in significantly greater reductions in bacterial loads ($p < 0.0014$) than isoniazid 25

mg/kg, which has potent antimycobacterial activity. When bedaquiline 25 mg/kg was added to the combination regimen of isoniazid, rifampin, and pyrazinamide, a significantly greater decrease in pulmonary bacterial load was seen ($p < 0.0018$).[42]

The bioavailability of bedaquiline is significantly affected by food. A standard meal with approximately 22 g of fat increased the bioavailability of bedaquiline by twofold compared with fasting conditions.[38] Current dosing recommendations include the administration of bedaquiline with meals in order to enhance oral bioavailability.

Bedaquiline is primarily metabolized by cytochrome P-450 isoenzyme 3A4 (CYP3A4).[53] Therefore, its metabolism can be affected by CYP3A4 inducers and inhibitors. The major metabolite, M2, is threefold to sixfold less active against *M. tuberculosis* than bedaquiline. In humans, the ratio for M2 to bedaquiline is 1:4 compared with mice, in which 80% of bedaquiline is converted to M2.[53]

Results from in vitro studies by Andreis et al.[42] suggest that bedaquiline has time-dependent, bactericidal activity. *M. tuberculosis* in log-phase growth was exposed to bedaquiline concentrations 10 and 100 times the MIC. Despite higher concentrations, samples exposed to bedaquiline concentrations at 100 times the MIC resulted in similar reductions of bacterial loads as 10 times the MIC on days 2, 6, and 12 when cultures were serially diluted and plated. At 6 and 12 days, bacterial loads were reduced by approximately 1 and 3 log colony-forming units (CFU)/mL, respectively.

Current FDA-approved indication. Bedaquiline is indicated in combination with at least three other antitubercular drugs in adults (age ≥ 18 years) with pulmonary MDR tuberculosis and when no other effective regimen is available.[38] Currently, there are no contraindications for bedaquiline; however, bedaquiline is not indicated in patients with latent, extrapulmonary, or drug-sensitive tuberculosis. The safety and efficacy of bedaquiline in the aforementioned settings have not been established.

FDA granted bedaquiline accelerated approval based on the surrogate endpoint of time to sputum conversion.[51,52] This surrogate endpoint was defined as the time between study drug initiation and the date of the first of two consecutive negative sputum cultures, taken at least 25 days apart with no confirmed positive intermediate cultures. Phase II trials assessing this surrogate endpoint showed greater sputum culture conversion up to week 24 for the bedaquiline group. This evidence suggests that bedaquiline provides an advantage over existing therapy for MDR tuberculosis. However, bedaquiline's accelerated approval remains contingent on confirmatory Phase III trials.

Approved dosing and administration. A course of bedaquiline requires 24 weeks of therapy in combination with other antitubercular drugs. The dosing of bedaquiline is 400 mg once daily for 2 weeks followed by 200 mg thrice weekly for 22 weeks. Bedaquiline is available as 100-mg tablets, which must be taken with food and swallowed whole with water.[38] The manufacturer recommends dispensing bedaquiline in its original container. If tablets are dispensed outside the original container, they should be placed in a light-resistant container with a maximum expiration date of three months. Tablets should be stored at room temperature (25 °C or 77 °F) with excursions permitted to 15–30 °C (59–86 °F).[38]

Clinical studies. Eleven Phase I studies have been conducted in which pharmacokinetic and pharmacodynamic parameters, dosing strategies, and drug–drug interactions of bedaquiline were assessed.[54] As these subjects were previously discussed in this review, the following section will focus on the Phase II studies that resulted in bedaquiline's accelerated approval by FDA.

Rustomjee et al.[50] assessed the bactericidal activity of bedaquiline in 75 treatment-naive patients with smear-positive pulmonary tuberculosis. Patients were randomized to one of five groups: once-daily bedaquiline (25, 100, or 400 mg), rifampin 600 mg, or isoniazid 300 mg for seven days. Sputum samples were collected at baseline and after each dose. Bedaquiline at 25 and 100 mg did not exhibit bactericidal effect. The 400-mg dose of bedaquiline correlated with greater bactericidal activity, thus displaying a linear relationship between dosage and effect. Specifically in patients who received 400-mg daily doses of bedaquiline, Rustomjee et al.[50] noted comparable decreases in bacterial load with isoniazid and rifampin on days 4 through 7. From days 0 through 7, decreases in bacterial load were 0.77 log CFU/mL for bedaquiline at 400 mg, 1.88 log CFU/mL for isoniazid, and 1.70 log CFU/mL for rifampin. This delayed bactericidal activity may potentially be attributed to bedaquiline's mechanism of action as ATP depletion and pH disruption usually take days to impact mycobacterial viability.[44]

A two-stage Phase II multicenter, placebo-controlled study was conducted, comprising of an exploratory stage (8 weeks) followed by a separate proof of efficacy stage (24 weeks) to assess the safety, pharmacokinetics, and antibacterial activity of bedaquiline. In stage I, Diacon et al.[51,52] randomized 47 newly diagnosed pulmonary MDR tuberculosis patients from South Africa to receive bedaquiline ($n = 23$) (400 mg daily for 2 weeks followed by 200 mg three times a week for 6 weeks) or placebo ($n = 24$) in combination with a background regimen that consisted of five second-line agents (kanamycin, ofloxacin, ethionamide, pyrazinamide, and cycloserine or

terizidone). After 8 weeks of double-blind treatment, bedaquiline was discontinued, and patients continued with their initial background regimen for 18–24 months. Final follow-up was at week 104. The addition of bedaquiline, as compared to placebo, resulted in reduced time to sputum culture conversion (hazard ratio, 11.8; 95% confidence interval, 2.3–61.3; $p = 0.003$) and significantly increased proportions of patients with negative sputum cultures (47.6% [10 of 21] versus 8.7% [2 of 23]) after 8 weeks.[51] Time to culture conversion at 24 weeks was significantly reduced in the bedaquiline group (hazard ratio, 2.25; 95% confidence interval, 1.08–4.71; $p = 0.031$). Negative sputum cultures at week 24 were observed in 17 (81%) of 21 patients versus 15 (65.2%) of 23 patients in the bedaquiline and placebo groups, respectively.[52] Accordingly, the 38.9% and 15.8% difference at weeks 8 and 24 in the percentage of culture conversion demonstrated reliably better microbiological responses with bedaquiline.

Similar to the first stage of the study, newly diagnosed MDR tuberculosis patients in stage 2 were randomized in a 1:1 ratio to receive bedaquiline or placebo for 8 weeks in combination with a background regimen of other second-line tuberculosis agents.[52] Patients continued on their background regimens for 18–24 months, and final follow-up occurred at week 120. A total of 160 patients from seven countries were enrolled in the study; 79 were treated with bedaquiline, and 81 received placebo. At week 24, a significantly greater percentage of patients in the bedaquiline group had culture conversion (78.8% [52 of 66 patients] versus 57.6% [38 of 66 patients], $p = 0.008$). Durable microbiological responses continued to be observed at week 72. The percentage of responders at week 72 was 71.2% (47 of 66 patients) in the bedaquiline group and 56.1% (37 of 66 patients) in the placebo group ($p = 0.069$). In both stages of the study, fewer patients receiving bedaquiline developed pre-XDR tuberculosis or XDR tuberculosis when compared with those receiving placebo (1 patient versus 4 patients in stage 1; 0 patient versus 7 patients in stage 2). Thus, the addition of bedaquiline may potentially decrease the risk of acquiring resistance to other background agents.[54]

A total of 233 patients with confirmed pulmonary MDR tuberculosis (newly diagnosed and previously treated) were enrolled in a single-group, open-label, uncontrolled Phase II trial.[54] Patients with XDR tuberculosis taking at least three susceptible antitubercular agents were also included. Patients received bedaquiline for up to 24 weeks in combination with background MDR tuberculosis regimens. The two-year follow-up period consisting solely of background regimens for MDR tuberculosis is currently ongoing.

Adverse effects. Pooled safety data from the two-stage Phase II trial revealed more hepatic disorders in patients receiving bedaquiline (9 of 102 patients [8.8%]) versus placebo (2 of 105 patients [1.9%]) (p not reported). Increases in liver function test values resolved in all but 2 patients. A Hy's law analysis identified elevated serum aspartate transaminase (greater than threefold the upper limit of normal) and total bilirubin (greater than twofold the upper limit of normal) as risk factors for drug-related liver injury.[54] Currently, no dosage adjustments for hepatic dysfunction are provided. However, increased laboratory test value monitoring, viral hepatitis testing, and discontinuation of concomitant hepatotoxic medications are recommended for patients with impaired liver function.[38]

Increases in mean Q-T interval, corrected using Fridericia's formula (Q-TcF), were more pronounced in the bedaquiline group.[51] The largest mean increase in Q-TcF at a predose time point occurred during the second stage of the study at week 18 (15.7 and 6.2 milliseconds in the bedaquiline and placebo groups, respectively) (p not reported).[54] The highest risk for Q-TcF prolongation correlated with the initial 24 weeks of bedaquiline treatment, after which Q-TcF prolongation persisted but increases became less prominent in the bedaquiline group. No Q-TcF absolute values exceeded 500 milliseconds, and no adverse events were associated with electrocardiographic changes in both stages of the study.[51,52,54] However, Q-TcF values over 500 milliseconds were reported in the single-group, open-label, uncontrolled Phase II trial.[54] Concomitant administration with the antimycobacterial agent clofazimine resulted in mean Q-TcF increases of approximately 30 milliseconds and values over 500 milliseconds.[54] Hence, additive effects of medications that can prolong the Q-TcF interval must be considered.

Of greatest concern is the increased risk of mortality reported with bedaquiline. In stage 2 of the Phase III, multicenter, placebo-controlled study, an increased risk of death was seen in the bedaquiline group (9 of 79 patients [11.4%]) compared with the placebo group (2 of 81 patients [2.5%]) within a 120-week window ($p = 0.03$).[38,55] One death occurred during bedaquiline administration. Five deaths in the bedaquiline group and all deaths in the placebo group appeared to be tuberculosis related.[54,55] In stage 1, none of the deaths due to hemoptysis secondary to tuberculosis, complications of tuberculosis, and acquired immune deficiency syndrome were considered to be bedaquiline related.[51] However, no clear relationship between these deaths and treatment response or underlying disease severity was found. The reason for the difference in mortality rates between the two study groups remains unclear. Nonetheless, the FDA-approved indi-

cation recommends bedaquiline use in patients with MDR tuberculosis who have not responded to effective first-line treatment regimens.

Drug interactions. Patients receiving multidrug regimens for the treatment of tuberculosis and HIV are at significant risk for drug–drug interactions that may require dosage adjustments or increased monitoring. Concerns regarding the concomitant administration of antiretrovirals and bedaquiline are substantial. Efavirenz, as a CYP3A4 inducer, may decrease levels of bedaquiline, a CYP3A4 substrate.

Dooley et al.[53] conducted a Phase I pharmacokinetic study to assess the potential for drug interactions in 33 healthy volunteers receiving bedaquiline and efavirenz. Two 400-mg doses of bedaquiline were given to each volunteer—the first dose alone and the second dose with efavirenz. Plasma sampling for bedaquiline and its metabolite, M2, was performed over 14 days following each dose. Efavirenz, at steady-state concentrations, did reduce the AUC of bedaquiline by 20% but the AUC of M2 remained unchanged, suggesting more rapid clearance. The clinical consequences of diminished bedaquiline concentrations in MDR tuberculosis are unknown.

As a CYP3A4 substrate, bedaquiline is susceptible to both CYP3A4 inducers and inhibitors. Dosage recommendations for bedaquiline are unchanged despite potential interactions. However, the manufacturer's recommendations state that coadministration of bedaquiline with strong CYP3A4 inducers (e.g., rifamycin) should be avoided.[38] Coadministration with strong CYP3A4 inhibitors (e.g., ketoconazole) for more than two weeks should be avoided unless the benefits outweigh the risks. Further in vivo evaluations with prolonged coadministration of bedaquiline need to be conducted before specific dosing recommendations can be made.

Place in therapy. Continual emergence of more-resistant tuberculosis, such as XDR and totally-drug-resistant tuberculosis, raises serious concerns regarding current practices for control and management of MDR tuberculosis. As the first novel antitubercular drug approved in over four decades, bedaquiline represents an important milestone in tuberculosis treatment.

Bedaquiline's unique mechanism of action presents a much-needed alternative approach to current antimycobacterial killing. By directly inhibiting ATP synthase, bedaquiline is effective against both replicating and dormant mycobacteria. Pulmonary cavitary lesions can contain heterogeneous populations. This potential mix of semireplicating and hypometabolic mycobacteria is more difficult to eliminate with conventional antitubercular drugs, thus increasing the risk of resistance.[56] No in vitro cross-resistance between bedaquiline and currently available antitubercular agents has been observed thus far. Because bedaquiline targets a completely different enzyme, cross-resistance with other conventional agents remains unlikely. Enhanced sterilizing capacity via synergistic depletion of ATP further exhibits the promising potential of bedaquiline with pyrazinamide. Thus, bedaquiline represents an important addition to the limited range of agents currently available against drug-resistant tuberculosis.

A major critique of MDR tuberculosis treatment is the significantly prolonged duration of therapy required in these patients. In Phase II studies, regimens containing bedaquiline resulted in greater reductions in bacterial load and greater proportions of sputum culture conversions. Of specific interest, 24 weeks of treatment with bedaquiline resulted in faster culture conversion and higher sputum conversion rates than those with placebo. The propagation of resistance through noncompliance is a major concern in complicated multidrug regimens. Shortening current therapy durations while improving efficacy can potentially improve patient outcomes.

Significant adverse effects are seen with MDR tuberculosis regimens that contain at least four antitubercular agents, none of which are benign. Bedaquiline was relatively well tolerated, with most adverse events thought to be associated with standard MDR tuberculosis agents. However, serious adverse events with bedaquiline therapy have culminated in black-box warnings for Q-T interval prolongation and an increased risk of mortality. The exact relationship between bedaquiline and increased risk of mortality are unknown. Considerable concern regarding the quality of the drug's safety data exists due to the risks of bias and imprecision (e.g., small sample size, use of modified intent-to-treat analysis, and the lack of quality evidence for the background regimens used in the trials).[57] Phase III studies that focus on safety data will have a significant impact on bedaquiline use in MDR tuberculosis.

Plans for a Phase III trial of 600 patients with sputum smear-positive pulmonary MDR or pre-XDR tuberculosis are underway. Pre-XDR tuberculosis is defined as MDR tuberculosis resistant to either a fluoroquinolone or a second-line injectable agent but not both. The objective of the trial is to confirm the efficacy of bedaquiline by comparing treatment outcomes at week 60 in patients randomized to receive bedaquiline or placebo added to a background regimen. The secondary endpoint will assess relapse-free cure at week 84. The total treatment duration of 36 weeks with 48 weeks of treatment-free follow-up will provide additional insight into patient outcomes associated with a shorter duration of MDR tuberculosis treatment while on bedaquiline. Moreover, safety data will provide additional focus on previously identified adverse events.[54]

Compared with older agents repurposed for the treatment of drug-resistant tuberculosis, bedaquiline has been shown to be effective against MDR tuberculosis in multiple randomized controlled studies. However, the overall evidence that led to bedaquiline's approval remains limited. An interim policy guidance recently compiled by WHO ranked the current evidence for bedaquiline use in adults with pulmonary MDR tuberculosis as "very low."[57] Contributing to this grade of evidence was the low confidence in bedaquiline's efficacy and safety (i.e., adverse events, mortality, emergence of resistance, and generalizability to other patient populations). Expert opinions emphasize bedaquiline use when an effective regimen containing four second-line drugs and pyrazinamide cannot be designed per WHO recommendations and when there is documented evidence of MDR tuberculosis with fluoroquinolone resistance. A maximum duration of six months of bedaquiline treatment in conjunction with MDR tuberculosis background regimens is recommended.[57] Preferred adjunct agents have yet to be indicated.

Current WHO interim recommendations are riddled with caveats for bedaquiline therapy in MDR tuberculosis. Without more comprehensive data from Phase III studies, provisions for the safe and effective use of bedaquiline must be implemented with special attention to pharmacovigilance.[57] Due to the limited data in patients with HIV and the elderly (age 65 years or older), particular caution should be employed with these populations.

Conclusion

The approval of bedaquiline represents a major milestone in MDR tuberculosis therapy. Bedaquiline should be considered in patients who have not responded to a regimen containing four second-line drugs and pyrazinamide and patients with documented evidence of MDR tuberculosis resistant to fluoroquinolones. The exact role of bedaquiline cannot be determined until further efficacy and safety data are obtained through ongoing Phase III trials.

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Appendix—Components of the Stop TB Strategy[a]

1. Pursue high-quality DOTS expansion and enhancement
   a. Secure political commitment, with adequate and sustained financing
   b. Ensure early case detection, and diagnosis through quality-assured bacteriology
   c. Provide standardized treatment with supervision, and patient support
   d. Ensure effective drug supply and management
   e. Monitor and evaluate performance and impact
2. Address TB/HIV, MDR-TB, and the needs of poor and vulnerable populations
   a. Scale up collaborative TB/HIV activities
   b. Scale up prevention and management of MDR-TB
   c. Address the needs of TB contacts, and of poor and vulnerable populations
3. Contribute to health system strengthening based on primary health care
   a. Help improve health policies, human resource development, financing, supplies, service delivery, and information
   b. Strengthen infection control in health services, other congregate settings and households
   c. Upgrade laboratory networks, and implement the Practical Approach to Lung Health
   d. Adapt successful approaches from other fields and sectors, and foster action on the social determinants of health
4. Engage all care providers
   a. Involve all public, voluntary, corporate and private providers through Public-Private Mix approaches
   b. Promote use of the International Standards for Tuberculosis Care
5. Empower people with TB, and communities through partnership
   a. Pursue advocacy, communication and social mobilization
   b. Foster community participation in TB care, prevention and health promotion
   c. Promote use of the Patients' Charter for Tuberculosis Care
6. Enable and promote research
   a. Conduct program-based operational research
   b. Advocate for and participate in research to develop new diagnostics, drugs and vaccines

[a]Reprinted, with permission, from reference 10. DOTS = directly observed treatment, short-course; TB = tuberculosis, HIV = human immunodeficiency virus, and MDR = multidrug resistant.