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Review Paper

Bedaquiline: A Promising new agent for the treatment of MDR-TB

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Abstract
Tuberculosis (TB) remains the single most infectious disease causing the highest mortality in humans. India is the highest TB burden country according to World Health Organization (WHO) statistics for 2011. The previous studies in India showed that 3% of multi drug resistant TB (MDR-TB) is seen in new tuberculosis cases and 17.2% among retreatment cases. The alarming increase in MDR-TB and the emergence of extensively drug resistant TB(XDR-TB) are man-made snags; therefore new drugs for the treatment of drug-resistant tuberculosis are obligatory.On 28thDecember 2012, the U.S. Food and Drug Administration approved bedaquiline (TMC207), as part of combination therapy to treat adults with MDR-TB when other alternatives are not available. Bedaquiline, a diarylquinoline has a unique mechanism of action and acts as a promising new agent in patients with MDR-TB.

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INTRODUCTION

Tuberculosis (TB) remains a major global health problem and stands a leading cause of death due to infectious disease, second only to human immunodeficiency virus and acquired immunodeficiency syndrome.[1]For several decades in the developing countries, eradication of tuberculosis remains to be a primary health challenge despite regular TB control programs adopted by governments. According to WHO-TB statistics for 2011, India has the highest TB burden country with an estimated incidence of 2.2 million cases out of a global incidence of 8.7 million cases and 1.4 million TB deaths.[2,3] The TB prevalence in India for 2011 is estimated to be 3.1 million cases.[3]In India,TB bares the highest mortality rate in humans among the infectious diseases, about 3 million deaths annually, 5 deaths every minute.[4]Therefore, to curtail the existing problem in India, a notification was sent to

all states, declaring TB to be a notifiable disease, which means all health care professionals treating a TB patient had to report immediately every case of TB to the government.[5]

Short-course regimens of first-line drugs that can cure around 90% of cases have been available since the 1980s.[3]Inadequate TB treatment or harboring drug resistant tubercle bacilli can lead to the development of drug resistant TB. TB control is challenged by MDR-TB and XDR-TB. MDR-TB is defined as resistance to isoniazid (INH) and rifampicin (RMP) two of the most effective anti-TB drugs, with or without resistance to other drugs.[6]Globally in 2011, there were an estimated 630,000 cases of MDR-TB among the world's 12 million prevalent cases of TB.[7]XDR-TB is defined as resistance to INH and RMP plus any fluoroquinolone and at least one of the injectable agents: kanamycin [KM], amikacin [AMK] or capreomycin [CPM]).[8, 9]Totally drug resistant TB(XXDR-TB or TDR-TB) is defined as resistant to a wider range of drugs has also now been detected. TDR-TB is resistant to all the first and second line TB drugs and it is extremely difficult to treat.[10, 11]

Novel TB drugs are obligatoryto tackle the major problem of prevention and treatment of drug resistance. The expansion of newer agents is an urgent priority for the restraint of MDR-TB and XDR-TB and also need for better and rapid diagnostic assays for early detection of TB.[12, 13]Several new molecules and early detection techniques are being researched in the management of TB; BEDAQUILINE is the first new FDA approved drug in 40 years to fight against MDR-TB.[14, 15]

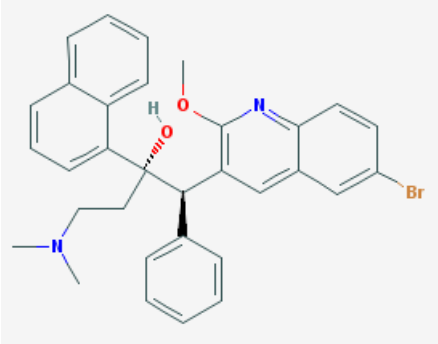
Drug review:

Adiarylquinoline anti-tuberculosis drug, Bedaquiline (also known as Sirturo, TMC207 or R207910)was discovered by a team led by the BelgianKoenAndries at Janssen Pharmaceutica.[16]It is manufactured by Johnson & Johnson (J&J), who sought accelerated approval of the drug for treatment of multi-drug-resistant tuberculosis.[17]On 28thDecember 2012, the U.S. Food and Drug Administration approved bedaquiline, as part of combination therapy to treat adults with multi-drug resistant tuberculosis (MDR-TB) when other alternatives are not available and also granted Sirturo fast track designation, priority review and orphan-product designation.[18] The drug demonstrated the potential to fill an unmet medical need, has the potential to provide safe and effective treatment where no satisfactory alternative therapy exists. [18]

Chemical structure: [19, 20]

IUPAC Name: (1R, 2S)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-naphthalen-1-yl-1-phenylbutan-2-ol.

Molecular Formula: $C_{32}H_{31}BrN_2O_2$



Mechanism of action:

TMC207 a diarylquinoline compound that offers a new mechanism of antituberculosis action by specifically targeting mycobacterial proton pump of adenosine triphosphate (ATP) synthase, leading to inadequate synthesis of ATP (reduced generation of energy in *Mycobacterium tuberculosis).*[21, 22]Its MIC for *M. tuberculosis* is 0.06 µg/ml and it has no cross resistance with existing anti-tuberculosis antibiotics. [21]Bedaquiline is active against most isolates of *Mycobacterium tuberculosis*. In vitro, TMC207 potently inhibits drug-sensitive and drug-resistant *M. tuberculosis* isolates [21, 23]and is also bactericidal against dormant (non-replicating) tubercle bacilli.[24]TMC207 has shown concentration-dependent anti-bacterial activity. [25]

Pharmacokinetics:[26]

Bedaquiline is well absorbed orally and post dose maximum plasma concentration (Cmax) is 5 hours. Food increases its bioavailability. The plasma protein binding of bedaquiline is > 99.9%. The volume of distribution in the central compartment is estimated to be approximately 164 L. Cytochrome P4503A4 metabolizes TMC207 into its major *N*-monodesmethyl metabolite, which is about five times less active than the parent compound. Both compounds are eliminated with long terminal half-lives of 50–60 hrs in mice, suggesting extensive tissue binding.[25]Based on preclinical studies, bedaquiline is eliminated mainly in feces. The urinary excretion of unchanged bedaquiline was < 0.001% of the dose in clinical studies, indicating that renal clearance of unchanged drug is insignificant.

Efficacy studies:

Preclinical studies: Bedaquiline exhibited potential antimycobacterial activity and also accelerated clearance of bacilli, as similar tothe combination of isoniazid, rifampin, and pyrazinamide in the murine model of tuberculosis.[21]TMC207 showed synergistic interaction with pyrazinamide. [27] Similarly, TMC207 enhances the antibacterial activity of second-line drug combinations in the murine model of drug-sensitive tuberculosis.[28]

Clinical studies:

The demonstration of antimycobacterial potential of bedaquiline in preclinical modelspaved way for further efficacy studies in humans.The drug has been approved on the basis of the results of two phase II trials. The study was randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability and efficacy of bedaquiline when it is added to a background regimen (BR) in newly diagnosed patients with MDR pulmonary TB was conducted in two stages. Both studies were designed to measure the time to conversion to a negative sputum culture.

In the first trial[29], newly diagnosed, smear positive MDR-TB (pulmonary) patients were randomly assigned to be treated with bedaquiline or placebo in combination with a standard five-drug regimen, second-line anti-tuberculosis regimen for 8 weeks. This study revealed, the addition of TMC207 (48%) to the standard drug regimen for MDR-TB resulted in quicker conversion to a negative sputum culture compared to placebo group (9%).The median rates of smear negative for acid-fast bacilli at week 4 were 77% and 57% for the TMC207 and placebo group and at week 8 were 84% and 68% for the TMC207 and placebo group respectively. Also TMC207had an acceptable side-effect profile. [29]

In the second trial[30], all patients received either bedaquiline or placebo for 24 weeks in addition to other anti-TB drugs. The median time of sputum culture conversion were 78 days for TMC207, compared with 129 days in patients treated with placebo.Those who received TMC207 were at lower risk of acquisition of additional drug resistance over the whole duration of follow-up. The side effects incidence was similar in the patients who received bedaquiline (82.6%) compared to those who had received placebo (79.2%). The majority of the adverse events recorded here were of mild or moderate intensity. A phase 3 trial of bedaquiline, TMC207-C210, is due to start in March 2013. It will be a double blind study of 600 patients with sputum smear positive MDR-TB, which will compare TB treatment with bedaquiline and a background regimen, with placebo and a background regimen.[31]

Safety and tolerability:[26]

The most common adverse reactions reported were nausea, arthralgia, and headache. Other adverse events reported were hemoptysis and chest pain in ≥10% of patients treated with bedaquiline, with a higher frequency than the placebo treatment group.[26,29] No clinically relevant heart rate changes or electrocardiographic QRS or PR interval were observed during the study. In both the treatment groups, mean increase in the corrected QT

interval was observed but was more pronounced in the TMC207 group (p> 0.05). No dosage adjustment is required in patients with mild to moderate renal or hepatic impairment. Caution in patients with severe renal or hepatic impairment. Alcohol and other hepatotoxic drugs should be avoided.

Dosage and precautions:

The recommended dose of bedaquiline for the treatment of pulmonary MDR-TB in adults is 400mg oncedaily for 2 weeks, followed by 200mg 3 times per week for 22 weeks, with a total duration of 24 weeks, taken with food and in combination with other anti-TB drugs. [26, 32]The drug bares a black-box warning for arrhythmias, therefore advised frequent ECG monitoring during the treatment. [18] Withdraw bedaquiline, when total bilirubin elevation > 2xULN or aminotransferase elevations are > 8xULN or aminotransferase elevations persist beyond 2 weeks. [26]

CONCLUSION

Adherence to appropriate standards of care and control is imperative and a top priority in order to prevent drug resistance in TB. The occurrence of MDR-TB and XDR-TB is related to poor TB control, due to improper use of second-line anti-TB drugs. The current need of an hour is the rational use of new drugs/regimens for the treatment of TB.Bedaquiline, a new FDA approved drug must be used in combination with other 2nd line anti-tubercular drugs to treat MDR-TB in adults, when other alternatives are not available and it is administered by DOTS. Future prospects include, clinical trials with good study design and large sample size are vital to rationalize the treatment, plus to reduce mortality, morbidity and economic losses, thereby improving TB scenario all over the world. The safety and efficacy of bedaquiline for the treatment of latent TB, drug sensitive TB and extra pulmonary TB has not been established, hence upcoming exploration is necessary in this area.

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