Bedaquiline: A novel drug to combat multiple drug-resistant tuberculosis

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ABSTRACT

Tuberculosis (TB) is among the most common infectious diseases and continues as a major global health problem. The scenario is worsened by the emergence and spread of multiple drug-resistant tuberculosis (MDR-TB) and extensive drug-resistant tuberculosis (XDR-TB). Cure rates are high for drug sensitive strains of *Myobacterium tuberculosis* if treatment protocols are adhered to, but treatment of MDR-TB and extensive drug drug-resistant strains is virtually impossible. The treatment of MDR-TB and XDR-TB relies on the drugs, which are less potent, more toxic and more costly and have to be administered for the longer duration. No new drug had come in to market for last 40 years, but the emergence of MDR-TB and XDR-TB has spurred interest in the development of novel drugs. For the effective treatment outcome, there is a dire need of new drugs with a different mechanism of action that can tackle both drug sensitive as well as drug-resistant strains. Bedaquiline is one such new drug with unique mechanism of action. Food and Drug Administration has approved bedaquiline for MDR-TB in December 2012. This article reviews the available evidence of efficacy and safety of bedaquiline.

Key words: Bedaquiline, multiple drug-resistant tuberculosis, tuberculosis

INTRODUCTION

The global burden of morbidity and mortality from tuberculosis (TB) remains enormous. Although, new cases of TB have fallen at the rate of 2.2% between 2010 and 2011,[1] still the treatment of TB faces many challenges due to the emergence of drug-resistant strains. The treatment of drug sensitive strains of TB requires minimum duration of 6 months. However, for multiple drug-resistant tuberculosis (MDR-TB) and extensive drug-resistance tuberculosis (XDR-TB) the duration is more than 20 months.[2] MDR-TB and XDR-TB are more difficult to manage, cure rate with second line drugs is very less and relapse rate is very high.[3] The burden of MDR-TB is increasing, especially in developing countries like India.[4] In addition, India has become the third country to report total drug-resistant TB.[5]

These situations demand for the development of new anti-tubercular drugs with a different mechanism of action. Unfortunately, no new drug had been introduced in last 40 years. There are a number of reasons for the slow development of new anti-tubercular drugs like duration of research is slow, long and expensive and pharmaceutical companies had scant interest. Moreover, the prevalence of TB is more in low-income countries.[1] Furthermore, research in this area has fastened up in last 10 years after launch of the global plan to stop TB.[6] There are nearly 11 new drugs in the pipeline for the better management of TB. One such drug from the new class, with a different mode of action, bedaquiline has been developed recently.

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BEDAQUILINE

It is also known as TM207 or R207910 and is the first compound from the new class diarylquinolines that acts by inhibiting bacterial adenosine triphosphate (ATP) synthetase enzyme, a novel mode of action.[7] Andries *et al*. at Jansen Pharmaceutical discovered it. This compound has shown high activity against both sensitive as well as resistant strain of mycobacterium.[8] ATP synthetase is the essential enzyme for the production for energy in the all-living organisms. ATP synthetase enzyme consists of two complexes, hydrophilic F1 and membrane embedded F0. The hydrophobic side of bedaquiline binds to c-subunit of the F0 complex and interferes with its rotatory movement leading to inadequate synthesis of ATP.[9] It is effective against replicating as well as dormant organisms as even dormant organisms require ATP for their survival.[8] Bedaquiline specifically inhibits the mycobacterium ATP synthetase as compared to mitochondrial ATP synthetase.[10] Bedaquiline is well absorbed after oral ingestion and is metabolized by hepatic CYP450 enzymes to less active metabolite N-desmethyl M2.[11] The average half-life over a dosing interval is about 24 hr. The terminal half-life of it is quite long approximately 173 hr.[11,12]

EFFICACY AND SAFETY IN CLINICAL TRIALS

The efficacy and safety of bedaquiline has been evaluated by clinical trials in MDR-TB patients.

Important aspect of any anti-tubercular drug is its ability to rapidly decrease bacillary load (early bactericidal activity [EBA] EBA). This ability of bedaquiline was assessed in newly diagnosed sputum positive patients. A total of 75 patients were randomized, they were given once daily either bedaquiline (25,100 or 400 mg) or 600 mg rifampicin or 300 mg isoniazid for 7 days. EBA of bedaquiline was similar to rifampicin and isoniazid from 4th day onwards onward at 400 mg dose.[11]

After that its efficacy was evaluated in phase 2 "multicentric trial of TMC 207 in adult patients with newly diagnosed smear positive pulmonary TB caused by MDR-TB strains." It was conducted in two phases; first phase was of 8 weeks, involved 47 patients. 23 patients were administrated bedaquiline, initially daily dose of 400 mg for 2 weeks, followed by 200 mg three times a week for 6 weeks, in addition to background regimen (BR) of the second line drugs while 23 patients received placebo and BR. The time for sputum conversion was shorter in bedaquiline group as compared with the placebo group (hazard ratio-11.8:95% confidence interval [CI]: 23-61.3, $P = 0.003$ by cox regression analysis). While the rate of sputum conversion was 48% in bedaquiline group as compared with 9% in the placebo group.[13] After 8 weeks, these patients were given only BR and were evaluated at 24 weeks; the rate of sputum conversion was more in bedaquiline treated group significant (hazard ratio-2.253:95% CI: 1.08-4.71; $P = 0.031$).[14]

In the second phase of this trial 161 patients were enrolled, 79 patients were administered bedaquiline at a dose of 400 mg daily for 2 weeks and then 200 mg three times a week and BR and 81 patients were given placebo and BR. Time for sputum conversion was 12 weeks in bedaquiline group as compared with 18 weeks in placebo ($P = 0.003$) and rates of sputum conversion were 79% in bedaquiline group and 58% in the placebo group ($P = 0.008$) at the end of 24 weeks.[12]

ADVERSE EFFECTS AND DRUG INTERACTION

The common adverse events seen with bedaquiline in clinical trials were nausea, diarrhea, bilateral hearing impairment, viral infections, pain, acne and non-cardiac chest pain. Except for nausea, which occurred more frequently in bedaquiline group as compared with the placebo group (26 vs. 4%; $P = 0.04$), there was no statistically difference in incidence of other adverse events in both groups. It was also found to increase QT interval, but no pathological increase in QT interval (>500 ms) was seen. Other matter of concern is its hepatotoxicity, it was found to increase the level of transaminases.[12-14] It was also found to increase the risk of death, 11.4% patients died in bedaquilne arm as compared to 2.5% in the placebo arm.[15]

As hepatic Cyp450 enzymes metabolize bedaquiline, many drug interactions can occur because of microsomal enzyme induction and inhibition. Rifampicin was found to decrease its plasma concentration to half, in spite of reduction in its plasma concentration in mouse model it was found to retain its activity when administered with rifampicin.[16]

CURRENT STATUS

Bedaquiline is the new anti-tubercular approved by USA Food and Drug Administration's accelerated approval program for MDR-TB patients, when no other drug is available. Experts are concerned about long-term safety, which will be clearer after phase 3 trial.[15] Recently, India has also decided to make bedaquiline available for drug resistant TB on experimental basis.[17]

CONCLUSION

There is a dire need of new anti-tubercular drug with a different mechanism of action, which can retard the emergence of the MDR- and XDR-TB patients as well can treat these patients. Bedaquiline is one such breakthrough drug, which can tackle

these issues, especially in countries like India where incidence and prevalence of MDR- and XDR-TB is increasing. But because of lack of enough safety data and to avoid the development of resistance against it, this drug should be used with caution.

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