Review Article

Bedaquiline – A Novel Promising Discovery in Multidrug-Resistant Tuberculosis

Sanjeev Kumar[1], *Seema Rani[2], Ram Chander Siwach[1], Prem Verma[2]

1. Department of Orthopaedics, Bhagat Phool Singh Government Medical College for Women, Khanpur Kalan (Sonepat), Haryana, India.
2. Department of Pharmacology, Bhagat Phool Singh Government Medical College for Women, Khanpurkalan (Sonepat), Haryana, India.

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ABSTRACT

After acquired immunodeficiency syndrome (AIDS), tuberculosis (TB) is the leading cause of death worldwide due to a single infectious agent. Recently, drug-resistant strains of mycobacterium tuberculosis reported more horrible version of tuberculosis. There is threatful increase in multidrug resistant tuberculosis (MDR-TB) and extensively drug-resistant TB (XDR-TB) all over the world, so better treatment options are needed to control the global MDR-TB and XDR-TB epidemic. Bedaquiline, a diarylquinoline has a unique mechanism of action i.e. causes inhibition of the proton pump activity of the ATP synthase in mycobacterium tuberculosis and targets the energy metabolism. It acts as a promising new agent in patients with MDR-TB came in market recently. Bedaquiline can be combined with antituberculosis and antiretroviral agents. The drug showed good oral absorption, long terminal half-life and is metabolized mainly by cytochrome $450P_3A_4$. It is recently been approved by U.S. Food and Drug Administration on 28th December, 2012 for treating multi drug resistant TB (MDR-TB) in adults ≥18 years. It seems to be good option for multidrug-resistant tuberculosis patients as it has earlier and sustained antitubercular action, shorten duration of treatment, less chances of resistance and better safety as compared to existing second line drugs. Long term studies are needed to explore its safety.

*Author for Correspondence:
Dr. Seema Rani
Associate Professor, Department of Pharmacology, BPS Govt. Medical College for Women, Khanpur Kalan (Sonepat) Haryana, India.
E-mail: seema17march@gmail.com

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INTRODUCTION

Tuberculosis (TB) remains a worldwide public health problem despite the fact that the causative organism tubercular bacillus was discovered more than 100 years ago and highly effective drugs and vaccines are available. In 1993, the World Health Organization (WHO) took an unprecedented step and declared TB to be a global emergency [1]. The emergence of resistance to drugs used to treat tuberculosis (TB), and particularly multidrug-resistant TB (MDR-TB) has become a significant public health problem in a number of countries especially in India and an obstacle to effective TB control. Multi-drug resistant tuberculosis (MDR-TB) is emerging as a possible threat to the global tuberculosis control efforts.

Multidrug-resistant tuberculosis (MDR-TB) is disease due to mycobacterium bacillus which shows high resistance to both isoniazid and rifampicin, with or without resistance to other anti-tubercular drugs [2]. The emergence of MDR-TB strains that reveal resistance to at least isoniazid and rifampicin (i.e. MDR-TB) plus resistance to any of the fluoroquinolones and any one of the second-line injectable drugs (amikacin, kanamycin, or capreomycin) is called as extensively drug-resistant TB (XDR-TB) [3]. In 2011, 220,000 - 400,000 MDR-TB cases were notified by World Health Organisation

and approximately 60% of these cases were found in Brazil, Russian Federation, China, India and South Africa [4]. Annual mortality from MDR-TB was estimated to be 150,000 worldwide [5]. Number of factors are responsible that lead to increase mortality in these patients including spontaneous mutations [6], relatively less effective, poorly tolerated and expensive drugs that may be needed for long period in MDR- TB patients [7,8]. So, it is dire emergency to develop new drugs for the treatment of drug-resistant tuberculosis.

The drug to become successful in MDR-TB should have special salient features including that a drug should have novel mode of action, good oral bioavailability, sensitive against drug resistant organisms, simplify and shorten treatment, lesser adverse effects, minimal interactions with other antituberculus and antiretroviral drugs, increase compliance and should have low cost [9,10].

Bedaquiline the first new drug with novel mechanism of action to treat drug resistant tuberculosis approved by the United States Food and Drug Administration (FDA) on 28 December, 2012 in over 40 years [11]. There is some controversy over the approval for the drug, as the FDA's ruling was based on a surrogate outcome means sputum cultures as opposed to patient deaths. In the clinical trials used for approval, the patients taking bedaquiline were more likely to die, even though they had resolution of TB based on sputum cultures [12].

History of Bedaquiline: In 2004, Bedaquiline, a novel diarylquinoline first came in limelight's with a name TMC207 then referred as R207910 for the research and development for potential use in the treatment of tuberculosis. It was discovered by Johnson & Johnson (J&J) via a screening prototype of more than 70,000 chemicals by inhibition of growth against mycobacterium smegmatis, a more rapidly growing mycobacterium compared with mycobacterium tuberculosis [13]. It was described for the first time in 2004 at the Inter science Conference on Antimicrobial Agents and Chemotherapy (ICAAC) meeting, after the drug had been in development for over seven years [14].

Mechanism of Action: Bedaquiline has unique and specific action against mycobacteria by inhibiting proton pump of mycobacterium tuberculosis's ATP synthase. It is an enzyme that is essential for the generation of energy in mycobacterium tuberculosis. Bedaquiline binds to the c-subunit of mycobacterium ATP synthase leads to inhibition of ATP synthesis and ultimately causes death of mycobacteria [15]. It is found to be active within macrophages as well as extracellularly so, a promising agent in shortening the duration of anti-tuberculosis treatment [16]. It is bactericidal and also has good sterilizing activity against the non-tuberculous mycobacteria like M. avium, M. Kansasii and rapidly growing mycobacteria like M. Abscessus that makes it an attractive drug in multi drug resistant-tuberculosis [17].

Pharmacokinetic properties: After oral dose of 400 mg/day it is found that maximum plasma concentration typically achieved at approximately (t-max) 4 hours post-dose and Cmax was 5.5 mg/L. It has long terminal half-life of 173 hours in human. This long terminal elimination phase likely reflects slow release of bedaquiline and *N*- mono desmethyl metabolite (M2) from peripheral tissues. The area under curve (AUC) and the Cmax have shown a linear pharmacokinetic profile in both single-and multiple-dose studies and the half-life is largely independent of the dose [18]. The volume of distribution is approximately 164 L and the plasma protein binding >99.9%. Bedaquiline is metabolized by oxidative metabolism via CYP3A4 to an active *N*-mono desmethyl which is 4 to 6-times less active in terms of antimycobacterial potency. Animal studies show that bedaquiline is mainly eliminated in faeces and renal clearance of unchanged drug is insignificant. When taken with food increased the relative bioavailability of bedaquiline increased by about 2-fold compared to administration under fasted conditions. Co administration with rifampicin leads to a 50% reduction in bedaquiline concentrations [19].

Pharmacodynamic properties: In vitro studies show that bedaquiline potently

inhibits drug-sensitive as well as drug-resistant mycobacterial TB at a minimal inhibitory concentration (MIC) of 0.002-0.06 µg/ ml [18]. It has been suggested that dormant mycobacteria have lower ATP stores so these bacteria becomes more vulnerable to ATP depletion even at nanomolar concentrations of bedaquiline [20]. That's reason it has shown an effective sterilizing agent against mycobacteria and a superior drug than other 1st line anti-TB drugs. The drug has shown a considerable strong inhibitory effect against many of non-tubercular mycobacteria e.g. M. avium and M. intracellulare, M. abscessus and M. Ulcerans [18]. In these conditions, it is almost as active as in mycobacteria tuberculosis. It also possesses good activity against MAC, M. leprae, M. bovis, M. marinum, M. kansasii, M. fortuitum, and M. szulgai. It has been found that it takes 2-4 days for its antibacterial activity to occur. This lag period may be due to its mechanism of action i.e. delayed ATP depletion and disruption of intracellular pH homeostasis. A significant bactericidal activity has been reported at days 4-7 after starting the treatment [21].

Pre-clinical studies: In mice model it was concluded that bedaquiline has superior bactericidal activities than isoniazid and rifampicin by at least 1 log unit. Single dose of bedaquiline inhibits mycobacterial growth for at least1 week [18].

It was concluded in murine model that four months of treatment with bedaquiline containing regimens was as effective as the six month treatment with standard regimen and more effective than four months of treatment with moxifloxacin containing regimens in the murine model. They also concluded that addition of bedaquiline in standard regimen (RHZ) or substitution of bedaquiline with rifampin may decrease duration of treatment in tuberculosis patients [22]. In guinea pig model, it was concluded that treatment of guinea pigs with bedaquiline was highly effective. There was complete eradication of the bacteria throughout both the primary and the secondary lesions in lung granulomas in their 6 week study [23].

In mice model, it was concluded that bedaquiline containing regimens were significantly more active than the non-bedaquiline containing regimens after 1 month of therapy. When bedaquiline alone was given for 2 months, it was found to be more active than the WHO standard first-line regimen. When it was given along with second-line drugs, the combinations were more active than the currently recommended regimen of MDR-TB [24].

Clinical studies: Diacon et al [25] studied in their first stage of a phase 2 trial, randomized, controlled trial, 47 newly diagnosed MDR-TB patients were randomly given either bedaquiline in dose of 400 mg daily for 2 weeks followed by 200 mg three times a week for 6 weeks or placebo in combination with a standard five-drug, second-line anti- TB regimen (total 8 weeks). The primary efficacy end point was culture conversion from positive to negative in liquid broth during the 8-week treatment period. It was reported that after adding bedaquiline to standard therapy the conversion time was significantly reduced as compared with placebo. The rates of conversion to a negative culture were 48% in the bedaquiline treatment arm and 9% in the placebo group. Also bedaquiline had an acceptable side-effect profile.

Diacon et al [26] studied in their second stage of a phase 2 trial, randomized, controlled trial, all patients received either bedaquiline or placebo for 24 weeks along with other anti-TB drugs. The median time of sputum culture conversion were 78 days for TMC207 compared with 129 days in patients with placebo. One patient receiving bedaquiline acquired drug resistance compared to five patients receiving placebo (4.8% versus 21.7%; p = 0.18) acquired drug resistance. Adverse effects occurred at almost comparable in both groups 54% in placebo group and (44%) in bedaquiline group discontinued the study in between. It was concluded that bedaquiline more rapid sputum culture conversion and prevents the development of resistance to the other drugs in the regimens. So may be a very effective therapy for MDR-TB.

Wallis et al [27], used a whole blood culture model to examine potential novel drug combinations that might ultimately be used to treat XDR-TB. The main findings were that combinations including PNU-100480,

TMC207, and SQ109 were highly active and fully additive. Further testing of these regimens needed.

Indication: Bedaquiline has been approved as part of combination therapy in adults (≥ 18 years) with multidrug-resistant strains of pulmonary tuberculosis (MDR–TB) when other alternatives are not available and also granted fast track designation, priority review and orphan product designation [28].

Dosage and Administration: Initial dosage is 400 mg once daily for 2 weeks, followed by 200 mg 3 times per week for 22 weeks for a total dose of 600 mg per week in pulmonary multi-drug resistant tuberculosis (MDR-TB). It is supplied as 100-mg tablets to be taken with food and swallowed whole with water. It is not indicated for the treatment of latent, extra-pulmonary or drug-sensitive tuberculosis [29].

Adverse effects: The adverse events noted are mild including nausea in 26% of patients and diarrhea in 13% of patients. Some patients reported with arthralgia, pain in extremities, and hyperuricemia [30].

Drug interactions: Bedaquiline is metabolized by CYP_3A_4; so strong CYP_3A_4 inducers may reduce its effect. Co administration with CYP_3A_4 inhibitors may increase systemic exposure and result in adverse effects. Dooley et al reported that when combination of bedaquiline and efavirenz was given to healthy volunteers no clinically significant effect of efavirenz observed on bedaquiline concentrations and both the drugs were well tolerated together too [31].

Special precautions: No dose adjustment is required in mild or moderate hepatic and renal impairment .But cautious use is recommended in severe hepatic impairment, severe renal insufficiency, undergoing dialysis, cardiovascular diseases, pregnancy, breast feeding females, children less than 18 years and elderly >65 years as safety and effectiveness have not been established in such patients [32].

CONCLUSION

Multi-drug resistant tuberculosis is a serious disease that can result in large number of mortality and for which there are few treatment options are available. Drug development for tuberculosis has stagnated for decades, but in recent years renewed commitment and coordinated research has generated a new drug, bedaquiline that hold the potential to make treatment more effective, shorter, less complex and less toxic in the near future. Bedaquiline is the first anti-tuberculosis drug with a novel mechanism to be approved by FDA on 28th December, 2012 in more in 40 years. It has shown good results and shortens the duration of antituberculus drugs when combined with these drugs in MDR and XDR- TB. Unfortunately, Bedaquiline has certain adverse effects like prolongation of QT interval, nausea and drug interactions with CYP_3A_4 inducers and inhibitors. Because the drug along with benefits also carries significant risks, physicians should ensure careful use of bedaquiline along with monitoring of the potential adverse effects and drug interactions.

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