WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 12, 265-268. Review Article ISSN 2277– 7105

A NEW WEAPON AGAINST RESISTANT TUBERCULOSIS-BEDAQUILINE

[1]Anand vardhan, [2]C. Dinesh M. Naidu, [3]Mangesh Bankar, [4]Sagar Sharma, [5]Vinay Raghuvanshi

[1,4,5]Senior Residents, [2]Professor, [3]Associate Professor

Department of Pharmacology, Andaman & Nicobar Islands Institute of Medical Sciences, Port Blair, India.

Article Received on
22 Sept. 2016,

Revised on 12 Oct. 2016,
Accepted on 01 Nov. 2016

DOI: 10.20959/wjpr201612-7403

***Corresponding Author**
Dr. Anand Vardhan
Senior Resident, Department of Pharmacology, Andaman & Nicobar Islands Institute of Medical Sciences, Port Blair, India.

ABSTRACT

Multidrug resistant tuberculosis is defined as resistance to at least isoniazid and rifampicin. Multidrug resistant Tuberculosis is becoming a challenging health problem. There is a need need for newer and more effective drugs for this deadly menance. Bedaquiline, first in a new class of drug, is approved by the US Food and Drug Association against MDR Tuberculosis. In phase III trials Bedaquiline is now known to bring about faster culture conversions. Accordingly, the FDA has approved bedaquiline as part of combination therapy to treat adults with MDR pulmonary TB but should be used only when other alternatives are not available. Bedaquiline a promising potential is also having a favourable outcome in Multi-Drug Resistant Tuberculosis.

KEYWORDS: Bedaquiline, multi drug reisitant, tuberculosis.

INTRODUCTION

Resistance to rifampicin with or without resistance to isoniazid is referred to as multidrug-resistant tuberculosis (MDR-TB). Both of them are the most effective bactericidal agents presently used in tuberculosis treatment. In current scenario, MDR-TB is one of the most challenging health problems consisting of 3.5% of all newly diagnosed patients with MDR-TB.[1] The treatment of MDR-tuberculosis is highly toxic and much expensive than the treatment regimen used to treat rifampicin sensitive TB.

The absence of drugs as effective as isoniazid and rifampicin for therapy leads to reduced chances of treatment success and increased death rate when compared to patients with rifampicin sensitive TB. The need for newer and more effective drug are the need of hour. The drug "Bedaquiline" to treat multi drug resistant resistant TB was approved by the US Food and Drug Administration (FDA) on December 28, 2012.[2] This drug was special and different from others as it had a different mechanism of action against tubercle bacilli. It was discovered by scientists at Janssen and was called as Sirturo. It is the first in a new class of drugs that aims to treat resistant TB. Mycobacterial adenosine triphosphate (ATP) synthase is required for the synthesis of ATP by Mycobacterium tuberculosis.

Bedaquiline, a diarylquinoline,[3] acts at this step by binding to the oligomeric and proteolipic subunit C of mycobacterial ATP synthase leading to inhibition of ATP synthesis and resulting in bacterial death. "atpE" is the gene encoding the subunit C of the ATP synthase and the amino-acid sequence is conserved even in nonrelated M. tuberculosis. Both replicating, as well as dormant Mycobacterium, are killed.[4]

In 440 patients in phase 2 clinical trials the Safety and efficacy of bedaquiline was seen. Random allotment of 160 patients with newly diagnosed, smear-positive, MDR to be given either bedaquiline 400mg once a day for 2 weeks, followed by 200 mg thrice a week for 22 weeks, or placebo, both in combination with a desired background regimen was done in the first trial. Bedaquiline was administered to 23 out of 47 patients enrolled in the second trial. The dosage was same as in the first trial, but the duration of use of bedaquiline was curtailed to 8 weeks. Safety, tolerability, and efficacy of this novel drug was tested in 233 patients in the third trial with dosage and duration same as used in the first trial. In these phase 2 trials, the end point was taken as median time to culture conversion, which was seen to be statistically significantly reduced, with acceptable adverse effects. Nausea, joint pain, and headache were the common side effects found in the clinical trials. [5] At a dose of 400 mg, early bactericidal activity of bedaquiline was similar to rifampicin and isoniazid from 4 th dayonwards.[6]

Bedaquiline is metabolised by Cytochrome 450 enzyme. Therefore plasma levels are affected by Microsomal enzyme induction and inhibition. Persons receiving bedaquiline should avoid alcohol and other hepatotoxic drugs.[7] Since it is minimally excreted by the kidneys, it is safe in patients with mild to moderate renal impairment (not requiring dialysis), and should be administered with vigilance in patients with severe renal impairment requiring dialysis.[8]

The risks included likely progression of disease and death, and the development of increased antimycobacterial resistance for the patient and the population at risk when improper and inadequate therapy was instituted. Bedaquiline is indicated in a patient population for which there is considerable unmet need and a positive benefit-risk balance. In several European countries and South Africa, bedaquiline is now available for use on a limited basis. In a study on five patients of MDR-TB the patients who were given bedaquiline had improvement in symptoms with acceptable microbiological conversion rates and without any adverseevents.[9] About 11.4% of patients taking Sirturo died during clinical trials compared with 2.5% of those taking placebos. As the drug carries some significant risks, it is mandated to be used only in patients who do not have other treatment options.[2]

CONCLUSION

Bedaquiline is a new weapon against MDR-TB but its use should be reserved for patients who do not have any other therapy options as the drug has shown some significant risks like cardiac arrhythmia attributable to QT prolongation. The patient with MDR-TB has limited treatment options low cure rates. In this scenario, bedaquiline has a promising potential in increasing sputum conversion rate and hence favourable outcome in therapy of this form of TB.

ABBREVIATIONS

MDR-TB – Multi Drug Resistant Tuberculosis

ANIIMS- Andaman & Nicobar Islands Institute of Medical Sciences, Port Blair

REFERENCES

1. WHO. Global Tuberculosis Report 2014. Vol. 5. Geneva: World Health Organization; 2014; p: 54.
2. Walker J, Tadena N. J and J tuberculosis drug gets fast-track clearance. Wall St J 2013. Available from:http://www.online.wsj.com/article/SB10001424127887323320404578213421059138236.html
3. Goel D. Bedaquiline: A novel drug to combat multiple drug-resistant tuberculosis. J Pharmacol Pharmacother 2014; 5: 76-8.
4. Koul A, Vranckx L, Dendouga N, Balemans W, Van den Wyngaert I, Vergauwen K, *et al*. Diarylquinolines are bactericidal for dormant mycobacteria as a result of disturbed ATP homeostasis. J Biol Chem 2008; 283: 25273-80.
5. US Food and Drug Administration. FDA news release. Available from:

6. Rustomjee R, Diacon AH, Allen J, Venter A, Reddy C, Patientia RF, *et al.* Early bactericidal activity and pharmacokinetics of the diarylquinoline TMC207 in treatment of pulmonary tuberculosis. Antimicrob Agents Chemother 2008; 52: 2831-5.
7. Food and Drug Administration. SIRTURO (bedaquiline) tablets label. Washington, DC: Food and Drug Administration; 2012.
8. Centers for Disease Control and Prevention. Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis. MMWR Recomm Rep 2013; 62: 1-12.
9. Udwadia ZF, Amale RA, Mullerpattan JB. Initial experience of bedaquiline use in a series of drug-resistant tuberculosis patients from India. Int J Tuberc Lung Dis 2014; 18: 1315-8.