DOI: 10.7860/JCDR/2016/19052.8286

Short Communication

Pharmacology Section

Bedaquiline: A Novel Antitubercular Agent for the Treatment of Multidrug-Resistant Tuberculosis

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ABSTRACT

The developing countries are having an abruptly growing number of drug resistant tuberculosis cases. Multidrug-resistant tuberculosis (MDR-TB) is a type of TB in which the strain of *Mycobacterium tuberculosis* is resistant to at least Isoniazid and Rifampicin, the two most effective of the four first-line TB drugs (the other two drugs being Ethambutol and Pyrazinamide). The management of such cases is complex and requires a treatment for 24-27 months. The current guidelines available for the management of this type of TB are largely based on the second line TB drugs which are relatively costly, less efficacious and are associated with greater side-effects. The introduction of newer drugs to cater to the high mortality and early sputum culture conversion in the MDR-TB cases is an absolute essential. In the present article, the authors discuss about the introduction of a newer drug named Bedaquiline for the control of MDR-TB.

Keywords: ATP Synthase, Diarylquinoline, Drug-resistance

INTRODUCTION

The developing world is having a heavy burden of infectious diseases. The diseases like HIV AIDS and Tuberculosis (TB) constitute the top two killers among all the infectious diseases [1]. TB is a disease of great significance and is a major public health problem in low income countries like India [1]. TB is caused by *Mycobacterium tuberculosis* and is commonly transmitted by aerosols [1,2]. In the year 2011, the World Health Organization (WHO) reported 8.7 million new TB cases worldwide, with around 1.4 million deaths (WHO 2012) [2]. Even though the efforts to control TB are in full swing yet the cases diagnosed and put on treatment represent only a tip of the iceberg [1]. The rising number of cases is mainly due to increased awareness, easily accessible and free of cost diagnostic and treatment options, etc., [1].

Since, 1990 the drug resistant TB (DR-TB) has become a major public health problem [3]. As per the WHO estimates of the year 2013 the prevalence of primary multi-drug-resistant TB (MDR-TB) in India around 3.5%; however, this prevalence is 20.5% among previously treated cases [3]. Thus, clearly showing that the MDR-TB is basically a man-made problem, as a result of improper or poorly administered treatment and it develops due to spontaneous mutations in the genes of the bacilli [3]. Also, the demographics of TB infection vary widely, with developing countries bearing the heaviest burden of disease [2].

Drugs used to treat both MDR- and XDR-TB are usually dismally tolerated and are linked with higher rates of unpropitious events resulting in an overall treatment success in only 50–80% of MDR-TB cases [4–7], and in less than 50% of XDR-TB cases [4,8]. The major contributor to these poor success rates has been high case fatalities. There has always been a need for the launch of newer and better drugs to solve this issue as highlighted in the Global Plan to Stop TB [4,9].

The Food and Drug Administration (FDA), granted accelerated approval to SIRTURO™ (Bedaquiline) tablets on 28th December 2012, to be included in the existing second line antitubercular therapy in the adult MDR-TB cases [10]. An accelerated approval is given to the Bedaquiline (BDQ) as the FDA believes that the clinical benefits of this drug should be used in the affected population. Thus BDQ (previously known as TMC207) becomes the first new anti-TB drug to be approved after Rifapentine which was approved in 1998 [4,10]. Also, BDQ is the first anti-TB drug with a novel mechanism of action to be approved after more than 40 years as Rifampicin was approved in 1974 [10]. BDQ is first of its type that has been specifically introduced for the management of MDR-TB in combination with other drugs [10].

BDQ, a diarylquinoline class of antitubercular drugs that inhibits the activity of mycobacterial ATP synthase enzyme by binding to the subunit c of the protein [4,10]. It inhibits both actively replicating and non-replicating mycobacteria, with one study showing inhibition of dormant cells in latent TB infection at a low concentration [11]. Thus, it has strong bactericidal and sterilizing activity and is highly bound to plasma, is metabolized in the liver and is eliminated mainly in faeces [10,12,13]. The BDQ has a novel mechanism of action thus making it less susceptible to have cross resistance to other antitubercular drugs used for the MDR-TB. Besides, the drug has an extended terminal elimination half-life for about 5.5 months because of a combination of a long plasma and tissue half-life and high tissue penetration (especially in the organs affected by *M. tuberculosis*) [4,14]. Thus, less frequent dosing may be practicable, but it may also lead to prolonged adverse events after the drug cessation [4]. However, further research into the resistance patterns developed to BDQ is required as reports of cross resistance with other drugs like Clofazimine are available in the literature [15].

BDQ is active against drug sensitive, MDR, Pre-XDR, and XDR strains of *M. tuberculosis* in vitro [10]. In the Programmatic Management of Drug-Resistant Tuberculosis (PMDT) cases in India BDQ was introduced for the first time on 21st March 2016 [16]. The drug has given good results with early culture conversion as per the reports published earlier [4]. Due to ever rising numbers of MDR-TB cases there is an urgent need to introduce BDQ extensively all over the country. BDQ will be introduced with the optimized background regimen which will be based on the baseline Drug-Susceptibility Testing (DST) results of Levofloxacin, Moxifloxacin (both 0.5mcg and 2.0mcg), Kanamycin, Amikacin, and Capreomycin and will be as per the PMDT guidelines. In case of resistance to these second line drugs an additional extended second line DST will be performed for Ethionamide, Linezolid, Clofazimine and PAS. The susceptibility of *M. tuberculosis* to BDQ is unchanged in the presence of resistance to other antitubercular drugs, including Isoniazid, Rifampicin, Ethambutol, Streptomycin, and Moxifloxacin [14]. The cultures are to be performed as per the PMDT and DST guided treatment guidelines as scheduled follow-

ups. If culture is found to be positive, then DST will be performed as a reflex every three months. BDQ is being introduced at six identified tertiary care centers across India [16]. In New Delhi the drug will be launched at two DOTS-Plus sites, i.e. National Institute of Tuberculosis and Respiratory Diseases (NITRD) and Rajan Babu Institute for Pulmonary Medicine & Tuberculosis (RBIPMT) covering 15 districts of Delhi and soon will be extended to other parts of New Delhi.

The BDQ will be given along with other drugs as per optimized background regimen which was considered to be most appropriate by treating clinicians in that setting, on a dose of 400mg per day orally for two weeks, followed by an alternate day regimen of 200mg/day orally for the next 22 weeks [10]. The maximum dose not to exceed 600mg per week [12]. Further, after completion of the 24 weeks of BDQ, MDR-TB regimen will be continued as per national TB treatment guidelines [10,13]. Only pulmonary MDR-TB cases more than 18 years of age after pretreatment evaluation and initiation at the DOTS-Plus site and after obtaining a written and an informed consent will be started on this new modified treatment.

The BDQ has certain adverse drug reactions (ADR) and a number of drug interactions. The most common side-effects reported with BDQ therapy are nausea (30%), arthralgia (26%), headache (22%), haemoptysis (14%), chest pain (9%), anorexia (7%), and rash (6%) [10]. Serious adverse events included elevated serum transaminase levels and rate-corrected QT-interval prolongation [10,13]. More details about these are published in medical literature [10,12,13]. Thus regular supervision is absolutely necessary for this new drugs inclusion in the program. Presently, as per the PMDT guidelines all the DR-TB cases after being detected are sent to DOTS-Plus site for pretreatment evaluation and treatment initiation as an indoor patients. In case of BDQ therapy the guidelines remain the same, but patients can be admitted for six months with monitoring at the DOTS-Plus site. Also, the minimum stay of 15 days in the IPD of DOTS-Plus site is also mandatory and the patients agreeing to it will only be included in this regimen. This is absolutely essential to monitor any untoward incident, especially due to BDQ therapy, which may affect the continuation of treatment or modification of the dose of other drugs of the optimized drug regimen.

In cases of private practitioners there is the provision of free medication which will be provided directly by the manufacturer. All the patients who will be discharged from the DOTS-Plus site will be carefully monitored at the DOT centers and will be given drugs as per the guidelines. Further, in case of any ADR or any problem the patients will be dealt immediately and for this the collaboration with the government hospitals with facility to manage emergency and also with private practitioners is underway. The patients discharged from the DOTS-Plus site will be given a list of drugs interacting with BDQ, which can be shown to any emergency physician, so that the drug interactions with BDQ can be avoided.

CONCLUSION

With the growing drug resistance patterns and given the suboptimal efficacy and toxicity of currently available regimens for MDR-TB, BDQ represents a novel and great addition to the existing armamentarium of anti-TB agents, particularly in areas of the world where the disease is endemic. Although, the drug will be included soon in India, but still the available scientific literature about its benefits creates a new hope for the patients suffering from the MDR-TB and also the clinical benefits of this drug are the main reason that the FDA has given accelerated approval after two phase-IIb trials. However, the traditional approval will come only after the phase-III trials are over which will prove its clinical benefits and answer the safety issues. Also, the drug has not been studied in pediatric cases, pregnant or lactating females, persons with extrapulmonary TB and persons with HIV or other co-morbid conditions, thus further studies are warranted before routine use of this new drug in these populations. While BDQ introduction to PMDT for pulmonary MDR-TB cases is a story of many firsts and certainly a welcome addition to the existing arsenal of anti-TB agents, a cautiously optimistic approach is required to assess the risk benefit profile of the drug.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Feb 24, 2016**
Date of Peer Review: **Apr 16, 2016**
Date of Acceptance: **Apr 21, 2016**
Date of Publishing: **Aug 01, 2016**