Drug Update

Bedaquiline for the Treatment of Multidrug Resistant Tuberculosis: Drug Update

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Abstract

Tuberculosis continues to be a major public health problem and the Increasing rates of drug-resistant tuberculosis has become a major threat to global tuberculosis care and control. To combat the treat of drug resistant TB effective new drugs and treatment regimens are urgently needed to improve success rates of the present treatment regimens and reduce mortality.

The US Food and Drug Administration approved **bedaquiline** as part of the treatment regimen for pulmonary MDR tuberculosis in December 2012 and WHO issued interim guidelines on the use of bedaquiline to treat MDR-TB in June 2013.

Bedaquiline has unique mechanism of action by directly inhibiting adenosine triphosphate synthase and is effective against both dormant and replicating mycobacteria. Bedaquiline has shown promising results in studies including two Phase IIb trials and more information related to safety and efficacy will be available ongoing Phase III trials. This review article summarizes the information available regarding bedaquiline and presents an update on its use in pulmonary multidrug resistant TB.

Key Words: Bedaquiline, Drug Update, Multidrug resistant TB treatment, FDA

Introduction:

Tuberculosis continues to be a major public health problem and the Increasing rates of drug-resistant tuberculosis has become a major threat to global tuberculosis care and control. Globally in 2012, there were an estimated 300 000 (range 220 000–380 000) MDR-TB cases among notified TB patients and at least one case of extensively drug-resistant TB (XDRTB) had been reported by 92 countries by the end of 2012.[1]

Among MDR-TB patients started on treatment globally in 2009, only 48% were treated successfully and among a subset of 200 XDR-TB patients in 14 countries, treatment success only reached 33% overall and 26% of cases died.[1]

Effective new drugs and treatment regimens are therefore are urgently needed to improve safe and effective treatment to reduce patient suffering and deaths moreover the scale up of new, rapid diagnostic tests for drug resistance, such as the Xpert MTB/RIF assay, will be increasing the demand for treatment of MDR-TB patients. The last time a drug was introduced specifically for the treatment of TB was in the late 1960s. The US FDA's accelerated approval of new drug Bedaquiline represents a major milestone in MDR tuberculosis therapy.

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Bedaquiline received accelerated approval by the US FDA in December 2012 based on phase II clinical trial data.[2]

Bedaquiline is indicated for treatment of pulmonary multidrug-resistant tuberculosis in adults as part of combination therapy only when an effective treatment regimen cannot otherwise be provided.[2]

WHO issued interim guidelines on the use of bedaquiline to treat MDR-TB in June 2013.[3]

Bedaquiline will get traditional FDA approval if results of phase III trial confirm that the drug actually provides clinical benefit.

Pharmacological Aspects:

Bedaquiline, the first compound in a diarylquinoline class, binds to subunit c of mycobacterial ATP synthase and inhibits its activity. It inhibits both actively replicating and non-replicating wild type and resistant M.Tuberculosis.[4]

The distinct target and entirely new mode of action of bedaquiline which belongs to the novel class of anti-TB compounds reduces the potential for cross-resistance with the existing anti-TB drugs. It is active against DS, MDR, Pre-XDR, and XDR strains of M. tuberculosis in vitro. It is metabolized by CYP3A4 to N monodesmethyl metabolite, which is 4-6 times less potent than the parent drug.[5]

Its bioavailability is enhanced in presence of food. It is eliminated mainly in faeces.

In placebo-controlled studies of MDR and XDR-TB patients 79% of patients given bedaquiline had negative TB cultures after 24 weeks. Culture conversion was 33% faster in patients taking bedaquiline as compared to the

standard WHO-recommended MDR-TB regimen.[3,6]

Dosage and Administration:

Bedaquiline tablets are taken in combination with other medications that are used to treat TB. Bedaquiline is available as 100 mg tablet for oral administration. The tablets should be taken with food and should be swallowed whole with water for a total of 24 weeks. During weeks 1 and 2, the dose is 400 mg (four tablets) one time each day. During weeks 3 to 24, the dose is 200 mg (two tablets) each day three times weekly (e.g., on a Monday, Wednesday and Friday every week).

Patients should not take more than 600 mg (six tablets) during a 7-day period. Other TB medications might need to be taken for longer than 24 weeks. Bedaquiline doses should not be skipped. If doses are skipped or if the 24-week treatment is not completed, TB might be more difficult to treat.

Patients are observed by a health care professional when they receive and take the drug as a way to reduce the risk of interrupted treatment and noncompliance.

There is no evidence as yet that this drug can reduce treatment duration. As with all other TB drugs, bedaquiline should not be used alone but as part of a combination therapy, and never added alone to a failing regimen.

Paediatrics: The safety and effectiveness of bedaquiline in children has not been established. There is no paediatric formulation currently available.

HIV co-infection :

Primary research shows that Efavirenz interacts with bedaquiline by reducing its blood concentration, while lopinavir/ritonavir slightly increases the concentration of the drug.[7,8] Efavirenz, may induce CYP3A, and there is possibility that efavirenz might adversely lower bedaquiline concentrations.[9,10]

Toxicity:

In one placebo-controlled trial, an increased risk of death was seen in 11.4% of bedaquiline- treated patients compared with 2.5% of placebo patients although it is not clear whether this was due to the drug.

QT interval prolongation: Bedaquiline prolongs the QT interval. Bedaquiline has not been studied in patients with ventricular arrhythmias or recent myocardial infarction. ECGs should be monitored closely.

Hepatic drug reactions:

More liver-related adverse drug reactions were reported with bedaquiline when it was used with other TB drugs compared with other TB drugs used without the addition of bedaquiline.

Alcohol and other hepatotoxic drugs should be avoided during bedaquiline therapy, especially in patients with diminished hepatic reserve. Liver function and related laboratory tests should be monitored closely.

Other most frequently reported adverse effects were nausea (35.3%), arthralgia (29.4%), headache (23.5%), hyperuricaemia (22.5%), and vomiting (20.6%).3

Due to the toxicity and adverse reactions it is important that patients are closely monitored and active pharmaco vigilance is ensured, particularly those that are serious and life-threatening. Clinical monitoring of symptoms, performance of special tests at appropriate intervals, and counselling of the patient to report untoward consequences of treatment to the treating physician are the important for the effective management of adverse effects of bedaquiline.

Patents:

Several patents have been filed by Janssen covering the basic compound, methods of use, formulation and preparation processes.

The basic patent has already been granted in several countries including Armenia, Azerbaijan, China, Kazakhstan, Russia, Africa, Tajikistan, Ukraine and a number of African Regional Intellectual Property Organization (ARIPO).In India, the patent application on the basic compound (220/DELNP/2005) was filed by Janssen Pharmaceutica N.V. in January 2005, and granted (IN236811) in November 2009. The patent application on the salt form was also filed by Janssen Pharmaceutica N.V. in June 2009.[11]

Other patent applications are still pending, including applications related to use of bedaquiline for treating drug-resistant mycobacteria, to the use of bedaquiline for treating latent TB, and for processes.

Conclusion:

The approval of bedaquiline represents a major milestone in MDR tuberculosis therapy. FDA speculates that bedaquiline has the potential to fulfil an unmet medical need for the treatment of MDR-TB and will reduce the risk of development of resistance to other anti-TB drugs in the standard regimen. Phase III trial of bedaquiline is planned to confirm the efficacy findings from previous phase II clinical trials and to obtain additional safety data.

There is an urgent need for further research (pharmacokinetics, pharmacodynamics, and safety data) into the use of this drug in paediatric population and HIV co-infected patients on EFV based regimens.

Conflict of interest:

The authors declare no conflicts of interest in preparing

this article.

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Table 1: Brief Information on Bedaquiline

Drug Class	Diaryl-quinoline anti- mycobacterial agent.
TM	Sirturo
Presentations available	100mg uncoated tablet.
Price (in US$)of the lowest unit (i.e. the price of one tablet, capsule or vial) 100mg tablet [11]	High-income countries: 159.574 Upper middle-income countries: 15.957 Least-developed/resource-limited countries: 4.787
Manufacturer	Janssen/Johnson & Johnson, Titusville, N.J.