Review Article

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Bedaquiline: New Approach for Treatment of Multidrug-Resistant Tuberculosis

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ABSTRACT

Multidrug-resistant tuberculosis is a highly infectious disease. It is related to increased morbidity and mortality and therefore, it is considered as one of the world's most serious public health problems. Bedaquiline is a new approach for MDR-TB. It has specific anti-mycobacterial activity against mycobacterial ATP synthase. However, the drug has potential risks, including increased risk of arrhythmias and death.

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is a form of tuberculosis (TB) caused by a *Mycobacterium tuberculosis* strain resistant to at least Rifampicin and Isoniazid.[1] Extensively drug-resistant (XDR) TB is the form of MDR-TB with additional resistance to fluoroquinolones (FQs) and second line injectable (SLI) drugs.[2] TB remains a global epidemic.[3]About 3% of new tuberculosis patients and about 20% of previously treated patients in the world have multi drug resistant strains.[4] WHO has estimated that in year 2014, 71000 cases of MDR-TB have emerged among the notified cases in India.[5] Current treatment for MDR-TB patients is still poor. Bedaquiline (BDQ) is a new drug for treatment of MDR-TB acting by novel mechanism. It is a bactericidal drug. It is the first member of a new class of drugs called the diarylquinolines.[6]

Safety and effectiveness

The safety and effectiveness of Bedaquiline has been established in 440 patients in two phase-2 clinical trials.[7,8,9] Patients in the first trial were randomly assigned to be treated with Bedaquiline plus other drugs used to treat TB, or a placebo plus other drugs used to treat TB. All patients in the second trial received Bedaquiline plus other TB drugs. Both studies were designed to measure the time taken for a patient's sputum to be free of *M. tuberculosis*, known as sputum culture conversion. Results from the first trial showed that patients treated with Bedaquiline combination therapy achieved sputum culture conversion in a median time of 83 days, compared with 125 days in patients treated with placebo combination therapy. Results from the second trial showed that the median time to sputum culture conversion was 57 days, supporting the efficacy findings of the first trial. Common side effects identified in the clinical trials included nausea, joint pain, and headache.

Mechanism of action

Bedaquiline is effective against mycobacteria including MDR strains of the pathogen. It blocks the proton pump for ATP synthase of mycobacteria.The drug inactivates the F_1/F_0-ATP synthase of the pathogen but has no inhibitory effect on mammalian F_1/F_0-ATP synthase. F_1/F_0-ATP synthase is the key enzyme in the process of oxidative phosphorylation and ATP production. The bacterial membrane-associated electron-transport chains generate protons. These protons are coupled to oxidative phosphorylation and captured by the membrane-embedded F_0 proton channel of the enzyme. Thereafter, they are transported to the catalytic F_1 component, which undergoes a conformational change resulting in synthesis of ATP. So ATP production is required for cellular energy production and its loss leads to cell death, even in dormant or non-replicating mycobacteria.[6,10,11]

Pharmacokinetic profile

Bedaquiline is well absorbed after oral administration. Food intake increases the oral bioavailability of

Bedaquiline. It is highly bound to plasma protein (>99.9%) and has a high volume of distribution including the spleen, lungs, and sputum. It is metabolized in liver by CYP3A4 enzyme. Bedaquiline has extended plasma half-life. It remains in plasma for up to 5.5 months after stopping the drug.[12]

Adverse reactions

Bedaquiline has organ specific toxicity to gastrointestinal system, musculoskeletal system, cardiovascular system, liver, and pancreas. It causes nausea, headache, joint pain, muscle tenderness, hepatitis, pancreatitis, chest pain, arrhythmias, and death, as it may prolong the QT interval. Studies have suggested that, liver function tests, serum amylase, serum lipase level, and ECG should be monitored during treatment.[13,14]

Drug interactions

Bedaquiline should not be co-administered with other drugs that are strong inducers or inhibitors of CYP3A4, the hepatic enzyme responsible for oxidative metabolism of the drug. MDR-TB and HIV co-infection is common, so safe dosing of Bedaquiline is important in these patients. Ritonavir-boosted Lopinavir (protease inhibitor) is CYP3A4 inhibitor, so dose of Bedaquiline should be reduced.[12,15] No dose adjustment is needed with nevirapine.[16,17] Bedaquiline can also prolong the QT interval, therefore, use of QT prolonging drugs like fluoroquinolones (FQs) (Moxifloxacin, Gatifloxacin), Clofazimine (Cfz), macrolides (Erythromycin, Clarithromycin, Azithromycin), 5HT3 antagonist (Ondansetron), azole agent (Ketoconazole), antimalarials (Quinine, Chloroquine), antipsychotic drugs (Chlor-promazine, Haloperidol), class I and class III antiarrhythmic drugs require caution.[18]

Resistance

The specific part of ATP synthase affected by Bedaquiline is subunit 'c' which is encoded by the gene atpE. Mutations in atpE can lead to resistance.[19,20] Mutations in drug efflux pumps have also been linked to resistance.[21]

Bedaquiline under Revised National Tuberculosis Programme (RNTCP)[22]

Indications

Bedaquiline (BDQ) is indicated in adults aged 18 or above as part of combination therapy of pulmonary tuberculosis due to multidrug-resistance (MDR-TB). Under RNTCP, the following subgroups of patients will be eligible for BDQ:

1. MDR-TB with resistance to all Fqs
2. MDR-TB with resistance to all SLI (second-line injectable drugs)
3. XDR-TB
   - XDR-TB (All FQs and all SLI resistance)
   - XDR-TB (All FQs and any SLI resistance)
   - XDR-TB (Any FQ and all SLI resistance)
   - XDR-TB (Any FQ and any SLI resistance)
4. Treatment failure of MDR-TB and FQ/SLI resistance
5. Treatment failure of XDR-TB

Regimen

Bedaquiline containing regimen for above subgroups would contain BDQ + at least four second line drugs (choice of drugs should be based on drug sensitivity test pattern in descending order)

1. Second line injectables (Group 2): Kanamycin (Km)/ Capreomycin (Cm)
2. Fluoroquinolones (Group 3): Levofloxacin (Lfx)/ Moxifloxacin (Mfx)
3. Two bacteriostatic drugs (Group 4): Ethionamide (Eto), Cycloserine (Cs), P-amino salicylic acid (PAS)
4. Group 5: Linezolid (Lzd)/ Clofazimine (Cfz)/ high dose Isoniazide (hINH)/ Clarithromycin (Clr)
5. Pyrazinamide (Z), if sensitive

Duration of treatment

- Week 0-2: BDQ 400 mg (4 tablets of 100 mg) daily + Optimized background regimen (OBR) of selected second line drugs.
- Week 3-24: BDQ 200 mg (2 tablets of 100 mg) 3 times per week (with at least 48 hours between) for a total dose of 600 mg per week + optimized background regimen (OBR) of selected second line drugs.
- Week 25 (start of 7 month) to end of treatment: Continue other second line anti-TB drugs only as per RNTCP recommendations.

CONCLUSION

A number of first and second-line drugs are available for treatment of tuberculosis infection. Development of resistance to these drugs is the major health problem. Bedaquiline is a new treatment modality for multidrug-

resistant (MDR) TB. Bedaquiline has specific anti-mycobacterial activity but it increases risk of arrhythmias and death. An important consideration in the use of Bedaquiline is its potential for drug interactions considering its metabolism through CYP3A4.

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