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Review Article

Sirturo- a diarylquinoline (bedaquiline): a novel approach for the treatment of MDR-TB and pre-XDR TB

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ABSTRACT

Sirturo (bedaquiline fumarate) is a new antitubercular class of medicine, lately, FDA, approved and indicated for use as a part of an appropriate applicable combination regimen along with other antitubercular medicines (i. e.; 2nd line anti-TB agents) for pulmonary multidrug-resistant tuberculosis (MDR TB) in grown up with age 12 years to less than 18 years of age and weighing at least 30 kg when an alternative treatment regimen cannot be considered for the reasons of resistance or tolerability. Bedaquiline, an enantiomer chemically belongs to the diarylquinoline (DAR) compound, which is nearly related to fluoroquinolones and chloroquine with differences in their side-chain moiety. Amongst all anti-TB medicines that have been approved, bedaquiline has a unique mechanism, which targets energy metabolism i. e.; adenosine triphosphate of mycobacteria, and eventually leads to bacterial cell lysis. ATP is an essential energy-producing molecule required for metabolic actions and survival of Mycobacteria and also for many other cells. Mycobacteria generally invade into well-encapsulated lung cavities and endosomes of macrophages, which can survive even under low oxygen levels leading to resistance against standard TB drugs. Bedaquiline has a spectrum of activity against drug-susceptible TB and MDR TB. Many clinical trials and studies demonstrated that bedaquiline is a crucial component of a combination regimen for multidrug-resistant TB.

Keywords: Bedaquiline, Mycobacterium TB, Anti-tubercular drugs, Multi-drug resistance, Diarylquinoline, Fluoroquinolones

INTRODUCTION

TB is mainly caused by *M. tuberculosis*, which is a non-spore-forming, aerobic bacillus that resists decolorization by acid-fast staining with basic fuchsin. Thus due to this reason, this organism is often referred to as an acid-fast bacillus (AFB). It is also different from other organisms in that it replicates slowly- once every 24 hours instead of every 20 to 40 min when compared to other organisms.[1] Transmission mainly occurs when a person inhales droplets that contain nuclei of *M. tuberculosis*, which further colonizes the nasal passages, upper respiratory tract, and bronchi and eventually reaches the alveoli of the lungs. Increased incidence of tuberculosis is seen in many HIV-epidemic countries.[2,3] The proven effectiveness of short-course chemotherapy, and the realization that tuberculosis control is one of the most cost-effective health interventions in developing countries.[4,5] Assuming lifelong infection, approximately 2.0 billion people (30% of the world's population) are infected with *M. tuberculosis*. TB is one of the most common causes of death from an infectious disease in the world, second only to HIV and AIDS. The era of medical therapy for TB began in 1944 with the discovery of streptomycin and, shortly later, p-aminosalicylic acid (PAS). The addition of isoniazid in 1952 and rifampin in the late 1960s has increased the treatment success rates and provide hope for the eventual elimination of TB. However, multidrug-

resistant TB (MDR-TB) i. e.; resistant to at least rifampicin and isoniazid emerged in the 1990s as a threat to the control of TB in the United States and other countries.[1-3] In the subsequent decade, reports were published describing the worldwide emergence of extensively drug-resistant TB (XDR-TB) and, more recently, the emergence of new forms of totally drug-resistant (TDR) or super XDR-TB strains. A better understanding of the prevalence of anti-tubercular drug resistance against mycobacterium tuberculosis is one of the key roles in controlling TB. Anti-Tb drug resistance, along with other factors like HIV, COPD, and immunosuppressed diseases, has contributed to increased morbidity and mortality due to tuberculosis. Drug-resistant strains of TB are rapidly emerging worldwide.[6] The WHO reported an intimidating rise of multidrug-resistant (MDR) TB and also XDR TB (extreme drug-resistant TB) globally. Considering globally, there were about 0.5 million cases of MDR TB, and increasing too.[7]

DRUG REVIEW

Chemistry

Bedaquiline is a pure enantiomer that contains two adjacent chiral carbon atoms that bridge three aryl rings (a naphthyl, a 6-bromoquinoline, and a phenyl ring which represent the core of the molecule, which shows high lipophilicity) and a dimethylamino ethyl moiety (Figure 1).[8-10] Bedaquiline molecular formula is C32H31BrN2O2 and IUPAC name is (1R, 2S)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-naphthalen-1-yl-1-phenylbutan-2-ol. Its molecular weight is 555.5 g/mol, physically white to almost white powder; practically insoluble in aqueous media (bedaquiline fumarate). ATC CODE: J04AK05.[11-14]

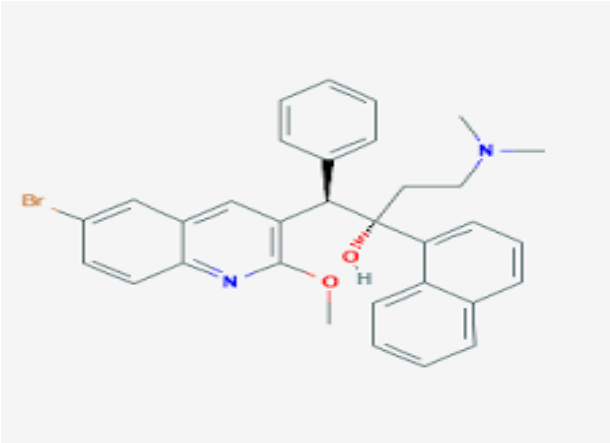

Figure 1: Chemical structure of bedaquiline.

Mechanism of action

Bedaquiline, a diarylquinoline antimycobacterial drug that inhibits mycobacterial ATP synthase by potentially binding to subunit C (at subunit c ATP synthase is oligomeric and proteolipid) of the enzyme, where ATP is the source of energy production in *Mycobacterium tuberculosis*. Which eventually leads to bacterial death. It has a transient bacteriostatic effect followed by a consistently maintained dose-dependent bactericidal effect.[11,12]

It binds to mycobacterial ATP synthase with more than 20,000 times more affinity than it binds to human mitochondrial ATP synthase.[15] It is the only reason for specific action in mycobacterium and minimum host cell damage.

Thus bedaquiline has become the focus of many synthetic studies and meta-analyses for its excellent activity and unique mechanism of action. Bedaquiline inhibits MTB at a MIC ranging from 0.002-0.06 µg/ml. Likewise, bacteria with smaller ATP stores (i. e.; generally dormant/nonreplicating bacilli) are found to be more susceptible to bedaquiline.[15,16]

SPECTRUM OF ACTIVITY

Bedaquiline targets the energy metabolism of mycobacteria- adenosine triphosphate (ATP). Based on minimum inhibitory concentration (MIC), bedaquiline shows excellent bactericidal activity against many strains of mycobacterium which includes *M. tuberculosis*, *Mycobacterium avium*, *Mycobacterium leprae*, *Mycobacterium intracellulare*. Its spectrum of activity also targets both rapid as well as slow growth among non-tuberculous mycobacteria (NTM). Also, bedaquiline is susceptible to NTM, and other mycobacterium strains as their MIC is less than 0.5 µg/ml, including *Mycobacterium chelonae*, *Mycobacterium fortuitum*, *Mycobacterium phlei* and *Mycobacterium vaccae*, *Mycobacterium kansasii*, *Mycobacterium gordonae*, *Mycobacterium simiae* and other strains belonging to slow growing NTM that are susceptible to bedaquiline.[17]

Pharmacokinetics and pharmacodynamics

Absorption

Bedaquiline orally is well absorbed with single and multiple doses and maximum plasma therapeutic concentration is observed within 5-6 hours after administration.[18] When administered with food can increase the oral bioavailability of bedaquiline. Bedaquiline has concentration-dependent killing and is bactericidal in nature.[21]

AUC of bedaquiline, when administered as a tablet formulation, is increased ~2.0- to 2.4-fold higher than compared to fasted conditions.[19,20] The usually available dose is 400 mg, when 400 mg is administered once daily for a week, the maximum plasma drug level (C_{max}) is attained at 5.5 µg/ml concentration and an AUC of 64.75 µg/ml.

Distribution

Bedaquiline has protein binding of nearly 99.9% and the volume of distribution is approximately 164L in the absence of fluid overload.[21]

Metabolism

Bedaquiline is generally metabolized in the liver by the enzyme P450 (CYP) isoenzyme 3A4 (substrate of CYP3A4) into the *N-mono desmethyl* metabolite i. e.; M2. The N-didesmethyl metabolite i. e.; M3 is another, quantitatively less important, metabolite. It is formed by *N*-demethylation of M2 and has nill therapeutic antimycobacterial activity.[22-25]

Route of elimination

Bedaquiline is primarily eliminated in the feces. The urinary excretion of the unchanged bedaquiline is 0.001% or less and has an insignificant renal clearance.[36,37] It is not a dialysable drug. It has a half-life (parent drug and M2 metabolite) of 5.5 months.

Indications

Bedaquiline is an FDA-approved drug for the treatment of multidrug-resistant TB in combination with other antimycobacterial agents.[26]

Dose, dosage forms, and strengths

Bedaquiline is generally administered orally. The recommended dosage is 400 mg once daily for 2 weeks followed by 200 mg three times per week for 22 weeks.[27] However, an alternative once-daily dosage of 200 mg for 8 weeks and then 100 mg for 18 weeks is currently being tested in two phases and 3 trials of bedaquiline-based regimens (for ≥18 years).[28]

Adverse effects and monitoring

Serious adverse effect is, increased liver enzymes (9-10% in adults, 33% in pediatrics) which is a concern with bedaquiline, thereby requiring patients to undergo baseline tests and subsequent monitoring of LFT throughout the treatment period.[29,32]

The regimen of bedaquiline when administered with other antituberculosis drugs has been associated with increased risk/rate of transient serum liver tests and probably liver injury. Another serious adverse effect is prolonged QT interval and should be avoided with drugs causing QT prolongation.

An electrocardiogram (ECG) should be performed and repeated monthly.[33] Gastrointestinal disturbances such as abdominal pain, nausea, and diarrhea have been commonly reported, arthralgia, headache, and chest pain are less common.[30,31]

Contraindications

Bedaquiline is contraindicated with the drugs that cause QT prolongation.

DRUG INTERACTION

Anti-TB drugs

Coadministration of rifampicin which is a potent inducer of CYP isoenzymes, including CYP3A4, with bedaquiline, was expected to reduce bedaquiline therapeutic concentration.[34] Whereas isoniazid, pyrazinamide, ethambutol, amikacin, and levofloxacin do not have many effects on pharmacokinetic interaction with bedaquiline.

Antiretroviral drugs

Lopinavir is both a substrate and an inhibitor of CYP3A4. As bedaquiline is primarily metabolized by CYP3A4, bedaquiline concentration increases when coadministered with lopinavir/ritonavir.[35-37] As it is metabolized by CYP2B6 and CYP3A and induction of CYP3A, the chronic coadministration of efavirenz can limit exposure to bedaquiline and its major metabolite M2 by approximately 50%.[38] Ketakonazole, a strong CYP3A4 inhibitor when coadministered with bedaquiline can result in an increase in AUC.[29] Additive/synergistic QT prolongation is observed when coadministered with medications like ketoconazole, fluoroquinolones, macrolide, and clofazimine.[39]

CONCLUSION

Infection of TB and multidrug resistance TB has been emerging in India. Bedaquiline was approved for DR-TB treatment under conditional access programme and was also implemented by the National Institute of TB and respiratory diseases. Many studies and meta-analyses performed all over the world have shown that bedaquiline with other combination drugs has reduced morbidity and mortality and increased the cure rates. Complete knowledge of bedaquiline and its rational use by physicians can enhance good therapeutic outcomes and decrease the chance of resistance.

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