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REVIEW ARTICLE

Bedaquiline: A Novel Addition to Anti-Tubercular Armamentarium

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ABSTRACT

In current scenario of rising trend of resistant tuberculosis (TB) and acquired immunodeficiency syndrome (AIDS) co infection with TB, a novel antitubercular drug is a prime need to effectively decrease the disease burden. In lieu of the fact that no new antitubercular drug has come up in last four decades, bedaquiline (TMC 207), an arylquinoline, seems an attractive option for TB patients because of its tendency to cause earlier and sustained antitubercular action, shorten treatment duration, less chances of resistance and better safety as compared to existing second line drugs. Bedaquiline has recently been approved by USFDA on 28th December, 2012 for treating multi drug resistant TB (MDR-TB) in adults ≥18 years. This review elucidates the available evidence on efficacy and safety of this drug after analyzing preclinical and clinical studies. Searches of pubmed, Cochrane database, Medscape, Google and clinicaltrial.org were made for terms like bedaquiline, TMC207 and MDR-TB.

KEY WORDS: Bedaquiline, TMC207, pulmonary tuberculosis, MDR-TB

INTRODUCTION:

Tuberculosis (TB), an ancient lethal infectious disease caused by '*Mycobacterium tuberculosis*' is emerging globally with an estimated prevalence of 8.7 million TB cases annually and 1.4 million deaths. [1] Directly Observed Treatment Strategy (DOTS) and Stop TB programs have substantially contributed to effectively improve the TB burden but rapid emergence of mycobacteria resistant to anti tubercular drugs and rising cases of Human Immunodeficiency Virus (HIV) co-infection with TB in last few decades has come up as a real threat in effective management of tuberculosis. [2,3]Rising trend of Multidrug resistant tuberculosis (MDR-TB) has been observed in European and Asian countries with 9-32% new cases and 50% previously treated cases being affected.[4]

Sensitive tubercular organisms respond well to the conventional treatment regimens as given by World Health Organisation(WHO) .Standard treatment of tuberculosis involves intensive phase of treatment of 2 months with first line drugs like rifampicin[R], isoniazid[H], ethambutol[E] and pyrazinamide[Z] followed by continuation phase with rifampicin and isoniazid for 6 months. The standard regimen is capable of curing 85% cases but being cumbersome and lengthy; it fails to result in complete compliance by majority of patients. Moreover, not all the first line drugs are capable against persistent bacteria. Latent TB is treated with isoniazid for 6-9 months where again patient compliance is a big question mark. [2,5] Management of tuberculosis seems more challenging when the patient develops drug resistant TB and HIV coexisting with TB. Drug resistant TB has been categorized by WHO as MDR, Pre Extensively Drug Resistant (Pre XDR) and XDR. MDR-TB refers to the resistance to at least isoniazid and rifampicin whereas XDR-TB is a subset of MDR-TB with resistance to any fluoroquinolones and at least one of three second line injectable drugs [capreomycin, kanamycin, and amikacin]. [6-8] Pre XDR TB refers to resistance to not only first line drugs but also to either fluoroquinolones or one of the second line injectables. [9] Resistant TB is treated by second line drugs which are less efficacious and poorly tolerated with devasting adverse effects resulting in rise in treatment defaulters. Cure rate with second line drugs has been demonstrated to be 54% with 15% mortality. [10]Besides this, treatment is too lengthy (for at least 20 months) and costly which has direct impact on the patient adherence.[8,11]Untreated /partially treated patients either end up in death or spread infection in community hence creating more alarming state.

Despite the rise in incidence of MDR-TB worldwide over the past few decades, no TB specific drug has been discovered in last 40 years. [12,13] After such a long waiting period, revival in research and development activity in this area has resulted in discovery of bedaquiline/TMC207, first compound from a new class of diarylquinolines, as a potential antitubercular candidate by scientists in Janssen discovery labs in Belgium in 2001. [14] This drug was reviewed by accelerated approval program which means

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approval of a promising drug based on a surrogate end point [time for sputum conversion] with additional studies to be conducted to confirm benefit and safety.[15]Bedaquiline has recently been approved by United states food and drug administration (USFDA) in December28, 2012 to be used as a part of combination therapy in MDR-TB in adults ≥18 years where other alternatives are not available. [16]

In lieu of the fact that no new antitubercular drugs has come up in last four decades despite of rising trend of MDR and XDR-TB, bedaquiline seems an attractive welcoming option to be used for both sensitive and resistant tuberculosis patients because of its tendency to cause earlier and sustained antitubercular action, shortening of treatment duration, less chances of resistance and better safety as compared to existing second line drugs. [12,13,15] Also bedaquiline offers the advantage of not only killing rapidly multiplying bacteria but also non replicating mycobacteria hence conforming it's both bactericidal and sterilizing action which shortens the duration of treatment, an important factor to improve patient adherence and ultimately the effectiveness of tuberculosis management.[10,17]

CHEMISTRY:

Chemically this novel agent is a diaryl quinoline anti tubercular agent with molecular weight 555.50 Da and chemical name as (1R, 2S)-1-(6-bromo-2 methoxy-3-quinolinyl)-4-(dimethylamino)-2-(1-naphthalenyl)-1-phenyl-2-butanol. [18]

MECHANISM OF ACTION:

Bedaquiline acts by novel mechanism of action by inhibiting mycobacterial ATP synthase enzyme needed for production of Adenosine triphosphate (ATP) from Adenosine diphosphate (ADP) and inorganic phosphate. ATP synthase has two major structural domains, F_0[a, b and c subunits] and F_1[α, β, γ, δ and ε sub units] linked together by central stalk [γ and ε] and peripheral stalk [b and δ].[18,19] This novel drug is proposed to bind to the proton translocating c subunit and forms a wedge between the two rotating subunits which otherwise move with speed of 100 revolutions /second. This binding stops the rapid rotation hence hindering the action of ATP synthase.[10] Mechanism has been confirmed by the observation that resistant mycobacteria differs in atpE gene coding for c subunit decreasing the binding of drug to target enzyme.

DRUG RESISTANCE:

Natural resistance is observed in certain mycobacterial species and human beings to the action of diaryl quinolines as these bear mutations in atpE gene coding for ATP synthase which is the target for drug action.[16,20] Out of 20 additional mycobacterial species. 3 were found to be naturally resistant to bedaquiline in a in vitro study. [21] Polymorphisms in genes regulating ATP synthase in human beings has resulted in selective action of bedaquiline in mycobacteria so mitochondrial ATP synthase is 20,000 fold less sensitive to bedaquiline than mycobacterial ATP synthase predicting its safety in human beings.[5,10,22] Due to it different mode of action with altogether different target of action, no cross resistance has been demonstrated with other antitubercular drugs.[10,15]

PHARMACOKINETICS:

Bedaquiline is an lipophilic compound which possesses high plasma protein binding [>99%] and volume of distribution [164 litres].[23]Maximum concentration of the drug is demonstrated in 5 hours post dose with initial decline due to tissue distribution. [12] It undergoes oxidation by CyP_3A_4 enzyme resulting in production of N – mono desmethyl metabolite M2 which is 4-6 times less potent than the parent drug. Bedaquiline and the metabolite possess terminal half-life ($t_{1/2}$) of 5.5 months. [10,16] In vitro inhibition of mycobacterium tuberculosis has been observed at 0.06 µg/ml concentration of Bedaquiline. [12]

DOSING RECOMMENDATIONS:

Bedaquiline is advised to be administered by DOTS for 24 weeks as combination therapy so as to decrease the chances of resistance. Recommended dose is 400 mg once daily for 2 weeks followed by 200 mg thrice weekly for 22 weeks with food as food has been found to enhance the plasma concentration of drug by two folds.[4]

PHARMACOKINETIC STUDIES:

A randomized, double blind, placebo controlled study was done on 6 cohorts of healthy male volunteers with 6 escalating doses of bedaquiline [10, 30,100,300,450 and 700 mg once daily] and placebo . Bedaquiline was found to be well absorbed after single oral dose with maximum plasma concentration (Cmax) achieved after 5 hours. Cmax and area under curve [AUC] increased proportionately with dose. No dose dependent change was observed in t1/2.Similarly study results of use of bedaquiline in three doses [50,150,400 mg daily] and placebo for 14 days demonstrated increase in AUC(0-24 Hrs) by factor of 2 between day 1 to 14 with bedaquiline suggesting an effective half life of 24 hours.[12]

ANIMAL STUDIES:

In mice study, bactericidal activity of bedaquiline has been found to exceed rifampicin and isoniazid by 1 log unit. Substitution of first line drugs by bedaquiline resulted in complete culture conversion in 2 months and single dose can inhibit the growth for 1 week. [12] In another murine study, four months of treatment with bedaquiline(J) containing regimens [JHRZ] was as effective as the 6-month standard regimen[HRZ] with relapse rate of 6% versus 17% ,p=0.54 and more effective than 4 months of treatment with moxifloxacin containing regimens[RMZ] with relapse rate of 6% versus 42%,p=0.03. Supplementation of standard regimen (RHZ) with bedaquiline or substitution of bedaquiline for H may shorten the treatment duration needed to cure TB patients. [24]

CLINICAL EFFICACY STUDIES IN TREATMENT NAIVE CASES:

Results of 7 day phase II study on treatment naive patients demonstrate that bedaquiline 400mg once daily is comparable in efficacy to rifampicin and isoniazid in treatment naïve patients with pulmonary TB during last days of treatment in terms of change in Colony Forming Units (CFU) count.[25] Another 14 day study on treatment naïve cases demonstrated bedaquiline inferior in Early bactericidal activity (EBA)than combination of PA824, moxifloxacin and Pyrazinamide but found to be safe and well tolerated [Table 1]. [26]

Table 1: Clinical studies in treatment naive pulmonary tuberculosis patients

Study	Study design	Patient details	Treatment details	Study results
Rustomjee et al ,2008 [25]	C202 trial Phase IIa Open label ,randomized, double blind, placebo controlled	N=67 Treatment naive patients with smear positive pulmonary TB	5 groups Bedaquiline 25mg,100mg,400 mg, Rifampicin[R] 600mg isoniazid [H]300 mg each drug once a day for 7 days	Mean decrease in CFU count over 7 day period in log10CFU/day± Standard deviation Bedaquiline 25mg 0.04±0.46 Bedaquiline 100mg 0.26±0.64 Bedaquiline 400mg 0.77±0.58 R600mg 1.70±0.71 H300mg 1.88±0.74 Bedaquiline 400mg was comparable in efficacy in later half of the treatment days.
Diacon et al, 2012 [26]	Phase IIa Open label randomized partially double blind Prospective study	N=85 Treatment naïve patients with smear positive pulmonary TB	64 patients completed the treatment 6 groups Bedaquiline[N=14] Bedaquiline and Z[N=14] PA-824 and Z[N=14] Bedaquiline and PA-824[N=14] and PA-824,M and Z[N=12] Unmasked standard ATT regimen[N=10] once daily for 14 days	Mean 14 day EBA of PA824-M-Z [0.233±0.128] was significantly higher than Bedaquiline [0.061±0.068], Bedaquiline and Z[0.131±0.102] and Bedaquiline and PA-824[0.114±0.50] Bedaquiline was well tolerated and safe.

CLINICAL EFFICACY STUDIES IN TREATMENT RESISTANT CASES:

A phase 2 trial conducted on newly diagnosed MDR-TB patients [C208] was done in two stages. Stage 1 demonstrated efficacy, safety and antibacterial activity of the study drug bedaquiline over 8 week period with final follow up at 104 weeks. Results of stage 1 study demonstrated early sputum conversion and higher conversion rates with bedaquiline than placebo at all time points over 8 weeks [48 versus 9%]. Mean log 10 CFU declined more rapidly with Bedaquiline than placebo. [27] During investigational period, bedaquiline was found to significantly reduce the time to culture conversion over 24 weeks; p=0.031.Resistance to companion drugs was also less (4.8%) with bedaquiline as compared to placebo (21.7%) (p=0.18)[Table 2].[28]

Stage 2 consisted of 24-week investigational treatment period with a follow-up at 120 weeks. Subjects from 7 countries with newly diagnosed smear positive pulmonary TB were enrolled. Results of stage 2 also showed the similar results of significantly earlier sputum conversion as well as higher conversion rates with bedaquiline as compared to placebo [79% versus 58% ,p=0.008]. Follow up after 96 weeks demonstrated

significantly higher sustained culture conversion with bedaquiline. In both the stages, few patients developed XDR-TB in bedaquiline group than placebo [1 versus 4 in stage 1 and 0 versus 7 in stage 2]. Cure rate for MDR-TB and pre XDR-TB was better in bedaquiline group [69% and 60%] than placebo [44% and 42%].Nausea was the most common adverse effect in both the stages followed by arthralgia, unilateral deafness, hyperuricemia, haemoptysis, rash and chest pain found with similar proportion in both the treatment arms. Though QTc prolongation was observed but these changes did not contribute to any adverse event during the treatment.[29]

Another trial [C209] was similar to C208 in all aspects but different in inclusion criteria because patients included were either newly diagnosed or old cases of MDR-TB. Significantly higher proportions of patients (79.5%) were found to have sputum conversion at week 24. Median time to sputum conversion was faster at 57 days as compared to C208 study because 86% of the patients in C209 groups were already taking treatment during screening phase. Response rate was higher in patients with no cavitations (p=0.0157), lower extent of resistance (p=0.0006) and patients on three or more active drugs (p=0.0376).Common adverse effects observed were nausea (11%), arthralgia(12%) and hyperuricemia(14%).QT c prolongation was also observed during treatment period which was not significant similar to that observed in C208 trial[Table 2] .[30]

Table 2: Clinical studies on drug resistant pulmonary tuberculosis patients

Study	Study design	Patient details	Treatment details	Study results
C208 trial [Stage 1] [28]	Phase II randomized placebo controlled, multicentre 8 week	N=47 Newly diagnosed cases of smear positive MDR-TB	41 patients completed the study Bedaquiline [N=23] 400 mg Placebo[N=24] once daily for 2 weeks followed by 200mg thrice weekly for 6 weeks in combination with standard 5second line drugs	Earlier sputum conversion with bedaquiline (p=0.003) Rate of sputum conversion: Bedaquiline -48% Placebo-9% Steady state plasma concentration of bedaquiline at concentration >600 mg /ml throughout the treatment
C208 trial [Stage 2] [29]	Phase II randomized placebo controlled 24 week treatment period followed by 96 week follow up period	N=160 Newly diagnosed cases of MDR-TB	Bedaquiline [N=79] 400 mg Placebo[N=81] once daily for 2 weeks followed by 200mg thrice weekly for 22 weeks in combination with standard 5second line drugs	Earlier culture conversion with bedaquiline at12 weeks versus 18 weeks with placebo(p=0.003) Rate of sputum conversion: Bedaquiline -79% Placebo-58% (p=0.008) Sustained culture conversion at 96 weeks Bedaquiline 62% Placebo 44%
C209 trial [30]	Phase II open label, single arm 24 week treatment study	N=233 Newly and previously iagnosed sputum smear-positive pulmonary MDR-TB including Pre-XDR (25%) and XDR-TB (21%)	Bedaquiline with optimized background regimen once daily for 2 weeks followed by 200mg thrice weekly for 22 weeks	Rate of sputum conversion with bedaquiline All cases 79.5% MDR-TB 87.1% Pre XDR TB 77.3% XDR-TB 55.6%

Phase 3 trials, trials on geriatric population , paediatric population , patients with HIV-TB co infection and severe hepatic /renal insufficiency ,are in pipeline in future so as to generate sufficient data to mark bedaquiline useful in such special population groups too.

SAFETY WARNING:

No dose adjustment of bedaquiline is needed in mild or moderate hepatic and renal impairment .But cautious use is recommended in severe hepatic impairment, severe renal insufficiency, undergoing dialysis, cardiovascular diseases, pregnancy , breast feeding females, children less than 18 years and elderly >65 years due to lack of data for its use in such patients.[10]

DRUG INTERACTIONS:

Bedaquiline though metabolised by microsomal enzyme CYP_3A_4, does not possess enzyme inducing or inhibiting action. Hence rather than being the culprit influencing other drug action, it can be a victim of drug interactions. Ketoconazole/lopinavir/ritonavir demonstrate enhancement of the action of bedaquiline whereas rifampicin has been found to decrease the exposure to bedaquiline .Till now no drug interactions have been observed with other antitubercular drugs in various studies.[10]Phase 1 pharmacokinetics drug interaction trial between bedaquiline and efavirenz in 33 healthy volunteers demonstrated no clinically significant effect of efavirenz observed on bedaquiline concentrations and both the drug were well tolerated together too.[31]

To conclude, bedaquiline is a promising drug which seems better than the conventional second line drugs in resistant cases of TB due to novel mechanism of action offering faster and sustained sputum conversion rates, absence of cross resistance and few treatment failures. But to mark it superior to existing drugs for drug sensitive, latent, extra pulmonary TB and TB HIV co-infection, more exploratory trials are needed to be conducted in future.

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