To Study Efficacy Of Bedaquiline Plus Optimized Background Regimen In Drug Resistant Tuberculosis Under National Tuberculosis Elimination Programme

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ABSTRACT:

Aims: Bedaquiline (BDQ) has been recently approved for drug resistant tuberculosis under programmatic management of drug resistant tuberculosis(PMDT). The present study was conducted to evaluate efficacy, safety and tolerability of bedaquiline plus optimized background regimen.

Methods: An observational study was conducted on cohort of pre-extensively drug resistant (XDR) pulmonary TB patients. Every patients was undergone pre-treatment evaluation. After initiation of regimen patients were follow up for sputum culture, adverse drug events and clinical improvement. Patients were closely monitored for cardiac safety during BDQ (I P Phase) and during continuation phase upto fifteen months.

Results : 93.39 % shows culture conversion within first 6 months. The treatment outcome could not be reached because none of the patient completed their regimen.Outof 116 patients enrolled,3 patients were declared as treatment failure. Culture reversion was seen in 1 patient. Previous history of anti-TB medications and low body mass index (BMI) have associated with delayed time for culture conversion.Hepatitis C virus negativity and normal serum albumin level were significantly associated with faster time to culture conversion. Baseline QTc interval was <420 ms in 86.21% patients. After initiation of treatment 12.93% cases shows QTc prolongation. 3 (2.59%)patients shows dangerous increase in QTc interval. Out of these, 2 patients required permanent discontinuation of BDQ.

1. INTRODUCTION

Tuberculosis(TB) is caused by a group of closely related bacterial species termed *Mycobacterium tuberculosis* complex. Today the principal cause of human tuberculosis is *Mycobacterium tuberculosis*[1].

Tuberculosis (TB) isone of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent (ranking above HIV/AIDS). In 2019, about 10 million people developed TB and 1.4 million died.[2]

The disease typically affects the lungs (pulmonary TB) but can also affect other sites (extrapulmonary TB). TB can affect anyone anywhere, but most people who develop the disease (about 90%) are adults; there are more cases among men than women.[2]

GLOBAL SCENARIO

Globally, an estimated 10.0 million (range, 8.9–11.0 million) people fell ill with TB in 2019, a number that has been declining very slowly in recent years.[2]

Men (aged ≥15 years) accounted for 56% of the people who developed TB in 2019; women accounted for 32% and children (aged <15 years) for 12%. Among all those affected, 8.2% were people living with HIV.[2]

Drug-resistant TB continues to be a public health threat. The three countries with the largest share of the global burden were India (27%), China (14%) and the Russian Federation (8%). Globally in 2019, 3.3% of

new TB cases and 17.7% of previously treated cases had MDR/RR-TB[2].

In 2014 and 2015, all Member States of WHO and the UN committed to ending the TB epidemic, through their adoption of WHO's End TB Strategy and the UN Sustainable Development Goals (SDGs). The strategy and SDGs include milestones and targets for large reductions in TB incidence, TB deaths and costs faced by TB patients and their households[2].An estimated 8.2% (range, 7.0–9.5%) of the incident TB cases in 2019 were among people living with HIV. Globally, the incidence of TB expressed per 100 person-years with HIV was 2.1% (range, 1.9–2.4%). The risk of developing TB among the 38 million people living with HIV was 18 (range, 15–21) times higher than in the rest of the global population.[2] In 2019, it caused 1.4 million deaths, including 208 000 among HIV-positive people.[2]

INDIAN SCENARIO

India is the highest TB burden country in the world having an estimated incidence of 26.9 lakh cases in 2019[3].In 2018 Revised National Tuberculosis Control Program (RNTCP) was able toachievea notification of21.5 lakh.[4]

India has moved closer to the target of notifying all TB cases through the on-line notification system (NIKSHAY) addressing the problems of missing millions[3]. 2019 marks another milestone year for TB surveillance effort in India, with a record high notification of 24 Lakh cases; an increase of over 12% as compared to 2018. Of the 24 lakh TB cases 90% (N=21.6 lakhs) were incident TB cases (New and Relapse/ Recurrent).[3]The emergence of drug resistance has been a major threat to tuberculosis worldwide and India.[5]

Bedaquiline (BDQ): This is new class of drug, diarylquinoline that was introduced by WHO interim policy for the treatment of DR TB in the year 2013 based on Phase IIb trials. The need of introducing bedaquiline was because of poor success rate among drug resistant patients.[6]

Bedaquiline, acts by binding to subunit c of mycobacterial ATP synthase (an enzyme essential for the supply of energy to *M. tuberculosis and most other mycobacteria*) and inhibits its activity. Strong bactericidal and sterilizing activities against M.tuberculosis have been shown in pre-clinical, laboratory and animal experiments.[7]. The drug has high volume of distribution, with extensive tissue distribution, high bound to plasma proteins and hepatically metabolized. Drug shows tri-exponential decline in plasma concentration with effective half-life of approximately 24-30 hours and terminal half-life ($t_{1/2}$, term) of approximately 4-5 months[8].

2. Material and methodology

2.1. Study design

It was an observational, continuous, prospective, single centre study in cohort of DR-TB patients conducted at Nodal DR-TB centre and Department of respiratory medicine, Dr. S.N. Medical College, Jodhpur, a tertiary carehospital.

Inclusion and exclusion criteria

Adult multidrug resistant Tuberculosis patients (18 years-65 years of age) with additionalresistant to either Fluoroquinolones (FQ) and/or Second Line Injectable (SLI) were enrolled. Patients having uncontrolled cardiac arrhythmia that requires medication and /or having QTcF interval >480 msec at baselineafter excluding other causes of Qtc prolongation and having evidence of chorio-retinitis, optic neuritis, or uveitis were excluded.Female not on effective hormonal birth control methods, Pregnant and Lactating women were also excluded.

Pre-treatment evaluation

After the approval of ethical committee, written informed consent taken from all participants. As per PMDT guidelines Pre-treatment evaluation comprising of Complete Blood Count , Blood sugar, Serum electrolytes, Liver function test, serum albumin , Renal function test, Hepatitis B virus status, Hepatitis C virus status, HIV status, Serum amylase and lipase , T3/T4/

TSH, Audiometry, Urine routine and microscopy, Urine pregnancy test (in females) were done.

2.2. SAMPLE SIZE

Sample size was calculated at 95% confidence interval at 10% precision / absolute allowable error. The calculated sample size was 62 subjects which was enhanced to 116 subjects.

3. Objectives

- To determine the Efficacy of the Bedaquiline plus optimized background regimen in Drug resistant Tuberculosis up to 15 months of treatment period in term of culture conversion.
- To determine any association between hepatitis C virus and serum albumin with time to culture conversion.
- To determine culture reversion rate of sputum of drug resistant TB patients who previously become culture negative.
- To assess the safety profile of anti-tubercular drugs used in Bedaquiline+OBR

4. Treatment initiation and follow up

All eligible patients were prescribed bedaquiline along with OBR according to PMDT treatment guidelines for DR-TB (2017) and DST results.

DST guided regimen

Intensive Phase - (6-9) Km Eto Cs Z Lzd Cfz + (6) Bdq

Continuation Phase- (18) Eto Cs Lzd Cfx

Bedaquiline was administered as 400 mg daily for initial fourteen days followed by 200mg thrice a week upto 24 weeks (total six months) along with OBR for mimimum 18 months. All patients receiving bedaquiline were hospitalised for initial seven days and monitored closely via any ECG changes.

RESULTS

A total of 127 DR-TB patients were enrolled. The characteristic of the patients is shown in Table 1. (No.= 116).

General characteristics of the DR-TB patients in the study population (No.= 116).

Table 1.

PARAMETERS	VALUES
Mean age ± SD (Years)	35.40±10.19
GENDER	
MALE	71.55%
FEMALE	28.45%
Mean Body weight ± SD (kg)	42.73±8.34
Body mass index (BMI)	
Underweight	98 (84.48%)
Normal weight	17 (14.66%)
Overweight	01 (0.86%)
Addictions	
smoking	38 (32.76%)
alcohol	33 (28.45%)
opium	24 (20.69%)
no addiction	21 (18.10%)
Co-morbidity	
Hypertension	13 (11.21%)
DM type 2	11 (9.48%)
HIV	0 (0%)
HCV	03 (2.59%)
Hypothyroidism	02 (1.72%)
contact history of TB (%)	13.79%
Previous history of anti-tubercular treatment	90.51%

A total of 116 patients were enrolled in this cohort.Majority of the patients were male having younger age group.

Age group distribution among patients ≤ 25 year,26-35 year,36-45 year,46-55 years, 56-65 years was 21 (18.10%), 43 (37.07%), 34 (29.31%), 13 (11.21%) and 04 (3.45%) respectively. Mean body weight was 42.73±8.34 kg with 84.48% patients were malnourished having BMI <18.4 kg/m^2.

In this cohort, 32.76% were smokers while 28.45% were having alcohol addiction. Three patients were coinfected with hepatitis C virus. Diabetes mellitus type 2 was present in 9.48% cases.

Disease status

Most of the cohort (90.51%) were having a history of previous TB treatment. Consolidation was most common (71.55%) finding in chest X-Ray. Fibrosis and cavitatory lung diseses was seen in 66.38% and 54.31% patients. Cough (56.03%) was

most consistent symptom followed by weight loss (39.65%).

Efficacy of BDQ plus OBR

1. **Sputum culture conversion:** At the end of 6 months of BDQ containing treatment regimen, sputum culture conversion was found in 99 (93.39%) patients.
2. **Weight gain:** In this studymeanweightgainwas2.86±3.02kg.

Impact of different variables on culture conversion

Table 2.

Variables	Status	Culture conversion time(In days)	P-value
Previous history of ATT	Present	101.03 ±20.00	0.635
	Absent	±21.21	
BMI	Underweight	100.00±20.50	0.232
	Normal	94.0±15.49	
HCV	Positive	150.0±42.42	0.0003
	Negative	99.67±18.32	
Serum albumin	Lower	93.42±9.68	0.010
	Normal	106.00±27.32	
Dose modification of OBR	Yes	106.80±32.49	0.174
	No	99.42±18.79	
Drug discontinuation of OBR	Yes	101.86±24.03	0.526
	No	96.66±13.22	

Treatment safety profile

The most common system affected was gasterointestinal in which nausea and vomiting followed by hepatitis was prominent adverse events. **(Fig.1)**

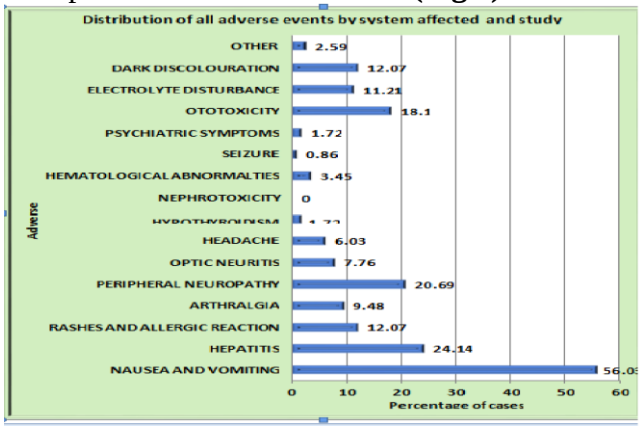

Fig.1

QTcF prolongation

At the time of pre-treatment evaluation, 87.95% male and 96.97% famales were having QTcF interval within normal range. 12.93% of total patients shows QTc prolongation more than 480 ms with a mean of 393.33±26.15msintheir baseline ECG. Three patient showed QTc prolongation having QTc interval more than 500 ms. BDQ was temporary withheld. Electrolytes was corrected and BDQ was rechallenged. Unfortunately one patient died and in remaining two, BDQ was permanent discontinued due to uncontrolled cardiac arrhythmia.

Interim outcome

Out of the 116 patients, 89 (76.72%) had lasttwoculturenegative. Remaining 17 unfavourable outcome (14.65%) patients include 06 (5.17%) death, 06 (5.17%) defaulter ,03(2.59%) treatment failure and two (1.72%) lost to follow up.In one patient, culture reversion occurs at 8th month of treatment.(Fig.2)

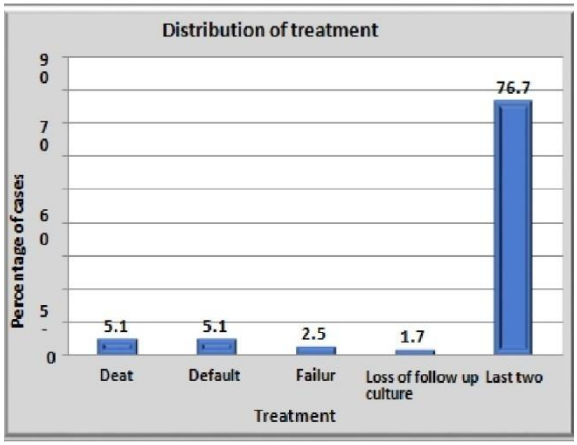

Fig.2

DISCUSSION

In the present study, the mean age of patients was 35.40±10.19 years with a median age of 33.50 years. In a study, the median age of patients was 35 years treated with BDQ **(Borisov et al, 2017)[9]**. In another study treated with BDQ **(charan et al, 2016)[10]**, the median age was 30 years. In another study treated with BDQ **(Ana-maria et al)[11]**, the median age was 30 years.

In this study, majority of patients were males (71.55%). Remaining 28.45% were females. **Borisov et al, 2017[9]**found that the most prevalent sex in the cohort was male (61.5%) in BDQ treated patients. **Charan et al, 2016[10]** found that 38% of patients were females treated with BDQ.

Mean weight gain in present study was 2.86±3.02 kg. Out of 116 patients 12 patients shows weight loss while 2 patients shows no changes in weight at all. **Udwadia et al (2016)[12]** reported that clinical improvement was seen in all 20 patients with a mean weight gain of 4.6 kg treated with BDQ. While another study by **Skrahina et al[13]** reported the mean weight gain of 3.8 kg after 6 month course of bedaquiline containing regimen.

The mean culture conversion time in patients with normal BMI was 94.0±15.49 days while the mean time was 100.00±20.50 days in patients having abnormal BMI. There is no significant difference in culture conversion time (P value = 0.232). Howeveras per report published in **PMDT 2019,** a BMI lower than 18 is significantly associated with unfavourable outcome[14].

In the present study hypertension was most frequently associated co-morbidcondition followed by diabetesmellitus typeII. Hepatitisc virus positivitywere seen in 2.59% patients of study population. Interestingly, none of thepatient were HIV positive. This finding is surprising as an estimated 8.2%(range,7.0–9.5%)oftheincidentTBcasesi n2019globallywereamongpeople living with HIV.[6] In one study carried out by **Borisov et al[9]**, 428culture-confirmed MDR-TB cases were analyzed in which 22.1% were HIV-positive.

Previous treatment history of ATT was present in 90.51% patients in the present study. The **National Drug Resistant Survey (NDRS)[15]** conducted for 2014-16 states that out of 4958 patients 307(6.19%) were MDR. In which 220 patients were previously treated while 87 patients not giving any history of anti-tubercular treatment In this study, consolidation on chest X-ray was seen in 71.55% patients. Cavityon chest X-ray was seen in 54.31% patients while 66.38% patients were havingfibrosis pattern in their chest X-ray. 47.41% patients were having bilateral lunginvolvement. **Udwadia et al (2016)[12]** found that radiographic status improvedin 17 patients; it was static in 3 patients treated with BDQ. The presence ofcavities or bilateral disease in chest radiography is used for defining severity ofdisease.[6]

In this study, QTc prolongation (QTc F>480 ms or 60 ms increase from baseline) seen in 12.93%patients.. A South African observational cohort reported minimal increase ofQT after bedaquiline initiation, but this study is flawed in that a third of thepatients were taking moxifloxacin, which is known to prolong QT, at the timeof baseline ECG. In 24 patients in that cohort, QT increased by more than 50msec after bed aquiline initiation,withQT>500msec in three patients (**Ndjeka et al [15], 2015**). QTcF> 500ms occurred in 11% ofpatients treated with bedaquiline in a French observational cohort but no arrhythmias werereported by (**Guglielmetti et al, 2017**)**[16].** A systematic review of the availableevidence on the cardiac safety of bedaquiline reported QTc prolongation > 500msec in 3.2% of patients **(Pontalietal,2017)[17]**.

Jones et al (2019)[18] found that QT prolongation was themostfrequentlyreported ADR. QT prolongation was reported in 1.4% of patients initiated onbedaquiline-containing TB treatment during the study period (8/549); severe QTc prolongation was

reported in1.2%(7/549)[18]. Previous studies have reported a similar pattern of ADR sattributed to bed aquiline.TheIndian study by **Sarin et al** [19] concluded that 29% of patients on bedaquiline had Qtc F of 480 msec to 500 msec. In a phase 2 randomised controlled trial of bedaquiline versus placebo (on a background of 5 additional anti-tuberculosis drugs) there was an increased risk of QTcF prolongation with bed aquiline **(Diacon etal,2014)** [20].

In a study treated with BDQ **(Mbuagbaw et al, 2019)**[21], up to 91.1% (95% CI82.2%-95.8%) of the patients experienced >1 adverse event, and 11.2% (95%CI5.0%-23.2%)experienced a serious adverse event. **Guglielmettietal**(2017) [16] found no significant differences in outcomes or adverse events rateswere observed between patients receiving standard and prolonged bed aquiline treatment. In this present study, most common adverse events were nausea andvomiting (56.03%) followed by hepatitis (24.14%) and peripheral neuropathy(20.69%). None of the patients suffered from nephrotoxicity during treatment course.

In the study by **Skrahinaetal**[13], 21%patients experience drenalandurinary disorders (creatinine clearance decrease being the most common).One another study by **diacon et al (2009)**[22] shows that with the exception of nauseareported in 26% of patients receiving bedaquiline and none receiving placebo,adverse events occurred at similar frequencies in both groups of patients: bilateral hearing impairment, extremity pain, acne, and noncardiac chest painoccurred in 13 and 21%, 17 and 13%, 9 and 17%, and 4 and 17% of patients,respectively, receiving bedaquiline or placebo. In the present study ototoxicitywere reported in 18.10% cases. In most of the studies, the severety of AE wasmild to moderate. Dark discolouration of skin was seen in 12.07% cases in thisstudy. Bedaquilinewas interrupted due to adverse events in 4.71% ofcases.Out of 116 cases, in 1.72% cases bedaquiline was permanently discontinued.Course of bedaquiline was interrupted in 5.8% cases in the study of **Borisov etal**(2017)[9].

Due to adverse drug reaction, dose of OBR drug was modified in 25% patients.In9.48%patients,symptomsnotimprovedevenafterdosemodificationsodrug was permanently discontinued in these patients. However no such data isavailabletocomparethisfinding.

In this study, the culture became negative in 66.04 % of patients on Bdq+OBRat the end of 3rdmonth.From 4thmonth onwardadditionally 16.04%, 6.60% &4.71% patients becomesculture negative in 4th,5th and 6th month respectively.The overall culture conversion rate after 6thmonth was 93.39%.In a studytreated with BDQ **(Mbuagbaw et al, 2019)** [21], the rate of culture conversion tonegativeat6 months(bytheendof6monthsoftreatment) was78%.

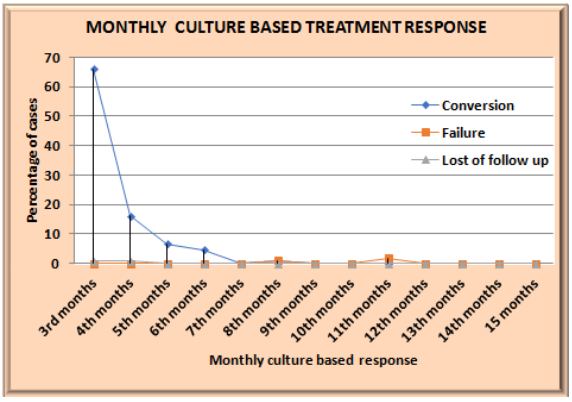

Fig.3

In a study **(Diacon et al, 2014)** [20], bedaquiline reduced the median time toculturecon version,ascomparedwithplacebo,from125daysto83days(hazard ratio in the bedaquiline group, 2.44; 95% confidence interval, 1.57 to3.80; P<0.001 by Cox regression analysis) and increased the rate of cultureconversion at 24 weeks (79% vs. 58%, P=0.008) and at 120 weeks (62% vs.44%, P=0.04). **Udwadia et al**[12](2016) found that 15 patients out of 27 patientsconvertedsputum while 5 patients failed to convert treated withBDQ. **Ferlazzo et al (**2018) [23]

reported that of 23 individuals with positivebaseline cultures, 17 (74%) converted to negative by month 6 of treatmenttreated with BDQ.

In present study the mean time of culture conversion in HCV positive patientswas 150.0±42.42 days while it is 99.67±18.32 days in HCV negative patients.With a significant (pValue=0.0003) differenceint imeto culture conversion.

Serum albumin level is significantly associated with time to culture conversion.In present study patients with normal serum albumin level has mean cultureconversion time of 93.42±9.68 days while patients with low albumin level havemean culture conversion time of 106.00±27.32 days with p value of 0.010. Inone multicentric cohort study done by **Lorengo Guglielmetti**, **Marie Jaspardetal[16].**

Under the title"Long term out come and safety of prolonged bed aquiline treatment for multidrug-resistant tuberculosis" in 2017, 45 MDR-TB patients were included. In a multivariate Cox proportional hazard model,factors independently associated with faster time to culture conversion were higher serum albumin level at treatment start (HR1.09,95%CI1.02-1.16;p=0.010) & HCV-negativity (hazardratio (HR) 2.64,95% confidenceinterval(CI) 1.34-5.19; p=0.021).

Borisova et al (2019) [9] described treatment outcomes and complications in a cohort of drug-resistant pulmonary tuberculosis(TB) cases treated with bed aquiline-containing regimens. In their study **Borisova et al** finds 21.8%cases as unfavorable outcomes (20.0% treatment failure, 1.8% lost to follow-up).

In the present study treatment failure seen in2.59%casesand1.72% cases as lost to follow up. 6 patients (5.17%) quit the course of treatment for more than 1 month& becomes defaulter.

Limitation of this study

This is an interim report at the end of the 15 months of regimen. We cannot comment on the treatment outcomes at the end of the treatment. These patients are under follow up for treatment outcome indicators, hope the full results of this study will be published sooner.

It was an observational open label single centre with absence of control arm and special populations in the study population.

CONCLUSION

This study suggests that BDQ in combination withan OBR has the betterefficacy to achieve higher and faster culture conversion rates in cases of DR-TB. The low toxicity profile (especially the cardiac toxicity interms of QTc prolongation) indicates that bedaquiline based regimen is well tolerated.In this study, the low mortality is also reassuring for effective and much safer treatment of DR TB. These results support the scale-up ofthe BDQ+OBR in the country and to give access to a wider group of patientswithMDR/RR-TBunderthe Programmatic Managementof DR-TBinthecountry's national program. Also, health care providers and patients need to beeducated about ADRs. Patient`s relatives should be explained about the ADRsand the early approach to health facility for timely interventions. So that severeADRscanbeprevented.

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