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Original Article

Efficacy of Bedaquiline Containing Regimen In MDR/XDR Tuberculosis Patients

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Abstract

A. Introduction: *India is the highest drug resistant tuberculosis (DR-TB) burden country. Outcomes of treatment for DR-TB are poor demanding new drug regimen for better outcome. Bedaquiline is the first antitubercular drug with novel mechanism of action developed specifically for treatment of DR-TB and has been shown efficacious.*

B. Aim: *To evaluate efficacy of bedaquiline containing regimen in MDR/XDR tubercular patients.*

C. Method: *An observational prospective study was conducted on 98 patients. Eligible patients were prescribed bedaquiline containing regimen and were monitored with strict adherence to follow up schedule for microbiological, clinical improvement and outcome during the treatment.*

D. Result: *In this study efficacy of bedaquiline containing regimen was observed in terms of increment in mean body weight, sputum culture conversion rate and treatment outcome at 6 and 12 months. Clinically significant increment in mean body weight occurred over period of 12 month. Culture conversion rate were 81.63% at 3m, 86.73% at 6m and 82.65% patients remain culture converted at end of 12m.At end of study period, 3 were culture reverted, 3 lost to treatment follow up and 8 died.*

E. Conclusion: *Bedaquiline containing regimen is associated with higher, faster sputum culture conversion rate. Early sputum culture conversion, high body mass index (BMI) and better immunity improve outcomes of treatment whereas extensive lung disease and low immunity negatively affects the outcome.*

Keyword - *Bedaquiline, BMI, Culture Conversion, Efficacy, MDR, XDR*

I. INTRODUCTION

Tuberculosis (TB) is an ancient infectious disease that is a major cause of ill health and is ranked as the leading cause of death worldwide among infectious diseases. About a quarter of the world population is infected with Mycobacterium Tuberculosis. India has the dubious distinction of being one of the high burden countries for TB, TB-HIV and MDR-TB as per WHO classification[1]. Every year around 3.1% of notified cases of pulmonary TB are multidrug resistant tuberculosis[2]. Although overall the TB rates are on decline but prevalence of MDR TB and more recently XDR-TB is increasing and spreading at an alarming rate which is a major threat to global TB care and control and has led to a setback in efforts to end TB[3].Treatment of MDR-TB is more challenging with second line drugs being less effective and more toxic than isoniazid and rifampicin based regimen. It becomes even more complex when MDR strains with additional resistance have emerged. The treatment success rate in India has been consistently below 50% in MDR TB, around 35% in MDR TB with FQ or SLI resistance and below 30% in XDR TB patients with mortality of nearly 50%[4].

In view of drug resistance and lack of effective therapy, a new drug bedaquiline was discovered. It defines a new class of antimycobacterial compounds, the diarylquinolines due to its novel mode of action. It selectively inhibits bacterialadenosine 5'-triphosphate synthase by binding to its c subunit, which is a novel antimycobacterial target. It has bactericidal effects for both replicating and dormant tubercular bacilli. It also has remarkable sterilizing capacity that makes it an attractive drug for MDR-TB treatment[5-7].Its distinct target also undermines the possibility of cross-resistance with existing anti-TB agents.

Government of India approved the use of bedaquiline in November 2015 under Conditional Access Programme (CAP) and after successful completion it was expanded nationwide through RNTCP programme.

The drug has been shown significant benefit in improving the time to culture conversion, outcomes and mortality rate in MDR-TB patients.. This study was undertaken to evaluate the efficacy of bedaquiline containing regimen, measured in terms of clinical(increment in mean body

weight), microbiological (sputum culture conversion time and rate) and treatment outcomes at 6 and 12 months.

II. METHOD

A. STUDY DESIGN

It was observational prospective non- randomized without control group study in cohort of DR-TB patients conducted at nodal DR-TB centre at Department of Tuberculosis and Respiratory Diseases, Sarojini Naidu Medical College Agra for a period of 18 months (September 2018 to March 2020). Data for 98 eligible patients had been studied.

B. PATIENT SELECTION (INCLUSION EXCLUSION)

Patients having laboratory confirmed diagnosis of pulmonary tuberculosis with resistance to rifampicin and additional resistance to any/all fluroquinolone and/or any/all second line injectable , treatment failure of MDR-TB + FQ/SLI resistance or XDR-TB, age 18 years or older, normal electrocardiogram and QTc interval below 450 ms where enrolled.

Patients with any of the following were excluded-

- patients having extra pulmonary TB
- patients who were pregnant or were breast feeding
- patients having uncontrolled cardiac arrhythmias that required medication
- repeated QTc interval > 450 ms at screening with history of additional risk factor for Torsade-de Pointes
- eye changes such as chorioretinitis, optic neuritis or uveitis at screening
- Significant laboratory abnormalities relating to kidney function, liver function, one marrow suppression as per the DIADS grading of adverse events.

C. PRE TREATMENT EVALUATION

All eligible patients were evaluated for detailed clinical examination, haematological, biological investigations, urine microscopic examination, chest X-ray, ECG, audiometry, urine pregnancy test among women of reproductive age and specialist consult with psychiatrist, ophthalmologistand ENT.

D. TREATMENT INITIATION

After pre treatment evaluation, counselling and written consent initiation of treatment was doneand the patient was closely monitored. All eligible patients were prescribed bedaquiline containing regimen according to national guideline for Programmatic Management of Drug resistant Tuberculosis (PMDT) 2017.

Bedaquiline 400 mg once daily was given for the first 2 weeks followed by 200 mg thrice a week for next 22 weeks (total 6 months) along with optimisedbackground regimen(OBR).The OBRwas continued beyond 24 weeks of bedaquiline administration for next 18 months.

Hospitalization was done for minimum of initial two weeks, sometimes longer as per requirement then patients were referred to their respective DOTS site for continuing the treatment and follow up on an ambulatory basis with strict adherence to follow up schedule.

E. FOLLOW UP

a) From second week to end of six months

Clinical examination, weight, sputum smear microscopy, sputum culture, CBC, liver and renal function test were repeated monthly till the end of six months. ECG was done at third week then monthly basis. Chest X-ray and thyroid function tests were repeated at the end of six months**.**

b) From 7th month to end of 18 months

Haematological investigations and sputum culture analysis was done at 7th, 9th and 12th months of treatment. ECG was done on quarterly basis. While chest X-ray was repeated at 12th month of treatment. All spontaneous adverse events reported by patient or treatment supervisor were recorded and followed up till recovery.

F. COHORT EVENT MONITORING

Each patient was monitored for clinical, microbiological, radiological improvement and treatment outcomes during bedaquiline phase and post bedaquiline phase.

G. STUDY DEFINITION

a) Sputum culture conversion was defined as 2 consecutive negative cultures at least 30 days apart during the course of treatment. Time to conversion was measured from the beginning of bedaquiline containing treatment regimen to the date of specimen collection of the first two consecutive results.

***b) Sputum culture reversion* :** Patient was considered to have culture reverted when, after an initial culture conversion, two consecutive cultures, taken at least 30 days apart , are found to be positive.

For the purpose of defining treatment failed, reversion is considered only when it occurs in the continuation phase.

III. RESULT

Characteristics of study population is shown in table 1, 2 and 3.Approximately half of patient were male and half were female with majority of patient being in younger age group and undernourished. 93.9% patient had previous exposure to second line injectable anti-tubercular drugs.74.5% patients had MDR TB and 25.5% had XDR TB.

Table 1. Baseline characteristics of the study population (n=98)	
Mean Age	31.6 years
Male	52
Females	46
Mean Body Weight	42.83
Mean Body Mass Index (BMI)	17.21
Body Mass Index (BMI) kg/m2 <16 16 to18.5 >18.5	 32 34 32
Personal Habit Smoking Alcohol consumption Chewing tobacco No Habit	 11 9 20 58
Co Morbidity Yes No	 11 87
HIV Positive	1
Previous exposure to Second line injectable anti-tubercular drugs	92

Table 2 :Distribution of patients according to their radiological extent of disease on chest X-ray (n=98)

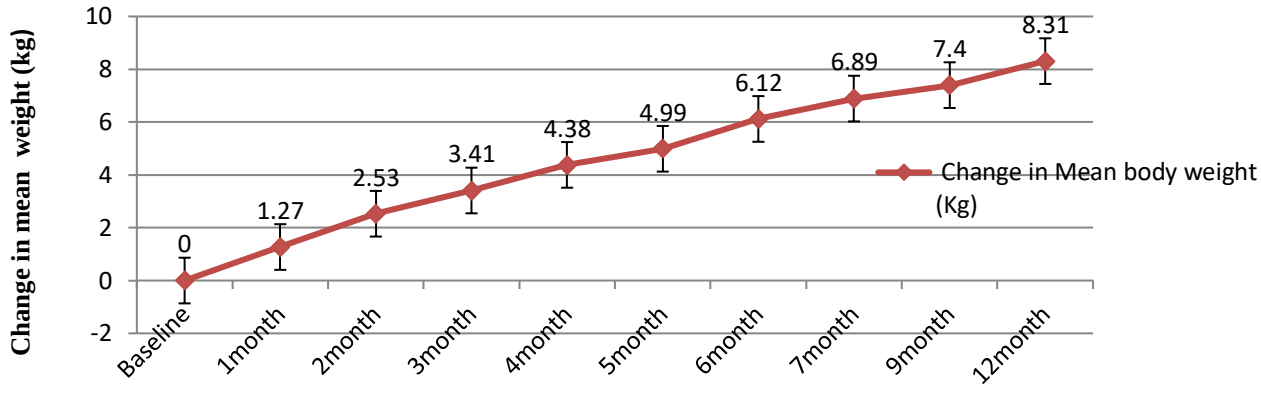
Radiological extent of disease	Number (No.)	Percentage (%)
<50% involvement with Cavitation	26	26.53
>50% involvement with Cavitation	40	40.82
<50% involvement without Cavitation	28	28.57
>50% involvement without Cavitation	4	4.08
Total	98	100

Table 3. Drug Resistance Profile of The Study Population

Type of resistance	Number
MDR_{FQ}	67
MDR_{SLID}	4
XDR	24
$MDR_{failure}$	2
$XDR_{failure}$	1

It was observed that patient had significant increment in mean body weight over period of 12 month (Fig.1).

Fig 1. : Relationship of increase in mean weight from baseline with time



Out of 98 patients 81.63% shows culture conversion after 3m and 86.73% at the end of 6m i.e.at end of bedaquiline phase while 82.65% patients remain culture converted at end of 12m (Table 4).

Table 4 : Sputum culture conversion time and rate in BDQ treated DR-TB patients (N = 98)

Time Period	Number of patients got culture converted	Percentage of patients converted (%)
3Month	80	81.63
4Month	83	84.69
5Month	84	85.71
6Month	85	86.73
12Month	81	82.65

Evaluation of the outcomes was done at 6^{th} and 12^{th} month (Table 5). 85 patients were sputum culture converted at 6 month. Later among those, 3 were culture reverted, 2 left the treatment follow up and 3 died. Further 4 patients that were previously not culture converted became culture negative. Thus at the end of 12 months, 81 patients remained culture converted.

Table 5: Outcomes of BDQ containing regimen in BDQ treated DR-TB patients (n=98)

Outcomes	At 6 month	At 12 month
Culture converted (or remain culture converted)	85	81
No conversion	4	0
Withdrawal of BDQ	3	3
LTFU	1	3
Culture reversion	0	3
Died	5	8
Total	98	98

An attempt has been made to correlate different factors with treatment outcome (Table 6). It was observed that early sputum culture conversion at 3rd month ($p < 0.0001$) and BMI >18.5Kg/m^2 ($p < 0.05$) were positive predictors of favourable treatment outcome. While low BMI (< 0.05) and >50% lung damage and cavitary lesions ($p < 0.0001$) were negative predictors of favourable treatment outcome.

Table 6: Correlation of various factors associated with treatment outcome in DR-TB patients at 12months (n=98)

Factors	Favourable outcome group (81,82.7%)	Unfavourable outcome group (17,17.3%)	P value
Gender			
Male	43	9	0.625
Female	38	8	
Age			
< or = 40	66	14	0.749
>40	15	3	
BMI			
<18.5(kg/m^2)	55	11	0.0312*
>18.5(kg/m^2)	26*	6	
Personal habit			
Yes	24	6	0.0923
No	47	11	
Resistance pattern			
MDR	61	12	0.764
XDR	20	5	
Cavitary lung lesion			
Yes	52	14**	0.0001*
No	29	3	
Lung involvement			
<50%	47	7	0.0001**
=>50%	34	10**	
Co morbidities			
Yes	9	2	0.0765
No	72	15	
Culture conversion within 3 months			
Yes	78**	2	0.0001**
No	3	15	

Values are absolute numbers. *p < 0.05 as compared to group I,**p < 0.0001 as compared to group I(Fisher's exact test).

IV. DISCUSSION

A cohort of 98 eligible DR-TB patients were enrolled for this study at nodal DR-TB centre at Department of TB and Respiratory Diseases, S N Medical College Agra for a period of 18 months (March 2018 to September 2020). Majority of the patients were in younger age group (46% patients in the age group of 18-25 years). Mean age of the study population was 31.6 years; similar to other studies[8,9,10]. 53% of the patients were males and 47% of the patients were femaleshaving increasing male female ratio with respect to age. It suggests that females are more susceptible to the disease in younger age as compared to males. The mean body weight and mean BMI were 42.83 kg and 17.21 kg/m^{2}respectively that indicate that majority of the patients were under nourished. Mean BMI was lower as compared to other studies [11,12,13].Only 1 patient was HIV positive and 11 patients had co-morbidities in which diabetes is most common. Baseline chest X-ray of patients reflected 67.35% having cavitation and 44.9% having more than 50% lung involvement.In present study, 74.5% patients were MDR-TB (MDR_{FQ}= 68.36%, MDR_{SLID} = 4.08% and MDR_f =2.04%)while 25.5% were extensively drug-resistant TB (XDR = 24.48%, XDR_f= 1.02%).XDR-TB patient was slightly higher as compare to study of RohitSarin et al [11]and V.S. Salhotra et al[14]but lower than the study conducted by Skrahina. A et al[15].In our study, efficacy of bedaquiline containing regimen was observed in terms of increment in mean body weight, sputum culture conversion rate and treatment outcome at 6 and 12 months which are as follows:

Mean body weight of study population was 42.83 kg and periodical significant increase in mean body weight was observed at 3rd, 6th and 12th month of treatment in patients treated with BDQ plus OBR which is similar to the study of Sandip V. Barvaliya et al [16].

In our cohort, culture conversion rate was found to be 81.63% and 86.73% at the end of 3rd and 6th month of treatment respectively. This is higher than that reported in clinical trials[17,18,12] as well as the South African Clinical access programme[9] but lower than the French cohort [19]and RohitSarin et al[11]. 63 patients (86.30%) out of 73 MDR TB patients and 22 patients (88%) out of 25 XDR TB patients got culture converted at the end of 6months of treatment. The results of this study are even more impressive in light of the fact that patients enrolled here included XDR-TB, which are often more difficult to treat than MDR-TB patients. Of note, it is reassuring that almost no difference in culture conversion rates after receiving bedaquiline-containing regimens was observed here between MDR- and XDR-TB patients, which aligns with results reported previously by Borisov and colleagues[18]and other studies[20,21]. Thus, the administration of bedaquiline might be associated with additional benefit for XDR-TB patients.

Median time for sputum culture conversion was 90 days which was higher than other studies [17,14,8,11] because we followed PMDT guidelines for sending the sputum culture in which first sample was sent at the end of 3rd month of treatment containing bedaquiline regimen.

High and faster culture conversion rate was observed in case of patients having high BMI which is in accordance with the study of V.S. Salhotra et al[14]**.** Previous pharmacokinetics research has confirmed that bedaquiline accumulates to relatively high concentrations in adipose tissue[22]. Considering that increased BMI is associated with a higher percent body fat, lipid partitioning of antibiotics may allow for slow, but extended, release from adipose cells into plasma; this extended slow release may maintain an effective drug concentration in extracellular fluids and subsequently improve culture conversion rates in patients with high BMIs. We also note that patients with low BMI had high risk of unfavourable outcomes in our cohort study.

At the end of 6 months of treatment, out of 98 patients, 85 got sputum culture converted, 4 had no culture conversion, 3 withdrawals from bedaquiline, 1 Lost to Follow Up (LTFU) and 5 mortalities occurred.

At the end of 12 months of treatment, out of 98 patients, 81 (82.65%) had favourable outcomes and remaining 17 (17.35%) had unfavourable outcomes which included 8 deaths (8.17%), 3 (3.06%) culture reversions, 3 (3.06%) Lost To Follow Ups (LTFU) and 3(3.06%) withdrawals from bedaquiline. High favourable outcomes may be attributed to individualized treatment regimen [23]**.** LTFU in present study was very low (3.06%) as compared to other studies[24,25,26,27]**.**

An attempt has been made to correlate different factors with treatment outcomes at the end of 12 months (Table 6). It was observed that early sputum culture conversion at 3rd month ($p < 0.0001$) and BMI >18.5 kg/m^2 ($p<0.05$) were positive predictors of favourable treatment outcome. While BMI<18.5 kg/m^2 ($p<0.05$) and >50% lung damage and cavitary lesions ($p<0.0001$) were negative predictors of favourable treatment outcome.This indicates that better nutritional and immune status of patients improves outcome.

The study supports that adding bedaquiline to optimized background regimen (OBR) shortened the typical time for sputum culture conversion, increased the rate of conversion at follow up and has shown significant benefit in improving survival and treatment outcomes in DR TB patients under clinical and programmatic settings.

V. CONCLUSION

We concluded that regimens containing bedaquiline have high and rapid sputum culture conversion rate and low mortality in comparison to previous treatment regimen for MDR/XDR tuberculosis further, the outcomes were encouraging in patients having early sputum culture conversion and high body mass index whereas low body mass index and extensive lung disease negatively affects outcomes. It strengthened the DR-TB treatment programme to new lengths.

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