Comparison of efficacy of bedaquiline and moxifloxacin in drug resistant pulmonary tuberculosis. A prospective observational study

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Abstract

Drug-resistant tuberculosis remains a major public health concern in many countries. We compared the efficacy and safety of bedaquiline plus optimized background regimen (Bdq+OBR) with high dose moxifloxacin and optimized background regimen (Mfx$^{(h)}$+OBR) for the treatment of patients with multidrug-resistant tuberculosis with additional resistance to fluoroquinolones. In this prospective observational study, newly diagnosed cases of multidrug-resistant tuberculosis with additional resistance to fluoroquinolone were enrolled. They received either Bdq+OBR or Mfx$^{(h)}$+OBR and were followed up for six months. The sputum culture conversion rate at the end of six months and the time to culture conversion in each group were studied. The safety profile of both regimens was also studied. The sputum culture conversion was achieved in 41 patients (100%) in the Bdq+OBR group and 36 patients (87.8%) in the Mfx$^{(h)}$+OBR group at the end of 6 months. The mean time to culture conversion was found to be 3.10±0.8 months in the Bdq+OBR group and 3.32±0.9 months in the Mfx$^{(h)}$+OBR group. Mortality was 6.8% in the Bdq+OBR group and 10.8% in the Mfx$^{(h)}$+OBR group at 6 months. Raised serum lipase and dark discolouration of skin were significantly more common in the Bdq+OBR group while vomiting and ototoxicity were more common in the Mfx$^{(h)}$+OBR group. Bdq+OBR was associated with higher success of sputum culture conversion at 6 months and faster sputum culture conversion rate as compared to the Mfx$^{(h)}$+OBR.

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Introduction

Tuberculosis (TB) is the leading global cause of death due to an infectious agent [1]. Multi drug-resistant TB (MDR-TB) is the TB that is resistant to both rifampicin and isoniazid and requires treatment with second-line anti-tubercular drugs. As per the Global Tuberculosis Report 2021 by the World Health Organization (WHO), about 150,000 people were started on treatment for drug resistant TB (DR-TB) and of these only 59% were treated successfully [2].

To combat the menace of DR-TB, the World Health Organization (WHO) has come up with regimens including newer drugs bedaquiline and delamanid along with other repurposed drugs like linezolid and clofazimine. Bedaquiline (Bdq) was approved in December 2012 by Food and Drug Administration (FDA), the first new TB drug in over forty years and is currently indicated for the treatment of drug-resistant tuberculosis [3]. It is a promising yet new drug in the management of DR-TB and very few studies concerning its efficacy and safety are published. In our study, we aimed to compare the efficacy and safety of bedaquiline plus optimized background regimen (Bdq+OBR) with high dose moxifloxacin plus optimized background regimen (Mfx$^{(h)}$+OBR) for the treatment of patients with multi drug-resistant tuberculosis

with additional resistance to fluoroquinolone under programmatic conditions. The primary objective was to study the rate of sputum culture conversion at the end of 6 months, and the time to sputum culture conversion in each group. The adverse events in each group over a period of six months were also studied.

Methods

This was a prospective observational study carried out between November 2018 to October 2019 in the DR-TB centre of a tertiary care hospital of Western India. Newly diagnosed cases of pulmonary tuberculosis between 18 to 65 years of age who were resistant to isoniazid, rifampicin, and fluoroquinolone, as demonstrated by line probe assay, Mycobacteria growth indicator tube (MGIT), or both were enrolled. Pregnant women, females not on effective hormonal birth control methods, not willing to continue practicing birth control methods throughout the treatment period, patients having uncontrolled cardiac arrhythmias, patients having prolonged QT/QTc interval (>450 msec at baseline for males and 470 msec for females after excluding other causes of Qtc prolongation), patients having evidence of chorioretinitis, optic neuritis, or uveitis as both regimens include linezolid, and patients who refused to give consent for the treatment were excluded from the study.

The patients were allocated into two groups by simple random sampling. One group received bedaquiline along with an optimised background regimen and the other group received high dose moxifloxacin along with an optimised background regimen. The optimized background regimen was developed according to the World Health Organisation (WHO) guidelines. The duration of intensive phase was 6 to 9 months while continuation phase was of 18 months, thus the total duration of treatment was 24 to 27 months. The Bdq + OBR regimen consisted of bedaquiline, kanamycin, pyrazinamide, ethambutol, ethionamide, cycloserine, linezolid and clofazimine. In the continuation phase, bedaquiline, kanamycin and pyrazinamide were not given. Bedaquiline was never given for more than six months. The $Mfx^{(h)}$+OBR regimen consisted of high dose moxifloxacin, kanamycin, pyrazinamide, ethambutol, ethionamide, cycloserine, linezolid and clofazimine. In the continuation phase, kanamycin and pyrazinamide were not given. The dose of moxifloxacin used was 400 mg for patients less than 30 kg, 600 mg for those between 30 to 45 kg and 800 mg for those weighing more than 45 kg. Baseline investigations like complete blood count, alanine transaminase, aspartate transaminase, creatinine, sodium, potassium, magnesium, HIV by ELISA, electrocardiogram was done for all the patients.

Patients were followed up for a period of six months. Early morning sputum samples were collected every month from the 3rd month onwards to assess the growth of *Mycobacterium tuberculosis* in liquid culture medium using *Mycobacterium* growth indicator tube (MGIT). Physical examination and complete blood count were performed every month. Serum creatinine was performed every month for three months and then after 3 months. Serum sodium, potassium, magnesium, lipase and amylase were performed every three months. ECG was performed at 2 weeks and then at monthly intervals. Fridericia's formula was used for correcting QT interval (QTcF). Audiometry was performed only when clinically indicated. The sputum culture conversion rate at 6 months in both groups was studied. The safety profile of both regimens was studied.

In patients who remained culture positive at six months, the culture isolate was subjected to second line- line probe assay (second line – LPA) and liquid drug susceptibility testing to check for amplification of resistance to second line drugs and presence of resistance to bedaquiline and accordingly the treatment was modified.

Written informed consent was obtained from all the patients prior to enrolment in the study. Institutional ethics committee approval was taken prior to commencing the study. The sample size of 70 was estimated assuming an 80% sputum culture conversion rate for DR-TB at 6 months [4] at 95% confidence interval, 10% relative precision and 10% contingency. The Chi-square test was used to compare the categorical variables. The unpaired *t*-test was used to compare continuous variables; $p<0.05$ was considered as significant. Statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 23 (IBM SPSS Statistics for Windows, Version 23.0, released 2015; IBM Corp. Armonk, NY, USA).

Results

A total of 90 patients were enrolled in the study. There were 44 patients in the BDQ+OBR group and 46 in the $Mfx^{(h)}$+OBR group. Three patients from the BDQ+OBR group and eight patients from the $Mfx^{(h)}$+OBR group expired during the initial six months of treatment. Thus, the mortality was 6.8% in the Bdq+OBR group and 10.8% in the $Mfx^{(h)}$+OBR group at 6 months. No deaths were related to any of the anti-tuberculosis drugs used. The deaths were due to type 1 respiratory failure due to extensive lung parenchymal destruction by DR-TB. One patient from the $Mfx^{(h)}$+OBR group was lost to follow-up. Thus, the sputum culture conversion rate, time to culture conversion and adverse event profile was studied in 78 patients with 41 patients in the BDQ+OBR group and 37 patients in the $Mfx^{(h)}$+OBR group.

The mean age of patients in the BDQ+OBR group and $Mfx^{(h)}$+OBR group was 36.71±11.49 and 41.14±14.33 years respectively. Majority of patients in both the BDQ+OBR (70.7%) and $Mfx^{(h)}$+OBR (70.3%) group were males. There was no significant ($p>0.05$) difference in age and gender distribution between the groups. There was no significant ($p>0.05$) difference in the anthropometric parameters between the groups (Table 1). All the patients in both groups had a history of intake of first-line anti-tuberculosis drugs in the past.

Weight gain was observed in all patients of the Bdq+OBR group and in 91.9% patients of the $Mfx^{(h)}$+OBR group at the end of 6th month. The mean weight gain was significantly higher in patients of the Bdq+OBR group (3.06±1.21 kg) than $Mfx^{(h)}$+OBR group (2.48±0.98 kg) (p 0.02). At the end of 3rd month, sputum culture became negative in 33 (80.9%) patients in the Bdq+OBR group and 24 (64.9 %) patients in the $MFX^{(h)}$+OBR group. All the patients (100%) in the Bdq +OBR became culture negative at the end of the 4th month while 30 (81.2%) patients became culture negative in the $MFX^{(h)}$+OBR group and this difference was statistically significant (p 0.04). The sputum culture conversion was achieved in 41 patients (100%) in the Bdq+OBR group and 36 patients (87.8%) in the $Mfx^{(h)}$+OBR group at the end of the 6 months (p=0.03). Four patients in the $Mfx^{(h)}$+OBR group remained culture positive at the end of 6th month (Table 2). The mean time to culture conversion was found to be 3.10± 0.8 months in the Bdq+OBR group and 3.32±0.9 months in the $Mfx^{(h)}$+OBR group (p=0.009).

The most frequent adverse events (>10% of patients) observed in the patients in Bdq+OBR group were dark discolouration of skin (39; 95.1%), vomiting (12; 29.26%), peripheral neuropathy (10; 24.4%), hyperlipasemia (8; 19.5%), hyperuricaemia (8; 19.5%),

raised QTcF interval (7; 17.1%), musculoskeletal (6; 14.6%), headache (5; 12.2%), and skin rash (5; 12.2%). The most frequent adverse events observed in the patients in Mfx(h)+OBR group were vomiting (22; 59.5%), dark discolouration of skin (21; 56.8%), headache (9; 24.3%), musculoskeletal (6; 16.2%) and peripheral neuropathy (5; 13.5%). Vomiting (22; 59.5% *vs* 12; 29.26%) (p=0.04) and ototoxicity (9; 24.3% vs 2; 4.9%) (p=0.01) were observed in a significantly higher proportion of patients in the Mfx(h)+OBR group as compared to Bdq+OBR group. The adverse events which were observed in a significantly higher proportion of patients in the Bdq+OBR group as compared to Mfx(h)+OBR group were hyperlipasemia (more than three times the upper limit of normal) (8; 19.5% *vs* 1; 2.7%) (p=0.02) and dark discolouration of skin (39; 95.1% *vs* 21; 56.8%) (p=0.0001). QTcF more than 480 msec was observed in 7 (17.1%) patients of Bdq+OBR group and in 2 (5.4%) patients of MFX(h)+OBR group and the difference was not statistically significant (p=0.10) (Table 3).

Discussion

The management of MDR-TB with additional resistance to FQ/SLI is complex as the treatment options are limited. As per the World Health Organisation (WHO), a regime for DR-TB should include at least four drugs to which the *Mycobacterium tuberculosis* (MTB) isolate is susceptible and to which the patient must not have been exposed in the past [5]. As in our study, most of these patients are exposed to first- or second-line anti-tuberculosis drugs in the past, thus further limiting the treatment options. Before the advent of bedaquiline, due to their good efficacy, fluoroquinolones and SLI's formed an integral part of a DR-TB regimen. High dose moxifloxacin has been shown to be effective even in FQ resistant cases [6]. The US-FDA approval of bedaquiline in 2012 lead to the addition of one more potent antimycobacterial drug to our armamentarium against DR-TB. Bedaquiline, a diarylquinoline, inhibits

Table 1. Demographic and baseline clinical characteristics of the patients.

Characteristics	BDQ+OBR (n=41)	MFX(h)+OBR (n=37)	p-value
Age (years) (mean±SD)	36.71±11.49	41.14±14.33	0.13
Gender			
Male sex, n (%)	29 (70.7)	26 (70.3)	0.96
Female sex, n (%)	12 (29.3)	11 (29.7)	
Weight, kg (mean±SD)	45.00±9.34	44.65±11.44	0.88
Height, m (mean±SD)	164.17±8.31	164.38±9.41	0.91
BMI, kg/m^2 (mean±SD)	16.63±3.07	16.48±3.98	0.85
Presenting symptoms			
Cough, n (%)	41 (100)	37 (100)	
Fever, n (%)	38 (92.7)	34 (91.9)	0.89
Night sweats, n (%)	2 (4.9)	2 (5.4)	0.91
Loss of weight, n (%)	41 (100)	35 (94.6)	0.13
Chest radiograph findings			
Consolidation, n	35	24	0.03
Cavity, n	15	23	0.02
Fibrosis, n	34	35	0.10
Bronchiectasis, n	2	3	0.56
Nodules, n	22	22	0.60
Bilateral involvement, n	12	13	0.57

Table 2. Comparison of culture results from 3rd months to subsequent time periods between the groups.

Time periods	BDQ+OBR (n=41)		MFX(h)+OBR (n=37)		p-value
	n	%	n	%	
3rd month					
Positive	8	19.5	13	35.1	0.12
Negative	33	80.5	24	64.9	
4th month					
Positive	0	0.0	7	18.9	0.004
Negative	41	100.0	30	81.1	
5th month					
Positive	0	0.0	4	10.8	0.03
Negative	41	100.0	33	89.2	
6th month					
Positive	0	0.0	4	10.8	0.03
Negative	41	100.0	33	89.2	

mycobacterial adenosine triphosphate (ATP) synthase and exerts bactericidal activity against mycobacteria. It's chemical structure and mechanism of action is different from fluoroquinolones and second line injectables and hence there is no cross-resistance between them [7]. The present study was conducted at a tertiary care hospital in western India with an objective to determine the 6th month sputum culture conversion in drug resistant PTB patients on Bdq+OBR regimen and Mfx(h)+OBR regimen. In our best knowledge, this is the first study comparing Bdq+OBR regimen and Mfx(h)+OBR regimen in the treatment of drug resistant TB patients.

In our study, weight gain was seen in all patients of the Bdq+OBR group and 91.9% patients of the Mfx(h)+OBR group at the 6th month. The mean weight gain was significantly higher in patients of the Bdq+OBR group than in the Mfx(h)+OBR group. At the end of 3rd month, sputum culture became negative in 80.9% of patients in the Bdq+OBR group and 64.9% patients in the MFX(h)+OBR group. All the patients in the Bdq+OBR group became culture negative at the end of the 4th month. The sputum culture conversion rate was 80.5% at 3 months with bedaquiline in patients with DR-TB in a multi-centric study by Borisov *et al*. [8]. At the end of 6 months, the sputum culture conversion rate was 100% in the Bdq+OBR group and 87.8% in the Mfx(h)+OBR group in our study. In a study from India with 290 DR-TB patients who received bedaquiline containing regime, the culture conversion rate at the six months was 98% [9]. The mean time to culture conversion was significantly less with Bdq+OBR than with Mfx(h)+OBR in our study. Thus, the Bdq+OBR was more efficacious than Mfx(h)+OBR.

US-FDA issued a black box warning for the use of bedaquiline because of the excess deaths in the bedaquiline arm in an initial trial and its QT prolonging effect [4]. Moxifloxacin [10,11], clofazimine [12] and delamanid [13] are also known to prolong QT interval. In our study, though raised QTcF interval was more commonly seen in the Bdq +OBR group as compared to the Mfx(h) + OBR group, the difference was not statistically significant. Also, none of the patients developed life threatening arrhythmias in both groups. There is now evidence that severe prolongation of QT interval is uncommon with bedaquiline [14]. In a prospective study based on the WHO active drug safety monitoring (aDSM) project, serious cardiological adverse events which required drug discontinuation were reported only in two out of 577 (0.35%) patients [15]. However, caution is to be exercised especially when bedaquiline is used with other QT prolonging drugs like moxifloxacin and clofazimine which are usually a part of the anti-TB regimen. In our study, seven patients (17.1%) in the Bdq+OBR group who were exposed to both bedaquiline and clofazimine had asymptomatic and transient QT prolongation (more than 480 msec). In a study by Udwadia *et al*., 15% of the patients of DR-TB who received bedaquiline and clofazimine along with other anti-tubercular drugs developed asymptomatic QT interval prolongation (more than 500 msec). Five out of the twenty had also received moxifloxacin [16].

Raised serum lipase and dark discolouration of skin were significantly more common in patients who received Bdq+OBR. Vomiting and ototoxicity were significantly more common in patients who received Mfx(h)+OBR. Bedaquiline or any other antitubercular drug leading to a rise in serum lipase levels has not been reported in the literature. Clofazimine is known to cause dark discolouration of the skin due to deposition of the free base form of the drug in the subcutaneous fat [17]. The mechanism of how bedaquiline potentiates these adverse events is still unknown.

We acknowledge a few limitations of our study. Ours was an observational study with a small sample size. Also, for a chronic disease like tuberculosis, the duration of follow-up of six months was short. A follow-up for at least two years after completion of treatment is prudential to detect relapse [18]. Hence, a randomised controlled trial with a large sample size and a follow up of at least two years after completion of treatment is advisable. The mechanism of bedaquiline induced or potentiated hyperlipasemia and dark discoloration of skin warrants further research.

Table 3. Adverse events among both groups.

Adverse events	BDQ+OBR (n=41)		MFX(h)+OBR (n=37)		p-value
	n	%	n	%	
Gastrointestinal					
Vomiting	12	29.26	22	59.5	0.04
Altered liver function tests	3	7.3	2	5.4	0.73
Raised serum lipase	8	19.5	1	2.7	0.02
Raised serum amylase	1	2.4	0	0.0	0.33
Mucocutaneous					
Dark discolouration of skin	39	95.1	21	56.8	0.001
Skin rash	5	12.2	3	8.1	0.55
Black hairy tongue	3	7.3	0	0.0	0.09
Nervous system					
Headache	5	12.2	9	24.3	0.16
Psychosis	0	0.0	1	2.7	0.28
Peripheral neuropathy	10	24.4	5	13.5	0.22
Hyperuricemia	8	19.5	2	5.4	0.06
Anaemia	3	7.3	2	5.4	0.73
Ototoxicity	2	4.9	9	24.3	0.01
Musculoskeletal	6	14.6	6	16.2	0.84
Raised QT interval (QTcF >480 msec)	7	17.1	2	5.4	0.1

Conclusions

Bedaquiline with an optimized background regimen was associated with the higher success of sputum culture conversion at 6 months and faster sputum culture conversion rate as compared to high dose moxifloxacin with the optimized background regimen. Thus, bedaquiline containing regimens should be preferred for the treatment of drug resistant tuberculosis. Vomiting and ototoxicity were more common with the $Mfx^{(h)}$+OBR regimen while raised serum lipase and dark discolouration of skin were more common with the Bdq+OBR regimen. Though life threatening arrhythmias are uncommon, caution must be exercised while using bedaquiline along with other QT prolonging drugs.

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