Original Article

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Safety and Efficacy of Bedaquiline in Drug Resistant Tuberculosis: A Hospital-based Prospective Observational Study

Internal Medicine Section

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ABSTRACT

Introduction: Tuberculosis (TB) is a chronic infectious disease that continues to cause significant morbidity and mortality in developing nations. The emergence of Drug Resistant Tuberculosis (DR-TB) has further aggravated the problem. The treatment of DR-TB is challenging due to poor compliance, stemming from drug toxicity and the long duration of treatment. Bedaquiline (BDQ), a novel drug, has shown promising results in terms of safety and efficacy for the treatment of Multidrug Resistant TB (MDR-TB).

Aim: To evaluate the safety and efficacy of BDQ in patients with DR-TB.

Materials and Methods: This was a prospective, observational, hospital-based study carried out in the Department of Respiratory Medicine at JNMC, Aligarh, Uttar Pradesh, India, over a period of two years from December 2020 to November 2022. A total of 303 patients were enrolled. BDQ treatment was initiated after satisfying the inclusion criteria and patients were monitored for Adverse Events (AE). The study evaluated outcomes in terms of sputum conversion and clinical improvement. A follow-up was conducted for six months after the completion of therapy. Data entry was performed on Microsoft Excel and the final analysis was conducted thereafter.

Results: Out of 303 patients, successful outcomes with BDQ were observed in 272 (89.77%) patients who were cured. Sixteen patients died (5.28%), 10 (3.30%) cases were lost to follow-up and in 5 (1.65%) patients, BDQ was discontinued due to adverse effects. Clinical improvement, in terms of an increase in body weight, improvement in symptoms and radiological improvement, was observed in 265 (97.43%) patients.

Conclusion: The study concludes that BDQ demonstrates promising safety and efficacy, establishing itself as a valuable option for the treatment of DR-TB.

Keywords: Adverse drug reaction, Antitubercular agents, Multidrug-resistant tuberculosis

INTRODUCTION

The TB is a chronic infectious disease that continues to cause significant morbidity and mortality in India and other developing countries [1]. It is still considered one of the top ten infectious disease-related causes of death in the world [2]. The emergence of DR-TB has exacerbated the situation. The burden of drug-resistant TB increased between 2020 and 2021, with 450,000 (95% UI: 399,000-501,000) new cases of Rifampicin-resistant TB (RR-TB) reported in 2021 [3]. The treatment of DR-TB is challenging due to poor compliance resulting from drug toxicity and the long duration of treatment.

For patients with MDR-TB, BDQ, a new diarylquinoline, was introduced into the World Health Organisation (WHO)-recommended all-oral regimen to replace injectable medications. Clinical trials have demonstrated improved sputum conversion rates with BDQ and some observational studies have shown enhanced treatment results [4-6]. BDQ is the first new class of anti-TB drugs in more than 40 years and works by inhibiting bacterial Adenosine Triphosphate (ATP) synthesis. It has demonstrated strong bactericidal and sterilising activities against *Mycobacterium tuberculosis* in preclinical, laboratory and animal experiments [7-9]. BDQ is now well incorporated within the National Tuberculosis Elimination Programme (NTEP) as part of the standard longer oral M/XDR-TB regimen for eligible patients.

Hepatotoxicity and delayed ventricular repolarisation (also known as QTc prolongation), which can lead to torsades de pointes and cardiac arrhythmia, are two severe side-effects that can develop from the administration of BDQ [10]. Regular electrocardiogram monitoring is thus mandatory during BDQ treatment and the drug should be discontinued if the QTc exceeds 500 ms. Given that BDQ is a new drug with limited clinical experience, active drug safety monitoring is essential to generate data for its continued use. A significant number of countries are currently participating in clinical BDQ trials at various levels.

This study was conducted to evaluate the safety and efficacy of BDQ in patients with DR-TB. This is the first such prospective study at our centre, which has a very high patient load of drug-resistant TB and accommodates patients who frequently default or present late.

The primary objective of this study was to evaluate the occurrence and severity of specific adverse effects, with a particular focus on QT prolongation and to monitor the overall safety profile of BDQ by assessing general adverse effects throughout the treatment course. The secondary objective was to assess microbiological improvement, defined by sputum culture conversion, whereby a patient is considered culture-converted when two consecutive cultures, taken at least 30 days apart, are negative for MTB.

MATERIALS AND METHODS

This was a prospective, observational, hospital-based study conducted over a period of two years, from December 2020 to November 2022, at the Nodal DR-TB Centre and the Department of Respiratory Medicine of JNMC, Aligarh, Uttar Pradesh, India involving 303 DR-TB patients. Approval from the Institute's Ethical Committee (IEC) was obtained under reference number IECJNMC/417, dated 19/10/2021.

Inclusion criteria: Patients aged 18 years or older, diagnosed with MDR/RR TB and confirmed through either CBNAAT (Cartridge-Based Nucleic Acid Amplification Test) or first-line LPA (Line Probe Assay) [11], as well as patients with controlled stable arrhythmias were included in the study.

Exclusion criteria: Patients with uncontrolled cardiac arrhythmias requiring medication, those with a QTc interval ≥500 ms at baseline despite normal electrolytes, patients with additional risk factors for Torsades de Pointes (such as heart failure, hypokalaemia, or a family history of long QT syndrome), pregnant or lactating women, as per the PMDT guideline of 2019 [12] and those whose initial ECG showed a QTc >500 ms (with a repeat ECG performed after six hours; if both ECGs showed a QTc >500 ms and the patient had not been given cardiotoxic drugs) were excluded from the study.

Pretreatment evaluation: Following written and informed consent, pretreatment evaluation was conducted for all eligible patients. This evaluation included a thorough history and physical examination, as well as laboratory investigations (complete blood count, renal function tests, liver function tests and sputum smear examination).

Drug regimen: BDQ was administered as 400 mg daily for the initial two weeks, followed by 200 mg thrice a week for the next 22 weeks (a total of six months), alongside other background regimen like levofloxacin, linezolid, clofazimine and ethionamide.

Treatment protocol: All patients receiving BDQ were hospitalised for the initial 14 days and monitored intensively. Daily ECGs and QTc intervals were measured while the patients were in a lying down position. The QTc interval was calculated using the Fredericia method (QTcF=QT/√ (3&RR) [13].

Follow-up monitoring: In the initial three days, each hospitalised patient was closely monitored for adverse effects like derangement of liver enzymes and QTc prolongation. Daily ECGs were obtained and QTc intervals were measured; patients were advised to attend follow-up appointments as per the schedule. During the six months following the completion of therapy, each patient was monitored for any possible adverse effects and clinical, bacteriological and radiological assessments were conducted to evaluate the response to treatment. Patients were encouraged to continue their treatment. Clinical improvement was assessed in terms of increases in body weight, improvements in symptoms and radiological enhancements. Microbiological improvement was evaluated in terms of sputum conversion and smear examination. Improvements were studied beginning two weeks after the initiation of therapy.

STATISTICAL ANAYLSIS

Data entry was performed using Microsoft Excel and the final analysis was conducted subsequently. The comparison of the variables which were quantitative were analysed using Independent t- test. For qualitative it was analysed using Pearson Chi-Square test. If any cell had an expected value of less than 5 then Fisher's exact test was used. The p-value <0.05 was considered statistically significant.

RESULTS

The demographic and clinical characteristics of the patients are shown in [Table/Fig-1]. The majority of patients were young (<35 years: 72.28%), male (59.74%) and had a low BMI (<18.5: 54.46%). Most of these patients presented with bilateral cavitatory lung lesions (83.17%) and a positive family history of TB (80.53%). Out of 303 patients, a successful outcome with BDQ, classified as cured, was observed in 272 (89.77%) patients, while 16 patients died (5.28%), 10 cases were lost to follow-up and in five patients, BDQ was discontinued due to adverse effects [Table/Fig-2]. Clinical improvement (in terms of increased body weight, improvement in symptoms and radiological enhancement) was observed in 265 (97.43%) patients, which was statistically significant [Table/Fig-3].

General profile		n (%)
Age (years)	≤35	219 (72.28)
	36-70	82 (27.06)
	>70	2 (0.66)
Sex	Male	181 (59.74)
	Female	122 (40.26)
Weight (kg)	≤35	9 (2.97)
	36-75	293 (96.70)
	>75	1 (0.33)
Height (cm)	≤145	98 (32.34)
	146-160	195 (64.36)
	>160	10 (3.30)
BMI (kg/m^2)	≤18.5	165 (54.46)
	18.6-24.9	137 (45.21)
	≥25.0	1 (0.33)
Family history of TB	Yes	244 (80.53)
	No	59 (19.47)
Site of disease	Pulmonary	285 (94.06)
	Extrapulmonary	8 (2.64)
	Extrapulmonary+Pulmonary	10 (3.30)
Radiological extent of disease	Cavitatory lung lesion present	262 (86.47)
	Cavitatory lung lesion absent	41 (13.53)
Laterality of lung involvement	Bilateral	252 (83.17)
	Unilateral	51 (16.83)

[Table/Fig-1]: Demographic and clinical profiles of enrolled patients.

Outcome	n (%)
Cured	272 (89.77)
Bedaquiline (BDQ) stopped	5 (1.65)
Lost to follow-up	10 (3.30)
Died	16 (5.28)

[Table/Fig-2]: Various outcomes in patients on Bedaquiline (BDQ) therapy.

Clinical improvement in patients	n (%)
Yes	265 (97.43)
No	7 (2.57)

[Table/Fig-3]: Percentage of patients with clinical improvements post-Bedaquiline (BDQ) therapy n=272.

During the initial two weeks of treatment with BDQ, a moderate increase in the QTc interval was observed in 10 (3.30%) patients; however, in 8 (2.64%) patients, there was a significant increase in the QTc interval. Of these eight patients, QTc was prolonged due to hypokalaemia in three patients, for whom the drug was temporarily stopped for one day and reintroduced after the correction of hypokalaemia. However, BDQ was permanently discontinued in five patients due to persistently prolonged QTc [Table/Fig-4]. After two weeks, none of the patients exhibited QTc interval prolongation. Liver enzymes showed temporary derangements in 19 (6%) patients during treatment; however, there was no serious impact on the outcome [Table/Fig-5]. After three months of treatment with BDQ, sputum culture and smear tests remained positive in approximately 44 patients.

QTc interval	n (%)
<450	285 (94.06)
450-499	10 (3.30)
>500	8 (2.64)

[Table/Fig-4]: QTc interval changes post-Bedaquiline (BDQ) therapy.

Deranged liver enzymes	n (%)
Increased AST	14 (4.62)
Increased ALT	5 (1.65)
Normal liver enzymes	284 (93.73)

[Table/Fig-5]: Derangement of liver enzymes after starting Bedaquiline (BDQ) therapy.

Following subsequent follow-up, all cured patients (272) were found to have negative sputum culture and smear results [Table/Fig-6].

S. No.	Sputum status post Bedaquiline (BDQ) therapy	Positive	Negative
1	At 3 months	44	228
2	At 4 months	39	233
3	At 5 months	3	269
4	At 6 months	0	272

[Table/Fig-6]: Sputum status post-Bedaquiline (BDQ) therapy.

DISCUSSION

DR-TB is a global health problem that poses a serious threat to the management of TB patients [14]. With the emergence of MDR and XDR-TB, the use of second-line drugs is becoming more prevalent. However, these drugs are associated with increased toxicity, high costs and prolonged treatment duration [15]. A meta-analysis conducted by Jacobson KR et al., noted that the mortality rate in XDR-TB patients on second-line drugs ranged from 14-27%, with only a 44% success rate [16]. Therefore, there was a need to identify agents that can lower costs, produce less toxicity and be more effective for patients with MDR and XDR-TB. In search of such agents, BDQ was proposed as a novel oral diarylquinoline antimycobacterial agent active against *Mycobacterium tuberculosis*, including MDR strains and was approved by the Food and Drug Administration (FDA) for the treatment of adults with MDR pulmonary TB as part of combination therapy [17]. Since then, various studies have been conducted to analyse the pharmacological profile, safety and effectiveness of BDQ. The present study observed that BDQ is relatively safe and more effective in patients with drug-resistant TB.

Sputum Status Pre- and Post-BDQ

The sputum status of the enrolled patients was compared before and after initiating BDQ therapy. Sputum smear tests were positive for acid-fast bacilli in 205 out of 303 patients (67.66%), while 98 patients (32.34%) were negative. In the study by Perrineau S et al., the sputum status before starting BDQ was positive in 77% of cases [18]. In another study by Li J et al., 60% of cases were sputum smear positive prior to BDQ therapy [19].

The sputum smear status post-BDQ therapy was assessed at three months, four months, five months and six months. At the three-month interval, sputum smear was positive in around 44 patients (16.2%) and negative in 228 patients (83.8%). At four months, positive sputum was observed in 39 patients (14.3%) and negative sputum smear was found in 233 patients (85.7%). At five months, only three patients (1.1%) were found to be sputum positive, while 269 were sputum smear negative. After this period, all 272 patients who survived were found to be sputum smear negative. These findings are comparable with various other studies. Barvaliya SV et al., noted sputum smear negativity in 93 out of 102 patients (91.17%) at three months post-BDQ, which was close to the findings of this study (84.6%) [20].

Adverse Effect (Safety Profile)

The safety of BDQ therapy was assessed in this study by analysing the QTc interval and serum levels of liver enzymes on the 14th day after initiating treatment. It was observed that out of 303 DR-TB patients who started BDQ therapy, the majority (n=285, 94.06%) had a QTc interval of less than 450 ms (normal, no prolongation). The number of patients with a QTc interval between 450-499 ms was 10 (3.30%) and only eight patients (2.64%) had a QTc interval greater than 500 ms (prolonged). This finding was statistically significant, with a p-value of 0.001.

Out of the eight patients with QTc prolongation, BDQ was discontinued in five cases (1.65%). In the three remaining patients, the QTc was prolonged due to hypokalaemia, for which the drug was temporarily stopped for one day and reintroduced after the correction of hypokalaemia. In the study conducted by Brust JCM et al., (2021), four participants out of 195 (2.05%) experienced a QTcF greater than 500 ms [21]. They concluded that severe QT prolongation was uncommon and did not necessitate the permanent discontinuation of BDQ. In the study by Zheng-Yu Shi et al., six patients (12.0%, 6/50) permanently discontinued BDQ due to a QTcF greater than 500 ms [22]; whereas, in this study, only 1.65% required the cessation of BDQ. In another study by Huynh J and Marais BJ, a 1% permanent discontinuation of BDQ due to QTc prolongation greater than 500 ms was observed [23]. In the study conducted by Pym AS et al., a QTc interval greater than 500 ms was observed in one out of 233 patients (0.42%) [24]. These findings suggest that BDQ does not cause significant QTc prolongation in most patients and can thus be considered a safe drug for use in DR-TB patients.

The serum levels of liver enzymes (AST and ALT) were analysed two weeks post-BDQ therapy. Out of 303 DR-TB patients who began BDQ therapy, only 14 patients (4.62%) showed an increase in AST and five patients (1.65%) showed an increase in ALT. However, this derangement did not lead to the cessation of BDQ therapy, while the rest of the patients showed no derangement of liver enzymes. This finding was statistically significant, with a p-value of 0.001. In the study by Pym AS et al., (2016), AST was elevated in nine out of 233 patients (3.86%) and ALT was increased in five out of 233 patients (2.14%), which is comparable to the findings of this study [25].

Outcomes after Bedaquiline (BDQ) Therapy

The outcomes of BDQ therapy in DR-TB patients were analysed in terms of those cured, those who died, those lost to follow-up and overall clinical improvement. Out of 303 patients, a total of 272 patients (89.77%) were cured after receiving BDQ therapy. Ten patients (3.30%) were lost to follow-up, BDQ was stopped in five cases (1.65%) and a total of 16 patients (5.28%) died during the study period while on BDQ therapy (p-value=0.001).

Out of the 272 patients who survived, the proportion of patients showing overall clinical improvement (which included an increase in body weight, improvement in symptoms and radiological improvement) post-BDQ therapy was significantly higher (n=265/272, 97.43%) compared to those with no clinical improvement (n=7/272, 2.57%), with a p-value of 0.001.

According to Barvaliya SV et al., out of 127 patients, 102 (80.3%) had a successful outcome, whereas death was noted in 14 (11.02%) cases, treatment failure was seen in 10 (7.9%) cases and one patient defaulted [20]. These findings are comparable to the current study, which noted a successful cure in 89.77% of cases and a death rate of 5.28%.

In a study by Kwon YS, a cure post-BDQ therapy was recorded in 125 out of 205 patients (61.00%) and death was reported in 14 out of 205 patients (6.8%) [25]. In the study conducted by Gao M et al., a favourable outcome was noted in 151 out of 177 patients (85.3%), with death recorded in 3 out of 177 patients (1.7%) [26]. A study by Zhao Y et al., reported death in 11 out of 145 patients (7.6%) at 12 months after BDQ therapy [27].

Lee HH et al., noted a favourable outcome in 68 out of 74 patients (91.90%), with one death reported in one out of 74 patients (1.35%), one patient lost to follow-up (1.35%) and treatment failure in four out of 74 patients (5.40%), which was comparable to the present study [28]. According to a study by Starshinova A et al., recovery was noted in 89.9% of cases of MDR-TB post-BDQ therapy, while in patients with XDR-TB, 71.9% of cases were cured [29].

Limitation(s)

This was a prospective study in which the cohort was under active safety surveillance and the patients were followed-up in the post-BDQ phase. However, there were certain limitations. It was an

observational, open-label, single-centre study. Additionally, the sample size was not calculated statistically. Future studies with a larger sample size could be conducted.

CONCLUSION(S)

The BDQ demonstrates promising safety and efficacy, establishing itself as a valuable option for the treatment of DR-TB. However, further studies with a control arm are needed to establish its safety and efficacy.

Authors' contribution: SE, IM-Conceptualisation; SE, IM, UB, RB-Methodology; ZA, MMA-Formal analysis; SE, MMA-Data curation; SE, MMA-Software; RB, ZA-Validation; SE, MMA, UB, RB, ZA-Investigation; SE, MMA-Writing - original draft preparation; ZA, MMA-Writing - review and editing; all authors- Approval of final manuscript.

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