ORIGINAL ARTICLE

Bedaquiline-related QTc Prolongation in Multidrug Resistant Tuberculosis Patients: A Prospective Study

Ayushi Gupta[1*], Christopher C Pais[2], Sharath Babu[3]

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Abstract

Introduction: Bedaquiline (BDQ) has revolutionized multidrug-resistant tuberculosis (MDR-TB) management in the Indian population with a high MDR-TB burden. However, its potential cardiotoxicity in the form of QTc prolongation warrants careful monitoring. This study aims to evaluate the prevalence, severity, and risk factors of BDQ-related QTc prolongation in MDR/rifampicin-resistant (RR)-TB patients. Given the genetic variability and diverse environmental factors, extrapolating foreign data to Indian patients is challenging; thus, local evidence is crucial.

Methods: A prospective analytical study was conducted over a period of 18 months on 55 adult patients with RR or MDR pulmonary or extrapulmonary TB initiated on BDQ-containing regimens. Electrocardiograms (ECGs) were performed at baseline, 1, 3, and 6 months. QTc intervals were calculated using Fridericia's formula at each time interval. Prevalence and severity of QTc prolongation were documented. Significant prolongation, defined as an absolute QTcF value ≥500 ms or a change from baseline of ≥60 ms, was also noted.

Results: The overall prevalence of QTc prolongation was 37.25%, with 13.7% of patients experiencing significant prolongation. The highest proportion of moderate to severe cases occurred at 3 months. Male gender and body mass index (BMI) >18.5 kg/m^2 were identified as statistically significant risk factors. All patients with significant QTc prolongation were under 60 years old, contrasting with prior research. Temporary withdrawal of BDQ was required in 1.96% of patients due to severe QTc prolongation, but no serious cardiac events were observed, consistent with previous studies.

Conclusion: This prospective study highlights that while QTc prolongation is a frequent occurrence in MDR/RR-TB patients receiving BDQ, severe cases necessitating treatment modification remain uncommon. These findings reaffirm the critical role of BDQ in MDR-TB management while emphasizing the necessity of stringent cardiac monitoring, particularly during the initial 3 months of therapy.

Limitations: The study's small sample size and concomitant use of other QTc-prolonging medications may have influenced the results. Further large-scale studies are needed to confirm these findings and explore additional risk factors.

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Introduction

Tuberculosis (TB) is an extremely infectious bacterial disease that is caused by *Mycobacterium tuberculosis*. It affects the pulmonary system but can also impact various other organ systems. TB is still a worldwide health concern, particularly in developing nations that have limited resources for prevention, diagnosis, and treatment.[1] Drug-sensitive TB, also known as drug-susceptible TB, refers to TB caused by strains that are susceptible to first-line antitubercular drugs, such as isoniazid, rifampicin, ethambutol, and pyrazinamide. These cases can be effectively treated with standard anti-TB regimens.[2]

The strains of *M. tuberculosis* that are resistant to rifampicin cause rifampicin-resistant TB (RR-TB). Rifampicin resistance is a significant concern, as it often indicates resistance to other first-line drugs as well.[3]

Multidrug-resistant TB (MDR-TB) is a more severe form caused by strains that are resistant to both isoniazid and rifampicin. MDR-TB is more difficult to treat and requires a longer treatment duration with second-line antitubercular drugs that are more toxic, more expensive, but often less efficacious.[2]

Both rifampicin-resistant and MDR-TB pose significant challenges in the global fight against TB. Effective management of these resistant forms requires prompt diagnosis, appropriate treatment regimens, strict adherence to treatment, and robust infection control measures to prevent further transmission.

The highest burden of TB cases worldwide is in India, with an ever-increasing proportion of drug-resistant TB (DR-TB) cases. 48,332 MDR/RR-TB cases were diagnosed in 2021, and 43,380 (90%) were started on treatment containing oral bedaquiline (BDQ) in the regimen.[4]

The evidence on incorporating a shorter oral BDQ-containing regimen with phasing out injectables is largely based on data from South African countries, which were studied by the World Health Organization (WHO). Initial studies done in South Africa show reduced time to culture conversion and improved cure rates with this drug.[5]

Since being approved by the US Food and Drug Administration (FDA), BDQ has expanded the limited range of treatment options available for the management of MDR-TB. However, the Center for Disease Control and Prevention (CDC) encourages expert consultation with regional health authorities prior to the use of BDQ due to its potential to cause serious adverse events.[6] Serious adverse events are categorized into grade III (severe), grade IV (disabling or life-threatening), and grade V (death related to adverse events).[7]

Bedaquiline has a favorable safety profile, but possible adverse reactions of BDQ include QT prolongation, which can lead to fatal arrhythmias like torsades de pointes, ventricular tachycardia, and ventricular arrhythmias, along with sudden cardiac death (for which a black box warning has been issued by the US FDA). Instances of hepatitis, jaundice, and increased serum transaminases have also been reported.[8] Hence, monitoring of electrocardiogram (ECG) and serum electrolytes (Na, K, Cl, Ca, and Mg) may be needed along with regular liver function test (LFT) monitoring.[8]

Sanctioned by the WHO, "Guidelines for Programmatic Management of Drug-resistant TB—PMDT in India—2021" were published.[4]

Bedaquiline is now incorporated in both the short and longer oral regimens for MDR-TB treatment for the initial 6 months under the programmatic management of drug-resistant tuberculosis (PMDT) guidelines.[4]

[1]Junior Resident; [2]Professor, Department of General Medicine, Kasturba Medical College, Mangaluru, Manipal Academy of Higher Education, Manipal; [3]Senior Pulmonologist, Department of Pulmonology, Wenlock District Hospital, Mangaluru, Karnataka, India; *Corresponding Author

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There are some published data on the cardiotoxic effects of BDQ; however, the consensus is that the benefits of the drug outweigh the potential risks of cardiotoxicity.[9]

This study was planned to determine the proportion of Indian patients with RR/MDR-TB who develop QTc prolongation related to the use of BDQ at the end of 6 months of therapy and to grade the severity of this adverse effect. It will also aid in identifying some of the possible risk factors that may be contributing to its cardiotoxicity.

The evidence on oral BDQ-containing regimen is largely based on data from South Africa. However, most of these studies, which establish the effectiveness and safety profile of BDQ, have been done outside of India, mainly in South Africa, and a few in Europe, China, and California.[6]

Hence, very little evidence exists in Indian MDR-TB patients, and considering the differences in genetic makeup and environmental factors, it becomes difficult to extrapolate data from other countries to the Indian population.

Keeping in mind that India has umpteen numbers of TB patients and increasing numbers of DR-TB, it becomes important to address these knowledge gaps. The current guidelines also emphasize that further data are needed, especially from resource-limited countries with rampant TB cases.

Methods

This prospective analytical study was conducted over 18 months from August 2022 to February 2024. The study population included Indian adult patients (>18 years) diagnosed with RR or MDR pulmonary or extrapulmonary TB who were initiated on treatment at Kasturba Medical College, Mangaluru teaching hospitals. Patients with baseline QTcF >500 ms, preexisting cardiac conduction abnormalities, or those not receiving BDQ were excluded.

Data collection was performed through direct interviews using a pretested, semi-structured questionnaire. Demographic data, clinical history, and baseline serum electrolytes were recorded. Baseline ECGs were taken as part of the pretreatment evaluation, and the QTc was calculated using Fridericia's formula. Follow-up ECGs were obtained at 1, 3, and 6 months after initiation of BDQ-containing treatment.

The primary outcomes were the number and proportion of subjects who developed an absolute QTcF value ≥500 ms or a change in QTc interval ≥60 ms from baseline after 6 months of BDQ therapy. The severity of QTc prolongation was graded according to PMDT guidelines.

Continuous variables were stated as mean ± standard deviation, and categorical variables as proportions and numbers. For comparison of the data, Chi-square tests were utilized, and $p < 0.05$ was considered significant. The calculated sample size for the study was 55 patients.

Results

In this prospective analytical study, data was collected from 55 adult patients with RR or MDR-TB who were initiated on BDQ-containing regimens. The population had a mean age of 40.9 years, with males constituting 61.8% of participants. Patient demographics, clinical characteristics, and ECG measurements were recorded at baseline and follow-up intervals of 1, 3, and 6 months. QTc intervals were calculated using Fridericia's formula, with significant prolongation defined as an absolute QTcF value ≥500 ms or a change from baseline ≥60 ms.

Table 1 outlines the baseline demographics and characteristics of the study population, highlighting that 58.2% of participants were underweight and the majority (63.6%) had RR-pulmonary TB. The distribution between long and short MDR regimens was 32.7% and 67.3%, respectively, with only 3.6% of patients being HIV positive.

Table 2 presents the key outcomes regarding QTc prolongation. Four patients were not included, as one patient was lost to follow-up and three patients died during the course of treatment. Data from 51 patients was analyzed. It revealed an overall prevalence of 37.25% for QTc prolongation. Notably, 13.73% of patients experienced significant QTc prolongation, with 11.76% showing a change in QTcF ≥60 ms from baseline and 1.96% reaching an absolute QTcF ≥500 ms.

The progression of QTc prolongation over time is detailed in Table 3, demonstrating that the peak of severity occurred at the 3-month interval. At this time point, 11.3% of patients experienced mild prolongation, 3.8% had moderate prolongation, and 1.9% had severe prolongation. By the 6-month mark, there was a noticeable improvement, with no severe cases and only 1.9% moderate cases remaining.

Table 4 analyzes the association between various clinical factors and significant QTc prolongation. The analysis identified male gender and body mass index (BMI) ≥18.5 as statistically significant risk factors (with $p < 0.001$ and $p = 0.005$, respectively). Interestingly, all patients who experienced significant QTc prolongation were under 60 years of age, although this was not statistically significant ($p = 0.43$). All patients with significant prolongation had normal calcium, potassium, and magnesium levels.

Discussion

Multidrug-resistant TB continues to be a major global health challenge, with BDQ emerging

Table 1: Patient demographics and characteristics

Characteristic		*Frequency (value)*	*Percentage (%)*
Mean age		40.9 ± 15.4 years	
Gender	Males	34	61.8
	Females	21	38.2
BMI	Underweight (<18.5)	32	58.2
	Normal (18.5–24.9)	23	41.8
Diagnosis	RR-pulmonary TB	35	63.6
	MDR-pulmonary TB	19	34.5
	Extrapulmonary RR-TB	1	1.8
HIV status	Positive	2	3.6
	Negative	53	96.4
MDR regimen	Long	18	32.7
	Short	37	67.3

Table 2: QTc prolongation prevalence and significance

QTc prolongation	*Prevalence*
Overall QTc prolongation	37.25% (19/51)
Significant QTc prolongation (≥500 ms absolute value or ≥60 ms change from baseline)	13.73% (7/51)
Absolute QTcF ≥500 ms	1.96% (1/51)
Change in QTcF ≥60 ms from baseline	11.76% (6/51)

Table 3: Severity of QTc prolongation over time

Time point	*Mild (%)*	*Moderate (%)*	*Severe (%)*
1 month	7.5	5.7	0
3 months	11.3	3.8	1.9
6 months	11.3	1.9	0

Table 4: Association of significant QTc prolongation with risk factors

Risk factor	*Significant QTc prolongation (%)*	*p-value*
Age ≤60 years	100	0.43
Male gender	71.4	<0.001
BMI ≥18.5	71.4	0.005
HbA1c >6.5	14.3	0.72
Calcium ≥8 mg/dL	100	–
Potassium 3.5–5 mEq/L	100	–
Magnesium 1.7–2.2 mEq/L	100	–

as a promising treatment option. However, its use has been associated with QTc interval prolongation, a potentially life-threatening adverse effect.[10–12] Our study aimed to detect the proportion of MDR/RR-TB patients developing QTc prolongation after 6 months of BDQ therapy and assess its severity and risk factors.

Our findings revealed a total QTc prolongation prevalence of 37.25%, with 13.7% experiencing significant prolongation. This prevalence is lower compared to some previous studies.[13–16] The severity of QTc prolongation varied over time, with the highest proportion of moderate and severe cases observed at the 3-month interval. Most patients with significant QTc prolongation were males and had a BMI >18.5 kg/m^2, both statistically significant risk factors. Interestingly, all patients with significant QTc prolongation were under 60 years old, contrasting with some previous research findings.[17]

While 1.96% of patients required temporary withdrawal of BDQ due to severe QTc prolongation, no serious cardiac events were observed. This aligns with other studies reporting low rates of therapy discontinuation due to QTc prolongation.[6,14,18,19]

However, the study's limitations, including a small sample size and concomitant use of other QTc-prolonging medications, necessitate further research to substantiate these findings and explore additional risk factors.

Conclusion

This prospective study demonstrates that while QTc prolongation is a frequent occurrence in patients receiving BDQ-containing regimens for MDR/RR-TB, severe prolongation necessitating treatment modification is rare.

The study identified male gender and BMI ≥18.5 as significant risk factors and observed that QTc prolongation typically peaks at 3 months before showing improvement.

Despite these cardiac effects, the absence of serious cardiac events suggests that BDQ can be safely administered with vigilant ECG surveillance and judicious patient selection.

These findings reaffirm the critical role of BDQ in MDR-TB management while emphasizing the necessity of stringent cardiac monitoring, particularly during the initial 3 months of therapy.

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