INT J TUBERC LUNG DIS 27(4):329–331
© 2023 The Union
http://dx.doi.org/10.5588/ijtld.22.0406

LETTER

QTc prolongation with bedaquiline treatment for drug-resistant pulmonary TB in a programmatic setting

Dear Editor,

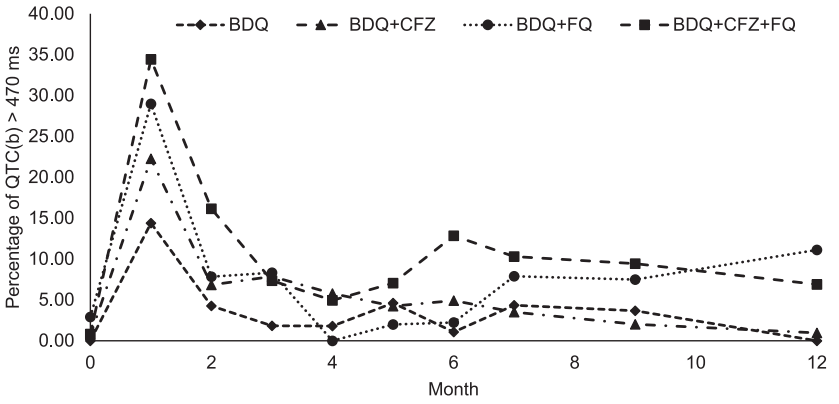
Bedaquiline (BDQ) in an optimised background regimen (OBR) achieves early sputum conversion in difficult to treat multidrug-resistant TB (MDR-TB) patients with additional resistance to fluoroquinolones (FQs).[1,2] However, BDQ has the potential to affect the QT interval of the cardiac cycle within days or weeks of initiating treatment.[2,3] The multi-drug treatment regimen includes other drugs that can also prolong the QT interval with an additive or synergistic effect on QT interval going beyond 500 ms (using either Bazett or Fridericia correction formulae).[4,5] This study aimed to characterise effects on the QTc interval when BDQ is used with other drugs to treat drug-resistant TB (DR-TB).

BDQ was introduced in India in 2016 under the Conditional Access Programme (BDQ-CAP) at six nodal DR-TB treatment centres. TB patients who were resistant to isoniazid and/or rifampicin, along with additional resistance to any or all FQ and/or second-line injectables, or with mixed pattern resistance, or patients declared as failures of prior MDR-TB treatment were eligible to receive a BDQ-containing regimen. For patients willing to participate in BDQ-CAP, after informed written consent, a pre-treatment evaluation was done, details of which are already published.[1] On the 12-lead electrocardiogram (ECG), QTc interval was noted and heart rate correction was applied using Bazett's formula. If the QTc(b) was found to be ≤470 ms, treatment was initiated with BDQ, along with an OBR. BDQ was administered at 400 mg once daily for 2 weeks, followed by 200 mg 3x weekly for 24 weeks. The drugs that were used in the OBR included clofazimine, levofloxacin or moxifloxacin, along with pyrazinamide and linezolid. Patients were classified based on the drugs in the OBR at the time of treatment initiation. After 24 weeks of treatment, BDQ was stopped and the remaining drugs in the regimen were continued for 18–24 months as per the standard of care. During the treatment period, QTc(b) intervals were regularly monitored. In patients with abnormal QTc(b), ECG was repeated to confirm the QTc(b) prolongation. Serum potassium, magnesium and calcium were checked and corrected if found to be abnormal. Other causes of prolonged QTc(b) were ruled out and a cardiologist's opinion was obtained. Division of AIDS criteria were used to assess the severity of the adverse events as mild (450–470 ms), moderate (>470–500 ms) or severe (>500 ms or a difference of ≥60 ms from baseline value), and patients were observed for any change within acceptable limits.[6] The study protocol allowed temporary withholding of treatment if QTc(b) was >470 ms until the abnormalities were corrected. The BDQ-containing regimen was permanently discontinued if QTc(b) was >500 ms and patients were given a regimen without QT-prolonging drugs.

Of the 620 patients enrolled in the BDQ-CAP between June 2016 to August 2017, five were excluded, either due to missing values of baseline QTc ($n = 3$), missing follow-up QTc ($n = 1$) and non-BDQ regimen ($n = 1$). Among the 615 patients, 346 (56.3%) were men and the mean body mass index (BMI) was 17.4 kg/m^2 (standard deviation [SD] 3.5). Pre-treatment investigation of the cohort included haemoglobin (mean ± SD: 11.5 ± 2.0 g/dL), platelet counts (mean ± SD: $2.5 \times 10^3 \pm 1.8 \times 10^3$) and liver enzymes: alanine aminotransferase (mean ± SD: 34.1 ± 21.6 U/L) and aspartate aminotransferase (mean ± SD: 23.9 ± 19.4 U/L). Varying degrees of QTc(b) prolongation were observed while on treatment: 195 (32%) patients showed an absolute QTc(b) interval of >470 ms, whereas 151 (25%) had ≥60 ms increase in QTc(b) from their baseline values. Although BDQ was temporarily withheld in a few patients in the study, unfortunately this was not documented. However, permanent discontinuation of BDQ was done in 14 patients due to prolonged QTc interval ($n = 2$), vomiting ($n = 2$), anaemia ($n = 1$), chest pain ($n = 1$), complete heart block ($n = 1$), death ($n = 1$), haemoptysis ($n = 1$), seizures ($n = 1$), thrombocytopenia ($n = 1$) and diarrhoea ($n = 1$). Two patients had peripheral neuropathy secondary to other drugs in the regimen, but the BDQ-containing regimen was permanently discontinued. Prolongation of QTc(b) interval was noticed more frequently during the first 6 months of treatment when BDQ was part of the treatment regimen as compared to later months (Figure).

BDQ was stopped after 6 months and during the 7–12 months post-BDQ treatment period, ECG data were available for 424 patients, of whom 33 (7.8%) had an absolute value of QTc(b) >470 ms; 48

Article submitted 23 July 2022. Final version accepted 24 October 2022.



Frequency of QTc (b) > 470 ms at each time point										
Month	Baseline	1	2	3	4	5	6	7	9	12
Frequency of QTc (b) > 470 ms	5	146	42	28	19	21	21	20	14	5
Patients, *n*	615	615	519	442	468	456	413	396	324	205

Figure Proportion of patients with ECG showing prolongation in QTc(b) above 470 ms. BDQ = bedaquiline; CFZ = clofamizine; FQ = fluoroquinolone; ECG = electrocardiogram.

(11.3%) had ≥60 ms increase of QTc(b) from their baseline values, while in the rest the values were within admissible range. Multivariate analysis was done to identify the predictors of QTc(b) prolongation. Female sex, age ≥25 years and use of FQs along with one or more QT prolonging drugs had a higher risk of QT interval prolongation, whereas weight ≥40.0 kg had a protective effect. Similarly, regimens with three potential QT-prolonging drugs had a significant effect on QTc interval as compared to two drugs or BDQ alone in the treatment regimen (Table). Variables such as age and alcohol use determined QT prolongation during the post-BDQ treatment period. Pre-treatment haematology and biochemical laboratory variables were not found to be statistically significant (with RR of 1) in the multivariable model.

This cohort of DR-TB patients was able to tolerate BDQ-containing regimens well, similar to other cohorts.[7–13] Although 21 patients (3.5%) developed QTc(b) >500 ms at any one time point during the entire treatment period, repeat ECG (triplicate ECG) showed QTc(b) of <470 ms; treatment was therefore continued, except in two cases. These two patients had QTc(b) >500 ms even in the repeat ECGs, and the BDQ-containing regimen was therefore permanently discontinued. This could be attributed to differences in ethnicity and racial variation. Similar to our findings, another study also that showed factors such as age, sex, concomitant anti-TB drug(s), and BMI determine QTc prolongation.[7] However, Njedka et al. reported that HIV status, age ≥50 years, and sex did not increase QTc values in the initial months of BDQ treatment,

Table Multivariable Poisson regression fitted to assess the effect of treatment regimen and other variables on prolongation of QTc(b) > 470 ms (*n* = 596)*

		First 6 months (BDQ usage)		Post-BDQ treatment period	
Variable		RR (95% CI)	*P* value	RR (95% CI)	*P* value
Age, years (≥25)		1.40 (1.08–1.808)	0.011	2.37 (1.02–5.51)	0.045
Female sex		1.49 (1.15–1.92)	0.002	0.69 (0.33–1.46)	0.336
Baseline weight, kg (≥40)		0.71 (0.56–0.9)	0.005	0.66 (0.32–1.36)	0.259
Excessive alcohol use in the past year (yes)		1.36 (0.69–2.71)	0.375	3.16 (1.19–8.4)	0.021
Tobacco use in the past year (yes)		0.55 (0.26–1.18)	0.123	0.19 (0.03–1.31)	0.091
Regimen	BDQ + CFZ	1.42 (0.98–2.06)	0.06	0.82 (0.31–2.19)	0.689
	BDQ + LVX	1.68 (0.84–3.4)	0.145	1.46 (0.22–9.55)	0.69
	BDQ + MFX	1.51 (0.92–2.5)	0.105	1.69 (0.52–5.49)	0.384
	BDQ + CFZ + LVX	1.88 (1.09–3.26)	0.024	2.61 (0.69–9.94)	0.158
	BDQ + CFZ + MFX	2.10 (1.41–3.13)	<0.001	2.24 (0.87–5.78)	0.094
	BDQ alone†	Reference	—	Reference	—

* Of the 615 patients, five patients had baseline QTc (b) above 470 ms, whereas in 14 patients alcohol and smoking status were not known and they were not considered for the univariate or multivariate analysis. Hence, 596 patients were analysed.
† BDQ alone denotes a regimen with combination of other drugs that do not have QTc prolongation effect.
BDQ = bedaquiline; RR = relative risk; CI = confidence interval; CFZ = clofazimine; LVX = levofloxacin; MFX = moxifloxacin.

whereas moxifloxacin-containing regimens did.[14] Diacon et al. and information from Janssen Pharmaceuticals Ltd. (Beerse, Belgium) has established an increased risk of QTc prolongation when BDQ is used with FQ and certain antimalarial drugs.[15] Pym et al. reported that patients with concomitant use of clofazimine had an increased risk of clinically significant QTcF prolongation.[2]

The WHO recommends monthly ECG monitoring for patients receiving BDQ along with other QTc prolonging drugs.[16] However, TB control programmes in many countries face a major obstacle in obtaining access to 12-lead ECG equipment and interpretation of results. There is no standard frequency of QTc monitoring and it varies between studies.[17] Our study indicates the need for a pre-treatment cardiac evaluation and supports less frequent ECG monitoring during and post-treatment periods. Limitations of the study includes the use of the Bazett formula for QT correction (as available in the ECG machine), which could have overestimated the QTc prolongation. The role of concomitant use of other potentially QT-prolonging drugs was also not analysed in this study, as they were not captured uniformly across the field study sites.

Considering current WHO recommendations for regimen composition and treatment monitoring of DR-TB patients, our study provides additional evidence on the safety of BDQ-containing regimens besides identifying high-risk categories for QT prolongation. On this basis, TB programmes can safely consider the widespread implementation of BDQ-containing regimens in the management of DR-TB under programmatic settings.

K. S. Sachdeva,[1,2] A. K. Bhatnagar,[3] A. Bhaskar,[4] N. Singla,[5] R. Sridhar,[6] B. Ramraj,[4] A. Athawale,[7] R. Solanki,[8] S. R. Baruah,[9] Y. Patel,[1,10] R. Ramachandran,[10] C. Padmapriyadarsini[4]

[1]Central TB Division, Ministry of Health and Family Welfare, Government of India, New Delhi, [2]The Union South East Asia, New Delhi, [3]Rajan Babu Institute of Pulmonary Medicine and Tuberculosis, New Delhi, [4]Indian Council of Medical Research-National Institute for Research in Tuberculosis, Chennai, [5]National Institute of Tuberculosis and Respiratory Diseases, New Delhi, [6]Government Hospital of Thoracic Medicine, Chennai, [7]Seth GS Medical College & KEM Hospital and Group of TB Hospitals, Mumbai, [8]BJ Medical College, Ahmedabad, [9]LG Chest Hospital, Guwahati, [10]WHO Country Office for India, New Delhi, India

Correspondence to: C Padmapriyadarsini, ICMR-National Institute for Research in Tuberculosis, No. 1, Mayor Sathyamoorthy Road, Chetput, Chennai 600031, India. E-mail: padmapriyadarsi.nic@icmr.gov.in

Conflicts of interest: none declared.

References

1 Salhotra VS, et al. Effectiveness and safety of bedaquiline under conditional access program for the treatment of drug-resistant tuberculosis in India: an interim analysis. Indian J Tuberc 2020;67(1):29–37.
2 Pym AS, et al. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. Eur Respir J 2016;47:564–574.
3 Tanneau L, et al. Exposure-safety analysis of QTc interval and transaminase levels following bedaquiline administration in patients with drug-resistant tuberculosis. CPT Pharmacometrics Syst Pharmacol 2021;10(12):1538–1549.
4 World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Geneva, Switzerland: WHO, 2013.
5 Li M, Ramos LG. Drug-induced QT prolongation and torsades de pointes. P & T 2017;42(7):473–477.
6 Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services. DAIDS table for grading the severity of adult and pediatric adverse events. Corrected version 2.1. Bethesda, MD, USA: 2017.
7 Barvaliya SV, et al. Early treatment outcome of bedaquiline plus optimized background regimen in drug-resistant tuberculosis patients. Indian J Tuberc 2020;67:222–230.
8 Udwadia ZF, Ganatra S, Mullerpattan JB. Compassionate use of bedaquiline in highly drug-resistant tuberculosis patients in Mumbai, India. Eur Respir J 2017;49(3):1601699.
9 Pontali E, et al. Cardiac safety of bedaquiline: a systematic and critical analysis of the evidence. Eur Respir J 2017;50(5):1701462.
10 Gao JT, et al. Bedaquiline-containing regimens in patients with pulmonary multidrug-resistant tuberculosis in China: focus on the safety. Infect Dis Poverty 2021;10(1):32.
11 Das M, et al. One step forward: successful end-of-treatment outcomes of patients with drug-resistant tuberculosis who received concomitant bedaquiline and delamanid in Mumbai, India. Clin Infect Dis 2021;73(9):e3496–e3504.
12 Jones J, et al. Adverse drug reactions in South African patients receiving bedaquiline-containing tuberculosis treatment: an evaluation of spontaneously reported cases. BMC Infect Dis 2019;19:544.
13 Motta I, et al. QT prolongation for old and new drugs: how much should we really worry? Int J Tuberc Lung Dis 2022;26(4):298–301.
14 Ndjeka N, et al. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. Int J Tuberc Lung Dis 2015;19(8):979–985.
15 Diacon AH, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med 2014;371(8):723–732.
16 World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Version March 2010. Geneva, Switzerland: WHO, 2014.
17 Isralls S, et al. QT interval prolongation in people treated with bedaquiline for drug-resistant tuberculosis under programmatic conditions: a retrospective cohort study. Open Forum Infect Dis 2021;8(8):ofab413.