Bedaquiline Effect on QT Interval of Drugs-Resistant Tuberculosis Patients: Real World Data

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ABSTRACT

***Background**: Bedaquiline (BDQ) is effective as part of treatment regimen for drug-resistant tuberculosis (DR-TB), but the cardiac safety profile of BDQ is not fully elucidated. This study aimed to analyse the cardiac safety of BDQ by examining its effect on the QT interval of DR-TB patients.* ***Methods**: This is a retrospective study cohort conducted in two DR-TB referral hospitals in Indonesia. The QT interval before and after therapy using BDQ was measured manually and corrected using the Fridericia formula (QTcF). The QT interval profile was analysed over time during BDQ treatment.* ***Results**: A total of 105 subjects participated in the study. The maximum mean difference (standard deviation) of QTcF after treatment with the baseline (ΔQTcF) is 34,06 (52,92) ms after three months of therapy. During BDQ treatment, clinically significant QTcF prolongations was observed in 37.1% subjects with neither arrhythmia nor any other adverse cardiac event occurred. The interval QT prolongation led to BDQ discontinuation in 15.2% subjects temporarily and in 6.7% subjects permanently. There were seven deaths (6.7%) during the treatment.* ***Conclusion**: During BDQ treatment, maximum QT prolongation was observed after three months of BDQ therapy. Therefore, more intensive cardiac monitoring is recommended during this period and afterwards.*

***Keyword**: bedaquiline, drug-resistant tuberculosis, QT interval prolongation.*

INTRODUCTION

Indonesia ranks among the 30 highest-ranking countries in the world when it comes to the burden associated with DR-TB, with the number of new cases increasing every year. In 2020, there were 8,200 new laboratory-confirmed DR-TB cases.[1] However, DR-TB treatment is still a challenge for clinicians due to the low effectiveness and the severe and life-threatening side effects.[2] These side effects may lead to additional morbidity, treatment withdrawal and even death of the patient.[3] In the last 50 years, a new TB drug has been developed from a new class of antibiotic, bedaquiline (BDQ). Clinical trials have shown that BDQ is effective in accelerating sputum conversion and improving success rate; however, BDQ may cause QT interval prolongation.[4] This poses a safety concern while using BDQ, as it may cause polymorphic ventricular tachycardia, also known as *Torsades de Pointes* (TdP), which may lead to sudden death.[5]

Another major concern is the long terminal half-life of BDQ (up to 5.5 months) due to tissue redistribution.[6]

This may lead to the generation of adverse effects of BDQ, including QT interval prolongation, which can last for a longer period or may even occur after the discontinuation of the drug.[4] Moreover, the cardiac safety profile of BDQ has not been fully elucidated by existing studies due to various limitations. Reports of drug-induced TdP were relatively rare, even though the drug is widely used.[5] Therefore, adequate data of cardiac safety of BDQ must be collected from all over the world, including Indonesia. The aim of this study was to analyse the effect of BDQ on the QT interval of DR-TB patients in pragmatic use from two DR-TB referral hospitals in Indonesia.

METHODS

This was a retrospective cohort study using real world data from patients' medical records. It was carried out at Dr. Saiful Anwar Malang Hospital (RSSA) and Dr. M. Goenawan Partowidigdo Cisarua Hospital (RSPG) between August 2020 and October 2020. Prior to its commencement, the study received ethical approval from the institutional review board in RSSA (No. 400/112/K.3/302/2020; April 6th 2020). All DR-TB patients who received BDQ as part of the treatment regimen were selected. The inclusion criteria were adult, aged >18 years, who were administered ECG before BDQ treatment and at least one ECG afterwards. Patients with unreadable ECG reports or incomplete medical records were excluded from the study. The QT intervals before and after the treatment were measured manually then were corrected to the heart rate using the Fridericia formula. According to the Indonesian technical guideline,[7] for cardiac safety monitoring during BDQ treatment, ECG should be performed on Day 2 (D2), in the first week (W1) and every month until the end of BDQ treatment (M1–M6).

The primary outcome was the QT interval profile consisted of QTcF, the difference of QTcF after treatment with the baseline (ΔQTcF) and the proportion of clinically significant QT prolongation over time during the BDQ treatment. The proportion of BDQ discontinuation related to adverse cardiac events was also considered as the primary outcome. According to the international harmonisation standard (ICH) clinical evaluation of QT/QTc interval prolongation and proarrhytmic potential for non-antiarrhytmic drugs (E14), clinically significant QT prolongation is defined as QTcF >500 ms, ΔQTcF >60 ms, or both.[8,9] However, as per WHO and the Indonesian guideline on DR-TB management, the criteria for the discontinuation of QT-prolonging drugs, including BDQ, are based on the absolute value of QTcF. The suspected drug should be interrupted for 7 to 14 days until the normal state is restored, if QTcF >500 ms in two measurements within 30-minute intervals and without cardiac symtoms.[10,11] This data of discontinuation was obtained from the clinician documentation on medical records.

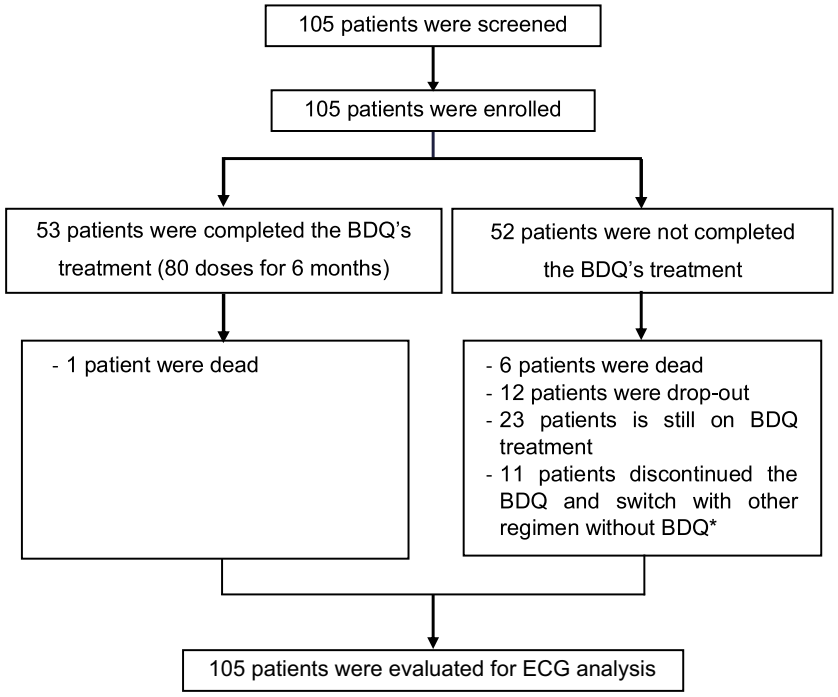
Based on formula of the mean difference between two paired groups (before and after), a minimum sample size of 66 subjects is necessary. The analysis of data was performed using SPSS software version 22. A t-test or Wilcoxon test was used to assess the difference in continuous variables, depending on the distribution of data.

RESULTS

Due to the ongoing COVID-19 pandemic in August to October 2020, there was limited mobility between regions in addition to limited data access to the study site. Therefore, it was not possible to carry out data selection as planned. Data were collected in a *convenient* manner, with support from data enumerators at RSSA. Due to the limited number of DR-TB patients treated with BDQ at each site, a small sample population of patients who received BDQ during the study period were finally selected. A total of 105 patients met the selection criteria (**Figure 1**). The baseline characteristics of the study subjects are presented in **Table 1**.

A total of 405 ECG reports from 105 subjects were analysed. During the six months of BDQ treatment, neither arrhythmia nor any other cardiac event occurred. The values of ΔQTcF tend to increase (Table 2), and its maximum values were observed after three months of the treatment (M3). The QT interval prolongation >500 ms during the treatment led to the interruption of BDQ treatment in 16 of the 105 subjects.

In this study, the prolongation of the QT interval was the common cause of the temporary



*The reason for switching the regiment in 11 patients:

- Failure of treatment (positive culture after BDQ treatment): 1 patient
- Adverse drug reaction:
  a. Persistence QT prolongation: 7 patients
  b. Inverted T wave with normal QT interval: 1 patient
  c. Renal impairment: 1 patient
  d. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome): 1 patient

Figure 1. Enrollment flowchart.

Table 1. Baseline characteristics of the subjects.

Variables	n (%)
Gender	
- Male	61 (58.1)
- Female	44 (41.9)
Age in years, median (minimum – maximum)	41 (18 – 68)
Comorbidity, n (%)	38 (36.2)
- Heart disease	1
- Kidney disease	3
- Subclinical hyperthyroidism	1
- Subclinical hypothyroidism	2
- DM	31
- Hypertension	2
- Asthma	1
Category of DR-TB, n (%)	
- MDR	79 (75.2)
- Pre-XDR	18 (17.1)
- XDR	8 (7.6)
Number of QT prolonging drugs, n (%)	
- One drug (BDQ)	2 (1.9)
- Two drugs	37 (35.2)
Lfx/BDQ	20
Mfx/BDQ	3
BDQ/Cfz	14

- Three drugs	65 (61.9)
Lfx/BDQ/Cfz	51
Mfx/BDQ/Cfz	14
- Four drugs	1 (1,0)
Lfx/BDQ/Cfz/Dlm	
Completing BDQ treatment (80 doses)	
- Yes	53 (50.5)
- No	52 (49.5)
QTcF baseline in ms, mean (sd)	414.52 (33.74)
Serum kalium baseline in mEq/L*, mean (sd)	4.02 (0.64)

DM: Diabetes mellitus; DR-TB: Drug Resistant Tuberculosis; MDR: Multi-Drug resistant, XDR: Extensively Drug Resistant; BDQ: bedaquiline; Lfx: levofloxacin; Mfx: moxifloxacin; Cfz: clofazimine; Dlm: delamanid; QTcF: QT corrected using Fridericia formula; sd: standard deviation. *was obtained from 96 subjects.

Table 2. QTcF interval profile during BDQ treatment.

Time of monitoring	ΔQTcF* ms Mean (sd)	p value (95%CI)	Temporary discontinuation of BDQ treatment** n/N (%)	Clinically significant QTcF prolongation n (%)
D2	3.55 (37.60)	0.671[W]	**1**/36 (2.8)	4/36 (11.1)
W1	19.76 (39.69)	0.002 (7.83 – 31.68)	**1**/45 (2.2)	6/45 (13.3)
W2	11.70 (41.67)	0.073 (-1.13 – 24.53)	**2**/43 (4.6)	5/43 (11.6)
M1	27.19 (45.65)	<0.001 (15.50 – 38.88)	**3**/61 (4.9)	10/61 (16.4)
M2	23.71 (37.51)	<0.001 (13.94 – 33.49)	**2**/59 (3.4)	10/59 (16.9)
M3	34.06 (52.92)	<0.001 (19.33 – 48.79)	**7**/52 (13.5)	13 /52 (25.0)
M4	22.52 (47.34)	0.003 (8.29 – 36.74)	-	8/45 (17.8)
M5	21.23 (33.26)	0.002 (8.58 – 33.8)	-	5/29 (17.2)
M6	23.97 (52.82)	0.011 (5.83 – 42.11)	-	8/35 (22.9)
Total			16/105 (15.2)	39/105 (37.1)

D: day 2; W: week; M: month; ΔQTcF: the difference of QTcF after treatment compared with baseline; sd: standard deviation; CI: confidence interval.
* the difference of QTcF after treatment with the baseline
**Discontinuation related to interval QT prolongation, if QTcF >500 ms[9,10]

discontinuation of BDQ treatment (95.8%). The prolongation of QT the interval was persistent and led to the permanent discontinuation of treatment in seven subjects (6.7%). However, most subjects with a regimen containing BDQ are still on treatment (70.4%). In total, there were seven deaths during the study period.

DISCUSSION

In this study, 53 of the 105 subjects had completed BDQ treatment for six months (80 doses). However, only three subjects (2.9%) had complete ECG data for each monitoring time. Even in developed countries such as the United States, monitoring during BDQ treatment is a challenge. In California, only three of 37 patients (8%) had complete ECG data at each point of monitoring.[12]

Recently, some studies have reported on the safety aspects of BDQ under programmatic conditions. These studies are from various countries, including Salhotra et al.[13] in India (2020), Gao et al.[14] in China (2021), Katrak et al.[12] (2021) in the United States, and Brust et al.[15] and Isralls et al.[16] (2021) in South Africa. The baseline characteristics of the subjects of this

study are similar to that of the participants of the aforementioned studies where BDQ was also used together with other QT-prolonging drugs in the DR-TB treatment regimen and the lengths of the BDQ treatment varied between subjects.

During the treatment with BDQ, clinically significant QTcF prolongation was observed in 37.1% of the subjects. Prolongation of QT and subsequent discontinuation of treatment temporarily and permanently by the clinician is in 15.2% and 6.7% subjects, respectively. Salhotra et al. reported a lower proportion of clinically significant QTcF prolongation (16.3%) compared to this study. Temporary discontinuation of BDQ treatment due to QT prolongation in the studies of Salhotra et al.[13], Gao et al.[14], Guglielmetti et al.[17] and Katrak et al.[12] amounted to 2.9%, 4.2%, 0.77% and 11%, respectively. Here, the variability effect of BDQ on subjects' QT interval from study to study is influenced by the subjects' baseline characteristics, with various risk factors. In this study, 61.9% of the subjects were on three QT-prolonging drugs (including BDQ), and 35.2% of the subjects had comorbidities related to QT interval prolongation, such as diabetes, hypertension, heart disease, kidney disease and hypothyroidism. These factors could have contributed to more cases of clinical significance in terms of QTcF prolongation as well as discontinuation of treatment.

According to ICH E14, the risk of TdP is associated not only with the absolute value of the QTc interval (QTcF > 500 ms) but also with ΔQTcF > 60 ms.[8,9] The incidence of ventricular arrhythmia increases by 5 to 7% for every 10 ms increase in QTc value.[18] The criteria for the discontinuation of treatment due to the prolongation of the QT interval may vary, depending on the level of risk and tolerance of the patient population, which is specific to the indication of the treatment.[8] According to WHO and the Indonesian technical guidelines,[10,19] ΔQTcF > 60 ms is an indicator of the need to perform ECG more often and manage other risk factors.[11,20] In this study, 38 subjects (36.2%) were detected with QTc > 60 ms. There were no reports of arrhythmia or other cardiovascular events in this group. A total of 24 of the 38 subjects (63.2%) continued the treatment; 17 of them completed the BDQ treatment. Additionally, 11 of them were also detected to have a QTc value > 500 ms; therefore, BDQ treatment in these subjects was temporarily discontinued. Finally, two subjects dropped out, and treatment in one subject was changed, as they experienced a failure of the BDQ treatment.

During BDQ treatment, seven subjects (6.7%) died (**appendix 1)**. The cause of death in one subject was not related to BDQ (sepsis and respiration failure). For the remaining (6/7; 85.7%), the cause of death could not be assessed, as they died at home, as reported by their families. It is difficult to establish the causal relationship of death with the prolongation of the QTc interval without recording the ECG at the time of the incident and evaluating complete the data before death. However, death in MDR-TB patients may occur due to various causes, including the progression of the TB itself, severity of comorbidities, and disease complications.[21] The use of cardiac holter monitoring could be an option for recording ECG in real time, although it will be limited by the cost.[22]

This study contributes to the literature by reporting the cardiac safety of BDQ in a systematic and complete manner. The QT interval profile was analysed over time during treatment in order to obtain a complete picture of the cardiac safety of BDQ. Most ECG machines can automatically calculate QTc intervals. Although it may seem practical, this automatic calculation can be inadequate due to inconsistencies in terms of the correction formula and algorithm used between ECG machine manufacturers. In addition, the ECG machine is not able to identify T and U waves when the two waves overlap. The U wave appears in hypokalemic conditions, which often occurs in DR-TB patients. Therefore, it is very important to identify these waves manually in order to calculate the QT interval correctly.[23]

This study has a few limitations. There were no assessments of the effect of genetic factors associated with QT prolongation, QT interval diurnal variation and the effect of the number of risk factors in each subject on QT-interval prolongation. In addition, the power of the study is diminished by the fact

that the number of subjects in each group at each monitoring was less than the targeted minimum sample size. Further cohort studies are required to evaluate the cumulative effect of QT prolongation due to the long elimination half-life of BDQ. Patients should be followed up with after the end of their treatment. This study could not assess this, as there was no ECG record after BDQ use (after six months). Furthermore, BDQ concentration was not measured.

CONCLUSION

Maximum QT prolongations were observed mostly after three months of BDQ therapy. Therefore, more intensive cardiac monitoring is recommended during this period and afterwards.

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Appendix 1. Clinical Data of Subjects Who Died during DR-TB Treatment with Regiment Containing Bedaquiline

Subject code	Sex/age (in year)	Weight (kg)	Comor-bidity	DR-TB cate-gory	DR-TB regiment	Clinical information	Period of death	Cause of death	QT interval during therapy	Supporting data
05	Male/59	59	DM on insulin	Pre-XDR	Lfx/Bdq/ Cfz/H/Z/E/ B6	Discontinued of BDQ in M4 due to decreasing liver function (SGOT/SGPT 775/337)	M5	Unknown	QTcF (ms): M2: 454,57 M3: 446,29 M4: 470,91 ΔQTcF (ms): M2: -29,98 M3: -38,56 M4: -13,94	Serum kalium (mEq/L): M2: 3,2 M3: 3,6 eGFR: M3: 83 ml/min
09	Female/36	56	DM on insulin	XDR	Lfx/Bdq/ Lnz/Cs/ Eto/H/Z/E/ B6	Had received full dose (80 doses)	M7	Respira-tory failure and sepsis	QTcF (ms): W1: 431,27 W2: 422,81 M1: 464,16 M3: 447,68 M5: 466,64 M6: 421,47 ΔQTcF (ms): W1: -39,64 W2: -48,10 M1: -6,75 M3: -23,23 M5: -4,27 M6: - 49,44	Serum kalium (mEq/L): - M1: 4,0 - M3: 4,0 - M5: 3,9 - M6: 3,5 eGFR: 119 ml/ min
23	Female/25	42	-	MDR	Lfx/Bdq/ Lnz/Cfz/ Cs/B6	On day 5, Lnz was switch to E due to anemia. However, BDQ was continued. Treatment duration: 25 days	D25	Unknown	On D2: QTcF:434,24 ms ΔQTcF: 50,2 ms No subsequent ECG data.	On day 5, the Hb subject was 6,6 mg/dl
25	Male/28	48	-	Pre-XDR	Bdq/Lnz/ Cfz/Eto/E/ B6	Total treatment duration: 15 weeks	M4	Unknown	QTcF (ms): - M1: 403,11 - M2: 428,34 ΔQTcF (ms): - M1: 0,00 - M2: 25,23 No subsequent ECG data.	Serum kalium: - M1: 3,5 - M2: 3,4 eGFR: M2: 81,8 ml/ min

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Subject code	Sex/age (in year)	Weight (kg)	Comor-bidity	DR-TB cate-gory	DR-TB regiment	Clinical information	Period of death	Cause of death	QT interval during therapy	Supporting data
27	Male/67	52	-	MDR	Lfx/Bdq/ Cfz/Eto/H/ Z/E	Discontinuation for 1 week on day 4 of therapy due to prolongation of the QT interval. The BDQ then was continued, Cfz was replaced with Cs. On M2, subject experiencing hypokalemia, but the QT interval is not prolonged. At that time, the hypokalemia was corrected.	2 weeks after the last visit for monitoring on M2.	Unknown	On M2: QTcF: 446 ms ∆QTcF: 28,26 No subsequent ECG data.	Serum Kalium (mEq/L): M2: 2,74 eGFR: M2:66 ml/min
83	Female/22	30	-	MDR	Lfx/Bdq/ Cfz/Cs/ Dlm	Discontinuation for 1 week on M1 and M4 due to QT interval prolongation and extreme tachycardia (130 beats per minute). On M5, BDQ was discontinued.	M7	Unknown	QTcF (ms): - W2: 395,42 - M1: 505,36 - M2: 436,76 - M4: 400,36 ∆QTcF (ms): - W2: 19,93 - M1: 61,27 - M2: 29,89 - M4:24,87 No subsequent ECG data.	Serum kalium (mEq/L): - M1: 4,4 - M2: 5,2 - M4: 4,3 eGFR: M6: 98 ml/min
93	Female/33	33	-	MDR	Lfx/Bdq/ Cfz/Cs/ Eto	Patients with a history of hydro-pneumothorax prior treatment. On M2, the subject was experiencing an asymtomatic prolongation of the QT interval (QTcB 582 ms) and T inversion in V2 – V5. BDQ treatment was discontinued, but the patient did not come for control a week after the discontinuation.	M3	Unknown	On M2: QTcF: 436,76 ms ∆QTcF: 83,98 ms No subsequent ECG data.	(-)

D: day 2; W: week; M: month; DM: Diabetes mellitus; DR-TB: Drug Resistant Tuberculosis; MDR: Multi-Drug resistant, XDR: Extensively Drug Resistant; BDQ: Bedaquiline; B6: Pyridoxine; Lfx: levofloxacin; Mfx: moxifloxacin; Cfz: clofazimine; Cs: cycloserine; Dlm: delamanid; Eto: Ethionamide; E: Ethambutol; H: Isoniazid; Z: Pyrazinamide; QTcB: interval QT correction using Bazett's formula; QTcF: interval QT correction using Fridericia's formula; ∆QTcF: the difference of QTcF after treatment compared with baseline; ms: milli second; ml/min: millilitre/minute; eGFR: estimation of Glomerular Filtration Rate; mEQ: milli equivalent.