ORIGINAL ARTICLE

Bedaquiline Correlation to QT Interval Prolongation in DR-TB Patients

Vandu Primadana[1*], Indra Yovi[1], Dyah Siswanti Estiningsih[2]
[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Riau/Arifin Achmad General Hospital, Pekanbaru, Indonesia.
[2]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Riau/Arifin Achmad General Hospital, Pekanbaru, Indonesia.

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ABSTRACT

Introduction: The regimen of drug-resistant tuberculosis (DR-TB) is Bedaquiline. One of the adverse events is QT interval prolongation, which can increase the risk of Torsade de Pointes (TdP) and lead to death. DR-TB patient screening before starting the treatment and monitoring QT interval during the treatment should be performed. This study aimed to determine Bedaquiline correlation to QT interval prolongation in DR-TB patients.
Methods: This was a retrospective study using an observational design by viewing medical records of DR-TB patients who underwent treatment from January 2019 to March 2022.
Results: This study involved 46 DR-TB patients with an average age of 41.4 years old, and 58.7% were males with a regimen of Bedaquiline. The comparison of Baseline QT intervals before and after one month of therapy showed QT interval prolongation (457.1 ± 18.2 ms and 443.8 ± 10.2 ms; $p < 0.001$). The comparison of QT intervals before the therapy and six months after the therapy showed prolongation QT intervals (443.8 ± 10.2 ms and 458.4 ± 23.7 ms; $p < 0.001$). QT intervals after one month of therapy compared to six months after the therapy showed insignificant slight prolongation (457.1 ± 18.2 ms and 458.4 ± 23.7 ms; $p = 0.587$).
Conclusion: QT interval prolongation occurred in DR-TB patients who received treatment using Bedaquiline regimen. It was seen significantly between baseline QT interval and after receiving the therapy for one month and six months.

INTRODUCTION

Bedaquiline is a drug approved for use as a treatment for drug-resistant tuberculosis (DR-TB). In 2012, Food and Drug Administration (FDA) released information about the good potency of Bedaquiline and its safety profile.[1–3] Previous studies that compared DR-TB regimens with and without Bedaquiline revealed the fastest conversion of culture result in a regimen with Bedaquiline and an increased recovery rate. At the same time, a significant difference in side effects was not found in both group.[4–6] Bedaquiline is the main drug in the DR-TB regimen, with the addition of four other drugs based on the patient's sensitivity.[7,8]

One of the side effects of Bedaquiline on the heart is the increasing QT interval prolongation incidence that can be seen on an electrocardiogram (ECG). QT intervals refer to ventricular systole cardiac electricity and combine measurement of heart depolarization and repolarization. The ventricle cardiac potential action phase described by ECG as the QT interval is measured from the beginning of the QRS complex to the end of the T wave when it returns

*Corresponding author: vandu.speed@gmail.com

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to the isoelectric line. The normal value for QT interval in males ranges from 350-450 millisecond (ms) and in females ranges between 360-460 ms, while the normal value for QT corrected (QTc) in males ranges from 350-450 ms and in females from 360-460 ms. Prolonging QT intervals of more than 500 ms will increase the risk by two to three times for Torsade de Pointes (TdP). This polymorphic interference of cardiac rhythm can be fatal for patients that can cause cardiac arrest.[9,10]

Bedaquiline will be bonded with the main energy source enzyme of *Mycobacterium tuberculosis* (MTB), thus, it has a bactericide effect. Action mechanisms against the target reduce cross-potential resistance to anti-tuberculosis drugs (ATD). Commonly Bedaquiline is well tolerated, with only a few cases where the treatment should be stopped due to bad tolerance and safety issue.[9,11,12] Pontali, *et al*. performed Bedaquiline safety aspect analysis towards cardiac based on 23 studies about Bedaquiline with 1,266 patients analyzed. Bedaquiline was stopped in 44 patients (3.5%) due to side effects. Only 8 from 1,266 (0.6%) patients experienced QT interval prolongation and stopped consuming Bedaquiline. Two of them restarted the treatment after the resolution of an acute episode.[9]

A study by Brust, *et al*. about cardiac safety in 195 DR-TB patients using Bedaquiline-based treatment revealed that the mean QT interval prolongation between baseline to six months of treatment was 22.7 ms. Four patients experienced QT interval prolongation of more than 500 ms, and 19 patients experienced prolongation of more than 60 ms. This study also revealed that age correlated with QT interval prolongation, therefore, conscientious observation is needed in elderly patients.[13] Bedaquiline has high efficacy in DR-TB treatment but also has QT interval prolongation side effects, thus, serial ECG observation is needed. This side effect became a consideration for us to undergo a study to analyze whether there is a correlation between Bedaquiline treatment with QT interval prolongation in DR-TB patients at our center. This study aimed to determine Bedaquiline correlation to QT interval prolongation in DR-TB patients.

METHODS

This was a retrospective study using an observational design performed in April 2022 to see the variance of QT intervals in DR-TB patients treated with a regimen of Bedaquiline for zero, one, and six months at Arifin Achmad General Hospital, Pekanbaru, Riau. The consecutive technique was used as a sampling method. The samples were collected from January 2019 until March 2022. 46 DR-TB patients who received Bedaquiline regimen at Arifin Achmad General Hospital and fully equipped medical records, including the patient's profile, drugs used, laboratory results, and ECG examination, were included in this study. Patients with a history of QT interval prolongation, congestive heart failure, atrial fibrillation or acute coronary syndrome, under 18 years old, and had incomplete medical records were excluded. The data were analyzed using a T-test to compare two mean values from two different groups. p-value < 0.05 was considered statistically significant. This retrospective study was approved by the Ethical Review Board for Medicine and Health Research, Faculty of Medicine, Universitas Riau, with signed ethical approval number B/036/UN19.5.1.1.8/UEPKK/2022.

RESULTS

The total samples were 65 DR-TB patients treated with Bedaquiline in the short treatment regimen, including the longer treatment regimen, but only 46 patients met the inclusion criteria. The patient characteristics of this study can be seen in Table 1.

The patient characteristics of this study were males (58.7%) compared to females (41.3%) with a mean age of 41.4 ± 13.2 years old. The electrolyte level in all patients was within normal (natrium 141.8 ± 3.5 mmol/L and kalium 4.0 ± 0.5 mmol/L). The mean of the patient's body weight was 49.7 ± 8.7 Kilograms. Patients who received BDQ-LFX-CFZ (89.1%) were more than patients who received BDQ-CFZ (10.9%). The renal function of all patients in this study was normal, with a mean serum creatinine of 0.7 ± 0.1 mg/dL and a glomerular filtration rate of 113.6 ± 14.4 ml/min/1.73 m^2.

The mean baseline QT interval in the age group of >45 years old was longer than the group of <45 years old, but the difference was not statistically significant (445.5 ± 11.5 and 442.3 ± 9.1; p = 0.099). The female group had a longer mean baseline QT interval value than the male group, but the difference was also not statistically significant (446.9 ± 10.8 and 441.5 ± 9.3;

Table 1. Patient's characteristics

Subject	N	%	Mean	SD
Sex				
Male	27	58.7		
Female	19	41.3		
Age (years old)			41.4	13.2
<45 years old	26	56.5		
>45 years old	20	43.5		
Natrium			141.8	3.5
Kalium			4.0	0.5
Body weight (Kg)			49.7	8.7
Regimen				
BDQ-LFX-CFZ	41	89.1		
BDQ-CFZ	5	10.9		
Serum creatinin (mg/dL)			0.7	0.1
Glomerular filtration rate			113.6	14.4
Normal	46	100		
Abnormal	0	0		

Table 2. QT interval mean values at baseline, after one month, and six months of therapy

Subject	N	%	Mean	SD
QT interval before the therapy (ms)			443.8	10.2
Prolongation	14	30.4		
No prolongation	32	69.6		
QT interval after one month of therapy (ms)			457.1	18.2
Prolongation	31	67.4		
No prolongation	15	32.6		
QT interval after six months of therapy (ms)			458.4	23.7
Prolongation	31	67.4		
No prolongation	15	32.6		

p = 0.867). Patients with QT interval prolongation had lower serum kalium levels before the treatment than patients with no QT interval prolongation (3.7 ± 0.5 mmol/L and 4.1 ± 0.4 mmol/L), but the difference was not statistically significant (p = 0.205).

This study revealed that patients with baseline QT interval prolongation had lower mean body weight than patients without QT interval prolongation, but it was not statistically significant. In contrast, patients who experienced QT interval prolongation after one and six months of therapy with Bedaquiline had higher mean body weight than patients with no QT interval prolongation, but the difference was insignificant.

Table 2 shows that in the female group, the baseline QT interval was longer than in the male group (446.9 ± 10.8 ms and 441.5 ± 9.3 ms; p = 0.867). After one month and six months of therapy, the female group also showed longer QT interval prolongation than the male group. The mean QT interval prolongation in the female group after one and six months of therapy compared to the baseline was 17.1 ms and 19.7 ms, while in the male group, the mean QT interval prolongation was 10.7 ms and 11.2 ms. These differences were not statistically significant.

In the male group, the mean QT interval after one month of therapy was longer than the baseline. This difference was statistically significant (p = 0.008). This study found prolongations after six months of therapy compared to the baseline with a p-value < 0.001. The prolongation of the mean QT interval after six months of therapy was longer than after one month of therapy, but this difference was not statistically significant (p = 0.365). These results were similar to what we found in the female group. The differences in the mean QT interval prolongation after one month and six months of therapy compared to the baseline were statistically significant (p < 0.001, p = 0.003). The comparison between the mean QT interval after one month and six months of therapy was not statistically significant (p = 0.195).

Table 3. Mean QT interval comparison between baseline, after one month, and six months of therapy based on the group of regimen (N = 46)

Subject	N	%	Mean	SD	P
Baseline					
BDQ-LFX-CFZ	41	89.1	445.1	9.8	0.236
BDQ-CFZ	5	10.9	432.8	5.9	
After one month of therapy					
BDQ-LFX-CFZ	41	89.1	458.4	18.5	0.442
BDQ-CFZ	5	10.9	445.2	10.2	
After six months of therapy					
BDQ-LFX-CFZ	41	89.1	459.7	24.5	0.452
BDQ-CFZ	5	10.9	447.4	13.0	

Table 4. Mean QT interval comparison before, after one month, and six months of therapy with Bedaquiline regimen (N =46)

Subject	Mean	SD	P
QT interval baseline	443.8	10.2	< 0.001
QT interval after one month of therapy	457.1	18.2	
QT interval baseline	443.8	10.2	< 0.001
QT interval after six months of therapy	458.4	23.7	
QT interval after one month of therapy	457.1	18.2	0.587
QT interval after six months of therapy	458.4	23.7	

Table 3 shows that the mean QT interval in patients who received regimen BDQ-LFX-CFZ was longer than in patients who received regimen BDQ-CFZ at baseline, after one month, and six months of therapy. However, these differences were not statistically significant (p>0.05).

Table 4 shows the mean QT interval prolongation with Bedaquiline regimen after one month and six months of therapy compared to the baseline (13.3 ms and 14.6 ms). The mean QT interval after six months of therapy was longer than after one month of therapy, but the difference was not statistically significant (p = 0.587).

RESULTS

31 (67.4%) patients with DR-TB experienced QT interval prolongation after receiving treatment with Bedaquiline regimen. This study revealed QT interval of patients with Bedaquiline regimen after one month and six months of therapy had prolonged than the baseline QT interval with a prolongation of as much as 13.3 ms and 14.6 ms (p < 0.001). These results were similar to a study by Isralls, *et al*., which involved 420 patients who showed that the mean baseline QT interval was 406.4 ms and prolonged to 430.5 ms (IQR= 414.4-445.1) after three months of therapy and 434.0 ms (IQR= 419.0-447.9) after six months of therapy. A study by Katrak, *et al*. aimed to see the QT interval value of patients at baseline after 2 weeks, 4 weeks, 8 weeks, 12 weeks, and 24 weeks of therapy. The QT interval prolongation happened on week 2 and 4, with a peak of prolongation on day 57.[14]

QT interval prolongation occurred due to cellular mechanism IKr component blockage. IKr blockading will cause prolongation of ventricular action potential duration, thus, natrium will enter the cell profusely and decline potassium level. Excess of positive ions causes prolongation of the repolarization phase; thus, the QT interval will be prolonged. M2 level influences QT interval prolongation.[15]

Patients in the age group of >45 years old showed longer QT interval values at baseline, after one month, and six months of therapy than the age group of <45 years old. This is because QT interval biological base will be prolonged due to the difference between potassium flew in cardiac, which is the main determining repolarization phase of the cardiac action potential.[16] This study showed that the QT interval after one month of therapy was longer than after six months of therapy in the age group of >45 years old. This is influenced by Bedaquiline doses given; thereafter, the QT interval value changed. A higher dose was given in the first two weeks of the treatment, which was 400mg once a day, and continued with 200mg three times a day for 22 weeks. This will cause alternating QT intervals

due to Bedaquiline M2 level declining. A higher dose will cause the prolongation of the QT interval to become longer.[17]

This study revealed that patients with prolonged QT intervals had a lower potassium level than patients who did not have QT interval prolongation (3.7 ± 0.5 mmol/L and 4.1 ± 0.4 mmol/L), but it was not statistically significant. Hypokalemia can cause QT interval prolongation; therefore, examining potassium levels is needed to eliminate the risk factor for QT interval prolongation in patients who receive Bedaquiline regimen.[18]

The renal function of the patients in this study was within normal limit. The mean serum creatinine level in this study was 0.7 ± 0.1 mg/dL, with a mean glomerular filtration rate of 113.6 ± 14.4 ml/min/1.73 m^2. Renal malfunction can cause QT interval prolongation and increase mortality. The patient characteristics in this study showed that all serum creatinine levels were normal, thus, it can reduce the bias of this study. This study showed that patients with prolonged QT intervals had a mean body weight of 48.2 kg, while patients with no prolonged QT interval had a mean body weight of 50.4 kg. The difference between this group was not statistically significant. Light body weight can cause QT interval prolongation to occur due to the disturbance of the potassium channel, therefore repolarization phase of cardiac potential action becomes prolonged.[19]

This study found that female has a risk factor to experienced QT interval prolongation compared to male. The female group had longer baseline QT intervals than the male group, but it was not statistically significant (446.9 ± 10.8 ms and 441.5 ± 9.3 ms; p = 0.867). After one month and six months of therapy, the female group's QT interval value was longer than the male group. QT interval value in the female group was prolonged as much as 17.3 ms between baseline and after one month of therapy, which was statistically significant. A prolonged QT interval also occurred after one month and six months of therapy, which was 19.7 ms. This result was statistically significant. QT intervals in the male group after one month of therapy were prolonged as much as 10.7 ms from baseline. This difference was statistically significant. A prolonged QT interval occurred after receiving six months of therapy with a mean prolongation value of 11.2 ms. It was also statistically significant. Comparison between QT intervals after one and six months of therapy in this group showed no significant difference.

Patients with the BDQ-LFX-CFZ regimen showed longer QT intervals than the BDQ-CFZ regimen. The former group experienced QT interval prolongation of as much as 13.3 ms after one month of therapy and 14.6 ms after six months of therapy. The latter group experienced QT interval prolongation of as much as 12.4 ms after one month of therapy and only 2.3 ms after six months of therapy. Other ATDs known to cause QTc prolongations are Fluoroquinolone and Clofazimine. Administration of drugs that have a risk of causing QT interval prolongation simultaneously can increase the risk of prolonged QT intervals.[9] A study by Udwadia, *et al*. showed the result of QT interval prolongation of as much as 49 ms in patients who received Bedaquiline and Clofazimine. Still, none of these patients had symptoms and needed to stop the therapy.[20] Another study by Guglielmetti, *et al*. reported a prolonged QT interval of 36.2 ms in patients who received therapy with Bedaquiline and Clofazimine.[21] This study used Bazett formula to calculate the QTc value.

A prolonged QT interval can cause the left ventricle to be more susceptible to premature electricity impulses. This can trigger polymorph ventricular tachycardia, known as TdP, which often occurs when the heartbeat reaches 160-240 times over a minute. This condition can be asymptomatic, not simultaneously, spontaneously disappear or worsen quickly, and change into ventricular fibrillation that causes sudden death.[22] A study performed by Gao, *et al*. on 1,162 patients who received Bedaquiline concluded that generally, Bedaquiline could be well tolerated with some safety issues in certain populations, therefore it could be used widely and supported the World Health Organization (WHO) recommendation of Bedaquiline usage.[23]

LIMITATION

This study had several limitations. First, this study only involved one center, therefore, the results of this study cannot be generalized to many populations. This makes us recommend other multicenter studies with a bigger sample and a longer study duration. Second, we did not analyze other risk factors like

smoking habits, amount of cigarettes in a year, previous history of QT interval prolongation, and more. Other ATDs known to cause QTc prolongations are Fluoroquinolone and Clofazimine. Administration of these drugs can increase the risk of causing QT interval prolongation.

CONCLUSION

Bedaquiline caused QT interval prolongation. In this study, 13.3 ms QT interval prolongation occurred after receiving therapy for one month, and 4.6 ms prolongation occurred after six months of therapy. This QT interval prolongation was statistically significant.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

Conceiving, designing the study, writing, and acquiring the data: VP. Revising the manuscript: IY and DSE. All authors contributed and approved the final version of the manuscript.

REFERENCES

1. Gotham D, McKenna L, Frick M, *et al*. Public Investments in the Clinical Development of Bedaquiline. *PLoS One* 2020; 15: e0239118-. [PubMed]
2. Mase S, Chorba T, Lobue P, *et al*. Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate (Sirturo) for the Treatment of Multidrug-Resistant Tuberculosis. *MMWR Recommendations and Reports*; 62. [PubMed]
3. Bélard S, Heuvelings CC, Janssen S, *et al*. Bedaquiline for the Treatment of Drug-Resistant Tuberculosis. *Expert Rev Anti Infect Ther* 2015; 13: 535–553. [PubMed]
4. Kwon Y. Clinical Implications of New Drugs and Regimens for the Treatment of Drug-resistant Tuberculosis. *Chonnam Med J* 2017; 53: 103. [PubMed]
5. Pym AS, Diacon AH, Tang SJ, *et al*. Bedaquiline in the Treatment of Multidrug- and Extensively Drug-Resistant Tuberculosis. *Eur Respir J* 2016; 47: 564. [PubMed]
6. Diacon A, Pym A, Grobusch M, *et al*. Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline. *N Engl J Med* 2014; 371: 723–732. [PubMed]
7. Wang MG, Wu SQ, He JQ. Efficacy of Bedaquiline in the Treatment of Drug-Resistant Tuberculosis: A Systematic Review and Meta-Analysis. *BMC Infect Dis* 2021; 21: 970. [PubMed]
8. Field SK. Bedaquiline for the Treatment of Multidrug-Resistant Tuberculosis: Great Promise or Disappointment? *Ther Adv Chronic Dis* 2015; 6: 170–184. [PubMed]
9. Pontali E, Sotgiu G, Tiberi S, *et al*. Cardiac Safety of Bedaquiline: A Systematic and Critical Analysis of the Evidence. *Eur Respir J* 2017; 50: 1701462. [PubMed]
10. Postema P, Wilde A. The Measurement of the QT Interval. *Curr Cardiol Rev*; 10. Epub ahead of print 13 May 2014. [PubMed]
11. Guo H, Courbon GM, Bueler SA, *et al*. Structure of Mycobacterial ATP Synthase Bound to the Tuberculosis Drug Bedaquiline. *Nature* 2021; 589: 143–147. [PubMed]
12. Lakshmanan M, Xavier A. Bedaquiline - The First ATP Synthase Inhibitor against Multi Drug Resistant Tuberculosis. *J Young Pharm*. Epub ahead of print 30 December 2013. [PubMed]
13. Brust J, Gandhi N, Wasserman S, *et al*. Effectiveness and Cardiac Safety of Bedaquiline-Based Therapy for Drug-Resistant Tuberculosis: A Prospective Cohort Study. *Clin Infect Dis*; 73. Epub ahead of print 21 April 2021. [PubMed]
14. Katrak S, Lowenthal P, Shen R, *et al*. Bedaquiline for Multidrug-Resistant Tuberculosis and QTc Prolongation in California. *J Clin Tuberc Other Mycobact Dis* 2021; 23: 100216. [PubMed]
15. Li M, Ramos LG. Drug-Induced QT Prolongation and Torsades de Pointes. *P T* 2017; 42: 473–477. [PubMed]
16. Rautaharju PM, Mason JW, Akiyama T. New Age- and Sex-Specific Criteria for QT Prolongation based on Rate Correction Formulas that Minimize Bias at the Upper Normal Limits. *Int J Cardiol* 2014; 174: 535–540. [PubMed]
17. Cunha JP. Sirturo. *RxList*, https://www.rxlist.com/sirturo-drug.htm (2021). [WebPage]
18. Priest B, Bell I, Garcia M. Role of hERG Potassium Channel Assays in Drug Development. *Channels (Austin)* 2008; 2: 87–93. [PubMed]
19. Kannankeril PJ, Norris KJ, Carter S, *et al*. Factors Affecting the Degree of QT Prolongation with Drug Challenge in a Large Cohort of Normal

Volunteers. *Heart Rhythm* 2011; 8: 1530–1534. [PubMed]
20. Udwadia ZF, Ganatra S, Mullerpattan JB. Compassionate Use of Bedaquiline in Highly Drug-Resistant Tuberculosis Patients in Mumbai, India. *Eur Respir J* 2017; 49: 1601699. [PubMed]
21. Guglielmetti L, Jaspard M, le Dû D, *et al*. Long-Term Outcome and Safety of Prolonged Bedaquiline Treatment for Multidrug-Resistant Tuberculosis. *Eur Respir J* 2017; 49: 1601799. [PubMed]
22. Cohen K, Maartens G. A Safety Evaluation of Bedaquiline for the Treatment of Multi-Drug Resistant Tuberculosis. *Expert Opin Drug Saf* 2019; 18: 875–882. [PubMed]
23. Gao JT, Du J, Wu GH, *et al*. Bedaquiline-Containing Regimens in Patients with Pulmonary Multidrug-Resistant Tuberculosis in China: Focus on the Safety. *Infect Dis Poverty*; 10. Epub ahead of print 1 December 2021. [PubMed]