Bedaquiline Effect Towards QT Interval in Drug Resistant Tuberculosis (DR-TB): A Systematic Review

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ABSTRACT

Objective: Bedaquiline is recommended by World Health Organization (WHO) to treat Drug-Resistant Tuberculosis (DR-TB). Bedaquiline is chosen due to its efficacy and safety in numerous studies. One adverse event that could happen is QT interval prolongation, which increases the risk of Torsade de Pointes (TdP) and leads to death. This study aimed to discuss the knowledge on the effect of bedaquiline on before-after and changes of QT interval.

Materials and Methods: This systematic review based on PRISMA guidelines through PubMed, Cochrane, Science Direct, ProQuest, Google Scholar, and Epistemonikos until April 10, 2023. The keywords used was ("Bedaquiline" AND "QT Interval"). We implemented inclusion and exclusion criteria by PICOS framework then assessed the studies by Joanna Briggs Institute (JBI) critical appraisal checklist tools.

Results: From 1.170 articles, eleven articles met the criteria. In total 2,449 patients assessed in this study. Most of the studies carried out treatment duration of 6 months. There was a change in the mean QT interval between 11ms to 52.5ms in patients using bedaquiline from the beginning to the end of treatment. The mean QT interval after treatment ranges from 409.7ms – 464.5ms.

Conclusion: The use of bedaquiline requires attention to the ECG before and during therapy. Regular monitoring is necessary to prevent QT prolongation.

Keywords: Bedaquiline; Drug-Resistant Tuberculosis; QT Interval (Siriraj Med J 2023; 75: 638-645)

INTRODUCTION

Bedaquiline is an anti-tuberculosis drug that is still recommended by the World Health Organization (WHO) today for Multi Drug-Resistant Tuberculosis (MDR-TB).[1] MDR-TB is a difficult case to treat and the incidence is increasing. Not only that, the genes of resistant TB that can mutate and present various variants of resistant mutations pose a potential ineffectiveness of current drugs in the future.[2] However, Bedaquiline is used because of its good efficacy in treating DR-TB and is better than kanamycin and bedaquiline could reduce the median time to culture conversion.[3,4] Result from clinical trial phase 2 in 2015 showed bedaquiline containing regimen considered well tolerated and led to good outcomes for DR-TB patients.[5] But behind a therapy with its efficacy, certainly has side effects that need to be considered in the provision of therapy. Meta-analysis by Lan *et al* in 2020 revealed the least amount of adverse events leading to long-term drug cessation occurred with bedaquiline (1.7% [0.7 – 4.2]),[6] However

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the QT interval prolongation, skin rash, hyperlactatemia, peripheral neuropathy, electrolyte depletion, and hearing loss are some adverse effects that need to be dealt with.[7,8]

The side effect of QT interval prolongation needs to be a concern for clinicians before giving the drug to patients. Issues arising from QT interval prolongation will progress to Torsade de Pointes (TdP), a heart arrhythmia that could be fatal and cause the patient to pass away. TdP is a distinctive polymorphic ventricular arrhythmia that is linked to delayed ventricular repolarization as shown by a prolonged QT interval on the surface electrocardiogram.[9] A retrospective cohort study by Darmayani *et al* showed 37.1% patients experienced clinically significant QTcF prolongation from 105 observed subjects.[10] Darmayani *et al*'s suggestion for therapy with bedaquiline is that patients require intensive cardiac monitoring during therapy period.[10]

The clinical question that will continue to arise is how much change in QT interval can be considered safe during Bedaquiline therapy? It has not yet been established exactly what is the limit or value that clinicians should be concerned about that can be considered "safe". Some opinions use the limitation that if the QT interval is above 500mm then the patient is stopped on treatment. We argue that this is potentially dangerous. This is due the risk of arrythmic events increases by 5% for every 10ms increase in the QT interval (normal QTc invervals are approximately 450ms for men and 460ms for women.[11] If 500mm is taken as the limit, men have a risk of arrythmia of 25% and 20% in women. Thus, this systematic review aims to discuss the knowledge on the effect of bedaquiline on before-after and changes of QT interval.

MATERIAL AND METHODS

Data sources and search strategy

For reporting in systematic reviews, we used Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and synthesis without meta-analysis. PubMed, Science Direct, Epistemonikos, Cochrane, ProQuest and Google Scholar were all searched for papers. Keywords like "Bedaquiline" AND "QT Interval" were utilized. We incorporate all research: (1) full text, (2) English or Indonesian Language, (3) Display the QT Interval value in numeric form, and (5) last 10 years. The search strategies are described in full in Fig 1. Unpublished data, duplicate research and reviews were disregarded. This systematic review registered at PROSPERO with number: CRD42023393217.

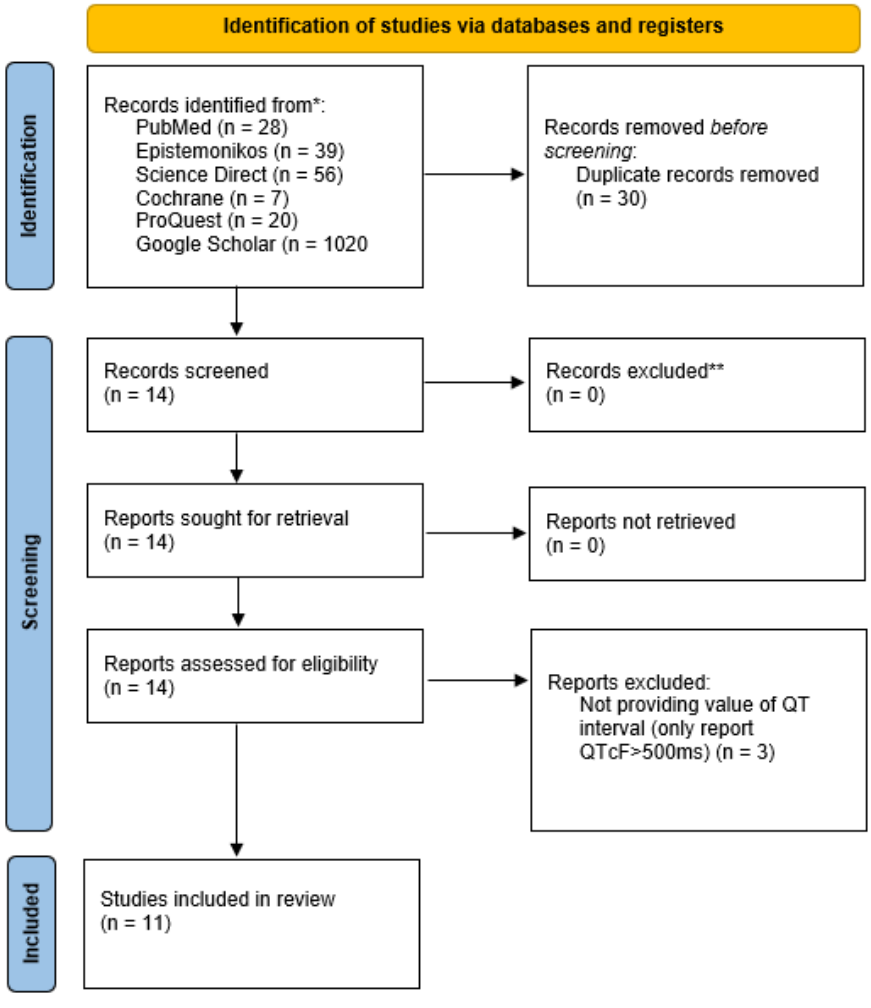

Fig 1. Flow diagram of included studies based on PRISMA flow chart.

Study Selection

Four researchers (AMS, RA, DTB, and RDH) independently evaluated eligibility based on titles and abstracts using the PICO framework (Population = DR-TB; Intervention = Bedaquiline; Compare = Not Specified; Outcome = QT interval). The consensus was reached between investigators to resolve disagreements, or supervisors (IY) were involved when consensus could not be reached.

Data extraction and risk of bias

From each included study, data were taken on: (1) country, (2) study design, (3) population, (4) study size, (5) Intervention, (6) time on treatment, (7) Regimen, (8) QT Interval before and after, and (9) QT interval changes. The primary outcome to determine QT interval changes after take Bedaquiline during obervation.

According to the type of articles received, AMS, RA, DTB and RDH examined full-text articles using the Joanna Briggs Institute Critical Appraisal Tool (jbi.global/critical-appraisal-tools). Consensus was reached to resolve the disagreements, or when consensus could not be established, supervisors (IY) were involved.

RESULTS

Study selection

A total of 1.170 studies were identified from the research database (Fig 1). After removing the duplicate records, 14 records were screened and assessed for eligibility. 11 studies were included in the review, after excluding three studies due to out of scope based on inclusion criteria. There are three articles that provide the effects of Bedaquiline in QT Interval but the form of QT interval they provided in categorical form, either >500ms or <500ms. Therefore we exclude those three articles.

Characteristics of included studies

A total of 1.170 studies were identified from the research database (Fig 1). After removing the duplicate records, and analyze the article based on title, abstract then proceed with full-text, we include 11 studies with 2,449 patients included. The studies we included have various types of study designs such as cohort and clinical trials originating from various countries such as Indonesia, South Africa, America, China, and so on. Patients included in this study were all patients with DR-TB and in some articles were specified according to findings such as Rifampicin-Resistant Tuberculosis (RR-TB), Multi Drug Resistant Tuberculosis (MDR-TB), and others. All studies conducted observations with a duration of six (6) months and there are some notes from several articles as compiled in Table 1.

QT interval changes in the use of bedaquiline

Of the patients included in this study, 405 out of 2,449 patients (16.5%) had QT Interval problems either QT interval ≥500ms or an increase in QT interval from baseline ≥60ms. Table 2 summarizes the results of each study included in this study including the QT interval values before therapy, after therapy, and the change in QT interval from baseline. The mean QT interval value after treatment with Bedaquiline in each article was rated as safe at <450ms. Only one article by Vandu et al.[12], 2022 which in their research found a mean QT interval value of 458.4ms, this according to the degree of QT interval display is considered as QT prolongation degree 1. When looking at the column of QT Interval changes from baseline also in each study can be said to be safe, no study found a mean increase in QT interval from baseline ≥60ms. The highest value of change in QT interval from baseline was 44.5 (23.8 - 63.8) from the study of Lee et al[13], 2021. Although on average both the change in QT interval after Bedaquiline therapy and the change in QT interval were said to be good, there were several cases of QT interval prolongation and some had to be discontinued. This shows that Bedaquiline can indeed increase the QT interval, but the number of cases can be said to be small, so it is necessary to monitor the QT interval of patients who are on therapy using Bedaquiline.

Risk of bias

All authors analyze risk-of-bias for every included study based on study design. The cutoff value we set has a risk of bias if it is less than 65%. The mean score of all articles was 89.9% with a lowest score of 84%. Fig 2 displays the JBI score of each article that has been analyzed.

DISCUSSION

Summary and interpretation of findings

This systematic review seeks to analyze the impact of Bedaquiline on QT Interval prolongation in patients with DR-TB. Of the various studies that have been included, the average QT Interval value after six months of observation with Bedaquiline is below 450ms, only two studies report the average post-treatment QT interval is above 450ms, namely Vandu et al., 2022 ranging from 458.4 (SD, 23.7) and Lee et al., 2021 with a median value of 462 (IQR, 443.3 - 492.0). Based on the degree of the average value of the two studies, it is categorized as QT

TABLE 1. Characteristics of the included studies.

Authors	Country	Design	Population	Study size	Intervention	Time on Treatment	Notes
Vandu, *et al.*[12], 2022	Indonesia	Retrospective Cohort	DR-TB	46	BDQ Regiment	6 Months	
Darmayani, *et al.*[10], 2022	Indonesia	Retrospective Cohort	DR-TB	105	BDQ Regiment	6 Months	52 Patients were not completed the BDQ's treatment
Dooley, *et al.*[16], 2021	South Africa and Peru	RCT	RR-TB/MDR-TB	50	BDQ Regiment (400mg for 14 days + 200mg thrice-weekly) BDQ+DLM Regimen	6.5 Months	Clofazimine was not allowes Moxifloxacin switched to levofloxacin
Katrak, *et al.*[17], 2021	America Cohort	Prospective	MDR-TB	37	BDQ Regiment	6 Months	
Isralls, *et al.*[18], 2021	South Africa Cohort	Retrospective	DR-TB	420	BDQ Regiment	6 Months	
Gao, *et al.*[19], 2021	China	Prospective Cohort	MDR-TB/XDR -TB	1162	BDQ Regiment	6 Months	
Brust, *et al.*[20], 2021	South Africa	Prospective Cohort	RR-TB/XDR-TB	195	BDQ Regiment	6 Months	
Lee, *et al.*[13], 2020	South Korea	Retrospective Cohort	MDR-TB	74	BDQ+DLM Regiment	6 Months	
Ndjeka, *et al.*[21], 2022	South Africa	Retrospective Cohort	XDR-TB	200	BDQ Regiment	6 Months	
Ferlazzo, *et al.*[22], 2018	Armenia, India, and South Africa	Retrospective Cohort	DR-TB	28	BDQ Regiment	6 Months	
Diacon, *et al.*[23], 2014	Brazil, India, Latvia, Peru, the Philippines, Russia, South Africa, and Thailand	RCT	MDR-TB	132	BDQ Regiment	6 Months	66 Patients are placebo

TABLE 2. Result of selected studies.

Authors	Regimen	n	QT Interval (Before), ms	QT Interval (After), ms	QT Interval Changes, ms	Notes
Vandu, *et al*.[12], 2022	BDQ Regiment	46	443.8 (SD, 10.2)	458.4 (SD,23.7)	NA	
Darmayani, *et al*.[10], 2022	BDQ Regiment	53	414.52 (SD, 33.74)	NA	23.97 (SD, 52.82)	1. 7 Patients had persistent QT Prolongation 2. 39 patients had clinically significant QTcF prolongation
Dooley, *et al*.[16], 2021	BDQ Regiment	26	397.4 (389.3 – 405.6)	409 (402.5 – 416.8)	12.3 (7.8 – 16.7)	1. Grade I QTC Prolongation: 9 (32.1%) 2. Grade 2 QTc Prolongation: 1 (3.6%)
	BDQ+DLM Regiment	24	391.7 (383.2 – 400.2)	412.4 (405 – 419.9)	20.7 (16.1 - 25.3)	1. Grade I QTC Prolongation: 10 (37%) 2. Grade 2 QTc Prolongation: 2 (7.4%)
Katrak, *et al*.[17], 2021	BDQ Regiment	37	Med, 428 (IQR, 414 – 458)	Med, 388 (IQR,376 – 400)	Med, 23 (IQR,12 - 41)	1.7 Patients had QTc Prolongation ≥500ms. 2. 3/7 had an increase of QTc interval from pre-drug baseline >60ms
Isralls, *et al*.[18], 2021	BDQ Regiment	420	Med, 406.4 (IQR, 389.1 – 421.3)	Med, 434.0 (IQR, 419 – 447.9)	Med, 29.5 (IQR, 9.6 – 47.2)	1. 2 Patients (11%) had QTcF >500ms 2. during 6 months, 18 patients (4.3%) experience QTc F >500ms 3. During 6 months, 110 patients (26.2%) had change of >60ms from base line
Gao, *et al*.[19], 2021	BDQ Regiment	1162	Med, 413 (IQR, 398 – 429)	NA	Med, 16 (IQR, -3 – 35)	32 patients experienced QTcF ≥500ms and 123 (15.7%) experienced QTcF ≥60ms from baseline 4 (2%) Patients

TABLE 2. Result of selected studies. (Continue)

Authors	Regimen	n	QT Interval (Before), ms	QT Interval (After), ms	QT Interval Changes, ms	Notes
Brust, *et al*.[20], 2021	BDQ Regiment	195	404.6 (SD, 22.2)	427.6 (SD,22.1)	23.7 (SD, 22.7)	experienced QTcF >500ms and 8 (4.4%) experience QTcF >60ms from baseline.
Lee, *et al*.[13], 2020	BDQ+DLM Regiment	74	420.8 (SD,24.7)	462 (SD,443.3 – 492.0)	44.5 (23.8 – 63.8)	23 (31.1%) patient had significant QT Prolongation and 1 (1.4%) patient discontinued due to QTcF Prolongation
Ndjeka, *et al*.[21], 2022	BDQ Regiment	200	Med, 403 (IQR, 389 – 422)	NA	Med, 11 (IQR, -6 – 27)	1 (6.3%) stopped because QTcF Prolongation. 5 Patients has QTcF >500ms
Ferlazzo, *et al*.[22], 2018	BDQ Regiment	28	Med, 401 (IQR,381 – 432)	Med, 434 (IQR, 408 – 446)	Med, 16 (IQR, -13 – 31)	No patients had QTcF >500ms.
Diacon, *et al*.[23], 2014	BDQ Regiment	66	NA	NA	15.4	

Abbreviations: DR-TB: Drug-Resistance Tuberculosis, MDR-TB: Multi Drug Resistance Tuberculosis, RR-TB: Rifampicin Resistance Tuberculosis, XDR-TB: Extensively drug-resistant Tuberculosis, BDQ: Bedaquiline, DLM: Delamanid, Med: Median, IQR: Interquartile Range, SD: Standard Deviation, NA: Not Available, QTcF : QT Interval Friderica Formula

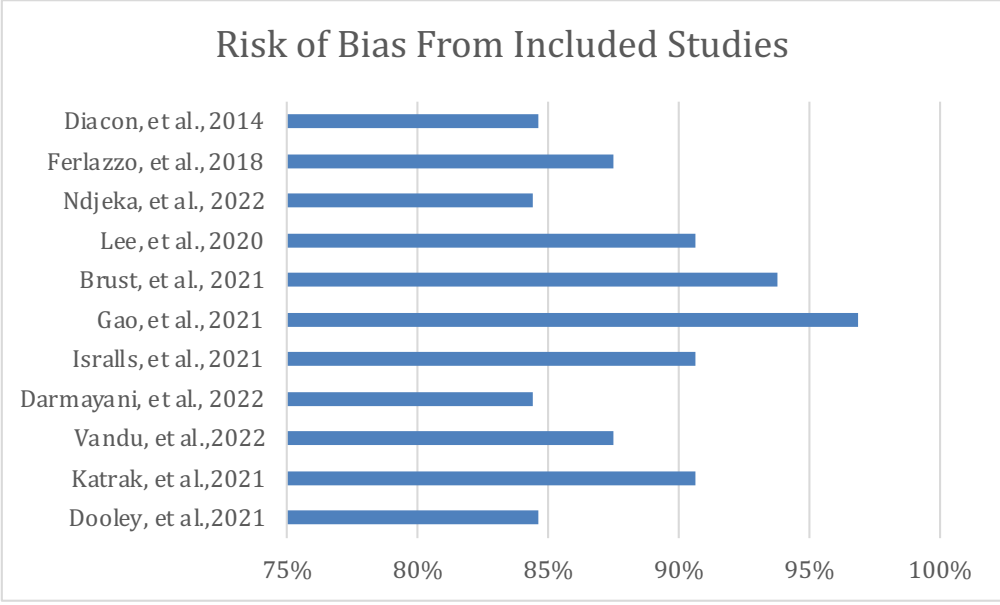

Fig 2. JBI scores of articles included in the study

interval Prolongation grade 1. Based on the change in QT Interval from the baseline, all studies assessed the average and there was no average value above 60ms. However, 405 out of 2,449 patients (16.5%) included in this study had QT interval problems ≥500ms or an increase in QT interval from baseline ≥60ms and some of them had to be discontinued.

As a result of this systematic review, it can be interpreted that the use of Bedaquiline may affect the QT Interval in its users, although few of these events have occurred or been reported. However, the use of Bedaquiline should still be cautioned in patients who have cardiovascular system problems, especially arrhythmias. The small number of cases does not mean that no patient will experience it, so clinician care in treating DR-TB patients is needed to ensure patient safety during therapy. Routine evaluation of the patient's ECG can be a good solution, especially in patients who are suspected of potentially facing adverse effects on the QT interval.

Bedaquiline mechanism on prolonging QT interval

A diarylquinoline called bedaquiline is an excellent treatment for DR-TB. This medication works by specifically inhibiting the mycobacterial ATP synthase enzyme.[14] The heart's hERG potassium channel can be blocked by bedaquiline, which can also influence the incidence of QT interval prolongation.[15] According to recent research, the QT interval is also accompanied with lower serum potassium levels and higher serum sodium levels, which may indicate a connection between the cardiac hERG channel and sodium currents and QT interval lengthening.[15]

Limitation, strength and future research direction

The limitation of this systematic review is that we did an analysis without using any statistics (without meta-analysis) so that a stratification or overall conclusion of the combined research was not obtained. Strength of this study. We summarize the characteristics of this systematic review of the use of Bedaquiline in DR-TB patients for changes in the current QT interval, which can be said to be safe and only a few cases have reported significant problems with the QT interval of its users. So with this systematic review providing evidence of the safety of using Bedaquiline in DR-TB while clinically careful in the condition before the patient received treatment. For future research, it is hoped that it will continue to report if QT interval prolongation occurs when using Bedaquiline and it is expected to be able to carry out a meta-analysis to determine the impact of using Bedaquiline on the QT interval in a combined manner from all existing data.

CONCLUSION

Of all the patients included, 16.5% had problems with the QT interval when using Bedaquiline and some of them had to stop treatment. The use of Bedaquiline is safe for the QT interval but requires the clinician's attention to the patient before giving the treatment with ECG both before and during therapy. Regular monitoring is important to prevent before QT prolongation occurs so that DR-TB treatment can be safer for patients.

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