

QTc Interval Prolongation in Drug Resistant-Tuberculosis Patients Treated with Shorter Treatment Regimen

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Abstract

Background: Shorter Treatment Regimen (STR) is a combination of treatments with a shortened period from 20-24 months to 9-11 months. Shortened treatment requires a higher dose of drug to kill resistant bacteria. Corrected QT (QTc) interval prolongation is one of the severe side effects of treatment.

Objective: This study aimed to find the factors of QTc prolongation in Drug Resistant-Tuberculosis (DR-TB) patients treated with STR during an intensive phase.

Method: An analytical retrospective study was conducted at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. DR-TB patients on the STR regimen were collected based on medical records between September 2017 to August 2018. QTc interval was calculated by Fredericia formula. The relationship between QTc interval at baseline and occurrence of QTc prolongation was analyzed using Chi-Square of fisher's exact test.

Results: Among 108 patients on the STR regimen, there were 20 (28%) patients experienced moderate QTc prolongation (471-500 ms), and 31 (28%) patients had severe QTc prolongation (>500 ms) during four months observation period in STR treatment. The prolonged QTc interval was significantly related to QTc interval at baseline ($p = 0.001$). The QTc interval at baseline correlated significantly with the start time of QTc prolongation ($p < 0.001$). Risk factors of age, gender, comorbid, hypertension, and potassium level at baseline had a significant negative correlation to QTc prolongation.

Conclusion: The prolonged QTc interval was significantly related to QTc interval at baseline. The QTc interval at baseline correlates significantly with the start time of QTc prolongation.

Keyword: Prolonged QTc, Drug Resistant-Tuberculosis, Shorter Treatment Regimen.

Introduction

Drug Resistant-Tuberculosis (DR-TB) is known for long-duration treatment (20-24 months) and unsatisfactory outcomes. Five hundred fifty-eight thousand new cases of DR-TB emerge each year globally, with success rate only 55%⁽¹⁾. In May 2016, World Health Organization (WHO) recommended Shorter DR-TB Regimen (9-11 months) with a success rate of 84% (95CLs:79%-87%)⁽²⁾. Indonesia start adopting and implementing a shorter DR-TB treatment regimen

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(STR) in September 2017. The Indonesia National TB Program is expecting STR can increase enrollment and success rate of treatment, also giving better outcomes rather than long-duration regimen⁽³⁾.

The STR contains new drugs such as a high dose of Moxifloxacin⁽³⁾. Moxifloxacin becomes an essential drug in the treatment of resistant tuberculosis⁽⁴⁾ that causes high bactericidal activity⁽⁵⁾. Nevertheless, these drugs have the ability to delay cardiac repolarization, represent as corrected QT (QTc) interval prolongation on electrocardiogram (ECG)⁽⁶⁾. QTc interval prolongation can disrupt normal cardiac rhythms and lead to fatal arrhythmias such as torsades de pointes⁽⁷⁾ and lead to sudden cardiac death⁽⁸⁾. Thus, TB program recommends monitoring QTc interval to ensure patient safety and optimum patient outcome⁽³⁾.

The risk of drug-induced QT interval prolongation appears to be frequently overlooked in clinical practice⁽⁸⁾. A literature review of 249 patients with TdP associated with non-cardiac QTc-prolonging drugs reported that, apart from the drugs, 71% had at least two other risk factors⁽⁹⁾. Clinically significant QTcF changes (QTcF > 500 ms or an increase 60 ms) were observed in 10/60 patients (17%, 95%CI; 8.0–30.7) without clinical events⁽¹⁰⁾.

However, there is not enough information regarding the relationship between QTc interval baseline, the occurrence of QTc prolongation among DR-TB patients on STR regimen, the dosage of moxifloxacin with QTc prolongation, and outcome treatment. This study aimed to find the factors of QTc prolongation in DR-TB patients treated with STR during the intensive phase.

Method

A descriptive retrospective study was conducted in 123 DR-TB patients treated with STR from September 2017 to August 2018 at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Only 108 patients were eligible for this study. DR-TB was confirmed by rapid molecular test XpertMTB/RIF and Drugs Sensitivity Test (DST). This study reviewed the medical records of patients with STR during the intensive phase.

STR is a 9-month regimen consisting of kanamycin, ethionamide, moxifloxacin, clofazimine, ethambutol, and high dose isoniazid⁽³⁾. The intensive phase lasts a minimum of four months and could be extended up to 6 months because of delayed sputum smear conversion⁽¹¹⁾.

This study obtained data on demographics, comorbidities, potassium (K⁺) baseline, baseline QTc interval, serial QTc interval, and the onset of QTc prolongation. Patient with missing serial ECG, incomplete medical record, and less than six-month treatment were excluded from this study.

Patient routinely has a 12-lead ECG before starting the treatment and each month when begin taking medication. QT interval defines as the time from the beginning of ventricular depolarization to completion of repolarization⁽⁷⁾. Measurement of the QT should be based on leads that normally show the earliest QRS onset and the latest end of the T wave (T-wave offset), which are II and V5. The end of the QT interval is the point at which the T wave reaches the iso-electric line⁽¹²⁾.

Baseline QTc was evaluated though first ECG recording before taking STR regimen therapy. QTc interval was measured from the onset of Q wave of QRS complex to the end of the T wave⁽¹³⁾. Frederica formula ($QTc_{Fri} = QT/RR^{1/3}$) was employed to count QT corection⁽¹⁴⁾.

QTc >500 ms is considered as severe prolongation; QTc 471-500 ms is considered as moderate prolongation that requires further evaluation⁽¹⁵⁾. QTc prolongation was classified according to the Common terminology criteria for adverse events (CTCAE) guidelines version 4.03 (grade 0, QTc < 450; grade 1, QTc 450–479 ms; grade 2, QTc 480–499 ms; grade 3, QTc > 500 ms; grade 4, QTc >500 ms with life-threatening signs or symptoms; grade 5, death)⁽¹⁶⁾.

Patient data were collected via Microsoft Excel and analyzed using IBM SPSS statistic 20.0 (IBM Corp., Armonk, NY, USA). A Multivariate logistic regression model was used to determine a risk factor relating to baseline QTc. The relationship between baseline QTc interval and occurrence of QTc prolongation was analyzed using Chi-Square of fisher's exact test. P-values < 0.05 were considered statistically significant.

Results

Of 123 patients with STR, only 108 patient were eligible for this study that consisted of 63 (58.3%) males and 45 (41.7%) females. In this study, patients were divided into two groups, normal QTc and prolonged QTc groups. There were 57 (53%) patients with normal QTc (<470msc) and 51 (47%) patients with prolonged QTc (>470msc). Thirty (28%) patients had severe

QTc prolongation (QTc > 500 ms), and 21(19%) had moderate QTc prolongation (QTc between 470-500 ms).

The demographic data from this study were noted in Table 1. The mean age patient was 46.4 ± 12.1 . There were 42 (38.9%) patients with diabetes mellitus and 8 patients with hypertension (7.4%). The mean of potassium at baseline was 4.08 ± 0.6 . Based on multiple regression model, there was no significant correlation between age, gender, diabetes mellitus, potassium at baseline, and smoking ($p > 0.05$).

Baseline QTc was divided into four groups (Table 2). There were 10 patients with baseline QTc with >470msc, 15 patients with QTc 451-470, 73 patients with QTc 400-450, and 10 patients with QTc < 400 ms. The results of chi-square of fisher exact showed that baseline QTc had a significant correlation with QTc interval prolongation after taking STR ($p = 0.001$).

This study found that baseline QTc had a significant correlation with the onset of QTc ($p < 0.001$). From 10 patients, 9 (90%) patients had QTc prolongation at first month after taking STR drugs and one patient (10%) in the second month. All patients developed into QTc prolongation as seen at Table 3. From baseline QTc 451-470, 2 (13.3%) patients had QTc prolongation at first month, and 3 (20%) patients had QTc prolongation at second month, and 6 (40%) patients did not develop into QTc prolongation. Forty-six patients with baseline QTc 400 – 450 ms did not have prolonged QTc during the intensive phase (63%), and 7 (70%) patients from baseline QTc < 400msc did not have prolonged QTc.

Of 109 patients with moxifloxacin, six (10.5%) patients with normal QTc had 400 mg oral moxifloxacin, 29 (50.9%) had 600 mg oral moxifloxacin, and 22 (38.6%) had 800 mg oral moxifloxacin. There were fifteen (71.4%) patients with moderate prolong QTc (471-500) had 600 mg oral moxifloxacin, 18 (58.1%) patients with severe prolong QTc > 500 ms had 600 mg. Almost all patients took 600 mg oral moxifloxacin (Table 4). There was no significant difference in the dosage of moxifloxacin with QTc interval prolongation.

There was a significant correlation between outcome therapy with QTc prolongation ($p < 0.001$; table 5). A favorable outcome was cured, while an adverse was defined as death. There were 22 (47.8%) patients on treatment had severe QTc prolongation (>500ms), 8 (44.4%) death patients had severe QTc prolongation and they were more likely died because of sudden death.

Compared with moderate QTc (471-500msc), 6 (13%) patients on treatment STR and 6 (28.6%) died.

Discussion

This study found that 47% patients with STR treatment developed into QTc prolongation. Cellular mechanism of QTc prolongation involves inhibition of rapid component of the delayed rectifier potassium current (IKr). Locking IKr leads to prolongation of the ventricular action potential duration, leading to an excess sodium influx or a decreased potassium efflux⁽¹⁷⁾. This excess of positively interaction with the ion channels is responsible for myocardial contractility that leads to an extended repolarization phase⁽¹⁸⁾, resulting in a prolonged QT interval and causing arrhythmias such as Torsades de Pointes⁽¹⁷⁾.

Table 1 showed that age, gender, diabetes mellitus, hypertension, smoking, and potassium at baseline had negative correlations with QTc prolongation. Therefore, the incidence of QTc prolongation might have been caused by the use of QT drugs. In this study, moxifloxacin was the strongest predictor of drug-induced QTc prolongation. Moxifloxacin inhibition of hERG/IKr occurred at concentrations higher than those observed clinically during treatment⁽¹⁹⁾.

A recent study demonstrated that the risk of cardiac arrest in hospitalized patients with several underlying diseases was increased two-times with the use of non-antiarrhythmic QT-prolonging drugs. The risk of cardiac arrest is higher if receiving more than one daily dose if treated with more than one QT-prolonging drug, and with drugs that interfere with the metabolism or elimination of the QT-prolonging agent⁽²⁰⁾. The individual variability in drug sensitivity and the variable influence of factors that affect QTc prolongation on each patient's drug exposure (e.g., dose, drug metabolism, and route of administration) might reduce the predictive accuracy of study⁽²¹⁾.

Moxifloxacin 400 mg is known to cause a mean increase in the QTc interval of between 10 and 14 ms in 2–4 hours after a single oral dose. In addition, a supratherapeutic dose of moxifloxacin (800 mg) results in a nearly two-times increase in the QTc interval from baseline compared with the 400-mg dose⁽²²⁾. Unfortunately, this study did not mention 600 mg dose.

Baseline QTc shown in Table 2 indicated that patients with longer baseline QTc significantly would develop

into prolonged QTc. Increased 10 ms from baseline on QTc interval results in 6% increase for the risk of a cardiac event. The risk of TdP also increases when the QTc interval lengthens more than 60 ms compared with the baseline value⁽¹⁹⁾ Therefore, physicians should anticipate this possible increase in QTc intervals and perform ECGs before treatment to identify baseline QTc which may be the result of drug-induced Long QT Syndrome⁽¹⁶⁾.

Treated patient with QTc Baseline > 470msc more likely developed QTc prolongation at first month of administered drugs (Table.3). Drug-induced QTc prolongation can occur at different times while the patient is receiving offending oral agent, as it usually corresponds with the expected time of the medication's peak concentration⁽¹⁷⁾. An increase in plasma moxifloxacin concentration is associated with QTc prolongation⁽²³⁾.

The regulatory of QTc study is identified by the EMA, the US FDA, and the International Conference on Harmonisation (ICH E14) of Technical Requirements for Registration of Pharmaceuticals for Human Use as a positive control in thorough QTc studies⁽²⁴⁾. The FDA further concludes that the risk of arrhythmias appears to increase with the extent of QT/QTc prolongation⁽⁶⁾.

Moxifloxacin, a new generation of fluoroquinolone, has been shown to have better activity against mycobacterium tuberculosis than floxacilin⁽²⁵⁾. Moxifloxacin is an 8-methoxy quinolone antimicrobial drug, which is often used as a positive control in thorough QT (TQT) studies⁽²⁶⁾. Moxifloxacin is a reversible blocker of the rapid component of the delayed rectifier, potassium current of the cardiac IKr potassium channel and causes a mean increase of the QTc interval of 10–14 ms between 2 and 4 hours after a single oral dose of 400 mg⁽²⁷⁾. Moxifloxacin binds to and inhibits the human ether-a-go-go-related gene (hERG) IKr α subunit and thereby prolongs the cardiac repolarization interval. Patch-clamp studies indicate that moxifloxacin can bind with high affinity to the open IKr and block the conductance⁽²⁸⁾.

The direct inhibition of hERG channel is the best-characterized mechanism by which drugs can inhibit cardiac repolarization⁽²⁸⁾. However, other inhibitory mechanisms, such as the IKr, interfere with hERG-protein intracellular trafficking or promoting the degradation of this protein and action on the autonomic

nervous system or the sinoatrial node⁽¹⁹⁾. Drugs block the delayed rectifier potassium channel, which is coded by human ether-a-go-go-related gene (hERG). The distinct molecular structure of the hERG channel makes it more susceptible to medications. IKr currently plays an important role in phase-3 of ventricular action potential (ventricular repolarization)⁽²⁹⁾.

The pharmacokinetics of this moxifloxacin make it suitable to be an anti-TB drug. The oral dosing achieves a peak serum concentration of >4 mg·L⁻¹. Maximum concentration in serum and the area under the concentration (AUC)–time curve from 0 to 24 h has been reported as 3.4 mg·L⁻¹ and 30.2 mg·h·L⁻¹. Respectively, high values were found on day 10. Peak concentrations of the drug are achieved rapidly, with all patients achieving this within two hours. The half-life is reported as ~12 h⁽⁵⁾.

Different absorption characteristics per dose were assumed, so a different parameter was estimated by dose in the absorption model. The absorption rate of 400 mg moxifloxacin was faster than that of 800 mg⁽³⁰⁾. Clinical vigilance and constant monitoring are important for all potential toxicities associated with high-dose moxifloxacin are imperative, especially for cardiotoxicity, which needs periodic electrocardiographic assessment throughout the treatment for all patients, with possibly 24 hours. Holter monitoring for selected cases is needed to comprehensively detect potentially dangerous arrhythmia⁽³¹⁾.

Yew and chang (2018) reported that 1-10% of patients with shorter MDR-TB treatment regimen containing high-dose moxifloxacin had QTc prolongation⁽³¹⁾. From systematic review, it summarises 15 years of research demonstrate that moxifloxacin is well absorbed orally and highly active against *M. tuberculosis*⁽⁵⁾.

QT prolongation has been described previously as a risk factor for all-cause mortality and more specifically, cardiovascular mortality⁽³²⁾. On a study of 172 patients, the most common cause for QTc prolongation was QTc interval-prolonging medication and was deemed most responsible in 48% of patients, with 25% of these patients taking \geq two offending drugs⁽²⁹⁾. A study conducted by Haugaa et al. showed the death diagnosis itself does not directly reflect arrhythmic death. It is important to analyze clinical courses in the group of patients with a QTc interval of 500 ms or higher to fill the gap between the death diagnosis and the real number of patients with

arrhythmia-related death⁽³³⁾. Thomas et al. found that acutely ill patients with prolonged QT intervals had nearly a three-time odds ratio for an adverse event in ICU⁽³⁴⁾. Patients with clinically significant QT prolongation should undergo continuous ECG monitoring⁽³⁵⁾.

In our study, 22 patients who were still undergoing STR and moxifloxacin treatment had severe QTc

prolongation. A cohort study in South Korea in 373 patients receiving anti-tuberculosis drugs found 16% incidence of ECG abnormalities, and 0.8% presented with cardiac adverse events. The study concluded that, despite QTc prolongation, clinically meaningful events appeared to be minimal⁽¹⁸⁾. Survival curves of those with/without prolonged QTc separated well within 50 days of hospital admission⁽⁷⁾.

Table 1. Demographics data

Characteristics	Total n (%)	Normal QTc n (%)	Prolong QTc n (%)	p
Age*	46.4±12.1	45.5±13.8	47.5±9.7	0.162
Gender				
Male	63(58.3%)	39(68.4%)	24(47.1%)	0.278
Female	45(41.7%)	18(31.6%)	27(52.9%)	
Diabetes Melitus				
Yes	42(38.9%)	20(35.1%)	22(43.1%)	0.836
No	66(61.1%)	37(64.9%)	29(56.9%)	
Hypertension				
Yes	8(7.4%)	4(7%)	4(7.8%)	0.946
No	100(92.6%)	53(93%)	47(92.2%)	
Smoking				
Yes	41(38%)	25(43.9%)	16(31.4%)	0.679
No	67(62%)	32(56.1%)	35(68.6%)	
Kalium Baseline*	4.08±0.6	4,12±0.6	4.03±0.6	0.200

*Mean±SD

Table 2. Correlation between baseline QTc and QTc interval prolongation

Baseline	Severe QTc >500	Moderate QTc 471-500	Normal QTc <470	p
QTc > 470 (n=10)	6(60.0)	3(30.0)	1(10.0)	0.001*
Tc 451-470 (n=15)	4(26.7)	7(46.7)	4(26.7)	
QTc 400-450 (n=73)	18(24.7)	10(13.7)	45(61.6)	
QTc < 400 (n=10)	3(30.0)	0(0.0)	7(70.0)	

*p < 0.05

Table 3. Correlation between baseline QTc with prolong QTc onset in DR-TB Patients

Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	No prolong QT	p
QTc >470 (n=10)	9(90.0)	1(10.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0.000**
QTc 451-470 (n=15)	2(13.3)	3(20.0)	1(6.7)	2(13.3%)	1(6.7)	6(40.0)	
Baseline QTc 400-450 (n=73)	6(8.2)	13(17.8)	5(6.8)	2(2.7%)	1(1.4)	46(63.0)	
Baseline QTc <400 (n=10)	1(10.0)	1(10.0)	0(0.0)	1(10.0)	0(0.0)	7(70.0)	

**p < 0.001

Table 4. Correlation between QTc prolongation with moxifloxacin dose

	Dosage moxifloxacin			p
	400 mg	600 mg	800 mg	
Normal QTc <470	6 (10.5)	29 (50.9)	22 (38.6)	0.565
Moderate prolong QTc 471-500	2 (9.5)	15 (71.4)	4 (19.0)	
Severe prolong QTc >500	3 (9.7)	18 (58.1)	10 (32.3)	

Table 5. Correlation between outcome therapy with QTc Prolongation

	Severe QTc >500	Moderate QTc 471-500	Normal QTc <470	p
Cured (n=9)	1 (11.1)	4 (44.4)	4 (44.4)	0.000**
Death (n=18)	8 (44.4)	6 (28.6)	4 (12.9)	
Dropout (n=20)	3 (15.0)	0 (0.0)	17 (29.8)	
Lost to Follow Up (n=16)	1 (6.2)	5 (31.2)	10 (62.5)	
On Treatment (n=46)	22 (47.8)	6 (13.0)	18 (39.1)	

**p < 0.001

Conclusions

Short term regimen DR-TB has the potential to prolong QT interval. The prolonged QTc interval is significantly related to the QTc interval at baseline. The QTc interval at baseline correlates significantly with the start time of QTc prolongation. This study presents different approaches that balance the need for life-saving regimens and medications, raise awareness of cardiac events, propose a strategy for ECG monitoring in STR DR-TB.

Conflict of Interest: The authors declare that they have no conflict of interest. The authors have written the ICMJE Authorship form.

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Data Availability: The data set used and/or analyzed during the current study are available from corresponding author on reasonable request.

Ethics Statement: All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (1491/KEPK/IX/2019).

List of Abbreviations: DR-TB = Drug Resistant-Tuberculosis, STR = Shorter, MFX = Moxifloxacin, ECG = Electrocardiography, WHO = World Health Organization, DST = Drug Sensitivity Test.

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