Correlation of Moxifloxacin Concentration, C-Reactive Protein, and Inflammatory Cytokines on QTc Interval in Rifampicin-Resistant Tuberculosis Patients Treated with Shorter Regimens

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ABSTRACT

Background: *Drug-resistant tuberculosis (DR-TB) is a global health concern. QTc prolongation is a serious adverse effect in DR-TB patients receiving a shorter regimen. This study aimed to evaluate the correlation of moxifloxacin concentration, CRP, and inflammatory cytokines with QTc interval in DR-TB patients treated with a shorter regimen.* ***Methods:*** *This study was performed in 2 groups of rifampicin-resistant (RR-TB) patients receiving shorter regimens. Correlation for all variables was analyzed.* ***Results****: CRP, IL-1β, and QTc baseline showed significant differences between 45 RR-TB patients on intensive phase and continuation phase with p-value of <0.001, 0.040, and <0.001, respectively. TNF-α and IL-6 between RR-TB patients on intensive phase and continuation phase showed no significant difference with p=0.530 and 0.477, respectively. CRP, TNF-α, IL-1 β, and IL-6 did not correlate with QTc interval in intensive phase (p=0.226, 0.281, 0.509, and 0.886, respectively), and also in continuation phase (0.805, 0.865, 0.406, 0.586, respectively). At 2 hours after taking the 48th-dose, moxifloxacin concentration did not correlate with QTc interval, both in intensive phase (p=0.576) and in continuation phase (p=0.691). At 1 hour before taking the 72nd-hour dose, moxifloxacin concentration also did not correlate with QTc interval in intensive phase (p=0.531) and continuation phase (p=0.209).* ***Conclusion:*** *Moxifloxacin concentration, CRP, and inflammatory cytokines did not correlate with QTc interval in RR-TB patients treated with shorter regimens. The use of moxifloxacin is safe but should be routinely monitored and considered the presence of other risk factors for QTc prolongation in RR-TB patients who received shorter regimens.*

Keywords: *Drug-resistant Tuberculosis, shorter treatment regimen, QTc interval.*

INTRODUCTION

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* strains resistant to anti-TB drugs is becoming a global health concern with an increasing number of cases. *World Health Organization* (WHO) reported 465,000 cases of Drug-Resistant Tuberculosis (DR-TB) in 2020 with a treatment success rate of 57%. Indonesia currently ranks 5th for countries with high DR-TB cases with a treatment success rate of less than 50%, due to the high mortality rate and loss to follow-up.[1] In 2016, the WHO recommended a standardized shorter regimen off 9-12 months to treat Multidrug-Resistant/Rifampicin-Resistant (MDR/RR-TB) patients with a specific inclusion criteria.[2] Indonesia started to implement the shorter regimen in 2017.[3] However, not all MDR/RR-TB patients were treated with shorter regimens until the end of treatment and 16/224 (7%) of patients switched their regimens from shorter regimen to individual regimens due to the presence of prolonged QT.[4] Another study reported the incidence of increased QTc interval of >30 ms in 21/98 (21.4%) and >60 ms in 10/98 (10.2%) of DR-TB patients who received shorter regimens.[5] Interval QT prolongation is a serious adverse effect and can potentially cause *Torsade de Pointes* (TdP) and sudden cardiac death.[6] Moxifloxacin is one of the components of shorter regimen and is often criticized for its higher risk of QTc interval prolongation and TdP.[4,6] According to the national program, moxifloxacin was given in 400 mg, 600 mg, or 800 mg dosages based on body weight.[3]

Inflammatory activation due to systemic inflammation was indicated as a new potential cause of acquired long QT syndrome via cytokine-mediated changes in cardiomyocyte ion channels.[7] Impaired expression and or function of several cardiac ion channels was affected by systemically or locally released inflammatory cytokines (mainly TNF-α, IL-1, and IL-6), resulting in a decrease of K+ currents and or an increase of ICaL. Cardiac or systemic inflammation promotes QTc-interval prolongation via cytokine-mediated effects, and this may increase sudden cardiac death risk.[8]

C-reactive protein (CRP) is one of the acute phase proteins that increases during systemic inflammation.[9,10] It is also commonly used as a prognostic marker in TB.[11] Elevated CRP serum level is a strong independent predictor of heart disease and cardiovascular disease in asymptomatic individuals.[9,10] Xie et al. (2015) suggested that CRP may directly or indirectly influence QTc interval via influencing the expression of K+ channel interaction protein 2 (KChIP2) and formation of transient outward potassium current (Ito.f) density of cardiomyocytes.[12]

Prolongation of QTc interval is usually asymptomatic and requires routine electrocardiography (ECG) monitoring during treatment using QT-prolonging drug.[2,13] Hence, it is very important to thoroughly assess DR-TB patients before attributing QTc prolongation solely due to anti-TB drugs.[14] Although several studies have reported QT prolongation in DR-TB, the correlation of inflammatory markers and QTc interval is still rarely being studied. In this study, we aimed to evaluate the correlation of moxifloxacin concentration, CRP, and inflammatory cytokines with QTc interval in DR-TB patients treated with shorter regimen.

METHODS

An observational analytic study with consecutive sampling was conducted from September 2019 to February 2020 in Dr. Soetomo Hospital Surabaya, one of East Indonesia TB referral hospitals. Study subjects were RR pulmonary TB patients based on the GeneXpert examinations with age 18 to 65 years old who will start the intensive phase and who are on the continuation phase of shorter treatment regimens. RR-TB patients with baseline QTc >500 ms, potassium <3.5 mmol/L, magnesium <1.7 mmol/L, calcium <8.5 mmol/L, creatinine clearance <30 cc/m, a*spartate aminotransferase* - alanine *aminotransferase* (AST-*ALT) >5x upper limit normal (ULN), body mass index (BMI) <18 kg/m*^{2}, on anti-arrhythmia therapy, anti-depressant therapy, with bradycardia, anti-fungal treatment (azoles), erythromycin therapy, and phenytoin therapy were excluded from this study.

The respondents were given an explanation of the research and publications to be carried out. All respondents information is kept confidential and only used for research purposes. After getting an explanation, the respondent is allowed to refuse the study or resign in the middle of the study. The respondents gave their written consent and permission for publication of the letters and to participate in the research. We confirm that all the research meets the ethical guidelines and in accordance with the Declaration of Helsinki.

Ethics

An informed consent was signed by all participants and the ethics committee of Dr. Soetomo Hospital with ethical clearance number 1444/KEPK/VIII/2019 on August 23rd, 2019.

Operational Definition

Rifampicin-resistant tuberculosis (RR-TB) was defined as the results of *Mycobacterium tuberculosis* detected with rifampicin resistance based on GeneXpert MTB/RIF.[15] RR-TB patients in intensive phase were defined as RR-TB patients who are eligible for shorter regimens and will start intensive phase of treatment. RR-TB patients in continuation phase were defined as RR-TB patients who have completed the intensive phase (4-6 months), i.e. those who have sputum smear conversion after the 4th, 5th, or 6th month. Shorter regimens were as recommended by the WHO in 2016 and the national program in 2019, consisted of 4-6 Km – Mfx – Eto(Pro) – HHigh Dose – Cfz – E – Z / 5 Mfx – Cfz – E – Z for 9-11 months.[2,16] Electrocardiography (ECG) was defined as a 12-lead surface heart recording using an ECG machine. The QT interval is that portion of the ECG that begins at the start of the QRS complex and ends at the termination of the T wave. The QTc referred to the corrected QT interval using the Fredericia formula.[14] The changes of QTc (ΔQTc) referred to the difference between the QT interval at baseline and the QT interval at 2 hours after taking the 48th-hour dose, and 1 hour before taking the 72nd-hour dose.

Concentration of Moxifloxacin

Blood samples were collected and put into heparin tubes at 2 hours after taking the 48th-hour dose and 1 hour before taking the 72nd-hour dose. Blood samples were centrifuged and the plasma was stored in the deep freezer with a temperature of -80^0 C. The moxifloxacin concentration was measured by a validated method using High-Performance Liquid Chromatography (HPLC). The separation of moxifloxacin from the plasma matrix using protein precipitation, followed by measurements using the Waters HPLC Alliance e2695 with a detector of Waters 2998 Photodiode Array (PDA). 240 µL of acetonitrile solution (100%) was added to the 200 µl of plasma sample. The sample was then vortexed for 1 minute and centrifuged at a speed of 10,000 g for 5 minutes. A total of 200 µl of supernatant was put into the vial and injected into the HPLC with an injection volume of 10 µl. Separation using a Sunfire™ C18 column (4.6 x 100 mm, 5 µm; Waters, Ireland). The mobile phase consisted of 0.4% TEA in aquabides with a pH of ±3 and 100% of acetonitrile (75%:25% (v/v)). The flow rate is 1 ml/min and the PDA detector was set at a wavelength of 296 nm. Accuracy for standard concentration curves is between 95.5% to 103.4%, depends on the standard concentration level. The coefficient of variation for intra- and inter-assay was less than 7.2% for the range from 0.204 to 10,200µg / mL. The lowest limit value which can be quantified was 0.204 µg/mL.

Measurement of CRP Levels

Venous blood samples from each subject were collected into heparin tubes. Serum was separated by centrifugation at 3,000 rpm for 5 minutes and stored at 4^0 C for 24 hours for the analysis.[9] CRP levels were determined by an immunoturbidimetric assay using SIEMENS Dimension clinical chemistry system for quantitative determination of CRP in serum and plasma. This instrument automatically calculates and prints the concentration of CRP in [mg/L] mg/dL. Analytical measurement range was 0.5-250.0 mg/L or 0.05-25.00 mg/dL.

Measurement of Inflammatory Cytokines Levels

Samples of venous blood with an amount of 5 cc were taken from each patient and put into EDTA serum tubes. All samples were stored in a deep freezer with a temperature of -80^0 C. After

the samples had sufficient amounts, all samples were put at room temperature for 2 hours or at 4^0 C for a night. The samples were centrifuged for 15 minutes to separate the blood plasma and serum. The cytokines levels were measured using the ELISA method with a kit of Elabsiences.

QTc Interval Measurement

QT interval was measured automatically using ECG machine merc BLT E30 (Guangdong Biolight Meditech, Germany, 2017) at baseline before treatment, 2 hours after taking the 48th-hour dose, and 1 hour before taking the 72nd-hour dose. Heart rate-corrected QT (QTc) interval was calculated using Fredericia formula,[14] manually by cardiologists.

Data Analysis and Ethical Statement

The data obtained in this study were presented as tables and graphics. Data were analyzed using SPSS 21.0 software (IBM Corp., Armonk, NY, USA). P-value <0.05 was considered as significant statistically. This study was conducted in accordance with the Declaration of Helsinki. An informed consent was signed by all participants. This study was approved by the ethics committee of Dr. Soetomo Hospital with ethical clearance number 1444/KEPK/VIII/2019 on August 23rd, 2019.

RESULTS

This study included 29 RR-TB patients on intensive phase and 16 RR-TB patients on continuation phase of shorter regimens. The clinical symptoms found in this study were cough, fever, chest pain, haemoptysis, weight loss, night sweats, dyspnea at rest, and dyspnea during activity. **Table 1** showed that the clinical symptoms of RR-TB patients improved in continuation phase, but there is no significant difference between the reported symptoms in intensive phase and continuation phase. Albumin, CRP, IL-1β, QTc baseline, and QTc at 2 hours after the 48th dose showed significant differences between RR-TB patients on intensive phase and continuation phase with p = 0.002, <0.001, 0.040, <0.001, and 0.026, respectively. While TNF-α, IL-6, moxifloxacin concentration at 2 hours after the 48th dose, moxifloxacin concentration and QTc at 1 hour before 72nd dose between RR-TB patients on intensive phase and continuation phase showed no significant difference with p = 0.530, 0.477, 0.686, 0.610, and 0.325. This was presented in **Table 1**.

Table 2 showed that CRP, TNF-α, IL-1β, and IL-6 did not correlate with QTc interval in intensive phase with p = 0.226, 0.281, 0.509, and 0.886, respectively. CRP, TNF-α, IL-1β, and IL-6 also did not correlate with QTc interval in continuation phase with p = 0.805, 0.865, 0.406, and 0.586, respectively. This result indicated that inflammatory markers could not predict QTc interval in our study.

At 2 hours after the 48th dose, it was known that moxifloxacin concentration did not correlate with QTc interval and ΔQTc, both in intensive phase (p = 0.576 and 0.415) and continuation phase (p = 0.691 and 0.353). At 1 hour before the 72nd- hour dose, moxifloxacin concentration also did not correlate with QTc interval and ΔQTc in intensive phase with p = 0.531 and 0.813, and in continuation phase with p = 0.209 and 0.464, as presented in **Table 3**.

Scatter plot in **Figure 1** showed that the distribution of CRP, TNF-α, IL-1β, and IL-6 did not correlate with QTc interval. Levels of CRP, TNF-α, IL-1β, and IL-6 are overlapping between intensive and continuation phases, while QTc interval showed an increased in continuation phase.

The distribution of moxifloxacin concentration and QTc interval at 2 hours after taking the 48th-hour dose and 1 hour before taking the 72nd-hour dose did not form a specific pattern as presented in **Figure 2**. This scatter plot showed that moxifloxacin concentration did not correlate with QTc interval, as the results of correlation analysis in **Table 3**.

DISCUSSION

Multidrug-Resistant/Rifampicin-Resistant TB (MDR/RR-TB) is an emerging threat to TB control, with clinical presentation of patients with MDR/RR-TB being identical to that of patients with drug-susceptible disease.[17] All patients with RR-TB in this study were symptomatic, most commonly with cough (66.7% in intensive phase and 33.3% in continuation phase), other symptoms including fever, chest pain,

Table 1. Characteristics of Study Subjects

Characteristics	RR-TB on Start of Intensive Phase (N=29)	RR-TB on Start of Continuation Phase (N=16)	P-value
Age (years)*	37 (18-62)	44 (19-56)	0.569
Sex**			0.673
Women	13 (59%)	9 (41%)	
Men	16 (70%)	7 (30%)	
BMI (m/kg^2)*	20.4 (18.03-28.65)	19.06 (18.26-27.68)	0.530
Diabetes mellitus**	14 (73.7%)	5 (26.3%)	0.429
Cough**	28 (66.7%)	14 (33.3%)	0.285
Fever**	12 (75%)	4 (25%)	0.272
Chest pain**	6 (100%)	0 (0%)	0.075
Haemoptysis**	9 (64.3%)	5 (35.7%)	1.000
Weight loss**	14 (60.9%)	9 (39.1%)	0.608
Night sweats**	10 (71.4%)	4 (28.6%)	0.738
Dyspnea at rest**	3 (60%)	2 (40%)	1.000
Dyspnea during activity**	7 (70%)	3 (30%)	1.000
Potassium (mmol/l)***	4.3 ± 0.45	3.96 ± 0.4	0.019
Calcium mg/dl)***	9.03 ±0.46	8.67 ± 0.2	0.001
Albumin***	3.43 ± 0.28	3.65 ± 0.14	0.002
CRP (mg/dl)*	1.5 (0.2-10.9)	0.15 (0.1-0.6)	<0.001
TNF-α (pg/mL)*	6.8 (0.13-36.22)	4.79 (0-43.34)	0.530
IL-1β (pg/mL)*	20.13 (2.23-708.7)	7.42 (0.6-113.47)	0.040
IL-6 (pg/mL)*	43.17 (10.14-1076)	40.61 (4.47-113.99)	0.477
QTc Baseline(ms)***	417.28 ± 31.2	455.94 ± 16.6	<0.001
Moxifloxacin **			0.727
600	17 (60.8%)	11 (39.2%)	
800	12 (70.6%)	5 (29.4%)	
Moxy Conc (48+2) (µg/mL)***	4.3 ± 2.32	4.61 ± 2.54	0.686
QTc 48+2 (ms)***	444.38 ± 31.25	467.94 ± 35.7	0.026
ΔQTc (48+2)-Baseline (ms)*	20 ((-17) – (81))	2.5 ((-44) – (115))	0.036
Moxy Conc (72-1) (µg/mL)*	1.01 (0.01 – 3.27)	0.91 (0.01 – 1.61)	0.610
QTc 72-1 (ms)*	448 (386-518)	447 (428-524)	0.325
ΔQTc (48+2) - (72-1) (ms)*	0 ((-75) – (60))	7.5 ((-77) – (52))	0.122

* Median (min-max) using Mann-Whitney Test; ** Chi-square; ***Mean ± Standard Deviation using T-test; BMI = Body Mass Index.

Table 2. Correlation Analysis at Baseline using Pearson or Spearman-rho Test

Intensive phase	QTc baseline		Continuation phase	QTc baseline	
	R	P		R	P
CRP (mg/dL)	-0.232	0.226	CRP (mg/dL)	0.067	0.805
TNF-α (pg/mL)	0.207	0.281	TNF-α (pg/mL)	0.046	0.865
IL-1β (pg/mL)	0.128	0.509	IL-1β (pg/mL)	-0.223	0.406
IL-6 (pg/mL)	-0.028	0.886	IL-6 (pg/mL)	-0.147	0.586

R: Correlation Coefficient; P: Sig. (2-tailed).

Table 3. Correlation Analysis at 2 Hours after the 48th Dose and at 1 Hour before the 72nd- Hour Dose

			Moxi Conc at 48+2			Moxi Conc at 72-1
Intensive phase	**QTc at 48+2**	**R**	**-0.108**	**QTc at 72-1**	**R**	**0.121**
		P	**0.576**		**P**	**0.531**
	ΔQTc ((48+2) – Baseline))	**R**	**-0.157**	**ΔQTc ((48+2) – (72-1))**	**R**	**-0.046**
		P	**0.415**		**P**	**0.813**
Continuation phase	**QTc at 48+2**	**R**	**0.108**	**QTc at 72-1**	**R**	**-0.332**
		P	**0.691**		**P**	**0.209**
	ΔQTc ((48+2) – Baseline))	**R**	**0.249**	**ΔQTc ((48+2) – (72-1))**	**R**	**-0.197**
		P	**0.353**		**P**	**0.464**

Correlation Analysis using Pearson or Spearman-rho Test; R: Correlation Coefficient; P: Sig. (2-tailed).

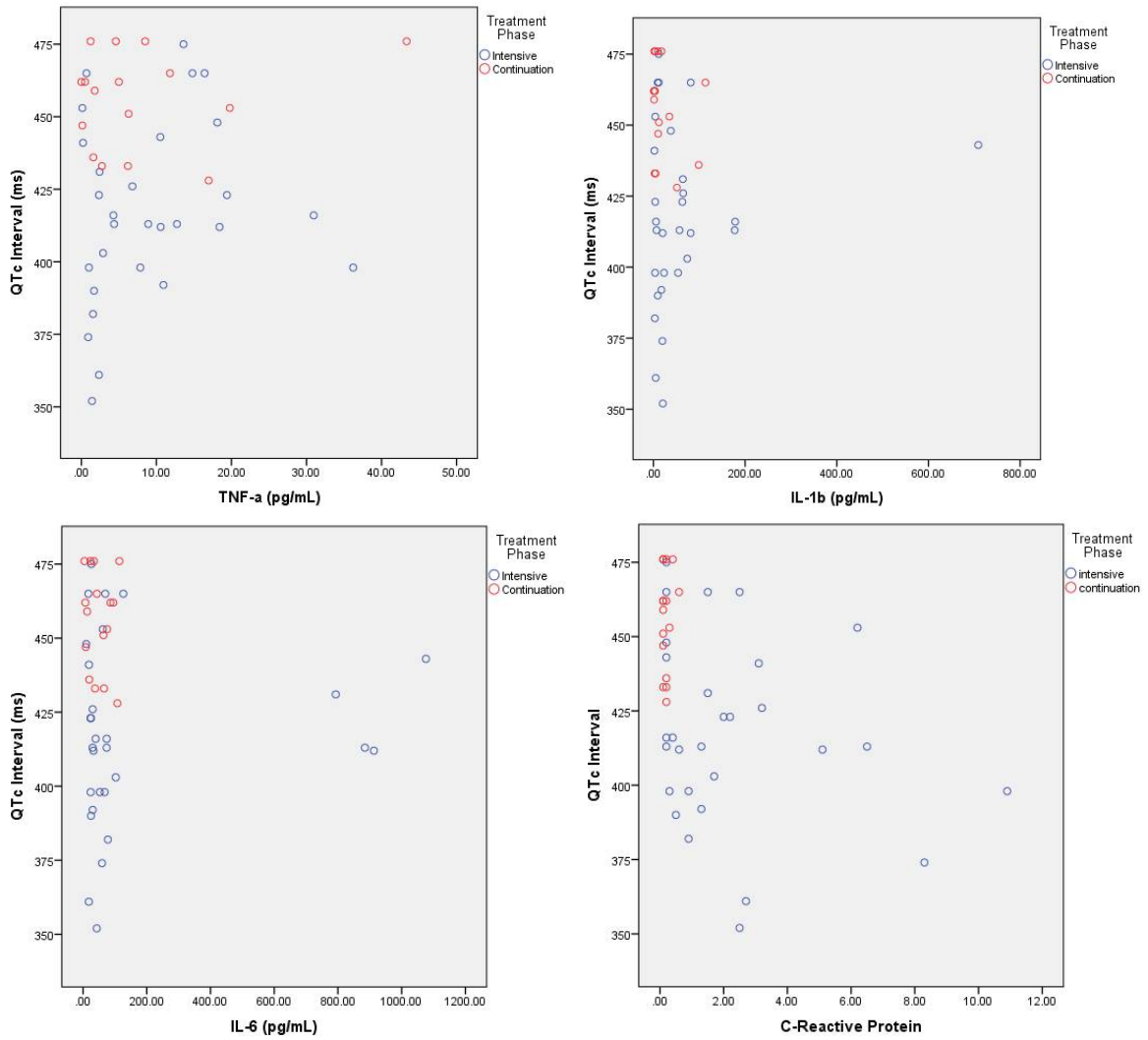

Figure 1. Scatter Plot of Inflammatory Cytokines (TNF-α, IL-1β, and IL-6), C-Reactive Protein, and Baseline of QTc Interval in RR-TB Patients.

haemoptysis, weight loss, night sweats, dyspnea at rest, and dyspnea during activity. A study in 93 MDR-TB patients by Brode et al. (2015) also reported productive cough as the most common symptoms in MDR-TB, followed by weight loss, malaise, fever, haemoptysis, night sweats, and chest pain.[18] The symptoms were more often reported in intensive phase, then improved in continuation phase (**Table 1**), as the intensive phase of RR-TB treatment aimed to significantly decrease the bacillary burden. The improved symptoms may results from the decreased bacillary burden and the decreased inflammation (inflammation caused by *Mycobacterium tuberculosis* infection) after intensive phase of treatment.

Interval QTc prolongation is a serious effect and is often reported in DR-TB patients treated with shorter regimens. Moxifloxacin is considered as a QT-prolonging drug and is often criticized to cause QTc prolongation in DR-TB patients.[1,6] Moreover, QT prolongation related to inflammatory factors also has been widely reported, as has been known that inflammation occurs as a response to injury, lipid peroxidation, and infection, including TB infection.[26]

In this study, RR-TB patients on intensive phase of shorter regimen have a higher level of CRP, TNF-α, IL-1β, and IL-6 levels, compared to those in continuation phase. CRP and IL-1β, and QTc baseline were significantly different between RR-TB patients on intensive phase and continuation phase with p-value of <0.001, 0.040, and <0.001, respectively. While TNF-α and IL-6

between RR-TB patients on intensive phase and continuation phase showed no significant difference with p = 0.530 and 0.477, respectively (**Table 1**). A higher level of inflammatory biomarkers in intensive phase showed that the inflammation due to *Mycobacterium tuberculosis* infection was still high because the patients have just received DR-TB treatment, while patients on continuation phase have been treated for a few months and have experienced sputum conversion which indicated decreased inflammation in lung tissue. Pulmonary TB infection ellicits an inflammatory process in lung tissue, which is correlated with CRP levels changes,[27] and induction of inflammatory cytokines to regulate immune system.[25] This immune process depends on Th1-cell activity, including TNF-α. IL-1β directly kills *Mycobacterium tuberculosis* in macrophages. IL-6 is a requirement in host resistance to infection. IFN-γ , TNF-α , IL-12.[28]

At baseline examination, QTc interval in continuation phase was found higher than intensive phase (**Table 1**), while correlation analysis in **Table 2** showed that CRP, TNF-α, IL-1β, and IL-6 did not correlate with QTc interval in intensive phase and continuation phase. This was different from previous studies that reported a correlation between inflammation marker and QTc prolongation. CRP levels were found higher and correlated with QTc prolongation in hypertensive and rheumatoid arthritis patients.[21-23] Other studies reported increased TNF-α in elderly general population, elevated IL-6 levels in patients who experienced TdP, and higher levels of IL-1β in patients with connective tissue diseases, all being risk factors for long QTc intervals.

The correlation between CRP and cardiovascular risk is through systemic inflammation. Inflammatory cytokines such as TNF-α, IL-6, and IL-1 act directly on cardiomyocyte ion channels expression and function, and may represent a risk factor for QTc prolongation.[7] Another study found that IL-6 negatively affected cardiomyocyte ion channel function and increased risk for QT prolongation, suggesting that patients with high levels of IL-6 should receive routine ECG and counseling if other QTc prolonging risk factors are present. Systemic inflammation promotes QTc-interval prolongation via cytokine-mediated effects. Released inflammatory cytokines are able to directly affect the expression and/or function of several cardiac ion channels, resulting in a decrease of K+ current and/or an increase of calcium current. While in this present study, it was shown that inflammation due to DR-TB infection did not correlate with QTc interval (**Table 2**).

Another factor was considered for acquiring QTc prolongation, and moxifloxacin as a component in the standardized shorter regimen was suspected to induce QTc prolongation. The mechanism of drug-induced QT prolongation is due to blockage of the human ether a-go-go gene (hERG) that is responsible for the inward potassium rectifier (IKr) repolarizing current.[31-33] Our study showed that at 2 hours after the 48th dose, moxifloxacin concentration did not correlate with QTc interval, both in intensive and continuation phases. At 1 hour before the 72nd- hour dose, moxifloxacin also did not affect QTc interval in intensive and continuation phases (**Table 3**). Yoon et al. (2017) also revealed the safe use of moxifloxacin on QTc changes in DR-TB patients. Moxifloxacin at the dosage of 400, 600, or 800 mg does not correlate with the QTc interval.

Moxifloxacin is relatively safe, and the prolongation caused by moxifloxacin is considered minimal or moderate, but should be carefully monitored when other risk factors are present. QT prolongation is usually asymptomatic and requires routine ECG monitoring during QT drug use, to ensure the safe use of moxifloxacin and prevent serious adverse effects which can be life-threatening.

CONCLUSION

Our study found that moxifloxacin concentration, CRP, and inflammatory cytokines did not correlate with QTc interval in DR-TB patients treated with shorter regimens. The use of moxifloxacin is safe but should be routinely monitored and considered the presence of other risk factors for QTc prolongation in DR-TB patients received shorter regimens.

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CONFLICT OF INTERESTS

The authors report no conflicts of interest in this work.

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