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Original Article

Clofazimine and QT prolongation in the treatment of rifampicin-resistant tuberculosis: Findings of aDSM in Taiwan

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KEYWORDS
Clofazimine;
QTcF prolongation;
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Abstract *Background:* Bedaquiline, delamanid and fluoroquinolones are associated with increased QTcF. Whether clofazimine is associated with QTcF prolongation is less clear.
Methods: All patients with rifampicin-resistant TB enrolled between May 2017 and Dec 2019 were included. ECGs were performed at baseline, month 1, month 3 and month 6 for patients treated with conventional regimens, and at additional timepoint for patients treated with

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tachycardia;
Torsades de pointes

bedaquiline, delamanid and short regimen. We estimated the maximum increase of QTcF and constructed cox proportional hazards models to assess factors associated with QTcF≥501ms.
Results: Among 321 patients, 59 (18.4%) patients had QTcF≥501ms during a mean follow-up of 242 days (median 189, range 4—1091). The median maximum increase of QTcF was 43.4 ms (IQR 31.3—65.9) in patients treated with clofazimine. Treatment with clofazimine was significantly associated with QTcF≥501ms as compared to without clofazimine (adjusted hazards ratio (adjHR) 4.35, 95% confidence interval (CI) 2.01—9.44). Among patients not treated with bedaquiline and delamanid, those treated with clofazimine and a fluoroquinolone (adjHR 3.43, 95% CI 1.61—7.34) and those treated with clofazimine and high dose moxifloxacin (adjHR 6.54, 95% CI 2.43—17.60) had a significantly higher risk of QTcF≥501ms as compared to those treated with a fluoroquinolone without other QTcF prolonging agents. Four (1.6%) patients had documented ventricular tachycardia, in which one was Torsade de pointes. One patient was found to have sudden death during hospitalization.
Conclusions: Clofazimine was significantly associated with an increased risk of QTcF prolongation. QTcF≥501ms was potentially associated with fatal event and needed to be managed cautiously.

Introduction

Treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) were difficult. With the introduction of new and repurposed drugs, such as linezolid, clofazimine, bedaquiline, delamanid and pretomanid,[1—5] and shorter regimens,[6,7] improvement of treatment outcomes of MDR/RR-TB has been reported.[8]

The use of new and repurposed drugs was associated with new challenges of adverse drug reactions.[3,4] WHO recommended implementation of active TB drug-safety monitoring and management (aDSM),[9] and monitoring for QT prolongation which should be corrected for heart rate (QTc).[10,11] Studies had reported that bedaquiline and delamanid were well-tolerated.[12—16] In the STREAM stage 1 trial, QTc ≥500 ms (ms) were observed in 11% of participants receiving the Short regimen, which involved the use of high-dose moxifloxacin (MFX) and clofazimine.[6] Fluoroquinolones were associated with QTc prolongation and were on the list of drugs that may cause Torsades de pointes.[17] Some studies reported that clofazimine may cause QTc prolongation, others reported conflicted findings.[18—21] Whether the use of clofazimine is associated with increased risk of clinically significant QTc prolongation is less clear.[22]

In Taiwan, the treatment outcome of MDR/RR-TB has improved substantially since the establishment of Taiwan MDR-TB Consortium (TMTC).[23,24] aDSM has been established in the TMTC in 2017. Adverse drug events have been closely monitored and comprehensive data collected, which provided an opportunity to assess QTc prolongation in the management of MDR/RR-TB.

Methods

The study has been approved by the Taipei Medical University — Joint Institutional Review Board (N201702047).

The structure and operation of the TMTC has been reported previously.[23] More than 90% of patients with MDR/RR-TB in Taiwan have been managed by the TMTC, and the proportion of MDR/RR-TB patients with treatment success has been ≥80% in past 15 years.[23,24]

For the implementation of an advanced package of aDSM,[9] a treatment initiation form was designed to capture baseline information. A treatment review form was designed to monitor symptoms, results of examinations and modification of regimens during treatment. An adverse event report form was designed for reporting serious adverse events, severe adverse events, and adverse events resulting in modification of treatment regimens. A treatment initiation form was filled in at the beginning of treatment and a treatment review form was completed on a monthly basis for every patient. An adverse event report form was submitted within 7 days of a serious adverse event, a severe adverse event, or an adverse event resulting in modification of treatment regimens.

aDSM was implemented in all health care facilities of the TMTC since May 2017. All MDR/RR-TB patients enrolled in the TMTC from May 2017 through December 2019 were included in this study. Treatment was either individualized tailored to results of drug susceptibility testing or standardized using a short MDR-TB regimen. For patients treated with conventional long regimens, ECGs were performed at baseline, month 1, month 3 and month 6. For patients treated with bedaquiline, delamanid or short regimen, ECGs were performed at baseline, every two weeks for 2 months, monthly in month 3 and 4, then every two months till treatment completion. QT interval and RR interval were determined automatically by the ECG machine reading. QT interval was corrected for heart rate by using the Fridericia formula (QTcF).

Serious adverse event was defined as an adverse event leading to death or a life-threatening experience; to hospitalization or prolongation of hospitalization; to persistent or significant disability; or to a congenital anomaly. Severity of adverse event was determined by using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, in which electrocardiogram QT corrected interval prolonged was classified as grade 3 if QTc ≥501ms, and grade 4

if QTc ≥501 ms or >60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia.

Treatment initiation forms, treatment monitoring forms and adverse event report forms were prospectively collected and entered into computer. Data collected in aDSM were used for the study. Collection of these form was discontinued in March 2020 in part due to the influence of the pandemic of COVID-19.

We monitored QTcF during treatment and quantified the change of QTcF as compared with baseline. We estimated the effect on QTcF of levofloxacin, moxifloxacin, clofazimine, high dose moxifloxacin and combined use of these agents by comparing the difference of drugs used at follow-up ECGs and that at baseline. If patients had a baseline ECG performed when the patient was not exposed to potential QT prolonging agent, and had a follow-up ECGs performed when the patient was treated with clofazimine without other QT prolonging agents, the difference of QTcF between that particular follow-up ECG and baseline was applied to estimate the effect of clofazimine. If patients had a baseline ECG performed when the patient was treated with levofloxacin, and had follow-up ECGs performed when the patient was treated with levofloxacin and clofazimine, the difference of QTcF between that particular follow-up ECG and baseline was also applied to estimate the effect of clofazimine. Similar approach was used to estimate the effect of other agent. We quantified the maximum increase of QTcF of exposure to each agent. Because the median maximum increase of QTcF in patients treated with levofloxacin was not significantly different from that in patients treated with normal dose moxifloxacin, we combined them as fluoroquinolone.

We analyzed the frequency of patients with QTcF≥501ms and assessed the association between exposure to each potential QTcF-prolonging agent and QTcF≥501ms by Kaplan—Meier survival curve and the log rank test. Patients were followed up till QTcF≥501ms, death, loss-to-follow-up or treatment completion. We constructed cox proportional hazard models to quantify the hazards of exposure to each QTcF-prolonging agent during treatment, adjusted for age, sex and other covariates.

Because multiple potential QTcF-prolonging agents were commonly used in combination, we analyzed the frequency of patients with QTcF≥501ms in those who were treated with different combination of potential QTcF-prolonging agents. We quantified the influence of clofazimine by comparing patients treated with fluoroquinolone plus clofazimine to those treated with fluoroquinolone without clofazimine. The influence of the combined use of clofazimine and other QT prolonging drugs on QTcF was assessed by comparing those treated with clofazimine and other QT prolonging drugs to those treated with fluoroquinolones alone as reference. We assessed the association between exposure to combined use of QTcF-prolonging agents and QTcF≥501ms by Kaplan—Meier survival curve and the log rank test. We constructed cox proportional hazard models to quantify the hazards of exposure to combined use of QTcF-prolonging agents during treatment, adjusted for age, sex and other covariates. Schoenfield residuals were used to test the assumptions of proportional hazards. Because the number of patients treated with bedaquiline, delamanid, and clarithromycin were relatively small, we repeated the same analysis after excluding patients treated with bedaquiline, delamanid, or clarithromycin.

Because potential QTcF-prolonging agents may be removed or added during MDR/RR-TB treatment due to adverse reactions or drug resistance, we constructed time-dependent cox proportional hazard models in a subset of patients who were not treated with bedaquiline, delamanid, or clarithromycin.

Among patients who had QTcF≥501ms, we tracked the change of regimens and the evolution of QTcF. We assessed outcome of treatment at 30 months after treatment initiation and analyzed factors associated with outcomes of treatment.

Results

Of the 333 patients enrolled in the TMTC between May 2017 and December 2019, 321 (96.4%) patients were included in this analysis; 12 patients were excluded, because 1 patient did not have information on the date of treatment initiation, 1 patient was not treated with second line anti-TB drugs, 4 patients had QTcF≥501ms before treatment initiation, and 7 patients had no ECG after treatment initiation.

Characteristics of the 321 patients were shown in Table 1. They had a mean age of 57 years. 245 (76.3%) were male. 221 (68.9%) had co-morbidities. 38 (11.8%) were treated with high dose moxifloxacin (600 mg or 800 mg), 224 (69.8%) with usual dose moxifloxacin (400 mg), 93 (29.0%) with levofloxacin, 165 (51.4%) with clofazimine, 26 (8.1%) with bedaquiline, 8 (2.5%) with delamanid, and 1 (0.3%) with clarithromycin.

Of the 321 patients, 182 (57%) had ECG examinations before initiation of QTcF-prolonging agents. 52 (28.6%) had QTcF≤400ms, 112 (61.5%) had QTcF between 401 ms and 450 ms, 18 (9.9%) had QTcF between 451 and 500 ms.

The mean number of ECG examinations performed after treatment initiation was 6.4 (median 4, interquartile range (IQR) 3—8); 5.1 (median 4, IQR 3—16) among patients treated with a fluoroquinolone, 8.7 (median 6, IQR 4—12) among patients treated with clofazimine, 14.8 (median 14, IQR 9—21) among patients treated with high dose moxifloxacin, 12.7 (median 12, IQR 6—15) among patients treated with bedaquiline, and 15.5 (median 13.5, IQR9-21) among patients treated with delamanid. During a mean follow-up of 242 days (median 189, IQR 111—345), 59 (18.4%) patients had QTcF≥501ms. The median interval between treatment initiation and occurrence of QTcF≥501ms was 111 days (IQR 68—242). The median maximum increase of QTcF was 27.1 ms (IQR 13.8—42.4) for treatment with fluoroquinolone, 43.4 ms (IQR 31.3—65.9) for clofazimine, 53.2 ms (IQR 36.2—73.2) for combination of clofazimine and a fluoroquinolone, and 41.8 ms (IQR 24.6—110.3) for combination of clofazimine and high dose moxifloxacin (Kruskal—Wallis rank test $p < 0.001$).

In univariable analysis, treatment with clofazimine (hazard ratio (HR) 3.69, 95% confidence interval (CI) 1.92—7.11), high dose moxifloxacin, older age groups, and comorbidities were significantly associated with increased risk of QTcF≥501 ms. In multivariable analysis, treatment with clofazimine (adjusted HR (adjHR) 4.35, 95% CI 2.01—9.44) and older age groups remained significantly

Table 1 Characteristics of patients.

	n	%
Total	321	100
Age (year)		
≤45	84	26.2
46-60	92	28.7
61-75	84	26.2
≥76	61	19.0
Sex		
Female	76	23.7
Male	245	76.3
Type of case		
Pulmonary TB	296	92.2
Extra pulmonary TB	25	7.8
History of TB		
New	255	79.4
Retreatment	66	20.6
TB treatment before current episode		
No	173	53.9
Yes	148	46.1
Smoking		
Never	158	49.2
Ex-smoker	80	24.9
Current	83	25.9
Alcohol intake		
Never	216	67.3
Ex-drinker	60	18.7
Current	45	14.0
Comorbidities		
No	100	31.1
Yes	221	68.9
Cardiovascular	73	22.7
Respiratory	34	10.6
Gastrointestinal/Hepatic	53	16.5
Renal/urinary	32	10.0
Nervous system	19	5.9
Muscularskeletal/connective tissue	16	5.0
Hematopoetic	7	2.2
Diabetes	87	27.1
Cancer	20	6.2
Others	62	19.3
Anti-TB medicines used		
Bedaquiline	26	8.1
Clofazimine	165	51.4
Delamanid	8	2.5
Levofloxacin	93	29.0
Moxifloxacin (400 mg)	224	69.8
Moxifloxacin (600 or 800 mg)	38	11.8
Clarithromycin	1	0.3
Capreomycin	30	9.4
Cycloserine	202	62.9
Kanamycin	256	79.8
Linezolid	77	24.0
Meropenem	12	3.7
Para aminosalicylic acid	25	7.8
Prothionamide	241	75.1
Rifabutine	3	0.9
Terizidone	52	16.2

associated with QTcF≥501ms (Table 2, Fig. 1, Supplement Table 1).

Levofloxacin was not significantly associated with QTcF≥501ms as compared with 400 mg moxifloxacin (Supplement Table 2). We combined usual dose moxifloxacin and levofloxacin as fluoroquinolone for further analysis on the association between combination of potential QT prolonging agents and QTcF≥501ms (Table 3). In multivariable analysis, treatment with clofazimine and a fluoroquinolone (adjHR 3.53, 95% CI 1.66—7.50), treatment with clofazimine and high dose moxifloxacin, and treatment with clofazimine, a fluoroquinolone, and other potential QTcF-prolonging agents were statistically significantly associated with QTcF≥501ms as compared with treatment with a fluoroquinolone without other potential QT prolonging agents. Restricting the analysis to patients not treated with bedaquiline, delamanid, and clarithromycin revealed similar findings (Table 4, Fig. 2).

In time dependent Cox proportional hazards model excluding patients treated with bedaquiline, delamanid, and clarithromycin, treatment with clofazimine and a fluoroquinolone (adjHR 3.51, 95% CI 1.64—7.51) and treatment with clofazimine and high dose moxifloxacin had an increased risk of QTcF≥501ms compared to treatment with a fluoroquinolone without other potential QT prolonging agents (Table 5).

Of the 59 patients who had QTcF≥501ms, 6 patients did not have further ECG examinations. Of the 53 patients with follow-up ECGs after having QTcF≥501ms, 25 (47.2%) had recurrence of QTcF≥501ms. Of the 25 patients with repeat QTcF≥501ms, 23 (92%) were on clofazimine when the first episode of QTcF≥501ms occurred. Of the 23 patients on clofazimine, 7 (30.4%) were continued with clofazimine, 13 (56.5%) had discontinuation of clofazimine, and 3 (13.0%) had dose reduction of clofazimine. Of the 7 patients without discontinuation of clofazimine, 4 had repeat QTcF≥501ms on multiple occasions. Of the 13 patients with discontinuation of clofazimine, 8 had re-introduction of clofazimine in whom 8 (100%) had recurrence of QTcF≥501ms after re-introduction of clofazimine.

Four (1.2% of 321) patients had had documented ventricular tachycardia (VT), in which three were monomorphic VT and one was torsade de pointes (Supplement Fig. 1). The highest QTcF of the four patients before ventricular tachycardia was 519 ms, 522 ms, 561 ms, and 508 ms, respectively. The patient with torsade de pointes was on fluoroquinolone without other potential QTcF prolonging agent when torsade de pointes occurred. Three patients with monomorphic VT were on a fluoroquinolone and clofazimine when VT occurred. The four patients survived the event of VT.

One 90 year-old patient had QTcF≥501ms and was found to have sudden death during admission in a participating hospital. The patient had repeat QTcF≥501ms for 6 months despite multiple withholding and re-introduction of anti-TB drugs. On the 64th day prior to sudden death, his regimen was modified as bedaquiline, clofazimine, linezolid, and terizidone. On the 4th day prior to sudden death, bedaquiline was discontinued due to QTcF≥501ms and vomiting. On the 2nd day prior to sudden death, QTcF was 545 ms and all anti-TB drugs were discontinued.

Table 2 Factors associated with QTcF≥501ms.

	Total	QTcF≥501ms N = (%)	HR[a] (95% CI)	*P* value	Adj HR[a] (95% CI)	*P* value
Age (year)						
≤45	84	7 (8.3%)	1		1	
46-60	92	17 (18.5%)	2.1 (0.87–5.08)	0.10	1.6 (0.62–4.13)	0.33
61-75	84	18 (21.4%)	3.04 (1.27–7.27)	0.01	2.36 (0.92–6.02)	0.07
≥76	61	17 (27.9%)	4.27 (1.77–10.29)	<0.01	3.27 (1.24–8.63)	0.02
Sex						
Female	76	12 (15.8%)	1		1	
Male	245	47 (19.2%)	1.21 (0.64–2.28)	0.56	1.13 (0.54–2.37)	0.75
BMI			0.97 (0.9–1.04)	0.35	0.95 (0.88–1.03)	0.21
Bedaquiline						
No	295	51 (17.3%)	1		1	
Yes	26	8 (30.8%)	1.43 (0.68–3.02)	0.35	1.08 (0.44–2.66)	0.86
Clofazimine						
No	156	11 (7.1%)	1		1	
Yes	165	48 (29.1%)	3.69 (1.92–7.11)	<0.0001	4.35 (2.01–9.44)	<0.01
Delamanid						
No	313	56 (17.9%)	1		1	
Yes	8	3 (37.5%)	1.65 (0.51–5.27)	0.40	0.9 (0.23–3.53)	0.88
Levofloxacin						
No	228	43 (18.9%)	1		1	
Yes	93	16 (17.2%)	0.86 (0.48–1.52)	0.60	0.86 (0.44–1.7)	0.6681
Moxifloxacin						
No	59	9 (15.3%)	1.27 (0.61–2.64)	0.53	2.62 (1.02–6.74)	0.05
400 mg	224	38 (17%)	1		1	
High dose	38	12 (31.6%)	2.1 (1.1–4.03)	0.03	2.03 (0.97–4.24)	0.06
Type of case						
Pulmonary TB	296	53 (17.9%)	1		1	
Extrapulmonary involvement	25	6 (24%)	1.72 (0.74–4.02)	0.21	1.74 (0.72–4.2)	0.22
History of TB						
New	255	45 (17.6%)	1		1	
Retreatment	66	14 (21.2%)	1.03 (0.57–1.89)	0.92	0.91 (0.44–1.87)	0.80
TB treatment before current episode						
No	173	30 (17.3%)	1		1	
Yes	148	29 (19.6%)	1.1 (0.66–1.83)	0.73	1.13 (0.61–2.09)	0.70
Smoking						
Never	158	28 (17.7%)	1		1	
Ex-smoker	80	15 (18.8%)	1.05 (0.56–1.96)	0.89	1.6 (0.69–3.7)	0.27
Current	83	16 (19.3%)	0.95 (0.51–1.76)	0.88	0.96 (0.42–2.2)	0.93
Alcohol intake						
Never	216	38 (17.6%)	1		1	
Ex-drinker	60	8 (13.3%)	0.73 (0.34–1.57)	0.42	0.4 (0.15–1.06)	0.07
Current	45	13 (28.9%)	1.37 (0.73–2.58)	0.33	1.31 (0.57–3.02)	0.52
Comorbidity						
No	100	11 (11%)	1		1	
Yes	221	48 (21.7%)	2.09 (1.08–4.02)	0.03	1.60 (0.79–3.26)	0.19

[a] HR, hazard ratio. Adj HR, adjusted HR.

Of the 321 patients, 257 (80.1%) were cured, 59 (18.4%) died, 5 (1.6%) were lost to follow-up. QTcF≥501ms was not associated with unfavourable treatment outcomes (Table 6).

Discussion

In this study, QTcF≥501ms occurred in 18.4% of MDR/RR-TB patients. Clofazimine was associated with a median maximum increase of QTcF of 43.4 ms. Treatment with clofazimine was significantly associated with QTcF≥501ms. The risk of QTcF≥501ms in patients treated with clofazimine and a fluoroquinolone was significantly higher than that in patients treated with a fluoroquinolone. After the first event of QTcF≥501ms, recurrence of QTcF≥501ms was observed in all patients with re-introduction of clofazimine after temporary discontinuation of clofazimine. Four patients (1.2%) had documented VT and one patient had sudden death. These findings indicated that clofazimine

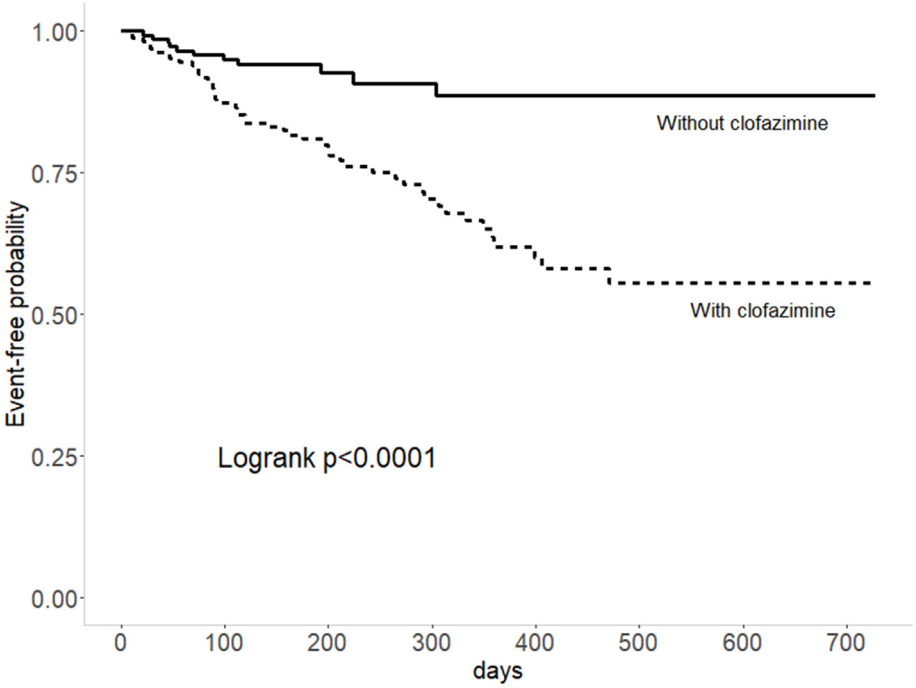

Figure 1. Time to the first event of QTcF≥501ms in patients treated with or without clofazimine.

Table 3 Combined use of potential QTcF-prolonging agents and the risk of QTcF≥501ms.

	Total	QTcF≥501 ms N= (%)	HR[e] (95% CI)	P value	Adj HR[e] (95% CI)	*P* value
Fluoroquinolone	148	10 (6.8%)	1		1	
Clofazimine and fluoroquinolone	103	28 (27.2%)	3.54 (1.72–7.29)	<0.01	3.53 (1.66–7.50)	<0.01
Clofazimine and high dose moxifloxacin[b]	35	10 (28.6%)	4.33 (1.80–10.42)	<0.01	6.36 (2.40–16.86)	<0.01
Clofazimine, fluoroquinolone, and others[c]	21	7 (33.3%)	3.87 (1.47–10.17)	<0.01	4.69 (1.67–13.21)	<0.01
Other combinations[d]	9	3 (33.3%)	3.52 (0.97–12.83)	0.06	5.09 (1.32–19.62)	0.02
None[a]	5	1 (20%)	4.26 (0.55–33.36)	0.17	11.72 (1.33–103.13)	0.03

[a] Note: none, no use of QT prolonging drugs; fluoroquinolone (FQ), normal dose moxifloxacin or levofloxacin.
[b] High dose moxifloxacin: 600–800 mg per day.
[c] Sixteen patients treated with clofazimine, fluoroquinolone and bedaquiline; two with clofazimine, fluoroquinolone and delamanid; two with clofazimine, fluoroquinolone, bedaquiline, and delamanid; one with clofazimine, fluoroquinolone and clarithromycin.
[d] Other combinations of 2–3 QT prolonging drugs: two patients treated with fluoroquinolone and bedaquiline; one with high dose moxifloxacin and bedaquiline; one with clofazimine and bedaquiline; one with clofazimine, high dose moxifloxacin, and bedaquiline; one with clofazimine, high dose moxifloxacin, and delamanid; three with clofazimine, bedaquiline and delamanid.
[e] HR, hazard ratio. Adj HR, adjusted HR, adjusted for age, sex, BMI, type of patients, history of TB treatment, smoking, alcohol, and comorbidities.

Table 4 Association between combined use of potential QTcF-prolonging agents and QTcF≥501 among patients not treated with bedaquiline, delamanid, and clarithromycin.

	Total N=	QTcF≥501msc N= (%)	Univariable		Multivariable	
			HR[a] (95% CI)	*P* value	Adj HR[a] (95% CI)	*P* value
Fluoroquinolone	148	10 (6.8%)	1		1	
Clofazimine and fluoroquinolone	103	28 (27.2%)	3.52 (1.71–7.26)	<0.01	3.43 (1.61–7.34)	<0.01
Clofazimine and high dose moxifloxacin	35	10 (28.6%)	4.28 (1.78–10.31)	<0.01	6.54 (2.43–17.60)	<0.01

[a] HR, hazard ratio. Adj HR, adjusted HR, adjusted for age, sex, BMI, type of patients, history of TB treatment, smoking, alcohol, and comorbidities. (Excluding 5 patients not treated with clofazimine and fluoroquinolone).

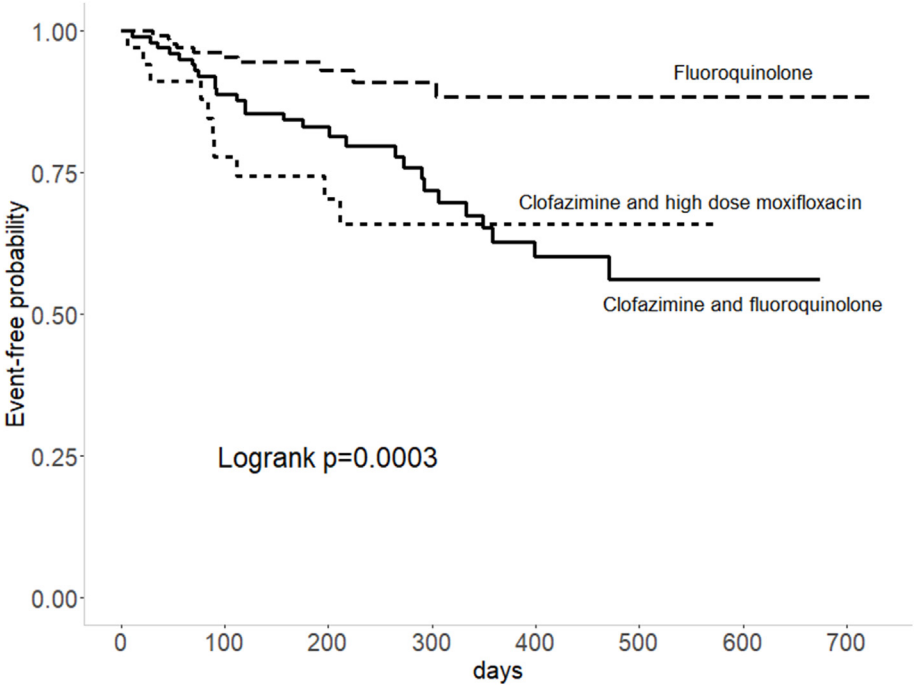

Figure 2. Time to the first event of QTcF≥501ms in patients treated with a) fluoroquinolone, b) clofazimine and fluoroquinolone, and c) clofazimine and high dose moxifloxacin.

Table 5 Time dependent Cox proportional hazards model on the association between combined use of potential QTcF-prolonging agents and QTcF≥501 among patients not treated with badaquiline, delamanid, and clarithromycin.

	Univariable		Multivariable	
	HR[a] (95% CI)	*P* value	Adj HR[a] (95% CI)	*P* value
Fluoroquinolone	1		1	
Clofazimine	4.60 (0.59–35.76)	0.15	4.08 (0.49–34.08)	0.20
Clofazimine + fluoroquinolone	5.12 (2.53–10.38)	<0.01	5.70 (2.73–11.94)	<0.01
Clofazimine + high dose moxifloxacin	3.96 (1.53–10.24)	<0.01	5.95 (2.06–17.21)	<0.01
None	1.76 (0.39–7.99)	0.46	1.84 (0.39–8.66)	0.44

[a] HR, hazard ratio. Adj HR, adjusted HR, adjusted for age, sex, BMI, type of patients, history of TB treatment, smoking, alcohol, and comorbidities.

was significantly associated with an increased risk of QTcF prolongation. Among patients treated for MDR/RR-TB, severe QTcF prolongation was not rare and should be monitored closely and managed carefully as potentially fatal arrhythmia may occur.

Although the extent of QTcF prolongation was not a perfect predictor of torsade de pointes, QTcF≥501ms had been recognized as a threshold of particular concern.[25,26] In most studies which examined cardiac safety in the treatment of MDR/RR-TB, the proportion of patients with QTcF≥501 ms was relatively low, usually less than 3%.[14,27,28] In STREAM stage 1 trial, QTcF≥501ms occurred in 6.4% of patients treated with Long regimen,[6] similar to that in those treated with a fluoroquinolone without other QTcF-prolonging agent in our study. However, the proportion of patients with QTcF≥501ms was higher among patients treated with Short regimen, and was strikingly high among Mongolian participants (45.5%) in STREAM stage 1,[6] which prompted the investigators to substitute levofloxacin for moxifloxacin in STREAM stage 2.[7] In our study, the proportion of patients with QTcF≥501ms was higher than that of most studies, perhaps because our participants were older and a high proportion of patients had comorbidities.

Studies have reported that fluoroquinolones may cause QT prolongation and were associated with an increased risk of serious arrhythmia and cardiovascular death.[29–31] Moxifloxacin has been reported to have a higher risk of QT prolongation and serious arrhythmia than levofloxacin and ciprofloxacin.[30–32] Our study did not detect significant difference between levofloxacin and moxifloxacin. Another study from Wuhan China using high-dose gatifloxacin-based short regimen reported a relatively high proportion of patients with QTcF≥501ms (21.4%),[33] in contrast with the OFLOTUB study which reported that the risk of QT prolongation in patients treated with gatifloxacin-base regimens was relatively small.[34] Of note is that clofazimine was part of the regimen in the Wuhan study, but not in the OFLOTUB trial.

Table 6 Factors associated with treatment success.

	Total	Treatment success N= (%)	OR[a] (95% CI)	*P* value	Adj OR[a] (95% CI)	*P* value
Age (year)						
≤45	84	80 (95.2)	Ref		Ref	
46-60	92	79 (85.9)	0.30 (0.09–0.97)	0.05	0.41 (0.12–1.36)	0.14
61-75	84	59 (70.2)	0.12 (0.04–0.36)	<0.01	0.16 (0.05–0.52)	<0.01
≥76	61	39 (63.9)	0.09 (0.03–0.28)	<0.01	0.12 (0.04–0.41)	<0.01
Sex						
Female	76	63 (82.9)	Ref		Ref	
Male	245	194 (79.2)	0.79 (0.40–2.67)	0.48	1.19 (0.53–2.66)	0.68
QTcF≥501ms						
No	262	214 (81.7)	Ref		Ref	
Yes	59	43 (72.9)	0.60 (0.31–1.16)	0.13	0.84 (0.42–1.70)	0.63
Type of case						
Pulmonary TB	296	238 (80.4)	Ref		Ref	
Extrapulomonary involvement	25	19 (76.0)	0.77 (0.30–2.02)	0.60	0.96 (0.34–2.72)	0.94
History of TB						
New	255	204 (80.0)	Ref		Ref	
Retreatment	66	53 (80.3)	1.02 (0.52–2.01)	0.96	0.67 (0.29–1.54)	0.34
TB treatment before current episode						
No	173	133 (76.9)	Ref		Ref	
Yes	148	124 (83.8)	1.55 (0.89–2.73)	0.12	1.72 (0.87–3.40)	0.12
Smoking						
No	158	130 (82.3)	Ref		Ref	
Ever	163	127 (77.9)	0.76 (0.44–1.32)	0.33	0.44 (0.21–0.95)	0.04
Alcohol intake						
No	216	169 (78.2)	Ref		Ref	
Ever	105	88 (83.8)	1.44 (0.78–2.65)	0.24	1.64 (0.75–3.57)	0.21
Comorbidity						
No	100	92 (92.0)	Ref		Ref	
Yes	221	165 (74.7)	0.26 (0.12–0.56)	<0.01	0.42 (0.18–0.97)	0.04

[a] OR, odds ratio. Adj OR, adjusted odds ratio.

Our study applied different analytic approaches and consistently demonstrated that clofazimine was associated with substantial QTcF prolongation and an increased risk of QTcF≥501ms. Clofazimine has the potential to prolong QT interval by inhibiting human ether-a-go-go-related (hERG) channel.[35,36] Population pharmacokinetic-pharmacodynamic modeling showed that clofazimine has a significant QT-prolonging effect driven by plasma concentrations.[35] Studies have reported that the extent of QTcF prolongation in patients treated with clofazimine in combination with bedaquiline was more prominent than those without clofazimine.[36] Our study revealed that the risk of QTcF≥501ms in patients treated with fluoroquinolone in combination of clofazimine was higher than that in patients treated without clofazimine. In the STREAM stage 1 trial, mean QTcF among patients treated with Short regimen remained higher than those with Long regimen for several weeks after treatment completion, likely due to clofazimine which has a long half-life. Furthermore, there was one case report that described clofazimine-related torsade de pointes in a patient with recurrent erythema nodosum leprosum.[37]

The effect of bedaquiline and delamanid on QT interval has been investigated.[12,15,20] Dooley et al. reported that mean change in QTc from baseline was 12.3 ms for bedaquiline, 8.6 ms for delamanid, and 20.7 ms for bedaquiline plus delamanid.[15] In our study, the number of patients treated with bedaquiline or delamanid was relatively small. However, patients treated with a fluoroquinolone and clofazimine in combination with bedaquiline or delamanid had a slightly higher risk of QTcF≥501ms than those without bedaquiline or delamanid, likely indicating addictive effects on QT prolongation.

To our knowledge, this is the first study that reports documented VT and sudden death among MDR/RR-TB patients with QTcF≥501ms. Our patients were older, commonly had comorbidities, and treated with two or more QT-prolonging drugs which may contribute to increased risks of severe QT prolongation. The four patients with VT were symptomatic, required hospitalization and immediate medical intervention. Fortunately, they all survived the event. However, one patient with severe QT prolongation had sudden death during admission, highlighting that the fatal threat of severe QT prolongation can not be neglected. Although we have identified serious adverse events related to QT prolongation, QTcF≥501ms was not significantly associated with overall treatment outcomes of MDR/RR-TB.

This study has limitations. First, it was based on programmatic data of TMTC in Taiwan, thus findings of our study may not be generalizable to other settings. Second, the timing of ECG differed between patients and some patients had a small number of ECG, which may result in under-detection of QT prolongation. Third, we did not consistently collect information of QT-prolonging drugs other than anti-TB medications. This study had its

strengths. This was a population-based study as more than 90% of MDR-TB patients in Taiwan were managed by the TMTC. Clofazimine were used in 51.4% of patients, providing an opportunity to examine its QT-prolonging effect against background influence of fluoroquinolones. Moreover, the TMTC has provided intensive medical services to MDR-TB patients, enabling timely documentation and management of grade 4 QT prolongation events, which may otherwise be missed in resource-limited settings.

In conclusion, our study has clearly documented the association between clofazimine and the risk of QTcF prolongation. Although severe QT prolongation was relatively uncommon, VT may occur, especially among patients with multiple risk factors receiving more than one potential QTcF prolonging agent. It is critical to stay vigilant in monitoring QT prolongation and take actions to mitigate the risk of torsade de pointes in patients with QTcF≥501ms.

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Availability of data

Data collected for the study will be made available upon reasonable request.

CRediT authorship contribution statement

Chou-Jui Lin: Writing — review & editing, Writing — original draft, Formal analysis, Data curation, Conceptualization. **Jin-Hua Chen:** Writing — review & editing, Methodology, Formal analysis. **Shun-Tien Chien:** Writing — review & editing, Investigation, Data curation. **Yi-Wen Huang:** Writing — review & editing, Investigation, Data curation. **Chih-Bin Lin:** Writing — review & editing, Investigation, Data curation. **Jen-Jyh Lee:** Writing — review & editing, Investigation, Data curation. **Chih-Hsin Lee:** Writing — review & editing, Investigation, Data curation. **Ming-Chih Yu:** Writing — review & editing, Investigation, Data curation. **Chen-Yuan Chiang:** Writing — review & editing, Writing — original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2024.08.002.