Cardiac safety of bedaquiline: a systematic and critical analysis of the evidence

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Bedaquiline is well tolerated: evidence indicates a minority of patients discontinue use due to QT extension http://ow.ly/9NRT30fNv4y

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Introduction

The treatment of multidrug-resistant (MDR) or extensively drug-resistant (XDR) tuberculosis (TB) remains a challenge for clinicians for several reasons, including the large number of drugs required, the cost, the tolerability of single drugs and their combinations, and the effectiveness and long treatment duration [1–6]. Therefore, fresh attention has recently been paid to new and repurposed anti-TB drugs [4, 5, 7–18].

Two recently approved anti-TB drugs, bedaquiline and delamanid, have the potential to affect cardiac electrophysiology by prolonging the QTc interval (the corrected measure of time between the start of the Q-wave and the end of the T-wave in the heart's electrical cycle). In addition, delamanid and bedaquiline can be part of complex multidrug regimens, including other drugs with a potential QTc prolonging effect such as clofazimine and the fluoroquinolones [19, 20].

It has been suggested that the potential for bedaquiline to prolong QTc might have been responsible for the 10 unexplained deaths in the bedaquiline-treated arm of a proprietary trial conducted to assess the efficacy of this drug [21]. Therefore, the World Health Organization (WHO) advises caution when administering this medication and recommends that strict monitoring procedures be put in place [22]. Furthermore, the current development of new antimicrobials is subject to stringent regulatory requirements by the relevant agencies, such as the Food and Drug Administration (FDA) in the United States and European Medicines Agency (EMA) in Europe. Specifically, drug manufacturers need to provide safety information on a drug's potential to prolong the QTc interval [23, 24].

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The published evidence on bedaquiline's effect in prolonging QTc among patients exposed to regimens with QTc extending capacity is still scant or anecdotal and no systematic review of the evidence on this topic has been ever conducted. This issue is decisively important when designing anti-MDR-TB regimens given the fact that several other anti-TB drugs such as fluoroquinolones, clofazimine, pretomanid, delamanid and macrolides have the potential to prolong QTc. This article is intended to accomplish the following: 1) Describe the basis of QTc monitoring and the risks associated with QTc being prolonged; 2) Summarise, *via* a systematic approach, the published evidence on bedaquiline's effect on the QTc interval.

Electrocardiography and the significance of prolonging QTc

Electrocardiogram (ECG) registration and graphic representation report the phases of the atrial and ventricular action potentials. When performing a 12-lead ECG, the QT interval can be measured as the interval from the beginning of the QRS-complex to the end of T-wave as it returns to baseline. The QT interval represents electrical ventricular systole and is a measure of the combination of cardiac depolarisation and repolarization [25]. The QT interval is not a constant and it varies depending on several factors, including gender, heart rate (HR), rhythm and conduction defects, and the physiologic and metabolic state of the patient. However, the primary factor affecting QT interval is HR. In this regard, the measure of QT interval variation needs to be corrected to account for HR changes. The HR-adjusted QT interval is named the corrected QT interval (QTc) and can be calculated with the Bazett formula (best between 60 and 100 beats·min^{-1}) or the Fredericia formula (best outside the previously mentioned range) [25]. QTc values are considered normal for males when they are between 350 and 450 ms and for females when they are between 360 and 460 ms [25]. Historically, ECG measurements of the QRS interval are preferably performed using lead II; however, when this is not feasible, leads V5, V6 or I can be used [25].

The main reason for monitoring QT intervals is the correlation with the third phase of ventricular repolarization. When the QT interval is abnormally long, the left ventricle becomes more susceptible to premature electrical impulses (*i.e.* early after-depolarizations). This event can eventually trigger a polymorphic ventricular tachycardia known as torsades de pointes (TdP) which was first described by F. Dessertenne back in 1966. The effect was described as a "twisting of the points" because the "points" of the QRS complexes on the ECG appeared to "twist" around the isoelectric baseline [26]. TdP results in a HR of between 160 and 240 beats·min^{-1}. It can be symptomatic with patients suffering from palpitations, dizziness, lightheadedness, shortness of breath, near-syncope and syncope. Notably, in some cases, TdP may be non-sustained and terminate spontaneously [27]. Nevertheless, TdP frequently degenerates in a very short time into ventricular fibrillation, thus resulting in sudden cardiac death.

Thus, the medical focus on the prolonging of QTc interval is explained by its risk of increasing the risk of TdP, particularly when the QTc interval exceeds 500 ms [28–30]. Actually, the vast majority of reported or published cases of TdP have occurred in patients where QTc interval has exceeded 500 ms and TdP remains rare when QTc interval is below 500 ms [23]. Furthermore, the TdP risk is associated not only with the absolute value of the QTc interval but also with an increase of greater than 60 ms compared with the pre-treatment value [23].

Several groups of drugs (*e.g.* anti-arrhythmics, antihistamines, antipsychotics and antimicrobial agents) can prolong the QTc interval and cause TdP [31]. In most cases, the repolarisation slowing is due to inhibition of the rapidly activating delayed rectifier potassium current in cardiac tissues at the level of the "ether-a′-go-go-related gene-encoded voltage-dependent potassium channel" (the hERG K channel) [31].

Systematic search on bedaquiline and prolonging of the QT interval

We carried out a scoping review in order to describe the main elements behind bedaquiline cardiac safety as a research topic. Using the PubMed search engine, the keyword "bedaquiline" was used to retrieve all studies reporting data on bedaquiline up to June 30, 2017. Due to the limited experience available so far, no restriction was initially applied as per the type of publication and no language restrictions were included. A total of 364 records were found and 299 were excluded because they did not fit the selection criteria (*i.e.* inclusion of manuscripts with a clear description of the safety profile of bedaquiline-containing regimens and an accurate assessment of any cardiac adverse events; epidemiologic, experimental or observational studies; case-series or case-reports. Exclusion of manuscripts with partial or missing information on QTc, or those focused on laboratory, animal or modelling studies). The remaining full-text manuscripts were assessed and only 23 were considered suitable for a qualitative/descriptive (but not meta-analytic) analysis of the main findings, whereas the others did not describe adequately the QTc issue or were model studies (figure 1). To improve the sensitivity of the analysis a search of the grey literature was carried out adopting the above-mentioned time period. We did not assess scientific abstracts submitted and presented at the main TB-related conferences, as the content provided was difficult to

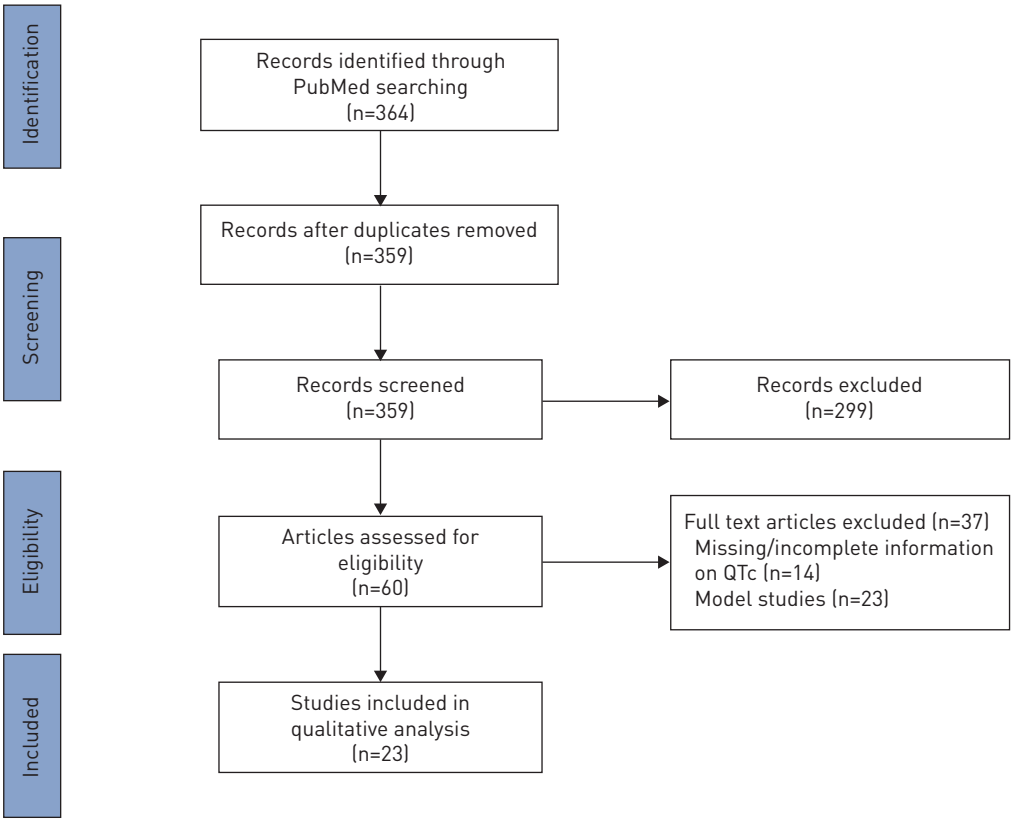

FIGURE 1 Selection process: PRISMA 2009 Flow Diagram.

retrieve in appropriate clinical and methodological form. One additional paper published during the revision of this editorial was added due to its relevance [32].

Summary of the published evidence

In the selected studies a total of 1303 subjects who received bedaquiline were assessed for cardiac safety and had information on QTc available [32–55] (table 1). Only a few were healthy volunteers (37; 2.8%) [35] or subjects affected by non-tuberculous mycobacteriosis (10; 0.8%) [46], while the vast majority were TB patients (1256; 96.4%). Some studies reported on preliminary experience of bedaquiline use with variable doses (ranging from 25 mg·day^{-1} to 400 mg·day^{-1}) and variable length of exposure (ranging from 7 to 56 days) [33, 34, 36–38, 45]. The length of bedaquiline administration was variable from 2 days, as in studies in healthy volunteers, to over 6 months in clinical experiences of prolonged MDR/XDR-TB treatment. The median time of exposure to bedaquiline in clinical studies was 24 weeks.

In general, bedaquiline was well-tolerated with a very limited number of treatments discontinued because of safety concerns or poor tolerability. In particular, 44 patients discontinued bedaquiline due to adverse events (3.5% of 1266 subjects) although the timing of discontinuation was not available [36, 37, 39, 43–45, 48, 50, 53, 54]. Although not always apparent in evaluated studies, only eight patients out of 44 (0.6% of 1266 subjects) discontinued bedaquiline because of prolonging of the QTc interval and two of these restarted bedaquiline after resolution of the acute episode [43, 44, 48, 50, 53]. One of the two patients obtained QTc normalisation after receiving verapamil [47], while the other patient presented spontaneous normalisation of QTc [44].

Patients receiving bedaquiline in clinical trials, case reports or cohort studies often received concomitant anti-TB drugs with an increased risk of QTc prolongation, *i.e.* fluoroquinolones, clofazimine, pretomanid, delamanid and azithromycin. Information on QTc was variable: most studies showed an average prolongation <20 ms regardless of concomitant drug use. Only a few studies reported higher QTc prolongation, *e.g.* 49 ms [52], 36.2 ms of average maximum increase in those with a prolongation [53], 31.9 ms for those with concomitant clofazimine [50], 28.5 ms of maximum increase in median values [54].

Information on QTc increase of at least 60 ms from baseline (regardless of baseline value) or of QTc prolongation of more than 450 ms was not systematically reported by authors. Nevertheless, all selected

TABLE 1 Effect of bedaquiline (BDQ) on the QT interval of the heart's electrical cycle

First Author, year, (Ref)	Subjects exposed to BDQ	Average BDQ exposure (days) / BDQ dose	Average QTc prolongation	Concomitant drug(s) prolonging QTc	n (%) subjects with QTc >450 msec	n (%) subjects with QTc >500 msec	BDQ discontinuation due to adverse events	n (%) subjects discontinuing BDQ because of QTc prolongation
Rustomjee, 2008 (Ref 33)	45	7/25, 200 or 400 mg once daily	25 mg: −1.9 +/-14.8 msec 200 mg: 7.1 +/-9.5 msec 400 mg: 18.8 +/-27.7 msec	None	0	0	None	0
Diacon, 2009 (Ref 34)	23	56/+	10.8 msec	Ofx (23/23; 100% of subjects)	Not reported	0	None	0
Dooley, 2012 (Ref 35)	37 (healthy volunteers)	2/400 mg daily	12.3–12.8 msec	None	2/37 (5.4%)	0	None	0
Diacon, 2012 (Ref 36)	45	14/700 mg on day 1, 500 mg on day 2, then 400 mg daily	No information reported	None	No information reported	0	1 (2.2%)	0
Diacon, 2012 (Ref 37)	23	56/+	No information reported	Ofx (most subjects)[¶]	No information reported	0	1 (4.3%) myocardial infarction – unrelated to BDQ	0
Diacon, 2013 (Ref 38)	68	14/loading dose for first 2 days, then 100 mg, 200 mg, 300 mg or 400 mg daily	No information reported	None	Not reported	0	None	0
Diacon, 2014 (Ref 39)	79	168/+	15.4 msec	FLQs (79/79; 100% of subjects)	Not reported	1 (1.3%)	4 (5.1%)	0
Tiberi, 2014 (Ref 40)	2	168/+	No prolongation reported	Cfz (2/2; 100% of subjects)	No information reported	0	0	0
van Halsema, 2014 (Ref 41)	1	168/+	No prolongation reported	Azh (1/1; 100%)	No information reported	0	0	0
Chua, 2015 (Ref 42)	1	168/+	No prolongation reported	Cfz (1/1; 100%)	0	0	None	0
Guglielmetti, 2015 (Ref 43)	35	168/+	Mean QTcB values increased by a median of 1.96 msec (range −64 to 71 msec); combined with FLQ (median, 4.9 msec) or Cfz (median, 7.3 msec); no significant difference	Cfz (5/35; 14.3% of subjects); FLQs (16/35; 45.7% of subjects)	No information reported	3 (8.6%)	2 (5.7%)	2 (5.7%)

Continued

TABLE 1 Continued

First Author, year, (Ref)	Subjects exposed to BDQ	Average BDQ exposure (days) / BDQ dose	Average QTc prolongation	Concomitant drug(s) prolonging QTc	n (%) subjects with QTc >450 msec	n (%) subjects with QTc >500 msec	BDQ discontinuation due to adverse events	n (%) subjects discontinuing BDQ because of QTc prolongation
Ndjeka, 2015 (Ref 44)	91 (54 HIV+)	168/+	Cfz was significantly associated with an 18.4 msec increase in QTcF; however, patients on Cfz were not more likely to experience a QTcF increase >50 msec	Lfx (76/91; 83.5% of subjects); Cfz (68/91; 74.7% of subjects)	No information reported	3 (3.3%) – spontaneous resolution	1 (1.1%) atrial fibrillation	1 (1.1%) temporary discontinuation
Diacon, 2015 (Ref 45)	60	14/400 mg on Day 1, 300 mg on Day 2, 200 mg on Days 3–14	No information reported	50% of subjects received Cfz +PA-824; 25% received Cfz; 25% received PA-824[¶]	No information reported	0	1 (1.7%)	0
Philley, 2015 (Ref 46)	10	168/+	Maximum change 6.5 msec	FLQs (3/10; 30% of subjects)	0	0	None	0
Lewis, 2016 (Ref 47)	1	126/+	QTc peaked after 10 weeks, introducing Cfz; decreased after a few weeks from peak and after Azh discontinuation	Azh, Cfz (1/1; 100%)	1 (100%)	0	None	0
Tadolini, 2016 (Ref 48)	1	175/+	Variable over time; concomitant low potassium at day 10	Dlm, Cfz (1/1; 100%)	1 (100%)	0	None	1 (100%); temporary BDQ discontinuation
Lachâtre, 2016 (Ref 49)	1	168/+	No prolongation reported	Dlm, Cfz (1/1; 100%)	0	0	None	0
Pym, 2016 (Ref 50)	233	168/+	The mean maximum change in QTcF interval from baseline was 14.2 msec. For those taking Cfz: 31.9 msec	FLQs (180/205; 87.8% of subjects with available information); Cfz (36/205; 17.6% of subjects with available information)	31 (13.3%)	2 (0.9%); both taking CFZ; one with low potassium	6 (2.6%)	1 (0.4%)
Henry, 2016 (Ref 51)	16	168/+	No information reported	Some subjects with Cfz and/or Mfx[¶]	No information reported	0	None	0

Continued

TABLE 1 Continued

First Author, year, (Ref)	Subjects exposed to BDQ	Average BDQ exposure (days) / BDQ dose	Average QTc prolongation	Concomitant drug(s) prolonging QTc	n (%) subjects with QTc >450 msec	n (%) subjects with QTc >500 msec	BDQ discontinuation due to adverse events	n (%) subjects discontinuing BDQ because of QTc prolongation
Udwadia, 2017 (Ref 52)	20	168/+	QTcF intervals increased by a mean of 49 msec	Cfz (20/20;100% of subjects); Mfx and Cfz (5/20; 25% of subjects)	No information reported	3 (15%) transient increase; reverted spontaneously by next week	None	0
Guglielmetti, 2017 (Ref 53)	45	360 days (range, 31-768- median duration of BDQ administration); 73% received prolonged treatment (>190 days)/+	QTcF prolongation occurred in 13 (28.9%) patients; median of the maximum QTcF increase was 36.2 (IQR 17.9–68.5) msec	#Mfx (14/45; 31.1% of subjects) 400 mg daily (10/45; 22.2% of subjects) 800 mg daily; Lfx (8/45; 17.8% of subjects) 1000 mg daily; Cfz (20/45; 44.4% of subjects); #Methadone (6/45; 13.3% of subjects)	No information reported	5 (11%), but neither arrhythmias nor symptomatic cardiac side effects occurred	3 (6.7%)	3 (6.7%)
Borisov, 2017 (Ref 54)	428	168/+	Maximum increase in median values: 28.5 msec	Mfx (250/428; 58.4% of subjects); Cfz (225/428; 52.6%; of subjects) Ofx (7/428; 1.6% of subjects)	No information reported	24 (9.7%)	25 (5.8%); one death with ECG abnormalities, but unrelated to BDQ	Not clearly reported
Olaru, 2017 (Ref 55)	30	At least 180/+	QTcB prolongation in 20/21 (95%); in one case QTcB >60 msec	No information reported	No information reported	1 (transient increase; spontaneous resolution)	None	0

Continued

TABLE 1 Continued

First Author, year, (Ref)	Subjects exposed to BDQ	Average BDQ exposure (days) / BDQ dose	Average QTc prolongation	Concomitant drug(s) prolonging QTc	n (%) subjects with QTc >450 msec	n (%) subjects with QTc >500 msec	BDQ discontinuation due to adverse events	n (%) subjects discontinuing BDQ because of QTc prolongation
Yoon, 2017 (Ref 32)	10	168/+	With Cfz 56.7±3.1 msec With MFX and macrolides −19 msec With MFX and CFZ +55 msec	Cfz (7/10; 70%): Mfx (4/10; 40%); Macrolides (1/10; 10%)	No information reported	0	No information reported	0
Total/median	Total: 1303 subjects	Median: 168 days			Total: 35/329 (10.6%) reporting information	Total: 42/1303 (3.2%)	Total: 44/1293 (3.4%) reporting information	Total: 8/875 (0.9%) In 2 patients out of 8 the discontinuation was temporary

Ref: reference.[#]: associated with >500 ms QTcF.[¶]: exact number not provided.+: standard BDQ dose, *i.e.* weeks 1–2: 400 mg once daily, then from week 3 to end of treatment: 200 mg 3 times per week.QTc: corrected measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle (see fig. 1 for details); QTcF: corrected QT using Fredericia formula; QTcB: corrected QT using Bazet formula; Ofx: Ofloxacin; FLQs: fluoroquinolones: Cfz: clofazimine; Azh: azithromycin; Lfx: levofloxacin; PA-824: pretomanid; Dlm: delamanid; Mfx: moxifloxacin; HIV: Human Immunodeficiency Syndrome.IQR. Interquartile range; ECG: Electrocardiogram.

papers had sufficient information to know if QTc prolongation greater than 500 ms occurred. In particular, QTc longer than 500 ms was reported in 42 patients (3.2%).

Some cardiac adverse events and even deaths were reported in the different cohorts, although the authors never attributed them to bedaquiline (table 1) [37, 44, 54]. It has to be underscored that, even if *post mortem* studies are carried out, it is impossible to determine whether death occurred due to an arrhythmia related to QTc prolongation. All the *post mortem* can do is to exclude other clear causes of death, such as myocardial infarction, pulmonary oedema, pulmonary embolism, *etc.*

Conclusions

The evaluation of the published studies highlighted the limited information provided on the cardiac safety of bedaquiline. Most often cardiac monitoring activities were not reported systematically and in sufficient detail to allow for easy comparisons. Other clinical studies (those discarded) did not even report on any relevant information on QTc or cardiac safety in general.

Clinicians and programme managers are in need of a standardised way to report cardiac safety from cohorts employing bedaquiline and delamanid; in particular, results of QTc monitoring and (cardiac) adverse events.

Unfortunately, as limited information was provided on the frequency of ECG monitoring, we cannot provide additional evidence regarding the ideal monitoring frequency. Nevertheless, we can confirm the current recommendation to perform ECG before starting bedaquiline and at least at weeks 2, 4 and every following month [56]. In addition, if the patient has other possible concurrent risks of QTc prolongation (*e.g.* receiving one or more concomitant drugs potentially prolonging QTc, having a serum potassium, calcium or magnesium level below the lower limits of normal, having a history of TdP, having congenital long QT syndrome, having hypothyroidism and bradyarrhythmias, or uncompensated heart failure) weekly ECGs can be recommended.

Clinical experiences on bedaquiline use and its safety in TB patients published so far remains scanty as it is available for only 1256 patients. Evaluation of the efficacy of bedaquiline-containing regimens requires time as multidrug regimens may last for up to 2 years. Nevertheless, information on cardiac safety could become available earlier since – in most patients – bedaquiline is employed for no more than 24 weeks.

In conclusion, analysis of collected information showed that bedaquiline is a relatively well-tolerated drug since its discontinuation occurred in only 3.4% and 0.6% of patients due to adverse events and QTc prolongation, respectively. Nevertheless, no complacency can be allowed, and strict ECG monitoring remains mandatory.

Hopefully, new larger cohorts reporting on safety of bedaquiline use under programme conditions will help in better defining the "cardiac safety profile" of bedaquiline.

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