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EDITORIAL

QT prolongation for old and new drugs: how much should we really worry?

Over the past decade, professionals dealing with TB have been forced to focus their attention on the cardiac safety of anti-TB drugs, especially the newer ones.[1–4] There have been several reports on the risk of increasing the QTc (corrected QT) interval of patients receiving anti-TB regimens, especially those being treated for multidrug-resistant TB (MDR-TB) or pre-extensively drug-resistant TB (XDR-TB) with bedaquiline (BDQ) and/or delamanid (DLM).[5–7] Although the clinical impact of this QTc increase is less than expected, it is not negligible.[8–11]

Until now, the QTc increase has been associated with newer drugs, and has not been extensively studied in other anti-TB regimens. This is addressed in this issue of the Journal in a paper by Hughes et al., which reports results from secondary analyses of QT interval prolongation of STREAM Stage 1 clinical trial.[12] The studied regimens included clofazimine (CFZ) and moxifloxacin (MFX). This is the first and largest dataset available from a clinical trial on QTc interval prolongation on the Short regimen with injectable, as approved in 2016 by WHO for the treatment of pulmonary rifampicin-resistant TB (RR-TB) with sensitivity to fluoroquinolones (FQs), later modified by replacing the injectable with BDQ.[13] Participants administered the Short regimen experienced a greater increase of QTc than the standard of care (SOC). Especially between Week 4 and Week 40, median QTc in the Short regimen arm was higher than the SOC arm (median maximum change in QTc from baseline of 50 ms in Short regimen vs. 30 ms in SOC), with a maximum difference of 24 ms at Week 28 between the two arms. After Week 40 (completion of the Short regimen), there was a decrease in QTc in this group; however, it remained higher than QTc in the SOC arm. During the study, 11% (31) of the participants reported QT/QTc $\geq$ 500 ms in the Short regimen arm compared to 5% (7) in the SOC, with a hazard ratio of 2.31 (95% CI 1.02–5.26) for the Short regimen arm. No statistically significant associations were found between QT $\geq$ 500 ms and sex, smoking status, diabetes, body mass index, MFX and CFZ dose, liver function tests, glucose, potassium or HIV status. Effect of dose per kg of MFX and CFZ was further investigated. In the lower weight group (33–50 kg) participants who experienced QTc above 500 ms received higher mg/kg doses both for MFX and CFZ, but this was not confirmed in the higher weight group (>50 kg). Association was found between QTc >500 ms at any point and baseline QTc $\geq$400 ms with OR 5.99 (95% CI 2.04–17.62) at univariate analysis, confirmed at multivariate analyses with OR 4.77 (95% CI 1.54–14.71). To note, significant statistical association was found also between QT >500 ms at any point and sites. Participants enrolled in Mongolia had 45.5% of ECGs with QTc >500 ms compared with participants from other sites (3.5–11.9%).

The QT interval

The QT interval, which on the ECG corresponds to the electrical depolarisation-repolarisation of ventricles, is measured from the beginning of the Q wave until the end of the T wave and this measurement must be corrected (QTc) according to the heart rate. Fridericia's (QTcF) and Framingham's formulas are considered the optimal correction factors;[14] Fredericia's correction is recommended for RR/MDR/XDR-TB patients. Accurate measurement of the QTc can be challenging in several scenarios:[15] identifying the end of the T wave and its potential overlapping with the U wave can be difficult; the recommendation is therefore to measure the QT interval in lead II, V5 and V6. The normal QTc duration is <450 ms in males and <470 ms in females. However, it must be kept in mind that the QTc can vary by up to 75 ms in the same person during the day; thus, if at screening a QTc >500 ms is detected, it is advisable to repeat the ECG within 24 h.[16]

It is well-known that prolongation of the QTc interval beyond 500 ms is a risk factor for 'torsade of pointes' (TdP), a form of polymorphic ventricular tachycardia. This arrhythmia usually terminates spontaneously, but sometimes it can occur in episodes with rapid succession and cause symptoms like palpitations, dizziness, syncope, and eventually, sudden death.[17–19] Prolonged QTc is a good predictor of risk of TdP.[20,21] Unfortunately, the correlation between length of the QTc interval and/or duration of QTc prolongation and TdP is not linear and depends on additional risk factors, which can be congenital and unmodifiable (e.g., being female, having long QT syndrome, etc) or acquired (e.g., hypopotassaemia, HIV infection, concomitant use of

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Table Risk factors for QTc prolongation and torsades de pointes

Baseline and unmodified predisposition	Acquired risk factors: clinical conditions
• Female sex • Advanced age (linearly increased risk after 60 years) • Underlying conduction abnormalities (subclinical long QT syndrome): genetic predisposition, family history of sudden death • Bradycardia	• Structural and functional heart problems o Ischaemic and congestive heart disease o Ischaemic cardiomyopathy o Dilated or hypertrophic congestive heart disease o Congestive heart failure o Recent conversion from atrial fibrillation • Electrolyte imbalance o Hypokalaemia o Severe hypomagnesaemia o Hypocalcaemia • Frequent conditions of TB patients o HIV infection (particularly in advanced disease and multiple medications) o Low BMI: malnutrition, starvation and wasting syndrome o Severe vomiting and diarrhoea creating low potassium levels • Other QTc prolonging drugs • Impaired renal function • Impaired hepatic function • Hypothyroidism

HIV = human immunodeficiency virus; BMI = body mass index

other QTc prolonging drugs) (Table). Fortunately, only a small minority of people with prolonged QTc interval are predisposed to TdP. 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.[22] Many TB drugs can potentially prolong the QT interval, especially if used in association with short intensive regimens. According to a review of studies, the prevalence of sudden death directly attributable to TdP by QTc-prolonging drug-resistant TB (DR-TB) drugs is likely less than 1%. The risk of TdP is likely not caused by the administration of specific drugs but to the cumulative number of several risk factors in the same patient. Thus, to assess individual risk it is important to carry out an initial screening combining a baseline ECG with some laboratory tests and patient's clinical history.

In light of what is known on risk factors for prolonged QTc, Hughes et al.'s[12] findings in the Mongolian group warrant further investigation into the genetic characteristics of the population through a pharmacogenetic approach towards personalised medicine. In addition, we should consider that the STREAM study was conducted between 2012 and 2015 and none of the participants across the sites received new or repurposed drugs such as BDQ, DLM or linezolid (LZD).[12] It is clear that we need to expand our knowledge of the impact of anti-TB regimens on QTc, not just the effect of a single drug (e.g., BDQ or DLM), but the effect of their variable combinations in the different regimens.

New anti-TB drugs

BDQ is becoming a key component of the new drug regimens to treat drug-susceptible and DR-TB. BDQ is a diarylquinoline, approved in 2012 by the US Food and Drug Administration, with an excellent efficacy profile and the WHO now recommends that all patients with RR-TB receive a BDQ-based regimen.[3,4,23] It has a favourable safety profile with known risk of increased liver enzymes shared with many other anti-TB compounds and risk of QTc interval prolongation, as CFZ, MFX, and, to a less extent, DLM.[1–5,8,10,11,22,24] Cardiac safety remains a major concern, especially when managing patients with several concomitant medications that could cause QTc interval prolongation, in particular when prescribing anti-RR/MDR/XDR-TB drug regimens containing also FQs and CFZ. Nevertheless, new information is becoming available, such as the recent report of a cohort study from South Africa that showed that severe QT prolongation was uncommon in 195 patients with RR-TB treated with BDQ and 97%, 94% and 92% of them received concomitant CFZ, levofloxacin and LZD, respectively.[25] Older age (above 30 years) was independently significantly associated with QTc $>$ 450 ms; the greatest effect was seen for participants above 50 years. In the large End TB observational cohort study (2015–2019), evaluating 2,296 patients that began RR/MDR-TB regimens containing BDQ or DLM in 17 countries, only 63 (2.7%) cases of Grade $\geq$3 (QTcF $\geq$ 501 ms with/without symptoms or 60 ms increase) QT interval prolongations were observed, and only one patient was reported to have had a fatal outcome.[26] The DELIBERATE Phase II controlled clinical trial investigated the effect of BDQ and/or DLM in 84 RR/MDR-TB patients from South Africa.[27] Mean change in QTc from baseline was 12.3 ms (95% CI 7.8–16.7) in BDQ-receiving group, 8.6 ms (95% CI 4.0–13.1) in DLM group, and 20.7 ms (95% CI 16.1–25.3) in BDQ+DLM group. There were no Grade 3 or 4 adverse QTc

prolongation events and no death during study treatment. Of note, none of the patients received CFZ, and MFX was replaced by levofloxacin. The NIX TB clinical trial on BPaL regimen for 24 weeks enrolled 109 XDR and failed MDR-TB patients and reported that the maximum increase in QTc interval was 10 ms at Week 16 and no participants had an increase of more than 480 ms.[28] Results on efficacy and safety of TB-PRACTECAL Phase II/III controlled clinical trial (24 weeks BPaL+MFX [BPaLM] regimen) were recently presented at the Union World Conference 2021 (I Motta, personal communication). Mean QTcF at 24 weeks was 441.8 ms (standard deviation [SD] 18) in SOC vs. 423.5 ms (SD 18.5) in BPaLM, with change in QTcF from baseline of 44.9 ms (SD 20.8) vs. 27 ms (SD 16.5), in SOC and BPaLM, respectively. Another recent finding comes from a prospective cohort study, BEAT India TB, in which 167 patients were enrolled and BDQ-DLM-LZD-CFZ (BDLC) regimen for 24 weeks in pulmonary pre-XDR-TB was investigated. Overall, cardiac safety was good and no patient had a QTc interval more than 500 ms.[29]

In conclusion, severe drug-related cardiac adverse events have rarely been reported in DR-TB patients and those that occur are largely associated with other additive risk factors. Clinicians should be trained to identify all situations likely to add risk of TdP. They should monitor and manage treatable existing conditions including gastroenteritis, malnutrition, hypothyroidism, review any medication as ancillary medication (e.g., methadone, hydrochlorothiazide, furosemide, metoclopramide), and promptly report if the patient presents palpitation, lipothymia and syncope. From the above it is clear that all-oral new regimens are safer than initially reported, at least from a QT perspective. A comprehensive evaluation of patients is mandatory at baseline and regularly during treatment, and this should be extended to allow continuous collection of information on cardiac safety of new and old drugs and their various combinations.

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