# QT prolongation and cardiac toxicity of new tuberculosis drugs in Europe: a Tuberculosis Network European Trialsgroup (TBnet) study

*To the Editor:*

There is concern that many second-line drugs used to treat multidrug-resistant tuberculosis (MDR-TB) may cause fatal arrhythmias linked to QT interval prolongation. The QT interval, measured on an electrocardiogram (ECG), represents the duration of the ventricular electrical systole. In order to have a more reproducible value across time and heart rates, the QT interval is adjusted according to heart rate (as QTc). Fluoroquinolones and, possibly, clofazimine can prolong the QTc interval [1, 2], as do bedaquiline (Bdq) and delamanid (Dlm) [3, 4]. A QTc interval >500 ms is considered a risk factor for ventricular arrhythmias such as torsades de pointes (TdP) [5]. Overall, 10–20% of patients with drug-induced TdP have a genetic predisposition and more than 70% have at least two other risk factors, like older age, female sex and electrolyte disturbances [6]. In smaller cohorts, no cases of fatal arrhythmia have been reported in association with new tuberculosis (TB) drugs and deaths in Bdq/Dlm registration trials were not linked to prolonged QTc nor arrhythmias [3, 4, 7]. The objective of the study was to evaluate the clinical impact of QTc prolongation and the number of cardiac events in patients receiving Bdq/Dlm treatment for MDR-TB in treatment centres of the Tuberculosis Network European Trialsgroup (TBnet), a clinical research collaboration of the European Respiratory Society, within the World Health Organization (WHO) Europe region.

In December 2016, a cross-sectional online survey was distributed in parallel to members of the TBnet and to a list of TBnet MDR-TB country representatives (chosen because of MDR-TB management expertise and previous participation in TBnet activities) in 45 countries belonging to the WHO Europe region, excluding Central Asia. No more than one participant was accepted from each centre and, in cases of multiple answers from the same centre, participants were contacted to confirm the correct answer. Participants who reported cardiac events in patients receiving MDR-TB treatment containing Bdq/Dlm were contacted to obtain additional information. The survey closed in July 2017. The questionnaire consisted of 10 questions on general information and QTc prolongation management; 32 questions on treatment experience with Bdq/Dlm; and three questions on the use of the Bdq/Dlm combination. The full questionnaire is available online (http://tb-net.org/images/TBnet_completed_projects_QT_survey/TBnet_Survey_on_QT_interval_monitoring_and_new_TB_drugs.pdf). Ethical approval was provided by the Institutional Review Board of Bligny Hospital, France.

Overall, 61 valid replies from different hospitals in 41 out of 45 (91%) targeted countries, out of the 53 included in the WHO Europe region, were retained. The most represented countries were Italy (seven participants), Denmark and Spain (four participants each). Most participants worked in teaching/university hospitals (49%) and in TB reference hospitals (24%).

Most physicians (50 out of 61 (82%)) routinely monitor the QT interval at their centre. Among them, 22 (44%) perform QT monitoring in all patients undergoing MDR-TB treatment, 20 (40%) perform it only in patients receiving new drugs or multiple QT-prolonging drugs, and eight (16%) do not perform it in MDR-TB patients. In MDR-TB patients monitored for QT prolongation, ECGs are repeated weekly

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**Few cardiac arrhythmias and no fatalities were observed in MDR-TB patients treated with bedaquiline and delamanid** http://ow.ly/2tC030koXJa

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(23 out of 42 participants (55%)) or monthly (19 out of 42 participants (45%)) during treatment, either before administering treatment (34 out of 42 participants (81%)) or 90–120 min after administration (eight out of 42 participants (19%)). Overall, 34 participants (68%) use the QTc interval while 16 (32%) use the uncorrected QT interval. Of the 34 participants measuring QTc, 41% use the Fridericia correction (QTcF), 23% use the Bazett correction (QTcB), 18% use both and 18% did not know which correction was used. Most physicians would stop Bdq and Dlm in case of QTc interval >500 ms (27 out of 61 participants (44%)), while 22 out of 61 participants (36%) would do so only in the case of symptomatic arrhythmias. Furthermore, 12 out of 61 participants (20%) would also stop the drugs for any prolongation above normal values (470 ms in women and 450 ms in men).

Overall, 35 participants (57%) had experience using Bdq and 20 participants (33%) had experience using Dlm. 15 out of 35 (43%) of those using Bdq and six out of 20 (30%) of those using Dlm require approval

TABLE 1 List of countries and centres taking part in the study, treatment with new drugs and QT-related adverse events

| Country | Centres | Treatment | | | QT prolongation[¶] | Cardiac events[+] |
|---|---|---|---|---|---|---|
| | | Bdq | Dlm | Bdq and Dlm[#] | | |
| **Albania** | 1 | | | | | |
| **Armenia** | 1 | 110 | 46 | 13 (9/4) | 1 (1/0) | |
| **Austria** | 1 | 13 | 1 | | | |
| **Belarus** | 1 | 297 | 33 | 2 (2/0) | | |
| **Belgium** | 1 | 7 | | | | |
| **Bosnia and Herzegovina** | 1 | | | | | |
| **Bulgaria** | 1 | | | | | |
| **Croatia** | 1 | | | | | |
| **Cyprus** | 1 | | | | | |
| **Czech Republic** | 1 | | | | | |
| **Denmark** | 4 | 9 | 3 | 2 (1/1) | | 1 (1/0) |
| **Estonia** | 1 | 20 | 13 | | | |
| **Finland** | 1 | 3 | | | | |
| **France** | 1 | 70 | 12 | 10 (4/6) | 5 (5/0) | |
| **Georgia** | 1 | 292 | 45 | | | 1 (0/1) |
| **Germany** | 3 | 39 | 15 | 4 (1/3) | | |
| **Greece** | 1 | | | 1 (1/0) | | |
| **Hungary** | 1 | | | | | |
| **Iceland** | 1 | | | | | |
| **Ireland** | 1 | 2 | 1 | 1 (1/0) | | |
| **Italy** | 7 | 14 | | | | |
| **Kosovo** | 1 | | | | | |
| **Latvia** | 1 | 53 | 34 | 4 (0/4) | | |
| **Lithuania** | 1 | 11 | 9 | | | |
| **Luxembourg** | 1 | 1 | | | | |
| **Macedonia** | 1 | | | | | |
| **Moldova** | 1 | 30 | | | 1 (1/0) | |
| **Montenegro** | 1 | | | | | |
| **Norway** | 1 | | | | | |
| **Poland** | 1 | | | | | |
| **Portugal** | 1 | 1 | 1 | | | |
| **Romania** | 2 | 40 | | | | |
| **Russia** | 2 | 13 | | | 1 (1/0) | |
| **Serbia** | 1 | | | | | |
| **Slovakia** | 1 | | | | | |
| **Spain** | 4 | | | | | |
| **Sweden** | 1 | 4 | 1 | | | |
| **Switzerland** | 1 | 1 | 1 | | 1 (0/1) | |
| **The Netherlands** | 3 | 10 | 4 | 1 (1/0) | | |
| **UK** | 3 | 3 | 1 | | | |
| **Ukraine** | 1 | 1 | | | | |
| **Total** | 61 | 1044 | 220 | 38 (20/18) | 9 (8/1) | 2 (1/1) |

Bdq: bedaquiline; Dlm: delamanid. [#]: values in parentheses are for concomitant/sequential treatment; [¶]: patients who had to stop a new drug for QT prolongation (Bdq/Dlm); [+]: patients with severe cardiac events while receiving a new drug (Bdq/Dlm).

from another health body to use the new drug, mainly national consiliums. While most physicians used new drugs for no longer than 24 weeks, nine out of 35 (26%) and four out of 20 (20%) had prescribed treatment durations up to 20 months for Bdq and Dlm, respectively.

Physicians who used Bdq had previously treated a limited number of patients with this drug (median: four patients (interquartile range (IQR) 2–25)). Out of a total of 1044 Bdq-treated patients, this drug had to be stopped in eight cases following QT prolongation (0.77% (95% CI 0.04–1.57)). One cardiac event was reported (0.10% (95% CI 0.01–0.63)) in a 55-year old diabetic patient from Somalia, treated for lymph node MDR-TB, who developed an asymptomatic first-degree atrioventricular block associated with QT interval prolongation (QTcF=460 ms) while receiving moxifloxacin, clofazimine, cycloserine, Bdq, ethambutol and prothionamide. The QT prolongation was recorded in association with an overdose of Bdq during the continuation phase of treatment, where the patient took 600 mg of Bdq daily for 5 days, instead of 200 mg three times a week, due to a misunderstanding of the prescription. The patient was hospitalised and, after 3 weeks, his QTcF normalised and he continued Bdq until the end of treatment.

Overall, 220 patients were treated with Dlm, with each physician seeing a median of two patients (IQR 1–13). Dlm was stopped in one case following QT prolongation (0.45% (95% CI 0.02–2.89)) and one significant cardiac event was reported (0.45% (95% CI 0.02–2.89)) in a 23-year old female patient from Georgia. The patient, treated for pulmonary MDR-TB with Dlm, linezolid, clofazimine, capreomycin, cycloserine and pyrazinamide, and receiving metoprolol, experienced multiple episodes of hypokalaemia and concomitant QT prolongation (QTcF >500 ms) with transient palpitations and dyspnoea but no evidence of ECG alterations, which resolved after temporary treatment interruption.

Overall, the use of the new drugs in association with other QT-prolonging drugs was common (26 out of 35 (75%) with Bdq and 18 out of 20 (90%) with Dlm), with 10 out of 35 (29%) and 9 out of 20 (45%) physicians reporting the use of Bdq and Dlm with two or more QT-prolonging drugs. In particular, 14 out of 61 physicians (24%) used the Bdq–Dlm combination in concomitant treatment and 11 out of 61 (19%) used it sequentially, for a total of 38 patients exposed to both drugs.

QT monitoring during MDR-TB treatment is commonly performed in Europe, although the frequency of ECG testing and the management of QT prolongation vary substantially across centres and countries. Experience with new drugs still appears to be limited, especially for Dlm. Although most participants reported the use of the new drugs in association with other QT-prolonging agents, Bdq and Dlm were stopped in only a few cases because of QT prolongation. Few clinically relevant cardiac adverse events and no fatal cases were reported. These findings support published results [8–10] and recent data from a Phase III clinical trial testing Dlm *versus* a placebo [11]. In addition, a relevant proportion of physicians used the new drugs for treatment for more than 6 months [12, 13] and in combination with QT-interval prolonging agents [14, 15]. Limitations of this study include retrospective data collection, the analysis of aggregate data, incomplete coverage of the WHO Europe region with over-representation of Western Europe, bias linked to surveys which may lead to underestimating the number of events and the absence of sudden death in the questionnaire.

In conclusion, QTc interval monitoring is regularly performed by physicians treating patients with Bdq and/or Dlm in the WHO Europe region. The frequency of clinically relevant cardiac events associated with the use of these drugs is low. Among 1044 patients treated with Bdq and 220 patients treated with Dlm as part of a MDR-TB treatment regimen, not a single case of a fatal cardiac event was observed.

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