Research Letter submission

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TITLE:

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

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Take-home message: Few clinically relevant cardiac arrhythmias and no cardiac fatalities were observed in patients with MDR-TB treated with bedaquiline and delamanid in Europe

Dear Editor:

Introduction:

There is concern that many second line drugs used to treat multidrug-resistant (MDR)-tuberculosis (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 (QTc). Fluoroquinolones and, possibly, clofazimine can prolong the QTc[1,2], as do bedaquiline and delamanid.[3,4] A QTc >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 genetic predisposition, and >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 TB drugs; deaths in bedaquiline/delamanid 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 bedaquiline/delamanid for MDR-TB treatment in TBnet treatment centres within the World Health Organization (WHO) Europe region.

Methods:

In December 2016, a cross-sectional online survey was distributed to members of the Tuberculosis Network European Trialsgroup (TBnet; a Clinical Research Collaboration of the European Respiratory Society), and in parallel 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; in case of multiple answers with differences in content, participants were contacted to confirm the correct answer. Participants who reported cardiac events in patients receiving MDR-TB treatment containing bedaquiline/delamanid 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 bedaquiline/delamanid; and 3 questions on the use of the bedaquiline/delamanid combination. The full questionnaire is available at: 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.

Results:

Overall, 61 valid replies from different hospitals in 41/45 (91%) targeted countries, out of the 53 included in the WHO Europe region, were retained. The most represented countries were Italy (7 participants), Denmark and Spain (4 participants each). Most participants work in teaching/university hospitals (49%) and in TB reference hospitals (24%).

Most physicians (50/61: 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%) only in patients receiving new drugs or multiple QT-prolonging drugs, and 8 (16%) do not perform it in MDR-TB patients. In MDR-TB patients monitored for QT prolongation, ECGs are repeated weekly (23/42: 55%) or monthly (19/42: 45%) during treatment, either before

administering treatment (34/42: 81%), or 90-120 minutes after administration (8/42: 19%). Overall, 34 (68%) of participants use QTc interval, while 16 (32%) use uncorrected QT interval. Out of 34 participants measuring QTc, 41% use Fridericia correction (QTcF), 23% Bazett correction (QTcB), 18% use both, and 18% did not know which correction was used. Most physicians would stop bedaquiline and delamanid in case of prolongation above 500 ms (27/61: 44%), or only in case of symptomatic arrhythmias (23/61: 37%); 19% (12/61) would also stop the drugs for any prolongation above normal values (470 ms in women, 450 ms in men).

Overall, 35 participants (57%) had experience using bedaquiline, and 20 (33%) using delamanid. 43% (15/35) and 30% (6/20) of those using bedaquiline and delamanid, respectively, require approval from another health body to use the new drug, mainly national consiliums. While most physicians used new drugs for no longer than 24 weeks, 26% (9/35) and 20% (4/20) had prescribed treatment durations up to 20 months for bedaquiline and delamanid, respectively.

Physicians who used bedaquiline had previously treated a limited number of patients with this drug (median: 4 patients (interquartile range (IQR): 2-25)). Out of a total of 1044 bedaquiline-treated patients, this drug had to be stopped in eight cases following QT prolongation (0.77%, 95% confidence interval (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, bedaquiline, ethambutol, and prothionamide. The QT prolongation was recorded in association with an overdose of

bedaquiline during the continuation phase of treatment, when the patient took 600 mg daily of bedaquiline for 5 days, instead of 200 mg thrice a week, due to a misunderstanding of the prescription. The patient was hospitalized and, after 3 weeks, his QTcF normalized and he continued bedaquiline until the end of treatment.

Overall, 220 patients were treated with delamanid, with each physician seeing a median of 2 patients (IQR: 1-13); delamanid 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-years old female patient from Georgia. The patient, treated for pulmonary MDR-TB with delamanid, 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 (26/35: 75% with bedaquiline, 18/20: 90% with delamanid), with 29% (10/35) and 45% (9/20) of physicians reporting to have used bedaquiline and delamanid with two or more QT-prolonging drugs. In particular, 24% (14/61) of physicians used the bedaquiline-delamanid combination in concomitant treatment, and 19% (11/61) sequentially, for a total of 38 patients exposed to both drugs.

Conclusions:

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

delamanid. Although most participants reported the use the new drugs in association with other QT-prolonging agents, bedaquiline and delamanid were stopped in only 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 delamanid versus placebo.[11] In addition, a relevant proportion of physicians used new drugs for treatment >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 and 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 bedaquiline and/or delamanid in WHO Europe region. The frequency of clinically relevant cardiac events associated with the use of these drugs is low. Among 1044 patients treated with bedaquiline and 220 patients treated with delamanid as part of a MDR-TB treatment regimen, not a single case of fatal cardiac event was observed.

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Table:
List of countries and centres taking part to the study.

Country	N. of centers	Patients treated with Bdq*	Patients treated with Dlm*	Patients treated with Bdq and Dlm (concomitant/ sequential)	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)
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)	
Netherlands	3	10	4	1 (1/0)		
United Kingdom	3	3	1			
Ukraine	1	1				
Total	**61**	**1044**	**220**	**38 (20/18)**	**9 (8/1)**	**2 (1/1)**