ECG findings in BPaL-based TB treatment regimens: the geographical effect on QT prolongation

Motta I[1], Cusinato M[2], Ludman A[3], Abdrasuliev T[4], Butabekov I[5], Tigay Z[4], Liverko I[5], Parpieva N[5], Moodliar R[6], Solodovnikova V[7], Kazounis E[1], Nyang'wa BT[8], Fielding K[2], Berry C[1]

1 Médecins Sans Frontières, London, UK; 2 London School of Hygiene and Tropical Medicine; 3 Royal Devon and Exeter NHS Foundation Trust, UK; 4 Republican Phthisiology Hospital, Nukus, Uzbekistan; 5 TB Institute, Tashkent, Uzbekistan; 6 TB and HIV Investigative Network, South Africa; 7 RSPCPT Minsk, Belarus; 8 Médecins Sans Frontières, Amsterdam, Netherlands

Introduction

QT prolongation is a known adverse effect of many tuberculosis (TB) drugs and the WHO has recommended monthly monitoring for RR (rifampicin resistant)-TB patients with electrocardiogram (ECG) since 2014. Newly recommended BPaL (Bedaquiline-Pretomanid-Linezolid)-based regimens also contain QT-prolonging drugs. In STREAM Stage 1 Clinical Trial more QTcF (QT corrected with Fridericia's formula) interval prolongation events occurred in Mongolia compared with other sites. We explored if there were differences in QTcF prolongation events in investigational arms according to country of enrolment in **TB-PRACTECAL clinical trial.**

In case you missed:

TB-PRACTECAL showed that participants receiving 6-month oral **BPaLM** had 89% of favourable outcomes versus 52% in WHO-Standard of Care.

BPaL and BPaLC also proven to be effective and safe.

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TB physicians should feel comfortable in prescribing these new regimens

Methods

We performed a post-hoc analysis of participants enrolled in investigational arms before 1st September 2020 across sites in Belarus, South Africa, and Uzbekistan. We assessed the direct effect of country of enrolment on QTcF >450 msec using Direct Acyclic Graphs to specify a causal framework identifying the sets of adjustment variables. This cut-off was chosen because of the paucity of observations with QTcF >480 msec and only 1 event>500 msec across investigational arms (BPaLC). The binary outcome was modelled using generalised linear mixed model with a logit link. Repeated measures were considered using random effects.

Full ethical approval was obtained for the main trial. For this post-hoc analysis of trial data, additional informed consent was not sought.

Uzbekistan observed a larger number of ECG with QTcF >450ms compared to Belarus and South Africa. Further studies investigating environmental site-related or genetic factors are warranted

Results

328 participants were included, with 112, 108 and 108 enrolled in BPaLM (BPaL-Moxifloxacin), BPaLC (BPaL-Clofazimine) and BPaL arms, respectively. 3,744 ECGs were recorded over the 24 weeks of treatment. Overall, the mean QTcF at baseline was 396.6, SD 18.6 msec. The average of the maximum QTcF value observed over 24 weeks was higher for BPaLC (mean 446.5, SD 19.4 msec) compared to BPaLM (mean 439.5, SD 20.7 msec) and BPaL (mean 436.0, SD 22.2 msec). 397 events of QTcF >450 msec were observed across the investigational arms over 24 weeks. Uzbekistan observed a larger number of events (323/1846, 17.5%) compared to Belarus (48/697, 6.9%) and South Africa (26/1201, 2.1%). The odds of QTcF >450 msec in a given patient in the investigational arm (regardless of treatment, baseline QTcF and creatinine) was 5.91 (95%CI .52;13.86) times higher in Uzbekistan compared to Belarus.

Discussion

QTcF interval in BPaL-based regimens may have a geographical determinant. The underlying mechanism is unclear. Further studies exploring whether the effect of country on QTcF interval is explained by environmental site-related factors or genetic determinants for drugs exposure are warranted.

Variables		BPaLM N=112	BPaLC N=108	BPaL N=108
Country	Belarus	20 (17.9%)	19 (17.6%)	20 (18.5%)
	South Africa	39 (34.8%)	38 (35.2%)	36 (33.3%)
	Uzbekistan	53 (47.3%)	51 (47.2%)	52 (48.1%)
Sex at birth	Male	63 (56.2%)	71 (65.7%)	56 (51.9%)
	Female	49 (43.8%)	37 (34.3%)	52 (48.1%)
Age (years)	Mean (SD)	36.1 (11.6)	33.5 (10.7)	37.5 (11.6)
	Median	34.2	32.1	36.6
	IQR	27.1, 44.7	25.3, 41.2	28.1, 45.0
	Range	18.2 - 61.2	15.5 - 68.0	15.7 - 72.5
BMI (kg/m²)	Mean (SD)	20.8 (4.7)	20.2 (4.2)	20.8 (3.7)
	Median	19.7	19.4	20.6
	IQR	17.6, 22.2	17.6, 21.9	18.1, 22.7
	Range	15.6 - 47.2	13.2 - 37.6	13.4 - 33.0
HIV status	Negative	83 (74.1%)	85 (78.7%)	74 (68.5%)
	Positive	29 (25.9%)	23 (21.3%)	34 (31.5%)

Summary of baseline characteristics across investigational arms. SD standard deviation, IQR interquartile range, BMI body mass index

Model	N_e	QTcF*	aOR	95% CI
Country[1]				
Belarus	863	52	1.00	--
South Africa	1364	33	0.97	(0.35 to 2.67)
Uzbekistan	2249	329	5.91	(2.52 to 13.86)

Model results for the direct effect of country in the investigational arms (over 108 weeks).
**** QTcF>450ms. Model estimating the effect of country, adjusting for baseline QTcF, baseline creatinine, regimen***

BPaL-based regimens caused few and predominantly mild QT-prolongation events

Acknowledgements

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References

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