Optimal longitudinal QT interval correction method considering changes in heart rate variability in patients treated for drug-resistant tuberculosis

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Introduction

- Active tuberculosis (TB) is associated with tachycardia, which diminishes with treatment
- Standard constant correction factors for QT interval, such as Bazett's (0.5). and Fridericia's (0.33), may result in sub-optimal correction in this population[1,2,3].
- A correction factor of 0.4081 has been proposed by Olliaro to optimally correct the QT interval in patients with TB pre-treatment[1].
- With a decrease in HR over time, QT-HR correlation also changes, suggesting the need for time-dependent correction.

Aim

To establish a time-dependent correction method for QT interval that optimally accounts for gradual changes in HR during the treatment period.

Methods

Data

- 440 Multidrug-resistant (MDR) TB patients received bedaquiline (BDQ) or a placebo for 8 weeks (C208, stage 1) or 24 weeks (C208, stage 2, or C209) on top of a background regimen.
  i. C208 (2-stage, randomized, double-blind, placebo-controlled)[4,5].
  ii. C209 (single-arm, open-label)[6].
- Baseline and on-treatment ECG measurements were included, and BDQ and M2 (main metabolite of BDQ) concentrations were predicted using a published pharmacokinetic model[7] at the time of ECG measurements.
- Two independent studies were used for external validation:
  i. The A5343 DELIBERATE study (N=82), a phase 2, open-label, randomized, controlled trial, in patients receiving BDQ, delamanid, or both for 24 weeks in addition to background treatment[8].
  ii. The PROBeX study (N=195), a prospective cohort study of patients in South Africa receiving a BDQ-containing regimen for 24 weeks[9].

Model and time-varying correction factor development

HR model was initially developed to describe the change in HR during treatment. Time-varying correction factor was then constructed using a parameter from the HR model that describes the rate of change in HR.

Correction Factor Evaluation

- Linear regression analyses in time intervals using QTc and HR.
- Linear regression of the interval-specific slopes (the slope between QTc and HR) accounting for standard error in the estimate was used.
- Successful correction was indicated by the slopes and r^2 values being close to 0.

Software

- Model development and simulation: NONMEM V. 7.4.4 & 7.5 and PSN 5.3.0.
- Visualization and analysis: R 4.2.2.

Result

The full HR model (eq. 1) included components describing;

- An asymptotic change in heart rate with time after study start (eq. 2)
- 24 & 12-hour circadian rhythm cycles (eq. 3)
- Effect of M2 (Emax-model) (eq. 4)
- Patient covariates (eq. 5, eq. 6)

$$HR(t) = (HR_{baseline} + TE(t) + DIUR(CTIME)) * (1 - M2EF) \quad \text{(eq. 1)}$$

$$TE(t) = (HR_{recovered} - HR_{baseline}) \cdot \left(1 - e^{\frac{-\log(2)t}{tprog}}\right) \quad \text{(eq. 2)}$$

$$DIUR(CTIME) = A_{24} \cdot \cos\left(\frac{2\pi(CTIME-\varphi_{24})}{24}\right) + A_{12} \cdot \cos\left(\frac{2\pi(CTIME-\varphi_{12})}{12}\right) \quad \text{(eq. 3)}$$

$$M2EF = \frac{E_{max,M2} \cdot Conc_{M2}}{EC50_{,M2} + Conc_{M2}} \quad \text{(eq. 4)}$$

$$P_j = \theta_0 \cdot \left(\frac{X_{ij}}{M(X_j)}\right)^{\theta_j} \quad \text{: for continuous covariates} \quad \text{(eq. 5)}$$

$$P_j = \theta_0 \cdot (1 + \theta_i X_{ij}) \quad \text{: for categorical covariates} \quad \text{(eq. 6)}$$

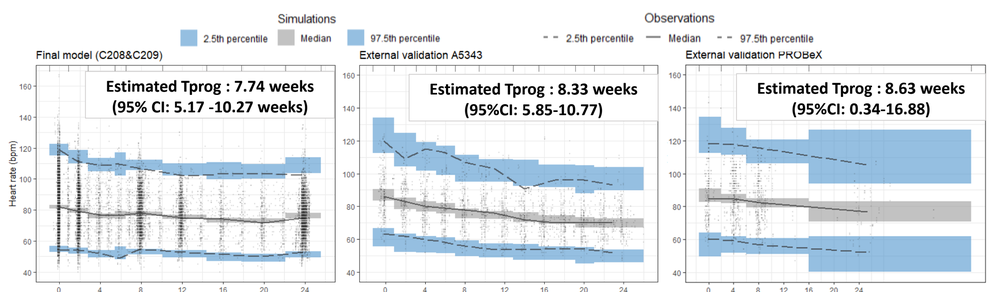
$HR_{baseline}$: Heart rate at baseline, $HR_{recovered}$: Heart rate at recovered (steady state), Tprog: the time to reach 50% of recovered HR from baseline (in weeks), A: Amplitudes(bpm), φ: acrophases(h), CTIME: clock time, $E_{max,M2}$: maximal effect of M2, $EC50_{M2}$: the M2 concentration producing 50% of maximal effect, $Conc_{M2}$: the predicted concentration of M2, Pj is the j^{th} population estimate of parameters, Xij is the covariate of subject i for the parameter Pj, M(Xj) is the median of covariate X for the population, θ_0 is the typical value of the parameter Pj, and θi is a constant that reflect the proportional covariate's effect on the parameter for i.

Table 1: Parameter estimates of the final HR model

	Description	Parameter Estimate (%RSE)	IIV %CV (%RSE)
Time on treatment	Baseline HR (bpm)	78.2 (1.2)	15 (4)
	Recovered HR (bpm)	73.1 (1.4)	15.4 (6)
	T_{prog} (weeks)	7.74 (16.8)	
Circadian rhythm	Amplitude 24 h (bpm)	6.2 (13.6)	95.3 (9)
	Peak time 24 h (clock time)	15.7 (1.3)	
	Amplitude 12 h (bpm)	1.65 (19.7)	95.3 (9)
	Peak time 12 h (clock time)	10.1 (4.8)	
	Box-cox shape for IIV amplitudes	−0.77 (20.9)	
M2 effect on HR	E_{max} (fraction)	0.179 (11.1)	
	EC_{50} (ng/mL)	2600 (13)	883.4 (2)
Covariate effects	Effect of study on HR (Study C209 vs C208)	0.047 (31.3)	
	Effect of changes in body weight on HR	−0.2 (15.2)	
	Effect of baseline serum albumin on HR	−0.22 (17.6)	
	Effect of baseline MGIT[b] on baseline HR	−0.05 (22.9)	
	Effect of age on recovered HR	0.08 (30.1)	
Residual error model	Proportional RUV (%)	8.4 (2)	23.6 (8)
	Additive replicated-specific RUV (bpm)	2.7 (1.9)	38.5 (4)

HR: heart rate, T_{prog}: time to reach 50% of recovered HR from baseline, EC_{50}: half maximum effect concentration, E_{max}: maximum effect, h: hour, MGIT: mycobacteria growth indicator tube, IIV: inter-individual variability CV: coefficient of variation, RSE: residual standard error, RUV: residual unexplained variability

Figure 1: Visual predictive check of the final model for C208 & C209 and external validation dataset (A5343, PROBeX), 1000 simulations, parameter re-estimated for validation dataset



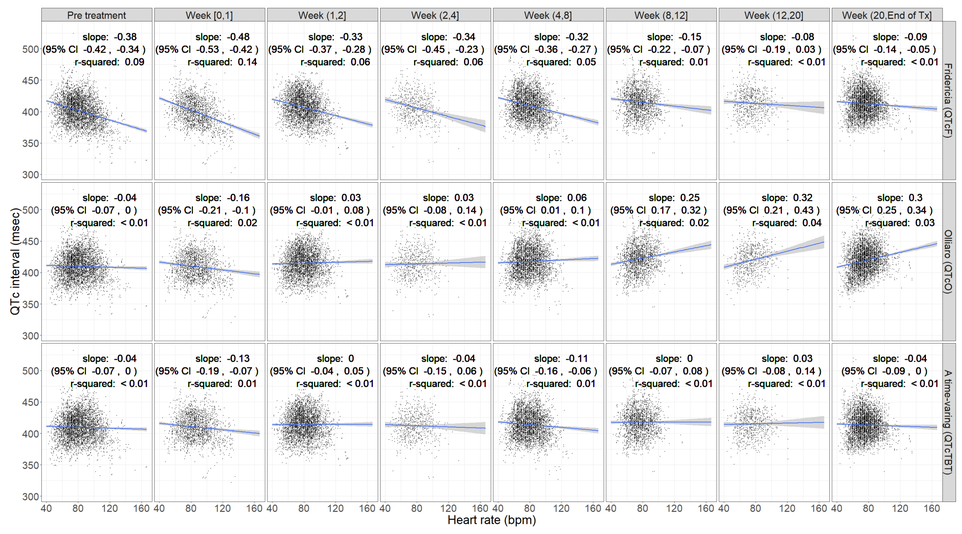
- The estimated T_{prog} from the final model (supported by comparable T_{prog} estimates from the base model, 8.15 weeks [95%CI 5.47-10.87], and from A5343 and PROBeX studies) was utilized to construct the time-varying correction factor, assuming that the estimated HR recovery rate represents the rate of change for the correction factor, as per the following formula:

$$CF(t) = 0.4081 - (0.0781) \cdot \left(1 - e^{\frac{-\log(2) \cdot t}{7.74}}\right)$$

Correction factor(CF) decreases asymptotically from 0.4081 (Olliaro's)[1] towards 0.33 (Fridericia's) over the time on treatment (t).

- The performance evaluation showed that the overall slope derived from the time-varying CF was not different from 0 (-0.008 [95%CI -0.004-0.003]), whereas the slope derived from QTcF was 0.013 (95%CI 0.009-0.016).

Figure 2: QTc versus heart rate plot with linear regression analysis, including slope, confidence interval, and r^2 values for Fridericia corrected (QTcF), Olliaro corrected (QTcO), and time-varying corrected QT (QTcTBT) from C208&C209 datasets.



Conclusion

- **The newly developed time-varying correction method can capture the natural change in QT-HR correlation that occurs during TB treatment, enhancing accuracy in QT prolongation determination**.
- It may alleviate the issue of QTcF underestimating the QT interval in early treatment and reduce the overestimation of QTc change from the baseline.
- As a result, this method enables more informative analysis of drug effects on QT in clinical trials and facilitates better treatment decisions for individual TB patients.

In collaboration with

Janssen | PHARMACEUTICAL COMPANIES OF Johnson&Johnson

ACTG AIDS CLINICAL TRIALS GROUP

The PROBeX study team

UPPSALA UNIVERSITET

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