Concentration-QT modelling of Bedaquiline, Clofazimine, and Pretomanid in TB patients

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Background and Objectives

Bedaquiline (BDQ), clofazimine (CFZ), and pretomanid (Pa) are used for drug-resistant TB (DR-TB).

BDQ, through its main metabolite M2, CFZ, and Pa have all been associated with QT interval prolongation.

Due to the multidrug nature of tuberculosis treatment, there is a risk of additive cardiac toxicity.

Limited information is available on the drug-drug interactions and combined toxicity of these drugs.

The objectives:

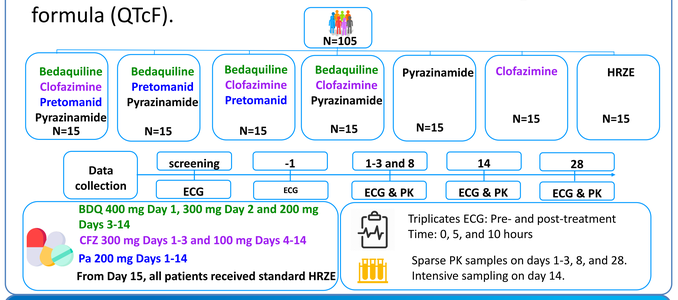
Describe exposure-QT relationship and possible drug-drug interactions between these drugs.

Evaluate the impact of optimized dosing regimen on QT

Methods

Adult drug-susceptible TB patients were enrolled in a 14-day early bactericidal activity study of CFZ, alone or in combination with BDQ or PRET.

The QT interval was corrected for the heart rate using Fridericia[1] formula (QTcF).



Results - Patient population

Table: Participant's baseline characteristics

Characteristics	**N = 105**
Age, years	30 (23 – 40)
Weight, kg	53.8 (46.9 – 60.4)
Fat-Free Mass, kg	30.1 (37.5 - 57.7)
Sex (% Males)	65 (62)
HIV Status - % Positive	11 (11)
Overall-Baseline QTcF (ms)	390 (379-401)
Overall-Baseline heart rate (bpm)	89.3 (77.4 – 100)

Data in median (IQR)/ n (%)

Results – Baseline and exposure-QT models

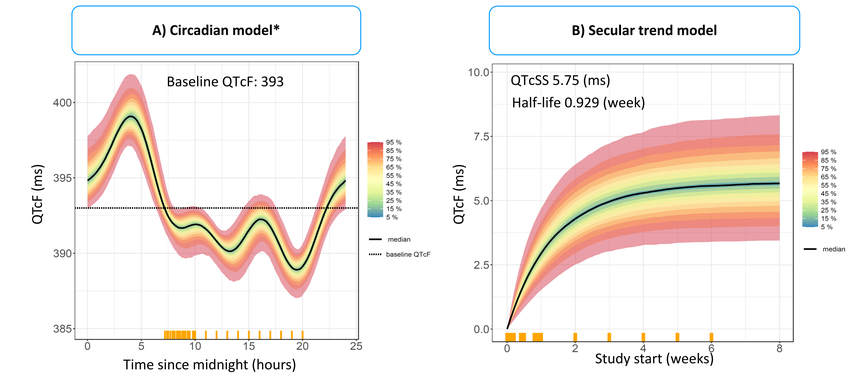


Figure 1: Baseline model accounting for circadian variations (left) in QT vs time since midnight and time-effect model (right) since study start in weeks. The solid black line represents the final median parameter estimate, the shaded colored areas reflect the overall uncertainty or different confidence intervals.

*Priors were used to guide parameter estimates[2]

Pre-treatment, pyrazinamide and HRZE arms were used to characterize the overall baseline and covariates known to affect QT.

Circadian variation in QT was described using a combination of cosine functions (Figure 1A).

The effect of time on treatment on QT, an effect known as a secular trend[3] was described using exponential model (Figure 1B)

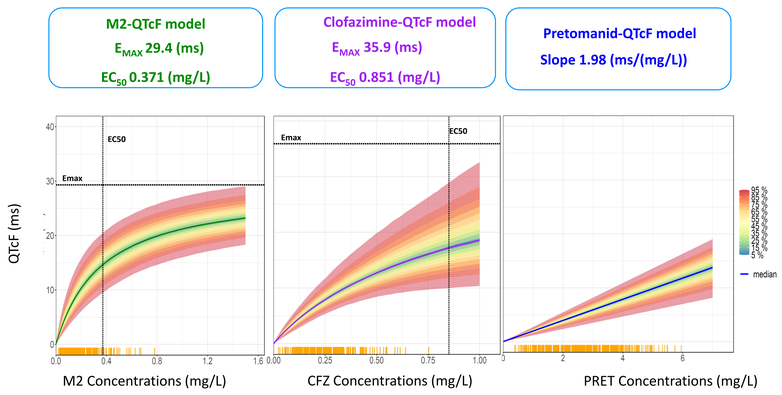


Figure: Exposure-QTcF models showing emax models between M2 and CFZ concentrations and QTcF and linear model between QTcF and pretomanid concentrations. The solid line represent the final median parameter estimate, the shaded colored area reflect the overall uncertainty or different confidence intervals.

- M2 and CFZ effect on QT were described by an Emax functions with a maximum QT prolongation up to 29 and 35 ms, respectively.
- Pa effect was mild and was described by a linear function.
- We characterized a competitive interaction between M2 and clofazimine, resulting in a less than additive effect of CFZ on QT.
- On average, the competitive interaction shifted CFZ EC50 by +26%

Results – PK/PD simulations

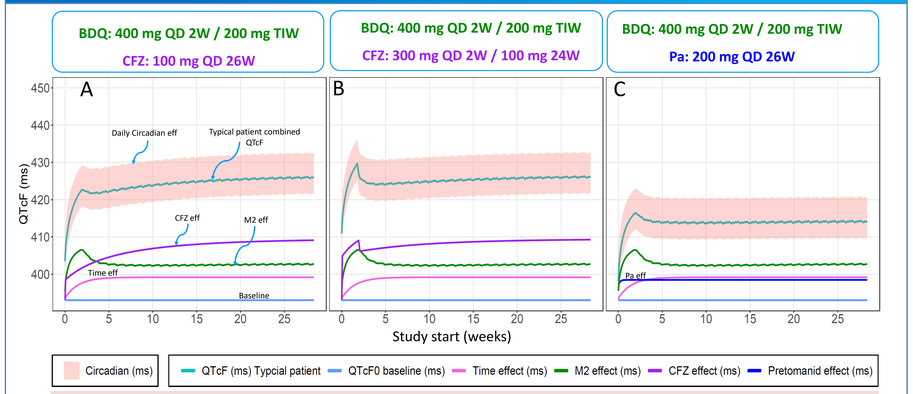


Figure: Simulated QTcF profile for a typical TB patient (weight 56 kg) receiving an oral standard (A and C) and optimized dosing (B) of bedaquiline, clofazimine and pretomanid. QD, once daily; TIW, three times a week. The figure shows the individual contribution to the QTcF interval and the overall combined effect vs time in weeks.

We simulated QT profile following:

- Standard dosing of BDQ and CFZ as part of MDR-TB regimen (A).
- Loading 300 mg dose of CFZ for two weeks with BDQ standard dosing (B).
- Standard dosing of BDQ and Pa as part of BPaL regimen (C).

Patients receiving bedaquiline and clofazimine as a loading dose had the highest increase in QT.

Patients receiving bedaquiline and pretomanid as part of the BPaL regimen showed mild increase in the QT.

Conclusions

- M2 QT effect is different from what is reported in literature[3]. Likely explanation is different companion drugs.
- Competitive interaction between BDQ and CFZ resulting in less than additive effect of CFZ on QT. However, these findings need to be further validated as BDQ was not given alone.
- Pa effect on QT is additive to BDQ/M2 and CFZ, with a slope similar to what was previously reported[4].
- Frequent safety monitoring especially during initial treatment period and in patients with lower weight is important to avoid cardiac related side effects.

References

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