Population pharmacokinetics of pretomanid in participants of a randomised controlled clinical trial for rifampicin-resistant tuberculosis.

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Background

Pretomanid is a nitroimidazole antibiotic with activity against both replicating and non-replicating Mycobacterium tuberculosis (TB) bacilli. Participants received pretomanid 200mg daily as part of a BPaL (bedaquiline 400mg daily for 2 weeks followed by 200mg three times a week for 22 weeks, pretomanid 200mg daily for 24 weeks, linezolid 600mg daily for 16 weeks then 300mg for 8 weeks) plus/minus M (moxifloxacin 400mg daily for 24 weeks) or C (clofazimine 100mg daily for 24 weeks) regimens. Participants with HIV received integrase inhibitor-based antiretroviral therapy.

We aimed to characterise pretomanid pharmacokinetics in rifampicin-resistant TB patients enrolled in the TB-PRACTECAL clinical trial.

Methods

Participants from five sites in South Africa and Belarus without severe renal or hepatic function impairment, provided serial venous blood at day 0 (0, 2, 23hrs), week 8 (0, 6.5, 23hrs), trough samples at the week 12, 16, 20, 24 and further samples at week 32 and 72 visits. Plasma was separated, stored at minus 60^0C and transported to a central bioanalytical facility. Quantification was conducted using high performance liquid chromatography-tandem mass spectrometry. Non-linear mixed effects modelling (saem and focei algorithms) of the data was conducted using nlmixr2 package in r.

Results

94 participants (36% female, 42% HIV positive, 55% Black, 42% Caucasian, mean BMI = 21) contributed 954 drug concentration observations. A one compartment, first order absorption and elimination model best described the data. Random effects on clearance (CL) and central volume of distribution (V) were included in the model to explain the inter-individual variability (IIV). A combined proportional and additive residual error model was used for unexplained variability. Fat free mass was the only covariate retained in backward elimination ($p < 0.001$) after BUN, Creatinine clearance, AST, race and treatment regimen were included in the forward analysis ($p < 0.05$).

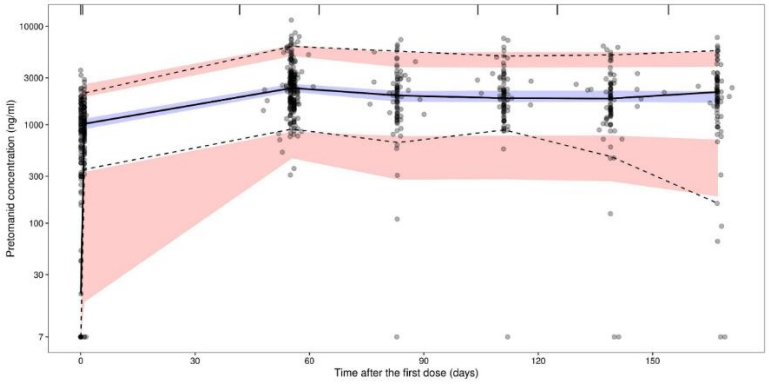

Figure 1: Visual Predictive Check plot of the final pretomanid model.
The black circles in the figure represents the observed plasma concentrations. Solid black line and dash black line represent the median and 95% confidence interval of observations, respectively. The purple area represents a simulation-based 95 % confidence interval for the median. Simulated prediction intervals for 5% and 95% percentiles are presented with pink

The final popPK model parameter estimates for the apparent absorption rate constant (Ka), clearance (CL/F) and volume of distribution (V/F) were 0.316 h^{-1}, 3.08 L/hr and 103 L respectively. Inter individual variability of CL and V (shrinkage) were 32.7% and 35.1%, respectively. The median (range) empirical Bayesian estimates of steady state C_{max}, AUC_{0-24} and C_{trough} were 3.18 (1.38 – 6.35) µg/mL, 63.8 (30.9 – 139) µg/mL and 1.97 (0.065 - 7.70)µg/mL.

Conclusions

An optimal design-led sparse sampling approach nested in a phase 3 randomised controlled trial facilitated development of a final pretomanid popPK model with acceptable primary and secondary PK parameter estimations. The PK parameter estimates in the rifampicin resistant patients were similar to those previously reported.