Drug effect of clofazimine on persisting mycobacteria explain an unexpected increase in bacterial load from patients

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Introduction

Clofazimine (CFZ) and pyrazinamide (PZA) are important components of recommended standard multi-drug treatments of TB. Paradoxically, in a Phase IIa clinical trial aiming to define the early bactericidal activity (EBA) of CFZ and PZA monotherapy over the first 14 days of treatment, no significant drug effect could be demonstrated for the two drugs using traditional statistical analysis [1]. An unexpected numerical increase in colony forming units (CFU) over time, was observed with CFZ monotherapy.

Objective

To link clinical pharmacokinetic (PK) and pharmacodynamic (PD) data, through the Multistate Tuberculosis Pharmacometric (MTP) model, in order to evaluate drug effects of CFZ and PZA in monotherapy on different bacterial substates, to explain change in colony forming units (CFU).

Methods

CFU and PK data from 14 and 15 patients receiving CFZ and PZA, respectively, was analyzed using non-linear mixed effects modelling. A population PK model was developed for CFZ, whereas a previously developed PK model was used for PZA. Individual PK profiles were linked to the MTP model[3,4] to explore exposure-response relationships on the killing of different mycobacterial substates, for both drugs in monotherapy.

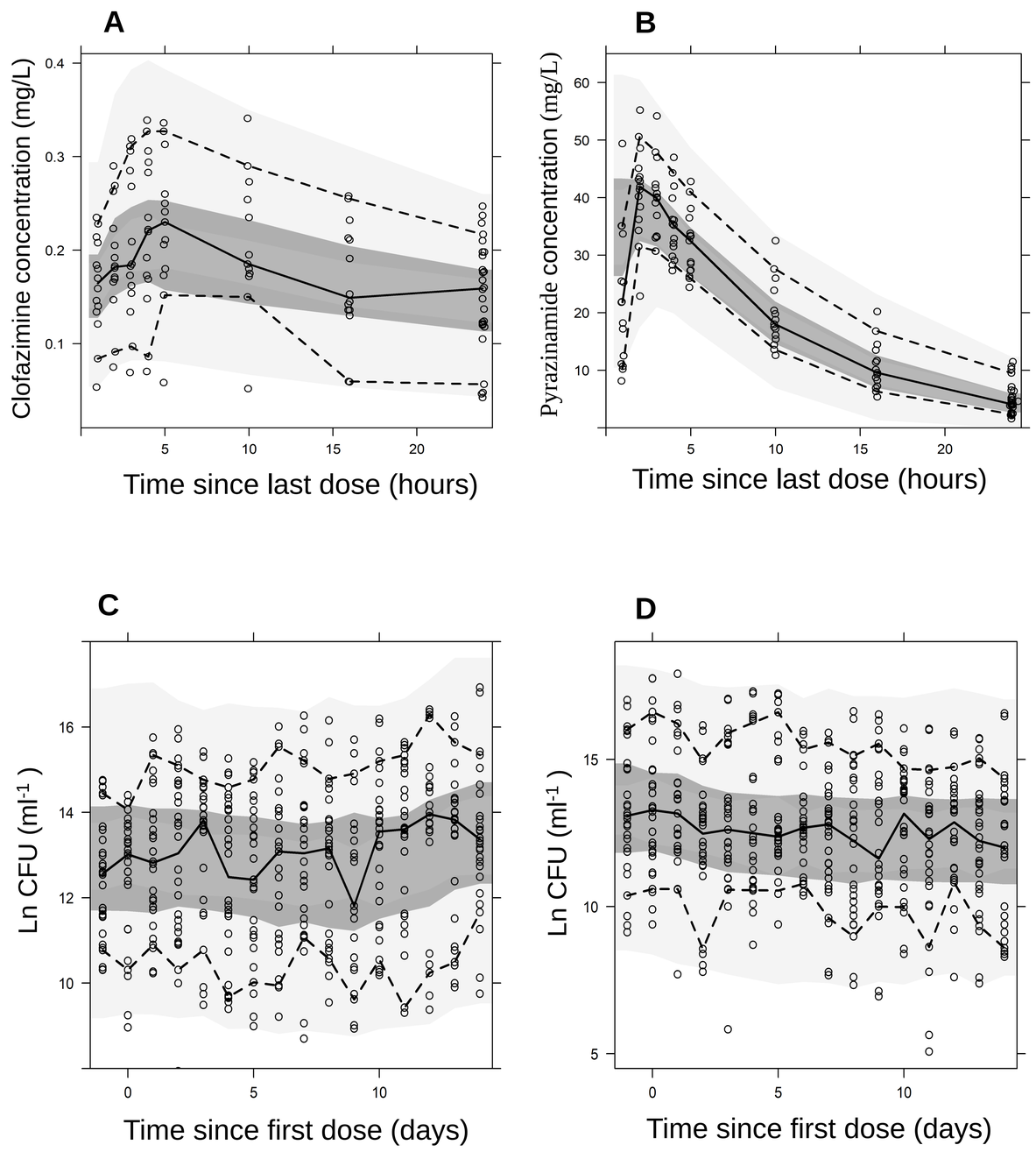

Figure 1. Visual predictive checks of the final MTP model of CFU data and population PK models. Top left and top right shows concentration versus time after (A) CFZ, and (B) PZA, respectively. The lower left and right show CFU over time after (C) CFZ, and (D) PZA, respectively. The solid and dashed lines are the median, 10th and 90th percentiles of the observed data. Shaded areas from top to bottom, are the 95% confidence interval of the 90th (light grey), median (dark grey) and 10th (light grey) percentiles of the simulated data. Observations are illustrated as open circles.

Acknowledgements

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Results

A two-compartment model with first order absorption and elimination together with an absorption lag-time was supported by the clofazimine PK data. Inter-individual variability (IIV) was supported for apparent oral clearance (CL/F), apparent volume of distribution (V/F) and the first-order absorption (ka) parameter. Inter-occasional variability (IOV) was supported for bioavailability. No statistically significant covariate relationship was found using body weight, age and sex on CL/F or V/F. Using the MTP model [3,4], statistically significant exposure-response relationships were characterized for both drugs, with a linear concentration-dependent killing effect for CFZ on persistent tubercular bacilli and a linear concentration dependent effect for PZA on semi-dormant mycobacteria. The final model could explain the original findings of paradoxical increase in CFU with CFZ treatment as well as no effect with PZA when the analysis did not include variables for different metabolic states of mycobacteria.

Conclusions

A novel semi-mechanistic model-based analysis of individual PK and sputum CFU counts revealed significant activity of CFZ and PZA on persistent and semi-dormant mycobacteria, respectively, which remained undetected with traditional methods of quantification, of anti-tuberculosis drug effect. Further, the drug effect on persistent tubercular bacilli explained the unexpected increase in CFU after CFZ monotherapy. We propose that this quantitative approach that provides a rational framework for analysing drug effects in Phase IIa EBA studies, can accelerate anti-TB drug development.

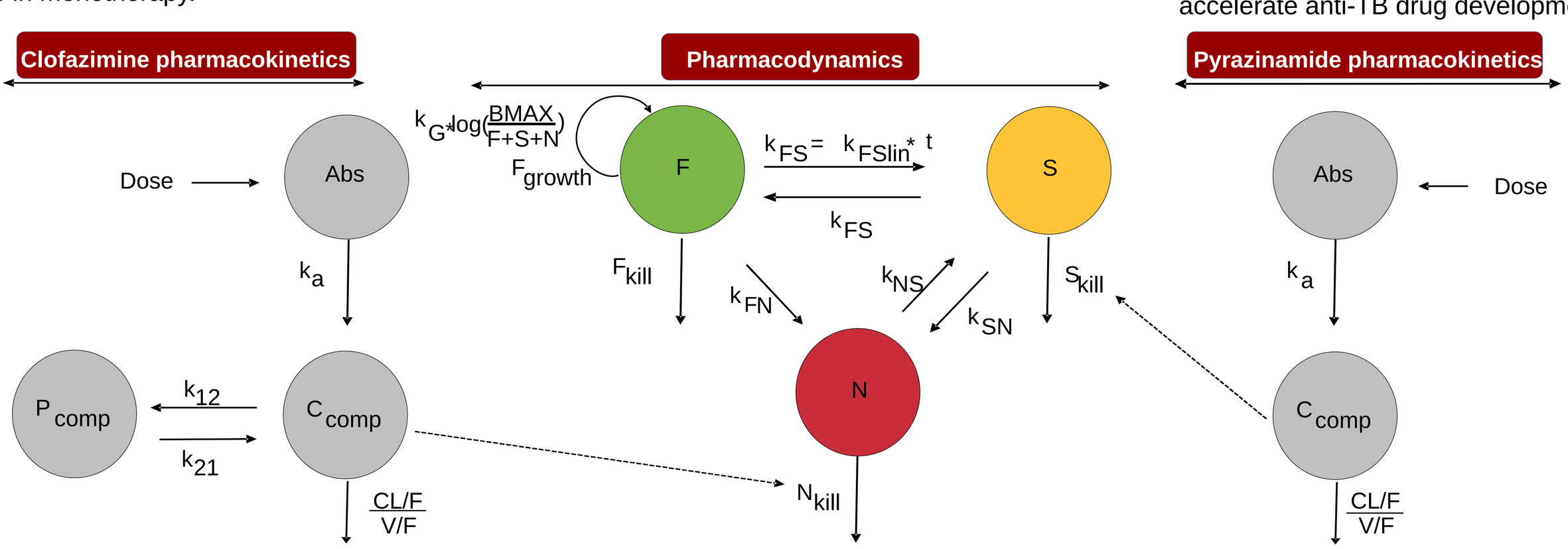

Figure 2. Illustration of the discovered exposure-response relationships discovered, driven by individual PK profiles generated from two separate population pharmacokinetic models of CFZ and PZA on The MTP model in the centre.

References

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