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

Alan Faraj\textsuperscript{1}, Robin J. Svensson\textsuperscript{1}, Andreas H. Diacon\textsuperscript{2} and Ulrika Simonsson\textsuperscript{3}

\textsuperscript{1}Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden; \textsuperscript{2}TASH Applied Science, Cape Town, and Division of Physiology, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa

Correspondence: alan.faraj@farmbio.uu.se

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.

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 (IVV) 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.

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\textsuperscript{1} Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden; \textsuperscript{2}TASH Applied Science, Cape Town, and Division of Physiology, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa

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