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

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### No conflicts of interests

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Sensitive and informative analyses are needed to accurately explore drug effects in early clinical trials in order to make the right decisions for advancement to further development and clinical trials.
Clofazimine and pyrazinamide

- Clofazimine (CFZ) and pyrazinamide (PZA) are recommended against MDR-TB\(^1\)

- Efficacy *in vitro* and *in vivo*\(^2,3\)

- Addition of CFZ to multi-chemotherapy regimens accelerate sputum culture conversion and improve treatment success rates\(^4\)

EBA study

- Paradoxically, no statistically significant EBA for CFZ and PZA
- Increase in CFU over time after CFZ monotherapy
Killing persisters cause increase in CFU
Clinical trial simulations of a hypothetical drug
Hypothesis

Is increase in CFU by CFZ caused by killing of persisters only?
Aims

• Find a model-based explanation for the numerical increase of CFU counts after CFZ monotherapy

• Characterize potential exposure-response relationships of CFZ and PZA during 14 days monotherapy using a model-based framework
Data

Phase IIa 14 day EBA, open-label, randomized

- PZA monotherapy 1500 mg (n=15)
- CFZ monotherapy 300 mg for 3 days followed by 100 mg (n=14)
- Plasma concentration sampling on days 1, 2, 3 and 8 with rich sampling on day 14
- Daily colony forming units (CFU) data

Diacon AH et al. 2015 Am J Respir Crit Care Med
Methods

Multistate Tuberculosis Pharmacometric model

\[ k_{FS} = k_{FSlin} \times t \]

\[ k_G \times \log\left(\frac{B_{MAX}}{F+S+N}\right) \]

Methods

Multistate Tuberculosis Pharmacometric model

MPN = F+S+N

CFU = F+S

Hu et al 2015 Front Microb, Clewe et al 2019 Manuscript
Results

Final PK-PD models

Clofazimine PK

Pharmacodynamics

Pyrazinamide PK

\[ k_{FS} = k_{FSlin} \times t \]

Statistically significant (p<0.05) killing of the N state

Statistically significant (p<0.05) killing of the S state

\[ k_G \times \log \left( \frac{BMAX_{F+S+N}}{F} \right) \]

\[ C \frac{L}{F} \times V/F \]

\[ C \frac{L}{F} \times V/F \]
Population PK model results
Visual Predictive Checks

Clofazimine

Pyrazinamide
PK-PD Results
Visual Predictive Checks

Clofazimine

Pyrazinamide

Ln CFU (ml⁻¹)

Time since first dose (days)

Ln CFU (ml⁻¹)

Time since first dose (days)
Results

Simulations of typical bacterial numbers based on models

Clofazimine

Pyrazinamide
Conclusions

• Sensitive analyses are crucial for exploring drug effects in early clinical trials to make right decisions for advancement to further development

• The original analysis could not demonstrate significant efficacy for CFZ or PZA

• If the substance was in development it might have been wrongly rejected
Conclusions

• Statistically significant efficacy of CFZ and PZA monotherapy using CFU as a biomarker

• The CFZ effect on persistent bacilli may explain the unexpected increase in CFU

• The true mechanism of action of CFZ is still unknown

• This quantitative semi-mechanistic approach provides a rational framework for analysing EBA studies, and can accelerate TB drug development
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