The Effect of Antitubercular Drug Exposure On Disease Regression In South African Tuberculosis Patients

Emmanuel Chigutsa¹, Paolo Denti¹, Gary Maartens¹, Carl M.J. Kirkpatrick², Helen McIlneron¹, Mats O. Karlsson⁴

¹ University of Cape Town Department of Medicine, Division of Clinical Pharmacology
² Monash University, Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences
³ University of the Western Cape, School of Public Health, Cape Town
⁴ Uppsala University, Department of Pharmaceutical Biosciences
Introduction

- There is a lot of *in vitro* and animal data showing relationships between drug exposure and mycobacterial kill

Shandil et al AAC, 2007

Drusano et al MBIO, 2011
• There is also data in patient studies comparing drug regimens (and doses)

Dietze et al AJRCCM, 2008

Rustomjee et al IJTL, 2008
• However no clinical studies investigating the effect of individual drug exposure
• We have recently developed a model describing treatment response in patients using **days to positivity** in MGIT culture (Chigutsa et al, WCOP 2012)
• We also described the pharmacokinetics of **rifampicin** (Chigutsa et al AAC, 2011), **pyrazinamide** (Chigutsa et al, PAGE 2010), **ethambutol** (modified from Jonsson et al, AAC, 2011) and **isoniazid** (modified from Denti et al, PAGE 2011) in the same group of patients
Objectives

• To investigate the effect of the pharmacokinetics of the first line antitubercular drugs on the rate of decline of viable *M. Tuberculosis* in patients
Methods

• 73 patients on first line regimen with PK data and MGIT culture days to positivity data weekly for 8 weeks

• Time to event model for disease regression developed (Chigutsa et al, WCOP 2012)

• AUCs for all 4 drugs were obtained by integrating the PK model (references above) predicted concentration of drug in the plasma over a 24h period after the dose
RESULTS (base model)

\[ Mtb \text{ no.} = 0.0425e^{-3.13t} + 0.0014e^{-0.11t} \]

Slope for fast kill, \( \alpha = 3.13 \)
Drug effect

- Rifampicin AUC significantly influenced alpha (p<0.05)
  - Linear covariate model on alpha
  - \[\text{ALPHA} = 3.89 \times (1 + 0.018 \times (\text{AUC}-45))\]
  - i.e. 1.8% (95% CI=0.85,2.8) change in alpha for every 1 mg.h/L change in AUC from the median of 45 mg.h/L
- Pyrazinamide had a (borderline) significant effect on beta, but not when rifampicin was included in the model
Discussion

• Simulations of higher rifampicin doses showed minimal changes in plots

• Expected since half life of fast kill was 1.25 days

• Thus a drug with increased early bactericidal activity is of little benefit when it comes to shortening regimens

• Lack of significance of effect of other drugs (or rifampicin on beta) is probably due to limited sample size, hence larger studies with wider dose ranges are required
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