Multivariate Adaptive Regression Splines Analysis of Drug Exposure and Sterilizing Effect in Tuberculosis

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Limited PK-PD data in humans

- Few clinical studies investigating the effect of individual drug exposure (Chideya et al, CID 2009, Weiner et al, CID 2005)

- We have recently developed a model describing treatment response in patients using **days to positivity** in MGIT culture (Chigutsa et al, AAC 2013)
PK variability

• 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 Wilkins et al, BJCP 2011) in the same group of patients
Aim

- To investigate the extent to which the pharmacokinetics of rifampin, isoniazid, pyrazinamide and ethambutol, in a combined multidrug regimen, individually influence the rate of bacillary decline in patients.
Methods

• Time to event model for disease regression developed (Chigutsa et al, AAC 2013) which we used to obtain individual beta slopes

• 54 patients on first line regimen with PK data (AUC and Cmax), MGIT culture days to positivity data weekly for 8 weeks and MICs

• Multivariate adaptive regression splines (MARS) implemented in Salford Predictive Modeler software was used for data analysis
Methods - MARS

- Standard linear regression is limited because of non-linearity of biological systems
- Traditional statistics less applicable to data with high dimensionality
- Traditional methods unable to look at ‘subregions of interest’ in the data. Local non-parametric vs global parametric modeling
- MARS is a combination of recursive partitioning with fitting of splines in the data
MARS analysis

• Variables tested in the MARS model were individual drug AUC, Cmax, AUC/MIC, Cmax/MIC, time above MIC

• Dependent variable was beta slope in patients (sterilizing activity)
RESULTS – $\beta$-slope stratified by week 8 sputum conversion
MIC distribution

Isoniazid MIC (mg/L)

Rifampin MIC mg/L

Pyrazinamide MIC (mg/L)

Ethambutol MIC mg/L
MARS findings

• In patients with low rifampin exposure (AUC <35.4 mg*h/L):
  – Higher isoniazid Cmax resulted in lower beta slope
  – Ethambutol Cmax/MIC positively correlated with kill
  – Rifampin AUC positively correlated with kill

• In patients with high rifampin exposure (Cmax >8.2 mg/L):
  – Higher PZA AUC/MIC resulted in higher beta slope, but for ratios >11.3
  – Higher rifampin Cmax resulted in higher beta slope
  – Isoniazid and ethambutol not significant
Odds ratios for MARS predicted cut-offs on sputum conversion

<table>
<thead>
<tr>
<th>Drug threshold</th>
<th>Odds ratio of negative 2 month culture (95% CI)</th>
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<tbody>
<tr>
<td><strong>Rifampin</strong> $C_{\text{max}} &gt; 8.2$ mg/L and pyrazinamide AUC/MIC ratio $&gt; 11.3$</td>
<td>6.0 (1.5-23.7)</td>
</tr>
<tr>
<td>Rifampin $C_{\text{max}} &gt; 8.2$ mg/L regardless of pyrazinamide AUC/MIC ratio</td>
<td>3.8 (1.1-13.3)</td>
</tr>
<tr>
<td>Pyrazinamide AUC/MIC ratio $&gt; 11.3$ regardless of rifampin $C_{\text{max}}$</td>
<td>2.9 (0.78-10.7)</td>
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Discussion

• First report to quantitatively describe effect of individual drugs in multidrug regimen on kill rates in patients

• Recommended thresholds for RIF and PZA agree with previous reports (Peloquin, Drugs 2002; Pasipanodya et al, JID 2013)

• PZA threshold of 363 mg*h/L → AUC/MIC of 9.7-14.5

• Studies with more patients are required to confirm our findings
Isoniazid antagonism

Grosset et al, PNAS 2012
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