Linking rifampicin exposure to treatment response over six months in patients with pulmonary tuberculosis

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Background

Rifampicin (RIF) is the most important component of first-line anti-tuberculosis (TB) therapy, but the optimal dosing of this pivotal drug is uncertain. The potential for TB treatment shortening with higher doses of RIF has been studied recently [1].

Objective

To characterize the relationship between **RIF plasma exposure** and treatment response measured over 6 months **as time to stable culture conversion** (TSCC, i.e. 2 sequential negative cultures) in this trial [1].

Methods

Study design and data

The study was an open-label multi-arm multi-stage study in newly diagnosed adult pulmonary tuberculosis patients. The experimental arms used RIF 20 or 35 mg/kg, and/or substitution of ethambutol (ETH) with moxifloxacin (MOX) or SQ109 (Table 1).

Table 1. Treatment per study arm

Arm	Treatment month 1-3	Treatment month 4-6
1 - R35HZE	RIF 35 mg/kg + HZ + ETH	RIF 10 mg/kg + H
2 - R10HZQ	RIF 10 mg/kg + HZ + SQ109	RIF 10 mg/kg + H
3 - R20HZQ	RIF 20 mg/kg + HZ + SQ109	RIF 10 mg/kg + H
4 - R20HZM	RIF 20 mg/kg + HZ + MOX	RIF 10 mg/kg + H
	Treatment month 1-2	**Treatment month 3-6**
0 - RHZE (control)	RIF 10 mg/kg +HZ + ETH	RIF 10 mg/kg + H

H, isoniazid; Z, pyrazinamide

Response was monitored with liquid cultures from sequential sputum samples and TSCC was derived. The dataset included **336 patients** (97 with full plasma PK curves, day 28).

Analysis

A sequential PK-PD analysis using multiple imputation (MI) methodology [2] for patients lacking PK data was performed in NONMEM 7.3. In the MI procedure 100 sets of AUCs were simulated for each patient missing PK observations, and each tested in the PD model. Parameter values ($\tilde{\beta}$) with uncertainity ($\tilde{b}$) from the MI procedure were averaged to final estimates according to the equations below where n is the number of imputed datasets, $\hat{\beta}_x$ is the x:th estimate of parameter and $\hat{b}_x$ is the x:th estimate of the uncertainty of parameter.

$$\tilde{\beta} = \frac{1}{n}\sum_{x=1}^{n}\hat{\beta}_x \qquad \tilde{b} = \frac{1}{n}\sum_{x=1}^{n}\hat{b}_x + \frac{n+1}{n(n-1)}\sum_{x=1}^{n}(\hat{\beta}_x - \tilde{\beta})^2$$

Results

RIF PK was described with a simplified version of a previously presented model, including fat free mass (FFM) [3]. The model's prediction of AUC was evaluated with ncappc [4] (median observed values within predicted 95%CI for each dose group) and individual predictions with and without variability (Figure 1).

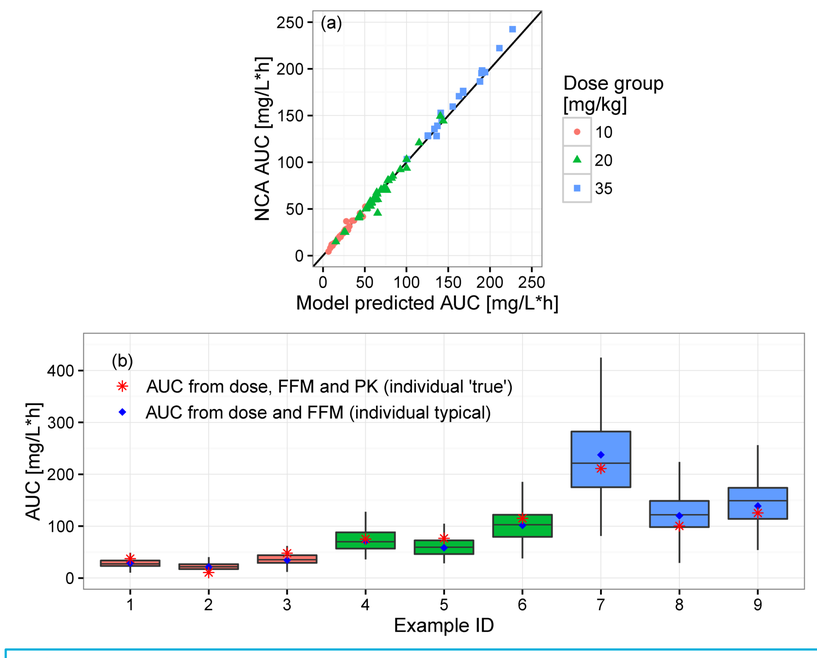

Figure1. Comparison between individual RIF AUC derived by non-compartmental analysis (NCA) and by the model, per RIF dosing level (red for 10 mg/kg, green for 20 mg/kg, blue for 35 mg/kg) (a), and distribution of AUCs (box-plots) simulated with inter-individual variability for nine example subjects and doses with corresponding individual typical and 'true' AUCs (b). All AUC values refers to 0-24 hours at day 28 for treatment.

TSCC was modeled with a time-to-event model; a three-parameter surge function defined the hazard (Table 2). The following covariates had significant (α=0.05) effects:

Shortening TSCC
- Higher RIF AUC (linear relation)
- Lower bacterial load at baseline (power relation)
- Lower proportion of missing sputum samples (power relation)
- Substitution with moxifloxacin

Increase TSCC
- Substitution with SQ109

The hazard function and the model fit per arm are illustrated in Figure 2 and 3.

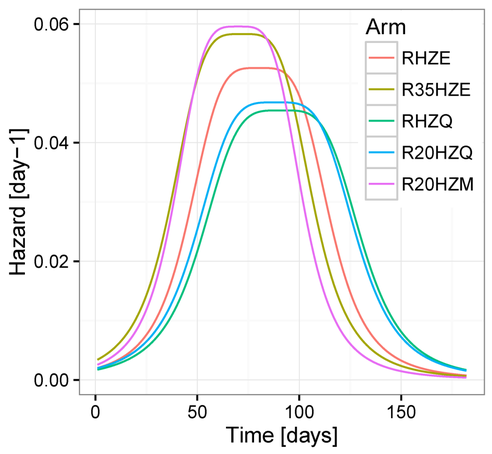

Table 2. Structural hazard model final estimates.

Parameter	Estimate	Uncertainity (RSE, %)
Surge amplitude [day^{-1}]	0.0539	12
Peak time [day]	78.3	4.1
Surge width[day]	35.4	7.0

Figure2. Hazard function for a patient with typical baseline bacterial load, proportion of missing sputum samples and RIF exposure per study arm.

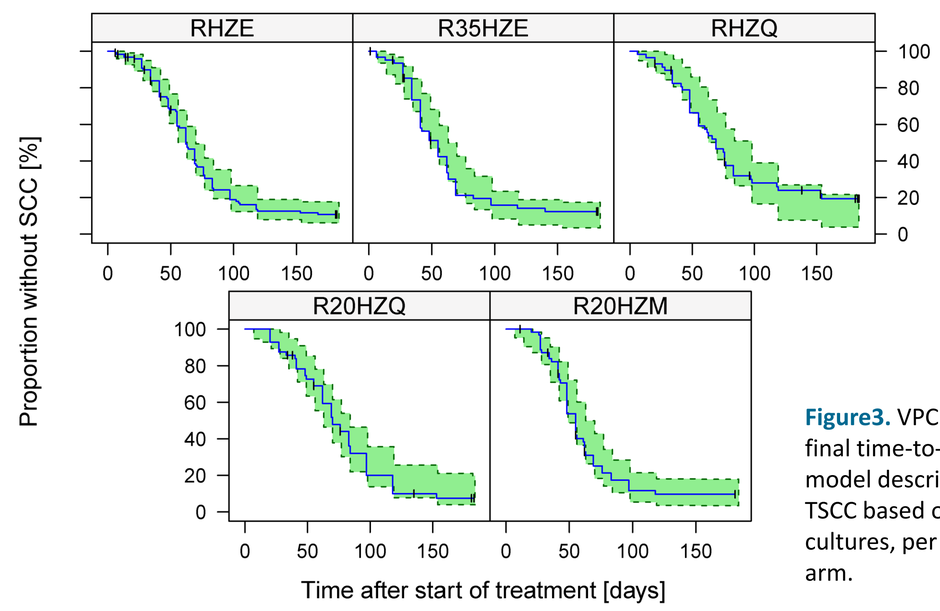

Figure3. VPC of the final time-to-event model describing TSCC based on liquid cultures, per study arm.

Simulations assuming standard regimen components, median baseline bacterial load and no missing sputum samples showed that the proportion of patients **with TSCC<8 weeks** is expected to **increase from 39% to 54%** when RIF dose is increased from **10 to 35 mg/kg** (Figure 4).

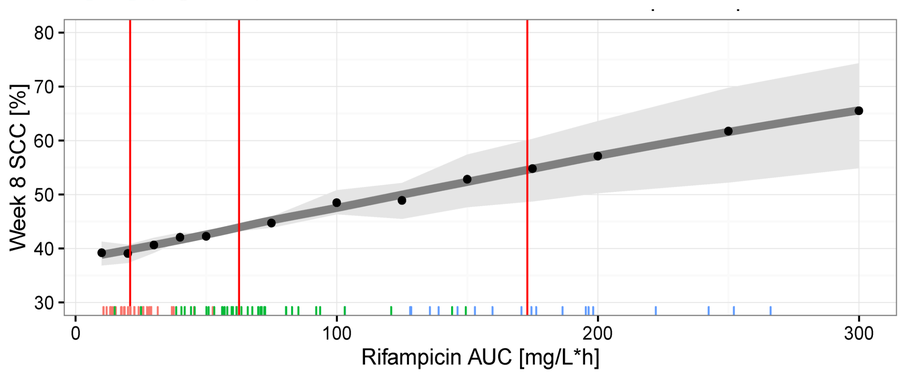

Figure4. Predicted week 8 SCC with 95% CI vs RIF exposure, given standard background, typical bacterial load, proportion of missing samples.

Conclusions

- **Higher RIF exposure leads to faster treatment response.**
- **No target exposure indicating maximal effect could be derived, probably due to limited range of exposures.**
- **RIF doses of 35 mg/kg, and higher if safe and tolerable, should be further studied in long-term trials for its potential to shorten TB treatment duration.**

References

[1] M Boeree *et al.*, Lancet infectious diseases, 2016, vol 17(1)
[2] Å Johansson *et al.*, The AAPS Journal, 2013, vol 15(4)
[3] R Svensson *et al.*, 25th PAGE 2016, abstract 5978
[4] C Acharya *et al.*, Computer Methods and Programs in Biomedicine, 2016, vol 127

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