Effect of Rifamycins on pretomanid exposure in patients with pulmonary Tuberculosis

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APT ASSESSING PRETOMANID FOR TUBERCULOSIS

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Background and Objectives

- Pretomanid is a potent new anti-TB drug recently FDA approved for treatment of drug-resistant TB at a dose of 200mg once-daily.
- It could potentially be a tool for treatment-shortening in drug-sensitive TB. But can it be used with rifamycins?
- Pretomanid is 20% metabolized by CYP3A4 isoenzyme
- In healthy volunteers[1], rifampicin reduced pretomanid AUC by 66% (from 13.7 vs. 42.5 mg·h/L) but there are no data in participants to guide pretomanid and rifamycin co-administration.
- **The objective** is to describe the effect of co-administration with rifabutin or rifampicin on the pharmacokinetics of pretomanid

Methods

APT (Assessing Pretomanid for Tuberculosis) is a phase IIB RCT assessing the safety and efficacy of pretomanid added to first-line drugs over 12 weeks among participants with pulmonary TB compared to standard of care with RHZE .

1. Arm 1 received pretomanid 200 mg (Pa) plus isoniazid (H), rifampicin (R), pyrazinamide (Z) = PaHRZ for 8 weeks, followed by PaHR (weeks 9-12);
2. Arm 2 received pretomanid 200 mg (Pa) plus isoniazid (H), rifabutin (Rb), pyrazinamide (Z) = PaHRbZ for 8 weeks, followed by PaHRb (weeks 9-12)

60 participant from Arms 1 and 2 underwent intensive PK sampling at predose and 1, 2, 5, 8, and 24 hr post-dose on day 14.

Results - Patient population

Table: Participant's characteristics

Characteristics	PaHRZ (n=30)	PaHRbZ (n=27)
Age, years	31 (18 -54)	29 (18 - 45)
Weight, kg	53 (41 - 77)	61 (38 - 118)
Fat-Free Mass, kg	30.1 (37.5 - 57.7)	38 (25 - 59)
Sex (% Males)	22 (73)	18 (67)
Race/Ethnicity %		
Black	20 (67%)	17(63)
Colored	10 (33%)	10 (37)
HIV Status - % Positive	2 (7%)	1 (4)
Cavitation >1 cm	25 (83%)	25 (83%)

Data in median (range)/%

Results – PK model

$$CL = TVCL \cdot \left(\frac{WT}{TVWT}\right)^{0.75} \qquad V = TVV \cdot \left(\frac{WT}{TVWT}\right)$$

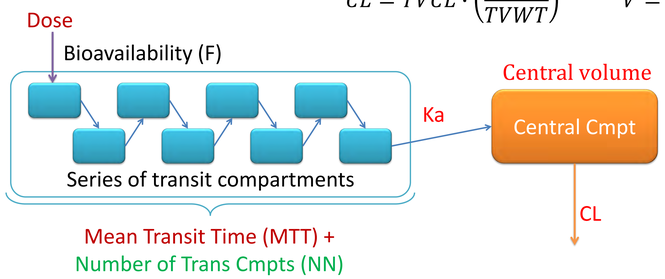

Figure: Structural model. Pretomanid absorption is modelled through a series of transit[4] compartments. Elimination is from central compartment with first-order kinetics

Population PK modelling in NONMEM [2]: one-compartment model with first-order elimination and transit compartment

Allometric scaling[3] was used to adjust of clearance (CL) and volume (V) for the effect body weight (WT)

Rifampicin vs rifabutin co-administration was tested on PK parameters

Table Final parameter estimates

Parameter	Typical Value	Parameter 95 Ci[c]
Clearance - CL (L/h)[a]	4.02	(3.58 - 4.51)
Central Volume of distribution - Vc (L)[a]	81.0	(76.5 - 85.5)
Absorption. rate constant - ka (1/h)	0.764	(0.585 - 0.983)
Absorption. mean transit time - MTT (h)	1.43	(1.09 - 1.87)
Number of abs. transit compartments - NN ()	4.49	(2.87 - 6.72)
Bioavailability - F ()	1 FIXED	-
Rifampicin effect on clearance (%)	+78.7	+(55.5 - 106)
Sex [Female] effect on clearance (%)	-20.8	-(30.7 - 10.5)
Proportional error (%)	6.84	(5.63 - 8.52)
Additive Error (mg/L)	0.032	(0.010 - 0.054)
Between subject variability of clearance (%CV)[b]	20.5	(17.1 - 26.4)
Between occasion variability (%CV)[b]		
Absorption rate constant	41.7	(29.7 - 52.5)
Mean transit time	78.1	(63.2 - 97.1)
Bioavailability	11.6	(8.32 - 14.5)

[a] The values of CL and V were allometrically scaled, so these typical values refer to the median body weight of the cohort (53 kg)
[b] Between-subject (BSV) or between-occasion (BOV) was assumed as lognormally distributed and is reported here as approximate %CV.
[c] 95 % confidence intervals obtained with sampling importance resampling technique using PsN software

Results – Exposure

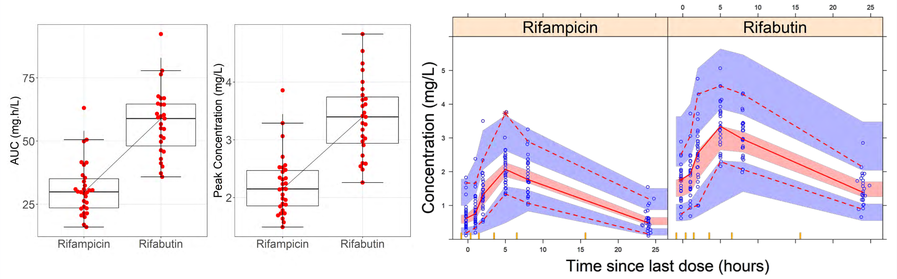

Figure: boxplots of the model-predicted estimates for AUC0-24 (on the left) and Cmax (on the right), stratified by treatment arm. The dots represent individual values, whiskers are 2.5th and 97.5th percentiles

Figure: Visual predictive check. Visual predictive check [5] of the pretomanid model, stratified by treatment arms.
The solid and dashed lines are the 5th, 50th, and 95th percentiles of the observations, while the shaded areas represent the 95% model-predicted confidence intervals for the same percentiles.

Participants taking rifampicin had 44% reduction in Pretomanid AUC compared to rifabutin (due to 79% faster CL).

Individual median (IQR) estimates of Cmax were 2.15 (1.86 – 2.47) and 3.40 (2.94 – 3.74) mg/L for rifampicin and rifabutin arms, respectively.

For the $AUC_{0\text{-}24}$, the values were 29.9 (23.6-35.1) and 58.9 (48.1-64.6) mg·h/L
CL was 20% higher in men than women.

Conclusions

- Co-administration of pretomanid with rifampicin increases the CL substantially compared to rifabutin.
- Exposures in the rifampicin arm in our study were similar to those seen in participants taking 200 mg of pretomanid alone, without food (AUC of 36 mg·h/L)[6].
- Pretomanid AUC with rifabutin in a fed state is higher than that seen in pretomanid monotherapy in a fasting state, likely due to food effect
- Pretomanid co-administered with rifabutin is more likely to maintain exposure levels equal to or exceeding regimens that do not contain rifamycins
- The difference in rifampicin effect on pretomanid exposure in APT is possibly due to food effect and reliable dosing with food may permit co-administration with rifamycin.

References

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