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Lack of a Clinically Important Effect of Rifabutin (RFB) on Raltegravir (RAL) Pharmacokinetics

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Abstract

Background: RAL is a HIV-1 integrase strand transfer inhibitor with potent in vitro and in vivo activity against HIV-1. A prior investigation of RAL (400 mg) co-administered with rifampin (600 mg), a commonly used agent to treat tuberculosis (TB), demonstrated a decrease in plasma concentrations of RAL likely secondary to induction of UGT1A1, the enzyme primarily responsible for the metabolism of RAL. Rifabutin (RFB), an alternative rifamycin used for the treatment of TB, is a less potent inducer of drug metabolizing enzymes, although little is known with regard to induction effect on UGT1A1. This study was conducted to assess the effect of RFB on plasma levels of RAL with co-administration.

Methods: Open-label, 2-period, fixed-sequence study in 16 healthy adults. Period 1: subjects received 400 mg RAL q12hr for 4 days. Period 2: same subjects received 400 mg RAL q12hr and 300 mg RFB qd for 14 days. Clinical safety evaluations were performed throughout the study. RAL plasma concentration data were collected.

Results: No serious adverse experiences (AEs) were reported and there were no discontinuations due to drug-related clinical or laboratory AEs. Compared to 400 mg RAL administered alone, multi-dose administration of RFB with RAL resulted in a 20% decrease in RAL C_{12hr} (GMR RAL + RFB/ RAL and 90% CI: 0.80 (0.68, 0.94)), a 19% increase in RAL $AUC_{0\text{-}12hr}$ (GMR 1.19 (0.86, 1.63)), and a 39% increase in RAL C_{max} (GMR 1.39 (0.87, 2.21)). The lower bound of the 90% CI for GMR C_{12hr} and the upper bound of the 90% CI for GMR $AUC_{0\text{-}12hr}$ were contained within the pre-specified bounds of clinical significance, defined as 0.40 for C_{12hr} and 2.0 for $AUC_{0\text{-}12hr}$.

Conclusions: Overall, co-administration of RAL and RFB does not alter RAL pharmacokinetics to a clinically meaningful degree. RFB may be co-administered with RAL without dose adjustment.

Background

- RAL is a novel HIV-1 integrase strand transfer inhibitor indicated for the treatment of HIV-1 infection.
- RAL is primarily metabolized by glucuronidation via UGT1A1.
- Tuberculosis (TB) is a common infection seen in the HIV-1 infected population.
  - Rifampin is a commonly used agent to treat TB.
- A prior investigation of RAL (400 mg) co-administered with rifampin (600 mg) demonstrated a decrease in plasma concentrations of RAL likely secondary to induction of UGT1A1.[1]
- Rifabutin (RFB) is an alternative rifamycin used for the treatment of TB with less potent inductive properties, in general, though little is known regarding the specific induction of UGT1A1
- This study was conducted to assess the effect of RFB on plasma levels of RAL with co-administration

Study Design

2-period fixed-sequence, open-label study in 16 healthy adult male and female subjects

Number of Subjects	Period 1	Period 2
N=16	RAL 400 mg q12hr for 4 days; Intensive pharmacokinetic sampling on Day 4	RAL 400 mg q12hr plus RFB 300 mg qd for 14 days (the Day 14 PM dose of RAL was not given); Intensive pharmacokinetic sampling on Day 14

Methods

Safety Assessment

- Safety and tolerability were assessed by measurements of physical examinations, vital signs, ECG, and laboratory safety tests (CBC, chemistry panel, urinalysis)
- Adverse experiences were evaluated as to their intensity, seriousness, and relationship to study drug

Analytical and Pharmacokinetic

- Plasma samples were analyzed for RAL concentration using a validated HPLC – MS/MS assay with a lower limit of quantitation of 4.5 nM (2 ng/ml).[2]
- C_{max}, T_{max}, and C_{12hr} determined by inspection
- $AUC_{0\text{-}12hr}$ calculated using linear up/log down trapezoidal method

Statistical Analysis

- A linear mixed-effects model was used with fixed effect of treatment and a random subject effect.
- Natural-log transformation was performed for $C_{12\ hr}$, C_{max}, and $AUC_{0\text{-}12hr}$ before analysis
- Two-sided 90% confidence intervals (CI) for the true mean difference (400 mg RAL + RFB/400 mg RAL) in RAL C_{12hr} on the log scale were calculated and then exponentiated to obtain a CI for the true geometric mean ratio (GMR) for RAL C_{12hr} (400 mg RAL + RFB/400 mg RAL)
  - C_{max}, and $AUC_{0\text{-}12hr}$ were analyzed in the same fashion
- Summary statistics and between-treatment comparison were provided for T_{max}

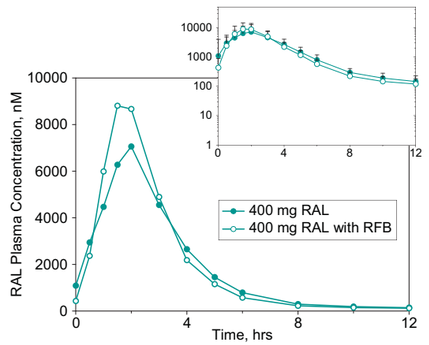
Results

Subject Disposition

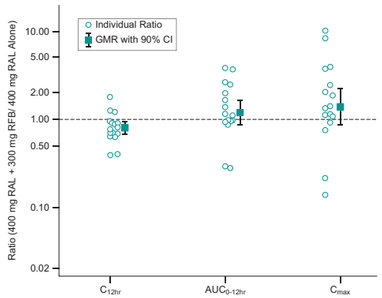
Randomized:	
Total (age range; mean):	19 (19 to 55 yrs; 35 yrs)
Male (weight range; mean)	6 (79 to 92 kg; 86 kg)
Female (weight range; mean)	13 (56 to 83 kg; 67 kg)
Completed:	16
Discontinued:	3
Protocol violation (smoking)	2
Withdrew consent	1
Drug-related adverse experience	0

Pharmacokinetics

Mean Plasma Concentration-Time Profiles for RAL Following Administration of Multiple Doses 400 mg RAL q12hr for 4 days and 400 mg RAL q12hr with 300 mg RFB qd for 14 days (Inset = Semilog scale)



Individual and Mean RAL $AUC_{0\text{-}12hr}$, Cmax and C_{12hr} ratios (400 mg RAL + 300 mg RFB / 400 mg RAL Alone) after Co-administration of Multiple Doses of 400 mg RAL q12hr and 300 mg RFB qd for 14 Days Compared with Administration of 400 mg RAL q12hr for 4 Days Alone



RAL Plasma Pharmacokinetics Following Administration of Multiple Doses of 400 mg RAL q12hr for 4 Days and Multiple Doses of 400 mg RAL q12hr + 300 mg RFB qd for 14 Days

Pharmacokinetic Parameter	RAL 400 mg N	RAL 400 mg GM† (95% CI)	RAL 400 mg + RFB 300 mg N	RAL 400 mg + RFB 300 mg GM† (95% CI)	RAL 400mg +RFB 300 mg/ RAL 400 mg GMR† (90% CI)
C_{12hr} (nM)	19	127.53 (100.00, 162.64)	16	102.08 (79.31, 131.40)	0.80 (0.68, 0.94)
$AUC_{0\text{-}12hr}$ (μM*hr)	19	18.12 (13.02, 25.23)	16	21.50 (15.10, 30.63)	1.19 (0.86, 1.63)
C_{max} (μM)	19	5.84 (3.90, 8.75)	16	8.10 (5.23, 12.56)	1.39 (0.87, 2.21)
T_{max}‡ (hr)	19	2.0 (0.0, 6.0)	16	1.5 (1.0, 3.0)	-0.75 (-1.25, -0.25)

† Geo mean=Geometric least-squares mean, GMR=Geometric mean ratio, CI=confidence interval
‡ Median (minimum, Maximum), Hodges-Lehman estimate of median treatment difference with corresponding 90% CI for true median treatment difference provided for T_{max}

Summary of Pharmacokinetics

- The coadministration of 400 mg RAL q12hr with 300 mg RFB qd resulted in a 20% decrease in mean RAL C_{12hr} relative to 400 mg RAL q12hr alone in healthy subjects
- RAL $AUC_{0\text{-}12hr}$ and C_{max} mean values were slightly higher after administration of 400 mg RAL q12hr with 300 mg RFB qd relative to 400 mg RAL q12 hr alone (increases of 19% and 39%, respectively)
- Median T_{max} values were slightly shorter after administration of 400 mg RAL q12hr with 300 mg RFB qd with a median of 1.5 hours compared to 2.0 hours for 400 mg RAL q12hr alone

Safety

- Co-administration of RFB and RAL was generally well tolerated in healthy subjects
- There were no discontinuations due to a drug-related adverse experience
- Three subjects discontinued due to reasons other than adverse experiences
- 19 subjects reported a total of 56 clinical adverse experiences
- 15 were considered by the investigator to be drug related
- The most commonly reported drug-related clinical adverse experiences (reported by ≥2 subjects) were headache, fatigue, nausea and vomiting
- No serious clinical or serious laboratory adverse experiences were reported

Conclusions

- Coadministration of 400 mg RAL q12hr with 300 mg RFB qd is generally well-tolerated
- Overall, co-administration of RAL and RFB does not alter RAL pharmacokinetics to a clinically meaningful degree
- RFB may be co-administered with RAL without RAL dose adjustment
- RFB represents an alternative to rifampin which modestly decreases RAL concentrations with co-administration

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References

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