Population Pharmacokinetic Analysis & Effects Of Raltegravir In HIV positive and Healthy Individuals

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Introduction

Raltegravir (RAL) pharmacokinetics (PK) are known to exhibit large inter and intra-individual variability.

The aims of the study were to :

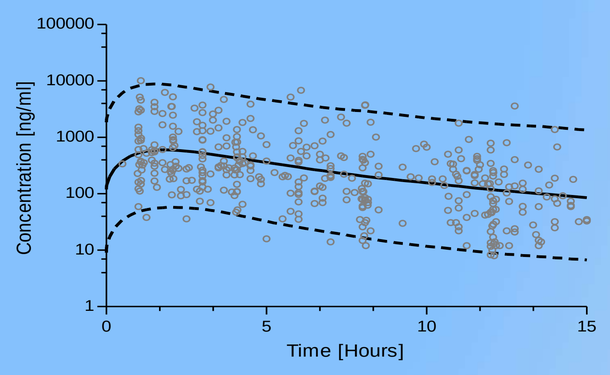
1. Quantify the variability affecting RAL PK parameters
2. Identify demographic factors that influence RAL concentration
3. Explore the correlations between exposure and markers of efficacy and toxicity
4. Simulate different dosage regimens for predicting and comparing drug levels at trough

Methods

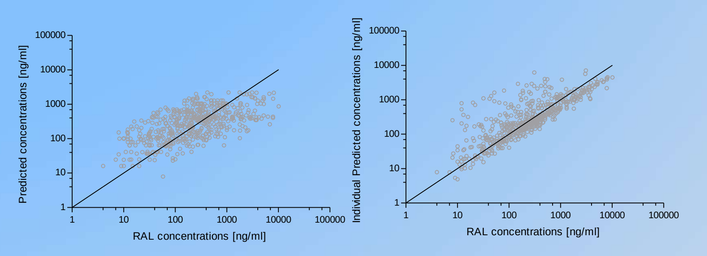
- 544 RAL plasma concentrations were collected in 145 HIV+ participants from the Swiss HIV cohort study and 19 healthy volunteers.
- One and 2 compartments with various absorption models were tested using NONMEM®.
- A relative bioavailability (F_{HIV+}) was introduced to capture a scale shift in the PK parameters observed in HIV+ patients compared to healthy individuals.
- Distinct absorption rate constants (ka) were also allowed.
- Demographic factors and co-medications were evaluated.
- Posterior Bayesian individual estimates of C_{min} and AUC_{0-24} were correlated with CD4+ count, viral load, total bilirubin, AST and ALT levels using linear regression analyses (Stata®)

Results

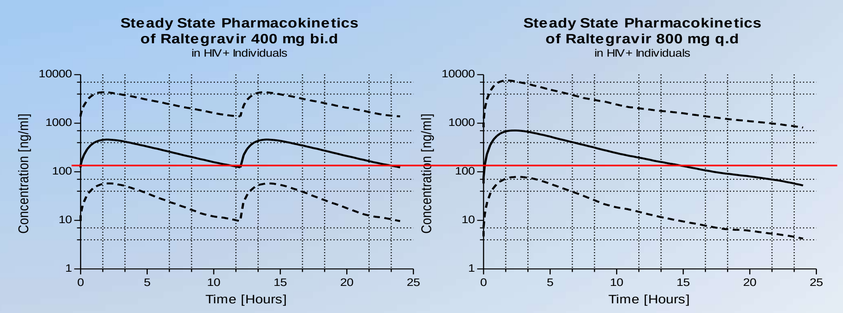
- A 2 compartment model with first order absorption adequately described the data.
- F_{HIV+} amounted to 80% of RAL bioavailability in healthy subjects (CV=86.4%).
- Average apparent clearance was 98.7 Lh^{-1}, volumes of distribution 393 L for the central compartment (CV= 76.8%), and 182 L for the peripheral compartment.
- Absorption constant (ka) amounted to 0.2 h^{-1} and 0.8 h^{-1} (CV= 100%) in HIV+ and healthy individuals, respectively.
- Atazanavir, female gender and hyperbilirubinemia (grade 1 or higher) affected $F_{HIV+,}$ yielding an increase of 40%, 60% and 30% in RAL bioavailability, respectively.
- No correlations were detected between RAL exposure and CD4+ and HIV RNA count or AST/ALT and total bilirubin.
- Model-based simulations predicted average trough concentrations of 124 ng/ml (95% prediction interval 9.7 - 1381) for the 400 mg b.i.d regimen and 52.2 ng/ml (4.2 - 817) for the 800 mg q.d regimen.



RAL Concentrations (open circles) vs. time standardized for a 400 mg b.i.d dosing in HIV + and HIV- individuals with population predictions (solid line) and the 95% prediction interval (dotted lines).



Plots of population (left panel) and individual (right panel) predictions versus the observations of the final model.



Model-based simulations of RAL 400 mg b.i.d (left panel) and RAL 800 mg q.d (right panel). Average RAL concentrations (solid line) with 95% prediction interval (dotted lines)

Conclusions

- RAL PK confirmed a large interpatient variability, of which only 4% was explained by atazanavir intake, female gender and by the association with high total bilirubin levels.
- The smaller relative bioavailability in HIV+ patients could result from HIV related pathophysiological differences, compliance or food.
- Due to large PK variability, some patients might exhibit very low RAL concentration with standard 400 mg b.i.d regimen.
- No clear correlation between RAL exposure and efficacy or toxicity markers could nevertheless be detected.