THE EFFECT OF EZETIMIBE (EZB) ON THE STEADY-STATE TROUGH LEVELS OF LOPINAVIR/RITONAVIR (LPV/r)

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ABSTRACT

Background: Hyperlipidemia in HIV-infected patients can be associated with the use of protease inhibitors (PIs). Ezetimibe (EZB) inhibits absorption of cholesterol in the intestine and can be added to statin therapy in patients who need further lowering of cholesterol. LPV/r is a highly lipophilic compound and the effect of EZB on LPV/r absorption and pharmacokinetics (PK) is unknown. This study evaluated effects of EZB on LPV/r trough concentrations.

Materials & Methods: HIV-infected adults stable on LPV/r and a statin (pravastatin 20mg/day or atorvastatin 10mg/day), who had not met their National Cholesterol Education Program III (NCEP) LDL goal were enrolled and treated with EZB 10mg/day for 18 weeks. Plasma trough levels (Cmin) of lopinavir and ritonavir were drawn at baseline and week 6. Differences in trough concentrations were analyzed using repeated measures ANOVA on ranks with Bonferroni adjustment.

Results: Thirteen subjects were enrolled; 8 (62%) men, median (range) age and body weight were 49 (32-63) years and 91 (56-152) kg, respectively. Mean (SD) Cmin of LPV at baseline and at week 6 were 5.7 (3.7) mcg/mL and 5.2 (4.4) mcg/mL, respectively (p=0.584). Mean (SD) Cmin of RTV at baseline and at week 6 were 0.44 (0.56) mcg/mL and 0.37 (0.41) mcg/mL, respectively (p=0.589).

Conclusions: Plasma trough levels of LPV and RTV are not affected by the concomitant use of ezetimibe.

BACKGROUND

- Hyperlipidemia in HIV-infected patients can be associated with the use of protease inhibitors (PIs)
- Use of HMG-CoA reductase inhibitors (statins) often fails to meet target lipid goals in HIV-infected patients
- Ezetimibe (EZB) inhibits absorption of cholesterol in the intestine, resulting in a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood[1]
- Lopinavir/ritonavir (LPV/r) is a highly lipophilic compound and is highly bound to plasma proteins (98-99%)[2]
- One clinical study reported no change in LPV C_{max} and AUC_{12h} after addition of EZB in 6 HIV-infected patients[3]
- Additional data regarding the effect of EZB on LPV/r PK are needed

METHODS

Study Design and Patients

- This was a PK substudy of a larger phase IV, prospective pilot study
  - Main study: HIV-infected adults (N=20) on stable PI-based antiretroviral therapy (ART) and statin (atorvastatin [ATR] 10mg/day or pravastatin [PRA] 20mg/day)
  - PK substudy: patients on LPV/r (N=13); goal was to evaluate LPV and ritonavir (RTV) trough concentrations at baseline and after EZB 10mg/day initiation

Study Screening
- PI-based HAART
- Statin
- Not at LDL goal

Baseline visit (BL)
- PI-based HAART and statin continued
- PK substudy: LPV, RTV trough drawn (N=13)
- EZB 10mg/day added
- Hematologic, renal, liver, cholesterol laboratory tests drawn

Week 6 visit
- LPV, RTV trough drawn
- Hematologic, renal, liver, cholesterol laboratory tests drawn

Study continued for a total of 18 weeks of EZB therapy
(additional cholesterol and safety laboratory evaluations at 12 and 18 weeks)

Laboratory Analysis

- Patients were instructed to take their last dose of LPV/r the evening prior to study visit (with or without food, based on their daily routine). Laboratory draws were performed during the study visit the following morning.
- LPV and RTV concentrations were determined using a validated HPLC method at the University of Alabama at Birmingham

Statistical Analysis

- Differences in LPV and RTV trough concentrations were analyzed using repeated measures ANOVA on ranks with Bonferroni adjustment

RESULTS

Study Participants

- The PK substudy included 13 patients who were receiving LPV/r
- LPV/r regimens: 11 patients on 400/100mg SGC BID; 1 patient on 533/133mg SGC BID; 1 patient on 400/100mg tablets BID
- Of 13 patients, 12 were on PRA 20mg/day and 1 patient was on ATR 10mg/day

Table 1. Demographics

	Patients Receiving LPV/r (N=13)
Male, n (%)	8 (62%)
Black, Non-Hispanic, n (%)	12 (92%)
Hispanic, n (%)	1 (8%)
Age [yr, median (range)]	49 (32-63)
Weight [kg, median (range)]	91 (56-152)

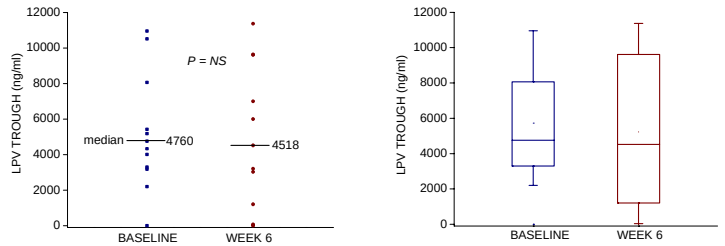
Safety

- Addition of EZB was safe and well tolerated
- All 13 patients completed the baseline and week 6 PK evaluations
- 2 patients experienced asymptomatic elevations in CPK (>5 x ULN): 1 likely to study drug; 1 likely related to concomitant cocaine abuse
- 1 patient expired after week 12 visit due to a myocardial infarction; this was not considered to be a drug-related adverse event

PK Results

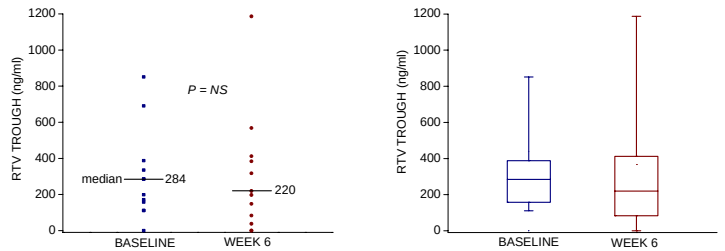
- Mean (SD) LPV trough concentrations at baseline and week 6 were 5,726 (3,717) ng/mL and 5,223 (4,430) ng/mL, respectively (*P*=0.584). Mean (SD) RTV trough concentrations at baseline and week 6 were 439 (560) ng/mL and 367 (407) ng/mL, respectively (*P*=0.589).
- Median (range) LPV trough concentrations at baseline and week 6 were 4,760 (0-12,524) ng/mL and 4,518 (0-12,216) ng/mL, respectively (Figure 1). Median (range) RTV trough concentrations at baseline and week 6 were 284 (0-2,126) ng/mL and 220 (0-1,214) ng/mL, respectively (Figure 2).

Figure 1. Lopinavir Trough Concentrations



Shown are the lower and upper quartiles (box), median (horizontal line in box), and 5th and 95th percentiles (whiskers)

Figure 2. Ritonavir Trough Concentrations



Shown are the lower and upper quartiles (box), median (horizontal line in box), and 5th and 95th percentiles (whiskers)

LIMITATIONS AND CONCLUSION

- **Study limitations:** small sample size, lack of intensive PK sampling to assess full PK profiles of LPV and RTV, lack of PK analysis for EZB, lack of a controlled research study setting during medication administration
- **Conclusion:** In our small cohort of minorities, high interpatient variability of LPV and RTV concentrations was observed, especially at week 6. Overall, plasma trough concentrations of LPV and RTV were not statistically affected by the concomitant use of EZB.

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