EZETIMIBE COMBINED WITH LOW DOSE STATIN EFFECTIVELY LOWERS LDL IN PROTEASE INHIBITOR TREATED PATIENTS

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ABSTRACT

Objectives: Ezetimibe (EZB) lowers cholesterol by blocking cholesterol absorption in the intestine. Data regarding its use are limited in HIV-infected patients. Our main objective was to assess LDL reduction 18 weeks after addition of EZB 10mg/day in statin-treated patients on protease inhibitor (PI)-based antiretroviral therapy (ART).

Methods: HIV-infected adults on stable PI-based ART were enrolled in this prospective pilot study if their LDL was not at goal (per National Cholesterol Education Program III guidelines) despite therapy with a statin (pravastatin 20 mg or atorvastatin 10 mg). In a subgroup of patients on lopinavir/ritonavir (LPV/RTV), trough LPV and RTV concentrations were obtained before and after addition of EZB. Data were analyzed using repeated measures ANOVA on ranks with Bonferroni adjustment.

Results: We enrolled 20 subjects; 12 (60%) men, 18 (90%) African American, 2 (10%) Latino; mean (SD) age was 49.1 (8.5) years. ART included RTV-boosted PIs in 17 (85%) patients, 3 (15%) were on nelfinavir; 19 were on pravastatin, 1 on atorvastatin. Cholesterol changes are described in the table. 13 patients were receiving LPV/RTV; LPV and RTV trough concentrations did not change after addition of EZB. One patient experienced elevated CPK possibly related to study medication; no other laboratory abnormalities or adverse effects were seen.

Table: Cholesterol Changes

Mean (SD)	BL (n=20)	Wk 6 (n=20)	p-value	Wk 12 (n=20)	p-value	Wk 18 (n=16)	p-value
TC (mg/dL)	228.8 (42.4)	203.4 (37.7)	0.003	206.9 (35.8)	0.008	208.1 (37.3)	0.031
LDL (mg/dL)	139.3 (25.4)	124.1 (33.6)	0.039	122.4 (28.8)	0.010	122.0 (26.8)	0.023
TG (mg/dL)	163.3 (112.6)	150.4 (70.9)	NS	162.4 (102.3)	NS	156.8 (64.6)	NS
HDL (mg/dL)	60.2 (23.9)	58.6 (16.6)	NS	58.3 (18.8)	NS	56.9 (17.6)	NS

Conclusions: Addition of EZB to low dose statin effectively lowers LDL and TC and appears to be safe and well-tolerated.

BACKGROUND

- Lipid abnormalities are common in HIV-infected patients
- Controlling this cardiovascular risk factor is essential in decreasing the risk of myocardial infarction (MI) and other atherosclerotic complications; however, HMG-CoA reductase inhibitor (statin) therapy often fails to meet target lipid goals in this patient population
- 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]
- Two clinical studies in HIV-infected individuals evaluating EZB monotherapy reported a 10-12% reduction in LDL cholesterol after 6 weeks of treatment.[2,3] A 24-wk study in 23 HIV-infected patients evaluated addition EZB to pravastatin 20mg/day and showed an additional 7% decrease in LDL.[4]
- Our main objective was to assess lipid changes in HIV-infected patients after addition of EZB to stable statin and PI-based HAART

METHODS

Study Design
- Prospective pilot study

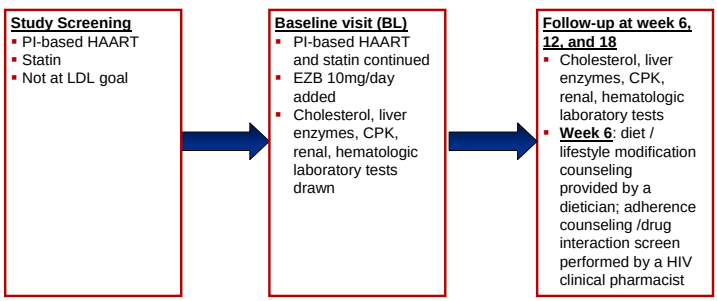
Inclusion criteria
- HIV-infected adults (≥ 18 years) on stable PI-based HAART for at least 6 weeks prior to study entry
- Hypercholesterolemia treated with atorvastatin (ATR) 10mg/day or pravastatin (PRA) 20mg/day, and LDL-cholesterol not at goal based on National Cholesterol Education Program III (NCEP)
- Laboratory values within normal limits

Exclusion criteria
- Pregnant or breast-feeding women
- Active alcohol or substance abuse
- Presence of decompensated heart failure, MI within 1year, severe vascular disease, poorly controlled diabetes mellitus

Primary Objective
- To assess LDL reduction at 18 weeks

Secondary Objectives
- To assess TC, LDL, TG, HDL reductions at 6, 12, and 18 weeks of EZB therapy
- To assess safety of the addition of EZB to statin therapy in HIV-infected patients on PIs
- To evaluate lopinavir and ritonavir trough concentrations before and after addition of EZB (baseline and week 6) in a subgroup of patients on LPV/r

Statistical Analysis
- Data were analyzed using repeated measures ANOVA on ranks with Bonferroni adjustment



RESULTS

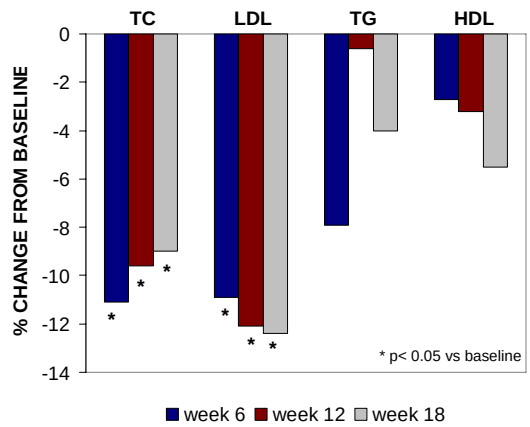
Table 1. Demographics (N=20)

Male, n (%)	12 (60%)
Black, Non-Hispanic, n (%)	18 (90%)
Hispanic, n (%)	2 (10%)
Age [yr, mean (SD)]	49 (8.5)
CD4 [cells/uL, mean (SD)]	428 (197)
<400 c/mL HIV-1 RNA, n (%)	15 (75%)
LDL-C [mg/dL, mean (SD)]	139 (25)
RTV-boosted PIs, n (%) Nelfinavir, n (%)	17 (85%) 3 (15%)
Pravastatin 20 mg/day, n (%) Atorvastatin 10 mg/day, n (%)	19 (95%) 1 (5%)
Current or former smokers, n (%)	8 (40%)
Hypertension, n (%)	12 (60%)
Diabetes, n (%)	4 (20%)
Weight [kg, median (range)]	91 (56-152)

Safety
- Addition of EZB was safe and well tolerated
- 4 patients did not complete week 18 study visit
  - 1 patient due to asymptomatic elevations in CPK (>5 x ULN) likely related to concomitant cocaine abuse
  - 2 patients due to protocol violation
  - 1 patient expired after week 12 visit due to a MI (not considered to be a drug-related adverse event)
- One patient experienced asymptomatic elevations in CPK (>5 x ULN) at week 18 study visit, possibly related to study medication. This patient completed the study and CPKs declined after EZB discontinuation

- ***Demographics (Table 1)***
  - Our cohort of minority patients had many baseline risk factors for cardiovascular disease
  - Based on the NCEP III guidelines, 18 of 20 patients (90%) had a LDL goal <100 mg/dL
- ***Cholesterol changes (Graph 1)***
  - Addition of EZB resulted in significant reduction of LDL and TC at all study visits (p<0.05), without significant changes in TG or HDL
  - 7 of 20 patients (35%) achieved their NCEP III LDL goal at study completion
- ***Pharmacokinetic substudy***
  - 13 of 20 patients were on LPV/r at study entry and completed the PK substudy. No changes in the trough concentrations of LPV or RTV were observed after addition of EZB.[5]

Graph 1. Cholesterol Changes



Cholesterol values [mg/dL, mean (SD)]

	TC	LDL	TG	HDL
Baseline (n=20)	228.8 (42.4)	139.3 (25.4)	163.3 (112.6)	60.2 (23.9)
Week 6 (n=20)	203.4 (37.7) (p=0.003)*	124.1 (33.6) (p=0.039)	150.4 (70.9) (NS)**	58.6 (16.6) (NS)
Week 12 (n=20)	206.9 (35.8) (p=0.008)	122.4 (28.8) (p=0.010)	162.4 (102.3) (NS)	58.3 (18.8) (NS)
Week 18 (n=16)	208.1 (37.3) (p=0.031)	122.0 (26.8) (p=0.023)	156.8 (64.6) (NS)	56.9 (17.6) (NS)

*all p values are versus baseline
** NS are p values >0.05

LIMITATIONS AND CONCLUSION

- **Study limitations:**
  - This pilot study was performed at a single institution, with a limited number of patients
  - Our strict inclusion criteria of low-dose statins (due to safety concerns) may have led to a blunted cholesterol-lowering response to combination therapy with statins and EZB
- **Conclusions:**
  - Adding ezetimibe to statins resulted in a significant reduction of TC and LDL in our cohort of minority HIV-infected patients with multiple risk factors for cardiovascular disease
  - Despite these reductions, only 35% of our patients achieved their NCEP III LDL goal at study completion
  - Addition of EZB to statins and PI-based HAART was safe and well-tolerated
  - No changes in the trough concentrations of LPV or RTV were seen after addition of EZB

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