Long-term use of proton pump inhibitors and increased immune activation in patients with chronic HIV-1 infection

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Abstract:
Background: Translocation of microbial products from the damaged gut causes increased systemic immune activation in HIV and is associated with increased mortality. Proton pump inhibitors (PPIs) predispose to microbial overgrowth in the gut. We hypothesized that long-term use of PPIs is associated with increased microbial translocation and immune activation in HIV-infected patients who have experienced ART-induced virologic suppression.

Methods: We recruited 37 HIV-infected subjects on long-term PPIs (cases), 40 HIV-infected subjects not taking any gastric acid reducers (controls), and 20 HIV-uninfected volunteers. Cases were older (55 vs. 50 years, P = 0.04) and more likely to have hypertension (55% vs. 34%; P = 0.04) and to receive statin therapy (44% vs. P = 0.035) than controls. Cases had higher levels of sCD14, LPS, LBP, LPS-binding protein (LBP, induced by LPS), soluble CD14 (sCD14, reflecting LPS- induced monocyte activation), and intestinal fatty acid binding protein (I-FABP, reflecting enterocyte turnover) by ELISA. Biomarker levels were log10-transformed prior to analysis. Characteristics of HIV-infected patients on long-term PPIs (cases) and those who did not receive any gastric acid reducers (controls) were compared by t-test and chi2 test. Variables that showed a P-value < 0.1 in the univariate analysis were considered in the elaboration of a multivariate logistic regression model.

Results: We recruited 37 HIV-infected subjects on long-term PPIs (cases), 40 HIV-infected subjects not taking any gastric acid reducers (controls), and 20 HIV-uninfected volunteers. Cases were older, and more likely to have hypertension, and receive statins than controls. Nadir and enrollment CD4+ cell counts and time receiving antiretroviral therapy did not differ between groups. Cases had higher concentrations of sCD14 (2.12 vs. 1.5 mg/mcl; P = 0.003) and LBP (21.78 vs. 18.28 mg/ml; P = 0.033) than controls. Higher sCD14 levels remained significantly associated with long-term PPI use after adjustment for age, hypertension and statin use in the multivariate model. Levels of activated CD8+ T-cells, LPS, LBP, and I-FABP were similar between HIV-infected cases and controls. HIV-infected cases and controls had higher levels of inflammation and the intestinal translocation markers than HIV-uninfected volunteers.

Discussion: Long-term use of PPIs was associated with higher concentrations of sCD14 and LBP but not with activated CD8+ T-cells. These results suggest that these drugs permit increased microbial translocation, resulting in increased monocyte activation in HIV- infected individuals. As I-FABP levels do not differ between cases and controls, enterocyte integrity is likely not disturbed by PPI use. Rather, bacterial overgrowth or dysbiosis may account for the increased microbial translocation and monocyte activation. High levels of sCD14 predict poor CD4 T cell recovery on ART and increased mortality. Whether the long-term use of PPIs, by increasing sCD14 levels, leads to impaired immunological recovery and/or mortality remains elusive. Some limitations of our study include using a convenience sample and a study population consisting of older male veterans only.

Conclusions: Long-term PPI use was associated with increased microbial translocation and innate immune activation but not with increased enterocyte turnover or T-cell activation in HIV-infected persons. Larger studies are needed to determine the clinical implications of our findings. In the meantime, cautious use of long-term PPIs is advised in this patient population.

Background:
Translocation of microbial products from the damaged gut causes increased systemic immune activation in HIV and is associated with increased mortality. Proton pump inhibitors (PPIs) predispose to microbial overgrowth in the gut. We hypothesized that long-term use of PPIs is associated with greater microbial translocation, resulting in increased systemic inflammation in chronic HIV.

Objective:
The main goal of this study is to investigate the potential association of long-term use of PPIs and increased microbial translocation and immune activation in HIV-infected patients who have experienced ART-induced virologic suppression.

Methods:
• Population: HIV-infected persons on antiretroviral therapy (HIV RNA < 50 copies/mm3) for at least one year prior to enrollment. Long-term use of PPIs was defined as filling six or more 30-day supplies of PPIs in the prior 12 months.
• Assays: We hypothesized decreased CD8+HLA-DR+ (activated) CD8+ T-cell frequency by flow cytometry and plasma levels of lipopolysaccharide (LPS, a component of Gram-negative bacteria) using the Limulus amebocyte lysate assay, and LPS binding protein (LBP, induced by LPS), soluble CD14 (sCD14, reflecting LPS-induced monocyte activation), and intestinal fatty acid binding protein (I-FABP, reflecting enterocyte turnover) by ELISA.

Statistical Analysis:
Biomarker levels were log10-transformed prior to analysis. Characteristics of HIV-infected patients on long-term PPIs (cases) and those who did not receive any gastric acid reducers (controls) were compared by t-test and chi2 test. Variables that showed a P-value < 0.1 in the univariate analysis were considered in the elaboration of a multivariate logistic regression model.

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References: