I. Introduction

HIV Race/Ethnicity Characteristic

Table 1. Baseline characteristics.

Hypothesis: Sevelamer, an LPS-binding compound, will reduce plasma LPS levels and LPS-associated monocyte and T cell activation in HIV-infected subjects.

II. Methods

Single arm study enrolling 40 subjects:

Male or female subjects ≥ 18 years with chronic HIV infection

CD4 + T-cell count ≥ 400 cells/mm³

HIV RNA > 50 copies/mL

No ART for 24 weeks before study entry

Intervention: 8 weeks of sevelamer carbonate 1600mg three times daily

8 weeks of follow-up

Statistical analysis: As-treated analysis

80% power to demonstrate a significant reduction in sCD14 or LPS from baseline to week 8

8 weeks of follow-up

Included in Primary Analysis?

Table 2. Effects of sevelamer on markers of inflammation

Sevelamer had no significant effect on markers of inflammation and cardiovascular disease. Median (Q1, Q3) values are reported.

Figure 1. Effects of sevelamer on circulating LPS and soluble CD14 levels

Sevelamer had no significant effect on LPS or sCD14 levels and no effect on endotoxin core antibody or LPS binding protein levels. Gray indicates treatment period. Red indicates median levels.

Table 2. Effects of sevelamer on markers of inflammation

Figure 3. Effect of sevelamer on soluble TF and D-dimer levels

Solute tissue factor decreased with sevelamer treatment and increased after treatment cessation whereas D-dimer increased minimally during sevelamer treatment. Gray indicates treatment period. Red indicates median levels.

Safety

- Well-tolerated
- No significant change in CD4 T-cell counts
- No significant change in HIV RNA levels
- No significant change in phosphate levels

IV. Conclusions

In patients not on ART, 8 weeks of sevelamer did not decrease microbial translocation or inflammation markers, possibly due to:

- Ongoing intestinal damage by viral replication
- Impaired LPS clearance due to defective phagocytosis, decreased endotoxin core antibody levels, hepatic dysfunction
- Alternatively, low levels of microbial translocation in this relatively healthy population may have precluded a significant effect.

However, 8 weeks of sevelamer carbonate decreased LDL and oxLDL levels with a comparable effect to statins.

Proposed Model:

1. Sevelamer decreases LDL and oxLDL cholesterol
2. Decreased oxLDL results in decrease surface tissue factor on monocytes and macrophages and in plaques
3. Decreased tissue factor is reflected by decreased soluble tissue factor
4. Decreased macrophage tissue factor may result in decreased formation of the thrombin/antithrombin complex
5. Thrombus formation is decreased, yielding a cardiovascular benefit

References


Sevelamer Does Not Decrease Plasma LPS or sCD14 but Does Decrease Soluble Tissue Factor and LDL

Netanya Sandler1,2, Xinyan Zhang3, Ronald Bosch3, Nicholas Funderburk4, Janet Robinson4, Daniel Douek1, Cara Wilson5, Steven Deeks6, Michael Lederman4, Rajesh Gandhi7, for the A5299 Study Team

1VRC/NAID/NIH, Bethesda, MD, USA, 2University of Texas Medical Branch, Galveston, TX, USA, 3Harvard School of Public Health, Statistical & Data Analysis Center, Boston, MA, USA, 4Case Western Reserve University, Cleveland, OH, USA, 5University of Colorado, Aurora, CO, USA, 6University of California, San Francisco, CA, USA, and 7Massachusetts General Hospital, Boston, MA, USA

Supported by NIH Grants U01-A168636, A168634