Rosuvastatin Reduces Immune Activation and Inflammation in Treated HIV Infection

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BACKGROUND

- Modest decrease in CD8+CD38+HLA-DR+ was reported after 8-weeks of statin therapy in 22 untreated HIV-infected subjects
- The effect of statins on immune activation and inflammation in HIV-infected subjects on antiretroviral therapy (ART) is unknown
- We have previously shown that 24 weeks of rosuvastatin treatment led to significant decreases in sCD14, Lp-PLA2 and the proportion of CD14dimCD16+ monocytes that express TF.
- We did not measure a significant change in markers of T cell activation or markers of systemic inflammation at 24 weeks of therapy.

OBJECTIVE

To assess the effect of 48 weeks of statin therapy on systemic and vascular inflammation and on monocyte and lymphocyte immune activation in HIV-infected subjects on antiretroviral therapy (pre-specified pre-planned analysis)

METHODS

STUDY DESIGN AND OBJECTIVES

- 147 subjects enrolled in the **S**topping **A**therosclerosis and **T**reating **U**nhealthy bone with **R**osuvastati**N** in HIV (SATURN-HIV) trial
- SATURN-HIV is a randomized double-blind placebo-controlled trial with the primary objectives to measure the effect of rosuvastatin 10mg daily on the progression of subclinical vascular disease and skeletal health. Secondary objectives included changes in systemic and vascular inflammation, coagulation, and in monocyte and lymphocyte immune activation.
- Randomization was stratified by PI use at entry.
- Enrollment spanned from March 2011 to. August 2012

INCLUSION CRITERIA

- ≥18 years of age, on stable ART with HIV-1 RNA < 1,000 copies/mL
- Evidence of heightened T-cell activation (CD8+CD38+HLA-DR+ ≥19%) or increased inflammation (high sensitivity C-reactive protein (hsCRP ≥2mg/L) at baseline
- LDL-cholesterol (LDL-C) ≤ 130 mg/dL

EXCLUSION CRITERIA

- Pregnancy
- Known coronary artery disease
- Uncontrolled diabetes
- Use of statin in the last 6 months
- Medication or diagnosis known to confound inflammation markers

MEASUREMENTS

- Systemic Inflammation: hsCRP (nepholometry), TNF-α, sTNFR-I and -II, and IL-6 (ELISA)
- Vascular inflammation: Lp-PLA2 (PLAC™ test)
- Monocyte Immune activation: soluble markers sCD14 and sCD163 (ELISA), and real time monocyte subpopulation distributions and tissue factor (TF) expression
- Lymphocyte activation: expression of CD38+ and/or HLA-DR+ and/or PD1+ on CD8+ and CD4+
- Coagulation: D-dimer (ELISA), fibrinogen (nepholometry)
- Other tests obtained but not used for the present analysis: Carotid intima media thickness, flow mediated dilation, calcium score, perivascular fat depots, lumbar spine and hip DXA scans, bone turnover markers, whole body DXA, oxidative markers, and markers of glucose and lipid metabolism.

Statistics: Analysis was by intent to treat. Differences in median percent changes at week 48 were assessed using the Wilcoxon Rank Sum test

Table 1: Baseline characteristics of study participants

	Statin n=72	Placebo n=75
Age (y)s)	45.6 (41.1, 51.4)	46.9 (39.2, 53.6)
Male sex	81%	76%
African American race	71%	69%
Body Mass Index (kg/m²)	26.6 (23.4, 30.0)	27.2 (23.5, 30.5)
Current Smoking	60%	72%
CD4+ count (cells/μl)	607.5 (439.5, 847.5)	627.0 (398.0, 853.0)
Nadir CD4+ count (cells/μl)	172.5 (83.5, 312.0)	189.5 (89.0, 281.0)
HIV-1 RNA <50 copies/mL	78%	77%
HIV duration (months)	133 (75, 199)	145 (73, 232)
Duration of ART(months)	63 (37, 119)	71 (39, 116)
On PI at entry	50%	48%
Duration of PI (months)	47 (13, 106)	39 (2, 80)
hsCRP (μg/mL)	1.6 (0.8, 4.9)	2.0 (0.7, 5.2)
IL-6 (pg/mL)	2.9 (1.9, 4.1)	2.7 (2.0, 5.3)
sTNF-RI (ng/mL)	1.59 (1.32, 2.15)	1.50 (1.23, 2.44)
sTNFR-II (ng/mL)	2.48 (1.78, 3.01)	2.16 (1.61, 2.62)
Lp-PLA2 (ng/mL)	165 (134, 199)	169 (142, 206)
CD8+CD38+HLA-DR+ (%)	13.3 (9.0, 19.1)	11.5 (8.0, 16.5)
CD4+CD38+HLA-DR+ (%)	5.3 (3.7, 6.8)	5.1 (3.5, 6.3)
sCD14 (ng/mL)	2178 (1783, 2497)	2138 (1611, 2455)
sCD163 (ng/mL)	645 (501, 822)	651 (475, 901)
CD14+CD16+ monocytes (%)	22.9 (18.1, 34.0)	23.4 (18.6, 35.9)
CD14dimCD16+ monocytes (%)	12.7 (8.8, 15.5)	10.0 (7.5, 14.3)
CD14+CD16+TF+ (%)	13.4 (7.9, 17.4)	10.9 (7.7, 15.9)
CD14dimCD16+TF+ (%)	21.8(15.6, 29.6)	18.9 (12.6, 25.3)
D-dimer (μg/mL)	0.19 (0.13, 0.33)	0.18 (0.09, 0.29)

Study arms were well balanced except for CD14dimCD16+TF+ (%); p=0.047

Data presented as median (Q1, Q3) or percent

Rosuvastatin treatment lowers several markers of immune activation including levels of sCD14 and lipoprotein-associated phospholipase A2 and proportions of activated monocytes and T cells

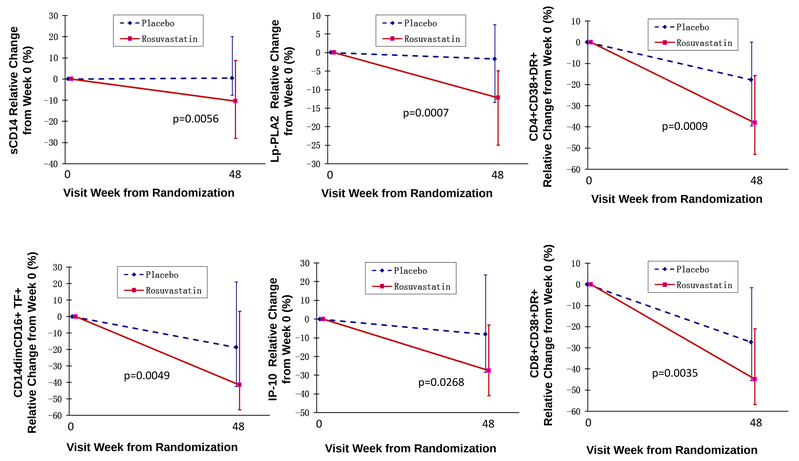

Table 2: Percent change in markers of inflammation and immune activation at week 48

	Statin n=72		Placebo n=75		P value Between two groups
	Median (Q1, Q3)	Within group p value	Median (Q1, Q3)	Within group p value	
Inflammatory molecules					
hsCRP (mg/L)	1.7% (-57.3, 69.4)	0.0256	28.6% (-30.2, 105.3)	0.0012	0.2018
IL-6 (pg/mL)	-12.3% (-44.6, 24.1)	0.3144	-3.7% (-31.6, 21.4)	0.0980	0.4444
sTNF-RI (ng/mL)	-0.7% (-33.3, 16.5)	0.0331	3.8% (-32.1, 14.7)	0.0703	0.6764
sTNF-RII (ng/mL)	25.5% (-3.6, 54.1)	<0.0001	34.8% (15.6, 55.8)	<0.0001	0.0908
IP-10	-27.5% (-40.9, -3.2)	0.0208	-8.2% (-28.4, 23.5)	0.7811	0.0268
Lp-PLA2 (ng/mL)	-12.2%(-25.0, -4.9)	<0.0001	-1.7% (-13.5, 7.5)	0.5921	0.0007
Lymphocyte Activation					
CD8+CD38+HLA-DR+ (%)	-44.8% (-56.9, -21.1)	<0.0001	-27.4% (-45.5, -1.6)	0.0188	**0.0035**
CD8+CD38+ (%)	-29.8% (-41.7, -19.0)	<0.0001	-19.5% (-34.7, -7.0)	<0.0001	**0.0178**
CD8+CD38+HLA-DR+PD1+ (%)	-45.5% (-58.3, -23.4)	<0.0001	-26.3% (-47.6, 28.8)	0.9325	**0.0016**
CD4+CD38+HLA-DR+ (%)	-38.1% (-53.0. -15.8)	<0.0001	-17.8% (-39.5 0)	0.0037	**0.0009**
CD4+CD38+ (%)	-15.3% (-22.2, -6.1)	0.0012	-13.6% (-23.4 -6.8)	<0.0001	0.8337
CD4+CD38+HLA-DR+PD1+ (%)	-42.5% (–57.2, -22.7)	0.0020	-24.1% (-43.0, 17.5)	0.3502	**0.0019**
Monocyte Activation					
sCD14 (ng/mL)	-10.4% (-27.9, 8.7)	0.0179	0.5% (-7.7, 20.1)	0.0882	**0.0056**
sCD163 (ng/mL)	-12.3% (-29.5, 0.8)	0.0099	-8.6% (-26.6, 9.9)	0.1566	0.6863
CD14+CD16+ monocytes (%)	-1.9% (-41.6, 29.4)	0.3081	-6.0% (-25.9, 24.1)	0.3701	0.9814
CD14dimCD16+ monocytes (%)	-7.5% (-35.1, 35.8)	0.1810	3.4% (-25.8, 43.6)	0.0387	0.2985
CD14+CD16-TF+ (%)	-52.1% (-64.1, -11.2)	0.0002	-31.2% (-67.3, 36.6)	0.5900	0.1739
CD14+CD16+TF+ (%)	-33.7% (-62.3, -7.8)	<0.0001	-29.9% (-57.6, 24.8)	0.4812	0.1978
CD14dimCD16+TF+ (%)	-41.6% (-56.7, 3.1)	<0.0001	-18.8% (-42.5, 21.0)	0.7998	**0.0049**

CONCLUSIONS

- In HIV-infected men and women with normal LDL-C and controlled plasma HIV-1 RNA levels , 48 weeks of rosuvastatin therapy resulted in:
  - A significant decline in the monocyte activation marker sCD14 and in the proportion of CD14dimCD16+TF+ monocytes
  - A significant decline in the vascular inflammation marker Lp-PLA2
  - A significant decline in levels of interferon gamma-induced protein 10 (IP-10)
  - A significant reduction in the proportions of activated CD4+ and CD8+ T cells
- We also report reductions in several markers of inflammation and immune activation within the statin arm between baseline and week 48.
- This is a 96 week study and we will continue to measure potential changes in inflammation, immune activation, and coagulation. We will also assess the relationships between the changes in inflammation and immune activation to those of cardiovascular markers and bone metabolism.

This study was funded by a grants from the National Institutes of Health (NR012642 to GM, 1K99HL108743 to NF) and by the CWRU Center for AIDS Research (P30 AI36219).