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The Effect of Hepatitis C Clearance on Macrophage Activation in HIV/HCV Coinfection

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Background

- HCV coinfection is associated with increased all-cause mortality in HIV-infected persons
- Cardiovascular disease (CVD) is a leading cause of non-liver, non-AIDS deaths in HIV/HCV-coinfected persons
- HCV coinfection may increase CVD risk and successful HCV treatment may reduce CVD risk
- Markers of macrophage activation are associated with atherosclerotic/arterial disease in HIV-infected persons
- We hypothesized that HCV virologic clearance reduces levels of soluble macrophage activation markers

Objectives

The aims of our study were to:

1) Characterize levels of soluble macrophage activation markers in a well-defined HIV/HCV-coinfected cohort.
2) Explore the potential benefit of HCV treatment on CVD outcomes by examining the effect of sustained virologic response (SVR) on markers of macrophage activation

Methods

Study Design and Subject Selection

- Retrospective case control analysis of stored serum and plasma samples and clinical data from 54 HIV/HCV-coinfected subjects who participated in ACTG A5178
- All subjects had ≥ 2 log reduction in or undetectable HCV viral load at 12 weeks and were assigned to receive up to 72 weeks of pegylated interferon plus ribavirin therapy
- EDTA plasma samples were collected prior to start of HCV treatment (baseline) and 24 weeks after end of HCV treatment (EOT+24 weeks)
- 27 HCV treatment responders (those with sustained virologic response (SVR) = HCV RNA <60 IU/mL at 24 weeks after EOT) and 27 non-responders (non-SVR) were selected those with available paired plasma samples from baseline and EOT+24 weeks, matched simultaneously on race/ethnicity and sex
- Outcome measures: Change in soluble CD163 (sCD163) and change in soluble CD14 (sCD14) levels from baseline to 24 weeks after EOT
- Hypothesis: SVR status is associated with change in sCD163 and sCD14 levels

Biomarkers:

- sCD163 and sCD14 were measured by ELISA (Macro163™, Trillium Diagnostics, LLC and Quantikine® Human sCD14 ELISA, R&D Systems, Inc.)

Methods

Data Analysis

- Baseline characteristics and biomarker levels were compared by Fisher's exact test or Wilcoxon tests
- Associations between biomarkers and baseline variables were explored using simple regression
- Within group (SVR/non-SVR) changes in each biomarker from baseline to 24 weeks after EOT were compared to zero by paired sample t-test
- Two-sample t-test was used for between group comparisons (SVR vs non-SVR) of changes in each biomarker
- Linear regression models were constructed to quantify the association between SVR and change in each biomarker, adjusting for selected covariates: sex and race/ethnicity (Model 1); further adjusting for baseline variables significantly different by SVR status at a 0.10 significance level with a backward variable selection (Model 2); further adjusting Model 2 for change in ALT from baseline to 24 weeks after EOT (Model 3); and adjusting Model 2 for duration of PEG/RBV therapy (Model 4)

Results

Table 1: Baseline characteristics of the study cohort

Characteristic	SVR (n=27) Median (Q1, Q3) or n (%)	Non-SVR (n=27) Median (Q1, Q3) or n (%)
Age (years)	47 (42, 52)	48 (45, 52)
Male sex	22 (81%)	22 (81%)
Race/ethnicity		
White Non-Hispanic	15 (56%)	15 (56%)
Black Non-Hispanic	12 (44%)	12 (44%)
Body mass index (BMI)	26.1 (23.2, 30.0)	25.5 (24.1, 28.5)
HIV-1 RNA <50 copies/mL	20 (74%)	22 (81%)
CD4 cell count	571 (378, 747)	536 (357, 734)
HCV genotype		
1	18 (67%)	23 (85%)
2	7 (26%)	2 (7%)
3	2 (7%)	1 (4%)
4	0 (0%)	1 (4%)
Cirrhosis	0 (0%)	2 (7%)
Fibrosis stage ≥ 3*	5 (19%)	13 (48%)
HCV RNA (log10 copies/mL)*	6.41 (5.73, 6.92)	6.70 (6.31, 7.04)
History of prior HCV treatment*	4 (15%)	11 (41%)
History of CVD	3 (11%)	4 (15%)
Hypertension	5 (19%)	9 (33%)
Diabetes	2 (7%)	5 (19%)
HOMA-IR	2.97 (1.43, 4.49) (n=22)	6.11 (3.73, 8.77) (n=16)
AST (U/L)*	41 (30, 60)	63 (42, 85)
ALT (U/L)*	58 (37, 73)	68 (51, 91)
PEG/RBV duration (weeks)	71.9 (71.0, 72.1)	71.4 (47.3, 72.3)

*Between group difference at 0.10 significance level, included in backward selection

Results

Table 2: Baseline biomarker levels by SVR status

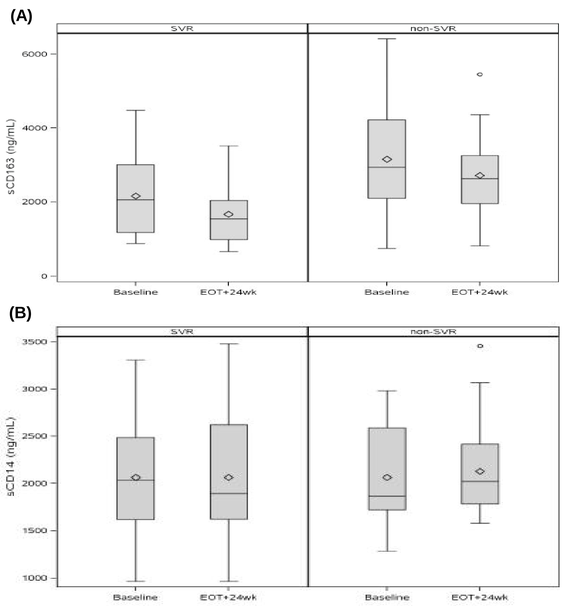
Biomarker	SVR (n=26)^ Median (Q1, Q3)	Non-SVR (n=27) Median (Q1, Q3)	P-value*
sCD163 (ng/mL)	2056 (1172, 3006)	2933 (2094, 4129)	0.013
sCD14 (ng/mL)	2032 (1622, 2484)	1866 (1724, 2591)	0.950

^One subject in the SVR group missing baseline measurements due to insufficient sample volume. *Wilcoxon rank sum test.

- In simple regressions, baseline sCD163 was positively associated with fibrosis stage, (p<0.001), baseline ALT (p<0.001), and baseline total cholesterol (p=0.0397).
- There was no difference in baseline sCD163 after controlling for baseline fibrosis (p=0.094).

Results: Effect of SVR on Biomarkers

Figure 1: Effect of SVR on sCD163 (A) and sCD14 (B)

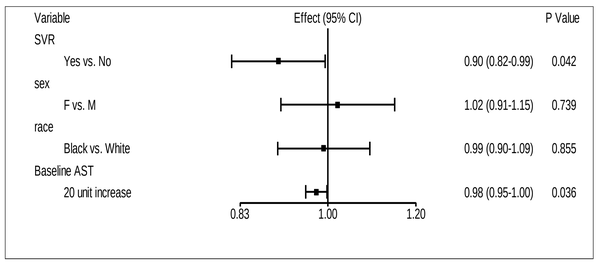


- Within group, log10 sCD163 levels decreased significantly in the SVR group (p=0.001), but not in the non-SVR group (p=0.20). There were no significant changes in sCD14 levels in either the SVR or non-SVR group.
- By t-tests, change in sCD163 and sCD14 comparing SVR and non-SVR was not statistically significant (p=0.162 and p=0.642).
- In regression analyses using backward selection (Model 2), the association between SVR and change in sCD163 persisted (p=0.042). The association was lost (p=0.096) after further adjusting for change in ALT with treatment (Model 3: association of ALT with change in sCD163 p=0.002).

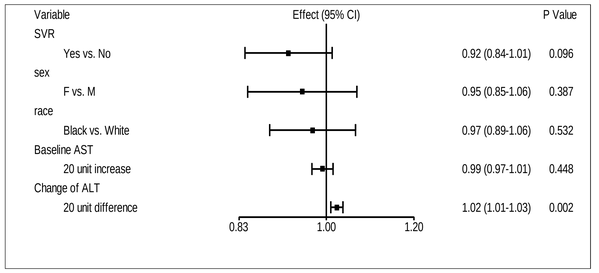
Results

Figure 2: Regression of change in $\log_{10}$ sCD163 with backwards selection (Model 2), adjusting for change in ALT (Model 3), and for duration of PEG/RBV therapy (Model 4)

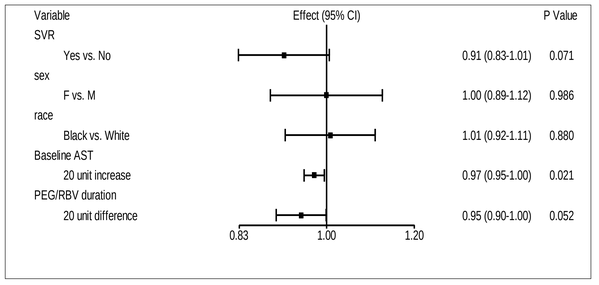
(Model 2)



(Model 3)



(Model 4)



Conclusions

- **HCV virologic clearance was associated with a significant decrease in plasma sCD163 but not sCD14 levels. Lack of association between HCV clearance and sCD14 may be due to variability in sCD14 and small sample size.**
- **Soluble CD163 but not sCD14 was associated with hepatic fibrosis and inflammation. The degree of liver disease should be considered in the interpretation of macrophage activation markers in HIV-infected persons.**
- **Effective HCV treatment may reduce hepatically-driven macrophage activation and systemic immune activation, with potential benefit in reducing cardiovascular disease risk in HIV/HCV-coinfected persons.**