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Decreases in Markers of Monocyte/Macrophage Activation after Hepatitis C Eradication in HIV/HCV co-infected Women

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Abstract

Objective: Eradication of hepatitis C virus (HCV) in HIV disease decreases liver and non-liver-related morbidity and mortality. Elevated markers of monocyte/macrophage activation (soluble CD163 and sCD14) are associated with excess non-AIDS morbidity and mortality in HIV. We examined the effect of HCV eradication on these markers in relation to change in hepatic fibrosis.

Design: Nested substudy within a longitudinal observational cohort

Methods: We studied 126 HIV/HCV coinfected women successfully treated for HCV, with undetectable HCV RNA at least 12 weeks after therapy completion. sCD163 and sCD14 were

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measured in serum collected before and after HCV eradication. Results were correlated with changes in markers of hepatic fibrosis.

Results: Mean age of participants was 56.3 years, mean CD4 was 615, 72% had suppressed HIV RNA. After treatment, sCD163 and sCD14 levels significantly decreased from pre-treatment levels in unadjusted analyses. After adjusting for age, race, hepatic fibrosis status, baseline HCV RNA, CD4 count and HIV RNA status, cigarette smoking, and alcohol use, the decreases in sCD163 and sCD14 remained significant. Decrease in pre-treatment to post-treatment sCD163 were significantly positively correlated with changes in FIB-4 (r=.250, p=.005) and APRI (r=.262, p=.003); similarly decrease in sCD14 was significantly positively correlated with changes in FIB-4 (r=.333, p=.0001) and APRI (r=.457, p<.0001).

Conclusions: HCV eradication is associated with significant reductions in monocyte/macrophage activation markers that correlate with reductions in markers of hepatic fibrosis. These findings support broad access to and early initiation of HCV treatment in order to decrease immune activation and improve health in HIV-infected persons.

Keywords

immune activation; microbial translocation; liver fibrosis; HCV; HIV; sCD163; sCD14

Background

Hepatitis C (HCV) infection is highly prevalent in HIV disease and is associated with excess liver-related and all-cause mortality.[1] HCV eradication not only reduces the risk of hepatocellular carcinoma and liver-related mortality in HIV but also reduces non-liver morbidity and mortality including cardiovascular and metabolic disease.[2, 3] Serum soluble CD163 (sCD163) and CD14 (sCD14) are biomarkers of innate immune activation including monocyte/macrophage activation.[4] These processes are associated with chronic immune activation in both HIV and HCV infection and are likely additive in co-infected patients,[4] and elevation of each of these markers has been independently associated with excess non-AIDS morbidity and mortality in HIV.[5–8]

Recently, Parisi et al, demonstrated that levels of sCD163 and sCD14 decline after HCV eradication in patients with and without HIV viral suppression suggesting that HCV plays a role in immune activation in co-infected patients.[9] Similarly, Lopez-Cortes, et al found the sCD14 decreases significantly after HCV eradication, along with proviral HIV DNA, cellular activation markers and lipopolysaccharide (LPS). We sought to confirm these findings in a large cohort of US women living with HIV (WLWH). We examined the effect of HCV eradication on sCD14 and sCD163 and the association between these biomarkers and hepatic fibrosis markers among participants in the Women's Interagency HIV Study.

Methods

The Women's Interagency HIV Study (WIHS) is a longitudinal prospective cohort study of US WLWH and demographically-similar HIV seronegative women.[11] The cohort was designed to reflect the demographics of women with HIV in the United States.[12] The WIHS in 1993, has been funded through five 5-year cycles to date and recently merged with the

Multicenter AIDS Cohort study to become the MACS/WIHS Combined Cohort Study. The current study includes the nine historical WIHS clinical sites: Chicago, IL; San Francisco, CA; Jackson, MS; Birmingham, AL; Miami, FL; Atlanta, GA; Washington, D.C.; Bronx, NY; and Brooklyn, NY. Semiannual visits include an extensive structured interview, physical exam, and collection of blood and genital specimens. All data for the current study were gathered from these semiannual visits. Demographic characteristics and clinical measures were assessed at pre- and post- HCV treatment WIHS visits, including the laboratory values required for calculation of fibrosis markers. HIV RNA is analyzed as a categorical variable (detectable/undetectable) and as a continuous variable with the LLD of detection of 20 cps/ml used for undetectable values. Hazardous drinking was defined by the National Institute of Alcohol Abuse and Alcoholism definition of >7 drinks/week for women.[13] The study was reviewed and approved by the Institutional Review Board of each institution and each participant provided written informed consent in accordance with US Department of Health and Human Services guidelines.

WIHS participants included in the current analysis were HIV/HCV co-infected women without active hepatitis B or acute infection at the time of blood draw. Each woman had undergone a course of therapy for HCV, had HCV eradication documented and had pre- and post-eradication serum available. HCV eradication was defined as undetectable HCV RNA ≥12 weeks after therapy completion. End of HCV treatment was self-reported at the semi-annual WIHS visit; at times, end of therapy had to be imputed based on when therapy was first reported. When there was any question that the end of treatment was less than 12 weeks prior to the visit, we measured markers from the next later semi-annual visit to assure that sustained HCV virologic response (SVR) had been achieved. Treatment included interferon-free and interferon-based regimens.

Non-invasive measures of fibrosis

Two validated, non-invasive tools that estimate the degree of hepatic fibrosis were chosen for correlation with sCD163 and sCD14 levels. The FIB-4 and aspartate transaminase (AST) to platelet ratio index (APRI) use routine biochemical laboratory values and, for the FIB-4, the patient's age. The data required are collected at each semiannual WIHS visit and values from the visits concurrent with the soluble marker levels were used to calculate each fibrosis marker. Though both tools have limitations, the correlation with liver biopsy histology is high in HIV/HCV-infected person and values can be followed serially. These markers have been used extensively in the WIHS to correlate with outcomes and have been shown to accurately predict liver-related mortality among HIV/HCV co-infected women.[14] The FIB-4 is calculated as (age x AST)/(platelet count x √alanine transaminase); a score greater than 3.25 is suggestive of significant fibrosis.[15–17] The APRI is calculated as (AST/upper limit of normal AST)/platelet count); a result greater than 1.5 is suggestive of significant fibrosis.[17,18]

Statistical Methods

Descriptive statistics were used to analyze demographic, behavioral, and clinical characteristics in the overall sample and summarized as frequencies for categorical variables and median (IQR) or mean (SD) for continuous variables. Bivariate analyses were

performed using Fisher's exact test for categorical variables and Wilcoxon signed rank tests for continuous variables. Non-normally distributed variables were transformed (log or square root) as needed. Unadjusted comparisons of biomarker means were assessed using Wilcoxon signed rank tests. For adjusted analyses, repeated measures analysis using general linear models were run to compare differences in pre- and post HCV treatment biomarker means. Multivariable analyses were adjusted for pre-treatment age, race, HCV RNA, and hepatic fibrosis status, post treatment CD4 and viral suppression, and hazardous drinking and smoking anytime between pre- and post-treatment visits. Correlations of change in biomarker levels with changes in APRI and FIB-4 scores from the pre-treatment to the post-treatment visit (post minus pre) were assessed using scatterplots and Spearman's rank correlation coefficients. All statistical analyses were conducted using SAS version 9.4.

Laboratory methods

sCD163 and sCD14 were measured in duplicate in pre- and post-treatment serum samples using the Quantikine CD14 and CD163 ELISA kits, respectively (R&D Systems, Minneapolis, MN). These serum samples had been frozen at the point of collection and stored at −80C.The final result used in analysis was the mean of the duplicate tests. If the duplicate results were more than 10% different the assays were rerun in duplicate and the results of the repeat assays used in analysis; only 8 of the 252 duplicate runs required repeating.

Results

One-hundred twenty-six WIHS participants met criteria for inclusion. Mean pre-treatment age was 56.3 years (Table 1). Participants were 52% African-American, 21% other/multiracial, 16% Latina, and 12% white. Prior to treatment, mean CD4 count was 636/μL and 72% of participants had undetectable HIV RNA. Thirteen (10%) had significant fibrosis by FIB-4 or APRI prior to HCV treatment. Thirteen (10%) received interferon-based therapy, the remainder received direct-acting antivirals (DAAs). Post-treatment biomarker levels were measured a median of 228 days (IQR: 164.5 – 365.5) after HCV therapy completion. The vast majority of women (94%) had genotype 1 HCV.

After HCV eradication, sCD163 and sCD14 levels significantly decreased from pre-treatment levels in unadjusted analyses (Figure 1A). Results were similar (data not shown) between women who received interferon-based and DAA therapy so the results from all women are presented together. Because the soluble markers were measured at least 12 weeks (and often much longer) after cessation of HCV therapy, we assumed that any inflammatory changes caused by interferon-based therapy had resolved and the changes reflected the effect of HCV eradication. After adjusting for age, race, pre-treatment fibrosis status, post-treatment CD4 count and HIV RNA status, and alcohol and tobacco use, the decreases in sCD163 and sCD14 remained significant (Figure 1A). We looked carefully at HIV RNA status; 35 women had detectable HIV RNA at the pre-treatment visit and 33 at the post-treatment, 16 of these were the same women and 17 and 19 women, respectively, were detectable only at the pre- or post-treatment visit. When we evaluated change in soluble markers including only the 52 women who had undetectable HIV RNA at both timepoints

the results of the unadjusted analysis was unchanged. The results of the analysis adjusted for all factors above excluding HIV RNA status revealed that the change in sCD14 remained significant at p=.014 but lost significance for change in sCD163 (p=.554).

Mean FIB-4 was 2.67 prior to treatment and 2.03 after (p<.0001). Mean APRI was 0.88 prior to treatment and 0.40 after (p<.0001). Change in pre-treatment to post-treatment sCD163 was significantly positively correlated with changes in FIB-4 (r=.250, p=.005) and APRI (r=.262, p=.003) (Figure 1B). Change in pre-treatment to post-treatment sCD14 was significantly positively correlated with changes in FIB-4 (r=.333, p=.0001) and APRI (r=.457, p<.0001) (Figure 1C).

Discussion

We demonstrated significant decreases in sCD163 and sCD14 after HCV eradication in a diverse and well-characterized cohort of HIV-infected US women. CD163 is a haptoglobin-hemoglobin scavenger receptor shed from the cell surface of monocytes and macrophages in response to inflammatory stimuli such as Toll-like receptor activation via lipopolysaccharides (LPS) or other microbial ligands.[5,9] In HIV disease levels of sCD163 have been consistently found to be associated with all-cause mortality and non-AIDS co-morbidities, independent of HIV RNA status in most analyses.[5–8] The cause of this association is unclear but sCD163 is associated with shortened telomere length in HIV.[19] In several studies tracking sCD163 levels after initiation of antiretroviral therapy (ART), the presence of HCV co-infection has been found to attenuate the antiretroviral induced decrease in sCD163.[6,21] Besides viral coinfections, microbial translocation and lifestyle factors (such as alcohol and tobacco use) have been hypothesized to contribute to the persistent immune activation in treated HIV.[9,21-23]

CD14 is a co-receptor for lipopolysaccharide and monocyte release of soluble CD14 is mediated by translocation of microbial products from the gut into the systemic circulation.[9,] Just as for sCD163, sCD14 has been associated with greater risk of all-cause mortality, as well as vascular disease, hematologic abnormalities and other non-AIDS co-morbidities.[5,8, 24, 25]

Decreases in sCD14 and sCD163 were associated with greater improvements in validated measures of hepatic fibrosis. While it is plausible that there is a causative relationship between the decrease in biomarkers and hepatic fibrosis regression given that products of microbial translocation (including LPS) are part of cascade leads to cleavage of CD14 and CD163, these may be two separate salutary effects of HCV eradication. Any direct causal relationship between hepatic fibrosis and decrease in biomarkers of macrophage activation remains to be determined.

Our study and its findings should be evaluated in the context of its limitations. We used calculated markers of fibrosis rather than transient elastography or liver biopsy as these markers are more widely available in WIHS and allowed us to include more women. These markers correlate well with biopsy, elastography and liver-related outcomes in HIV but

do not directly measure hepatic fibrosis.[14–18] We were unable to include data on hepatic steatosis which may have influenced the markers, the fibrosis outcomes or both.

Our study demonstrates a potential mechanism- a decrease in monocyte/macrophage activation by translocated microbial products as a consequence improved hepatic fibrosis status- by which HCV eradication leads to reductions in non-AIDS-related events. Further studies are needed to determine the precise mechanism and the full range of immunologic benefits of HCV eradication. This study supports broad access to and early initiation of treatment for HCV in order to decrease immune activation and improve health of HIV-infected persons.

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A. Pre- and Post-HCV Treatment sCD163 and sCD14

Median (IQR)	Pre-Treatment	Post-Treatment	Unadjusted[a] p-value	Adjusted[b] p-value
sCD163 (ng/mL)	1,258.4 (887.2-1,759.5)	825.9 (530.9-1,128.6)	**<.0001**	**.016**
sCD14 (pg/mL)	2,190,784 (1,901,281-2,544,132)	2,064,231 (1,741,339-2,400,766)	**<.0001**	**.029**

[a]p-value by Wilcoxon test

[b]Controlled for age, race/ethnicity, HCV RNA, and fibrosis at pre-treatment visit, detectable HIV viral load and CD4 count at post-treatment visit, cigarette smoking and hazardous alcohol use at any visit between pre- and post-treatment.

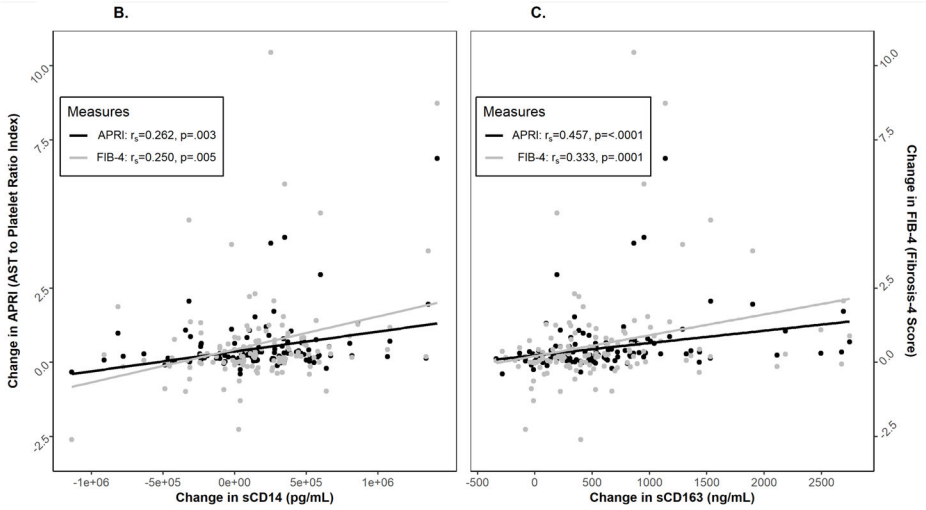

Figure 1:

(A) Comparison of sCD163 and sCD14 levels before and after HCV eradication (B) Association between pre- to post-treatment change in sCD14 and FIB-4 (gray) and sCD14 and APRI (black) (post minus pre) (C) Association between pre-to post-treatment change in sCD163 and FIB-4 (gray) and sCD163 and APRI (black) (post minus pre) *Negative values indicate a decrease from pre-treatment to post-treatment.

Table 1.

Characteristics of co-infected patients before and after HCV eradication (n=126)

	Pre-Treatment n (%)	Post-Treatment n (%)	p value
Age, mean (SD)	56.3 (5.9)	58.2 (5.9)	
Race/Ethnicity			
Black	65 (51.6)		
Hispanic	20 (15.9)		
Other/Multiracial	26 (20.6)		
White	15 (11.9)		
Income, ≤$12,000 annually	70 (57.9)	74 (60.7)	.696
Current Hazardous Drinking at Visit [a]	6 (4.8)	8 (6.5)	.594
Any Hazardous Drinking [b]		18 (14.6)	
Current Cigarette Smoker at Visit	53 (42.1)	49 (38.9)	.700
Any Cigarette Smoking [b]		60 (47.6)	
Current Hard Drug [c] **Use at Visit**	7 (5.6)	4 (3.2)	.540
Any Hard Drug Use [b]		11 (8.9)	
Body Mass Index, mean (SD)	29.7 (7.8)	30.0 (8.1)	.375
APRI, mean (SD)	0.88 (1.04)	0.40 (0.36)	**<.0001**
FIB-4, mean (SD)	2.67 (2.41)	2.03 (1.64)	**<.0001**
Significant fibrosis (APRI >1.5 and FIB-4 >3.25)	13 (10.3)	5 (4.0)	.084
Log baseline HCV RNA (IU/mL), mean (SD)	14.15 (1.7)		
HCV Genotype (n=78)			
1	73 (93.5)		
2	1 (1.2)		
3	2 (2.5)		
4	2 (2.5)		
HCV Therapy			
Any Interferon-Based Therapy		13 (10.3)	
Ribavirin + any Direct Acting Agent (DAA)		11 (8.7)	
Harvoni (ledipasvir/sofosbuvir)		77 (61.1)	
Other DAAs		21 (16.7)	
Unknown oral therapy		4 (3.2)	
CD4+ T Lymphocyte Count (/μL), mean (SD)	636.5 (331.6)	679.1 (334.0)	**.013**
Detectable HIV RNA	35 (28.2)	33 (26.8)	.887
Log HIV RNA (copies/mL), mean (SD)	5.39 (2.1)	5.54 (1.7)	.639

Data are presented as n (%), unless otherwise noted.

[a] Reported >7 alcoholic drinks per week at the visit

[b] Ever reported between pre- and post-treatment visits

[c] Crack, cocaine, and/or heroin