Association between sCD163 and CMV IgG in Virologically Suppressed HIV+ Patients

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ABSTRACT #319

Abstract

Background: HIV+ patients with controlled viremia have ongoing chronic inflammation which has been associated with an increased risk for cardiovascular and neurocognitive disease. Cytomegalovirus (CMV) has been implicated as a potential driver of this inflammation. Soluble CD163 (sCD163) is a marker of monocyte/macrophage activation and is upregulated in inflammatory states. We explore the relationship between CMV and sCD163 in HIV+ pts with well controlled viremia.

Methods: Patient samples and data from existing cohorts of HIV+ subjects with undetectable HIV RNA were utilized for this study. Specimens were collected between 2009 and 2013. ELISA was used to measure sCD163 level in plasma and CMV immunoglobulin G (IgG) level in serum. All subjects underwent plasma CMV PCR testing. Bivariate analysis (Pearson Correlation and Kruskal Wallis Test) and multivariate linear regression analysis were performed to identify variables associated with CMV IgG level. Variables included in the multivariate model are sex, race, age, duration of antiretroviral use, and sCD163 level.

Results: Of 139 adult, virologically suppressed HIV+ subjects, 130 (94%) were CMV seropositive and were included in our analysis. The median age was 55 (51-59) years, 63% male, 61% black, 18% Hispanic, 12% white, and 2% other race. The median CD4 count was 511 (196-686) cells/mm^3, median sCD163 was 1165.9 ng/mL (884.4-1553.1), and median CMV IgG level was 38.8 IU/mL (31.6-45.5) (results reported as median (IQR) unless stated otherwise). No subjects had detectable plasma CMV DNA. Bivariate analysis revealed a significant, positive correlation between sCD163 and CMV IgG levels (r = 0.19, p = 0.03) and a trend towards increased CMV IgG among those with coronary disease (H = 2.99, p = 0.08). Multivariate analysis also identified a positive relationship between CMV IgG levels and sCD163 (coef. 0.004; 95%CI 0.001-0.003 p = 0.01).

Conclusions: Among HIV+ adults with undetectable HIV RNA, increased CMV IgG level (even in the absence of CMV viremia) is associated with increased sCD163 level. Our finding adds to the body of evidence suggesting that CMV is involved in the complex pathophysiology of chronic inflammation in HIV. Cellular correlates of these elevated CMV IgG levels deserve further exploration.

Background

- HIV infection causes increased inflammation and immune activation that persists despite virologic suppression with antiretroviral therapy (ART)
- This ongoing inflammation and immune activation results in increased rates of cardiovascular disease, neurocognitive dysfunction, and other non-AIDS morbidities
- Chronic CMV infection has been proposed as a driver of chronic inflammation:
  - Elevated CMV immunoglobulin G (IgG) antibody levels have been associated with an increased incidence of ischemic heart disease, Alzheimer disease, and all-cause mortality in the general population
  - Elevated CMV IgG antibody levels have been associated with subclinical carotid artery disease among HIV+ patients
- Macrophage and monocyte activation have also been postulated to play a role in the development of cardiovascular disease among HIV+ patients
- Soluble CD163 (sCD163) and soluble CD14 (sCD14) are markers of monocyte/macrophage activation and are upregulated in inflammatory states
- In this pilot study, we explore the relationship between CMV, sCD14, and sCD163 in HIV+ patients with well controlled HIV infection

Materials and Methods

- Location:
  - All patients were enrolled from the Ruth M. Rothstein CORE Center, Chicago, IL, USA
    - Subjects for this study were drawn from two existing cohorts
  - CMV IgG ELISA and CMV PCR testing was performed at Rush University Medical Center, Chicago, IL, USA
  - sCD163 and sCD14 ELISA testing was performed at The Blood Systems Research Institute, San Francisco, CA, USA
- Study Period: Enrollment for the two original cohorts occurred in 2009-2011 and 2011-2013
- Study Population: 139 HIV+ patients with undetectable HIV RNA
- Data Collected:
  - Demographics, social history, HIV-related variables (CD4 count, ART regimen, time on ART), co-morbidities, and various laboratory values (lipids, hsCRP, FIB-4 score)
  - Serum was tested for sCD163, sCD14, and quantitative CMV IgG level via ELISA
  - Plasma specimens underwent PCR testing to assess for the presence of CMV DNA

Statistical Analysis:

- Bivariate analysis (Pearson Correlation and Kruskal Wallis Test) and multivariate linear regression analysis were performed to identify variables associated with CMV IgG level

Results

Table 1. Characteristics of CMV Seropositive Patients

Characteristic	n =130
Age, years	55 (51-59)
Race n (%)	
White	16 (12)
African American	79 (61)
Hispanic	23 (18)
Other	2 (2)
Gender n (%)	
Male	82 (63)
CD4 Count, cells/mm^3	511 (196-686)
Duration of ART, years	9 (5-12)
HCV Ab Positive n (%)	51 (39)
CAD/MI n (%)	22 (17)
sCD163, ng/mL	1165.9 (884.4-1553.1)
sCD14, ng/mL	1876.0 (1615.1-2235.6)
CMV Quantitative IgG, IU/mL	38.8 (31.6-45.5)
Detectable CMV DNA n (%)	0

Results reported as median (interquartile range) unless otherwise stated

Abbreviations: Ab, antibody; ART, antiretroviral therapy; CAD, coronary artery disease; CMV, cytomegalovirus; HCV, hepatitis C virus; IgG, immunoglobulin; MI, myocardial infarction

Table 2. Bivariate Analysis of CMV IgG and Patient Characteristics (n=130)

Characteristic	CMV_IgG (Coef.)	p-value
Age ^	-0.04	0.66
Race ±	5.71	0.13
Gender ±	1.44	0.23
CD4 Count^	-0.09	0.32
Nadir CD4 Count	-0.09	0.31
Duration of ART, years^	-0.01	0.90
HCV Ab Positive	0.06	0.81
CAD/MI ±	2.99	0.08
DM±	0.12	0.73
HTN±	0.12	0.73
BMI	-0.03	0.88
Smoking±	3.8	0.05
Alcohol Use±	0.04	0.84
hsCRP	-0.07	0.43
sCD163^	0.19	0.03
sCD14^	-0.001	0.99
FIB-4*	0.14	0.10

^ Presented as Pearson Correlation Coefficient and corresponding p-value
± Kruskal Wallis Test
* FIB-4 is a non-invasive assessment of liver fibrosis utilizing alanine aminotransferase (ALT) level, aspartate aminotransferase (AST) level, platelet count and age

Abbreviations: Ab, antibody; ART, antiretroviral therapy; BMI, body mass index; CAD, coronary artery disease; CMV, cytomegalovirus; DM, diabetes mellitus; HCV, hepatitis C virus; hsCRP, high sensitivity C reactive protein; HTN, hypertension; IgG, immunoglobulin; MI, myocardial infarction

Table 3. Multivariable Linear Regression of Factors Associated with CMV IgG Level

Characteristic	Coef.	95% CI	*p*-value
Male	-3.91	-8.61-0.79	0.10
Race			
African American	-5.85	-12.54-0.83	0.09
Hispanic	-5.50	-13.34-2.25	0.17
Other	5.86	-11.51-23.20	0.51
Age	-0.04	-0.42-0.35	0.86
Duration of ART Use	-0.17	-0.70-0.36	0.53
sCD163[a]	0.004	0.001-0.006	0.01

[a]Model selection considered sCD163, sCD14 considered in separate analysis due to colinearity between the markers

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; CMV, cytomegalovirus; IgG, immunoglobulin

Study Limitations

- Small sample size and lack of longitudinal follow up prevent assessment of clinical outcomes associated with increased immune activation and inflammation
- There are not enough CMV seronegative subjects to allow for comparison of sCD163 and sCD14 levels between CMV seropositive and CMV seronegative subjects

Conclusions

- Among HIV+ adults with undetectable HIV RNA, detectable CMV replication in the blood is rare
- Despite this lack of CMV viremia, increased CMV IgG levels are associated with increased macrophage/monocyte activation as assessed by sCD163 level
- We did not find a relationship between CMV IgG and the macrophage/monocyte activation marker sCD14 in this cohort
- There appears to be a trend towards higher CMV IgG levels in smokers and patients with cardiovascular disease
- These findings suggest that CMV is involved in the complex pathophysiology of chronic inflammation in HIV
- Larger studies are needed to further explore the relationship between CMV and macrophage/monocyte activation and the potential clinical implications

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