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Pre-vaccine plasma levels of soluble inflammatory indices negatively predict responses to HAV, HBV, and tetanus vaccines in HCV and HIV infection

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ABSTRACT

Background: Chronic hepatitis C virus (HCV) and HIV infections are associated with impaired responses to neo-antigens contained in hepatitis A virus (HAV)/hepatitis B virus (HBV) vaccines, yet responsible mechanisms are unclear.

Methods: ACTG 5232 and CFAR0910 were clinical trials where pre-vaccine levels of plasma IP10, IL-6, sCD163 and sCD14 were measured in viremic HCV- (n = 15) or HIV-infected participants (n = 24) and uninfected controls (n = 10). Accelerated dosing HAV/HBV vaccine and tetanus booster were administered and antibody response was measured at 0, 1, 3, 8, and 24 weeks.

Results: Pre-vaccine plasma IP10, IL-6, and sCD14 levels were elevated in both HCV and HIV-infected participants, while sCD163 was also elevated in HCV-infected participants. Pre-immunization tetanus antibody levels were lower in HIV-infected than in uninfected participants, while vaccine induced antibody responses were intact in HCV and HIV-infected participants. After HAV/HBV vaccination, HCV and HIV-infected participants had lower and less durable HAV and HBV antibody responses than uninfected controls.

Among HCV-infected participants, pre-vaccine plasma IP10, IL-6, sCD14, and sCD163 levels inversely correlated with HAV, HBV and tetanus antibody responses after vaccine. Low HAV/HBV vaccine responses in HIV-infected participants prohibited assessment of immune correlates.

Conclusions: During HCV and HIV infection markers of systemic inflammation reflect immune dysfunction as demonstrated by poor response to HAV/HBV neo-antigen vaccine.

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1. Introduction

HCV-infected persons co-infected with HAV or HBV have more severe hepatic damage and increased risk for hepatocellular carcinoma [1], while HIV disease progression and mortality are, in some studies, associated with co-infection with HBV and HCV [2]. Therefore vaccination against HAV and HBV is standard of care for these patient populations. Chronic HCV and HIV infections are associated with impaired responses to many vaccines [3–6] including HAV/HBV vaccines [3–5,7,8]. In the case of HCV infection, these impaired responses are not related to cirrhosis or serum HCV RNA levels, suggesting mechanisms of immune dysfunction unrelated to liver synthetic function or portal hypertension may be involved [9]. During HIV infection, vaccine responses improve with antiretroviral therapy (ART) but remain impaired compared to the responses seen among uninfected controls [8,10]. During HIV infection, poor vaccine responses are associated with low CD4 T cell counts, low nadir CD4 T cell counts, low resting memory

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B cells and higher plasma HIV levels [4,10–12].Elevated proportions of exhausted T cells have been implicated in reduced responses to vaccine in HCV infection [7].

Elevated plasma levels of inflammatory mediators like IL-6 and soluble CD14 (sCD14) are associated with morbidity and mortality in both HCV and HIV infection [13–19]. Whether these factors relate to vaccine response is unclear. We examined the pre-vaccination levels of soluble inflammatory indices that have been associated with morbidity or mortality in HIV or HCV infection and determined their association with neo-antigen HAV/HBV and recall antigen tetanus booster vaccine antibody responses in untreated HCV, untreated HIV and uninfected control participants in the context of an exploratory clinical trial (AIDS Clinical Trials Group A5232 and the companion clinical trial CFAR 0910). Soluble inflammatory indices that we found elevated in either patient group and were associated with vaccine antibody responses are reported on here. We found that pre-vaccination plasma levels of IL-6, sCD14, sCD163, and IP10 were inversely associated with antibody responses to HAV/HBV vaccines and tetanus booster in HCV and HIV-infected participants.

2. Methods

2.1. Study participants

AIDS Clinical Trials Group (ACTG) A5232 "Optimizing Vaccine Responsiveness in HIV-1 and HCV Infections by Identifying Determinants of Responsiveness: A Pilot Study" and Case CFAR CFAR0910 "Optimizing Vaccine Responsiveness in HIV-1 and HCV Infections by Identifying Determinants of Responsiveness: A Pilot Study" trials were approved by the institutional review boards at University Hospitals/Case Medical Center, Cleveland VA Medical Center, MetroHealth Medical Center, University of Cincinnati, and ACTG Sites. All participants provided written informed consent in accordance with the Declaration of Helsinki. This was a pilot study specifically designed to identify determinants of vaccine responsiveness to neo-antigen in the form of hepatitis A-hepatitis B immunization (Twinrix®) and memory recall antigen in the form of diphtheria/tetanus toxoid immunization (Decavac™). Data from the two protocols were combined to examine untreated HCV-infected (n = 15), untreated HIV-infected (n = 24), and uninfected (n = 10) participants. Diptheria/tetanus toxoid vaccine was administered intramuscular (IM) in the deltoid on day 0; and HAV/HBV (Twinrix®) vaccine was administered IM (contralateral deltoid) on days 0, 7, and 21, with booster at 1 year. Participants were age 18–65. They were excluded if they were positive for hepatitis B surface antibody or antigen, hepatitis A antibody, had a known history of HAV or HBV vaccine, were taking systemic antineoplastic treatment, or had therapeutic radiation within 24 weeks of study entry. Chronic HCV-infected participants had detectable HCV RNA in plasma and were without prior anti-HCV therapy. Chronic HIV-infected participants had no contemporary standard of care indication for antiretroviral therapy (ART), or were off ART for at least 3 months and had CD4+ T cell counts >300 cells/mm^3.

2.2. Vaccine induced antibody levels

Stored serum samples were batch tested for anti-tetanus, -hepatitis A, and -hepatitis B antibody levels at days 0, 7, 21, and weeks 6, 8, 12, and 24 for participants in A5232, and at days 0, 7, 21 and weeks 8 and 24 for participants enrolled in CFAR0910. Anti-Hepatitis B surface (anti-HBs) antibody levels were quantified by ELISA (ADVIA Centaur Anti-HBs2 assay, Siemens Diagnostics, Malvern, PA) at the Cleveland VA Medical Center. Antibody against Hepatitis A antigen was measured by a competitive ELISA using the anti-HAV enzyme immunoassay kit, ETI-AB-HAVK PLUS (DiaSorin, Italy). Tetanus antibodies (IgG) titers were quantified by ELISA (Alpha Diagnostic, Intl, San Antonio, TX).

2.3. Soluble inflammatory indices

Plasma IL-6 was measured by high sensitivity ELISA (Quantikine HS, R&D Systems, Minneapolis, MN), and soluble CD14 (sCD14), soluble CD163 (sCD163), and IP-10 were measured by ELISA (Quantikine, R&D Systems, Minneapolis, MN).

2.4. Statistical analysis

Continuous variables were compared between 2 groups using the Mann-Whitney U test, and among multiple groups using a Kruskal-Wallis test (GraphPad Prism software, version 5.04). We assessed the associations between continuous variables by Spearman's rank correlation coefficient, and proportions of groups with vaccine response were compared using Pearson Chi-Square analysis or a Fisher Exact Score (SPSS version 22). Paired week 0 and week 24 tetanus responses were analyzed using a Wilcoxon matched-pair sign-rank test. A "p" value <.05 was considered significant.

3. Results

3.1. Study participant clinical characteristics

Fifteen untreated HCV-infected, 24 untreated HIV-infected, and 10 healthy control participants were enrolled. Characteristics of the participants are shown in Table 1. HCV-infected participants were older than HIV-infected participants (p = .004) and controls (p = .04). Although all HIV-infected participants had CD4 counts >300 cells/mm^3, CD4 T cell counts in this group were less than among uninfected donors and HCV-infected participants (p = .023 and p = .0007, respectively), while HCV-infected participants had higher CD4 T cell counts than among uninfected donors (p = .022). The HIV-infected group had 4 Hispanic participants whose antibody responses to the HBV antigen were particularly low (no response detected).

3.2. Antibody responses to HAV/HBV vaccine are impaired in viremic HCV and HIV-infected participants

Vaccine responses to HBV in HCV infection [7,9] and HIV infection [4,5] have been previously described as impaired, and our results confirm this (Fig. 1). Participants were examined for antibody responses after receiving accelerated HAV/HBV vaccine given at weeks 0, 1, and 3 and tetanus booster given at week zero. Participants with HAV antibody levels >20 mI U/mL or HBV antibody levels >10 mI U/mL by week 12 or 24 were considered responders. The proportion of HCV-infected participants that responded to the HAV (78%) and HBV component of the HAV/HBV vaccine (73%) by week 24, tended to be lower than the proportion of uninfected participant responders to HAV (100%) and HBV (88%) (Fig. 1). The proportion of HIV-infected participants responding to HAV (88%) and HBV (38%) vaccine by week 24 also tended to be lower than uninfected participants (HAV 100% and HBV 88%) (Fig. 1).

We next evaluated the antibody levels specific to the vaccines. HAV antibody titers were significantly lower in HIV-infected participants at weeks 1, 8, and 24 compared to those in uninfected controls (p = <.05, <.05, and <.0001, Fig. 1A); and change in HAV antibody titers after vaccination were significantly lower at weeks 8 and 24 (supplemental Fig. 1A). At week 24 HAV antibody titers (and change from baseline) were also significantly lower in

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