Cytokine Profiles in Asymptomatic Acute Hepatitis B Infection

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Eric C. Seaberg[2], **Katherine Cascino**[1], Tanner Grudda[1], Jose Barillas[1], Mallory Witt[3], Claudia Hawkins[4], Bernard J. Macatangay[5], Chloe Thio[1]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [3]Harbor-UCLA Medical Center, Torrance, CA, USA, [4]Northwestern University, Chicago, IL, USA, [5]University of Pittsburgh, Pittsburgh, PA, USA

BACKGROUND

Hepatitis B Virus (HBV) co-infection occurs in 5-20% of HIV-infected individuals globally. Prior studies found that elevated proinflammatory cytokines are associated with spontaneous control (SC) of symptomatic HBV, but the majority of acute HBV infections are asymptomatic. A better understanding of cytokine profiles in early asymptomatic HBV will provide insight into immune responses important for natural resolution of infection and may suggest immune targets for curative HBV therapies. Using men enrolled in the Multicenter AIDS Cohort Study/Women's Interagency HIV Study Combined Cohort Study (MWCCS) with asymptomatic incident HBV, we compared cytokine profiles between men who either had SC or developed chronic hepatitis B (CHB).

METHODS

- To identify incident HBV infection, plasma samples were tested by ELISA for serological markers of HBV infection: hepatitis B surface antigen (HBsAg), antibodies against hepatitis B core antigen (anti-HBc) and hepatitis B surface antigen (anti-HBs)[1].

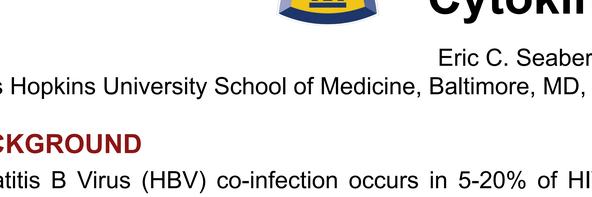


Figure 1. Breakdown of MWCCS samples by stage of HBV infection.

- Samples were analyzed based on HBV infection state determined by serological markers as follows: uninfected (186 total), early acute infection (33 total), acute infection (36 total), and resolved infection (162 total) (Figure 1).
- Circulating levels of 24 cytokines/chemokines were tested by ELISA or electrochemiluminescence assay (MSD, Rockville MD) on samples obtained within the HBV infection period for each subject.
- Statistical comparisons of the log-transformed cytokine data were performed using linear regression with generalized estimating equation methods to account for within subject correlations.
- Statistical significance was calculated after correction for multiple comparisons considering dependent cytokine interactions. 7 functional cytokine groups were determined for a significance level of p<0.007.

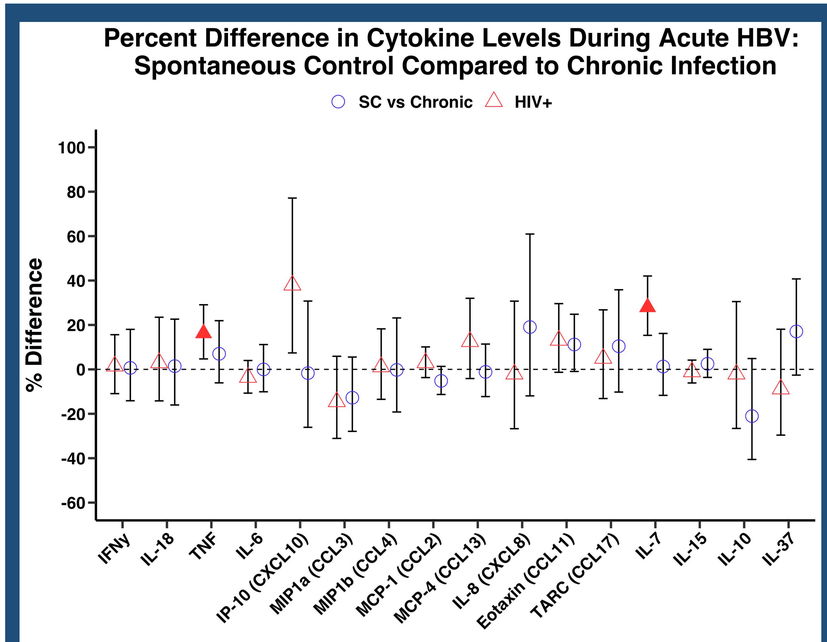


Figure 3. Acute stage HBV cytokine levels are not predictive of outcome. Blue circles represent all men in the acute HBV stage who spontaneously controlled (SC) HBV infection compared with all men who developed CHB as reference. Red triangles are HIV+ men in the acute stage compared with HIV- men as the reference group. Values are reported as % Difference in cytokine levels with positive values indicating higher levels in SC (blue) or in HIV+ (red). Error bars are 95% confidence intervals. Filled markers represent statistical significance (p<0.007). Models were adjusted for age, race, HBV antiviral medication and CD4 counts.

RESULTS

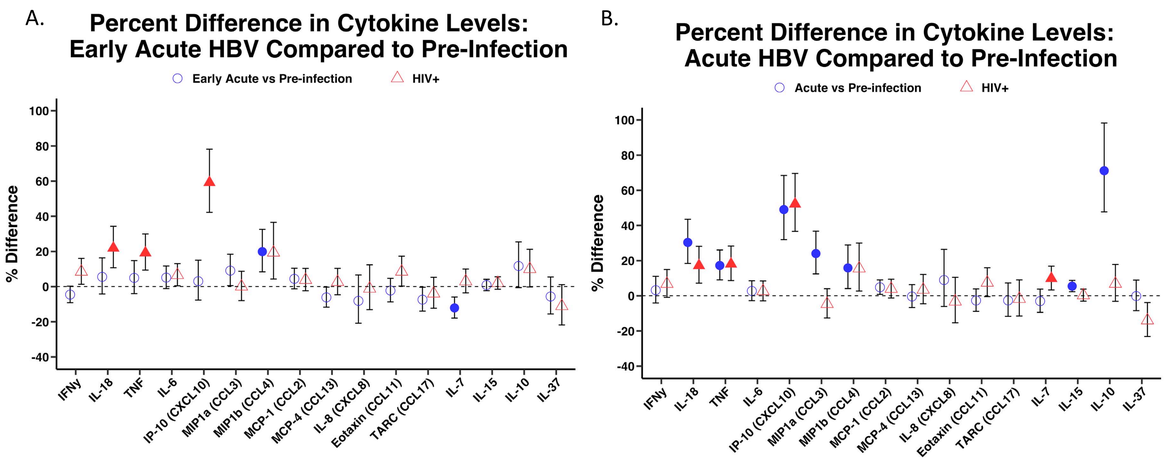


Figure 2. Increased cytokine induction at acute HBV stage of infection is not observed in early acute HBV. Blue circles are all men at either A) the early acute stage of HBV infection or B) the acute stage, compared to all men pre-infection as a reference group. Red triangles are HIV+ men compared to HIV- men as reference. Values are reported as % Difference in cytokine levels in early acute or acute HBV compared to pre-infection. Positive values indicate higher levels in either acute HBV stage compared to pre-infection (blue) or in HIV+ men compared with HIV- (red). Error bars are 95% confidence intervals. Filled markers represent statistical significance (p<0.007). Models were adjusted for age, race, HBV antiviral medication and CD4 counts.

RESULTS

- 8 of 24 cytokines had insufficient data above lower limit of quantification and were excluded (IL-1b, IL-2, IL-4, IL-12, IL-13, IL-5, LTa, IFNa)
- In early acute HBV, MIP1b was significantly elevated and IL-7 was significantly decreased
- In HIV+ men, IL-18, TNF, and IP-10 were significantly higher at early acute HBV infection
- In acute HBV, IL-18, TNF, IP-10, MIP1b, IL-15, and IL-10 were significantly elevated
- In HIV+ men, IL-18, TNF, IP-10, and IL-7 were significantly elevated at acute HBV infection
- In the acute stage of HBV, there were no significant differences in cytokine levels between SC compared to CHB subjects, but
  - IL-10 had >20% difference in SC vs CHB men
- In acute stage of HBV infection for HIV+ men, TNF and IL-7 were significantly higher in SC compared to CHB subjects, and
  - IL-7 had >20% difference in HIV+ vs HIV- men
  - IP-10 had <-20% difference in HIV+ vs HIV- men

CONCLUSIONS

- In early acute HBV infection there was little change in cytokine levels compared to pre-infection baseline
- In acute HBV infection when an immune response begins to be generated against HBV (anti-HBc) there is an upregulation of inflammatory response
- This inflammatory response is not predictive of outcome of infection (CHB or SC)
- After infection resolves, cytokines return to baseline levels
- HIV infected individuals have higher overall cytokine levels than HIV uninfected

REFERENCES

1. Falade-Nwulia et al. Incident Hepatitis B Virus Infection in HIV-Infected and HIV-Uninfected men who have sex with men from Pre-HAART to HAAART periods. Ann Intern Med. 2015;163(9):673-680.

ADDITIONAL KEY INFORMATION

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