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BRIEF ARTICLE

Predictors of loss of hepatitis B surface antigen in HIV-infected patients

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Abstract

AIM: To study factors associated with loss of hepatitis B surface antigen (HBsAg) in patients co-infected with human immunodeficiency virus (HIV) and hepatitis B virus (HBV).

METHODS: We retrospectively reviewed the medical records of 5681 patients followed up at two New York City HIV clinics from January 1999 to May 2007. Clinical and laboratory parameters including baseline and follow-up HIV viral loads, CD4 cell counts, alanine transaminase levels, demographics, presence of hepatitis C infection, and treatment with highly active antiretroviral therapy dually active against both HIV and HBV infection, were analyzed to determine factors associated with loss of HBsAg.

RESULTS: Three hundred and fifty five patients (355/5681, 6.84%) were co-infected with HIV and HBV and were evaluated. Of these, 226 patients with more than 12 mo follow-up were included in further analysis to determine factors associated with loss of HBsAg in the long-term follow-up. In the univariate analysis, baseline CD4 cell count was associated with loss of HBsAg (P = 0.052). Cox regression analysis revealed that loss of HBsAg was associated with baseline CD4 cell count > 500 cells/mm^3 (P = 0.016, odds ratio: 76.174, 95% confidence interval: 2.233-2598.481).

CONCLUSION: Our study showed an interesting association of loss of HBsAg in HIV-HBV co-infected patients with higher CD4 cell count, suggesting that T-cell cytolytic activity against HBV may still be effective in clearing HBV infection.

Key words: Human immunodeficiency virus; Hepatitis B; Viral antigens; Surface antigens

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INTRODUCTION

Co-infection with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) poses a treatment challenge. In Western Europe and the United States, chronic HBV infection has been found in 6%-14% of HIV-positive patients[1]. Increased HBV carriage rates, greater levels of HBV viremia, more rapid decline in hepatitis B surface antibody (HBsAb), increased reactivation episodes, faster progression to liver cirrhosis, and development of hepatocellular carcinoma at a younger age leading to increased

liver-related morbidity and mortality, are all characteristic of HIV and HBV co-infected patients. Also, there are lower incidences of spontaneous loss of HBV e antigen (HBeAg) or HBV surface antigen (HBsAg) because of impaired host innate and adaptive immunity[2-4]. However, factors associated with HBsAg loss in HIV and HBV co-infected patients remain unclear. In this study, our aim was to analyze the characteristics of patients dually infected with HIV and HBV, and to determine factors associated with loss of HBsAg on follow-up.

MATERIALS AND METHODS

We conducted a retrospective medical chart review of 5681 patients followed in 2 HIV/AIDS clinics that comprise the Center for Comprehensive Care at St. Luke's-Roosevelt Hospital Center in New York City, from January 1999 to May 2007. All HIV-infected patients had positive enzyme-linked immunosorbent assay (ELISA) [HIVAB™ HIV-1/HIV-2 (rDNA) EIA, Abbott Laboratories, Abbott Park, IL, USA] and confirmatory Western blotting test (HIV 1/HIV 2 Western blot/Immunoblot, Quest Diagnostics, USA). HIV and HBV co-infection was defined as having both positive HIV infection and HBsAg serology as determined by an ELISA kit (VITROS® Immunodiagnostics, Ortho-Clinical Diagnostics, USA) for at least 6 mo of follow-up. Hepatitis C virus (HCV) serology was determined using ELISA (VITROS® Immunodiagnostics, Ortho-Clinical Diagnostics, USA). We compared patients that lost HBsAg to the rest of the cohort, at baseline and at time of loss of HBsAg. Clinical and laboratory parameters including baseline and follow-up HIV viral loads, CD4 cell counts, alanine aminotransferase (ALT) levels, HCV co-infection, demographics, and duration of anti-HBV therapy were analyzed to determine factors associated with loss of HBsAg. In the earlier study years, HBV DNA viral load, HBV genotype, and HBeAg determinations were not available for every patient, therefore these variables were excluded from the final analysis.

Statistical analysis

Statistical analysis was performed using SPSS, version 15.0 for Windows (SPSS). Dichotomous variables were compared using Fisher's Exact test or the Pearson χ^2 test. For continuous variables, the independent *t* test was used. Univariate analysis and then multivariate Cox regression analysis, with data censored at the time of loss of HBsAg, were conducted to determine factors associated with loss of HBsAg. Odds ratio (OR) and 95% confidence interval (CI) were calculated. A P value < 0.05 was considered to be statistically significant.

RESULTS

Of the 5681 HIV infected patients in our cohort, 355 patients (355/5681, 6.84%) who were co-infected with both HIV and HBV were evaluated. Of these, 226 patients with more than 12 mo follow-up were included in the further analysis to determine factors associated with loss of HBsAg in the long-term follow-up. The patients were observed for a mean duration of 45.6 mo (range, 20.8-61.1 mo). During the follow-up period, 21 (9.3%) of the 226 co-infected patients lost HBsAg. Of these 21 patients, 8 patients (38.1%) were noted to have developed HBsAb.

Table 1 Demographic, virological, immunologic characteristics, and outcomes of HIV and HBV co-infected patients in 2 groups according to HBsAg status

	Persistent HBsAg	Loss of HBsAg	*P*
Number of patients (%)	205 (90.7)	21 (9.3)	
Median age (IQR)	46 (42-51)	41 (33-55)	0.305
Gender (%)			0.353
Female	32 (15.6)	5 (23.8)	
Male	173 (84.4)	16 (76.2)	
Ethnicity (%)			
White	25 (12.2)	3 (14.3)	0.731
Hispanic	42 (20.5)	6 (28.6)	9.404
Black	134 (65.4)	12 (57.1)	0.453
Other	4 (2.0)	0 (0.0)	
HIV risk factor (%)			
Hetero	59 (28.8)	5 (23.8)	0.630
MSM	81 (39.5)	12 (57.1)	0.118
IDU	27 (13.2)	3 (14.3)	0.747
IDU and hetero	10 (4.9)	0 (0.0)	
IDU and MSM	6 (2.9)	0 (0.0)	
Other	5 (2.4)	0 (0.0)	
Unknown	17 (8.3)	1 (4.8)	1.000
HCV co-infection (%)			0.789
HCV positive	49 (23.9)	4 (19.0)	
HAART (%)			0.746
No HAART	30 (14.6)	2 (9.5)	
HAART	175 (85.4)	19 (90.5)	
ALT baseline			0.469
Median ALT baseline (IQR)	44.50 (26.00-79.00)	24.50 (17.50-100.50)	
CD4 baseline			
Median CD4 baseline (IQR)	270 (115-439)	271 (63-594)	0.449
CD4 baseline > 500 (%)	25 (12.2)	5 (23.8)	0.078
HIV viral load baseline			
Median HIV VL (log) (IQR)	4.47 (3.01-5.45)	4.03 (2.70-5.39)	0.841
HIV VL ≤ 400 (%)	40 (19.5)	3 (14.3)	0.763

Hetero: Heterosexual; MSM: Male sex with male; IDU: Intravenous drug use; HIV: Human immunodeficiency virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HBsAg: Hepatitis B surface antigen; HAART: Highly active antiretroviral therapy with dually active agents against both HIV and HBV including lamivudine, tenofovir or both for more than 6 mo; ALT: Alanine aminotransferase; CD4 baseline: CD4 cell count baseline cells/mm^3; HIV VL: HIV viral load copies/mL; IQR: Interquartile range.

Table 1 shows demographic, virological and immunologic characteristics, and outcomes of the HIV and HBV co-infected patients in 2 groups according to HBsAg status. There were no differences in terms of age, gender, ethnicity, risk factor, HCV co-infection, CD4 cell count, HIV viral load, and ALT level at baseline between these 2 groups. Additionally, patients were categorized by CD4 cell count and HIV viral load. With regard to the patients with a CD4 cell count baseline > 500 cells/mm^3, 25 patients (25/205, 12.2%) had persistent HBsAg, and 5 patients (5/21, 23.8%) had seroclearance of HBsAg. Although a higher CD4 cell count, > 500 cells/mm^3, was observed in the HBsAg seroclearance group, this difference was

Table 2 Univariate analysis of factors associated with loss of HBsAg

	P
ALT baseline	0.737
HCV co-infection	0.660
HIV VL baseline	0.981
HIV VL end of follow-up	0.790
CD4 cell counts baseline	0.052
CD4 cell count end of follow-up	0.064
CD4 cell count gain	0.118
HAART	0.764

not statistically significant ($P = 0.078$). With regard to the patients with a baseline HIV viral load ≤ 400 copies, 40 patients (40/205, 19.5%) had persistent HBsAg, and 3 patients (3/21, 14.3%) had seroclearance of HBsAg, but there was no statistical significance, $P = 0.763$.

One hundred and ninety four HIV and HBV co-infected patients (194/226, 85.8%) received dually active antiretroviral therapy against HIV and HBV, including either lamivudine or tenofovir or both, for more than 6 mo as part of their highly active antiretroviral therapy (HAART) for HIV. Treatment with these dually active antiretroviral drugs did not differ between the 2 groups.

During the study period, more deaths in the persistent HBsAg group were noted (21/205, 10.2%) than in the HBsAg seroclearance group (1/21, 4.8%) although this was not statistically significant ($P = 0.702$).

In the univariate analysis, baseline CD4 cell count was associated with loss of HBsAg ($P = 0.052$). Other factors, including baseline ALT, presence of HCV co-infection, baseline HIV viral load, HIV viral load at end of follow-up, CD4 cell count at end of follow-up, CD4 cell count gain, and treatment with dually active antiretrovirals were not correlated with loss of HbsAg (Table 2).

Cox regression analysis revealed that baseline CD4 cell count > 500 cells/mm^3 ($P = 0.016$, OR: 76.174, 95% CI: 2.233-2598.481) was associated with loss of HBsAg (Table 3).

Table 3 Multivariate Cox regression analysis of factors associated with loss of HBsAg

	Odds ratio (95% CI)	*P*
ALT baseline		
Normal ALT (ref)		
Elevated ALT	0.157 (0.013-1.829)	0.139
HCV co-infection		
HCV negative (ref)		
HCV positive	0.073 (0.002-2.802)	0.160
HIV VL baseline (copies/mL)		
HIV VL ≤ 75	3.018 (0.028-325.768)	0.644
HIV VL 76-500	9.195 (0.037-2289.798)	0.431
HIV VL 501-100 000	1.026 (0.009-118.554)	0.991
HIV VL > 100 000 (ref)		
HIV VL end of follow up (copies/mL)		
HIV VL ≤ 75	1134.708 (0.000-1.43E+151)	0.968
HIV VL 76-500	4403. 835 (0.000-5.55E+151)	0.962
HIV VL 501-100 000	3338.767 (0.000-4.19E+151)	0.963
HIV VL > 100 000 (ref)		
CD4 baseline (cells/mm^3)		
CD4 < 200 (ref)		
CD4 200-350	0.983 (0.042-22.809)	0.992
CD4 351-500	0.000 (0.000-1.35E+034)	0.834
CD4 > 500	76.174 (2.233-2598.481)	0.016
CD4 end of follow-up (cells/mm^3)		
CD4 < 200 (ref)		
CD4 200-350	9.113 (0.141-587.310)	0.299
CD4 351-500	0.521 (0.018-15.301)	0.705
CD4 > 500	0.003 (0.000-0.631)	0.034
CD4 gain (cells/mm^3)		
CD4 gain ≤ 150 (ref)		
CD4 gain > 150	2.800 (0.122-64.365)	0.520
HAART		
No HAART (ref)		
HAART	0.117 (0.004-3.105)	0.199

Data for 226 patients. Data censored at the time of HBsAg loss.

DISCUSSION

Our clinics serve a large number of ethnically diverse HIV-infected patients in New York City. In our study, the prevalence of HIV and HBV co-infection was 6.84%. These results are consistent with previous data[1], suggesting that our adult study cohort was representative of the current HIV and HBV co-infection epidemic in the United States.

The results of our study demonstrates that higher baseline CD4 cell count was significantly associated with loss of HBsAg in HIV and HBV co-infected patients. These results correspond with earlier studies which reported that higher initial CD4 cell count was associated with HBeAg seroconversion in HIV and HBV co-infected patients receiving lamivudine therapy[5,6]. CD4 T-cell responses are believed to play a critical role in maintaining actively functioning cytotoxic T-lymphocytes (CTLs), which aid in release of antiviral cytokines[7]. Interestingly, HBV-specific CD4 T-cell responses are thought to be reduced in HIV and HBV co-infected patients[8]. However, a recent study showed that the frequency and quality of HBV-specific T-cell responses increased with a higher CD4 cell count and there was no relationship between circulating HBV-specific T cells and liver damage as measured by fibrosis scores[9]. Therefore a functioning immune system in HIV and HBV co-infected patients with very high CD4 cell count may enable a robust T-cell cytolytic response with production of anti-HBV cytokines such as interferon-gamma to help clear HBV infection in HIV co-infected patients.

Our study showed no significant association between elevated baseline ALT levels and loss of HBsAg. These results differ from those of Lau *et al*[10] and Bonino *et al*[11], which have shown a greater treatment response to either interferon or lamivudine in the setting of elevated ALT levels in chronic HBV patients without hepatitis C or HIV co-infection. However, none of our HIV and HBV co-infected patients were treated with interferon. It is also important to note that 53 patients out of our 226 studied patients (23.5%) were also co-infected with HCV. Therefore, findings from previous studies are not directly applicable to our study. A recent review article suggested that baseline ALT levels were not associated with treatment response in patients treated with nucleos(t)ide ana-

logues[12]. There is conflicting and limited data regarding the utility of baseline ALT levels as a predictor of treatment response especially in the HIV and HBV co-infected patients. Further study is necessary to clarify the role of baseline ALT levels as a predictor of treatment response in this population.

Current guidelines[13-15] recommend that HIV and HBV co-infected patients should be started on antiretroviral therapy with dually active agents such as lamivudine, tenofovir as part of HAART for HIV treatment regardless of CD4 cell count when treatment of HBV is indicated, based on HBV DNA levels, histological lesions, and serum ALT levels. Also, a significant number (50%) of expert panel members in the guidelines favor starting HAART in patients with CD4 cell count > 500 cells/mm^3. Therefore, our study results would support initiating HAART earlier in the HIV and HBV co-infected patients with dually active agents against both HIV and HBV, even in patients with CD4 cell count > 500 cells/mm^3 to maximize the T-cell response to both HIV and HBV.

There were some limitations to our study. It was a retrospective chart review. As previously mentioned, many patients did not have determination of HBV genotype, HBV viral load, HBeAg, or HBeAb. Therefore, we were not able to analyze these factors in our univariate and multivariate Cox regression analysis.

In summary, our study showed an interesting association of HBsAg loss in HIV-HBV co-infected patients with higher CD4 cell count, suggesting that T-cell cytolytic activity against HBV may still be effective in clearing HBV infection.

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COMMENTS

Background

Co-infection with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) is associated with increased morbidity and mortality.

Research frontiers

The aim of this study was to determine factors that influence loss of hepatitis B surface antigen (HBsAg) in an HIV and HBV co-infected population.

Innovations and breakthroughs

In this large retrospective study, a strong association between high baseline CD4 cell count (CD4 cell count > 500 cells/mm^3) and seroclearance of HBsAg in HIV and HBV co-infected patients was found, suggesting that very high CD4 cell count may enable a robust T-cell cytolytic response with production of anti-HBV cytokines such as interferon-gamma to help clear HBV infection in HIV co-infected patients.

Applications

The authors' study results would support initiating highly active antiretroviral therapy earlier in HIV and HBV co-infected patients with dually active agents against both HIV and HBV, even in patients with CD4 cell count > 500 cells/mm^3, to maximize the T-cell response to both HIV and HBV.

Terminology

HBsAg seroclearance, loss of HBsAg; one of the criteria used for determination of resolution of hepatitis B virus infection.

Peer review

This is a large retrospective cohort study demonstrating that HBsAg seroclearance was associated with higher baseline CD4 cell counts in patients with HIV-HBV co-infection.

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