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Hepatitis A vaccine response in HIV-infected patients: Are TWINRIX® and HAVRIX® interchangeable?

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ABSTRACT

Introduction: Hepatitis A virus (HAV) infection remains a health risk for human immunodeficiency virus (HIV)-infected persons. Seroconversion rates among HAV vaccinated HIV-infected patients have been shown to be reduced compared to the general population. Current guidelines regard HAV vaccines as interchangeable, however there no published data comparing their efficacy in HIV patients. Our study evaluated the impact of different factors, including type of vaccination, on the immunologic response to hepatitis A vaccination in HIV-infected patients in the HAART era.
Methods: This was a retrospective review of 226 HIV-infected patients at our clinic in Newark, NJ. Patients were eligible if at least one dose HAVRIX® (1440 ELISA units) or TWINRIX® (720 ELISA units) was administered and had anti-HAV antibody data pre- and post-vaccination. Numerous variables were evaluated for their effect on seroconversion.
Results: Seroconversion developed in 53.5% of the population. Responders had higher baseline median CD4 counts (446 versus 362 cells/mm^3; $P = 0.004$) and lower median HIV RNA levels (475 copies/mL versus 5615 copies/mL; $P = 0.018$) than non-responders. Patients with CD4 counts > 350 cell/mm^3 were more likely to respond than those with CD4 counts < 200 cell/mm^3, 60% and 35%, respectively ($P = 0.0498$). Responders were also more likely to be virologically suppressed (48% versus 32%; $P = 0.0024$). TWINRIX® recipients had a 7-fold increased probability of seroconversion when virologically suppressed and less likely to respond if the vaccination series was not completed (OR 0.42; 95% CI 0.18–0.96).
Discussion: Seroconversion rates to HAV vaccination are significantly impaired among HIV-infected patients. CD4 cell count and virologic suppression at vaccination impact response. Seroconversion among TWINRIX® recipients appeared to be more sensitive to these factors and vaccine series completion in comparison to those administered HAVRIX®. Among HIV-patients requiring hepatitis a and b vaccination, the advantage of TWINRIX® over HAVRIX® as a combination product should be reevaluated.

1. Introduction

Hepatitis A virus (HAV) infection remains a health risk for many human immunodeficiency virus (HIV)-infected patients, particularly men who have sex with men (MSM), injection drug users (IDU), hemophiliacs receiving plasma-derived concentrates, and international travelers [1–3]. Although acute HAV infections are typically self-limiting, they appear to cause significantly more morbidity and mortality among patients with chronic liver disease [4]. Thus, vaccination is recommended for all HIV-infected patients at increased risk for HAV infection without anti-HAV antibodies, and those a risk of severe disease (i.e. chronic liver disease) [5]. Immunization with a single dose of the inactivated hepatitis A vaccine (HAVRIX®) has been shown to lead to HAV antibody seroconversion rates of 80–100% in healthy volunteers. After a completed vaccination series, response rates in healthy individuals are 98–100% [6]. Although there are studies concluding that inactivated hepatitis A vaccination is generally safe and well tolerated in HIV-infected patients with no effect on the course of HIV infection, the data on efficacy are conflicting [7–10]. Several studies have illustrated impaired responses to the hepatitis A vaccine with lower seroconversion rates and antibody titers among HIV-infected patients compared with healthy subjects, especially those with CD4+ T cells below 500 per mm^3 [8–14]. In addition, conflicting data exist on whether viral suppression increases the likelihood of seroconversion after vaccination against the hepatitis A virus [13,14]. Another factor that has not been well studied is the response rates of

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HIV-patients administered the hepatitis A and B recombinant vaccine (TWINRIX®), which contains a lower hepatitis A dose than HAVRIX® (720 enzyme-linked immunosorbent assay (ELISA) units compared with 1440 ELISA units) given more frequently. The purpose of this study was to evaluate the impact of various factors on the immunologic response to hepatitis A vaccination in HIV-infected patients.

2. Methods

This study was a retrospective review of patients cared for at an urban, ambulatory care HIV clinic from 2002 until 2008, inclusive. Given that the study was retrospective in nature, written consent from individual patients for use of data was not required; the study was approved by the Institutional Review Board of Saint Michael's Medical Center, Newark, NJ (USA) where the study was conducted.

Patients were included in the study if they had at least one dose of hepatitis A vaccine administered and had antibodies for HAV measured pre- and post-vaccination using a Vitros ECi immunodiagnostic system the through Laboratory Corporation of America (LabCorp). This system qualitatively measures for both anti-HAV IgM and anti-HAV total antibodies. A positive test is entails an antibody cutoff <0.80 for anti-HAV total antibodies and a no detection of anti-HAV IgM at a cutoff of <0.80). Exclusion criteria included any patient who did not have HAV antibodies measured prior or after the administration of the vaccine. The majority of the data was extracted using electronic medical records whereas the rest was obtained though paper chart reviews. In addition to seroconversion rates, medical records were assessed for patient demographics, HIV transmission risk, hepatitis B and C status, CD4 cell count at baseline, plasma viral load at baseline, type of vaccine administered, indication for vaccination, and antiretroviral therapy at time of vaccine doses. Hepatitis C virus (HCV) coinfection was defined as a positive antibody or detectable HCV RNA level, and Hepatitis B virus (HBV) coinfection as a positive hepatitis B surface antigen or a detectable HBV DNA.

Since several assays were utilized to measure HIV RNA throughout the study period, with varying sensitivity thresholds, viral suppression was defined as a viral load less than 400 copies/mL. Two types of vaccine were administered intramuscularly in the deltoid; patients with preexisting hepatitis B virus immunity received HAVRIX®, containing 1440 ELISA units (1 mL) of hepatitis A virus antigen at months 0 and 6–12 months, and patients lacking immunity to both viruses were given TWINRIX®, containing 720 ELISA units of hepatitis A virus antigen and hepatitis B surface antigen 20 mcg (1 mL) at 0, 1 and 6 months. Patients who received any of the two vaccines were included in the study.

Categorical data were analyzed in 2×2 contingency tables for univariate comparisons and tested for statistical significance with Fisher's exact test or, for 2×3 tables (race/ethnicity), the chi squared test for contingency tables. Odds ratios (OR) thus obtained were adjusted (by logistic regression) for potential confounders based on differences in baseline characteristics of the responders and non-responders for each vaccine studied. The criterion for inclusion as a confounding variable was a P-value for the between-response differences of 5α. As the α level for rejection of the null hypotheses (no difference between response for CD4 and for viral load for each vaccine) was set at 0.05, consideration of any baseline characteristic as a potentially confounding variable required that $P \leq 5\alpha$ ($P \leq 0.25$). For interval variables (such as age), dichotomization was based on receiver operating characteristic curve analysis.

Continuous variables were tested for fit-to-normality by the D'Agostino-Pearson omnibus normality test and found to be non-normally distributed. Consequently, nonparametric methods were used. Decision levels ("cut-offs") were determined from receiver-operating characteristic (ROC) curve analysis.

Analyses were done using either Prism® software (GraphPad Corp., San Diego, CA, USA) or SPSS® v.15 (IBM Corp., Armonk, NY) on a personal computer Windows 7® platform.

3. Results

Of 427 patients that received a hepatitis A vaccine, 226 met the inclusion criteria and were included in the study. Of the patients excluded, 129 only had HAV antibody information prior to vaccination and 72 patients did not have documented HAV antibody information either pre- or post-vaccination. Distribution among the sexes was 53.5% male and 46.5% female. The mean age of the population studied was 41.8 years (range from 18 to 58 years). The most common risk factor for HIV transmission was heterosexual contact (57%), followed by sexual exposure among MSM (13%), IDU (12%), both heterosexual and injection drug use (11%), and others/unknown (7%). The majority of the cohort was Black (78%), followed by Hispanic (14%), and White (8%). The median baseline CD4 cell count and HIV RNA level was 410 cells/mm^3 (IQR 280 – 596 cells/mm^3) and 1287 copies/mL (IQR 400 – 15,425 copies/mL), respectively. Hepatitis C and B virus coinfection was identified in 104 patients (46%) and 12 patients (5.6%), respectively. At baseline, 40.5% of patients were virologically suppressed. Overall, only 53.5% of the HIV patients developed anti-HAV antibodies after hepatitis A vaccination.

Baseline characteristics were similar between responders and non-responders, with the exception of CD4 count, median HIV RNA level, and HIV viral load undetectable status at vaccination (Table 1). Responders to the vaccine had a higher median CD4 count at baseline than non-responders, 446 cells/mm^3 versus 362 cells/mm^3, respectively ($P = 0.004$). Patients with CD4 counts above 350 cell/mm^3 were more likely to respond than those with CD4 counts below 200 cell/mm^3 ($P = 0.0498$). HIV RNA was significantly lower in responders, 475 copies/mL versus 5615 copies/mL, respectively ($P = 0.008$). Moreover, HIV viral suppression was seen in 48% of patients achieving anti-HAV antibodies, in comparison to 32% of those who did not ($P = 0.024$). Hepatitis C coinfection did not seem to affect the response to the hepatitis A vaccine and seroconversion rates were comparable among patients with or without HCV coinfection (55% versus 52%).

One hundred twenty-five patients (55%) received HAVRIX® whereas 101 patients (45%) were given TWINRIX®. Likelihood of seroconversion appeared comparable among patients who received HAVRIX® (54%) and those administered TWINRIX® (53%) (P = NS). In Fig. 1, the values for baseline CD4+ cells and viral load are shown for responders and non-responders by vaccine type. Neither variable is significantly different in responders and non-responders for patients receiving HAVRIX® (Fig. 1A and 1B). However, CD4 cell counts and HIV RNA at vaccination were both significantly different for TWINRIX®, with CD4 cell counts higher and HIV RNA lower for responders (Fig. 1C and 1D). The mean CD4 cell count was 525 cells/mm^3 in the responder group versus 243 cells/mm^3 in the nonresponder group ($P = 0.024$). Responders also had a median HIV RNA below 400 copies/mL compared to 8389 copies/mL in non-responders ($P = 0.018$).

A univariate analysis was performed evaluating the effect of CD4 cell count and HIV RNA on response to either vaccination option. For both vaccination options, a CD4 cell count above 300 cells/mm^3 was associated with response. HIV RNA level, by log fold, was not predictive of response. When adjusted for viral suppression (HIV RNA < 400 copies/mL), patients with a CD4 cell count above 200 cell/mm^3 that received TWINRIX® were significantly more likely to respond than those with 200 cell/mm^3 or less, with an OR of 6.86 (95% CI 1.76–26.7). This effect by viral load < 400 copies/mL was not seen among HAVRIX® with a CD4 cell count above 200 cells/mm^3, with an OR of 1.84 (95% CI 0.47–7.52).