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Low Immune Response Rate of HIV-Infected Patients to a Single Injection of Hepatitis A Vaccine

Short Title: HAV Vaccine in HIV-Infected Patients

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Declaration of interest: none.

Abstract

Objectives

We aimed to evaluate the immune response of HIV-1 positive patients to a single injection of HAV vaccine in a context of vaccine shortage during the 2017 European outbreak.

Methods

We retrospectively enrolled all HIV-1 positive patients vaccinated by a single injection of HAV vaccine Vaqta 50[®]. HAV serology was performed before and >30 days after the vaccine injection.

Results

Among the 73 patients, HIV-1 viral load was ≤ 50 copies/mL in 93.2% of the cases. Medians of CD4 and median ratio of T CD4/CD8 cells were 658/mm³ and 0.9, respectively. A low immune response rate (59.7%) was observed among the patients. Responders had a significantly higher CD4/CD8 cell ratio than non-responders.

Conclusions

A serologic control should be recommended in this population in the event of a single injection vaccination schedule. During routine follow-up, and prior to any untoward event, physicians should assess the vaccination coverage of HIV-infected patients.

Key words: Hepatitis A; HIV infection; Immune Response; Vaccine; Hepatitis A antibodies; Disease outbreak.

I. Introduction

Hepatitis A virus (HAV) can be responsible for acute forms of hepatitis among unimmunized adult populations. The virus is mainly transmitted globally via the fecal-oral route either through ingestion of contaminated food or water or through direct contact with an infectious person. Epidemiology is strongly correlated with socioeconomic indicators, access to clean water and adequate sanitation [1]. In high-income regions, HAV seroprevalence is very low but infections may occur in individuals or groups at particularly high risk, such as unimmunized travelers to areas of high endemicity, men who have sex with men (MSM) or injection drug users, possibly reaching epidemic proportions [2–4].

Since 2015, numerous HAV outbreaks have been occurring among MSM, affecting Europe, the United States and the Asia-Pacific region [5–7]. During the year 2017, three different HAV strains were spreading out over 22 countries in Europe [8]. In France, 2060 cases were reported between January and August. Because of a concomitant shortage of inactivated HAV vaccines, national recommendations reduced the vaccination scheme from two injections to one injection of HAV vaccine, except for immunocompromised patients. Indeed, all inactivated HAV vaccines have been shown in the general population to be highly immunogenic, with protective immune responses approximating 90% one month after a single dose [9].

Even after 2 HAV vaccine injections, HIV-positive patients' vaccine response can be inferior to that of the general population, with HAV seroconversion rates in the literature ranging from 48.5% to 93.9% [10,11]. Nevertheless, many previous studies were conducted several years ago, under circumstances where immune recovery and HIV replication control were not optimal (CD4 cell count $<500/\text{mm}^3$ and/or HIV-1 plasma viral load >50 copies/mL).

The present study is aimed at evaluating the immune response of HIV-1 positive patients to a single injection of HAV vaccine in the 2017 epidemic context.

II. Methods

In this observational single center study, we retrospectively enrolled all HIV-1 positive patients vaccinated by a single injection of HAV vaccine in 2017 (n=73; Vaqta 50[®], MSD, Kenilworth, NJ, USA). HAV serology was performed on a serum sample before and >30 days after the vaccine injection, using the routine system Architect[®] (Abbott, North Chicago, IL, USA) by chemiluminescent microparticulate immunoassays. Response to vaccine was defined by a ratio (signal of the sample/signal of the threshold value) ≥ 2 .

To compare responder and non-responder patient characteristics, Student (continuous variables: age, HIV infection duration, median CD4 cell count, median nadir CD4 cell count, and T CD4/CD8 ratio) or Chi 2 (categories: HIV viral load ≤ 20 copies/mL, CDC stage) tests for univariate statistical analyses were performed. For characteristics with $p < 0.20$ in univariate analysis, logistic regression for multivariate analysis was carried out.

III. Results

In 2017, 73 mainly MSM (93.2%) patients with a median age of 49.4 years (IQR 36.0-57.1) received a single injection of HAV vaccine. HIV-1 viral load was ≤ 50 copies/mL in 93.2% of the cases. Patients had been diagnosed HIV positive for 14.9 years in median (IQR 7.4-27.6) and 16.4% of them had been classified as stage C in the CDC system. Medians of CD4 and nadir CD4 cell counts were $658/\text{mm}^3$ (IQR 465-838) and $270/\text{mm}^3$ (IQR 93-381) respectively. Median ratio of T CD4/CD8 cells was 0.9 (IQR 0.56-1.21). One patient already had positive HAV serology before the vaccine injection and was excluded from the analyses.

The rate of immune response was 59.7% (n=43/72) 106 days after the injection in median (IQR 68-171).

Responders had a significantly higher T CD4/CD8 cell ratio than non-responders in univariate and multivariate analyses (0.63 vs 1.00; p=0.019 and 0.024, respectively, with a median of 28 days between T CD4/CD8 cell measurements and vaccination). All characteristics of responder and non-responder patients and statistical analyses are presented in Table 1.

IV. Discussion

Compared to the general population [9,11], a lower immune response rate (59.7%) was observed in this study after a single injection of HAV vaccine in well-controlled HIV-positive patients.

Similar results have been described during a HAV outbreak among a comparable HIV-infected population by Lin *et al.*, with 57.3% of responders 21 weeks after an injection of Vaqta 50[®] or Havrix[®] 1440 ELISA units. However, another recent study showed a markedly better response rate to a single injection of Havrix[®] 1440 (83.2% at 175 days after the vaccination) [12]. Interestingly, the authors had previously observed a response in 53/129 patients (41.1%) 97 days after 1 dose of Havrix[®] 1440, exterior to any epidemic context and in a population less controlled for HIV replication (54% HIV-1 viral load \leq 50 copies/mL; median CD4 cell counts 592/mm³).

While immune response has been shown to be dependent on immune status and HIV infection control [13–16], it might also depend on the vaccine used [17] and the epidemic context. In our work, some patients may have been contaminated by HAV shortly before or during the study, leading to vaccine-independent seropositive status and possible overestimation of the response rate.

A low T CD4/CD8 cell ratio represents a risk factor for non-response, as previously reported by Neukam *et al.* [12] and Fritzsche C *et al.*[18], which could reflect the immune system activity linked to CD4 cell count recovery and to chronic activation during HIV infection.

CD4 cell counts were high among the studied population (658 cells/mm³ in median; 2/72 CD4 counts <200 cells/mm³ only) and their impact on vaccine response was not significant as a continuous variable ($p=0.124$). Nevertheless, when CD4 cell counts were stratified into four groups, the group with the lowest CD4 counts showed a lower vaccine response compared to the other groups, as previously reported ($p=0.008$) [19]. We were not able to assess the impact of HIV viral load as 93.2% of the cases were <50 copies/mL [20].

However, our study provides information on the immune response to a single injection of Vaqta 50[®] HAV vaccine among well-controlled HIV-infected patients. In this specific context, the immune response rate turned out to be low.

V. Conclusions

During a vaccine shortage, control of response to HAV vaccination should be recommended for this population to ensure their protection in the overall framework of a single injection vaccination scheme. In routine follow-up, and before any HAV outbreak or other untoward event occurs, physicians should closely assess the vaccination coverage of HIV-infected patients.

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Table 1. Characteristics of responder and non-responder patients and statistical analyses

	Non-responders (n=29; 40.3%)	Responders (n=43; 59.7%)	Univariate analysis, p	Multivariate analysis of continuous variables, p
Age, median (years)	52.9	45.5	0.311	NA
HIV viral load ≤20 copies/mL (%)	82.8	83.7	0.914	NA
HIV infection duration (years)	20.4	11.6	0.320	NA
CD4, median (cells/mm³)	594	671	0.124	0.607
Nadir CD4, median (cells/mm³)	188	294	0.386	NA
T CD4/CD8, cells (ratio)	0.63	1.00	0.019*	0.024*
CDC stage (%)	24.1	11.6	0.162	NA

NA: not applicable

* Statistically different between responder and non-responder patients