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Short communication

Evaluation of a convenient vaccination schedule against hepatitis B in HIV-patients with undetectable HIV viral load

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ABSTRACT

Vaccination against hepatitis B virus (HBV) is recommended for all HIV-positive individuals but the standard schedule is not satisfactory. High or more doses have also been studied with variable results. We compared a vaccination schedule with a higher dose but fewer shots to the standard scheme (HBVaxPro 40 μg versus Engerix 20 μg at 0, 1, and 6 months). Of the 63 patients vaccinated with HBVaxPro 79%, 65% and 47% seroconverted at month 1, 12 and 24 after vaccination, respectively. A total of 137 patients received Engerix and showed lower response rates (68%, 53% and 38%, respectively). Anti-HBs titers in the Engerix group were also lower with a statistically significant difference.

In patients younger than 55 years HBVaxPro was 3 times more likely to provoke a response compared with Engerix (OR = 3, p = 0.006). In conclusion, HBVaxPro 40 μg at 3 doses could be proposed as a more robust and acceptable alternative.

1. Introduction

The co-existence of HIV with Hepatitis B virus (HBV) infection is frequent due to the common modes of transmission of the two viruses. It is estimated that almost 10% of HIV-patients have also been infected by HBV [1].

In the era of highly active antiretroviral therapy (HAART), liver disease (including chronic hepatitis B) is one of the leading causes of death for HIV-patients [2]. Hence, immunization against HBV is recommended to all non-immune HIV-patients. However, compared with healthy individuals, patients with HIV-infection have lower seroconversion rates and decreased Hepatitis B surface antibody (anti-HBs) titers [3].

The standard HBV vaccine schedule consists of three doses of 20 μg administered at 0, 1, and 6 months; however, high rates of non-responders have been reported.

Several studies have been carried out, evaluating the immune response thereby providing alternative vaccination regimens and schedules. Findings from recent reports favored the administration of high or more (four) doses [4–6]. However, in the clinical practice, a schedule with many shots may be inconvenient and therefore unsuccessful.

Therefore, the aim of this research was the evaluation of a high dose vaccination with fewer shots using a schedule with a 40 μg dose (and not 2 × 20 μg) at 0, 1, and 6 months. We preferred to evaluate the vaccine regimen in patients with complete suppression of HIV as this is the vast majority of the patients.

2. Methods

This prospective study was conducted in the HIV/AIDS Unit of the Andreas Syggros University Hospital (Athens, Greece) from 2012 to 2016 and included HIV-patients eligible for vaccination against HBV. The study protocol was reviewed and approved by the hospital's ethics committee (IRB approval number: 324/2012). Before enrollment all participants completed an informed consent form.

Eligibility criteria included blood tests (chemiluminescent immunoassay method, Architect i-system, Abbott, Ireland) that confirmed no past infection or immunity to hepatitis B, history of no previous HBV vaccination, CD4 T-cell counts of more than 200

Abbreviations: Anti HBs, antibody titers; BMI, body mass index; CI, confidence interval; GMT, geometric mean antibody titers; HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; OR, odds ratio.

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cells/mm^3, HAART administration, and undetectable viral load (HIV RNA < 20 copies/ml determined by NASBA, NucliSENS Easy Q HIV-1 V2.0, bioMérieux, Marcy l'Etoile, France) within six months prior to the first dose of the HBV vaccine.

Patients were vaccinated using 40 μg of HBVaxPro (Sanofi Pasteur MSD SNC, France) or 20 μg of Engerix B (GlaxoSmithKline, Brentford, United Kingdom) administered intramuscularly at 0, 1, and 6 months. Both vaccines contain HBsAg protein (40 and 20 μg/ml respectively) which is produced in yeast cells (Saccharomyces cerevisiae) by recombinant DNA technology and adsorbed on aluminum hydroxide which acts as an adjuvant. A serum sample was collected at months 1, 12, and 24 after the completion of vaccination. Anti-HBs titers were determined with a commercial chemiluminescent immunoassay method (Architect i-system, Abbott, Ireland).

Seroconversion was confirmed if anti-HBs titer was ≥ 10 mIU/ml.

Potential factors evaluated for their influence on the response to vaccination were: CD4 T-cell count, the lowest (nadir) CD4 count, CD4/CD8, type of HAART, history of AIDS-defining conditions, age, smoking status and body mass index (BMI).

Table 1
Patients characteristics.

Characteristics	HBVaxPro 40 μg[a] [n = 63]	Engerix 20 μg[a] [n = 134]
Age, yrs	47.0 [28–71]	42.6 [27–65]
Gender		
Men	61 [97%]	122 [91%]
Women	2 [3%]	12 [9%]
Smoking	28 [44%]	62 [46%]
Hepatitis C	0 [0%]	2 [1.5%]
Body Mass Index (BMI)	25.2 [19.1–36.9]	24.8 [18.2–32.1]
History of AIDS-defining condition	10 [16%]	17 [13%]
Kaposi's sarcoma	3	4
Pn. jirovecii[b]	2	4
Candidiasis, eosophageal	4	6
Pneumonia, recurrent[c]	–	2
Herpes, mucocutaneous[d]	1	1
HAART at vaccination		
PI	30 [48%]	68 [51%]
NNRTI	17 [27%]	38 [29%]
INI	16 [25%]	27 [20%]
CD4 T-cells at vaccination, cells/mm^3	636 [311–1462]	591 [60–1801]
Nadir CD4[e], cells/mm^3	242 [21–934]	319.5 [30–881]
CD4/CD8 at vaccination	0.66 [0.20–1.91]	0.63 [0.19–2.15]

Note: Categorical variables are shown as numbers [percentages] and continuous as means [min-max].
Key to Acronyms: HAART = Highly Active Antiretroviral Therapy, PI = Protease Inhibitors, NNRTI = Non-nucleoside reverse transcriptase inhibitors, INI = Integrase inhibitors.
[a] All patients received 3 doses (0, 1 and 6 months).
[b] Pn. Jirovecci = Pneumonocystis jirovecii pneumonia.
[c] Pneumonia, recurrent ≥ 2 episodes in 1 year.
[d] Herpes simplex with mucocutaneous ulcer > 1 month.
[e] Nadir CD4 = The lowest CD4.

2.1. Statistical analysis

Anti-HBs levels were log transformed for geometric mean titers (GMTs) and compared with Wilcoxon rank-sum tests. Data were analyzed based on immune response (anti-HBs ≥ 10 mIU/ml) and the GMT with 95% confidence intervals (CIs). Logistic regression was also used to explore the factors affecting response. All statistical analyses were conducted using STATA software version 11.

3. Results

The demographic and immunologic characteristics of 63 patients vaccinated with HBVaxPro 40 μg and 134 vaccinated with Engerix 20 μg are summarized in Table 1. Seroconversion was detected 1 month after the last dose of the HBV vaccine in 79.3% (50/63) of the HBVaxPro patients versus 68.7% (92/134) of Engerix patients. Seroprotective titers of anti-HBV antibodies were measured at months 12 (65.1%) and 24 (47.6%) in the HBVaxPro population. Among patients who received Engerix, 53.0% maintained antibody titers one year (12th month) after vaccination while two years later (24th month), 38.8% had persisting antibody titers.

Estimation of anti-HBV antibodies titer showed that HBVaxPro vaccinated patients had higher GMTs compared to Engerix patients. A gradual decrease of GMTs was confirmed in both groups with the difference between them being statistically significant ($p < 0.05$) (Table 2). The Wilcoxon rank-sum test also showed the significant difference among repeated measurements of GMTs (p-value < 0.01, Fig. 1).

A statistically significant interaction of vaccination type with age was found. At centered age (44 years), odds ratio (OR) for immune response was 3.3 (95% CI: 1.03–4.6, p = 0.015). This result decreased at older ages. A subgroup analysis for patients younger than 55 years old (n = 171, 49 on HBVaxPro and 122 on Engerix) showed that those receiving HBVaxPro were 3 times more likely to respond to vaccination compared with those who received Engerix (OR = 3, 95% CI: 1.45–9; p = 0.006).

4. Discussion

Many vaccination schedules with various vaccines, doses or routes of administration have been studied in HIV patients.

Currently available HBV vaccines for adults include: 20 μg HBsAg, Engerix (GlaxoSmithKline, Brentford, United Kingdom) and Fendrix (GlaxoSmithKline, Belgium); 10 μg HbsAg, Recombivax HB (Merck, USA) and HBVaxPRO (Sanofi Pasteur MSD SNC, France), 40 μg HBVaxPRO (Sanofi Pasteur MSD SNC, France). There is also Twinrix (GlaxoSmithKline, Belgium), which contains 20 μg HBsAg and 720 ELISA units of inactivated HAV.

In this study, vaccination with three doses of 40 μg HBVaxPro led to a protective serologic response in 79% of patients. This immune response was higher compared to the response (68%) in participants who received the standard schedule (20 μg Engerix at 0, 1, and 6 months).

Table 2
Response rate to Hepatitis B vaccination and Geometric Mean Titers of anti-HBs antibodies.

Months after vaccination termination		HBVaxPRO 40 μg[a]	Engerix 20 μg[a]	p-value
1	Seroconversion rate	50/63 (79.37%)	92/134 (68.66%)	
	GMT[95% CI]	200 (125–318)	107 (80–142)	p = 0.0086
12	Seroconversion rate	41/63 (65.08%)	71/134 (52.99%)	
	GMT[95% CI]	180 (114–285)	87 (66–115)	p = 0.0077
24	Seroconversion rate	30/63 (47.62%)	53/134 (39.55%)	
	GMT[95% CI][	154 (91–261)	51 (37–71)	p = 0.0008

Note: Seroconversion rate: number seroconverted/number estimated (%).
[a] All patients received 3 doses (0, 1, 6 month).

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