Vaccine 37 (2019) 2278–2283

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Immune response to hepatitis A vaccine in patients with HIV

Carlos Fritzsche [a,*], Lisa Bergmann [a], Micha Loebermann [a], Aenne Glass [b], Emil C. Reisinger [a]

[a] Division of Tropical Medicine and Infectious Diseases, Department of Medicine, All University Medical School of Rostock, Germany
[b] Institute for Biostatistics and Informatics in Medicine and Ageing Research, All University Medical School of Rostock, Germany

ARTICLE INFO

Article history:
Received 3 January 2019
Received in revised form 10 February 2019
Accepted 19 February 2019
Available online 16 March 2019

Keywords:
HIV
Hepatitis A
Vaccine
Seroconversion rate
Hepatitis B

ABSTRACT

Objectives: The aim of this study was to evaluate the impact of various factors that may influence the immunologic response to hepatitis A mono-vaccine or hepatitis A/B co-vaccine (Twinrix®) in HIV-infected patients.
Design: Retrospective cross-sectional study.
Methods: HIV positive patients with a full course of hepatitis A vaccine were tested for HAV antibodies. The seroconversion rates were determined, and the influence of several factors including CD4 cell counts, CD4/CD8 ratio, plasma viral load, type of vaccine, and antiretroviral therapy at the time of vaccine, was evaluated.
Results: After vaccination, 80.2% of the patients developed anti-HAV antibodies, 81.5% in the mono-vaccine group and 79.2% in the hepatitis A/B co-vaccine group. In the mono-vaccine group, factors significantly associated with a better response to the vaccine were higher CD4 cell count, higher CD4/CD8 ratio, and shorter time interval from vaccine to serological control. In patients who received the hepatitis A/B co-vaccine, younger age and female sex were significantly associated with better vaccine response. Multivariable logistic regression analysis revealed time interval from vaccine to serological control of more than 5 years vs. less than 1 year to be significantly associated with decrease of seroconversion after HAV vaccine.
Conclusions: The response to hepatitis A vaccine is impaired in HIV positive patients. HIV patients, at least those older than 30, should be tested for seroconversion after receiving the hepatitis A vaccine. As hepatitis A titers may rapidly decline, control serology during follow-up should be proposed, possibly within two years. However, vaccine type does not play a role in vaccine response.

1. Introduction

Although hepatitis A virus (HAV) infections are typically self-limiting, vaccination is recommended for all HIV-infected patients without anti-HAV antibodies who are at increased risk of HAV infection or at risk of severe disease. It is also recommended for intravenous drug users, hemophiliacs receiving plasma-derived concentrates, travelers to endemic areas, and men who have sex with men [1–5]. Immunization with a single dose of the monovalent hepatitis A vaccine leads to HAV antibody seroconversion rates of 80–100% in healthy volunteers, with response rates rising to 98–100% after completion of a vaccine series [6]. Similar results have been shown for the combined hepatitis A and B vaccine (Twinrix®) and other HAV combination vaccines [6–8]. Although various studies conclude that the monovalent hepatitis A vaccination is generally safe and well tolerated in HIV patients and has no effect on the course of HIV infection, the data on efficacy are conflicting [9–12]. Numerous studies point to impaired responses to the hepatitis A vaccine among HIV-infected patients, especially those with CD4+ T cells below 500/μl. Seroconversion rates and antibody titers have regularly been found to be lower in HIV patients than in healthy subjects and range between 48.5% and 94% [10–16]. These lower seroconversion rates are of clinical significance since acute hepatitis A occurs in HIV patients even after complete vaccination against HAV [2,17]. One factor that has not been well studied is the response rate of HIV-patients after administration of Twinrix®, which contains a lower hepatitis A dose than Havrix® (720 enzyme-linked immunosorbent assay (ELISA) units compared to 1440 ELISA units) [18,19].

The aim of this study was to evaluate the impact of various factors on the immunologic response to hepatitis A vaccination, monovalent and hepatitis A/B co-vaccine (Twinrix®), in HIV-infected patients.

* Corresponding author at: Division of Tropical Medicine and Infectious Diseases, Department of Medicine, University of Rostock Medical School, Ernst-Heydemann-Str. 6, D-18057 Rostock, Germany.
E-mail address: Carlos.Fritzsche@med.uni-rostock.de (C. Fritzsche).

https://doi.org/10.1016/j.vaccine.2019.02.064
0264-410X/

2. Patients and materials

This retrospective cross-sectional study was conducted on HIV positive patients attending care at the University of Rostock Medical School. The study was approved by the Ethics Committee of the University of Rostock Medical School (A 2018-0021) and patients gave written consent.

HIV-positive patients older than 18 years were included in the study if they had received a documented primary series of hepatitis A vaccination after being diagnosed HIV positive, and had had negative antibodies for HAV measured before vaccination. Post-vaccination measurement of anti-HAV was carried out during the regular appointments in the outpatient department from September 2017 to June 2018 using a chemiluminescence immunoassay (HAV Ab-IgG, HAV Ab-IgM; ARCHITECT, Abbott). According to the manufacturer, a positive test entailed an antibody cut-off >1.0. Patients who received the hepatitis A/B co-vaccine (Twinrix®) were also tested for anti-HBs antibodies, with an antibody cut-off >10 IU/ml considered to be a positive titer.

Patients who had not had HAV antibodies measured both prior to and after administration of the vaccine, those who had HAV antibodies without prior vaccination, those on whom data was missing or unavailable, those who received an incomplete primary series of hepatitis A vaccination, and those who had already received a booster vaccination after a complete series of HAV vaccination were excluded from the study. The data was extracted by reviewing both electronic medical records and paper charts. In addition to seroconversion rates, extracted data included patient demographics, CD4 cell counts at baseline [absolute (cells/μl) and relative (in %)], CD4/CD8 ratio at baseline, HIV plasma viral load at baseline, type of vaccine administered, and antiretroviral therapy at the time of the first vaccine dose.

Since several assays with different sensitivity thresholds were used to measure HIV RNA throughout the study period, viral suppression was defined as a viral load of 50 copies/ml. Vaccines were administered intramuscularly in the deltoid muscle. Patients with preexisting hepatitis B virus immunity received 2 doses of an HAV mono-vaccine (Vaqta® containing 50 E, HAV-Pur® containing at least 24 IE, or Havrix® containing 1440 ELISA units of hepatitis A virus antigen), and patients lacking immunity to both viruses were given 3 doses of Twinrix® (HAV/HBV co-vaccine, containing 720 ELISA units of hepatitis A virus antigen and 20 μg of hepatitis B surface antigen).

3. Statistical analysis

Data are expressed as frequencies or proportions (%) for categorical variables, and median and quartiles (Q1 and Q3) for quantitative variables. Categorical data were analysed in 2×2 contingency tables for univariate comparisons and tested for statistical significance with Fisher's exact test, or in 2×3 contingency tables and tested with the chi-squared test. Differences in means between hepatitis A vaccine responders and non-responders, and between patients vaccinated with monovalent vaccine and bivalent vaccine were compared using the *t*-Test (or Mann-Whitney *U* test for non-normal distributions). Candidates associated with response to vaccination were analysed using a binary logistic regression analysis. Odds ratios (OR) are given with their respective 95% confidence intervals (CI) and the p-values for OR = 1. Variables presumed to have a potential association with the outcome variable response/non-response in the univariate model (p-value < 0.2) were assessed jointly in a multiple approach. The factor "vaccine" was additionally included to control for treatment. Adjusted ORs (OR_{adj}) and their 95% CIs and p-values are given here.

P-values ≤ 0.05 were considered significant. Analyses were performed using either Prism® software (GraphPad Corp., San Diego, CA, USA) or SPSS® v.23 (IBM Corp., Armonk, NY).

4. Results

Of the 340 patient charts reviewed, 131 met the inclusion criteria. Of the 209 patients excluded, 60 had received a prior HAV vaccine, 124 patients were already positive for HAV antibodies (in 31 of whom it was not possible to establish whether through prior vaccine or infection), and another 25 patients did not meet the criterion of having received a complete hepatitis A vaccine.

Of the 131 eligible patients, 77 (58.8%) had been vaccinated with HAV/HBV co-vaccine, and 54 (41.2%) with the HAV mono-vaccine. Hundred and ten (84%) patients were male, and 21 (16%) were female, all coming from Europe. The median age of the population studied was 37 years ranging from 18 to 68 years (HAV mono-vaccine: 18–65 years; HAV/HBV co-vaccine: 21–68 years; p = 0.031). The median baseline CD4 cell count and HIV RNA level were 490 cells/μl (Q1-Q3 350 – 680 cells/μl) and 66 copies/mL (Q1-Q3 50–22400 copies/mL), respectively. 62 patients (47.3%) were virologically suppressed at the time of the first HAV vaccine. The median time between last vaccine and serological control was 865 days and ranged from 17 to 6581 days (HAV mono-vaccine: 23–6581 days; HAV/HBV co-vaccine: 17–6031 days; p = 0.646). The baseline characteristics of the patients are shown in Table 1. Beside HIV, no other immunosuppressive conditions were seen at time of vaccination.

Overall, 80.2% of the HIV patients developed anti-HAV antibodies after vaccination, 81.5% in the HAV mono-vaccine group and 79.2% in the HAV/HBV co-vaccine group (p = 0.826). In the mono-vaccine group, factors significantly associated with response to the vaccine were absolute CD4 cell count (p = 0.003), CD4/CD8 ratio (p = 0.032), and time interval from vaccine to serological control (p = 0.016). In contrast, in patients who received the HAV/HBV co-vaccine, only age and sex were significantly associated with vaccine response (p = 0.043 and p = 0.033 respectively) (Table 2).

In those patients in whom HAV antibodies were tested within a year of vaccination the seroconversion rate reached 88.9%, 94.4% in the mono-vaccine group and 85.2% in the HAV/HBV co-vaccine group (p = 0.634). Taking both groups together, factors significantly associated with response to the vaccine were higher relative CD4 cell counts (23.5% vs. 13%, p = 0.013) and higher CD4/CD8 ratio (0.43 vs 0.21, p = 0.014). Since only one patient did not respond in the HAV mono-vaccine group statistical analysis was not appropriate. However, this patient had lower CD4 cell counts (absolute and relative), a lower CD4/CD8 ratio, and a higher viral load than those who responded to the vaccine. In those patients who received the HAV/HBV co-vaccine, non-responders were older and had a lower CD4/CD8 ratio than responders. However, the difference was not statistically significant (Supplemental Table 1).

Patients whose titers were checked within a year of vaccination were significantly more frequently seropositive than those checked more than 5 years after vaccination [88.9% (40/45) vs. 66.6% (20/30); p = 0.037]. This difference was highly significant within the mono-vaccine group [94.4% (17/18) within first year vs. 37.5% (3/8) $\geq$ 5 years; p = 0.005], but not in patients vaccinated with HAV/HBV co-vaccine [85.2% (23/27) within first year vs. 77.3% (17/22) $\geq$ 5 years; p = 0.713].

Factors potentially associated with response to hepatitis A vaccine (Table 2) were assessed in a logistic regression analysis. Multivariable regression analysis revealed time between vaccine and titer control to be the only significant factor. The chance to have positive antibody titers after vaccination was significantly lower for patients whose titers were checked after more than 5 years

Table 1
Study population characteristics by type of hepatitis A virus vaccine.

Characteristics	Total n = 131 (100%)	HAV mono-vaccine n = 54 (41.2%)	HAV/HBV co-vaccine n = 77 (58.8%)	p-value
Age, y	37 (29–48)	31 (25–46)	39 (31–48)	0.031
Sex, male	110 (84%)	49 (44.5%)	61 (55.5%)	0.093
female	21 (16%)	5 (23.8%)	16 (76.2%)	
CD4 cell count/μl at vaccination	490 (350–680)	535 (375–713)	440 (325–670)	0.095
CD4 cell count in % at vaccination	24 (18–32)	26 (20–31)	24 (18–32)	0.144
CD4 cell count < 200/μl	10 (7.6%)	3 (30.0%)	7 (70.0%)	0.195
CD4 cell count 200–499/μl	58 (44.3%)	20 (34.5%)	38 (65.5%)	
CD4 cell count > 500/μl	63 (48.1%)	31 (49.2%)	32 (50.8%)	
CD4/CD8 ratio at vaccination	0.47 (0.29–0.77)	0.49 (0.32–0.80)	0.45 (0.27–0.74)	0.337
HIV RNA copies/ml at vaccination	66 (50–22400)	187 (50–25500)	50 (50–7398)	0.06
HIV RNA ≤ 50 copies/ml	62 (47.3%)	32 (51.6%)	30 (48.4%)	0.021
HIV RNA ≥ 1000 copies/ml	50 (38.2%)	16 (32.0%)	34 (68.0%)	0.092
cART at vaccination	88 (67.2%)	41 (46.6%)	47 (53.4%)	0.09
Interval between first and last dose, d	214 (180–293)	216 (185–333)	214 (179–290)	0.917
0–6 months	34 (26.0%)	11 (32.4%)	23 (67.6%)	0.453
>6 months–1 year	73 (55.7%)	33 (45.2%)	40 (54.8%)	
>1 year	24 (18.3%)	10 (41.7%)	14 (58.3%)	
Interval between last vaccine dose and control, d	865 (191–1634)	782 (184–1170)	897 (199–2013)	0.646
0–1 year	45 (34.4%)	18 (40.0%)	27 (60.0%)	0.109
>1–5 years	56 (42.7%)	28 (50.0%)	28 (50.0%)	
>5 years	30 (22.9%)	8 (26.7%)	22 (73.3%)	

HAV = hepatitis A; HBV = hepatitis B; y = year; d = days; cART = combined antiretroviral therapy.
Categorical variables are shown as frequencies (percentages) and continuous values as medians (Q1-Q3).
p-values for comparison of HAV mono-vaccine vs. HAV/HBV co-vaccine groups.

Table 2
Baseline characteristics of patients by response to hepatitis A vaccines.

Characteristics	Total N = 131			HAV mono-vaccine N = 54			HAV/HBV co-vaccine N = 77		
	Responders N = 105 (80.2%)	Nonresponders N = 26 (19.8%)	p-value	Responders N = 44 (81.5%)	Nonresponders N = 10 (18.5%)	p-value	Responders N = 61 (79.2%)	Nonresponders N = 16 (20.8%)	p-value
Age, y	35 (28–47)	42 (32–49)	0.055	30 (25–48)	34.5 (30–42)	0.300	37 (29–47)	47 (38–49)	0.043
Sex									
Female	20 (95.2%)	1 (4.8%)	0.074	4 (80.0%)	1 (20.0%)	1.000	16 (100.0%)	–	0.033
Male	85 (77.3%)	25 (22.7%)		40 (81.6%)	9 (18.4%)		45 (73.8%)	16 (26.2%)	
CD4 cell count/μl at vaccination	510 (350–710)	455 (358–590)	0.171	580 (460–788)	355 (188–498)	0.003	440 (290–680)	490 (380–667.5)	0.390
CD4 cell count (%) at vaccination	25 (19–32.5)	22.5 (13–28)	0.035	26.5 (21–32)	19 (11.8–28.8)	0.063	24 (18–33)	23 (14–28)	0.288
CD4 cell group									
CD4 cell count < 200/μl	6 (60.0%)	4 (40.0%)	0.134	1 (33.3%)	2 (66.7%)	0.009	5 (71.4%)	2 (28.6%)	0.815
CD4 cell count 200–499/μl	45 (77.6%)	13 (22.4%)		14 (70.0%)	6 (30.0%)		31 (81.6%)	7 (18.4%)	
CD4 cell count > 500/μl	54 (85.7%)	9 (14.3%)		29 (93.5%)	2 (6.5%)		25 (78.1%)	7 (21.9%)	
CD4/CD8 ratio at vaccination	0.48 (0.31–0.82)	0.42 (0.2–0.56)	0.038	0.54 (0.33–0.82)	0.37 (0.18–0.53)	0.032	0.46 (0.29–0.79)	0.44 (0.21–0.69)	0.349
HIV RNA copies/ml at vaccination	66 (50–22650)	101 (50–23025)	0.843	50 (50–10333)	50 (50–14460)	0.476	149 (50–28850)	847 (50–24275)	0.543
HIV RNA at vaccination < 50 copies/ml	51 (82.3%)	11 (17.7%)	0.663	25 (78.1%)	7 (21.9%)	0.501	26 (86.7%)	4 (13.3%)	0.256
HIV RNA at vaccination > 1000 copies/ml	40 (80.0%)	10 (20.0%)	1.000	14 (87.5%)	2 (12.5%)	0.704	26 (76.5%)	8 (23.5%)	0.778
cART at vaccination	71 (80.7%)	17 (19.3%)	0.819	33 (80.5%)	8 (19.5%)	1.00	38 (80.9%)	9 (19.1%)	0.775
Interval between first and last vaccine dose, d	222 (61–300)	202 (169–298)	0.212	232 (185–352)	204 (177–273)	0.436	219 (180–284)	195 (168–315)	0.327
0–6 months	25 (73.5%)	9 (26.5%)	0.527	9 (81.8%)	2 (18.2%)	0.726	16 (69.5%)	7 (30.5%)	0.347
>6 months–1 year	60 (82.2%)	13 (17.8%)		26 (78.8%)	7 (21.2%)		34 (85.0%)	6 (15.0%)	
>1 year	20 (83.3%)	4 (16.7%)		9 (90.0%)	1 (10.0%)		11 (78.6%)	3 (21.4%)	
Interval between last vaccine dose and control, d	587 (180–1282)	1198 (525–2660)	0.010	562 (136–1077)	2025 (772–3786)	0.016	589 (187–1909)	1099 (255–2250)	0.261
0–1 year	40 (88.9%)	5 (11.9%)	0.061	17 (94.4%)	1 (5.6%)	0.002	23 (85.2%)	4 (14.8%)	0.626
>1–5 years	45 (80.4%)	11 (19.6%)		24 (85.7%)	4 (14.3%)		21 (75.0%)	7 (25.0%)	
>5 years	20 (66.7%)	10 (33.3%)		3 (37.5%)	5 (62.5%)		17 (77.3%)	5 (22.7%)	

HAV = hepatitis A; HBV = hepatitis B; y = year; d = days; cART = combined antiretroviral therapy.
Categorical variables are shown as frequencies (percentages) and continuous values as medians (Q1-Q3).

compared to those whose titers were checked within 1 year after vaccination (OR_{adj} = 0.185, 95%CI 0.052–0.661, p = 0.009). Patients older than 30 years seemed to respond less to the vaccine than younger ones (OR_{adj} = 0.317, 95%CI 0.087–1.12, p = 0.072) (Table 3).

Among the patients who received the HAV/HBV co-vaccine, only 48.7% (37) seroconverted for hepatitis B (HBV). Of the HAV responders, 55.7% responded to HBV (34 of 61), while only 18.8% (3 of 16) HAV non-responders seroconverted for HBV (p = 0.011). Factors significantly associated with anti-HBs seroconversion were

Table 3
Multivariable analysis of factors associated with response to hepatitis A vaccine. *Reference.

Potential factors associated with response	Unifactorial model			Multiple model		
	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Interval between last vaccine and titer control			0.054			0.034
1-5ys vs. < 1y*	0.499	0.160–1.56	0.231	0.356	0.107–1.19	0.093
>5ys vs < 1y*	0.232	0.070–0.772	0.017	0.185	0.052–0.661	0.009
Age	0.308	0.994–0.959	0.042	0.312	0.087–1.12	0.075
>30 ys vs ≤ 30 ys*						
Sex	0.170	0.022–1.33	0.091	0.235	0.027–2.01	0.186
Male vs Female*						
CD4%	0.481	0.197–0.959	0.109	1.90	0.726–5.98	0.191
>24% vs. ≤ 24%*						
Vaccine	0.866	0.359–2.09	0.750	1.29	0.465–3.56	0.628
HAV/HBV co-vaccine vs. HAV mono-vaccine*						

OR = odds ratio.
y/ys = year/years.

younger age (p = 0.003), female sex (p = 0.032), and HIV RNA below 50 copies/ml (p = 0.016) (Supplemental Table 2).

5. Discussion

Both, HAV mono-vaccine and HAV/HBV co-vaccine are well tolerated, with seroconversion rates of 98–100% in healthy volunteers [6,7]. However, seroconversion rates in HIV patients are significantly lower, ranging from 48.5 to 94%, and most studies have focused on HAV mono-vaccines only [16,20–22].

In our cohort, the overall seroconversion rate for the HAV mono-vaccine and HAV/HBV co-vaccine was 80.2%. This is better than that obtained in a study in HIV patients from 2013 where Havrix® and Twinrix® were compared and the overall seroconversion rate only reached approximately 53% [19]. The reason for a higher seroconversion rate in our study might have been the exclusion of patients with an incomplete vaccination series. In children with HIV or other immunosuppressive conditions, the seroconversion rate for HAV after the HAV/HBV co-vaccine Ambirix® has been found to be 99% [23]. In contrast to our study, that latter was a prospective study, and serological testing was consistently performed 4 to 6 weeks after the last vaccine dose. In our cohort, on the other hand, the median time between completion of the HAV/HBV co-vaccine series and serological testing was approximately 2 years (897 days). In those cases in our cohort in which serological testing was performed within a year of vaccination, the seroconversion rate reached 94% for the HAV mono-vaccine and 85% for the HAV/HBV co-vaccine. This difference was not statistically significant, and comparable to the results of other studies [20,23,24].

Various factors have been discussed as potentially having an influence on the seroconversion rate after HAV vaccine, including CD4 cell counts, CD4/CD8 ratio, viral load, hepatitis C coinfection, and sex, but the results to date have been conflicting [15,16,19,22].

In our cohort, the univariate model revealed CD4 cell counts (absolute and relative), CD4/CD8 ratio, sex, age, and time between last vaccine and serological testing to be factors that significantly affected the response to the vaccine. Age and sex were only significantly associated with seroconversion in patients who received the HAV/HBV co-vaccine, and CD4 cell counts, CD4/CD8 ratio and time interval between last vaccine and serological testing were significant factors for patients that received the HAV mono-vaccine. With regard to sex as an influencing factor, the results were inconsistent. While two studies have shown female sex to be associated with a better response [15,16], one study found male sex to be associated with a better response [25]. In our cohort, female sex was associated with a better response in the HAV/HBV co-vaccine group and no difference was detected in antibody response between men and women following HAV mono-vaccine. Interestingly, CD4 cell count, CD4/CD8 ratio and time between vaccine and serological testing were only significant factors in the HAV mono-vaccine group. This association is consistent with other studies in which CD4 cell counts and CD4/CD8 ratio significantly influenced seroconversion after HAV mono-vaccine [15,19,22,26]. It is not clear, why - in contrast to the HAV mono-vaccine group – in the HAV/HBV co-vaccine group non-responders had similar CD4 cell counts (absolute and relative) compared to responders. One explanation might be the significantly older age of the non-responders, resulting in an immunosenscence with a poorer antibody response despite similar CD4 cell counts [27].

Conflicting data exist on whether viral suppression increases the likelihood of seroconversion after vaccination against HAV [15,16]. In several studies viral suppression (viral load below 400 copies/ml) was an important predictor of seroconversion [16,19,28]. In our cohort, however, this was not the case, which is in agreement with another study from Greece, where viral load had no influence on seroconversion after hepatitis A vaccine [26].

Several studies revealed sex, viral load > 1000 copies/ml, CD4 cell count < 200/μl, CD4/CD8 ratio, and HCV co-infection to be significantly associated with decrease of antibody response [15,16,22]. In our cohort, multivariable analysis revealed only time, especially of more than 5 years between vaccination and serological testing to be a factor that significantly influence seroconversion. Age is a crucial factor that influences the immunogenicity of vaccines. In elderly individuals, immunosenescence combined with the progressive increase of a proinflammatory status characteristic of the aging process are responsible for most age-related diseases and correlate with poor response to vaccination [27]. HIV-associated immune activation is characterized by an increase in proinflammatory mediators, dysfunctional T regulatory cells, and a pattern of T-cell-senescent phenotypes similar to those seen in the elderly [29]. This might explain our finding that age over 30 years, even though not significant, seems to be associated with a decrease of antibody response.

However, vaccine type (HAV mono-vaccine or HAV/HBV co-vaccine) has no significant impact on the seroconversion rate for HAV antibodies confirming the results of a study by Jimenez et al. in which seroconversion rates for Havrix® and Twinrix® were similar [19].

Data on the durability of HAV vaccine in HIV patients is scarce and mainly available for the monovalent HAV vaccine. Between 75% and 88% of patients vaccinated with the HAV mono-vaccine have been reported to have positive HAV antibody titers 5–10 years after vaccination [20,24,30]. We did not test longitudinally in our cohort, making it difficult to interpret results obtained from non-responders tested more than 5 years after vaccination, as

it was not clear whether these patients had lost their protective antibody titers over time or failed to develop these in the first place. However, in the subgroup of patients tested within a year of vaccination, 89% had positive HAV titers – 94.4% in the HAV mono-vaccine group and 85.2% in the HAV/HBV co-vaccine group, which is similar to other studies [20,24,30]. Among those patients serologically tested 5 years or more after vaccination, 66.6% (10/30) had positive titers – 37.5% (3/8) in the HAV mono-vaccine group and 77.3% (17/22) in the HAV/HBV co-vaccine group. This almost significant difference between the mono-vaccine group and the HAV/HBV co-vaccine group (37.5% vs 77.3%, $p = 0.078$) remains unclear, but might be explained by the small number of patients in these groups, especially in the HAV mono-vaccine group. In a large study on HAV mono-vaccine in more than 2000 HIV patients, approximately 7% of patients with CD4 cells < 350/μl lost their antibodies after a median time of 611 days after the first dose of vaccine. Patients who lost the HAV antibodies after vaccination were less likely to have achieved HIV viral suppression, and had a lower median CD4 cell count at vaccination, than those who were able to maintain seroresponses after vaccination [31]. This median time of 611 days is consistent with our finding, that serological control five years after vaccination is associated with a negative antibody titer after vaccination, either due to nonresponse or to loss of antibodies after primary response. In a smaller study with viremic HIV patients, only 88% responded with development of HAV antibodies after an accelerated HAV/HBV co-vaccine, and antibodies waned over time until week 24 after vaccination. Like in our cohort, there was no association between CD4 cell count and antibody response, but age was inversely correlated with HAV antibody titers at week 24 [32].

With regard to the HBV seroconversion rate, our results are in agreement with those of various other studies in which seroconversion rates among adults range between 17.5% and 90% [33–35]. As in other studies, non-responders in our cohort were more likely to be older and to have lower CD4 cell counts. We found a suppressed HIV viral load to be associated with a better response to vaccine, which again is in agreement with other studies [34,35].

Several limitations of our study need to be mentioned. Unbalanced groups as shown here for both age and HIV RNA below 50 copies/ml occur frequently in cross-sectional studies. Since patients with preexisting HBV immunity receiving HAV mono-vaccine may have better immunity in general than those without preexisting immunity, our investigations concerning HAV mono-vaccinated group may be biased towards better immunity. However, the proportion of non-responders after 5 years of vaccination was higher in the HAV mono-vaccine group. We were not able to draw conclusions about the durability of the vaccine since no baseline titers after a primary series of vaccinations were available as longitudinal data. Since the rate of hepatitis C co-infection was rather low in our cohort we did not analyze these subjects separately, although it has been shown that HCV co-infection is associated with a lower probability of response to the vaccine [15,20,21].

Furthermore, the antibody titer is only a surrogate marker of protection against HAV infection, the vaccine efficacy was not evaluated in this study.

6. Conclusion

The response to the hepatitis A vaccine is impaired in HIV positive patients. As a result, HIV patients, especially those older than 30, should be tested for seroconversion after receiving the hepatitis A vaccine. As hepatitis A titers may rapidly decline, control serology during follow-up should be proposed, possibly within two years. However, vaccine type (HAV mono-vaccine or HAV/HBV co-vaccine) does not seem to influence vaccine response.

Conflict of interest

ML received personal fees from Pfizer Pharma GmbH, AbbVie Deutschland GmbH, Gilead Sciences GmbH, and Astellas Pharma outside the submitted work. CF received personal fees from MSD, and Gilead Sciences GmbH outside the submitted work. ECR received personal fees from Pfizer, Infectopharm, Metaplan, and from Falk Foundation outside the submitted work.

LB and AG have no conflicts of interest to declare.

Acknowledgements

All authors contributed substantially to the manuscript. All authors helped in acquiring analyzing, and interpreting the data for the work. The manuscript was revised critically by all authors and all authors approved the final version before publication.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.02.064.

References

[1] Bordi L, Rozera G, Scognamiglio P, Minosse C, Loffredo M, Antinori A, et al. Monophyletic outbreak of Hepatitis A involving HIV-infected men who have sex with men, Rome, Italy 2008–2009. J Clin Virol 2012;54(1):26–9.
[2] Mor Z, Lurie Y, Katchman E. A case of hepatitis A vaccination failure in an HIV-positive man who had sex with men in Israel. Int J STD AIDS 2012;23(7):529–30.
[3] Fonquernie L, Meynard JL, Charrois A, Delamare C, Meyohas MC, Frottier J. Occurrence of acute hepatitis A in patients infected with human immunodeficiency virus. Clin Infect Dis 2001;32(2):297–9.
[4] Aberg JA, Kaplan JE, Libman H, Emmanuel P, Anderson JR, Stone VE, et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV medicine association of the infectious diseases society of America. Clin Infect Dis 2009;49(5):651–81.
[5] Vento S, Garofano T, Renzini C, Cainelli F, Casali F, Ghironzi G, et al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. N Engl J Med 1998;338(5):286–90.
[6] Clemens R, Safary A, Hepburn A, Roche C, Stanbury WJ, Andre FE. Clinical experience with an inactivated hepatitis A vaccine. J Infect Dis 1995;171(Suppl 1):S44–9.
[7] Beran J. Bivalent inactivated hepatitis A and recombinant hepatitis B vaccine. Expert Rev Vaccines 2007;6(6):891–902.
[8] Loebermann M, Kollaritsch H, Ziegler T, Rendi-Wagner P, Chambonneau L, Dumas R, et al. A randomized, open-label study of the immunogenicity and reactogenicity of three lots of a combined typhoid fever/hepatitis A vaccine in healthy adults. Clin Ther 2004;26(7):1084–91.
[9] Bodsworth NJ, Neilsen GA, Donovan B. The effect of immunization with inactivated hepatitis A vaccine on the clinical course of HIV-1 infection: 1-year follow-up. AIDS 1997;11(6):747–9.
[10] Kemper CA, Haubrich R, Frank I, Dubin G, Buscarino C, McCutchan JA, et al. Safety and immunogenicity of hepatitis A vaccine in human immunodeficiency virus-infected patients: a double-blind, randomized, placebo-controlled trial. J Infect Dis 2003;187(8):1327–31.
[11] Shire NJ, Welge JA, Sherman KE. Efficacy of inactivated hepatitis A vaccine in HIV-infected patients: a hierarchical bayesian meta-analysis. Vaccine 2006;24(3):272–9.
[12] Wallace MR, Brandt CJ, Earhart KC, Kuter BJ, Grosso AD, Lakkis H, et al. Safety and immunogenicity of an inactivated hepatitis A vaccine among HIV-infected subjects. Clin Infect Dis 2004;39(8):1207–13.
[13] Neilsen GA, Bodsworth NJ, Watts N. Response to hepatitis A vaccination in human immunodeficiency virus-infected and -uninfected homosexual men. J Infect Dis 1997;176(4):1064–7.
[14] Rimland D, Guest JL. Response to hepatitis A vaccine in HIV patients in the HAART era. AIDS 2005;19(15):1702–4.
[15] Weissman S, Feucht C, Moore BA. Response to hepatitis A vaccine in HIV-positive patients. J Viral Hepat 2006;13(2):81–6.
[16] Overton ET, Nurutdinova D, Sungkanuparph S, Seyfried W, Groger RK, Powderly WG. Predictors of immunity after hepatitis A vaccination in HIV-infected persons. J Viral Hepat 2007;14(3):189–93.
[17] Fritzsche C, Loebermann M, Reisinger EC. A case of acute hepatitis A infection in an HIV-positive patient despite complete hepatitis A vaccination. Infection 2018;46(4):565–7.
[18] Hess G, Clemens R, Bienzle U, Schonfeld C, Schunck B, Bock HL. Immunogenicity and safety of an inactivated hepatitis A vaccine in anti-HIV positive and negative homosexual men. J Med Virol 1995;46(1):40–2.

[19] Jimenez HR, Hallit RR, Debari VA, Slim J. Hepatitis A vaccine response in HIV-infected patients: are TWINRIX and HAVRIX interchangeable? Vaccine 2013;31(9):1328–33.
[20] Jablonowska E, Kuydowicz J. Durability of response to vaccination against viral hepatitis A in HIV-infected patients: a 5-year observation. Int J STD AIDS 2014;25(10):745–50.
[21] Mena G, Garcia-Basteiro AL, Bayas JM. Hepatitis B and A vaccination in HIV-infected adults: A review. Hum Vaccin Immunother 2015;11(11):2582–98.
[22] Mena G, Garcia-Basteiro AL, Llupia A, Diez C, Costa J, Gatell JM, et al. Factors associated with the immune response to hepatitis A vaccination in HIV-infected patients in the era of highly active antiretroviral therapy. Vaccine 2013;31(36):3668–74.
[23] Belderok SM, Sonder GJ, van Rossum M, van Dijk-Hummelman A, Hartwig N, Scherpbier H, et al. Evaluation of immune responses to combined hepatitis A and B vaccine in HIV-infected children and children on immunosuppressive medication. Vaccine 2013;31(38):4156–63.
[24] Cheng A, Chang SY, Sun HY, Tsai MS, Liu WC, Su YC, et al. Long-term durability of responses to 2 or 3 doses of hepatitis a vaccination in human immunodeficiency virus-positive adults on antiretroviral therapy. J Infect Dis 2017;215(4):606–13.
[25] Armstrong KE, Bush HM, Collins JD, Feola DJ, Caldwell GC, Thornton AC. Role of CD4 count in immunity development after hepatitis A and B vaccination among HIV-infected patients: Kentucky, 2002–2007. J Int Assoc Physicians AIDS Care (Chic) 2010;9(3):179–86.
[26] Kourkounti S, Mavrianou N, Paparizos VA, Kyriakis K, Hatzivassiliou M, Kordosis T, et al. Immune response to hepatitis A vaccination in HIV-infected men in Greece. Int J STD AIDS 2012;23(7):464–7.
[27] Ciabattini A, Nardini C, Santoro F, Garagnani P, Franceschi C, Medaglini D. Vaccination in the elderly: The challenge of immune changes with aging. Semin Immunol 2018;40:83–94.
[28] Weinberg A, Allshouse AA, Mawhinney S, Canniff J, Benning L, Wentz EL, et al. Responses to hepatitis A virus vaccine in HIV-infected women: effect of hormonal contraceptives and HIV disease characteristics. J Acquir Immune Defic Syndr 2012;60(1):e15–8.
[29] Sokoya T, Steel HC, Nieuwoudt M, Rossouw TM. HIV as a Cause of Immune Activation and Immunosenescence. Mediators Inflamm 2017;2017:6825493.
[30] Crum-Cianflone NF, Wilkins K, Lee AW, Grosso A, Landrum ML, Weintrob A, et al. Long-term durability of immune responses after hepatitis A vaccination among HIV-infected adults. J Infect Dis 2011;203(12):1815–23.
[31] Huang SH, Huang CH, Wang NC, Chen TC, Lee YT, Lin SP, et al. seroreversion after 2 doses of hepatitis A vaccination in HIV-positive patients: incidence and associated factors. Hepatology (Baltimore, MD) 2019.
[32] Shive CL, Judge CJ, Clagett B, Kalayjian RC, Osborn M, Sherman KE, et al. Pre-vaccine plasma levels of soluble inflammatory indices negatively predict responses to HAV, HBV, and tetanus vaccines in HCV and HIV infection. Vaccine 2018;36(4):453–60.
[33] Catherine FX, Piroth L. Hepatitis B virus vaccination in HIV-infected people: A review. Hum Vaccin Immunother 2017;13(6):1–10.
[34] Kim HN, Harrington RD, Van Rompaey SE, Kitahata MM. Independent clinical predictors of impaired response to hepatitis B vaccination in HIV-infected persons. Int J STD AIDS 2008;19(9):600–4.
[35] Mena G, Llupia A, Garcia-Basteiro AL, Diez C, Leon A, Garcia F, et al. Assessing the immunological response to hepatitis B vaccination in HIV-infected patients in clinical practice. Vaccine 2012;30(24):3703–9.