Immunogenicity of Sci-B-Vac (a Third-Generation Hepatitis B Vaccine) in HIV-Positive Adults

Danny Alon MD[1,2], Gideon Y. Stein MD PhD[2,3], Vered Hadas-Golan RN1, Luba Tau MD[1,3], Tal Brosh MD[1,3] and Dan Turner MD[1,3]

[1]Kobler AIDS Center, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[2]Department of Medicine B, Rabin Medical Center (Beilinson Campus), Petah Tikva, Israel
[3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT: **Background:** Guidelines recommend hepatitis B virus (HBV) vaccination of all adults positive for human immunodeficiency virus (HIV). Immune responses to single-antigen HBV vaccine among HIV-positive patients are low when compared with HIV-negative adults. Sci-B-Vac™ is a recombinant third-generation HBV that may be advantageous in this population.

Objectives: To examine the immune responses to Sci-B-Vac among HIV-positive adults.

Methods: We conducted a prospective cohort study involving HIV-positive adults who had negative HBV serology (HBSAg, HBSAb, HBcoreAb). Sci-B-Vac at 10 µg/dose was administered intramuscularly upon recruitment and after 1 and 6 months. HBSAb levels were checked 1 month after each dose; a level › 10 mIU/ml was considered protective. Data regarding age, gender, CD4 level, and viral load were collected.

Results: The study group comprised 31 patients. Average CD4 count was 503 ± 281 cells/ml, and average viral load was 44 copies/ml. Median interquartile range (IQR) HBVAb titers after the first, second and third immunizations were 0 (0, 3.5), 30 (6, 126) and 253 (81, 408) mIU/ml. Significant titer elevations were found between the second and third immunizations (P = 0.0003). The rate of patients considered protected was 16% after the first, 65% after the second (P ‹ 0.0001), and 84% after the third dose (P = 0.045). No adverse events were reported. More patients under the age of 40 years responded to the first immunization (28% vs. 0%, P = 0.038). CD4 level had no influence on immunization rates.

Conclusions: Sci-B-Vac might achieve better immunization rates among HIV-positive adults compared to the single-antigen vaccine and thus deserves further evaluation in a randomized, double-blind study in this population.

IMAJ 2017; 19: 143–146

KEY WORDS: hepatitis B virus (HBV), vaccine, human immunodeficiency virus (HIV), immunogenicity, Sci-B-Vac™

Both hepatitis B virus (HBV) and human immunodeficiency virus (HIV) are chronic viral infections that share similar modes of transmission, resulting in frequent co-infection [1]. HIV-infected patients are more likely to develop chronic hepatitis B from an acute infection and are at increased risk of developing cirrhosis and hepatocellular carcinoma and of dying prematurely [2]. Conversely, HBV might be a co-factor for HIV disease progression [3]. Hence, hepatitis B vaccination is universally recommended in all HIV treatment guidelines (www.aidsinfo.nih/gov) because it can prevent HBV infection and its sequelae [4].

The widely used recombinant single-antigen hepatitis B vaccine (Engerix B®, GlaxoSmithKline, UK) has been extensively used among HIV-infected individuals. However, the three-dose vaccination schedule (0, 1 and 6 months) among HIV-positive adults is not as effective as it is among HIV-negative individuals. Whereas 90–95% of healthy adults are protected after vaccination, only 17.5%–53% of HIV-positive adults develop protective antibody titers, defined as hepatitis B surface antibody (HBsAb) > 10 mIU/ml [5-7], mostly depending on CD4 T cell counts, HIV viral loads [8], and age of the patient (response declines significantly with age) [9].

A number of strategies have been used to achieve higher immunization rates among HIV-positive individuals, with varying, yet modest degrees of success. These include postponing vaccination with hepatitis B vaccine until CD4 counts exceed 200 cells/ml [3], increasing the number of doses given [10], or using a higher dose of the vaccine [11].

Sci-B-Vac™ is a recombinant third-generation hepatitis B vaccine derived from a mammalian cell line and containing hepatitis B surface antigen as well as preS1 and preS2 antigens (thus termed a triple-antigen vaccine). The vaccine was found to be accompanied by a more rapid onset and pronounced antibody response in healthy children and newborns [12-14]. Third-generation vaccines have proven to be superior among individuals at risk for suboptimal response to vaccination [15]. This result was also shown in a study of health care workers who had failed to respond to a previous recombinant vaccination series [16]. Thus, Sci-B-Vac may be advantageous in HIV-positive individuals, whose response to the single-antigen vaccine is poorer and in whom a faster immunization is desirable. The immunogenicity of Sci-B-Vac among HIV-positive adults, however, has never been tested. The aim of the study was therefore to examine the immune responses to Sci-B-Vac among HIV-positive adults.

PATIENTS AND METHODS

The Kobler AIDS clinic at Tel Aviv Sourasky Medical Center employs seven infectious disease physicians who follow approximately 1500 HIV-infected patients. All new patients are screened for previous exposure to HBV and for hepatitis B immunity. Screening is then repeated on a yearly basis. Patients who are non-immune are offered vaccination.

Between January 2012 and June 2013 all consecutive asymptomatic HIV-positive patients over 18 years who were negative for HBsAg, HBsAb or HBcAb and who were not vaccinated with any hepatitis B vaccination in the past were invited to join the study. Women of childbearing age were excluded unless a pregnancy test was negative.

Sci-B-Vac was provided by the manufacturer Scigen (Rehovot, Israel) at no charge. Scigen personnel had no access to study data, nor did they participate in its analysis in any way. The study was approved by the Institutional Review Board of Tel Aviv Sourasky Medical Center. All participants signed an informed consent form and were instructed to observe local signs and general symptoms associated with vaccine administration.

VACCINATIONS, FOLLOW-UP AND RESPONSE DEFINITIONS

Sci-B-Vac was administered at a dose of 10 μg intramuscularly (IM) upon recruitment and after 1 and 6 months. HBsAb levels were checked for 1 month after each administered dose of Sci-B-Vac. Levels above 10 mIU/ml were considered protective. Data regarding age, gender, CD4 count and viral load were also collected, including whether patients were treated with highly active antiretroviral therapy (HAART) at the time of vaccine administration.

STUDY OBJECTIVES

The overall immunogenicity of Sci-B-Vac among HIV-positive individuals was compared to that achieved with single-antigen recombinant vaccines in historic patient cohorts. Immune response rates were evaluated after one, two and three doses of Sci-B-Vac. Demographic and laboratory parameters that might be associated with response rate were also analyzed.

STATISTICAL ANALYSIS

Statistical analysis was performed with SPSS software for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as a mean ± 1 standard deviation (SD) and as a median [interquartile range (IQR)] when indicated. Categorical variables are presented as percentages. Comparisons between two groups were performed by Student's *t*-test for continuous variables and the chi-square test for comparison of categorical values. All tests of significance were two-tailed with *P* value < 0.05 considered significant.

RESULTS

The cohort included 31 patients (3 females, 28 males). Study patients had a mean age of 37 ± 11 years. All patients were Caucasians.

The average CD4 count at first vaccination dose was 503 ± 218 cells/ml and the median viral load was 44 copies/ml. Twenty-five (80%) of the patients were on HAART at the first vaccination dose.

Median (IQR) titers measured 1 month after the first, second and third vaccination doses were 0 (0, 3.5), 30 (6, 126) and 253 (81, 408) mIU/ml, respectively. A significant elevation of the titers was found between the second and third vaccination doses ($P = 0.0003$) but not between the first and second doses (P = NS) [Figure 1].

The percentage of patients considered protected (i.e., HBsAb titer > 10 mIU/ml) increased from 16% after the first vaccination dose to 65% after the second dose ($P < 0.0001$) and further to 84% after the third vaccination dose ($P = 0.045$) [Figure 2].

More patients under the age of 40 years responded to the first vaccination dose as compared to those 40 years or older (28% vs. 0%, respectively, $P = 0.038$). Age-dependent differences after the second and third vaccination doses were not significant. Both viral load measurements and CD4 counts were not associated with immunogenicity rates in our cohort. Local reactions were reported by two patients. No systemic reactions were reported by any patient.

Figure 1. HBVsAb titers after first, second and third dose of Sci-B-Vac

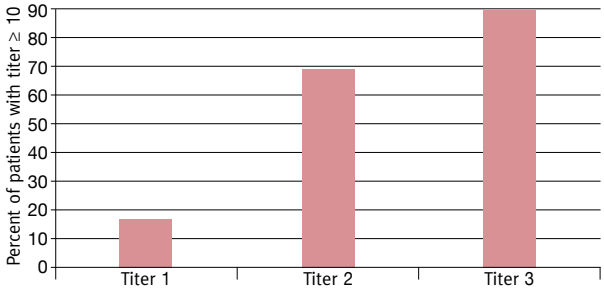
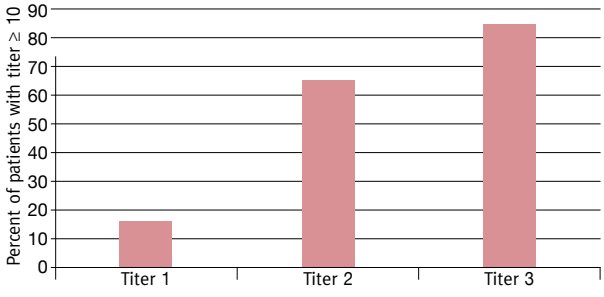


Figure 2. Hepatitis B immunization rates after first, second. and third dose of Sci-B-Vac



DISCUSSION

Immunization of HIV-positive patients with hepatitis B vaccine could protect them from HBV infection and significantly reduce morbidity and mortality [17]. However, immunization response to standard single-antigen hepatitis B vaccines among HIV-infected individuals has been consistently unsatisfactory compared to that in HIV-negative persons (17.5–53% vs. 90–95%) [6-8].

In this single-center prospective cohort study of 31 HIV-positive adults, the rate of protection against HBV obtained using Sci-B-Vac – a third-generation, triple-antigen recombinant hepatitis B vaccine – was 84% after completion of a full vaccination series consisting of three doses. This rate exceeded the response rates observed in previous studies in patients with HIV infection, using the single-antigen recombinant hepatitis B vaccine [18]. Moreover, a series of two doses of Sci-B-Vac, given 1 month apart, resulted in seroconversion in 64% of our cohort. No serious adverse events were reported.

Risk factors for lack of response to the standard hepatitis B vaccine among HIV-positive individuals identified in previous reports included low CD4 counts, high viral load measurements, female gender, and age above 40 years [7,19-21]. Similarly, age above 40 at the time of the first dose was significantly associated with diminished response in our cohort, but with the first dose only, again reflecting an increased potency of the triple-antigen vaccine.

CD4 counts were not associated with a diminished response in our study, although one should bear in mind that the lowest CD4 count in our cohort was 285 cells/ml only. Thus, the lack of an association in our study may be explained by the relatively immunocompetent population, or it may indeed indicate that the CD4 cell count is not the predominant factor responsible for vaccine responsiveness. Previous studies have shown conflicting results regarding how well CD4 counts can predict immunization response to HBV vaccine: both a positive correlation [22,23] and no correlation between successful response and pre-vaccination CD4 counts were observed, albeit in an older publication [24].

Concomitant HAART was not associated with response in our cohort either, a result that probably reflects the large proportion of patients who were treated with antiretroviral therapy at the time of the first vaccination dose. Lack of association between HAART use and vaccine response has been shown before [19,25]. The lack of association between viral load measurements and the response rate is likely due to the wide range of viral load measurements observed in our cohort.

Limitations of our study include its small sample size and its inherent lack of control. In this respect it is a modest observational study that can serve as a proof of concept necessitating a randomized study comparing a single-antigen vaccine group with a triple-antigen vaccine group in a blinded and prospective manner. This type of study, however, would not have been feasible due to our relatively small population of HIV patients who had not been already vaccinated against HBV upon presentation.

In conclusion, Sci-B-Vac, a third-generation triple-antigen hepatitis B vaccine, might be associated with better immunization rates among HIV-positive adults and therefore deserves further study in this patient population.

Acknowledgments

Scigen (Rehovot, Israel) supplied the vaccinations free of charge but was not involved in the study and had no influence whatsoever on study design, conduct or data analysis.

Correspondence

Dr. D. Alon

Kobler AIDS Center, Tel Aviv Sourasky Medical Center, Tel Aviv 64239, Israel

Fax: (972-3) 937-6612

email: dr.danny.alon@gmail.com

References

1. Jansen K, Thamm M, Bock CT, et al. High prevalence and high incidence of coinfection with hepatitis B, hepatitis C, and syphilis and low rate of effective vaccination against hepatitis B in HIV-positive men who have sex with men with known date of HIV seroconversion in Germany. *PLoS One* 2015; 10 (11): e0142515.
2. Soriano V, Labarga P, de Mendoza C, et al. Emerging challenges in managing hepatitis B in HIV patients. *Curr HIV/AIDS Rep* 2015; 12 (3): 344-52.
3. Parvez MK. HBV and HIV co-infection: impact on liver pathobiology and therapeutic approaches. *World J Hepatol* 2015; 7 (1): 121-6.
4. Mena G, García-Basteiro AL, Bayas JM. Hepatitis B and A vaccination in HIV-infected adults: a review. *Hum Vaccin Immunother* 2015; 11 (11): 2582-98.
5. Lopes VB, Hassing RJ, de Vries-Sluijs TE, et al. Long-term response rates of successful hepatitis B vaccination in HIV-infected patients. *Vaccine* 2013; 31 (7):1040-4.
6. Irungu E, Mugo N, Ngure K, et al. Immune response to hepatitis B virus vaccination among HIV-1 infected and uninfected adults in Kenya. *J Infect Dis* 2012; 207 (3): 402-10.
7. Bailey CL, Smith V, Sands M. Hepatitis B vaccine: a seven-year study of adherence to the immunization guidelines and efficacy in HIV-1-positive adults. *Int J Infect Dis* 2008; 12 (6): e77-83.
8. Chonwattana W, Raengsakulrach B, Holtz TH, et al. Hepatitis B vaccination uptake and correlates of serologic response among HIV-infected and uninfected men who have sex with men (MSM) in Bangkok, Thailand. *Vaccine* 2016; 34 (17): 2044-50.
9. Fisman DN, Agrawal D, Leder K. The effect of age on immunologic response to recombinant hepatitis B vaccine: a meta-analysis. *Clin Infect Dis* 2002; 35 (11): 1368-75.
10. Chaiklang K, Wipasa J, Chaiwarith R, et al. Comparison of immunogenicity and safety of four doses and four double doses vs. standard doses of hepatitis B vaccination in HIV-infected adults: a randomized, controlled trial. *PLoS One* 2013; 8 (11): e80409.
11. Ni JD, Xiong YZ, Wang XJ, Xiu LC. Does increased hepatitis B vaccination dose lead to a better immune response in HIV-infected patients than standard dose vaccination: a meta-analysis. *Int J STD AIDS* 2013; 24 (2): 117-22.
12. Madalinski K, Sylvan SP, Hellstrom U, Mikolajewicz J, Dzierzanowska-Fangrat K. Presence of anti-preS1, anti-preS2, and anti-HBs antibodies in newborns immunized with Bio-Hep-B vaccine. *Med Sci Monit* 2004; 10 (1): PI10-7.
13. Madalinski K, Sylvan SP, Hellstrom U, Mikolajewicz J, Zembrzuska-Sadkowska E, Piontek E. Antibody responses to preS components after immunization of children with low doses of BioHepB. *Vaccine* 2001; 20 (1-2): 92-7.
14. Hellstrom UB, Madalinski K, Sylvan SP. PreS1 epitope recognition in newborns after vaccination with the third-generation Sci-B-Vac vaccine and their relation to the antibody response to hepatitis B surface antigen. *Virol J* 2009; 6: 7.

15. Krawczyk A, Ludwig C, Jochum C, et al. Induction of a robust T- and B-cell immune response in non- and low-responders to conventional vaccination against hepatitis B by using a third generation PreS/S vaccine. *Vaccine* 2014; 32 (39): 5077-82.

16. Zuckerman JN, Zuckerman AJ, Symington I, et al. Evaluation of a new hepatitis B triple-antigen vaccine in inadequate responders to current vaccines. *Hepatology* 2001; 34 (4 Pt 1): 798-802.

17. Soriano V, de Mendoza C, Fernández-Montero JV, Labarga P. Management and treatment of chronic hepatitis B in HIV-positive patients. *Ann Med* 2014; 46 (5): 290-6.

18. Launay O, Rosenberg AR, Rey D et al. Long-term immune response to hepatitis B virus vaccination regimens in adults with human immunodeficiency virus 1: secondary analysis of a randomized clinical trial. *JAMA Intern Med* 2016; 176 (5): 603-10.

19. de Vries-Sluijs TE, Hansen BE, van Doornum GJ et al. A prospective open study of the efficacy of high-dose recombinant hepatitis B rechallenge vaccination in HIV-infected patients. *J Infect Dis* 2008; 197 (2): 292-4.

20. Okulicz JF, Mesner O, Ganesan A, et al Hepatitis B vaccine responsiveness and clinical outcomes in HIV controllers. *PLoS One* 2014; 9 (8): e105591.

21. Fuster F, Vargas JI, Jensen D et al CD4/CD8 ratio as a predictor of the response to HBV vaccination in HIV-positive patients: a prospective cohort study. *Vaccine* 2016; 34 (16): 1889-95.

22. Fonseca MO, Pang LW, de Paula Cavalheiro N, Barone AA, Heloisa Lopes M. Randomized trial of recombinant hepatitis B vaccine in HIV-infected adult patients comparing a standard dose to a double dose. *Vaccine* 2005; 23 (22): 2902-8.

23. Rey D, Krantz V, Partisani M, et al. Increasing the number of hepatitis B vaccine injections augments anti-HBs response rate in HIV-infected patients. Effects on HIV-1 viral load. *Vaccine* 2000 18 (13): 1161-5.

24. Wong EK, Bodsworth NJ, Slade MA, Mulhall BP, Donovan B. Response to hepatitis B vaccination in a primary care setting: influence of HIV infection, CD4+ lymphocyte count and vaccination schedule. *Int J STD AIDS* 1996; 7 (7): 490-4.

25. Cruciani M, Mengoli C, Serpelloni G, et al. Serologic response to hepatitis B vaccine with high dose and increasing number of injections in HIV infected adult patients. *Vaccine* 2009; 27 (1): 17-22.