

Seroconverting nonresponder of high-dose intramuscular HBV vaccine with intradermal HBV vaccine

A case report

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Abstract

Introduction: Liver disease is a leading cause of death among human immunodeficiency virus (HIV)-infected patients in the United States. Patients with HIV and hepatitis B virus (HBV) coinfection have accelerated liver disease, higher rates of cirrhosis, and liver cancer, and markedly increased liver-related mortality. The CDC and US Advisory Committee on Immunization Practices recommend hepatitis B vaccination for all HIV-infected individuals. Unfortunately, HIV-infected patients have a worse response rate after standard HBV vaccination. Intradermal (ID) vaccination continues to emerge as an important modality in such difficult to vaccinate individuals and should be considered whenever permissible. Herein, we report a case of a 46-year-old male with HIV who failed to mount an immune response to standard intramuscular vaccine, standard booster dose, and repeat high-dose booster vaccine but subsequently mounted an immune response to the ID vaccine which was sustained at 3 months postvaccination.

Conclusion: ID vaccination continues to emerge as an important modality in difficult to vaccinate individuals and should be considered in all applicable cases

Abbreviations: HBV = hepatitis B virus, HIV = human immunodeficiency virus, ID = intradermal, IM = intramuscular.

Keywords: hepatitis B vaccine, human immunodeficiency virus, intradermal, intramuscular, nonresponder

1. Introduction

Human immunodeficiency virus (HIV) is a global epidemic with an estimated 35 million individual carriers.^[1] Due to shared routes of transmission, the risk for coinfection with hepatitis B virus (HBV) is approximately 20 times that of the general population (8.4%).^[2] Over 90% of immunocompetent individuals will spontaneously clear HBV infection but HIV-infected patients have less than a 50% chance of clearing the virus.^[3,4] World-wide, approximately 10% of HIV-infected individuals are coinfecting with HBV,^[1] and these patients have accelerated liver disease, higher rates of cirrhosis, and liver cancer along with markedly increased liver-related mortality.^[1,5] Additionally, many antiretroviral regimens increase the risk of drug induced liver disease in HIV patients.^[2,6]

These factors underline the importance of recommending primary prevention of HBV in HIV-infected individuals. Vaccination for HBV is universally practiced, and the CDC and US Advisory Committee on Immunization Practices recommend hepatitis B vaccination for all HIV-infected individuals.^[7] The Infectious Disease Society of America recommends routine serologic testing for HBV in men who have sex with men, and vaccination of susceptible individuals.^[8] Five to ten percent of immunocompetent patients fail to mount an appropriate antibody response to the vaccine.^[9,10] Some studies in HIV-infected patients have a worse response rate ranging from 33.3% to 65% after standard HBV vaccination schedules.^[5,11] Both patient and vaccine factors have been studied to play a role in failed immune response to vaccination. The location of vaccine inoculation and the storage conditions have shown decreased rates in seroconversion. Patient factors such as drug abuse, smoking, infections, chronic illness, and genetics also play a role.^[12,13]

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2. Case report

A 46-year-old homosexual Caucasian male with a 10-year history HIV infection was referred to Hepatology Clinic for chronically elevated liver function tests. He initially started on treatment with efavirenz/emtricitabine/tenofovir at the time of his HIV diagnosis and later changed to tenofovir/emtricitabine/raltegravir due to elevated liver function tests. He reported compliance and remained asymptomatic with stable virologic suppression. On subsequent primary care office visits, he was noted to have persistently elevated transaminases prompting the referral to hepatology clinic. At the time of consultation his AST was 69 units/L, ALT 245 units/L, and alkaline phosphatase was

Table 1**Vaccine dose and antibody titers.**

Route of delivery	IM*	Repeat IM†	Booster IM‡	Intradermal‡
Vaccine dose	20 µg	20 µg	40 µg	40 µg
No of doses given	3	3	1	2
Anti-HBs titers	<10 mIU/mL	<10 mIU/mL	<10 mIU/mL	126 mIU/mL

HB = hepatitis B, IM = intramuscular.

* Initial IM injection was historic reporting per electronic records.

† Repeat IM and booster IM doses were office-based observed administrations.

‡ Intradermal doses were office-based observed administrations.

119 units/L. He denied any IV drug use, excess alcohol consumption, or recent blood transfusions. He was otherwise asymptomatic, and there was no family history of chronic liver disease.

A liver biopsy was performed which demonstrated macro- and microvesicular steatosis involved 70% to 80% of hepatic parenchyma with ballooning degeneration and some periportal inflammation, mild interface, and lobular activity. This was consistent with moderate steatohepatitis with marked steatosis. Concomitant chronic liver disease workup including autoimmune and viral titers was negative except for elevated aldolase levels – deemed to be due to myositis from his current antiretroviral therapy. Hepatitis B serologies demonstrated negative hepatitis B surface antigen and hepatitis B surface antibody – indicative of vaccine nonresponse despite prior documentation of receiving standard 3 dose (20 µg) intramuscular (IM) vaccine.

During our office visit, we repeated a standard (20 µg) 3 dose IM regimen however, no surface antibody was detected on 3 different occasions (Table 1). He subsequently received an increased dose (40 µg) booster vaccine with no seroconversion noted. His CD4 count was normal with the most recent over 800, and his viral load was undetectable. The patient was then considered to be a nonresponder and in order to develop a protective antibody against HBV he was vaccinated with 2 intradermal (ID) inoculations (1 month apart) of high dose (40 µg) HBV vaccine over each deltoid after obtaining informed consent. Serum antibody titers were obtained 3 months after the series of ID vaccine was administered and antibody titer was 126 mIU/mL indicative of seroconversion. Patient's consent was obtained to include data in this case report. IRB approval was waived (not required) as this was a case report not involving any experimental intervention.

3. Discussion

The recombinant HBV vaccine is made from yeast *Saccharomyces cerevisiae* and is made of the purified, nonglycosylated molecule, of the hepatitis B surface antigen.^[14,15] It is typically administered via IM route with 20 µg dosage at 0, 1, and 6 months. This creates an immunogenic response to the protein inducing anti-HBs antibodies. Protective HBs antibody response is considered a serum level of >10 IU/mL. The vaccine stimulates a long-term immune response in healthy individuals. Often, a 4th dose is administered for those patients at high risk for virus exposure or those that are immunocompromised.^[14] High-risk patients should have antibody titers rechecked 1 to 3 months after completion of the series and if the titer is less than 10 mIU/mL then the series should be repeated again and the antibody titers should be rechecked. Patients who do not respond to standard

regimen or the 4th booster or repeated course are considered “nonresponders.”^[14]

Several methods have been proposed to achieve seroconversion in nonresponders. The most commonly used is IM administration of the double dosage hepatitis B vaccine. Bonazzi et al^[16] showed a 68% response rate with double dosing (40 µg IM) at 0, 1, and 6 months in pretransplant cirrhotic patients. The ID route has been tested in several clinical trials especially in patients with chronic kidney disease who have suboptimal response to HBV vaccine.^[17] Barraclough et al^[17] screened 297 end-stage renal patients on hemodialysis who were nonresponsive to IM HBV vaccination, and administered ID 10 µg dosage with a 79% seroconversion rate. These patients also had a trend toward longer duration of protective antibody titer compared to the IM group. In patients with chronic liver disease, Dhillon et al^[18] administered HBV vaccine at 40 µg ID and had a 69% seropositive response rate.

The French National Agency for Research on AIDS and viral hepatitis performed one of the first randomized control trial exploring alternative HBV vaccination strategies in patients with HIV.^[19] They compared standard vaccination series to low-dose 4-injection ID versus a 4-injection double-dose IM administration and noted improved antibody response in the ID and double-dose IM group compared with the standard HBV vaccination regimen.

Although the IM route is more common and preferred, the skin is more immunogenic site due to the presence of dendritic cells. The protein in the vaccine interacts with the antigen presenting cells in the dermis, stimulating innate and adaptive immune responses. Langerhan cells and macrophages in the dermis express high levels of class II major histocompatibility complex. They process the vaccine antigen and eventually present it to CD8+ and CD4+ T lymphocytes in local lymph nodes.^[2] Due to concentration of antigen in the dermis, there is increased migration of dendritic cells causing CD8+ cells to become effector and memory T cells, while CD4+ promotes the differentiation of B cells into antibody producing plasma cells.^[2]

Our patient was on antiretroviral therapy with undetectable HIV viral loads and CD4 counts of over 800 cell/µL, but was still nonresponsive to standard and repeated vaccination regimens. He expressed a robust and lasting antibody response to 2 ID injections with no side effects. HIV and HBV coinfection is associated with higher morbidity and mortality and significantly impacts on healthcare resource utilization. ID vaccination continues to emerge as an important modality in such difficult to vaccinate individuals and should be considered in all applicable cases.

References

- [1] Martins S, Livramento A, Andrigueti M, et al. Vaccination coverage and immunity against hepatitis B among HIV-infected patients in South Brazil. *Braz J Infect Dis* 2015;19:181–6.
- [2] Filippelli M, Lionetti E, Gennaro A, et al. Hepatitis B vaccine by intradermal route in non responder patients: an update. *World J Gastroenterol* 2014;20:10383–94.
- [3] Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. *J Hepatol* 2006;44(1 Suppl):S6–9.
- [4] Bodsworth N, Donovan B, Nightingale BN. The effect of concurrent human immunodeficiency virus infection on chronic hepatitis B: a study of 150 homosexual men. *J Infect Dis* 1989;160:577–82.
- [5] 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;34:2044–50.

- [6] Bonacini M. Diagnosis and management of cirrhosis in coinfecting patients. *J Acquir Immune Defic Syndr* 2007;45(Suppl 2):S38–46. discussion S66–S67.
- [7] Mast EE, Weinbaum CM, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. *MMWR Recomm Rep* 2006;55(RR-16):1–33. quiz CE1-4.
- [8] Masur H, Brooks JT, Benson CA, et al. Prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Updated Guidelines from the Centers for Disease Control and Prevention, National Institutes of Health, and HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* 2014;58:1308–11.
- [9] Das K, Gupta RK, Kumar V, et al. Immunogenicity and reactogenicity of a recombinant hepatitis B vaccine in subjects over age of forty years and response of a booster dose among nonresponders. *World J Gastroenterol* 2003;9:1132–4.
- [10] Rendi-Wagner P, Kundi M, Stemberger H, et al. Antibody-response to three recombinant hepatitis B vaccines: comparative evaluation of multicenter travel-clinic based experience. *Vaccine* 2001;19:2055–60.
- [11] Fonseca MO, Pang LW, de Paula Cavalheiro N, et al. Randomized trial of recombinant hepatitis B vaccine in HIV-infected adult patients comparing a standard dose to a double dose. *Vaccine* 2005;23:2902–8.
- [12] Yu AS, Cheung RC, Keeffe EB. Hepatitis B vaccines. *Infect Dis Clin North Am* 2006;20:27–45.
- [13] Wood RC, MacDonald KL, White KE, et al. Risk factors for lack of detectable antibody following hepatitis B vaccination of Minnesota health care workers. *JAMA* 1993;270:2935–9.
- [14] Walayat S, Ahmed Z, Martin D, et al. Recent advances in vaccination of non-responders to standard dose hepatitis B virus vaccine. *World J Hepatol* 2015;7:2503–9.
- [15] McAleer WJ, Buynak EB, Maigetter RZ, et al. Human hepatitis B vaccine from recombinant yeast. *Nature* 1984;307:178–80.
- [16] Bonazzi PR, Bacchella T, Freitas AC, et al. Double-dose hepatitis B vaccination in cirrhotic patients on a liver transplant waiting list. *Braz J Infect Dis* 2008;12:306–9.
- [17] Barraclough KA, Wiggins KJ, Hawley CM, et al. Intradermal versus intramuscular hepatitis B vaccination in hemodialysis patients: a prospective open-label randomized controlled trial in nonresponders to primary vaccination. *Am J Kidney Dis* 2009;54:95–103.
- [18] Dhillon S, Moore C, Li SD, et al. Efficacy of high-dose intra-dermal hepatitis B virus vaccine in previous vaccination non-responders with chronic liver disease. *Dig Dis Sci* 2012;57:215–20.
- [19] Launay O, van der Vliet D, Rosenberg AR, et al. Safety and immunogenicity of 4 intramuscular double doses and 4 intradermal low doses vs standard hepatitis B vaccine regimen in adults with HIV-1: a randomized controlled trial. *JAMA* 2011;305:1432–40.