Vaccine 38 (2020) 112–114

Contents lists available at ScienceDirect

Vaccine

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

Short communication

Case report of delayed seroprotection rather than non-response after primary three-dose hepatitis B vaccination

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ARTICLE INFO

Article history:
Received 10 January 2019
Received in revised form 3 October 2019
Accepted 8 October 2019
Available online 21 October 2019

Keywords:
Hepatitis B
Vaccine
Non-responder
Humoral Immunity
Delayed seroprotection

ABSTRACT

We describe a delayed hepatitis B seroprotection 12 weeks after the primary vaccination schedule in a 57-year-old male with smoldering multiple myeloma. Based on undetectable anti-HBs antibodies 6 weeks after the third vaccination, the index person was previously considered to be a hepatitis B vaccine non-responder. Because hepatitis B vaccination started in the 1980s, many hepatitis B vaccine non-responders have received a revaccination regimen. If more cases of genuine delayed hepatitis B seroprotection surface in patients with hematologic malignancies, delayed seroprotection should be considered before the commencement of hepatitis B revaccination.

1. Introduction

Hepatitis B virus (HBV) vaccination is the only strategy to prevent HBV infection. In the Netherlands, the primary hepatitis B vaccination schedule in adults consists of three vaccinations at 0, 1, and 6 months and is able to induce a seroprotection response (hepatitis B surface antibody (anti-HBs) level ≥10 mIU/mL) in over 95% of immunocompetent individuals [1]. Compared with immunocompetent individuals, humoral response to HBV vaccination is reduced in haemodialysis patients and other immunocompromised patients (e.g. HIV-infected subjects) [2]. Individuals who mount an inadequate immune response (anti-HBs < 10 mIU/mL) within 1–2 months after three doses of HBV vaccine are defined as non-responders and thereby susceptible for HBV infection [1]. Here we report a delayed hepatitis B seroprotection 12 weeks after the primary HBV vaccination schedule in a male adult with smoldering multiple myeloma (MM). Based on undetectable anti-HBs antibodies 6 weeks after the third vaccination, the index person was considered to be a hepatitis B vaccine non-responder.

2. Case presentation

At 57-years of age, a male adult who was born and raised in the Netherlands presented to a study screening visit for the assessment of a new adjuvanted hepatitis B vaccine in registered healthy adult non-responders (defined as anti-HBs antibody level <10 mIU/mL 1–2 months after three hepatitis B vaccinations) (this study is registered at clinicaltrials.gov, NCT03415672). Table 1 illustrates individual's history of vaccination, hepatitis B vaccine response and relevant status.

After inquiring the digital records, the individual had received three commercially available Engerix-B© 20 μg HBsAg/mL, 1 ml vaccines (GlaxoSmithKline, Zeist, the Netherlands) at 0, 1 and 6 months. According to the local guidelines, the vaccines were

Abbreviations: Anti-HBc, antibodies to hepatitis B core antigen; anti-HBs, antibodies to hepatitis B surface antigen; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgG, Immunoglobulin G; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma.

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https://doi.org/10.1016/j.vaccine.2019.10.022
0264-410X/

Table 1
History of hepatitis B vaccination, hepatitis B vaccine response and relevant status.

Date	Vaccine	Anti-HBs	Relevant status
21-06-2017	Engerix-B© 20 μg HBsAg/mL, 1 ml vaccine		
26-07-2017	Engerix-B© 20 μg HBsAg/mL, 1 ml vaccine		
03-01-2018	Engerix-B© 20 μg HBsAg/mL, 1 ml vaccine		
14-02-2018		<2 mIU/mL Reanalysis: <2 mIU/mL	Negative: HBsAg and anti-HBc
26-03-2018		12.75 mIU/mL Reanalysis: 12.72 mIU/mL	Negative: HBsAg, anti-HBc, anti-HCV, HIV Ag/Ab
01-06-2018		20.91 mIU/mL	
03-07-2018		23.88 mIU/mL	

Abbreviations: anti-HBs: antibodies to hepatitis B surface antigen; HBsAg: hepatitis B surface antigen; anti-HBc: antibodies to hepatitis B core antigen; anti-HCV: antibodies against hepatitis C virus; HIV Ag/Ab: HIV antigen/antibody.

injected into the deltoid muscle of the non-dominant arm with adequate 23 gauge needle with a length of 25 mm. The anti-HBs antibody level 6 weeks after the third vaccination was <2 mIU/mL. Hepatitis B surface antigen (HBsAg) and hepatitis B core antibodies (anti-HBc) were negative (Table 1). The individual was consequently diagnosed as a hepatitis B vaccine non-responder. The individual's reported medical history was as follows: idiopathic small fiber neuropathy, hypertension and seasonal allergic rhinitis. His chronic medication consisted of duloxetine 30 mg once daily, amlodipine 5 mg once daily and desloratadine 5 mg once daily.

In addition to inquiring the medical history, the first study screening visit consisted of a complete physical examination, assessment of in-/exclusion criteria and blood sampling. No abnormal findings were encountered during physical examination. The verification of the in-/exclusion criteria showed the absence of the following conditions: known or suspected immune deficiency, known or suspected disease that influences the immune system, dialysis patient, use of medication that influences the immune system (immune suppressive treatment or daily use of corticosteroids, including chronic use of local corticosteroids), any vaccination within 3 months before screening, administration of plasma (incl. immunoglobulins) or blood products within 12 months before screening. Consecutive blood sampling demonstrated an anti-HBs antibody level of 12.75 mIU/mL and a negative screening test for HBsAg, anti-HBc, antibodies against hepatitis C virus (anti-HCV) and HIV antigen/antibody. In view of protective anti-HBs antibody levels in the last blood analysis, the individual was excluded from participating in a new adjuvanted hepatitis B vaccine study in registered healthy adult non-responders.

Reanalysis of anti-HBs on the same analyser (Elecsys® anti-HBs II, cobas e 601 module, Roche Diagnostics GmbH, Mannheim, Germany) and in the same laboratory confirmed undetectable anti-HBs antibodies in the first blood sample and an anti-HBs antibody level 12.72 mIU/mL in the second blood sample. Five months after the third vaccination, we reviewed the hospital's medical records and a diagnosis of smoldering MM was revealed after the study visit on March 26, 2018. Subsequent analyses by serum protein electrophoresis of both blood samples, 6 and 12 weeks after the third vaccination, indicated an identical monoclonal peak in the gamma fraction. The M-protein was typed as IgG-kappa and quantified at 17.4 g/L; total serum IgG was 22.5 g/L. Five and six months after the third HBV vaccination, additional blood samples were collected and tested for anti-HBs and serum protein electrophoresis. Together with a further increase in anti-HBs antibody level, a comparable peak in the gamma fraction as to the previous two blood samples was detected.

3. Discussion

To our knowledge, this is the first genuine report of delayed hepatitis B seroprotection after primary three hepatitis B vaccinations. Despite an undetectable anti-HBs antibody level 6 weeks after a complete primary hepatitis B vaccination schedule, the individual developed seroprotection with an anti-HBs antibody level of 12.75 mIU/mL 12 weeks after the last vaccination, with a further increase in the subsequent months. There are four plausible explanations for this delayed hepatitis B seroprotection: (1) booster hepatitis B vaccination, (2) HBV infection, (3) laboratory error and (4) delayed immune response.

1. In most countries, the administration of three additional doses of commercially available hepatitis B vaccines at one-month intervals is the recommended revaccination regimen to improve response in non-responders [1,2]. Our male participant did not receive a hepatitis B vaccine or any other vaccine within 3 months of the last anti-HBs measurement. Thus, seroprotection due to booster hepatitis B vaccination can be excluded as reason for hepatitis B seroprotection.
2. HBV infections have been reported in individuals with an anti-HBs <10 mIU/mL after the primary vaccination schedule [3–5]. The estimated risk of HBV infection for persons with an anti-HBs antibody level <10 mIU/mL was 6.9 infections per 100 person-years [5]. In this matter, two studies were conducted in high endemic regions, such as Alaska and Gambia. Another study was conducted in a low endemic region determining the long-term immunogenicity and efficacy of hepatitis B vaccine in men who have sex with men. Our individual does not belong to a HBV infection risk group, and, is born and raised in the Netherlands, a low endemic region with a HBsAg prevalence of 0.2% [6]. Moreover, on the basis of a negative HBsAg and anti-HBc analysis, we can exclude seroprotection due to HBV infection.
3. Lippi and colleagues published that the laboratory practice error rate ranged from 0.1 to 3.0% [7]. However, in our case labelling error is very unlikely as the subsequent blood samples all had a similar migration of the M protein in the protein spectrum and the M protein was identified as IgG kappa. Serum protein electrophoresis is used in the diagnostic evaluation of multiple myeloma and the separation of proteins into multiple bands is based on their charge, size, and shape. Reanalysis of both anti-HBs measurements maintained to demonstrate an initial undetectable anti-HBs antibody level (<2 mIU/mL) and a second anti-HBs antibody level of 12.72 mIU/mL, 12 weeks after the third vaccination. This difference could not be ascribed to assay variation of the chemiluminescence assay (Elecsys® anti-HBs II, cobas e 601 module, Roche Diagnostics GmbH, Mannheim, Germany) (3.3–3.6%). Our assay variation is in line with those stated by the company (2.1–7.9%). The chance of a false positive value of the second anti-HBs level is further minimized by the observation of a further increase in anti-HBs levels in subsequent samples. We can therefore exclude laboratory error as reason for the observed hepatitis B seroprotection.

4. Serum analysis 6 weeks after the third vaccination showed undetectable anti-HBs antibodies (<2 mIU/mL). However, serum analysis 12 weeks and 6 months after the last vaccination showed an anti-HBs antibody level of 12.75 mIU/mL and 23.88 mIU/mL, respectively. Our case clearly had a delayed hepatitis B seroprotection. Smoldering MM is the most likely cause of this delayed hepatitis B seroprotection in our participant. Smoldering MM is a key stage of high clinical relevance in the monoclonal gammopathy of undetermined significance (MGUS)-MM transition. Smoldering MM fulfills the diagnostic criteria for MM, with serum paraprotein ≥30 g/L and/or clonal plasma cells ≥10% on bone marrow biopsy however without clinical CRAB symptoms (hypercalcemia, renal insufficiency, anemia and bone lesions) or end organ damage that can be attributed to plasma cell disorder. The progressive competition and replacement of normal bone marrow polyclonal plasma cells by clonal (tumor) plasma cells as disease advances from MGUS to MM might explain the encountered delayed seroprotection [8]. The increase of clonal plasma cells has multiple effects on the bone marrow, which is involved in multiple immunologic functions, including haematopoiesis, B-cell development, antibody production and depot for memory T cells [9,10].

Delayed hepatitis B seroprotection may be more common than thought, since other cases may not have been recognized or may not have been published due to incomplete data on vaccination of the individuals. Based on this case report, we conclude that delayed seroprotection should be considered previous to the diagnosis of hepatitis B vaccine non-responders in patients with hematologic malignancies. Because hepatitis B vaccination started in the 1980s, many hepatitis B vaccine non-responders have received a revaccination regimen. If more cases of genuine delayed hepatitis B seroprotection surface in patients with hematologic malignancies, a new postvaccination antibody level analysis (e.g. 1–3 months after initial blood sampling) in initially diagnosed non-responders should be considered to secure the diagnosis of hepatitis B vaccine non-responder before the commencement of a revaccination regimen. The authors also acknowledge that a panel of international experts should be nominated to work on a practice guideline on the management of hepatitis B vaccine non-responders in order to achieve consensus on diagnosis and treatment of this group. Several approaches have been proposed to induce antibody response in hepatitis B vaccine non-responders and these include increased dose of hepatitis B vaccination, intradermal injection and alternative adjuvants [11,12].

Conflicts of interest

Özgür M Koc has received research grants and travel grants from Gilead to attend scientific Congresses. All payments were invoiced by Hasselt University and were all outside the submitted work.

Jan Damoiseaux has received honorarium for lectures from Thermo Fisher Diagnostics, all payments were invoiced by the Central Diagnostic Laboratory, Maastricht UMC. All lectures were outside the submitted work.

Inge HM van Loo has no conflicts of interest.

Heloise IL Masquillier has no conflicts of interest.

Astrid ML Oude Lashof has received honorarium for lectures from GSK and Janssen-Cilag, all payments were invoiced by the department of medical microbiology, Maastricht UMC. All outside the submitted work.

Financial support

None.

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report. A copy of the written consent is available for review by the Editor of this journal.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.10.022.

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