Nonresponse to intramuscular vaccination: An unmet need in hepatitis B vaccination

Hepatitis B virus (HBV) infection afflicts about 400 million people worldwide, half of which are infected perinatally or during early childhood via vertical and/or horizontal routes, respectively. HBV infection is also responsible for 500,000 to 1.2 million deaths/year due to chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC).[1] Antiviral agents and interferon represent the drugs of choice for the treatment of HBV infection, however, these may be ineffective in some clusters; therefore, prophylactic approaches, such as vaccination, become essential to prevent viral infection.[1] According to the National Vaccine Prevention Plan (PNPV) schedule, the vaccine is administered intramuscularly in three doses of 20 μg HBV vaccine at 0, 1, and 6 months intervals, ensuring a long lasting serologic immunity in 95% of healthy individuals.[2,3] Nevertheless, the response to HBV vaccine is variable among vaccinated subjects, and only anti-HBs antibody level greater than 100 IU/L is considered "protective." Although anti-HBs antibody level greater than 10 IU/L is defined as "appropriate" immune response, data suggest that anti-HBs antibody level between 10 and 100 IU/L might indicate an incomplete response to the HBV vaccine and places patients at risk of loss of immunity against HBV infection.[2,3] Accordingly, it has been reported that 5% of the general population, especially in advanced age, and 20% of population suffering from chronic diseases, including those affected by diabetes, human immunodeficiency virus infection, end-stage renal disease (ESRD), hypoalbuminemia, celiac disease, and inflammatory bowel disease, are unable to mount a protective response and they can be defined as "nonresponders."

The causes of nonresponse are not fully understood and many confounding factors, including the lack of prospective findings between time of vaccination and development of the immune response, have contributed to maintaining this uncertainty.[4] The inability to mount anti-HBs antibody following conventional vaccination, the development of mutants, the decline of antibody response rates after age 40 years, and predisposing genetic factors (human leukocyte antigen [HLA] alleles, cytokine and chemokine gene polymorphisms), are the mechanisms most commonly hypothesized causing an "imperfect-vaccine response" in vaccinated subjects.[4] Moreover, it is also possible that a person who does not respond to the HBV vaccine may already be infected with HBV.[4]

Several strategies to vaccinate patients who did not respond to standard HBV vaccine have been proposed. These studies provided robust findings on increased dose vaccination and accelerated frequency to stimulate an appropriate immune response in high-risk individuals.[4,5] Taking advantage of the high number of antigen presenting dendritic cells resident in the dermis as well as their ability to activate the immunogenic cells, the intradermal (ID) administration of the HBV vaccine has been proposed, resulting in a significantly higher immune response when compared to the intramuscular (IM) route, while also associated with a good safety profile.[4] Firstly, the combined use of the ID and IM routes in patients suffering from ESRD provided very promising effects as assessed by the evidence that all enrolled patients developed sero-protection (anti-HBs antibody titre >100 mIU/mL).[6] Successively, in their randomized study performed on 50 chronic dialysis patients who did not develop a seroconversion rate after a reinforced protocol of HBV vaccine given by IM route, Fabrizi *et al*.[7] showed that seroconversion rates and proportion of patients who developed protective anti-HBs titers were significantly higher in ID compared to IM patients. Similarly, a higher percentage of "responders" in the group of patients who were administered the HBV vaccine intradermally, as well as a trend toward longer duration of seroprotection, in spite of a lower amount of antigen administered with ID route, was also reported.[7]

An improved immunogenicity has also been reported in a study performed on 100 nonresponsive health care workers to standard vaccine who failed to seroconvert after 3 doses plus booster vaccine; a single dose of the triple S recombinant produced seroconversion in more than half of the participants ($n = 69$).[8] In this issue of the Journal, Hanif *et al*[9] firstly documented the effectiveness of ID HBV vaccination in patients not responding to the conventional IM route, suggesting that this approach might allow a decrease in infection rate not only in the

general population but also in the vulnerable subjects such as the hemodialysis (HD)-dependent population. However, although a better ID response was documented in HD-dependent population with anti-HBs antibody titer >100 IU/L, this finding was not statistically relevant. In addition, the authors did not investigate the long-term effect of HBV vaccination. Follow-up completeness is a pre-requisite for reliable outcome assessment, and the lack of a follow-up period in the previous studies correlates inversely with the accuracy of outcome estimates, with the risk of selection bias, and with the credibility of study data. Moreover, this study did not explore the role of HLA on negative response to HBV vaccine, currently hypothesized as one of the most reasonable cause of lack of response to HBV vaccination. Lastly, although the authors stated that the absence of hypertension and a younger age seemed to be a better predictor of immune response, they documented neither the potential effect of anti-hypertensive treatment nor the influence of age on the immune response in patients receiving HBV vaccine, thus providing insufficient data on these issues.[9] What is the benefit of vaccinating patients with chronic liver disease, which specific vaccinations should be given to these patients, what are some of the obstacles to vaccination among this cluster of subjects, and how clinicians can improve the response rates in this population remain research fields to be investigated.[10,11]

Alternative routes of administration, such as nasal and oral vaccines, are also being actively investigated.[4] The co-administration of adjuvants or another vaccine in addition to the common HBV vaccine would seem to enhance the immune response globally.[4] Finally, a booster vaccination might be required for a complete prevention of HBV infection and it is recommended if antibody concentration declines to below 10 mIU/mL, according to the risk of exposure to HBV.[4]

However, currently, there is not sufficient evidence that these alternative approaches can significantly improve seroconversion to immune status and, moreover, no cost-effectiveness studies are still available to support them. Future studies, including randomized controlled clinical trials, should be specifically designed to investigate seroconversion rates with different therapeutic management options. Despite the fact that the control of HBV infection *via* vaccination has significantly decreased the new infection rates as well as chronic liver disease and HCC worldwide, to date, the unresponsiveness to HBV vaccination still represents a critical issue, because non-responder subjects represent a significant reservoir of viral agent. Moreover, although checking the post–HBV vaccination status for anti-HBs antibody is recommended in populations with risk factors for HBV transmission or those at risk for HBV reactivation, and several biomarkers have recently been proposed to reflect the immune impairment that results in failure of the HBV vaccination,[12] to date, these strategies have not sufficiently ameliorated the problem. Hence, the need for an improved vaccine persists, especially in high-prevalence countries and high-risk individuals.

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