

Hepatitis B vaccine in celiac disease: Yesterday, today and tomorrow

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Abstract

Some studies showed that in celiac patients the immunological response to vaccination is similar to that one found in general population except for vaccine against hepatitis B virus (HBV). The non-responsiveness to HBV vaccine has also been described in healthy people, nevertheless the number of non-responders has been demonstrated to be higher in celiac disease (CD) patients than in healthy controls. Several hypothesis explaining this higher rate of unresponsiveness to HBV vaccine in CD patients have been described, such as the genetic hypothesis, according with CD patients carrying the disease-specific haplotype HLA-B8, DR3, and DQ2, show a lower response to HBV vaccine both in clinical expressed CD patients and in healthy people carrying the same haplotype. On the other hand, it has been demonstrated that the gluten intake during the vaccination seems to influence the response to the same vaccine. Moreover, it has been demonstrated a possible genetic predisposition to hepatitis B vaccine non-responsiveness likely due to the presence of specific human leukocyte antigen haplotypes and specific single nucleotide polymorphism in genes of cytokine/cytokine

receptors and toll like receptors, but the pathogenic mechanism responsible for this low responsiveness still remains unclear. The aim of this review is to focus on the possible pathogenic causes of unresponsiveness to HBV vaccine in CD patients and to propose an alternative vaccination schedule in order to improve the responsiveness to HBV vaccine in this at-risk patients.

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Key words: Celiac disease; Non responders; Hepatitis B vaccine; Vaccination schedules

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INTRODUCTION

It is estimated that more than one third of the world's population has been infected with the hepatitis B virus (HBV), causing acute and chronic liver diseases, ranging from fulminant hepatitis to cirrhosis and eventually hepatocellular carcinoma, with an incidence of 620 000 death per year^[1-3].

On this regard, in order to prevent this serious health problem, since 1982 a safe and effective hepatitis B vaccine has been available. The first vaccines were plasma-derived, which contained purified hepatitis B surface antigen (HBsAg) obtained from the plasma of people with chronic HBV infection. In the following years, recombinant DNA hepatitis B vaccine has been developed, containing purified HBsAg obtained by culturing genetically engineered yeast or mammalian cells carrying the *HBsAg* gene. Currently recombinant DNA hepatitis B vaccines are predominant-

ly being used, while plasma-derived hepatitis B vaccines are still being used in several low-income countries^[4].

At the beginning, the hepatitis B vaccine was considered for use in high risk individuals for acquiring HBV infection. Actually, it has become more widely used and recommendations for hepatitis B vaccination have been extended to all infants in an attempt to achieve protection against HBV infection^[5]. Despite these recommendations, 8 countries in Northern Europe (Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, and the United Kingdom) have yet to implement such a policy, currently adopting an “at-risk” strategy. In 2007, Zuckerman *et al*^[6] recommend a reassessment in these country of their hepatitis B prevention strategies considering the difficulty in identifying all at-risk individuals and the lack of effectiveness of the vaccination on at-risk subjects in reducing the overall incidence of hepatitis B.

Italy was one of the first countries to implement an universal strategy of hepatitis B vaccination^[7]. Since 1984 HBV vaccination has been recommended and offered free of charge by the National Health Service to high-risk groups-*e.g.*, family members of HBsAg carriers, healthcare workers and in 1991, vaccination became mandatory for all new born and for twelve year-old adolescents^[8].

Consequent to this global strategy, a decrease in prevalence of chronic HBV infection among vaccinated children and adolescents has been documented, including people living in high risk area such as China, Hong Kong, Taiwan, the Gambia, Senegal, Alaska and Italy^[9].

Usually, a single course of three doses of hepatitis B vaccine administered in a variety of schedules, such as at birth, 1 and 6 mo schedule, the 6, 10 and 14 wk doses and the 2, 4 and 6 mo schedule induces protective levels of antibody to HBsAg in nearly 95% of healthy infants and children^[10].

The antibody response to hepatitis B vaccine has been found occurring in more than 90% of the healthy vaccinated subjects^[11-13]. However some studies showed that serum anti-HBs levels decreases with the time following vaccination^[14,15]. Several factors, such as age, body mass index and smoking at the time of vaccination, have been found to be associated with a lower rate of antibody response to hepatitis B vaccine^[16,17], and the decline of HBs antibody titer seemed mainly to be proportional to the antibody titer originally obtained^[18].

Long-term follow-up studies of newborn vaccination showed that antibodies become negative in 15%-50% among the vaccine responders within 5 to 10 years^[19-21].

The clinical significance of the disappearance of specific antibodies in immunocompetent patients responders to previous vaccination remains object of discussion.

Successfully vaccinated people who have lost antibodies after primary vaccination, usually show a rapid anamnestic response when boosted. This means that the immunological memory for HBsAg can outlast antibody

detection, providing long-term protection against the disease. Hence, there is consensus that there is no need to administer booster doses of vaccine to ensure long-term protection in immunocompetent patients^[22-25].

On the other hands some authors suggest specific strategies for the vaccination of certain groups of people at high risk such as haemodialysis, celiac and thalassemia patients^[26-31].

Vaccinated subjects with an anti-HBs titer less than 10 mIU/mL after completion of primary vaccine series are called “no responders”.

Several factors have been associated with a non response to the HBV vaccine. These include inappropriate vaccine storage conditions, vaccination in buttocks, obesity, smoking, drug abuse, infections^[32]. There are also chronic conditions, such as chronic alcoholism, chronic kidney disease, human immunodeficiency virus infection, immune-suppression, type I Diabetes Mellitus and Celiac disease that are characterized by a lower response to HBV vaccination^[33-45]. Recently, it has been demonstrated a possible genetic predisposition to hepatitis B vaccine non-responsiveness likely due to the presence of specific human leukocyte antigen (HLA) haplotypes and specific single nucleotide polymorphism (SNP) in genes of cytokine/cytokine receptors and toll like receptors (TLR)^[42,46], but the pathogenic mechanism responsible for this low responsiveness still remains unclear.

CELIAC DISEASE AND HBV VACCINE: THE HISTORY

Celiac disease (CD) is an autoimmune disorder characterized by a permanent intolerance to ingested gluten, which results in immunologically mediated inflammatory damage to intestinal mucosa^[47]. Genetic, environmental and immunological factors seem to be responsible for the disease.

CD is usually characterized by various gastrointestinal (GI) symptoms (*e.g.*, diarrhea, malabsorption, weight loss) associated with consumption of grains containing gluten (wheat, barley, rye). Although some CD patients may have primarily GI symptoms, CD may be detected due to associated extra intestinal disorders, even without GI symptoms, or due to screening for CD based on a positive family history. CD has a strong association with HLA-DQ2 and HLA-DQ8^[48]. HLA-DQ2 is present in 90% to 95% of patients with CD^[49].

The link between HBV infection and celiac disease seems to be controversial. Relatively little data exist on the relationship between HBV and CD, although one third of the world's population (around 2 billion people) have been infected with HBV. It has been reported that the response rate to HBV vaccination in CD-infected individuals is lower (30%-50%) than in the general population (4%-10%)^[42,43] (Table 1). Recently, it has been hypothesized that non intestinal inflammatory diseases may trigger immunologic gluten intolerance in suscepti-

ble individuals, and HBV as far as hepatitis C virus (HCV) were thought to be suitable candidates. However this assumption is still matter of debate. Relatively few data exist on the relationship between HBV and CD. It could be speculated that HBV as well as HCV infections may trigger immunologic gluten intolerance in genetically susceptible people and that chronic HBV segregates a higher percentage of CD patients^[50,51]. However this assumption is still a matter of debate.

Possible activation of CD due to the treatment of hepatitis infection is another controversial point. There have been some reports indicating that autoimmune disorders such as insulin-dependent diabetes mellitus and celiac disease can develop during treatment with interferon (IFN)- α for viral hepatitis because of its immune modulatory properties^[52,53]. CD activation during interferon α or interferon α plus ribavirin therapy has recently been observed in HCV-positive patients^[54], confirming that IFN- α therapy could trigger CD in susceptible subjects during treatment. In the study of Leonardi *et al.*^[30], although evidence suggested that IFN- α can activate CD4T cells in the lamina propria and cause intestinal tissue damage^[55], no patient treated in childhood showed any serological marker of CD at the time of the present study. Due to the small sample size authors could not claim that there was no association between CD and HBV, although a sample size more representative of the prevalence of CD in Italy should help to better examine the relationship between CD and HBV.

Some studies showed that in celiac patients the immunological response to vaccination is similar to that one found in general population except for vaccine against HBV^[42,56]. On this regard, it is well known that unresponsiveness to hepatitis B vaccine in healthy people has been attributed to failure of class II major histocompatibility complex molecules in the interaction with processed protein antigen, in the stimulation of T-helper cells, or in both^[57,58].

Analysis of previous studies suggested a very high incidence of a particular extended HLA haplotype in non responders to hepatitis B vaccine. In fact, homozygotes for HLA-B8, DR3, and DQ2 were found to have a significantly higher incidence of hepatitis B vaccine non-response^[58]. In 1989, Alper *et al.*^[59] prospectively vaccinated 5 homozygotes and 9 heterozygotes for extended MHC haplotype (HLA-B8, SC01, DR3). Four of the 5 homozygotes produced low levels of HBsAb two months after their third HBV vaccination, whereas all 9 heterozygotes had significantly higher titers of HBsAb. In 1995, Livenson *et al.*^[60] studied 153 patients with end-stage renal disease immunized with a recombinant HBV vaccine. Homozygotes for HLA-A1, HLA-B8, HLA-DR3 and HLA-DQ2 were found almost exclusively in the non-responder group and a significant higher number of heterozygotes for these alleles was found in the non-responder group compared to the responders^[59]. In the same year, Martinetti *et al.*^[61] performed an HLA study in

Table 1 People who have anti-HBs titre after completion of primary vaccine series less than 10 mIU/mL

	Celiac patients (no responders, %)	Control subjects (no responders, %)
Leonardi <i>et al.</i> ^[30]	30/60 (50)	7/60 (11.7)
Ahishali <i>et al.</i> ^[42]	8/25 (32)	0/20 (0)
Zingone <i>et al.</i> ^[43]	31/51 (60.7)	13/48 (27.08)
Ertekin <i>et al.</i> ^[44]	20/52 (38.5)	2/20 (10)
Noh <i>et al.</i> ^[56]	13/19 (68.4)	-

9 absolute non-responder (serum titer of anti-HBsAg < 2 mIU/mL) and 8 low-responder (serum antibody level between 2 and 9.9 mIU/mL) infants who underwent, in neonatal period, HBV vaccination. The investigation pointed out that many of these subjects carry HLA haplotypes classically involved in autoimmune diseases: HLA DR7, DQ2, DR4, DQ8 and DR3. Further Godkin *et al.*^[58] investigated the binding affinities of envelope and core peptides of HBV to particular HLA glycoproteins, and their data supported the direct involvement of HLA-DR3 in HBV vaccine non responsiveness.

Since the HLA-DQ2 haplotype is over-represented in celiac population, it has been postulated that this genetic profile may play a crucial role in predisposing celiac patients to a lower grade of immunization to hepatitis B vaccine^[62].

On the other hand some studies argue that in celiac individuals gluten intake at the time of vaccination may influence the vaccine-induced immune response^[41,44].

Nevertheless all these hypotheses are still argument of debate and no responsiveness of celiac patients to the HBV vaccine remains a significant public health problem, since the worldwide spread of the disease although there is no convincing evidence that patients with viral hepatitis B carry an increased risk of celiac disease^[63].

In 2003, Noh *et al.*^[62] studied 19 celiac patients and found that 13 did not respond to vaccination. HLA typing was performed on 15 of these subjects (13 non responders and two responders). All tested subjects were apparently either homozygous or heterozygous for DQ2. The authors postulated that the non responsiveness to the hepatitis vaccine in celiac patients is due to the suppression of the Th2 response and to the B cell differentiation due to the high protection performed by the IFN-gamma.

In 2009, Leonardi *et al.*^[30] retrospectively analysed the response to HBV vaccine in 60 celiac patients and they found that 30 of 60 CD patients (50%) and 7 of 60 control subjects (11.6%) were non-responders to HBV vaccination ($P < 0.0001$).

It is well known that in celiac disease the intestinal damage is caused by interaction between specific deaminated glutamine residues of gliadin and HLA-DQ2 or DQ8 molecules^[63].

Both HBsAg protein fragments and gliadin peptides bind to HLA-DQ2 molecules, and their competition

may result in a defective antibody response against the recombinant HBsAg vaccine in active CD^[49].

In 2008, Nemes *et al*^[41] studied 128 children and adolescent with celiac disease and 113 age-matched control subjects. For all celiac patients diet compliance and CD activity were monitored by measurement of antibodies against transglutaminase and endomysium. The authors demonstrated that the rate of primary non-response to the standard regimen of recombinant HBV vaccination was surprisingly high (74.1%) in undiagnosed and untreated celiac adolescents.

In 2010, Ertem *et al*^[64] evaluated anti-HBs titer in celiac patients and healthy children. They found that anti-HBs negativity was significantly higher in celiac patients than in healthy controls. They also demonstrated that response to HBV vaccine in children with CD who were compliant with the gluten free diet (GFD) was not different from that found in the healthy population.

In 2010, even Zingone *et al*^[44] hypothesized the possible role of dietary gluten in induction of a suboptimal immune response in celiac patients. They studied 51 celiac patients who were on a GFD and were negative for anti-transglutaminase-IgA antibody at the time of testing. Eleven years after primary vaccination the proportion of vaccinated subjects with anti-HBs antibody ≥ 10 mIU/mL was significantly lower in celiac than in controls (68.6% *vs* 91.7%; $P < 0.01$). Only three (5.9%) celiac patients were on GFD at the time of primary vaccination. Fourteen out of 16 (87.5%) celiac patients and all controls with anti-HBs < 10 mIU/mL received a booster dose of vaccine. Two weeks after the booster dose, 4 (28.6%) celiac patients and 3 (75%) controls showed an anamnestic response. Three out of 10 celiac patients who did not respond to the booster dose agreed to complete a new vaccine cycle. One month after vaccination completion, all showed anti HBs between 10 and 100 mIU/mL. Thus, the authors concluded that the gluten intake at the time of vaccination could decrease the efficacy of the same vaccination.

To confirm the role of gluten in the unresponsiveness to HBV vaccine in celiac patients, Ertekin *et al*^[45] observed 52 children with CD and 20 age healthy children who received HBV vaccination according to the standard immunization schedule. They found that anti-HBs positivity was significantly higher in celiac patients who were compliant to GFD than in those who were noncompliant.

Even in the study led by Leonardi *et al*^[30], the authors found a significantly higher number of responders in patients younger than 18 mo at diagnosis and a significantly lower number of responders in adolescent patients older than 14 years at diagnosis. This data confirms that in celiac patients a complete cycle of revaccination during a well controlled GFD might be more effective than the primary vaccination performed on a gluten-containing diet.

FUTURE DIRECTION

We have underlined how celiac disease is characterized by a low responsiveness to vaccinations such as HBV vaccine, and both for the widespread of celiac disease, that is high in prevalence of morbidity, and for the wide range of not response to HBV vaccine. The problem of unresponsiveness could represent a matter of world health, because the group of non-responders patients could be considered as a large reservoir of HBV-susceptible people that will persist as healthy carriers, leading to a diffusion of the diseases even in healthy subjects.

This problem drew the literature research towards possible reassessments of immunization strategies to protect this population and to achieve the goal of universal protection.

It would be important, therefore, to assess the possible vaccination strategy in order to reduce this “healthy-reservoir” of infection. On this regard, new vaccination strategies for celiac patients were proposed in literature: the first one the use of booster doses of HBV vaccine by intramuscular route (IM), the second one is the performance of booster doses of HBV vaccine by intradermal route (ID).

In their scientific paper, Zingone *et al*^[44] gave an IM dose of HBV vaccine to celiac patients with anti HBs titre < 10 mIU/mL and found that, one month after vaccination completion, all showed anti-HBs titer between 10 and 100 mIU/mL. They concluded that celiac patients may require higher doses of vaccine and/or more injection to achieve full protection. Supporting this hypothesis, in 2008, Ashaili *et al*^[43] studied 25 celiac patients and control subjects who were negative for anti-HBs. HBV vaccine was administered to all celiac patients and control subjects in three doses, at month 0, 1, 6 by intramuscular injection into the deltoid muscle. Four weeks after the last dose, anti-HBs was measured quantitatively. Seventeen celiac patients (68%) and all control subjects (100%) were found to respond to HBV vaccination^[44].

On the other hands, supporting the hypothesis of a possible role of gluten in the unresponsiveness to HBV vaccine in celiac patients and in severe liver disease^[40], Nemes *et al*^[41] recommended a revaccination by IM route for celiac patients after treatment with gluten-free diet. They administered a dose of IM vaccine to anti-HBs-negative patients with CD during a controlled gluten-free diet and found that 97.3% of them seroconverted after revaccination. They concluded that the no responder status to primary HBV vaccination is not permanent in CD and may improve after gluten exclusion.

The second strategy addresses on the use of ID booster of HBV vaccine in non-responders patients. The rationale of this is that in contrast to IM, which relies on a T-cell mediated response, vaccines introduced directly into the skin activate a dendritic-cell-mediated immune response through a lower doses of antigen^[65].

According to these results, in 2010, Leonardi *et al*^[66]

revaccinated celiac patients who were non-responders to HBV vaccination with a 2 mg dose of recombinant hepatitis B vaccine administered intradermally. After the first ID dose we found that 40% of patients achieved anti-HBs titer ≥ 1000 mIU/mL, 20% between 100 and 1000 mIU/mL, and 15% between 10 and 99 mIU/mL.

In order to compare the efficacy and the safety of the two HBV vaccination strategy (IM *vs* ID) in a non-responder population, in 2011, Leonardi *et al.*^[67] re-vaccinated non-responder celiac patients with ID or IM vaccine. The Authors found a higher percentage of “responders” after the first booster dose (ID = 76.7% *vs* IM = 78.6%) and a deeper increase after the third dose (ID = 90% *vs* IM = 96.4%) of vaccine in both groups. These data seem to suggest that both ID and IM route are effective options to administer a booster dose of HBV vaccine in celiac patients. However the ID route seems to be a better vaccination strategy, as demonstrated by the higher percentage of patients with an anti-HBs titer > 1000 IU/L found in ID than in IM group.

In literature there are no other studies comparing the efficacy of HBV vaccination administered by IM or ID route in celiac patients. The two different methods are extensively compared in other pathologic conditions in which we observed a low responsiveness to HBV vaccination. For example in a meta-analysis about the HBV vaccination response in patients with chronic kidney disease, the authors found that pooling of study results demonstrated a decreased risk of failure to respond to HBV vaccine among patients who were vaccinated by intradermal *vs* intramuscular route^[27].

There is another topic that should be considered. Actually it is still not clear if non-responder patients are characterized by an immunological anergy since birth, or they lose their immune competence during the time. With this regard, there is general consensus in literature that successfully vaccinated people who have lost antibodies years after primary vaccination usually show a rapid anamnestic response when boosted^[68]. This means that the immunological memory for HBsAg can outlast antibody detection, providing long-term protection against the disease and the development of the carrier state. Hence, there should be no need to administer booster doses of vaccine to ensure long-term protection in subjects initially responding to vaccination^[22-25]. Thus, it is still not clear if celiac non-responders show an immunity anergy since birth and do not respond since the first dose of vaccination or they lose their antibody protection with the flow of time, as physiologically happens in normal people, even if in a shorter period of time, remaining, thus, protected by an intra-cellular immunity.

For this reason it would be important an early identification of potential “pure” non-responsive patients through the identification of specific markers of unresponsiveness. Recent acquisitions show a possible role of toll-like receptors, cytokines and cytokine receptors polymorphisms associated with no response to hepatitis B

vaccine in healthy population. As a matter of fact, Chen *et al.*^[46] hypothesized that the variations in these structures may act individually or cooperatively in the influence of the duration and intensity of immune response elicited by the hepatitis B vaccine, finding that 4 specific SNPs in the *IL-4*, *IL-4RA*, *IL-13* and *TLR2* genes were closely associated with the serum anti HBsAg response to HBV vaccine. These cytokines and TLR2 seemed to be associated with a status of hepatitis B vaccine-induced protective humoral immune response. If an early identification of responsiveness to HBV vaccine could be speculated in general population by the analysis of specific SNPs, it could be postulated the use of the same analysis in celiac patients, in whom the rate of non-responsiveness is higher, representing a specific marker of the “pure” non-responders. Nevertheless, further studies should clarify the role of these polymorphisms and their possible use as markers of unresponsiveness to HBV vaccine.

In conclusion, we suggest that all patients with CD should be revaccinated to achieve the goal of universal protection. In consideration of the possible relationship between anti-HBs titers and compliance with GFD, they should be revaccinated after the decrease of specific celiac antibodies, that usually occurs after about 1 year of a strict GFD. We also suggest the use of the intradermal route for the revaccination of these patients. The increase of anti-HBs antibodies is in fact satisfactory after ID injection in all patients, a lower dose of the vaccine can be used for immunization and the cellular immune responsiveness to HBsAg can be easily assessed by the development of a skin reaction at the injection site^[31]. Thanks to the appearance of this reaction there is no need to test the serum anti-HBs concentration after the booster dose to value the vaccine efficacy, and this could represent a less expensive strategy for the Health Organization to perform HBV booster doses^[69]. A recent retrospective cost-benefit analysis of ID hepatitis B vaccination reported a cost reduction exceeding 50% compared with a standard IM vaccine regimen^[63]. Moreover the ID route would allow a lower performance of venous withdraws in all patients, reducing the costs linked to serial follow-up withdraws. In literature it is also demonstrated that strong immunological memory persists more than 10 years after immunisation of infants and adolescents with a primary course of vaccination^[70]. Furthermore, we suggest to administer a booster dose of vaccine every 10 years to all celiac patients, independently their status of “pure” unresponsiveness, and as they are genetically predisposed to lose their anticorporeal memory, these boosters would favour a better immunologic strategy in order to protect celiac non-responders from a possible HBV infection.

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