

WJG 20<sup>th</sup> Anniversary Special Issues (9): Hepatitis B virus**Hepatitis B vaccine by intradermal route in non responder patients: An update**

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Author contributions: Filippelli M and Leonardi S participated in the conception and design of the review, manuscript writing and revision; Lionetti E, Gennaro A, Lanzafame A, Arrigo T, Salpietro C and La Rosa M participated manuscript writing; all authors read and approved the final manuscript.

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Received: November 29, 2013 Revised: March 12, 2014

Accepted: April 27, 2014

Published online: August 14, 2014

**Abstract**

Vaccination is the main prophylactic measure to reduce the mortality caused by hepatitis B virus (HBV) infection in healthy subjects since the immune response to hepatitis B recombinant vaccination occurs in over 90% of general population. Individuals who develop an anti-HBs titer less than 10 mIU/mL after primary vaccination cycle are defined "no responders". Many factors could cause a non response to the HBV vaccination, such as administration of the vaccine in buttocks, impaired vaccine storage conditions, drug abuse, smoking, infections and obesity. Moreover there are some diseases, like chronic kidney disease, human immunodeficiency virus infection, chronic liver disease, celiac disease, thalassaemia, type I diabetes mellitus, down's syndrome and other forms of mental retardation that are characterized by a poorer response to HBV vaccination than healthy subjects. To date it is still unclear how

to treat this group of patients at high risk of hepatitis B infection. Recent studies seem to indicate that the administration of HBV recombinant vaccine by the intradermal route is very effective and could represent a more useful strategy than intramuscular route. This review focuses on the use of anti hepatitis B vaccine by intradermal route as alternative to conventional intramuscular vaccine in all non responder patients. A comprehensive review of the literature using PubMed database, with appropriate terms, was undertaken for articles in English published since 1983. The literature search was undertaken in September 2013.

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**Key words:** Hepatitis B virus; Vaccine; Intradermal route; Non responders; Update

**Core tip:** Vaccination is the principal strategy to reduce the morbidity and mortality caused by hepatitis B virus. Vaccinated subjects with an hepatitis B surface antibody titer less than 10 mIU/mL after primary vaccine series are considered "no responders". There are chronic conditions that are characterized by a poorer response to hepatitis B virus vaccination than healthy subjects. To date it is still unclear how to treat this group of patients at high risk of hepatitis B infection. This review focuses on the use of anti hepatitis B vaccine by intradermal route as alternative to conventional intramuscular vaccine in all non responder patients.

Filippelli M, Lionetti E, Gennaro A, Lanzafame A, Arrigo T, Salpietro C, La Rosa M, Leonardi S. Hepatitis B vaccine by intradermal route in non responder patients: An update. *World J Gastroenterol* 2014; 20(30): 10383-10394 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i30/10383.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i30.10383>

## INTRODUCTION

More than 10<sup>12</sup> of people in the globe are infected by hepatitis B virus (HBV), of which more than 400 million become chronic carriers and more than 700000 individuals die annually due to complications caused by acute or chronic HBV infection<sup>[1,2]</sup>. In spite of improvements in hygienic conditions and in anti-viral therapy, eradication of HBV has not been obtained and to date vaccination is the only strategy to prevent this infection<sup>[1]</sup>. Since HBV vaccination was introduced, many advances (*e.g.*, use of recombinant technology) have been made in order to increase its safety and immunogenicity<sup>[3]</sup>. HBV vaccination is able to stimulate a long-term immune response in healthy individuals, since the antibody response occurs in over 90% of the immune-competent individuals after three doses of 20 µg HBV vaccine administered at 0, 1, and 6 mo intervals<sup>[4,5]</sup>. Considering this percentage of vaccine efficacy in healthy subjects, it has been postulated that between 537000 and 660000 HBV-related deaths could be prevented each year with a mass vaccination<sup>[6]</sup>. For this reason health authorities in the world suggest to vaccinate also all people with chronic conditions<sup>[1,7,8]</sup>.

A sero-protection response is defined by an hepatitis B surface antibody (anti-HBs) titer  $\geq 100$  IU/L. An anti-HBs titer  $> 10$  IU/L is considered as a “protective” titer, although it could not confer protection after HBV contact in every case (poor response)<sup>[9,10]</sup>.

Individuals who develop an anti-HBs titer less than 10 mIU/mL after three doses of vaccine are defined “no responders”. Many factors could cause a non response to the HBV vaccination, such as administration of the vaccine in buttocks, impaired vaccine storage conditions, drug abuse, smoking, infections and obesity<sup>[11]</sup>. In recent years it has been suggested an important role of genetic factors in predisposing to hepatitis B vaccine unresponsiveness. This factors are represented by specific human leukocyte antigen (HLA) haplotypes and specific single nucleotide polymorphism in genes of cytokine or cytokine receptors and toll like receptors<sup>[12,13]</sup>.

The unresponsiveness to hepatitis B vaccination is an important problem, because non-responder subjects represent a great container of HBV-carriers. This problem led the researchers to propose new immunization strategies in order to reach the “universal protection”.

## INTRADERMAL ROUTE VACCINATION: THE RATIONAL

Many vaccines are administered by intramuscular route although the muscle is a poorly immunogenic organ<sup>[14,15]</sup>. On the other hand the skin is a more immunogenic site for vaccination due to presence in the dermis of dendritic cells, capable of presenting antigens and stimulating innate and adaptive immune responses. In fact skin protects the body from microbial infection using both its physical barrier and its immunological function performed by dendritic cells<sup>[16]</sup>.

The main target of intradermal vaccination is represented by Langerhans cells and macrophages in the dermis that are specialized in antigen presentation due to their ability to express high levels of class II major histocompatibility complex (MHC) and CD1 molecules<sup>[17,18]</sup>. These dendritic cells process the antigens released in the dermis, re-expressing part of them as peptide-MHC complexes on the surface and after they have acquired immune stimulatory capacity, migrate to the para-cortical area of the regional lymph nodes, where they present the antigens to CD8<sup>+</sup> and CD4<sup>+</sup> T-lymphocytes<sup>[19,20]</sup>. Different signaling pathways are involved in promoting this mechanism, such as increased expression of MHC antigens, interleukin (IL)-1 $\beta$ , IL-6, IL-12 and tumor necrosis factor- $\alpha$ <sup>[21]</sup>. Furthermore the release of antigens directly in the dermis affects the migration of dendritic cell precursors from the blood stream to the dermis<sup>[19,22,23]</sup>. CD8<sup>+</sup> T cells clonally expand and become effector and memory T cells, while CD4<sup>+</sup> T cells promote the differentiation of B cells into antibody producing plasma cells<sup>[20]</sup>. This route is more immunogenic, due to the direct release of antigens to the skin immune system, compared with intramuscular vaccination that stimulates T-cell response, due to the lack of dendritic cells in muscles. Studies conducted on smallpox, rabies, Bacillus Calmette-Guérin and hepatitis B vaccines supported this hypothesis<sup>[24,25]</sup>.

After the introduction of the Mantoux method<sup>[26]</sup> and the experience with intradermal administered “typhoid fever” vaccine<sup>[27]</sup>, the intradermal route has been investigated in order to evaluate safety and immunogenicity of several vaccines which could be administered by intradermal route. These studies were conducted on vaccination against measles<sup>[27,28]</sup>, cholera<sup>[29]</sup>, rabies<sup>[30,31]</sup>, hepatitis B<sup>[32,33]</sup> and poliomyelitis<sup>[34,35]</sup>.

Vaccination by intradermal route was used during the smallpox eradication campaign by employing a bifurcated needle to deposit a dose of live vaccine into the skin<sup>[36]</sup>. In addition Bacillus Calmette-Guérin vaccination is to date administered by intradermal route using the Mantoux technique, which is based on the injection of a hypodermic needle directly into the skin<sup>[37,38]</sup>.

Since 1991, the World Health Organization has promoted in developing countries the use of the Mantoux method as a less expensive and effective practice for vaccination against rabies<sup>[39]</sup>.

In recent years the administration of influenza vaccine by intradermal route has been introduced in many parts of the world due to its greater immunogenicity compared to vaccination by intramuscular route<sup>[40]</sup>. In this case, intradermal administration of the vaccine is performed using a micro-needle syringe directly injected into the skin<sup>[41]</sup>.

Moreover economic studies seem to suggest that the cost-savings advantages of administering vaccines by intradermal (ID) route, could be significant<sup>[42,43]</sup>.

In addition the cellular immune response to hepatitis B surface antigen (HBsAg) evoked by ID route can be

**Table 1** Studies published since 1983 on vaccination against hepatitis B virus by intradermal route and percentage of positive response

Ref.	Categories of patients	Patients (n)	Dose for ID administration	Positive response
Marangi <i>et al</i> <sup>[72]</sup>	Chronic kidney disease	5	5 ig/dose until the protective titer	100%
Fabrizi <i>et al</i> <sup>[76]</sup>	Chronic kidney disease	25	16 doses of 5 ig/dose	100%
Chanchairujira <i>et al</i> <sup>[74]</sup>	Chronic kidney disease	25	7 doses of 10 ig/dose every 2 wk	92% at 7 mo
Barracough <i>et al</i> <sup>[75]</sup>	Chronic kidney disease	30	10 ig/dose every week for 8 wk	79% at 24 mo
Bunupuradah <i>et al</i> <sup>[109]</sup>	HIV- children	41	2 ig/dose at mo 0, 2 and 6	90.2% at month 7
Launay <i>et al</i> <sup>[108]</sup>	HIV- adults	144	4 ig × four doses at weeks 0, 4, 8, and 24	77% at week 28
Dhillon <i>et al</i> <sup>[113]</sup>	Chronic liver disease	42	40 ig/dose maximum of three doses	69% after the third dose
Leonardi <i>et al</i> <sup>[123]</sup>	Celiac disease	20	2 ig/dose maximum of four doses	90%
Leonardi <i>et al</i> <sup>[126]</sup>	Celiac disease	30	2 ig/dose x four or five doses every 4 wk	90% after the third dose
Li Volti <i>et al</i> <sup>[130]</sup>	Insulin-dependent diabetes mellitus	9	3 ig/dose at the start of the study and at two, four, and six or eight week intervals	77.7%
Leonardi <i>et al</i> <sup>[148]</sup>	Thalassaemia	54	5 ig/dose every two weeks until the protective titer	96.4%
Ghebrehewet <i>et al</i> <sup>[142]</sup>	Healthcare workers	23	Two doses of 20 ig	91.3% after 1 or 2 doses
Hayashi <i>et al</i> <sup>[134]</sup>	Mentally retardation	63	4 ig/dose maximum of three doses	93.5%
Heijntink <i>et al</i> <sup>[135]</sup>	Mentally retarded patients	92	2 ig/dose maximum of four doses	92%
Hayashi <i>et al</i> <sup>[134]</sup>	Mentally retarded patients	62	4 ig/dose maximum of three doses	93.5%

ID: Intradermal; HIV: Human immunodeficiency virus.

determined by the appearance of a skin reaction at the injection site, as demonstrated by Leonardi *et al*<sup>[44]</sup> and Vitaliti *et al*<sup>[45]</sup>. The development of this reaction on the site of the intradermal injection may represent a cost-savings practice for the Health Organization to test serum anti-HBs response after the booster dose<sup>[43]</sup>.

Recently new devices for intradermal vaccination have been introduced in order to make the skin an effective and safe route for vaccine administration<sup>[46]</sup>.

## ID VACCINATION IN NON RESPONDERS PATIENTS: A REVIEW OF THE LITERATURE

There are some diseases, like chronic kidney disease, human immunodeficiency virus infection (HIV), chronic liver disease, celiac disease, thalassaemia, type I diabetes mellitus, down's syndrome and other forms of mental retardation that are characterized by a poor response to HBV vaccination<sup>[47-49]</sup>.

This review focuses on the use of anti hepatitis B vaccine by intradermal route as alternative to conventional intramuscular vaccine in all non responder patients. A comprehensive review of the literature using PubMed database, with appropriate terms, was undertaken for articles in English published since 1983. The literature search was undertaken in September 2013. All studies published on PubMed are reported on Table 1.

### Chronic kidney disease, hemodialysis and renal transplantation

Patients with advanced chronic kidney disease (CKD) have an impaired immune response to hepatitis B vaccination. In fact even using higher vaccine doses, only 50% to 85% of dialysis patients achieve a protective titer (> 10 IU/L) after hepatitis B vaccination<sup>[50-54]</sup>. Moreover

anti-HBs titer in dialysis patients tends to fall quicker than in healthy subjects<sup>[50,53,55]</sup>.

Numerous genetic and acquired factors are involved in unresponsiveness to hepatitis B vaccination. In the 70-ties of the past century, immune response to HBsAg in HBV infected hemodialysis (HD) patients was linked to HLA<sup>[56,57]</sup>. In 1990, non responders HD patients had shown to have a higher frequency of HLA-A1, B8 and DR3 than responders<sup>[58]</sup>. More recently, interleukin genotypes (examples IL10, IL-12, IL-18) were related to the anti-HBs development in response to HBsAg in HD patients<sup>[59,60]</sup>. Another factor that negatively affect the response to hepatitis B vaccination seems to be an increasing of age<sup>[61-63]</sup>. Seroconversion rate to anti-HBs positivity after vaccination was 84% in HD patients below 40 years and only 33% in those ≥ 60 years<sup>[52]</sup>. Moreover poor response to hepatitis B vaccination in dialysis patients has been linked to male gender<sup>[58,64]</sup>, low serum albumin concentration, bad nutritional status<sup>[65,66]</sup>, serological positivity for hepatitis C virus (HCV)<sup>[67]</sup> or HIV<sup>[68]</sup>, and diabetes mellitus<sup>[59,69]</sup>. Furthermore vitamin D deficiency could negatively affect antibody formation upon hepatitis B vaccination in stage 3-5D CKD patients<sup>[70]</sup>. It is well known that dialysis patients have an impaired immune function and there is a positive correlation between increase of immune abnormalities and deterioration of renal function. The best example is correlation of serum soluble CD40 levels with creatinine in non-dialyzed CKD patients. Soluble CD40 is capable to inhibit immunoglobulin production by CD154-activated B lymphocytes *in vitro* and there is a positive correlation between the serum levels of soluble CD40 and the poor response to hepatitis B vaccination<sup>[71]</sup>. The decline of the immune system in the course of CKD should represent a valid reason for vaccinating CKD patients in early stages of their renal diseases. According to European Best Practice Guidelines (2002) "patients with progres-

sive renal failure should be vaccinated against HBV preferably before the start on HD<sup>[51]</sup> and the United States Center for Disease Control and Prevention suggests to administer three further doses of intramuscular vaccine in hemodialysis patients<sup>[55]</sup>.

For CKD patients who do not respond to six doses of vaccine, there are no evidences about the use of further intramuscular doses. Different strategies have been suggested in order to increase the vaccine-induced seroconversion rate in patients with advanced CKD. In particular the ID vaccination was studied either alone or in combination with conventional intramuscular route.

Hepatitis B vaccination schedule based on the combined use of the intradermal and intramuscular routes, was elaborated in 1994 by Marangi *et al*<sup>[72]</sup> in CKD patients with serum creatinine concentration  $\geq 4$  mg/dL and gave very promising effects. The intramuscular dose of 40 micrograms of a DNA-recombinant vaccine was administered to all chronic uremic patients at 0, 1, 2 and 6 mo and two further IM booster dose at 12 and 18 mo in order to achieve an antibody titre  $> 100$  mIU/mL. Moreover intradermal inoculation of 5 micrograms of vaccine every 2 wk was administered for those patients who did not have a protective titre ( $\geq 10$  mIU/mL) even after 19 mo. All patients developed sero-protection.

Another strategy is the administration of HBV vaccination only by intradermal route. In 1997 Fabrizi *et al*<sup>[73]</sup> conducted a randomized study on 50 chronic dialysis patients who did not develop a sero-conversion rate after a reinforced protocol of hepatitis B vaccine given by IM route. These patients were randomly re-vaccinated by intradermal or intramuscular route. Patients of ID group received 16 doses of 5  $\mu$ g of HBs antigen weekly, whereas patients of the IM group received two doses of 40  $\mu$ g of vaccine monthly. One month after the end of re-vaccination protocol, sero-conversion rates and proportion of patients who developed protective anti-HBs titers were significantly higher in ID compared to IM patients (100% *vs* 48% and 96% *vs* 40% respectively). More recently Chanchairujira *et al*<sup>[74]</sup> revaccinated non responder hemodialysis patients with ID or IM vaccine: 25 patients were treated with 7 doses of 10  $\mu$ g of HBV vaccine by intradermal route every 2 wk and other 26 patients were treated with 40  $\mu$ g by intramuscular route at 0, 1, 2 and 6 mo. The Authors found a higher percentage of "responders" in the group of patients who were treated by intradermal administration of the vaccine. At 7 mo after the first vaccination, good (anti HBs titer between 10-999 IU/L) and excellent responders (anti HBs titer  $> 1000$  IU/L) in the ID group were respectively 72% (18/25) and 20% (5/25) compared with 34.5% (9/26) and 34.5% (9/26) of IM group ( $P > 0.05$ )<sup>[74]</sup>. In 2009 Barraclough *et al*<sup>[75]</sup> revaccinated 59 hemodialysis patients non responsive to primary HBV vaccination, with either ID (10  $\mu$ g of vaccine every week for 8 wk) or IM (40  $\mu$ g of vaccine at weeks 1 and 8) HBV vaccine. Seroconversion rates to 24 mo, were 79% ID *vs* 40% IM ( $P = 0.002$ ). Moreover they found a trend toward longer

duration of seroprotection with ID vaccination. The authors concluded that ID vaccination should become the standard of care in this population.

Finally a recent meta-analysis conducted by Fabrizi *et al*<sup>[76]</sup> on 12 controlled trials in order to compare intramuscular *vs* intradermal HBV vaccination in 640 CKD patients, demonstrated that intradermal route provides an higher seroconversion rate than intramuscular route. This result occurred in spite of a lower amount of antigen administered with intradermal route.

### HIV infection

HBV vaccination has been extensively investigated in patients with HIV infection due to the high prevalence of co-infection. In fact the United States HIV Outpatient Study cohort<sup>[77]</sup>, between 1996 and 2007, showed that the prevalence of co-infection with HBV was 20 times higher than in general population (8.4%). In another US study between 1998 and 2001<sup>[78]</sup>, the incidence of hepatitis B infection in patients with HIV, was 370 times higher than in the general population (12.2/1000 persons each year). HIV infection negatively influences different phases of hepatitis B infection, promoting virus replication, the development of chronic infection and the loss of HBs antibody. Furthermore co-infection of hepatitis B and HIV provides an higher incidence of complications, such as hepatocellular carcinoma, cirrhosis and liver-related mortality compared to HIV mono-infection<sup>[79,80]</sup>. In addition, the probability of developing hepato-toxicity after highly active antiretroviral therapy (HAART) is higher in patients with HIV infection who are also infected by hepatitis B virus<sup>[80,81]</sup>. For all these reasons individuals with HIV infection should receive vaccine against hepatitis B with the conventional three doses<sup>[82-86]</sup>. Despite this prophylactic measure, patients with HIV infection develop protective anti-HBs titers in only 18%-71% of cases after three doses of vaccine<sup>[87-89]</sup>. Individuals with HIV who are non-responders to hepatitis B vaccination, are not protected from infection because they become infected with hepatitis B virus as unvaccinated subjects with HIV<sup>[90]</sup>. Different factors, such as viral load, CD4 cell count and HAART, can impair the response to hepatitis B vaccination.

Some studies have demonstrated a link between low viral load of HIV and the development of an anti-HBs protective titer for either standard-dose<sup>[87,91-94]</sup> or double-dose vaccinations<sup>[95-98]</sup>.

B cell dysfunction has been shown in patients with HIV<sup>[99,100]</sup>. This immunological dysfunction may result in a decreased antibody response among HIV-infected patients<sup>[101]</sup>. On this regard Mehta *et al*<sup>[102]</sup> showed a lower number of hepatitis B virus specific memory B cells after vaccination in adolescents with HIV.

On the other hand some studies have suggested that the poor response to HBV vaccination could be attributed to impaired T-cell function<sup>[103]</sup>. In fact the higher number of T regulatory cells in individuals with HIV is often associated with unresponsiveness to HBV vaccina-

tion<sup>[104,105]</sup>. T regulatory cells inhibit B cell proliferation by inducing their apoptosis<sup>[106]</sup>.

Although HIV-infected patients who do not respond to the conventional three doses may develop a protective immune response after revaccination, they could lose anti HBs titres faster than patients who respond to the first vaccination series, as showed by Cruciani *et al*<sup>[95]</sup> and Rey *et al*<sup>[89]</sup>.

In patients with HIV infection, the intradermal route seems to have a greater immunogenicity compared to intramuscular route<sup>[107]</sup>.

In 2011 Launay *et al*<sup>[108]</sup> performed a randomized study on 437 patients in order to compare the safety and immunogenicity of 4 intramuscular double-dose (40 µg) and 4 intradermal low-dose (4 µg) regimens *vs* the standard hepatitis B vaccine regimen (20 µg × three doses). They found that intradermal vaccine recipients had significantly better sero-conversion rates compared with the standard dose group at week 28 (77% *vs* 65%) but there was no difference between the 4 intramuscular double-dose regimen and the 4 intradermal low-dose regimen.

However intradermal route permit to elicit a better immune response using only 20% of the dose compared to intramuscular route.

In only one pediatric randomized study conducted in order to compare ID *vs* IM HBV vaccination in children with HIV infection, the percentage of responders to ID route resulted similar to IM route at the end of the third dose of vaccine (90.2% ID *vs* 92.3% IM)<sup>[109]</sup>.

### Chronic liver disease and liver transplantation

With regard to liver transplantation, a de novo HBV infection increases post-transplant morbidity and mortality<sup>[110]</sup>. For this reason pre-transplant vaccination represent a valid prophylactic measure, although there are currently few data about the efficacy of HBV vaccination among patients with advanced liver disease<sup>[111,112]</sup>. On this regard Dhillon *et al*<sup>[113]</sup> in a recent retrospective review administered HBV vaccination by intradermal route in individuals with chronic liver disease (CLD) who had not developed a protective anti-HBs titer after three doses of 40 µg IM vaccine and booster doses of either 40 or 80 µg IM. 42 patients were treated with a 40 µg ID total dose for a maximum of three doses. 29/42 (69%) subjects developed an anti HBs titer > 10 mIU/mL and 15 (51%) of the responders developed an anti HBs titer > 100 mIU/mL. The authors conclude that high-dose ID HBV vaccination in patients with CLD is efficacious and safe.

### Celiac disease

Some studies documented that in celiac disease (CD) the immune response to vaccination does not differ from that one found in healthy subjects except for HBV vaccination<sup>[12,114]</sup>. It has been postulated that HLA-DQ2 haplotype, over-represented in celiac population, could predispose celiac patients to a poorer response to hepatitis B vaccination<sup>[115]</sup>. On the contrary other studies

suggest that in celiac patients gluten consumption could affect the immune response to HBV vaccine<sup>[116,117]</sup>. Since in celiac patients the interaction between specific deaminated glutamine residues of gliadin and HLA-DQ2 or DQ8 molecules is responsible for the development of intestinal damage<sup>[118]</sup>, it has been postulated that gliadin peptides compete with HBsAg protein fragments for binding to HLA-DQ2 molecules, and this competition could result in an impaired immune response to HBV vaccination in CD<sup>[119]</sup>. To support this hypothesis recent data of the literature suggest to revaccinate celiac patients during a correct gluten free diet<sup>[48,117,120,121]</sup>. For this reason new vaccination strategies for non responders celiac patients have been suggested<sup>[100,101,106]</sup>. In 2010 Leonardi *et al*<sup>[122]</sup> revaccinated 20 celiac patients who had not responded to HBV vaccination with a 2 µg dose of HBV vaccine by intradermal route. The authors found that after the first booster dose 8/20 patients (40%) developed anti-HBs titer ≥ 1000 mIU/mL, 4/20 (20%) between 100 and 1000 mIU/mL, and 3/20 (15%) between 10 and 99 mIU/mL. Moreover in 2011 the same authors<sup>[123]</sup> revaccinated 58 non-responder celiac patients with ID (2 µg) or IM vaccine (10 µg) for a maximum of three booster doses, in order to compare the safety and the efficacy of these two different vaccine routes (ID *vs* IM). The Authors found a similar percentage of “responders” after the third booster dose (ID = 90% *vs* IM = 96.4%), although they documented an higher percentage of patients with an anti-HBs titer > 1000 IU/L in ID (40%) than in IM (7.1%) group.

## OTHER CONDITIONS

The immune response to hepatitis B vaccination seems to be poorer in patients with insulin dependent diabetes mellitus (IDDM) than in healthy population<sup>[124-126]</sup>. This seem to depend on genetic factors: in fact HLA-A11, which favors the immune response to hepatitis B vaccination, is present more frequently in responder subjects, while HLA-DR3, DR4, DR7, and B8 have an higher prevalence in patients who respond poorly or do not respond completely as those with diabetes mellitus<sup>[127-129]</sup>. However there is in literature only one study which evaluated the effectiveness of intradermal route in diabetic patients and compared the immune response to hepatitis B vaccine by intradermal or intramuscular route<sup>[130]</sup>. All the children enrolled in this trial were divided into four groups: A, B, A1 and B1. Nine children with diabetes mellitus in group A received 3 µg of a recombinant DNA hepatitis B vaccine by intradermal route at 0, 2, 4 and 6 or 8 wk, while other 9 children affected by diabetes mellitus in group B received three doses of 10 µg (for patients younger than 10 years) or 20 µg (for patients older than 10 years) of the same vaccine by intramuscular route at 0, 1 and 6 mo. In addition 24 normal children of which 12 in group A1 and 12 in B1 received the same vaccine schedule as groups A and B. The authors found that there was a poorer immune response to intra-

dermal hepatitis B vaccine in children with IDDM when compared with controls ( $P < 0.001$ ) and with group B children with IDDM ( $P < 0.001$ ). Recently Fabrizi *et al.*<sup>[131]</sup> conducted a meta-analysis on 12 studies involving 1002 unique patients, in order to assess whether diabetes mellitus could affect the immune response to HBV vaccination in dialysis patients. The authors found a significant decrease in seroconversion rates in patients with diabetes mellitus *vs* non diabetic patients.

Thalassaemic subjects who have been vaccinated against hepatitis B virus often show a loss of anti HBs titer; moreover, between 5% and 20% of subjects who have been immunized against hepatitis B virus do not respond to the hepatitis B vaccine after either conventional or booster vaccination<sup>[132,133]</sup>. In literature is reported only one study about the use of anti-hepatitis B intradermal route to vaccinate non responder thalassaemic patients<sup>[44]</sup>. The authors studied 56 children with thalassaemia who had been vaccinated against hepatitis B virus by IM route. In these patients the vaccine was administered in doses of 5 µg by intradermal route and the inoculations were continued every two weeks until the titer had risen above 10 U/L. 45/56 children (80%) with thalassaemia developed HBs antibody titer > 10 U/L two weeks after the first intradermal dose. In other 9 of 11 (82%) non-responding thalassaemic patients the anti- HBs titre was > 10 U/L two weeks after the second intradermal dose. This study showed that low doses of vaccine against hepatitis B virus administered by intradermal route produce an effective immune response in thalassaemic patients.

In addition there are in literature four studies which investigate the use of intradermal hepatitis B vaccination in patients with Down's syndrome and other forms of mental retardation (OMR), but the available data are still discordant. In fact two studies suggest that low dose vaccination against hepatitis B by intradermal route, seems to be a suitable cost-reducing immunization system in institutes for mentally retarded patients and its use is safe and effective<sup>[134,135]</sup>. In another study on follow up the authors concluded that using the intradermal route the antibody response persisted for 2 years in the OMR patients, while decreased remarkably in the DS patients<sup>[136]</sup>. Only the fourth study concluded that intradermal vaccination is not warranted in persons with DS, especially not in middle aged and older persons<sup>[137]</sup>.

Knowledge of non-response to hepatitis B vaccination is critical also for healthcare workers (HCWs) who are at continuous risk of infection. Around 10%-15% adults do not respond to three doses of anti hepatitis B vaccination or respond poorly<sup>[138,139]</sup>. Alternative vaccination programs have been studied for non-responders HCWs.

Three studies, have shown that high dose (20 µg) of intradermal vaccine are immunogenic in persons who did not respond to IM vaccination<sup>[140,141]</sup>.

More recently Ghebrehewet *et al.*<sup>[142]</sup> conducted an observational study on 23 non-responding HCWs. All eligible HCWs were vaccinated with two doses of 20 µg

of recombinant hepatitis B vaccine intradermally. The authors found that 21/23 (91.3%) of all non-responders developed protective titers ( $\geq 10$  mIU/mL) after 1 or 2 doses of IDRv.

The most recent Cochrane review<sup>[143]</sup> identified 7 randomized studies that compared the two different routes (ID *vs* IM) evaluating the anti-HBs sero-conversion. The review concluded that the 20 µg vaccine by intramuscular route elicits a better anti-HBs response than the 2 µg vaccine by intradermal route. Despite these results, the authors suggest to further investigate the intradermal route because the doses used by the two routes differ 10 fold while the seroconversion rates differed less than two-fold.

## CONCLUSION

It is imaginable that within the not too distant future all people in the world will be vaccinated on the mandatory basis. The World Health Organization has recommended that hepatitis B vaccination should be performed for all children in the world and cost-benefit analyses have supported the introduction of universal vaccination against HBV to newborns<sup>[144,145]</sup>. Results of children's vaccination, which were evaluated in the six-year outcome of the program, showed neither new cases of HBsAg *de novo* nor seroconversion to anti-HBc positivity<sup>[146]</sup>.

According to the European Consensus Group on hepatitis B immunity<sup>[147]</sup> a sustained protection against hepatitis B infection is based on immunological memory. Since antibody memory seems to last for at least 15 years in immune-competent subjects using vaccine by intramuscular route, we might expect that also who respond to intradermal vaccination with an anti-HBs titer  $\geq 10$  mIU/mL will develop a prolonged protection.

To date anti hepatitis B intradermal vaccination seems to be an effective alternative to intramuscular route in non responder patients. Vaccines administered by intradermal route promote a dendritic-cell-mediated immune response and require lower amount of antigen compared to vaccines administered by intramuscular route that activate a T-cell-mediated response. In addition economic studies seem to suggest that the cost-savings advantages of administering vaccines by intradermal (ID) route, could be significant<sup>[42,43]</sup>. Moreover the immune response to HBV vaccination can be determined by the appearance of a skin reaction at the injection site<sup>[148]</sup>. The development of this reaction on the site of the intradermal injection could represent a cost-savings measure for the Health Organization to test serum anti-HBs response after the booster dose<sup>[45]</sup>. As many literature data suggest that intradermal vaccines improve sero-conversion rates, it would be reasonable to promote this procedure. However further studies should be conducted in particular focusing on: the ideal dose and timing of the ID vaccination schedule; and the sustainability of the immune response achieved and the need of administering further booster doses.

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ISSN 1007-9327



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