REVIEW ARTICLE

Hepatitis Monthly 2006; 6(1): 25-29

HBV Vaccination in Chronic Renal Failure Patients

Shahnaz Sali MD

Infectious Disease Specialist, Fayyaz Bakhsh Hospital, Tehran Social Security, Tehran, Iran

HBV infection in chronic renal failure (CRF) becomes chronic in 30 to 60% compared with less than 10% in nonuremic patients.
Immunological dysfunction in patients on hemodialysis may be related to imbalanced cytokine systems, such as tumor necrosis factor (TNF-α) and interleukin (IL) 6,1 by retention of renal metabolite in uremia and chronic inflammation and have a poor immunological reaction to T-cell-dependent antigens, like hepatitis B vaccination.
Immunocompromised patients who are unresponsive to hepatitis B vaccination seem to be unable to enhance IL-10 synthesis for control of monokine overproduction.
Moreover, human leukocyte antigen (HLA) genes, which play a major role in the antigen presentation to immunocompetent cells, have also been shown to modulate this immune response.
Unfortunately, seroconversion to anti-HBS has been reported to occur in only 40 to 50% of the vaccine, a significantly lower rate than that observed in healthy adults. Various methods including adjutants such as zinc, gamma interferon, thymopentine, GM-CSF and Levamisol for improving immune responses have been advised.
Experience with $Pres_1/s_2$, third-generation vaccines is limited and they have not been proven more effective than intradermally (ID) administered second-generation S antigen vaccines.
Both intramuscular (IM) and intradermal (ID) vaccinations against hepatitis B have variable efficiency in hemodialysis and non-responders should be retreated by ID route.

Keywords: **CRF, Vaccination, Hepatitis B, Immunoresponse, TNFa, Interleukin, Pre-S Vaccine**

Introduction

Patients with end stage renal disease (ESRD) who undergo hemodialysis are prone to blood-borne infectious diseases, such as hepatitis B virus, because they are normally exposed to blood products and hemodialysis apparatus [1].

HBV infection in hemodialysis patients become chronic in 30% to 60% compared to less than 10% in nonuremic patients with complications including cirrhosis, hepatocellular carcinoma (HCC) and end stage liver failure (ESLF) [2]. For this reason, HBV vaccination is mandatory in such patients [3,4].

In these patients impaired responsiveness to HBV vaccination is in agreement with the known impaired cellular immune response and compromised immunological system of uremic as well as hemodialysis patients [2,5].

Chronic inflammation associated with renal failure, leads to impaired monokine production and decrease immunity. Non-responders to hepatitis B vaccination express increased levels of HLA Class II alleles (T-Cell immune response modulators) DR_1-DR_{15} [2].

Various methods including immune modulating agents for improving both humoral and cellular immune responses have been devised to increase the response rate to HBV vaccination in hemodialysis; for example, adjutants such as zinc [6,7], gamma interferon[8], thymopentin[9], Gm-Csf [10] and levamisol [3].

HBV vaccination reinforcement technique evolved from an initial intramuscular (IM) double/multiple-dosing regimen to more frequent intradermal smaller dose injections. This newer regimen achieves a higher and almost complete seroconversion rate, although frequent booster shots are necessary to maintain protective levels [11,12,13,14,15].

Correspondence:
Shahnaz Sali, Infection Specialist, Social Security Center, Karaj, Iran

Tel: *+98 21 8895 1290*

E-mail: *drsh_sali@yahoo.com*

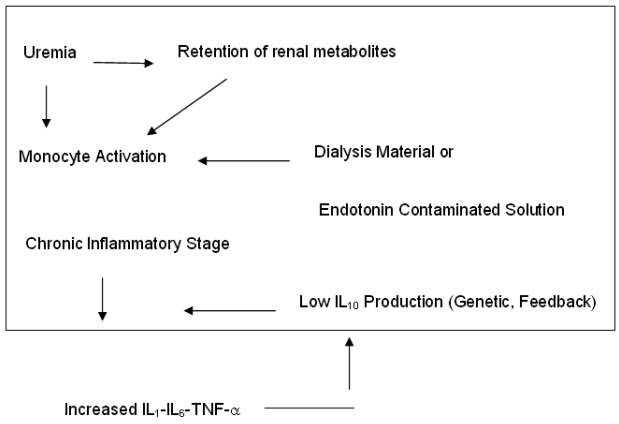
Hep Mon 2006; 6 (1): 25-29

Experience with $Pres_1/s_2$, third-generation vaccines is limited and they have not been proven more effective than intradermally (ID) administered second-generation S antigen vaccines.

Immune Response in Renal Failure and Hemodialysis Patients

Chronic renal failure (CRF), in the earlier stage, exhibits specific and non-specific humoral and mainly cellular immune deficiency. Cellular immune deficiency, worsened by dialysis, is based on reduced T cell activation of the accessory antigen presenting cells (APC) in most patients [1,3]. Most immunocompetent cells show a paradoxical coexistence of a functional deficiency, together with phenotypic signs of T cell activation [3]. (Table 1).

Table 1. Immune Deficiency in Uremic-Mechanism



Monocyte activation is a part of the uremic syndrome even before end stage renal disease (ESRD) and dialysis have been reached. When patients start dialysis, complement activation by membrane material or endotoxin contaminated solution lead to additional monocyte activation.

Monokines, like IL_1, IL_6 and TNF-α, activated by the retention of renal metabolites in uremia and by chronic inflammation (induced by dialysis material), are systematically released in patients with renal failure or on hemodialysis (Table 1).

Overproduction of proinflammatory cytokines, at least partially, genetically defined (by gene polymorphism) is associated with a heavily impaired system and explaining the variable presence of the inflammatory state in renal failure patients [16,17].

Genetically defined inability to produce the necessary IL_{10} (a cytokine feedback mechanism resulting in better B cell function) in order to control the overproduction of proinflammatory monokines (IL_6, TNF-α) both in renal failure and in end stage renal disease is linked to the immune defect[18].

Patients producing higher levels of IL_{10} exhibit reduced uremia and dialysis induced chronic inflammation, and respond better to vaccines (Table-1) [16,17,19].

Hemodialysis patients, by the presence of a dominant immune gene in major histocompatibility complex (MHC), responsible for normal response (helper T cells activated) and, when present in MHC extended haplotypes on both chromosomes, responsible for low or no response (suppressor T cells activation) to HBV vaccine antigens[20].

At least in Caucasian populations various studies showed non-response to HBV recombinant vaccine to be related to $HLA\text{-}DR_3$ and/or DR_7 alleles, especially when they were found to be present on extended haplotypes; $HLAB_8\text{-}SC_{01}\text{-}DR_3$ and $HLAB_{44}\text{-}FC_{31}\text{-}DR_7$ [20].

These genetic findings could be explained by the presence of a dominant immune gene in MCH, responsible for normal response (helper T cells activation) and when present in MCH extended haplotypes on both chromosomes, responsible for low or no response (suppressor T cells activation) to HBV vaccine antigens[20].

Specific antibody production, often HBV vaccination, is generated via B-cell activation by CD4 + Th_1 - helper (class II) and CD8 + CTL - Cytotoxic T cell (class I restricted T-cell) responses. Insufficient B and T-cell responses lead to chronic liver disease in 5-15% of the general population and in 30% of HBV infected dialysis patients [14,18].

Immune suppression is associated with uremia and dialysis (Table-2) and leads to high susceptibility to infections, life-threatening sepsis and reduced response to vaccination [5,18]. The number of blood transfusions and the presence of a hepatitis C virus infection or diabetes mellitus are considered additional factors for the decreased immune response [21]. Indeed, response to hepatitis B vaccine is reported to be very low, in patients with hepatitis C virus infection, which suggests a possible genetic basis for low responder status to both viruses (Table 2).[4,21,22].

Scanty information exists concerning the relationship between dialysis adequacy, immune function and antibody response to vaccinations. There is, however, indirect evidence that more frequent dialysis may lead to an enhanced response because dialysis helps to restore impaired B7-2 expression[5].

In a study of peritoneal dialysis patients immunized with the hepatitis B vaccine, the initial weekly Kt/V was 2.37 and 2.01 in responders and non-responders respectively, although other

Table 2. Causes of immune suppression associated with uremia and dialysis

Uremic Syndrome (Inflammation, anemia, malnutrition, hyperparathyroidism)
Age (old)
Sex (Female)
Body weight (Overweight)
Iron (Overload)
HCV+
Diabetes
Genetics (MHC;HLA DR_3/DR_7 presence, B_{18},51-DRB_1 0101-DR_{15} absence
Dialysis (Method, efficiency, biocompatibility)

investigators could not confirm such a favorable action of dialysis on immune function.

Because of depressed immunity, dialysis patients are not able to respond to HBV vaccination and when they do respond, they develop lower antibody titers and do not maintain adequate antibody levels over time, compared to a healthy population [22,23].

The immune response in patients with ESRD is generally defined wherever T cell activation is required (hepatitis B, tetanus, influenza vaccine)[19], while it is found almost normal when non-T dependent immunity mechanisms are activated (pneomococcal vaccine). Despite the evidence for deceased efficiency, current recommendations are to vaccinate patients with ESRD [4,25].

HBV vaccination, when applied together with the other preventive measures, resulted in an up to 10 fold drop in the number of new HBV case in hemodialysis patients and renal unit staff in Western Europe and in the United States [20,26].

Although the incidence of the disease is actually low in Iran, a high percentage of susceptible patients are still not vaccinated. CDC suggests that the cost of vaccinating patients is mitigated by the reduced need for monthly surveillance of antigen and antibody status in those who develop specific antibodies [15,20,26,27].

Hepatitis B is still a threat for dialysis patients; despite prophylactic measures, HBV could also infect dialysis patients due to its prevalence in the general population. Infected patients can then spread the disease in their unit before HBV infection has been detected if patients are not actively protected by a successful vaccination program [28].

A high percentage of dialysis patients becoming HBV positive will be unable to eliminate their virus (developing chronic hepatic disease). They are considered high risks for renal transplantation and are virus reservoirs to both other patients and non-protected staff [26].

A completely non-protected vaccination program is essential for patients and personnel protection against this chronic, persistent and potentially lethal disease [1,4,28].

Hepatitis B Vaccination

Hemodialysis patients and renal failure patients not yet on dialysis reached similarly to the injected antigen and produced similar levels of antibody [5].

Controversy exists concerning the overall effectiveness, including the cost/benefit ratio, of hepatitis B vaccination in patients with ESRD[15,20,21,27,28].

The first vaccine for HBV was plasma-derived vaccine (first Generation vaccine-1980). Already second generation recombinant vaccines (expressing the "S" gene), have replaced plasma-derived vaccines (Table 1). These vaccines are safe and result in immunogenicity levels similar to those seen in control patients [1,15].

Pre-S components have been found to be more immunogenic than simple S containing vaccines by some authors, as they could overcome genetically defined unresponsiveness and protect even against emerging HBV mutant (G14SR vaccine relate mutations in 5% of vaccinated infants) resistant to anti-S antibodies [29].

Table 3. Recommendation protocols of HBV vaccinations in ESRD.

Intramuscular:	
	Single dose (20 µgr) 3 (doses)
	Double dose (40 µgr) (3 doses)
	Adjuants-immunostimulants
	(IL-2, IFN-γ, G-M Csf, Thymopentine, Levamisol)
Intradermal:	
	5-10 µgr per 7-15 days (4-8 doses)
Intramuscular booster dose:	
	20- 40 µgr in 6-12 months
	additional if fall of antibody

Mettang *et al.* and others also point out the importance of a strict intradermal vaccination technique (Table 4) [11,12,21].

Intradermal antigen presentation lasts longer, possibly because it mobilizes dendrotic Longerhans cells, leading to a more sustained stimulant that overcomes the "uremic" immune defect.

Immune response strength to hepatitis B vaccine in hemodialysis patients is equivalent when immunization is conducted via either the IM or ID methods. However, later, antibody titers are found significantly lower in the ID immunization group[14]. Consequently, these patients need more

Table 4. Difference in intradermal vs. intramuscular protocols in HBV vaccination in uremia.

Less vaccine (economy)
Difficult techniques
More doses
100% Response
Earlier response
Lower peak antibody levels
Need for more frequent boosters

frequent, yearly serum HBV (S) Ab measurements and booster doses when titers are found un-protective.

Both intramuscular and intradermal vaccinations against hepatitis B have been used with variable efficiency in hemodialysis. Combination of IM and ID (for non-responding) vaccination protocols succeeded, in some studies, in protecting up to 100% of the renal failure population.

Multiple intradermal vaccinations against HB virus, using a smaller total vaccine doses, is a safe, quick, cost effective and successful approach that can be used in all susceptible pre-dialysis and dialysis patients. The disadvantage of this method is that specific antibody titers decrease over time, thus necessitating the administration of additional boosters.

Thus, vaccination against HBV with recombinant (S) vaccine, first with the IM method and then, in non-responders to IM, with the ID method, protects immunocompromised end stage renal disease patients as efficiently as it does in the health population [1,12,13,20].

Conclusions

End stage renal disease (ESRD) patients have been low or no response to HBV vaccine as an index of immune suppression in dialysis in patients and poor dialysis adequacy. These patients with low producing IL-10 genotypes, who show no response to hepatitis B vaccines may harbor an immune defect that is generally defined T-cell CD4 dysfunction and abnormal antigen presenting cells are the main causes of this immune defect. In addition, impaired immunity is considered an additional risk factor, together with inadequate dialysis, inflammation and resulting malnutrition, for other sclerosis, poor cardiovascular outcome and survival in ESRD. Second-generation recombinant HBV vaccines, intradermaly administrated, can overcome the immune defect in all renal failure patients.The combination of IM and ID (in non-responders) vaccination protection succeeded in ESRD patients. Alternatively, combination of immunomodulatory, for example, IL2-thymopentin, zinc, GM-Csf, levamisol may provide enhanced vaccination efficiency.

Abbreviations:

HB ≡	Hepatitis B
HBV ≡	Hepatitis B Virus
HBS Ag ≡	Hepatitis B Surface Antigen
HD ≡	Hemodialysis
CRF ≡	Chronic Renal Failure
ESRD ≡	End Stage Renal Disease
IM ≡	Intramuscular
ID ≡	Intradermal
TL ≡	Intraleukin
IFN ≡	Interferron
TNF ≡	Tumor Necrosis Factor
G-M CSF ≡	Granulocyte Macrophage Colony Stimulating Factor
APC ≡	Antigen Presenting Cell
MCH ≡	Major Histocompatibility Complex
HLA ≡	Histocompatibility Locus A
HCV ≡	Hepatitis C Virus

References

1. Rapicetta, M, "hepatitis B Vaccination in Dialysis Centers; Advantages and Limits" Nephron 1992, 61, 284-286
2. Caillat-Zuckerman, S; Gimenez, J.J; Wambergue, F.; Albouze, G.; Lebkin, B.; Naret C., Moynot, A.; Jungers, P. and Bach, J-F. "Distinct HLA Class II alleles determine antibody response to vaccination with hepatitis B surface antigen". *Kidney Int* 1998. **53:** 1626-1630
3. Mansur Kayats, "Levamisole Treatment Enhances Protective Antibody Response to Hepatitis B Vaccination in Haemodialysis Patients", International Society for Artificial Organs 2002, **266**: 492-496
4. Miller, E.R.; Alter, M.J. and Tokars, J.T. "Protective effect of hepatitis B vaccine in chronic haemodialysis patients" *Am. J. Kidney Dis* 1999.; **32**: 356-360
5. Vanholder, R.; Van Loo, A.; Dohndt, A.M.; Desmet, R. and Ringoir, S. "Influence of uremic and haemodialysis on host defense and infection". (1996) Nephrol Dial. Transplant, 11, 593-598
6. Rawer P.; Willems WR, Breidenback T.; Guttmann W.; Pabstw, Schutterle G. "Servoconversion rate, hepatitis B vaccination, haemodialysis and zinc supplementation". *Kidney Int.* 1987; **32**: 149-152
7. Brodersen HP.; Holtkamp W.; Larbig D.; Beckers B.; Thiery J.; Lautenschlager J.; Probst HJ., Robertz S.; Yauari A. "Zinc supplementation and hepatitis B

vaccination in chronic haemodialysis patients (letter)". Nrephrol. Dial. *Transplant* 1995; **10**: 1780-83
8. Quirage JA.; Castillo I.; Porres JC.; Casadio S.; Saez F.; Gracia MM.; Gomez M.; Inglade L. "Recombinant gamma interferone as adjuavant to hepatitis B vaccine in haemodialysis patients". *Hepatology* 1990; **12**: 667-673
9. Donati D.; Gastaldi L; "Controlled trial of tymopentin in haemodialysis patients who fail to respond to hepatitis B vaccination". *Nephron*. 1988; **50**: 133-6
10. Hasan MS.; Agosti JM. "Granolocyte macrophage colony stimulating factors as an adjuvant for hepatitis B vaccination of healthy adults". *J. Infect. Dis.* 1999; **180**: 2023-6
11. Propst, T.; Propst, A.; Lhotto, K.; Vogel W. and Konig, P. "Reinforced intradermal hepatitis B vaccination in haemodialysis patients is superior in antibody response to intramuscular or subcutaneous vaccination" *Am. J. Kidney Dis.* 1998; **32**: 1041-1045
12. Charest, A.F.; MC Dougall, J. and Goldstein, M.B. "A randomized comparison of intradermal and intramuscular vaccination against hepatitis B virus in incident chronic haemodialysis patients". *Am. J. Kidney Dis* 2000.; **36**: 976-982
13. Vlassopoulos, D.; Arvamitis, D.; Lilis D.; Loxizox, K. and Hadji Constanti "v. lower long-term efficiency on intradermal hepatitis B vaccine compared to the intramuscular rate in haemodialysis patients". *Int. J. Artif. Org.* 1999; **22**: 739-743
14. Rohman, F.; Dahmem, A.; Herzog-Houff, S.; Bocher, W.O.; Gall, P.R. and Lohr, H.F. "Cellular and humoral responses induced by intradermal or intramuscular vaccination with the major hepatitis B surface". *Heptology*, 2000; **31**, 521-527
15. Dakes, C.S.; Street A.C.; Starling, J.F. and Hamilton J.D. "Hepatitis B vaccination and booster in pre-dialysis patients: a 4-years analysis". *vaccine*, 1993; **11**: 1229-1232
16. Girndt, M; Sester, V.; Sester, M; Deman, E.; Kaul, H. and Kohler, H. "The interleukin-10 promotor genotype determines clinical immune function in haemodialysis patients". *Kidney Int.*, 2001; **60**, 2385-2391
17. Van Riensdijk-van Overbeeke, T.C.; Baan, C.C.; Knoop, C.J.; Loonen, E.H.M.; Ziestse, R. and Vreimar, W. "Quantitative flow cytometry shows activation of TNF-α system but not of the IL-2 system at the single cell level in level I in renal replacement therapy". *Nephron. Dial. Transplant*, 2001; **16**, 1430-1435
18. Descamps-Latscha, B. and Chatenoud "L.T cells and B cells in chronic renal failure". *Semin. Nephrol* 1996.; **163**: 183-191
19. Girdt, M.; H.; Scheid Helm-weick, E; Schleak, J.F.; Meyerzum Buschenfede, K.-H. and Fleischer, B. "Production of interleukin-6, tumor necrosis factor ? and interleukin-10 in vitro correlates with the clinical immune defect in chronic haemodialysis patients". *Kidney Int* 1995.; **47**, 559-565
20. Pol, S.; Legendre, C.; Nattlinger, B.; Berthelot, P. and Kresis, H. "Genetic basis to hepatitis B vaccine in haemodialysis patients". (1990) 7, *Hepatol.*; **11**, 385-387
21. Navarro JF, Teruel JL, Mateos ML, Marcen R, Ortuno J. Antibody level after hepatitis B vaccination in hemodialysis patients: influence of hepatitis C virus infection. *Am J Nephrol*. 1996; **16**: 95-7
22. Peces, R,; de la Torre, N; Alcazar, R. and Urra, J.M. "Prospective analysis of the factors influencing the antibody response to hepatitis B vaccine in haemodialysis patients". *Am. J. Kidney Dis* 1997,; **29**: 239-245
23. Buti, M.; Viladomix, L.; Jardi, R.; Olmos, A; Rodriguez, J. A.; Bartolone, J.; Esteban, R. and Guardia, J. "Long-term immunogenicity and efficiency of hepatitis B vaccine in haemodialysis patients". *Am. J. Nephrol* 1992;. **12**, 144-147
24. Girndt, M.; Pietsch, M. and Kohler, H. "Tetanus immunization and its association to hepatitis B vaccination in patients with chronic renal failure". *Am. J. Kidney Dis* 1995;. **26**: 454-460
25. Fivush, B.A. and Neu, A.M. "Immunization guidelines for pediatric renal disease".Seminars in Nephrology 1998;, 18: 256-264
26. Kohler, H. "Hepatitis B immunization in dialysis patients, is it worthwhile?". *Nepral Dial. Transplan* 1994t; **9**, 1719-1720
27. Katkow, W.N. and Dientag J.L "Prevention and therapy of viral hepatitis". *Semin. Liver Dis.* 1991; **11**: 165-174
28. Jibani, M.M; Heptonstall, J.; Walker, A,M.; Bloodworth, L.O. and Howard, A.J. "Hepatitis B immunization in UK renal units: failure to put policy into practice". *Nephrol. Dial. Transplant* 1994; **9**, 1765-1768
29. Zuckerman, J.N.; Sabin, C.; Craig, F.M.; Williams. A. and Zuckerman, A.J. "Immune response to a new hepatitis B vaccine in healthcare workers who had not responded to standard vaccine:randomized double blind dose-response study". *B.M.J* 1997;. **314**, 329-330