HBV Vaccination in Chronic Renal Failure Patients

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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 adjuvants such as zinc, gamma interferon, thymopentine, GM-CSF and Levamisol for improving immune responses have been advised.

Experience with PreS1/S2, 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, TNFα, 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 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) DR1-DR15 (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, adjuvants such as zinc (6,7), gamma interferon (8), thymopentin (9), Gm-Csf (10) and levamisol (9).

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).
Experience with Pres/s, 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).

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 IL1, IL6 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 IL10 (a cytokine feedback mechanism resulting in better B cell function) in order to control the overproduction of proinflammatory monokines (IL6, TNF-α) both in renal failure and in end stage renal disease is linked to the immune defect(18).

Patients producing higher levels of IL10 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-DR and/or DR alleles, especially when they were found to be present on extended haplotypes; HLAB8-SC01-DR3 and HLAB44-FC31-DR7 (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 + Th1 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).

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...
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 (pneumococcal vaccine). Despite the evidence for decreased 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 2. Causes of immune suppression associated with uremia and dialysis

| Uremic Syndrome (Inflammation, uremia, malnutrition, hyperparathyroidism) | Age (old) | Sex (Female) | Body weight (Overweight) | Iron (Overload) | HCV+ | Diabetes | Genetics (MHC,FLA DR,DR; presence, B6,L, DR, 0101,DR, absence) | Dialysis (Method, efficiency, biocompatibility) |
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Intramuscular:

- Single dose (20 μg) 3 (doses)
- Double dose (40 μg) (3 doses)
- Adjuvants-Immunostimulants (IL-2, IFN-β, GM-CSF, Thymopentin, Levamisole)

Intradermal:

- 5-10 μg per 7-15 days (4-8 doses)

Intramuscular booster dose:

- 20-40 μg 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 dendritic 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
frequent, yearly serum HBV (S) Ab measurements and booster doses when titers are found unprotective.

Both intramuscular and intradermal vaccinations against hepatitis B have been used with variable efficiency in hemodialysis. Combination of IM and ID (for non-responders) 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, intradermally 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
6. Rawer P.; Willems WR, Breidenback T.; Guttmann W.; Pabstw, Schutterle G. "Seroconversion 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)." Nephrol. 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 adjuvant to hepatitis B vaccine in haemodialysis patients". Hephatology 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
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