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Overcoming Strategies for Non-responders in HBV Vaccination

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Authors' contributions

This work was carried out in collaboration among all authors. Author VB designed the study, performed the statistical analysis, literature searches and wrote the protocol and the first draft of the manuscript. Author RS managed data validation and critical revision of the manuscript. Authors KVL and TJ managed the frame work of the study and technical editing of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Non-responder refers to an individual did not develop their anti HBs, even after administration of a 2 complete series of the HBV vaccine. Due to mutant variants, vaccine failure occurred in numerous reports but the incidence of these mutants were unknown. Primary HBV vaccine series failed for nearly 5% of immunocompetent people. There is no clear vision on nonresponse but certain individuals are at major risk, those with persistent diseases, immunosuppressant medication and genetic predisposition. CD-4 T-helper cells that was obtained from viral peptides played an important role in Human Leukocyte antigen (HLA) along with Major Histocompatibility Complex (MHC) and individuals who failed to respond had defect in T helper cells stimulation or antigen presentation. After administration of a course of vaccine, antibody will be produced against major hydrophilic domain of HBsAg in determinant epitope cluster. As upcoming approaches, antigen dose were increased, alternative vaccination, new adjuvants such as immunostimulatory DNA sequences and accelerating vaccination schedules are followed in practice. Increased dosage vaccines, upgraded immunogenicity, adjuvants, surrogate mechanism, combined vaccines and administration of intradermal vaccines are the relevant approaches for a non-responder. Further studies has to be conducted on HLA alleles that can overcome the obstacles in HBV therapeutics.

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1. INTRODUCTION

Among viral hepatitis, the only double stranded DNA virus is Hepatitis B Virus (HBV). In 1963, Blumberg had discovered Hepatitis B Surface Antigen (HBsAg) while studying yellow jaundice and later he showed that a virus could cause liver carcinoma [1]. Hepatitis B infection (HBI) is a developing life-threatening liver infection caused by the HBV. It causes chronic infection and that leads to death by causing Liver cirrhosis (LC) and hepatocellular carcinoma (HCC) [2]. Vaccine of hepatitis B prevents serious diseases and decrease the number of infections. World Health Organization (WHO) reports show that in 2015, about 257 million people were residing with chronic HBI (defined as HBsAg positive). In the same year, hepatitis B resulted in 887 000 deaths, mainly from LC and HCC. As of 2016, 27 million people (10.5% of people estimated to be living with HBV infection) were aware, while 4.5 million (16.7%) of the people diagnosed were on treatment [3]. Non-responder refers to an individual who didn't develop their anti HBs, even after administration of a 2 complete series of the HBV vaccine. About 5-15% of the individual estimated did not respond to vaccine because of smoking, obesity, chronic illness and older age [4].

Host immunity is divided into antigen specific adaptive immune system (ASAIS) (which generates immunological memories for antigen exposure) and innate immune system (IIS) (which responds quickly and nonspecific). It is mediated by antigenic receptors, which has a germ line encoded pattern recognition receptors in case of IIS and ASAIS generated by rearrangements of receptor gene on B or T cells that shows immunological memory [5]. The IIS can also alter its function by pathogenic, to impose reinfection by nonspecific protection, hence it is named as Innate immune memory (IIM) or Trained immunity (TI) [6-8]. Natural Killer Cells (NK) are the pre-eminent effectors of IIS that shows both ASAIS and TI [9,10]. Cytokine stimulation or vaccination occur for pre-activation of NK cells that can stimulate TI in humans and enhance the production of interferon. In contrast, ASAIS has only report in in-vitro model. In humans, NK cell response remains undefined but it has potency in cell mediated therapies that improvise the vaccine response or viral infection and targeting carcinoma [11-13].

In Infants, 80 % – 90% of HBV infection are caused by chronic infection [14]. Due to effective vaccination there is a significant decline in the prevalence of chronic infection but HBV immunity is not developed for immunocompetent individuals (~5%) [15]. Meanwhile NK cells play a vital role in inducing early defense against HBV infection [16], an impaired viral activity is initiated in chronic infection [17-19]. This review will discuss various approaches to vaccinate non responders by standard therapy to overcome the non-responsiveness of HBV vaccine.

2. PECULIARITY OF HEPATITIS B VIRUS

HBV is a DNA virus and a member of the Hepadnavirus family. An icosahedral nucleocapsid core and Outer lipid envelope are composed of protein present in virion. The diameter of the virions are 30–42 nm [20]. They are HBsAg, HBcAg, and HBeAg. In older days surface antigen is otherwise called Australia antigen because it was observed in Australian Aboriginal person. HBsAg contains two components – 'a' epitope from reactive antigen and two pairs namely d/y and w/r from type specific antigens. It has 4 sub types that are named as adw, ayw, adr and ayr. Typing of HBV are serotype and genotype. In serotype, adr, adw, ayr and ayw are the four major divisions from HBV [21]. It shows distinct geographical distribution. In India, southern and eastern part prevalent subtype is adr whereas in western, northern region prevalent is ayw. There are eight types (A-H) of genotypic divisions in HBV and their geographical distribution shows that in India, genotypes are A and D [22].

Genome of HBV consist of partially a circular dsDNA of 3200 bp in length. It has two strands, long or L strand and Short or S strand. L strand is minus strand of DNA that is complete, full length and identical in all HBV isolates. For S strand it is incomplete and variable in length [23]. HBV genome has four genes that overlaps each other, they are S, C, X, P genes. S gene has three regions (i) S gene (ii) Pre S1 (iii) Pre-S2 and Surface antigen is coded by these genes. C gene consist of pre-C (precore antigen, HBeAg) and C (core antigen, HBcAg) region coding for two nucleocapsid. X gene codes HBxAg. P gene that codes polymerase protein and it is the largest gene which has three enzymatic activites

- DNA polymerase activity, RNase H activity and reverse transcriptase activity [24].

HBV mutants are precore mutants which abolish HBeAg production that tend to have severe chronic hepatitis. Escape mutants that mutate in S gene alters in HBsAg that cause infection in vaccinated individuals as anti HBs present in them cannot neutralize these HBsAg negative mutants. Tyrosine-methionine-aspartate-aspartate locus is present in the HBV transcriptase region of polymerase gene [25].

3. BACKGROUND OF HBV VACCINE

The 1st anti-cancer vaccine to prevent LC is Hepatitis B Vaccine. In 1963, Dr. Baruch Blumberg who discovered HBV, initially called this virus as "Australian Antigen" due to blood sample of Australian aborigine's that reacts with an antibody present in the American hemophilia patient's serum. Irving Millman and Dr. Baruch Blumberg developed a blood test for the HBV. In blood banks, HBV screening test was initiated in 1971 to decrease 25% of the risk to HBV infection from blood transfusion. After 4 years, the 1st HBV vaccine was developed in the form of heat treated HBV by Dr. Baruch Blumberg and Irving Millman.

In the year 1981, plasma derived HBV vaccines were approved by Food and Drug Administration (FDA) in human. The blood was collected from HBV infected donors to develop "inactivated" type of vaccine and pooled blood undergoes several steps to inactivate the viral particles. The commercially available 1st plasma derived HBV vaccine is "Heptavax". The 2nd generation of DNA recombinant HBV vaccine were developed in 1986. These vaccines were not employed for HBV infected blood and is prepared by synthetic method. Yeasts like *Saccharomyces cerevisiae*, *Pichia pastoris* or Chinese hamster ovary (mammalian cells), *Hansenula polymorpha* express the HBsAg in all recombinant vaccines nowadays.

In the year 1991, National Immunization Program (NIP) for HBV vaccination were held in all countries and World Health Organization (WHO) suggested vaccination as a course of 3 series to be provide on day 0 and 1, 6 months. HBV infection is prevented by effective strategy in Infant immunization by NIP. Vaccine immune response or seroprotection were provided by both combined and monovalent vaccines. Single Antigen Formulation (SAF) and in Combination with Other Vaccines (COV) are available. At birth, SAF is recommended but COV is not recommended usually [26].

4. HBV VACCINATION AFTER SUFFICIENT RESPONSE

Various clinical trials were performed to investigate the effective vaccine dose and its optimal vaccination schedule for different individuals like infants, neonates, adults and immune suppressed individuals. HBV vaccine will produce adequate titer and remain persistent. Vaccine Induced immunity or immunity due to infection is observed by serological marker called anti-Hbs (Antibody to hepatitis B Surface antigen). ≥10 mIU/mL is the antibody titre that shows protective immune response after vaccination as per Centers for Disease control and prevention (CDC). 3 courses are required minimally for the immune response [27].

5. VACCINATION OF LIVER TRANSPLANTED INDIVIDUALS

After administration of a course of HBV vaccine, requires a booster dose for ensuring a year later based on the serological test. For these individuals, their seroconversion is particularly low contrast to healthy individual [28]. The seroconversion rate had low intensity due to immunosuppressant medication as well as disease severity. To control vaccine failure, repeated vaccination and intensified doses were given. Individuals who has undergone liver transplantation before for chronic HBV infection were merely dependent on immunosuppression drugs or hepatitis B immune globulin (HBIG) but recent vaccine that have been succeed to decrease use of HBIG [29-31].

6. VACCINATION OF INDIVIDUALS WITH POOR IMMUNE RESPONSE

In initial course, the individual having < 10 mIU/mL Anti-Hbs is considered to be unresponsive to vaccine. Smoking, old age, gender, Body mass index, immunodeficiency, hemodialysis, celiac diseases, chronic HBV infection and inappropriate storage etc., are the constraining effect of Anti Hbs response [32]. After HBV vaccination, there is a high risk for cirrhotic patients due to flare from immune mediated hepatitis. In Major histocompatibility complex (MHC), genetic predisposition is occurred by absence of a satisfactory response [33].

7. MUTANTS OF HBsAG

Due to mutant variants, vaccine failure occurred in numerous reports but the incidence of these mutants were unknown. After administration of a course of vaccine, antibody will be produced against major hydrophilic domain of HBsAg in determinant epitope cluster [34]. A survey conducted in Taiwan about hepatitis B surface variant in children and their prevalence shows that significantly raised vaccine escape mutant from pre vaccination to post vaccination in these days. In the year 1984, prevalence shows 7.8%, in 1989 - 19.6% and in 1999 - 23.1%. Prevalence of 32% of vaccinated children group is higher compared to 9% of unvaccinated group.[35] Another study was conducted in prevalence of G145 R mutation in Italy and their result shows 3.1% from 256 patients [36]. Prevalence of escape mutants were studied in China by post mass vaccination in children, results showing that in 1992 it was 6.5% and in 2005 it was 14.8% by their G145 R – predominant mutation [37].

8. INDIVIDUALS WHO ARE NON-RESPONDERS

Primary HBV vaccine series failed for nearly 5% of immunocompetent people. There is no clear vision on nonresponse but certain individuals are at major risk, those with persistent diseases, immunosuppressant medication and genetic predisposition. For these population, the observations found was quite interesting. CD-4 T-helper cells that was obtained from viral peptides played an important role in Human Leukocyte antigen (HLA) along with Major Histocompatibility Complex (MHC) and individuals who failed to respond had defect in T helper cells stimulation or antigen presentation. Various studies show that individuals who are homozygous have non-responsiveness due to increased predisposition by HLA DRB1*0301, SC01, HLAB44, DR-7, FC-31 and HLA –B8 [38]. In a study conducted among > 60 years old, out of 70 individuals, 32 developed anti-Hbs [39]. In another study among >59 years old, out of 106 individuals, only 60% developed anti-Hbs after post vaccination [40]. About 8% to 72 % of the seroconversion rate varied in HIV patients depending on their immune status. The individuals who are not receiving HAART therapy, their immune response rate is 30% - 50% while of those receiving therapy shows increase in response about 60% to 70% and it is inversely proportional to their viral load and directly proportional to their CD-4 Count [41,42]. Blunted response was observed in individuals with chronic liver disease (CLD) [43]. In a study conducted among hepatitis C infected patients who were vaccinated, their seroconversion results were 55%. Out of these individuals, robust response was observed only in 37%. Interestingly, Genotype 1 had a poor response rather than other genotypes. Moreover, immune response to vaccination was measured by MELD score that is inversely proportional to advanced liver disease [44,45]. In a study conducted by evaluating response rate to HBV vaccine, Creatinine level was 1.5 to 3.0 mg/dL, > 6.0 mg/dL, 3.0 to 6.0 mg/dL, resulting mild, severe, moderate respectively to chronic kidney disease (CKD). After administration of third dose, it shows 87.5, 35.7% and 66.6% respectively. Rates were improved after administration of fourth dose, 100%, 36.4% and 77% respectively [46].

9. APPROACHES TO VACCINATE NON-RESPONDERS BY STANDARD THERAPY

9.1 Increased Dose

Individuals in high risk groups have an elicit immune response by raising dosage with the considerable data. A study was conducted, results showing that 68% of individuals had response while double dosing in pre transplant patients shows that 41% of the individuals had robust response [47]. Another study shows 80% of the chronic hepatitis C patients responded after administration of a high booster dose [48]. Another study was conducted in CLD patients by shorter interval and higher dose that resulted in 72% response. Non-cirrhotic has a higher immune response rather than the cirrhotic (80% vs 54%), after administered booster dose, 74% and 88% respectively were increase in their response [49].

9.2 Intradermal Administration

Various studies show that the antigen presenting dendritic cells (APCs) present in skin, especially in the dermis layer further activates the immunogenic cells in lymph node, which enhances the immune cascade activation and protective antibodies [50-52]. In another study, the efficacy is compared both intra dermally (ID) and intra muscularly (IM), the resulting IM has the high immune response. T & B cell response, IM form has lower ID form. Recommending ID in

the dermis may result in antigen trapping in the skin that might develop robust and cell mediated immune response along with humoral immunity [53]. In 42 CLD patients were administered a course ID in each arm (20µg), 29 of 42 patients induced immune response and 15 patients produced robust response [54]. Hemodialysis patients who were non responsive primarily, after administered a standard dose showed response rate of 40% in IM vs. 79% in ID, 5µg of dose were injected ID weekly for 8 weeks and was compared to IM (40µg) dose at 1st and 8th week. IM group were less powerful than the ID group [55].

9.3 Upgraded Immunogenicity

Most of the researches were concentrated on upgrading the immune response by pre-S1, nucleocapsid containing HBcAg, pre-S2 particle to the S-protein to emphasize effectiveness of the vaccine [56-58]. A study conducted in 100 non responsive health care professionals, who failed in immune response after administered 3 doses and booster dose. Triple S recombinant vaccine were administered as a single dose that produces response in 69 patients. In parallel, immune response rates were 71% and 65%, after 3rd and 4th dose of pre-S2 & pre-S1 recombinant vaccine in chronic renal failure patients who were non-responders [59].

9.4 Adjuvants and their Uses

Currently, Aluminum (Al) is used as an adjuvant in HBV vaccine to enhance immune response. A combination of Al with 3-deacylatedmonophosphoryl lipid A (3D-MPL) shows more immunogenicity than Al in non-responsive individuals, with immune response up to 98% of the individuals after administered 3 doses. Delta inulin and polysaccharide adjuvant, shows immunogenicity by Advax™ with robust response in preclinical trials contrast with conventional Al [60].

9.5 Surrogate Mechanism

A study was conducted in liver and spleen of transgenic mice that was infected by HBV, comparing immunity production between HepBcAg and HepBsAg with pulsed dendritic cells. Their results show that the stimulated cells of surface antigen in account with production of surface antibodies stimulated cells of core antigen with both surface and core antibody titers high. For the development of next generation HBV vaccine by using core antigen, there are undergoing researches [61].

9.6 Vaccine Combination

HepBsAg and HepBcAg were employed to induce cell mediated/humoral immune response which controls infection by stimulating memory B cells (antibody production) as well as CD-8 T cells. A novel vaccine that contain HepBcAg and HepBsAg has proven to be effective (a saponin-based ISCOMATRIX adjuvant). Chronic HBV infected mice induces plasma cells as well as HBcAg and HBsAg specific CD-8 T cells to produce antibodies as high titres against the antigen [62]. A study was conducted in 44 individuals, with 3 doses of hep B & Hep A vaccine in IM who were non responders for four doses of ID vaccine. 42 (95%) individuals shows an immune response against vaccination with high titers. Hence Hep A antigen induces response against immune system, it can also act as an adjuvant [63]. A research was done in combination of HPV 16/18 with HBV vaccine and administered to the non-responder women, in two groups there was no difference. This concluded that immunogenicity is not affected by co-administration of vaccine [64].

10. CONCLUSION

HBV is a serious global threat for human population. In attribute to both mortality and morbidity by HBV infection, vaccines are readily available and efficacious against this virus. In worldwide, CLD and hepatocellular carcinoma were remarkably decreased via vaccination. 95% of the immune response that is induced by vaccine shows long lasting and durable immunity. For high risk individuals such as health care professionals, patients with IV drugs, patients with CKD and diabetes mellitus, efforts should be made to ensure the immunity against vaccination. Therapeutic potential and long lasting immunity were demonstrated by different vaccines. Pre-S1 and pre-S2 portions of HBsAg are used for the improvement of HBV vaccination. As upcoming approaches, antigen dose were increased, alternative vaccination, new adjuvants such as immunostimulatory DNA sequences and accelerating vaccination schedules are followed in practice. Increased dosage vaccines, upgraded immunogenicity, adjuvants, surrogate mechanism, combined vaccines and administration of intradermal vaccines are the relevant approaches for a non-

responder. Further studies has to be conducted on HLA alleles that can overcome the obstacles in HBV therapeutics.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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