


Immunological Review on Non-responder Phenomenon to Hepatitis B Vaccination

Adika Zhulhi Arjana,[1] Ninda Devita[2]

[1]Department of Clinical Pathology, Faculty of Medicine, State University of Yogyakarta,
[2]Department of Microbiology, Faculty of Medicine, Indonesia Islamic University, Yogyakarta, Indonesia

ABSTRACT

Hepatitis B vaccine has been highly effective in preventing HBV infection. However, a subset of individuals fails to develop adequate protective antibodies after complete vaccination series (anti-HBs ≥ 10 mIU/mL), termed as non-responders. Non-responder phenomenon is influenced by a complex interplay of genetic, immunological, and environmental factors. This narrative review aims to delve into the immunological aspects of the non-responder phenomenon, exploring the factors influencing vaccine response, the immunological mechanisms involved, and potential approaches to managing and overcoming non-responders.

Keywords: Hepatitis B vaccine, immune response, non-responders.

ABSTRAK

Vaksin Hepatitis B sangat efektif mencegah infeksi HBV. Namun, beberapa individu yang disebut kelompok *non-responden* gagal mencapai titer antibodi yang memadai (anti-HBs ≥ 10 mIU/mL) setelah vaksinasi lengkap. Fenomena non-responden dipengaruhi oleh interaksi kompleks antara faktor genetik, imunologi, dan lingkungan. Tinjauan pustaka ini bertujuan untuk menelaah aspek imunologi fenomena non-responden, mengeksplorasi faktor-faktor yang memengaruhi respons vaksin, mekanisme imunologi yang terlibat, dan langkah untuk mengatasi fenomena non-responder. **Adika Zhulhi Arjana, Ninda Devita. Tinjauan Imunologik Fenomena Non-responden Terhadap Vaksinasi Hepatitis B.**

Kata Kunci: Vaksin hepatitis B, respons imun, non-responder.

INTRODUCTION

Hepatitis B is a significant global health issue, caused by hepatitis B virus (HBV), which can lead to chronic liver disease, liver cirrhosis, and hepatocellular carcinoma.[1] World Health Organization (WHO) estimated 254 million people were living with chronic hepatitis B infection in 2022, resulting in over 1,1 million deaths primarily due to cirrhosis and liver cancer.[2] Effective prevention of HBV infection through vaccination has been a cornerstone in the global effort to reduce the burden of this disease.[3]

Hepatitis B vaccine, first introduced in the early 1980s, has been highly effective in preventing HBV infection. It is typically administered in a three-dose series, eliciting protective antibody levels (anti-HBs ≥10 mIU/mL) in over 90% of healthy individuals.[4] The vaccine induces an immune response that generates memory B cells and long-lasting protection against HBV.[5]

Despite the high efficacy of the Hepatitis B vaccine, a subset of individuals fails to develop adequate protective antibodies after the complete vaccination series. These individuals are termed "non-responders." The prevalence of non-responders varies but is generally estimated to be between 5% and 10% of vaccinated individuals.[6–8] This phenomenon poses significant public health challenges, as non-responders remain susceptible to HBV infection despite vaccination efforts.

The non-responder phenomenon is influenced by a complex interplay of genetic, immunological, and environmental factors.[6] Understanding the underlying mechanisms that contribute to non-response is crucial for developing strategies to enhance vaccine efficacy and ensure broader protection against HBV. This narrative review aims to delve into the immunological aspects of the non-responder phenomenon, exploring the factors influencing vaccine response, the immunological mechanisms involved, and potential approaches to managing and overcoming non-responsiveness.

DISCUSSION

Mechanism of Action of the Hepatitis B Vaccine

The Hepatitis B vaccine is primarily composed of the hepatitis B surface antigen (HBsAg), which is produced using recombinant DNA technology. When administered intramuscularly, the HBsAg is recognized as a foreign antigen by the immune system, initiating a cascade of immune responses.[9,10]

Upon injection, the vaccine's HBsAg is taken up by antigen-presenting cells (APCs), such as dendritic cells and macrophages, in the muscle tissue. These APCs process the antigen and migrate to the nearest lymph nodes, where they present the antigenic peptides to naïve

Alamat Korespondensi *email: adikazhulhiarjana@uny.ac.id*

T cells via major histocompatibility complex (MHC) molecules.[11] These cells process the antigen and present it on their surface using MHC class II molecules. The binding of HBsAg to pattern recognition receptors (PRRs) on the surface of APCs triggers their activation. This activation leads to the secretion of pro-inflammatory cytokines, such as IL-6, IL-12, and TNF-α, which enhance the recruitment and activation of additional immune cells.[12]

In the lymph nodes, APCs present the HBsAg-MHC complex to naïve CD4+ T cells (helper T cells) and CD8+ T cells (cytotoxic T cells). This interaction, along with co-stimulatory signals provided by the APCs, activates the T cells. Activated CD4+ T cells differentiate into various subsets, including Th1 and Th2 cells. Th1 cells produce cytokines like IFN-γ, which support cell-mediated immunity and the activation of cytotoxic T cells. Th2 cells produce cytokines like IL-4 and IL-5, which support humoral immunity and B cell activation. Although the primary role of cytotoxic T cells is in targeting infected cells, they also contribute to the overall immune response by eliminating cells that may transiently express HBsAg during the immune response.[13,14]

B cells with receptors specific for HBsAg bind the antigen and internalize it, processing and presenting it on MHC class II molecules to helper T cells. This interaction, along with cytokine signals from Th2 cells, leads to B cell activation, proliferation, and differentiation into plasma cells. Plasma cells secrete large quantities of anti-HBs antibodies, which bind to HBsAg, neutralizing the virus and preventing its entry into hepatocytes. These antibodies also facilitate opsonization and the clearance of the virus by phagocytic cells.[15,16]

Factors Influencing Vaccine Response

The response to the Hepatitis B vaccine is influenced by a variety of factors, including genetic, demographic, health-related, and environmental elements.

1. Genetic Factors

The human leukocyte antigen (HLA) system plays a crucial role in the immune response to vaccines. Certain HLA types have been associated with a higher likelihood of non-response to the Hepatitis B vaccine. Individuals with HLA-DRB103 and HLA-DRB107 alleles have been found to have a lower response rate.[17] The HLA system affects antigen presentation to T cells, influencing the subsequent immune response. Variations in HLA genes can lead to differences in how the immune system recognizes and processes the HBsAg, impacting the effectiveness of the vaccine.[18]

Specific genetic polymorphisms in immune-related genes, such as those encoding cytokines and their receptors, can also influence vaccine response. Polymorphisms in the IL-10 gene, which encodes an anti-inflammatory cytokine, have been associated with variations in vaccine response. Genetic variations can affect the production and function of immune system components, altering the overall immune response to the vaccine.[19,20]

2. Demographic Factors

The age of the vaccine recipient significantly influences the immune response. Infants and young children generally have a higher response rate compared to older adults. As age increases, the likelihood of non-response also rises. Age-related decline in immune function, known as immunosenescence, affects the ability of older individuals to mount an effective immune response to the vaccine.[21]

Females tend to have a higher immune response to the Hepatitis B vaccine compared to males. This difference is thought to be due to hormonal and genetic factors that influence immune function. Estrogen and other sex hormones can modulate immune responses, potentially enhancing vaccine efficacy in females.[8,22]

Higher BMI has been associated with a reduced response to the Hepatitis B vaccine. Obesity can impair the immune system's ability to respond effectively to vaccination. Adipose tissue produces inflammatory cytokines and adipokines, which can interfere with immune function and vaccine response.[6]

3. Health-Related Factors

Individuals with chronic diseases, such as diabetes, chronic kidney disease, and liver disease, often have a lower response rate to the Hepatitis B vaccine. Patients undergoing hemodialysis for chronic kidney disease have a significantly lower seroconversion rate compared to the general population.[7,23]

Immunocompromised individuals, including those with HIV/AIDS, cancer patients undergoing chemotherapy, and organ transplant recipients on immunosuppressive therapy, are at a higher risk of non-response. The compromised immune system in these individuals may be unable to mount a sufficient response to the vaccine, necessitating alternative vaccination strategies or additional doses.[21,24]

4. Environmental and Lifestyle Factors

Smoking has been shown to negatively affect the immune response to the Hepatitis B vaccine. Smokers often have lower antibody titers and a higher rate of non-response. The toxic compounds in cigarette smoke can impair immune cell function and reduce the overall effectiveness of the vaccine.[4]

Excessive alcohol consumption can also impair immune function and reduce vaccine response. Chronic alcohol use is associated with a higher likelihood of non-response to the Hepatitis B vaccine. Alcohol can suppress various aspects of the immune system, including the function of APCs, T cells, and B cells.[25,26]

Malnutrition and micronutrient deficiencies can also adversely affect the immune response to the Hepatitis B vaccine. Adequate nutrition is essential for maintaining a healthy immune system. Specific nutrients, such as vitamin A, vitamin D, and zinc, play important roles in supporting immune function and vaccine efficacy.[27,28]

Immunological Mechanisms in Non-responders

Deficient immune signaling pathways significantly contribute to non-responsiveness to hepatitis B vaccination by disrupting the critical steps needed for an effective immune response.[17] One of the key components involved in the initial immune response is the family of Toll-like receptors (TLRs), which are a type of pattern recognition receptor (PRR) expressed on various immune cells, including dendritic cells and macrophages. TLRs recognize pathogen-associated molecular patterns (PAMPs) present on the hepatitis B surface antigen (HBsAg) and play a crucial role in activating innate immune responses. When these receptors function properly, they trigger signaling cascades that lead to the production


of cytokines and the activation of adaptive immune cells.[29]

However, in non-responders, polymorphisms or mutations in the genes encoding TLRs or their downstream signaling molecules can impair this process. Variations in TLR2, TLR3, TLR4, and TLR9 have been studied for their roles in recognizing viral components and initiating immune responses. Deficiencies in these receptors or their signaling pathways can lead to reduced activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and interferon regulatory factors (IRFs), which are transcription factors critical for the production of pro-inflammatory cytokines and type I interferons. These cytokines are essential for the maturation and activation of dendritic cells, which in turn present antigens to T cells, initiating the adaptive immune response.[30–32]

The interferon (IFN) pathway is another critical signaling mechanism that can be impaired in non-responders. Type I interferons, such as IFN-α and IFN-β, are produced in response to viral infections and play a vital role in antiviral defense by enhancing the presentation of viral antigens and the activation of T cells. Defects in the production or signaling of type I interferons can lead to insufficient activation of the adaptive immune response, thereby reducing the effectiveness of the hepatitis B vaccine.[29,33]

T-cell and B-cell dysfunctions also play a critical role in the failure to develop protective immunity in non-responders to hepatitis B vaccination. CD4+ helper T cells are essential for initiating and sustaining a robust immune response. These cells assist in the activation and differentiation of B cells into plasma cells that produce antibodies. In non-responders, several dysfunctions can impair the role of CD4+T cells.[33–35] Suboptimal activation of these T cells can occur due to insufficient interaction with antigen-presenting cells (APCs), such as dendritic cells and macrophages, which present the hepatitis B surface antigen (HBsAg) to T cells. This inadequate interaction can be caused by inefficient antigen processing or presentation, or due to intrinsic defects in the T cells themselves.[33]

The proliferation and differentiation of CD4+ T cells can also be compromised in non-responders due to genetic polymorphisms. Several key molecules involved in T-cell receptor (TCR) signaling pathways could be the source of polymorphisms. Defects in these signaling pathways can result in reduced T-cell activation, proliferation, and cytokine production, leading to an insufficient helper function for B cells.[11,36]

Regulatory T cells (Tregs), which help maintain immune homeostasis and prevent autoimmunity, can also impact the efficacy of the hepatitis B vaccine. An overactive Treg response can suppress the activation and proliferation of effector T cells and B cells, thereby dampening the overall immune response. Elevated levels of Tregs or enhanced Treg activity in non-responders can contribute to the failure to generate a robust immune response to the vaccine.[37,38]

The role of cytokines and other immunomodulatory factors further underscores the complexity of the immune response to hepatitis B vaccination. Cytokines are critical signaling molecules that orchestrate the immune response by promoting or inhibiting various immune functions. An imbalance between pro-inflammatory cytokines (such as IL-2, IFN-γ) and anti-inflammatory cytokines (such as IL-10) can skew the immune environment, potentially suppressing the necessary immune activation and effector functions.[39,40]

Finally, the formation and maintenance of long-lived plasma cells and memory B cells, which are crucial for sustained immunity, can be compromised in non-responders. Memory B cells are responsible for the rapid and robust production of antibodies upon subsequent exposures to the antigen. If these cells are not adequately formed or maintained, the individual may not develop long-term protective immunity despite initial vaccination.[41,42]

Strategies to Managing Non-responders

Non-responders to the Hepatitis B vaccine remain at risk of HBV infection and its associated complications, despite completing the vaccination series. This poses significant clinical and public health challenges. Identifying and managing non-responders is crucial for ensuring adequate protection against HBV. The following approaches are commonly used:

1. Post-Vaccination Testing:

Routine testing for anti-HBs antibodies 1-2 months after completing the vaccination series can help identify non-responders. Those with anti-HBs levels below 10 mIU/mL should be evaluated for potential re-vaccination or alternative strategies.[43] However this strategy is high cost, therefore it is not mandatory in Indonesia Immunization Programme. Many vaccine recipient was labelled as complete without knowing their anti-HBs level.[44]

2. Re-Vaccination Strategies:

Non-responders may benefit from re-vaccination with an additional series of Hepatitis B vaccine doses. Studies have shown that administering up to three additional doses can result in seroconversion in many non-responders.[45] Alternatively, using a different vaccine formulation, such as an adjuvanted vaccine or a vaccine with a higher antigen content, may improve the immune response.

3. Booster Doses:

For secondary non-responders, booster doses may be necessary to maintain protective antibody levels. Regular monitoring of anti-HBs levels can guide the timing and need for booster vaccinations.[46,47]

4. Individualized Approaches:

Personalized vaccination strategies, considering individual risk factors and health status, can optimize vaccine efficacy. This may involve tailored vaccination schedules, higher doses, or the use of adjuvants to enhance the immune response.

Genetic screening for HLA types and other genetic markers associated with non-response can help identify individuals who may benefit from alternative vaccination strategies. Personalized vaccination plans can then be developed based on genetic risk factors. Screening for HLA-DRB103 and HLA-DRB107 alleles can help identify individuals at higher risk of non-response, allowing for tailored vaccine regimens.[48,49]

SUMMARY

The phenomenon of non-responsiveness to the Hepatitis B vaccine presents a significant challenge to global efforts aimed at controlling HBV infection. Despite the vaccine's high efficacy

in the general population, a notable proportion of individuals fail to mount an adequate immune response, leaving them vulnerable to infection and its severe complications.

In addition to genetic and immunological factors, environmental and lifestyle influences can also affect vaccine responsiveness. Factors such as nutrition, stress levels, and exposure to other infections can modulate immune function, potentially impacting the effectiveness of the vaccine. Understanding the intricate interplay of these genetic predispositions, deficient immune signaling pathways, T-cell and B-cell dysfunctions, and the regulatory roles of cytokines and other immunomodulatory factors is essential for developing targeted strategies to enhance vaccine efficacy. Such strategies may include personalized vaccination approaches, the use of adjuvants to boost immune responses, and the administration of additional booster doses. Rigorous monitoring and follow-up of individuals who do not respond to the initial vaccination series are crucial to ensuring that protective immunity is achieved. By addressing the underlying immunological mechanisms, healthcare providers can improve vaccination outcomes and protect all individuals from hepatitis B infection.

Conclusion

While the challenge of non-responsiveness to the Hepatitis B vaccine remains, ongoing advancements in vaccine technology, personalized medicine, and public health strategies offer promising solutions. Continued research, innovation, and global collaboration are essential to overcoming this obstacle and ensuring that all individuals receive effective protection against Hepatitis B.

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