Research Article

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An Evaluation of the Efficacy of High-dose Hepatitis B Vaccine in Patients Using Biological Agents

Biyolojik Ajan Kullanan Hastalarda Yüksek Doz Hepatit B Aşısının Etkinliğinin Değerlendirilmesi

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ABSTRACT

Objectives: Hepatitis B virus (HBV) vaccination is efficient in the normal population, whereas lower humoral response rates in immunosuppressed patients. Biological agents used in the treatment of several diseases in recent years are a significant cause of immunosuppression in patients. In this study we aimed to evaluate the efficacy of double-dose HBV vaccination at months 0, 1, 2, and 6 in patients using biological agents.

Materials and Methods: The patients who were using biological agents and seronegative for HBV received double-dose HBV vaccine (40 µg) on months 0, 1, 2 and 6, and response rates were assessed. Patients with anti-HBs titers >10 mIU/mL one month after completion of the vaccine plan were regarded as vaccine-responsive.

Results: Eighty-four patients were evaluated. Forty patients (47.4%) were men and 44 (52.4%) were women. The mean age of the patients was 43.1±12.5 years. The most common underlying inflammatory rheumatic disease was ankylosing spondylitis at 51.2% (n=43). The most commonly used biological agent was adalimumab at 36.9% (n=31). Vaccine response was achieved in 85.7% (n=72) of the patients, while no response was achieved in 12 patients (14.3%). Sex, comorbidities, type of underlying inflammatory disease and biological agents had no effect on vaccine response.

Conclusion: Administration of 40 µg HBV vaccine at months 0, 1, 2, and 6 to HBV seronegative patients using biological agents was found to be effective. This efficacy was found to be independent of the type of biological agent, the time of onset of the biological agent and the length of use of the biological agent.

Keywords: Hepatitis B vaccines, biological factors, vaccination, hepatitis B virus, rheumatic diseases

ÖZ

Amaç: Hepatit B virus (HBV) aşısı normal popülasyonda etkin iken, immünosüpresif hastalarda humoral yanıt oranları daha düşüktür. Son yıllarda birçok hastalıkta kullanılan biyolojik ajanlar önemli bir immünosüpresyon nedenidir. Bu çalışmada, biyolojik ajan kullanan hastalarda 0, 1, 2 ve 6. aylarda çift doz HBV aşılamasının etkinliğinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Biyolojik ajan kullanan ve HBV için seronegatif olan hastalara 0, 1, 2 ve 6. aylarda çift doz (40 µg) HBV aşısı uygulanarak yanıt oranları değerlendirildi. Aşı şeması tamamlandıktan bir ay sonra bakılan anti-HBs titresi >10 mIU/mL olan hastalar aşı yanıtlı olarak kabul edildi.

Bulgular: Seksen dört hasta değerlendirildi. 40 hasta (%47,4) erkek ve 44 hasta (%52,4) kadındı. Hastaların yaş ortalaması 43,1±12,5 idi. Altta yatan enflamatuvar romatizmal hastalıklarından en sık görüleni %51,2 (n=43) oranında ankilozan spondilit idi. Biyolojik ajanlardan en sık %36,9 (n=31) oranında adalimumab kullanılmıştı. Çalışmada hastaların %85,7'sinde (n=72) aşı yanıtı sağlanırken 12 hastada (%14,3) aşı yanıtı alınamadı. Cinsiyetin, komorbiditelerin ve altta yatan enflamatuvar romatizmal hastalığın ve biyolojik ajanın türünün aşı yanıtını etkilemediği saptandı.

Sonuç: Biyolojik ajan kullanan HBV seronegatif hastalarda; 0, 1, 2 ve 6. aylarda 40 µg HBV aşı uygulamasının etkin olduğu saptanmıştır. Bu etkinliğin biyolojik ajanın türünden, biyolojik ajana başlama zamanından ve biyolojik ajanı kullanma süresinden bağımsız olduğu görülmüştür.

Anahtar Kelimeler: Hepatit B aşıları, biyolojik faktörler, aşılama, hepatit b virüsü, romatolojik hastalıklar

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Introduction

Hepatitis B virus (HBV) infection is a serious global health problem. Chronic HBV infection is a frequent cause of cirrhosis and hepatocellular cancer (1).

Since HBV is a disease that can be prevented by vaccination, contemporary guidelines recommend that high-risk groups should be screened and immunized. According to these guidelines, all patients considered for immunosuppressive therapy should be screened for HBV, and HBV-seronegative patients must be vaccinated. It is also recommended that, if possible, vaccination should be initiated before immunosuppressive therapy (2,3,4,5,6). The risk of HBV reactivation varies depending on the class of immunosuppressive therapy. Cancers and inflammatory and autoimmune diseases play a determining role in the incidence of HBV reactivation (5). Many drugs used in the treatment of these diseases such as antimetabolites, tumor necrosis factor (TNF) inhibitors, steroids, systemic chemotherapy and biological agents lead to immunosuppression (7).

Biological agents are drugs that inhibit specific molecules or cellular targets in the pathogenesis of diseases. They make a positive contribution to prognosis by targeting TNF, interleukin-1 and 6, and cytotoxic T lymphocyte antigen-4 and B cells (8). Biological agents have become increasingly used in the treatment of inflammatory rheumatic diseases, and are a significant cause of immunosuppression in these patients (7).

Humoral response rates to HBV vaccination are >90% in the normal population, but lower in immunosuppressed patients (9). In some studies, response rates were found between 34-49% in immunosuppressive patients (10,11,12). Higher-dose or reinforced vaccines may be required to achieve anti-hepatitis B surface (HBs) response in immunosuppressed patients (13). Antigen specific B and T lymphocytes play important roles in the antibody response to HBV vaccine (14). TNF inhibitors suppresses the T-cell and B-cell mediated immune response (15,16). The Centers for Disease Control and Prevention currently recommends that since vaccine response is low in patients receiving immunosuppressive therapy, vaccination should be applied in a double dose (two concomitant adult HBV vaccine doses) at months 0, 1, 2 and 6 (17).

There are very few studies in the literature evaluating the HBV vaccine response in patients using biological agents. In these studies, it was found that the vaccine response decreased in patients using biological agent therapy (15,18). However, no study evaluating the effectiveness of the high-dose vaccine administered four times was found. Regardless of the type of biological agent used in our study, all patients were administered double dose HBV vaccine for 4 times. The purpose of this study was to evaluate the efficacy of double-dose HBV vaccination at months 0, 1, 2, 6 and to evaluate the factors affecting the vaccine response in patients using or scheduled to be started on biological agents due to underlying diseases.

Materials and Methods

The patients who were using biological agents and followed up in infectious diseases outpatient clinic between January 2017 and July 2018 were evaluated retrospectively in this study.

Hepatitis B surface antigen (HBsAg), hepatitis B core antibody immunoglobulin G, and anti-HBs were investigated using the Enzyme-Linked Immunosorbent Assay method (Roche, Hitachi- Cobas 6000). Patients seronegative for HBV received double-dose HBV vaccine (40 µg) on months 0, 1, 2 and 6, and response rates were assessed. Vaccination was performed both on patients already started on biological agents and on those scheduled to begin using such agents within the following two weeks. Patients' demographic data, underlying diseases, and comorbidities were recorded. Patients' anti-HBs titers were investigated one month after completion of the vaccine schedule. Subjects with anti-HBs titers >10 mIU/mL were regarded as vaccine-responsive.

The study protocol was approved by Karadeniz Technical University Scientific Research Ethics Committee (approval number: 2019-253). Informed consent wasn't obtained.

Statistical Analysis

SPSS 23.0 software was used for statistical data analysis. Student's t test was employed to compare numerical variables between two independent groups, and the chi-square test in the comparison of qualitative data. P-values <0.05 were regarded as statistically significant.

Results

Eighty-four patients who had received vaccination were evaluated. Forty patients (47.4%) were men and 44 (52.4%) were women. The mean age of the patients was 43.1±12.5 years, with a median value of 42 years. The most common underlying inflammatory rheumatic diseases were ankylosing spondylitis at 51.2% (n=43), followed by psoriasis at 25% (n=21), and rheumatoid arthritis at 22.6% (n=19). Reactive arthritis was diagnosed in only one patient. Patients' underlying diseases, comorbidities and biological agents are summarized in Table 1.

The most commonly used biological agent was adalimumab at 36.9% (n=31). No relation was observed between biological agents used and patients vaccine responses (p=0.152).

HBV vaccination was performed a mean two weeks before biological agent use in 43 (51.2%) patients, and during biological agent use in 41 (48.8%). These patients had been using biological agents for a median 36 months. Comparison of these two groups revealed response rates of 81.4% in patients started on vaccine before biological agent use and of 90.2% in those starting vaccine during biological agent use. The difference between the two groups' vaccine responses was not statistically significant (p=0.397).

Thirty-nine (46.4%) patients were using immunomodulatory therapies such as methotrexate and prednisolone before starting on biological agents (Table 1). Use of these therapies prior to biological agents had no effect on vaccine response (p=0.392).

Vaccine response in the form of anti-HBs>10 mIU/mL was achieved in 85.7% (n=72) of the 84 patients receiving HBV vaccine, while no response was achieved in 12 patients (14.3%). Anti-HBs levels in the patients with vaccine response ranged between 19 and 1000 mIU/mL, with a mean value of 740.9±379.9 mIU/mL. The relation between anti-HBs level and biological agent used in patients with vaccine response is shown in Figure 1. Vaccine response was higher in young patients than elders (p=0.049). Sex, comorbidities, and type of underlying inflammatory disease had no effect on vaccine response (Table 2).

Table 1. Clinical and demographic characteristics of patients	
Characteristics of patients (n=84)	
Mean age	43.1±12.5
Median age	42
Gender	n (%)
Male	40 (47.6)
Female	44 (52.4)
The underlying rheumatic disease	
Rheumatoid arthritis	19 (22.6)
Anklylosing spondylitis	43 (51.2)
Psoriasis	21 (25)
Reactive arthritis	1 (1.2)
Comorbid diseases	
Diabetes mellitus	5 (6)
Hypertension	6 (7.1)
Coronary artery disease	3 (3.6)
Chronic lung disease	3 (3.6)
Hypothyroidism	3 (3.6)
Biological agents	
Infliximab	10 (11.9)
Adalimumab	31 (36.9)
Etanercept	21 (25)
Ustekinumab	3 (3.6)
Tofacitinib	7 (8.3)
Golimimab	7 (8.3)
Tocilizumab	3 (3.6)
Sertolizumab	1 (1.2)
Abatacept	1 (1.2)
Drug used before biological agent	
Prednisolone	3 (3.6)
Methotrexate	12 (14.3)
Prendisolone and methotrexate	12 (14.3)
Infliximab	2 (2.5)
Etanercept	4 (4.8)
Abatacept	1 (1.2)
Adalimumab	1 (1.2)
Result	
Vaccine responsive	72 (85.7)
Vaccine unresponsive	12 (14.3)
The mean level of anti-hepatitis B surface in vaccine responders (IU/l)	**740.9 ± 379.9**

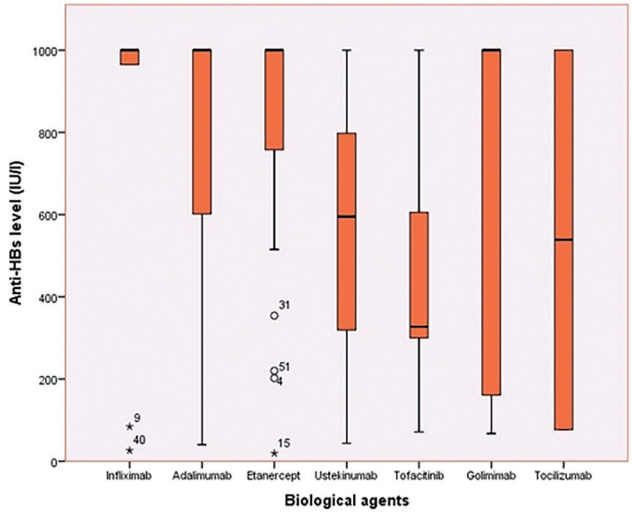

Figure 1. Relation between biological agents and anti-hepatit B surface titers in patients with vaccine responders
Anti-HBs: Anti-hepatit B surface

Discussion

HBV infection is a serious global health problem. Approximately 6% of the world population is chronically infected with HBV (19). HBV is widely transmitted by body fluids such as blood, sperm, and vaginal secretions. The most effective method for protection against this infection is vaccination (17). With its "Global Health Sector Strategy" announced in 2016, the World Health Organization aims for the elimination of viral hepatitis by 2030, and vaccination is the best way to achieve that (20). Thanks to universal HBV vaccination in newborns, the epidemiology of chronic HBV infection has altered dramatically in several parts of the world (19). Due to HBV vaccination at 0, 1, and 6 months, the response rate in healthy adults under 40 now exceeds 90%, although response rates are known to decrease with age. Response rates are lower in immunosuppressed patients (21). Various strategies have been developed in order to increase vaccine response rates in subjects with some chronic diseases or receiving immunosuppressive therapy, including increasing the vaccine dosage, intradermal administration, alternative adjuvants, alternative routes of administration, concomitant administration with other vaccines, and novel therapies (22). One of the methods employed to increase vaccine response in immunosuppressive patients is double-dose (40 µg) HBV vaccination at months 0, 1, 2 and 6 (17).

Biological agents that have become increasingly used in the treatment of inflammatory rheumatic diseases are an important cause of immunosuppression in these patients (7). There are no specific recommendations regarding HBV vaccination in patients using biological agents. As set out in the current guidelines patients receive immunosuppressive therapy must be screened for HBV, and HBV seronegative subjects must be immunized. The guidelines also state that commencing immunization before immunosuppressive therapy increases antibody response (2-4). Two weeks are required for immune response to develop in inactive vaccines. It is therefore recommended that immunization commence two weeks prior to the start of immunosuppressive therapy. However, when immunosuppressive therapy is completed, the timing of vaccination may vary depending on the biological agent employed (23). In contrast to other guidelines, the American College of Rheumatology guideline strongly recommends HBV vaccination in patients with rheumatic arthritis already using biological agents. The reason for this recommendation in the

Table 2. Comparison of vaccine responder and non-responder patients

Characteristics of patients	Anti-HBs positive (n=72, 85.7%)	Anti-HBs negative (n=12, 14.3%)	p
Mean age	42.01±11.75	49.67±15.38	**0.049**
Median age	41.5	51	
Gender	n (%)	n (%)	
Female	40 (55.6%)	4 (33.3%)	0.265
Male	32 (44.4%)	8 (66.7%)	
The underlying rheumatic disease			
Rheumatoid arthritis	13 (18.1%)	6 (50%)	0.108
Anklylosing spondylitis	39 (54.2%)	4 (33.3%)	
Psoriasis	19 (26.4%)	2 (16.7%)	
Reactive arthritis	1 (1.4%)	0	
Comorbidities			
Diabetes mellitus	4 (5.6%)	1 (8.3%)	0.743
Hypertension	5 (6.9%)	1 (8.3%)	
Coronary artery disease	2 (2.8%)	1 (8.3%)	
Chronic lung disease	3 (4.2%)	0	
Hypothyroidism	3 (4.2%)	0	
Biological agents			
Infliximab	10 (13.9%)	0	0.152
Adalimumab	27 (37.5%)	4 (33.3%)	
Etanercept	19 (26.4%)	2 (16.7%)	
Ustekinumab	3 (4.2%)	0	
Tofacitinib	5 (6.9%)	2 (16.7%)	
Golimimab	5 (6.9%)	2 (16.7%)	
Tocilizumab	2 (2.8%)	1 (8.3%)	
Sertolizumab	1 (1.4%)	0	
Abatacept	0	1 (8.3%)	
Start vaccination before using biological agents	35 (48.6%)	8 (66.7%)	0.397
Start vaccination while using biological agents	37 (51.4%)	4 (33.3%)	
Use of immunomodulatory drug before biological agent	29 (40.3%)	7 (58.3%)	0.392

HBs: Hepatitis B surface

guideline is the documented benefit of inactivate pneumococcal vaccine in patients with rheumatic arthritis already using biological agents and the absence of any major concern over damage (24). In our study, HBV vaccination was also administered to patients already using biological agents for a long time in addition to those schedules to receive biological agent therapy. Vaccine response analysis at the end of the study revealed no difference in responses between subjects started on vaccination before biological agent use and those started on vaccination while already using biological agents (81.4% and 90.2%, respectively). Although rituximab was not being used in our study, the type of agent employed and the duration of use had no effect on vaccine response. This shows that high-dose HBV vaccination (40 µg) at months 0, 1, 2 and 6 may be beneficial in patients using biological agents, independently of the type of agent or the length of use.

Haykir Solay and Eser et al. (10) evaluated the results of HBV vaccination in patients with inflammatory rheumatic disease using immunomodulatory therapy. Three doses of 20 µg and 40 µg HBV vaccine were applied on months 0, 1 and 6. Response rates were 49.3% in patients receiving the standard schedule, and 61.1% in the high-dose group. The difference between the two groups was not statistically significant. In addition, response rates in patients using infliximab were lower than in patients using ustekinumab and etanercept. In our study, a four-dose vaccination schedule was employed and a higher vaccine response rate was achieved, but no difference was determined in vaccine responses in terms of biological agents. However, in one study infliximab use was found not to affect the HBV vaccine response rate in children with inflammatory bowel disease (25).

A similar study comparing the efficacy of double-dose HBV vaccine administration at 0, 1, and 2 months in patients with inflammatory bowel disease reported anti-HBs >10 IU/l in 59% of patients. A response rate of 45% was determined in patients using TNF inhibitors (11). The vaccine response rate in the present

study being higher than in that study may be due to our vaccination schedule involving a further double-dose at six months.

Studies of the efficacy of high-dose HBV vaccination in immunosuppressive individuals have largely focused on HIV-positive individuals. Four prospective studies on that subject applied 40 µg HBV vaccine at 0, 1, and 6 months, with response rates ranging between 46.9% and 63.8% (12,26,27,28). Protective antibody response rates of 89.4% and 90.8% were determined n two observational studies in which 40 µg HBV vaccine was administered to HIV-positive patients at 0, 1, 2, and 6 months, (29,30). High-dose HBV vaccination has also been studied and shown to be effective in chronic kidney diseases, cancer patients receiving chemotherapy, drug abusers, nondrug-responsive subjects and cirrhosis patients (31,32,33,34,35). Although the underlying diseases are not the same, these data from the immunosuppressive patient group support our own findings.

Study Limitations

This study has several limitations. The retrospective nature of the study and the small number of patients are main limitations of the study. This study needs to be investigated in a larger number of patients to provide detailed clarification on the relationship of vaccine response with underlying rheumatic disease, age, biological agent used etc. In this study, hepatitis B vaccination was performed in double dose (40 µg) at 0, 1, 2 and 6 months. If a group of patients were given 20 µg of vaccine in the same scheme and these two groups were compared, a better contribution would be made to the literature.

Conclusion

High antibody levels were achieved with the administration of 40 µg HBV vaccine at months 0, 1, 2, and 6 to HBV seronegative patients using biological agents, independently of the type of biological agent and length of use. Our scans of databases such as Pubmed, Google Scholar, Web of Science, and Research gate revealed no similar studies of the efficacy of 20 µg or 40 µg HBV vaccine at months 0, 1, 2, and 6 in patients using biological agents. Vaccination in this patient group should not be overlooked in daily practice. Further studies with larger patient numbers comparing different vaccine doses and schedules are now needed to identify the appropriate schedule and effective dosage.

Ethics

Ethics committee approval: The study protocol was approved by Karadeniz Technical University Scientific Research Ethics Committee (approval number: 2019-253).

Informed Consent: Informed consent wasn't obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices - M.A., Concept: M.A., F.A., Design: F.A., Data Collection or Processing: Z.Y., M.A., Analysis or Interpretation: İ.K., Literature Search: M.A., F.A., Writing: M.A., F.A.

Conflict of Interest: The authors declare no conflict of interest.

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