

# Reactivation rates in patients using biological agents, with resolved HBV infection or isolated anti-HBc IgG positivity

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## ABSTRACT

**Background/Aims:** Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) inhibitors and ustekunimab are widely used in autoimmune diseases. It is known that these biological agents cause the reactivation of hepatitis B virus (HBV). There is no standardized strategy to prevent the reactivation in patients with evidence of a previous HBV infection. In our study, anti-HBc IgG-positive patients who received a biological agent were evaluated in terms of HBV reactivation.

**Materials and Methods:** Patients who were followed up for the use of biological agents in our clinic were evaluated retrospectively. Patients with isolated anti-HBc IgG positivity were included in the study. The HBV reactivation data were recorded from the patients' files retrospectively.

**Results:** Two hundred and seventy-eight patients who received biological treatment were evaluated. Twenty-nine patients with isolated anti-HBc IgG positivity or resolved HBV infection were included in the study. The HBV reactivation was seen in 5 patients (17.2%). Of these patients, 3 were using adalimumab, 1 infliximab, and 1 ustekunimab. It was controlled by antiviral therapy that was started in the early period.

**Conclusion:** Drugs that block TNF- $\alpha$  and ustekunimab cause an increase in viral replication. In literature, the HBV reactivation rate was approximately 1% in HBsAg-negative, anti-HBc IgG-positive cases, whereas it was found to be as high as 17.2% in our study. Patients receiving the immunomodulator therapy should be evaluated for HBV serology before treatment and carefully monitored for HBV reactivation during and after treatment.

**Keywords:** Biological agent, hepatitis B, reactivation

## INTRODUCTION

Hepatitis B virus (HBV) infection is a global public health problem. It is estimated that there are 300 million HBV carriers in the world, of whom roughly 600,000 die annually from liver disease caused by HBV (1). An efficient control of HBV infections requires a concerted action of both innate and adaptive immune responses. During the course of HBV infections, innate immunity induces an antiviral state in infected cells by producing type I interferons, and it supports the efficient maturation and site recruitment of adaptive immunity through the production of pro-inflammatory cytokines, in particular, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Thus, TNF has long been considered a key cytokine in the HBV eradication (2). On the other hand, clinically, a biological agent regimen, such as anti-TNF, reportedly increased the number of HBV reactivation cases

(3-8). TNF- $\alpha$  antagonists, such as infliximab, etanercept, and adalimumab have been widely used for the treatment of rheumatologic, gastrointestinal, and dermatologic autoimmune diseases (4). Infliximab is a chimeric mouse/human monoclonal antibody against TNF- $\alpha$ , clinically used for the treatment of Crohn's disease and ulcerative colitis. Etanercept is a fully human recombinant molecule consisting of two soluble TNF receptor (p75) subunits fused with the Fc portion of human IgG1. Adalimumab is a humanized monoclonal TNF- $\alpha$  inhibitor containing constant and variable regions of human monoclonal antibody (9). Ustekunimab, another biological agent, inhibits the TNF- $\alpha$  production indirectly by the interleukin (IL) blockade and is used in the management of psoriasis and psoriatic arthritis (10). These biologic agents are known to cause HBV reactivation (11).

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Reactivation occurs in 1% to 10% of individuals positive for hepatitis B surface antigen (HBsAg) during the biological agent therapy, and it may lead to severe hepatitis and/or hepatic insufficiency in 25% to 50% of patients who do not receive preemptive or prophylactic antiviral treatment (12). Therefore, anti-hepatitis B core antigen antibody (anti-HBc IgG) screening and close monitoring of these patients is of critical importance, especially in the HBV endemic areas (13). In the present study, anti-HBc IgG-positive patients receiving ustekinumab or other TNF-α inhibitors were evaluated in terms of HBV reactivation.

**MATERIALS AND METHODS**

The records of patients treated with biologic agents in the infectious disease and clinical microbiology clinics were evaluated retrospectively.

Those patients who had a serologically proven past HBV infection (anti-HBc IgG positive, HBsAg negative, hepatitis B surface antibody [anti-HBs] positive or negative), were treated with a TNF-α inhibitor or ustekinumab, and whose HBV DNA levels were measured at the beginning of the treatment and during follow-up were included in the study. Patients who were HBsAg negative, anti HBc IgG positive, anti-HBs negative, and HBV DNA negative are described as isolated anti-HBc IgG positive, while pa-

tients with HBs Ag negative, anti-HBc IgG positive, anti-HBs positive and HBV DNA negative are described as resolved HBV infection.

Patients diagnosed with chronic HBV infection and those positive for HBV DNA and/or signs of hepatitis at the beginning of treatment were excluded.

Anti-HBs levels above 10 IU/mL were considered positive, and those below were considered negative.

Reactivation was defined as the detection of HBV DNA and/or HBsAg conversion in blood analysis during the follow-up. Hepatitis was defined as alanine aminotransferase (ALT) elevation at or exceeding the normal level 5 times (14).

Age, gender, primary disease, type of biologic treatment (adalimumab, etanercept, infliximab, ustekinumab), and treatment duration were recorded retrospectively from the patients’ medical records. The ALT levels measured at baseline and every 3 months, HBsAg, anti-HBc IgG, anti-HBs, and HBV DNA values measured at baseline and every 6 months were recorded.

This study was conducted with the local ethical committee approval of our hospital in December 2017.

**Statistical analysis**

Statistical analysis was performed using the SPSS package version 20.0 (IBM Corp.; Armonk, NY, USA). Descriptive analyses were presented using percentages, minimum-maximum, means, and standard deviations.

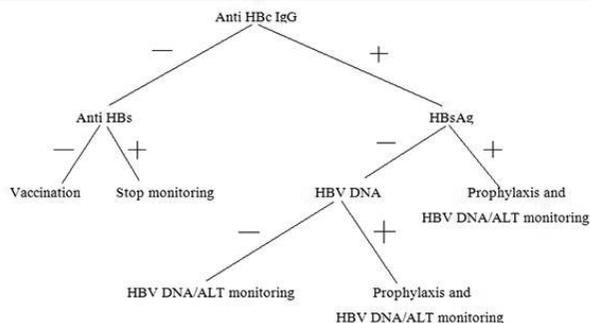
**RESULTS**

The files of 278 patients who received biologic treatment for various reasons were screened. Sixty patients had evidence of past HBV infection. Of these, we excluded 13 patients whose viral load was not assessed at the beginning of treatment, 11 patients who had hepatitis findings due to the use of an additional drug (isoniazid in 10, methotrexate in 1), 5 patients who had chronic HBV infection, and 2 who were positive for HBV DNA at the beginning of treatment. Therefore, our analysis included a total of 29 patients who had evidence of past HBV infection and were using a biologic agent.

Eight of the 29 patients had isolated anti-HBc IgG positive, and 21 had HBV infection. The mean age of the patients was 50.7 years. All were anti-HBc IgG positive and HBsAg negative. Twenty-one (72.4%) patients were

**Table 1.** Patients’ diagnoses

Disease	n (%)
Psoriasis	23 (79.4%)
Hidradenitis suppurativa	2 (6.8%)
Ankylosing spondylitis	2 (6.8%)
Rheumatoid arthritis	1 (3.4%)
Crohn’s disease	1 (3.4%)



**Figure 1.** Algorithm for HBV infection monitoring in patients using biologic agents

**Table 2.** Evaluation of patients receiving antiviral therapy

Patient No.	Primary diagnosis	Immunosuppressive Agent	Prophylaxis	Reactivation	HBV DNA (copy/ml)	Time to reactivation (months)	Antiviral agent
1	Psoriasis	Adalimumab	+	-	0	-	Lamivudine
2	Psoriasis	Adalimumab	+	-	0	-	Lamivudine
3	Psoriasis	Adalimumab	-	+	28	12	Entecavir
4	Psoriasis	Adalimumab	-	+	72	12	Entecavir
5	Psoriasis	Infliximab	+	-	0	-	Tenofovir
6	Rheumatoid arthritis	Infliximab	-	+	46	18	Entecavir
7	Psoriasis	Ustekinumab	-	+	53	6	Entecavir
8	Psoriasis	Adalimumab	-	+	78	12	Entecavir

male, and 8 (27.6%) were female. The mean follow-up time was 22 weeks (12-120 weeks). The diagnoses details of these patients are summarized in Table 1. The biological agents used in our study are adalimumab (n=19, 65.5%), ustekinumab (n=7, 24.1%), infliximab (n=2, 6.8%), and etanercept (n=1, 3.4%).

Two patients who started adalimumab and 1 patient who started infliximab were given prophylaxis, and no reactivation was observed during the follow-up. Five patients became positive for HBV DNA during the follow-up (3 were taking adalimumab, 1 infliximab, and 1 ustekinumab). The reactivation rate was 17.2% among all patients treated with a biologic agent, and it increased to 19.2% when only patients who did not receive prophylaxis were evaluated. In patients without ALT elevation or HBsAg conversion, viral load returned to zero 6 months after the antiviral treatment was initiated (Table 2). Four (80%) of these patients were being treated for psoriasis and 1 (20%) for rheumatoid arthritis.

The HBV reactivation occurred in 50% (4/8) of isolated HBe IgG-positive patients, but only in 4.7% (1/21) of patients with resolved HBV.

## DISCUSSION

TNF- $\alpha$  stimulates the acute phase reaction and is an essential cytokine for the host defense against infective pathogens (15). It is synthesized by active macrophages and T cells, and it stimulates the release of inflammatory cytokines such as IL-1, IL-6, and IL-8. It induces inflammation and apoptotic cell death, while suppressing tumorigenesis and viral replication (9). TNF- $\alpha$  is necessary for the proliferation of HBV-specific T lymphocytes (16). HBV is eliminated through mechanisms such as destabilization of the viral capsid, degradation of viral proteins by

protease and nitric oxide activity, and post-transcriptional DNA fragmentation (17). For these reasons, reduced TNF- $\alpha$  production is associated with chronic HBV infection (18).

Hepatitis B virus infection is one of the most common viral infections in humans. There are 248 million carriers of HBV worldwide (1). In Turkey, this number is approximately 3 million, and the average of exposure to HBV infection has been reported as 30.6%, similar to the global average. The isolated anti-anti-HBe IgG positivity is 4.6% (19). The virus genome remains in covalently closed circular form (cccDNA) in the nuclei of infected cells throughout the patient's lifetime (18). Increases in the TNF- $\alpha$  production are detected in these patients (6). Therefore, the HBV reactivation is expected with drugs that cause the TNF- $\alpha$  blockade; the HBV antigen presentation decreases and leads to increased viral replication (7).

Chronic inflammatory diseases such as psoriasis, ankylosing spondylitis, and rheumatoid arthritis are associated with high TNF- $\alpha$  levels. As this indicates that the TNF- $\alpha$  elevation may be a factor in tissue damage, treatments aim to inhibit this cytokine (9). There are five drugs that block TNF- $\alpha$ : adalimumab, golimumab, certolizumab, etanercept, and infliximab (18). Ustekinumab inhibits the TNF- $\alpha$  production indirectly by IL-12 and IL-23 blockade (10).

The HBV reactivation while using a TNF- $\alpha$  inhibitor or ustekinumab has been reported at rates ranging from 1% to 10% in the HBsAg-positive patients and 1% in patients negative for HBsAg and positive for anti-HBe IgG (1). Of all the TNF- $\alpha$  inhibitors, infliximab is the most commonly reported reason of reactivation in the literature (2). However, it should be noted that these patients also used other immunosuppressive drugs such as corticosteroids

or methotrexate (8). Moreover, infliximab was the first TNF- $\alpha$  inhibitor to gain an approval by the Food and Drug Administration and enter the market (2). For this reason, more experience and reports on side effects are expected. Two of the patients in our study were using infliximab. One received prophylaxis and experienced no reactivation. Other was being treated for rheumatoid arthritis and was also taking prednisone at 4 mg/day. This patient was considered at moderate risk of HBV reactivation due to infliximab use and low risk due to prednisone use; however, the patient developed reactivation. This suggested that the combined use of two immunosuppressive agents may have increased the likelihood of reactivation. There are few case series and case reports in the literature concerning the HBV reactivation after adalimumab use (8). Nineteen of the 29 patients we followed were using adalimumab. Two of those patients received prophylaxis. Reactivation occurred in 3 patients (16.6%) who did not receive prophylaxis. Reports of HBV reactivation with ustekinumab are also very limited, and reactivation reportedly occurs more in patients who are HBsAg positive (20). However, it is accepted that it can also cause reactivation in cases with isolated anti-HBc IgG positivity due to its mechanism of action. Reactivation occurred in 1 (14.2%) of the 7 patients using ustekinumab in our study. The rates of HBV reactivation identified with etanercept therapy are similar to those of adalimumab (21). Since there was only 1 patient in our study with etanercept, no comment could be made on the specific rate. We determined a reactivation rate of 17.2% when all patients using biologic agents were analyzed collectively, which is higher than reports found in the literature. This may be due to the low number of patients or the paucity of previous reports. Larger studies are needed, especially in areas where HBV infection is endemic.

Among anti-HBc-positive patients using biologic agents, more than two-thirds of those had detectable anti-HBs. Among such patients, the HBV reactivation was observed in approximately 5%, a frequency that is slightly lower than isolated total positive (anti-HBc) patients (10). This suggests that the presence of anti-HBs cannot be protective against reactivation. A small number of studies have reported fewer cases of severe hepatitis among patients positive for anti-HBs (11). In our study, 4 (80%) of the 5 patients who experienced reactivation were negative for anti-HBs. In other words, 4 of the 8 who were anti-HBs negative experienced reactivation. However, reactivation occurred in only 1 of 21 anti-HBs-positive patients (4.7%). These findings suggest that anti-HBs may be protective against reactivation.

Viral burden is the first sign of the HBV infection reactivation, followed by a transaminase elevation and seroconversion (22). In our study, the ALT level was measured every 3 months, and HBV DNA and HBsAg were assessed every 6 months. The HBV DNA positivity was detected before the ALT elevation in all patients. This algorithm is thought to allow early detection of reactivation and possibly prevent unnecessary antiviral treatment. As a result, this method should be effective both in terms of limiting costs and in preventing resistance development (Figure 1).

Lamivudine resistance is reported to be 20% in the first year and 30% in the second year in immunocompromised patients. Due to the extended duration of treatment, entecavir or tenofovir are recommended when antiviral therapy is needed for patients taking biologic agents (10). In our study, reactivation was treated and successfully suppressed with entecavir.

Patients who are to begin treatment with biologic agents should be evaluated for HBV infection. HBV DNA should be assessed in patients with evidence of past HBV infection, regardless of anti-HBs titers. Antiviral prophylaxis should be initiated in patients who are HBV DNA positive, and potent drugs are preferable due to the long duration of immunosuppression. The American Gastroenterology Association suggests antiviral prophylaxis over monitoring for patients at moderate risk undergoing immunosuppressive drug therapy (4). For patients who are negative for HBV DNA, the ALT levels should be measured every 3 months, and HBV DNA and HBsAg every 6 months.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Ethical Committee of the Dışkapı Yıldırım Beyazıt Training and Research Hospital (Decision Date: December 2017).

**Informed Consent:** Written informed consent was obtained from the patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

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**Conflict of Interest:** The authors have no conflict of interest to declare.

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