



The frequency of hepatitis B virus reactivation in patients receiving anti-TNF treatment: A single center, retrospective study

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Abstract

Aim: The equilibrium between the host immune response counter the hepatitis B virus (HBV) and the amount of viral replication is a crucial factor in the pathogenesis of HBV-associated liver disease. Tumor necrosis factor-alpha (TNF- α) is a considerable proinflammatory and immune regulatory cytokine in the pathogenesis of various inflammatory and autoimmune conditions. There is no consensus on using antiviral prophylaxis treatments in cases who have been exposed to hepatitis B but have not become chronically ill, and are thus planned to receive anti-TNF- α treatment. The aim of this study is to determine the frequency of reactivation after anti-TNF treatment in cases with isolated anti-HBc total positivity who have been exposed to hepatitis B virus.

Materials and Methods: Serological HBV infection markers (HBsAg, anti-HBc IgG and anti-HBs) of 1467 adult cases who received anti-TNF therapy for the indications of various rheumatological diseases in the rheumatology and physical therapy clinics between the years 2010-2021 were retrospectively screened using the hospital's electronic information system.

Results: 140 rheumatologic disease cases who took a TNF- α inhibitor (infliximab, adalimumab, etanercept, golimumab, certolizumab) treatment were included in this study. Before the cases were started on TNF- α treatment, all cases were anti-HBc total positive, 110 were anti-HBs positive, 30 were anti-HBs negative, and 4 were HbsAg positive and HBV-DNA negative. The median pre-treatment anti-HBc total and anti-HBs values of the cases were 5.6 IU/L and 79.29 IU/L, respectively. No HBV reactivation was observed in any of the 140 cases after a median follow-up duration of 71.5 (min. 8, max. 185) months.

Conclusion: In conclusion, HBV reactivation was not detected in any of the anti-HBc positive cases included in this study, which suggest that anti-HBc positive cases can be followed up with close follow-up without starting them on anti-TNF therapies and antiviral prophylaxis.

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Introduction

Hepatitis B (HB) is a widespread disease worldwide, affecting roughly 2 billion people and of which 240 million are chronically infected (chronic hepatitis B, CHB) [1].

The equilibrium between the host immune response counter the hepatitis B virus (HBV) and the amount of

viral replication is a crucial factor in the pathogenesis of HBV-associated liver disease [2]. HBV reactivation, which is defined as a abrupt increase in HBV replication, often accompanied by clinical manifestations of hepatocellular injury, is a well-known complication in inactive hepatitis B surface antigen (HBsAg) carriers taking immunosuppressive treatment for autoimmune inflammatory diseases, malignancies, or organ transplantation [3].

Tumor necrosis factor-alpha (TNF- α) is a considerable proinflammatory and immune regulatory cytokine in the

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pathogenesis of diverse inflammatory and autoimmune conditions [4]. TNF- α inhibitors have been incorporated into the treatments of a variety of autoimmune and inflammatory diseases [4]. Serologic test results pertaining to HBV-specific antigens and antibodies, i.e., HBsAg, total hepatitis B core antibody immunoglobulin G (anti-HBc IgG) and hepatitis B surface antibodies (anti-HBs), should be evaluated to determine the risk of reactivation in cases who are scheduled for anti-TNF therapy [5].

Contrary to some guidelines, European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Disease (AASLD) guidelines recommend using antiviral prophylactic treatments in cases who have been exposed to HBV but have not become chronically ill, that is, patients who were serologically tested positive (+) for anti-HBc total, negative (-) for HBsAg, and (+/-) for anti-Hbs [6–11]. Hence, there is no consensus on using antiviral prophylaxis treatments in cases who have been exposed to hepatitis B but have not become chronically ill, and are thus planned to take anti-TNF- α treatment.

In this context, the objective of this study is to examine the frequency of HBV reactivation in cases who have been exposed to HBV, took anti-TNF- α therapy and followed up in physical therapy and rheumatology clinics but did not take prophylactic antiviral therapy.

Materials and Methods

Ethical approval was received for the study from Inonu University Health Sciences Non-invasive Clinical Research Ethics Committee (Decision no: 2022/2872). Serological HBV infection markers (HBsAg, anti-HBc IgG and anti-HBs) of 1467 adult cases who received anti-TNF therapy for the indications of various rheumatological diseases in the rheumatology and physical therapy clinics between the years 2010-2021 were retrospectively screened using the hospital's electronic information system.

“Chronic HBV infection” was described as having HBsAg positivity for more than 6 months, whereas “past HBV infection” was described as having HBsAg negativity, anti-HBc IgG positivity, and anti-HBs positivity [11,12]. On the other hand, “exposure to HBV infection” was described as having HBsAg negativity, anti-HBc IgG positivity and anti-HBs positivity or negativity (both cases with past HBV infection and cases with isolated anti-HBc IgG positivity) [12,13].

Of the study population, 215 vaccinated patients, 65 patients who received prophylactic antiviral treatment, 72 cases who were not screened for HBV, 106 patients who were screened for HBsAg and anti-HBs but not for anti-HBc total, and 869 patients who were neither vaccinated with HB vaccine nor exposed to HBV were excluded from the study. In the end, 4 patients with HBsAg positivity, 26 patients with anti-HBs negativity and anti-HBc total positivity, and 110 patients with both anti-HBs and anti-HBc total positivity were included in the study sample. None of the cases included in the study sample had any malignancy or additional immunosuppressive illness.

Statistical analysis

The analyses were evaluated in the SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL) 22 package program. Descriptive data were presented as number (n) and percentage values for categorical data and mean \pm standard deviation (mean \pm SD) and median (minimum-maximum) values for continuous data. Since none of the patients developed reactivation, a comparative analysis could not be performed between the two groups. The patients were examined as a single group.

Results

A total of 140 rheumatologic disease cases who took a TNF- α inhibitor (infliximab, adalimumab, etanercept, golimumab, certolizumab) treatment were included in this study. The basic demographic characteristics and primary diseases of the cases are summarized in Table 1. Before the cases were started on TNF- α treatment, all patients were anti-HBc total positive, 110 were anti-HBs positive, 30 were anti-HBs negative, and 4 were HbsAg positive and HBV-DNA negative. The median pre-treatment anti-HBc total and anti-HBs values of the cases were 5.6 IU/L and 79.29 IU/L, respectively. No HBV reactivation was observed in any of the 140 cases after a median follow-up duration of 71.5 (min. 8, max. 185) months.

Table 1. Basic demographic characteristics and primary diseases of the cases.

Demographic and clinical variables	Study Sample (n=140)	n	%
Age Median	55 (min-max)(32-83)		
Gender			
Male		73	52.1
Female		67	47.9
Primary disease			
Rheumatoid arthritis		49	35
Ankylosing spondylitis		90	64.3
Systemic lupus erythematosus		1	0.7

Discussion

TNF- α plays a key role as a proinflammatory cytokine in the host defense mechanism against infectious agents and in the pathogenesis of immune-mediated diseases, as well as in the inhibition of HBV replication through HBV-specific cytotoxic T lymphocytes (CD8⁺) [14]. Suppression of TNF- α can lead to HBV reactivation by reducing the clearance of HBV-infected hepatocyte and eradicating the suppression of viral replication [15]. However, the studies on cases who have been exposed to HBV and have received anti-TNF treatment are limited, and there is no agreement between the findings of these studies.

HBV reactivation prevention and treatment guidelines of the American Gastroenterology Association (AGA), as in EASL guidelines, included HBsAg positive individuals in the high reactivation risk group, and anti-HBc IgG positive individuals, who have been exposed to HBV, in the moderate risk group featuring a reactivation risk between

1-10%, and recommended the use of prophylactic treatment in both patient groups [9,11].

In a study conducted with patients receiving anti-TNF- α treatments, Alvarez et al. determined that HBV reactivation developed in 35 of the 87 patients with HbsAg positivity, and in 9 of 168 patients with HbsAg negativity/anti-Hbc positivity, of whom 1 died due to fulminant liver failure [16].

Similarly, in a retrospective study of 152 HbsAg -/anti-Hbc + cases with rheumatoid arthritis, HBV reactivation was reported in 3 of the 98 patients treated with anti-TNF- α therapies [17]. Additionally, in a recent study by Fidan et al., HBV reactivation was observed in only 1 of the 241 HbsAg -/anti-Hbc + cases who did not take any antiviral treatment [18].

AASLD and EASL guidelines consider exposure to HBV a moderate HBV reactivation risk and therefore recommend prophylactic antiviral treatments in cases who have been exposed to HBV. On the other hand, European Crohn's and Colitis Organization (ECCO) and American College of Rheumatology (ACR) guidelines recommend vaccination over antiviral prophylaxis in these patients [6,7,9,11].

In comparison, among the 4 HBsAg positive patients included in this study, who were considered to be high risk patients, none had HBV reactivation. Similarly, none of the 136 cases with anti-HBc total positivity had HBV reactivation during a median follow-up duration of 71.5 months. These findings support the findings reported in the study by Fidan et al.

Conclusion

In conclusion, HBV reactivation was not observed in any of the anti-HBc positive patients included in this study, which suggest that anti-HBc positive patients can be followed up with close follow-up without starting them on anti-TNF therapies and antiviral prophylaxis. However, randomized controlled studies are still needed to determine the groups at risk for HBV reactivation that need to be given antiviral prophylaxis.

Ethical approval

Ethical approval was received for this study from Inonu University Health Sciences Non-Interventional Clinical Research Ethics Committee (Decision no: 2022/2872).

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