Risk of hepatitis B reactivation during anti-TNF therapy; evaluation of patients with past hepatitis B infection

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ABSTRACT

Background/Aims: Hepatitis B reactivation (HBVR) is an important risk of treatment with tumor necrosis factor inhibitors (anti-TNF). While antiviral prophylaxis is recommended before treatment in hepatitis B surface antigen (HBsAg) positive patients, there is no clear approach for the follow-up or prophylactic treatment of patients with past hepatitis B virus (HBV) infection. This study aimed to evaluate patients with past HBV infection treated with anti-TNF for HBVR and/or HBVR-associated biochemical breakthrough.

Materials and Methods: Patients who received anti-TNF therapy and had past HBV infection (HBsAg negative, anti-HBc IgG positive, anti-HBs negative or positive) were screened and evaluated at 3-month intervals for viral and biochemical breakthrough according to a liver function test (ALT) and HBV DNA level.

Results: A total of 653 patients who received anti-TNF therapy were screened. Ninety of these patients had past HBV infection and had not received antiviral prophylaxis. Anti-HBs positivity and isolated anti-HBc IgG positivity were seen in 87.7% (n: 79) and 12.2% (n: 11) of these patients, respectively. No HBVR was seen in 20% (n: 18) of patients who were followed up regularly, and no HBVR-associated biochemical breakthrough was found in patients who were not followed up regularly in terms of HBV DNA level (80%, n: 72) during the follow-up period (26±16 months).

Conclusion: The use of anti-TNF in patients with past HBV infection has a low risk for HBVR. A follow-up for the ALT and HBV DNA levels at 3-month intervals may be more reasonable than administering antiviral prophylaxis to all patients.

Keywords: Anti-tumor necrosis factor alpha, Hepatitis B virus infection, Hepatitis B reactivation

INTRODUCTION

Hepatitis B virus reactivation (HBVR), which can be seen under immunosuppressive therapy, is a condition characterized by necroinflammation of the liver and viral replication and may result in liver failure (1). Immunosuppressive therapies are currently used in many clinical disciplines. The risk of developing HBVR under these treatments is related to the serological and replication indicators of the current infection status and the type of immunosuppressive therapy (2).

Tumor necrosis factor alpha blockers (anti-TNF) are immunosuppressive agents that have been used for more than 20 years in the treatment of rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and inflammatory bowel diseases (IBD). These drugs may cause weakening of the cytokine cascade involved in HBV clearance, decreased hepatocyte clearance with decreased apoptosis, and inadequate cytotoxic T lymphocyte response to HBV, resulting in HBVR (3). Therefore, prophylactic antiviral treatment is recommended because of the high risk of HBVR in patients with hepatitis B surface antigen (HBsAg)-positive patients who are treated with anti-TNF (4).

According to current treatment guidelines, there is no standardized approach for prophylactic treatment in patients with past HBV infection (patients with negative HBs Ag and positive IgG anti-HBc, with or without positive anti-HBs antibody) in terms of the risk of HBVR (5). This study aimed to evaluate patients with past HBV infection who were treated with anti-TNF in terms of HBVR and/or HBVR-associated biochemical breakthrough.

MATERIALS AND METHODS

A total of 653 adult patients who received anti-TNF treatment between 2013 and 2019 were retrospectively screened for serologic HBV infection markers (HBsAg, anti-HBc IgG, and anti-HBs) from the files recorded in the hospital computer database. Those with past HBV infection (n: 90) were included in this study. Serologic and biochemical follow-up results of these patients were assessed for HBVR and/or biochemical breakthrough.

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HBsAg positivity was defined as "chronic HBV infection". HBsAg negativity, anti-HBs negativity, and anti-HBc IgG positivity was defined as "isolated anti-HBc IgG positivity", and HBsAg negativity, anti-HBs positivity and anti-HBc IgG positivity was defined as "resolved HBV infection" (1, 5). Past HBV infection was defined by the coexistence of negative HBs Ag and positive IgG anti-HBc with or without positive anti-HBs antibody (both patients with resolved HBV infection and patients with isolated anti-HBc IgG positivity) (1, 5).

Patients were excluded from the study if they had not experienced HBV (anti-HBc IgG negative) or were immunized against HBV (anti-HBc IgG negative and anti-HBs positive), had received antiviral prophylaxis due to HBVR risk, had chronic HBV infection and unscreened HBV serology or had not undergone biochemical tests for more than 4 months while they were under treatment.

The demographic characteristics of the patients included in the study, the treatments used before and during the anti-TNF therapies, the results of the liver function tests (ALT and AST) taken at three-month intervals, and the HBV DNA levels measured at any given time under the treatment were recorded.

Biochemical breakthrough was defined as the occurrence of a ≥3-fold increase compared with the normal upper limit of the serum alanine aminotransferase (ALT) level or ALT ≥100 IU/mL (6). HBVR was defined as the presence of any of the following criteria: a) an increase of >1 log10 IU/mL in the HBV DNA level compared with the past value; b) positivity in those who were HBV DNA negative; and c) detection of any positive HBV DNA level in patients whose baseline HBV DNA level was not studied (6).

HBVR-unrelated enzyme elevation or HBVR-unrelated biochemical breakthrough was considered a negative HBV DNA level with a ≥3-fold increase in the ALT level compared with the upper normal limit or ALT ≥100 IU/ml.

MAIN POINTS

- *The HBsAg, anti-HBc IgG, and anti-HBs titers should be evaluated to determine the reactivation risk in patients planned to be administered anti-TNF treatment.*
- *There is no standardized approach for prophylactic treatment in patients with past HBV infection (patients with negative HBs Ag and positive IgG anti-HBc, with or without positive anti-HBs antibody) in terms of the risk of HBVR.*
- *Treatment with anti-TNF in patients with past HBV infection seems to be low risk in terms of HBVR.*

Anti-HBs, anti-HBc IgG, and HBsAg were detected by chemiluminescent microparticle immunoassay (Architect- i2000 SR system; Abbott, Ireland). Seropositivity was defined as anti-HBs and anti-HBc IgG antibody concentrations ≥10 mIU/mL and 1≥s/CO, respectively. Seropositivity or HBsAg was defined as 1≥s/CO. Real-time polymerase chain reaction (PCR) was used for quantification of serum HBV DNA (Real-Time HBV Viral Load Assay Kit; Abbott Laboratories, USA). The detection range of HBV DNA was 10- 1.000.000.000 IU/mL.

This study was approved by the local ethical committee of Umraniye Training and Research Hospital (decision number: B.10.1.TKH.4.34.H.GP.0.01/136;24-07-2019).

Statistical Analysis

The analyses were performed using MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba; Ostend, Belgium; http://www.medcalc.org: 2013). Descriptive statistics (mean, standard deviation, minimum, median, and maximum) were used to define the continuous variables.

RESULTS

Of all the patients who received anti-TNF (n: 653), 86 (26 RA, 12 PsA, 37 AS, and 11 IBD patients) who were not screened for HBV serology were excluded from the study. HBsAg seroprevalence was then determined as 0.8% (n: 5), isolated anti-HBc IgG seroprevalence as 2.2% (n: 13) and resolved HBV infection seroprevalence as 15.6% (n: 89). Patients with negative HBV serology (n: 460, 81.1%) and those who had received prophylactic antiviral therapy (n: 15; 5 patients with HBsAg positivity, 2 with isolated HBC IgG positivity, and 8 with resolved HBV infection) and patients who did not attend a follow-up appointment for more than 4 months within the period when the anti-TNF was used (n: 2) were excluded from the study. The serological profile of all screened patients and the flow chart of the study are shown in Figure 1.

The study included a total of 90 patients, comprising of 52 males (53.3%) and 38 females (46.7%), with a mean age of 46±13 years and mean duration of treatment with anti-TNF of 26±16 months. Of these patients, 14.4% (n: 13) were diagnosed with IBD, 18.8% (n: 17) with RA, 56.6% (n: 51) with AS, and 10% (n: 9) with PsA. The records showed 8.8% of the patients (n: 8) treated with infliximab, 34.4% (n: 34) with adalimumab, 14.4% (n: 13) with golimumab, 10% (n: 9) with certolizumab pegol, and 28.8% (n: 26) with etanercept. Anti-TNF monotherapy was administered to 67.7% of the patients (n: 61), while 32.2% of the patients (n: 29) received combined therapy

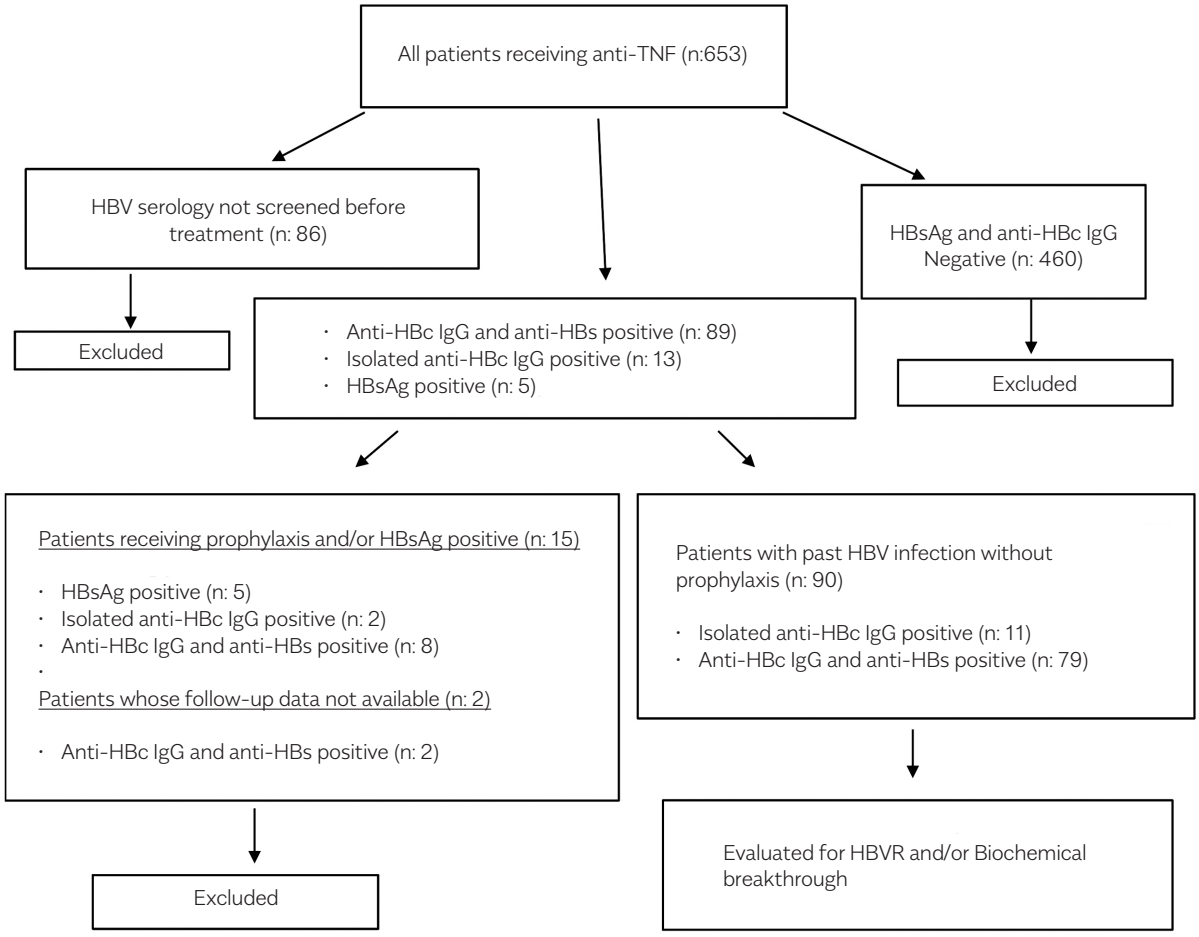

Figure 1. The serological profile of all screened patients (n:653) and the flow chart of the study.

of anti-TNF and corticosteroid and/or immunomodulator. Of the patients receiving combined therapy, 27.5% (n: 8) used corticosteroids (methylprednisolone or prednisone <7.5 mg/day), 20.6% (n: 6) azathioprine, 24.1% (n: 7) methotrexate, and 27.5% (n: 8) methotrexate and corticosteroid (methylprednisolone or prednisone <7.5 mg/day). Resolved HBV infection was seen in 87.8% (n: 79) and isolated anti-HBc IgG positivity in 12.2% (n: 11) of the patients.

Forty-nine (54%) of the patients were negative for HBV DNA before treatment, and 41 (46%) patients did not have HBV DNA levels before the treatment. Eleven patients had isolated anti-HBc IgG positivity. Ten of these patients had negative HBV DNA levels before treatment, and only one patient did not have an HBV DNA level before treatment. The HBV DNA level and liver function tests were followed up regularly at three-month intervals. No HBVR was seen in 20% of the patients (n: 18) during the follow-up period (Table 1). No HBVR-associated biochemical breakthrough was found in patients who were not followed up regularly in terms of HBV DNA level (80%, n: 72). HBVR-unrelated ALT elevations were seen in three patients during the anti-TNF treatment and were attributed to methotrexate use in two patients and isoniazid use in one patient. The follow-up results in terms of HBVR and biochemical breakthrough according to the serologic features are shown in Figure 2.

DISCUSSION

TNF-α plays a key role in the defense mechanism of the host against infectious agents and as a proinflammatory cytokine in the pathogenesis of immune-mediated diseases. TNF-α is involved in the inhibition of HBV replica-

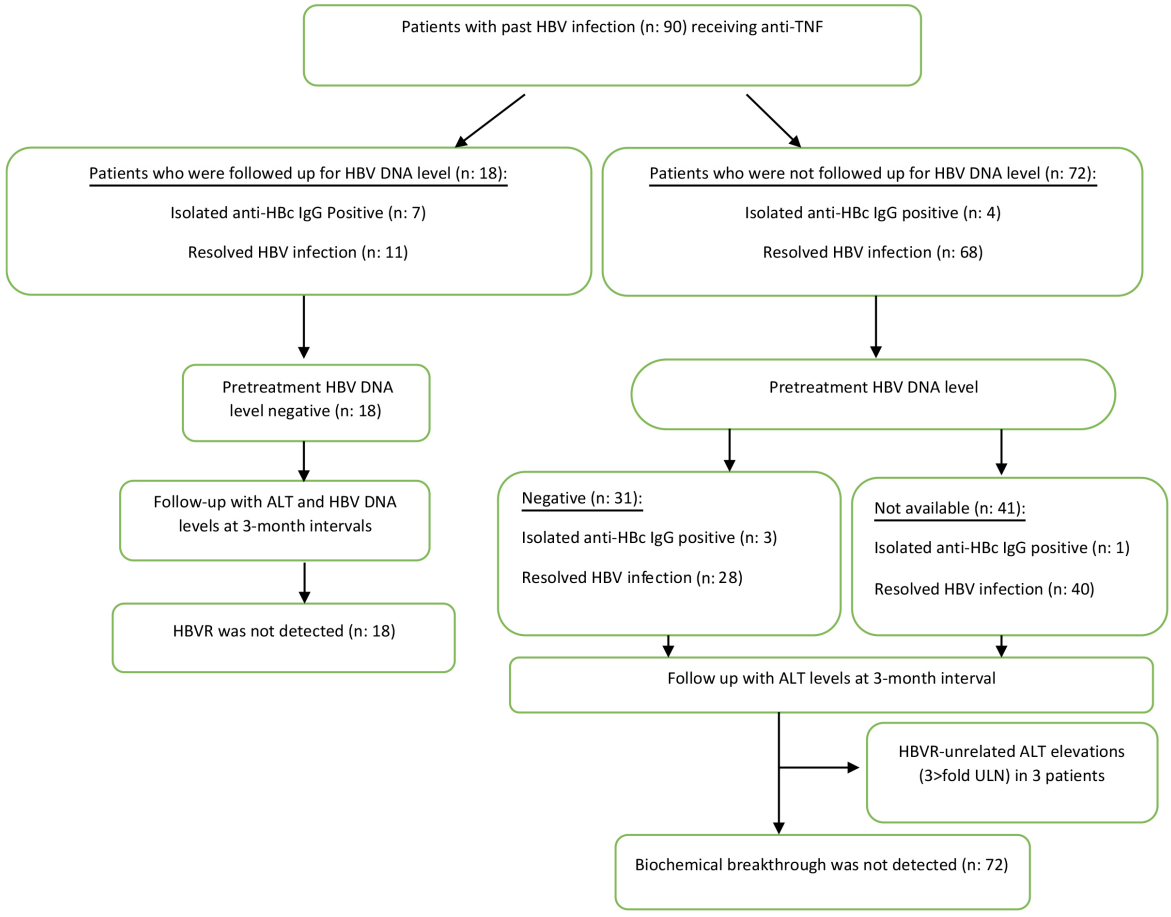

Figure 2. The follow-up results of patients (n:90) in terms of HBVR and biochemical breakthrough according to the serologic features.

tion by means of HBV-specific cytotoxic T lymphocytes (CD8+) (7). Suppression of TNF-α may lead to HBVR by decreasing HBV-infected hepatocyte clearance and eliminating the suppression of viral replication (8).

In various studies, the HBVR ratio has been reported to be between 27 and 39% in HBsAg-positive patients treated with anti-TNF (9, 10). It is a rational approach to give these patients prophylactic antiviral treatment due to the high risk of HBVR. In patients with past HBV infection, the risk of HBVR is reportedly lower (0-5%) (1, 11). The HBsAg, anti-HBc IgG, and anti-HBs titers should be evaluated to determine the reactivation risk in patients planned to be administered anti-TNF treatment (12).

Current RA and IBD treatment guidelines recommend that patients with past infections should be followed up with liver function tests and HBV DNA levels and that antiviral therapy be initiated in the presence of HBV DNA or in case of the elevation of the HBV DNA at a detectable level (HBVR) during the follow-up period (12, 13). In contrast, the HBVR prevention and treatment guidelines of the American Gastroenterology Association (AGA) recommend the administration of prophylactic treatment rather than follow-up (4). However, this recommendation is based on an insufficient number of studies that have evaluated the risk of HBVR in patients with past infections who were treated with anti-TNF (11).

In the present study, HBVR and/or associated biochemical breakthrough was investigated in patients with past HBV infection who received anti-TNF treatment. The results of this study showed that 90 patients who received anti-TNF, who were followed up for a mean

Table 1. The characteristics and follow-up results of patients (n: 18) who were followed up regularly in terms of HBV DNA level for hepatitis B virus reactivation

Patient Number	Age/Gender/ Diagnosis	Anti-HBc IgG/ Anti-HBs	Anti-TNF	DMARD/IM	TD (Month)	HBV DNA (Baseline)	ALT	HBVR
1	46/F/CD	+/-	IFX	-	12	Negative	Normal	ND
2	50/M/RA	+/-	ADA	-	16	Negative	Normal	ND
3	33/F/CD	+/-	ADA	AZA	56	Negative	Normal	ND
4	43/F/PsA	+/-	ETN	-	12	Negative	Normal	ND
5	50/M/RA	+/-	ETN	**CS	6	Negative	Normal	ND
6	34/M/AS	+/-	ETN	-	39	Negative	Normal	ND
7	45/M/AS	+/-	ETN	-	6	Negative	Normal	ND
8	48/F/RA	+/+	GOL	MTX	12	Negative	Normal	ND
9	58/F/AS	+/+	GOL	MTX	18	Negative	Normal	ND
10	48/F/RA	+/+	CTP	-	22	Negative	Normal	ND
11	63/F/AS	+/+	GOL	-	27	Negative	Normal	ND
12	39/M/AS	+/+	ETN	-	24	Negative	Normal	ND
13	27/M/AS	+/+	CTP	MTX	27	Negative	*2 <ULN	ND
14	31/M/AS	+/+	ADA	-	30	Negative	Normal	ND
15	44/M/AS	+/+	ADA	-	32	Negative	*2 <ULN	ND
16	36/F/RA	+/+	ADA	***CS	30	Negative	Normal	ND
17	47/M/AS	+/+	ADA	MTX	24	Negative	Normal	ND
18	61/F/AS	+/+	ADA	-	42	Negative	Normal	ND

F: female; M: male; RA: rheumatoid arthritis; AS: ankylosing spondylitis; PsA: psoriatic arthritis; CD: Crohn disease; IFX: infliximab; ADA: adalimumab; ETN: etanercept; GOL: golimumab; CTP: certolizumab pegol; CS: corticosteroid; ** prednisolone 5 mg; *** methylprednisolone 4 mg; MTX: methotrexate; AZA: azathioprine; TD: treatment duration; HBVR: hepatitis B virus reactivation; anti-TNF: tumor necrosis factor inhibitor; DMARD: disease-modifying anti-rheumatic drug; ALT: alanine aminotransferase; ULN: upper limit of normal; * less than 2-fold ALT elevation; not associated with HBVR; ND: not detected.

of 26±16 months, did not have HBVR or biochemical breakthrough.

In a study by Charpin and Caporali et al. (14, 15), a total of 88 rheumatic patients with past HBV infection were evaluated, and it was reported that no HBVR was found in patients with negative HBV DNA before the treatment. In a recent study by Papalopoulos et al. (16), HBVR was evaluated according to biological treatments. No HBVR was detected in any of the 82 (73.9%) patients with past HBV infection who received anti-TNF treatment, and 29 (26.1%) patients had isolated anti-HBc IgG positivity. Lan et al. (17) evaluated HBVR and treatment-related viral kinetics in patients treated with anti-TNF and reported that no HBVR was detected in the patient subgroup (n: 58) with anti-HBs positivity (resolved HBV infection). In the same study, it was reported that HBVR was detected in one of the patients with positive isolated anti-HBc IgG (n: 12) and positive pretreatment HBV DNA (n: 4).

One result shared in common by those three studies is that no HBVR was found in patients with positive anti-HBs. Similarly, most of the patients in our study cohort (n: 79, 87%) were composed of patients with positive anti-HBs, and HBVR was not detected in these patients.

One of the important factors that affect the immunosuppressive treatment associated HBVR risk in patients with

past HBV infection is whether the pretreatment HBV DNA level is at a detectable level (18). In a meta-analysis by Lee et al. (19), 468 HBsAg-negative/anti-HBc IgG-positive rheumatic patients who were treated with anti-TNF were evaluated, and 8 patients (1.7%) were determined to have HBVR. In that analysis, the only factor determined as predictive of reactivation was the detectable HBV DNA level. In the present study, the pretreatment HBV DNA level was negative in 54% of the patients, and the remaining patients were not tested for pretreatment HBV DNA levels. In addition, the pretreatment HBV DNA level was negative in 10 of 11 patients with positive isolated anti-HBc IgG (the pretreatment HBV DNA had not been tested in 1 patient). In the present study, the high rate of anti-HBs-positive patients, along with the presence of undetectable pretreatment HBV DNA levels in patients with isolated anti-HBc IgG positivity, may be associated with a low risk of HBVR.

This study has some limitations as it was a retrospective and single-center study. The fact that most of the patients were not followed up for HBV DNA level limits the study. However, no HBVR-related biochemical breakthrough was determined in any of the patients included in the present study.

Literature is scarce about anti-TNF-associated HBVR in our country. In addition to HBVR data, this study provides screening and follow-up practices for patients with past HBV infection who receive anti-TNF treatment in our country.

In conclusion, according to the results of the present study, treatment with anti-TNF in patients with past HBV infection seems to be low risk in terms of HBVR. Therefore, it would be more rational to follow-up these patients with ALT and HBV DNA levels at three-month intervals rather than giving antiviral prophylaxis to all patients.

Ethics Committee Approval: This study was approved by the local ethical committee of Umraniye Training And Research Hospital (decision number and date: B.10.1.TKH.4.34.H.GP.0.01/136;24-07-2019).

Informed Consent: Informed consent couldn't obtained due to the retrospective nature of this study.

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