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RESEARCH ARTICLE

Evaluation Risk of Hepatitis B Reactivation in Anti-HBc (+) Patients Receiving Anti-TNF Therapy*

Anti-TNF Tedavisi Alan Anti-HBc (+) Hastalarda Hepatit B Reaktivasyon Riskinin Değerlendirilmesi*

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ABSTRACT

Objective: Anti-TNF agents are increasingly used for the treatment of many autoimmune diseases. HBV reactivation may occur by different mechanisms in anti-HBc (+) patients receiving anti-TNF therapy. In our study, we aimed to retrospectively evaluate how patients who received anti-TNF agents were managed in terms risk of HBVr.
Material and Method: The results of 2084 patients who used anti-TNF at Erciyes University were scanned. HBV management in 319 HBsAg(-) anti-HBc(+) patients was analyzed retrospectively.
Results: The mean duration of follow-up was 40.61±26.73 months. The most commonly used anti-TNF agents were adalimumab and etanercept. HBVr occurred in 8 patients (2.5%). HBVr was diagnosed as HBV-DNA increase in six patients and HBsAg seroconversion in two patients. HBVr occured 18.25±9.95 months after commencing the treatment. None of the patients who experienced reactivation had severe complications such as transaminase elevation, liver failure, death. Prophylactic antiviral treatment was used 88 of the 319 patients. Other patients were followed up with a preemptive treatment approach. HBVr occurrence rates were 1.13% (n =1) in the group receiving prophylaxis and 3.03% (n =7) in the group not receiving prophylaxis.
Conclusion: In a study evaluating anti-HBc (+) patients, no morbidity or mortality and no transaminase increase were encountered; however, the HBVr rate was slightly above 1%. Anti-TNF agents can be followed with a preemptive treatment strategy without antiviral prophylaxis in anti-HBc (+) patients. HBV-DNA, ALT, and serology should be used during follow-up. Randomized controlled trials are needed to reach a consensus.
Keywords: Hepatitis B, HBV, Reactivation, Tumor Necrosis Factor, Immunosuppression.

ÖZET

Amaç: Anti-TNF tedaviler birçok otoimmün hastalıkta giderek kullanımı artmaktadır. HBV reaktivasyonu (HBVr), anti-TNF tedavi alan anti-HBc (+) hastalarda farklı mekanizmalarla meydana gelebilir. Çalışmamızda anti-TNF tedavi alan hastalarda HBVr riski açısından nasıl yönetildikleri retrospektif olarak değerlendirilmesi amaçlanmıştır.
Gereç ve Yöntem: Erciyes Üniversitesi Hastanesi'nde 2007-2018 yılları arasında anti-TNF tedavi alan 2084 hastanın sonuçları tarandı. HBsAg (-) anti-HBc(+) 319 hastanın verileri retrospektif olarak analiz edildi.
Bulgular: Hastaların ortalama anti-TNF kullanım süresi 40,61±26,73 aydı. En fazla adalimumab, etanersept kullanılmıştı. Toplam 8 hastada HBVr gelişti (%2.5). Bu hastaların 6'sında HBV-DNA artışıyla, 2'sinde HBsAg serokonversiyonuyla HBVr tanısı kondu. Tedavi başlangıcından ortalama 18.25±9.95 ay sonra HBVr geliştiği saptandı. Reaktivasyon gelişen hastaların hiçbirinde transaminaz yüksekliği, karaciğer yetmezliği, ölüm gibi ciddi komplikasyonlar gelişmedi. 319 hastanın 88'inde profilaktik antiviral tedavi kullanımı varken diğer hastalar preemptif tedavi yaklaşımıyla izlenmişti. HBVr oranları antiviral profilaksi alan grupta %1.13 (n =1) iken antiviral profilaksi almayan grupta %3.03 (n =7) olarak bulundu.

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Sonuç: Anti-HBc (+) hastaların değerlendirildiği çalışmamızda HBVr oranı %1'in biraz üzerinde saptanmakla birlikte herhangi bir morbidite veya mortaliteyle karşılaşılmamıştır. Hatta transaminaz yüksekliği dahi görülmemiştir. AntiHBc(+) hastalarda anti-TNF ajanlar antiviral profilaksi verilmeden preemptif tedavi stratejisi ile izlenebilir. Takipte HBVDNA, ALT, hepatit serolojisi izlenmelidir. Ortak bir görüş oluşabilmesi için randomize kontrollü çalışmalara halen ihtiyaç vardır.

Anahtar Sözcükler: Hepatit B, HBV, Reaktivasyon, Tümor Nekrozis Faktör, İmmünosüpresyon.

Hepatitis B is one of the most common infectious diseases in the world that affects the liver and is caused by hepatitis B virus (HBV), which is a partially double-stranded enveloped DNA virüs(1). HBV is transmitted parenterally, vertically or horizontally (2).HBV infection is increasing worldwide, and it is estimated that 2 billion people are exposed to this virüs and approximately 296 million people have chronic hepatitis B (3).

HBV reactivation (HBVr) often occurs as a result of immunosuppressive treatments and was first described 50 years ago in patients undergoing chemotherapy and transplantation. Although HBVr is a frequent problem among HBsAg (+) patients, it can also occur in individuals with resolved Hepatitis B infection, characterized by HBsAg negativity and the presence of anti-HBc antibodies. HBVr can cause serious morbidity and mortality after immunosuppressive treatment and can manifest in various ways, ranging from mild and asymptomatic to severe conditions that could potentially lead to liver failure and even death (4).

Anti-TNF drugs are one of the immunosuppressive treatments that cause HBVr. Although it is not clear exactly how the mechanism of HBVr develops, the initiating factor is thought to be loss of immune control over viral replication. HBV-specific cytotoxic T lymphocytes are largely involved in the immune control of HBV infection. Inhibition of TNF-α causes reactivation of latent infections such as HBV (5, 6).

Data regarding HBVr in patients receiving anti-TNF is limited. The optimal management of this group of patients is unclear. According to current treatment guidelines, antiviral prophylaxis is recommended before anti-TNF-α treatment in HBsAg-positive patients, but there is no standard approach for prophylactic treatment in patients with resolved HBV infection (7-11). In our research, we conducted a retrospective analysis with the objective of examining the management of patients who had received anti-TNF therapy in relation to their risk of HBVr.

MATERIAL AND METHOD

Study population

The data of 2084 patients over the aged > 18 years who received anti-TNF treatment in various clinics at xxx between 2007 and 2018 were retrospectively examined from the files in the hospital computer database. There were 378 HBsAg-negative and anti-HBc-positive patients, and their clinical findings were investigated. The following information was obtained from patient and laboratory files: demographic data, pre- and post-treatment HBV markers, viral load status, results of transaminase tests and other laboratory tests, presence of comorbidities, and antiviral prophylaxis status. In this study, 59 individuals were excluded owing to insufficient clinical information. The remaining 319 patients who were initially core antibody-positive and surface antigen-negative during anti-TNF therapy were analyzed retrospectively.

Patients with hematological or oncological malignancies, chronic liver diseases, rituximab treatment, and incomplete medical records were excluded from the study.

Definitions

The definition of HBV reactivation is as follows:

1) The reappearance of HBsAg in the serum.

2) The new detection of quantifiable HBV DNA, particularly if it was previously undetectable.

3) The presence of HBV DNA at a concentration of greater than 100 IU/ml, particularly if this value was previously unknown

The definition of a hepatitis flare was established as an alanine aminotransferase (ALT) level increase exceeding three times the baseline value of 45 U/L for serum ALT.

Acute liver failure is characterized by an abrupt and severe loss of liver function, which is accompanied by coagulopathy and encephalopathy

Ethics Committee Approval

The study protocol received ethics approval from the local ethics committee (reference number: 2018/76). Informed consent could not be obtained since it was a retrospective study.

Statistical analysis

Data analyses were performed using IBM SPSS version 22.0 statistical software (IBM Corp., Armonk, NY, USA). The basic characteristics of the patients were evaluated using descriptive statistics. Descriptive statistics (mean, standard deviation, minimum, median, and maximum) were used to define the continuous variables. Continuous variables were presented as the mean± standard deviation, and categorical variables were expressed as total numbers and percentages. The Shaphiro wilk test and graphical methods were used to check the normal distribution of quantitative data Student's t-test or Mann–Whitney U-test (if t-test assumptions were not met) was used. The chi-square test for categorical variables was used for between-group comparisons. A p-value less than 0.05 was considered statistically significant.

RESULTS

In a retrospective analysis of data from 2084 patients who were treated with anti-TNF agents, 319 individuals who showed evidence of resolved hepatitis B infection were selected for the study. The study's participants included 129 individuals with ankylosing spondylitis, 127 with rheumatoid arthritis, 32 with psoriasis, 14 with inflammatory bowel diseases, and 17 with other conditions. The most commonly used anti-TNF agents were adalimumab and etanercept. The duration of anti-TNF use was 12955 months, which was determined as 1079 patient years. The mean anti-TNF agent exposure time was 30 (range: 3-101) months. Of the 319 patients using anti-TNF agents, 43.8% (140 patients) used DMARDs, whereas 2.5% (8 patients) used azathioprine. Clinical and demographic parameters are reported in table 1.

Table 1. Characteristics of patients included in the study.

Charactristics	n =31
Female/ Male	190 (59,6%) / 129 (40,4%)
Age, mean±SD, years	53.73±10.40
Age, mean±SD, female / male	55,47±10,12 / 51,16±10,30
Indication for anti-TNFα	
Inflammatory bowel diseases	14 (4.4%)
Ankylosing spondylitis	129 (40.4%)
Rheumatoid arthritis	127 (39.8%)
Psoriasis	32 (10%)
Other diseases	17 (5.3%)
Anti-TNF α agents	
Adalimumab	161 (50.5%)
Etanercept	128 (40.1%)
Golimumab	67 (21%)
İnfliximab	92 (28.8%)
Certolizumab	41 (12.9%)
Concomitant immunosuppressants	148 (46,4%)
DMARDs	140 (43,8%)
Azathioprine	8 (2,5%)
Time on anti-TNF α, mean±SD, months	40,61±26,73
Antiviral prophylaxis	88 (27,6%)
Tenofovir	25 (7.8%)
Lamivudine	30 (9,4%)
Entecavir	35 (10,9%)
HBV-DNA availability at onset of anti-TNF α	92 (28,8%)

SD: standard deviation, DMARDs: Disease-modifying antirheumatic drugs.

The hepatitis serology screening rates by department were 92% in dermatology, 84% in physical therapy and rehabilitation, 80% in rheumatology, and 69% in gastroenterology. In our study, we observed a significant rise in the rates of HBc IgG screening in recent years, which increased from 58.5% to 80.6%. ($p < .001$). Similarly, we observed a notable rise in HBV-DNA testing, with rates increasing from 28.8% to 62.3%.

Of the 319 patients in the study, 88 (27.5 %) received antiviral prophylaxis. The most commonly administered antiviral medication was entecavir, with 35 patients (10.9%) using it.

HBV reactivation was observed in 8 (2,5%) of the 319 patients. Six patients were diagnosed with an increase in HBV-DNA, while two patients tested positive for HBsAg during treatment. The onset of HBVr occurred 18.25 ± 9.95 months after initiating therapy. Three patients had RA, 3 had AS,1 had IBD and 1 had psoriasis. Three patients received infliximab, 2 adalimumab,2 golimumab, and 1 certolizumab (Table 2).

Table 2. Characteristics of patients who developed HBVr.

Patients	1	2	3	4	5	6	7	8
Age	57	38	63	65	51	55	70	45
Gender	M	M	M	F	M	F	M	M
Indication	UC	AS	PsA	RA	AS	RA	RA	AS
Department	G	P	P	R	P	R	P	P
Anti TNF	ADA	INF	GOL	GOL	CTP	INF	INF	ADA
Anti-TNF agent duration (months)	58	63	71	47	41	20	64	81
Concomitant immunomodulators	DMARDs+Az	None	DMARDs	DMARDs	none	DMARDs	DMARDs	none
Antiviral prophylaxis	No	No	No	No	No	No	No	Lam
Ast/Alt (baseline) (U/L)	18/15	23/30	15/13	31/22	14/20	61/31	23/29	17/19
Ast/Alt (reactivation) (U/L)	21/17	17/25	24/21	14/16	16/17	69/87	14/13	19/18
HBV-DNA reactivation (IU/mL)	122	42	149496	Neg	475	Neg	61	179
HBsAg (reactivation)	Neg	Neg	Neg	Pos	Neg	Pos	Neg	Neg
Time to reactivation (months)	7	18	22	18	17	12	40	12
Type of HBVr	HBV-DNA ↑	HBV-DNA↑	HBV-DNA↑	HBsAg +	HBV-DNA↑	HBsAg +	HBV-DNA↑	HBV-DNA↑
Has anti-TNF been discontinued?	No	No	No	No	No	No	No	No
HBVr management	No	No	No	Etv	No	Lam	Lam	Lam to Tdf

UK: Ulcerative colitis, AS: Ankylosing spondylitis, PsA: Psoriatic arthritis, RA: Rheumatoid arthritis, G: Gastroenterology, P: Physical therapy and rehabilitation, R: Rheumatology, ADA: Adalimumab, İNF: Infliximab, GOL: Golimumab, CTP: Certolizumab, ETA: Etanercept, Az: Azathioprine, NA: not avaliable HBsAg: Hepatitis B surface antigen; Anti-HBs: hepatitis B surface antibody; Anti-HBc: hepatitis B core antibody, HBV: hepatitis B virus; AST: aspartate aminotransferase, ALT: alanine aminotransferase, F: female, M: male, DMARDs: Disease-modifying antirheumatic drugs, Neg: negative, Pos: positive.

The occurrence of HBVR was found to be lower in the patient group administered prophylactic antiviral therapy (1 HBVr in 88 patients, equivalent to 1.13%) compared to the patient group not administered prophylactic antiviral therapy (7 HBVr in 231 patients, equivalent to 3.03%) (p =0.334) (Table 3).

Table 3. Characteristics of patients with or without HBVr.

Characteristics	HBVr (n =8)	No HBVr (n =311)	P value
Age, mean±SD, years	55,5±10,66	53,68±10,40	0,643
Female	3 (%37.5)	187 (%60.1)	0,198
Anti-TNF agent			
Adalimumab	2 (25%)	159 (51.1%)	0,144
Etanercept	1 (12.5%)	127 (40.8%)	0,106
Golimumab	3 (37.5%)	64 (20.5%)	0,246
İnfliximab	4 (50%)	88 (28.3%)	0,181
Certolizumab	2 (25%)	39 (%12.5)	0,298
2 or more agents	3 (37.5%)	123 (39.5%)	0,907
Anti-TNF agent duration	40,23±26,81	55,63±19,15	0,053
Concomitant immunosupresants	5 (62.5%)	143 (45.9%)	0,355
Antiviral prophylaxis	1 (12.5%)	87 (27.9%)	0,334
Baseline Anti-HBs titers, mIU/ml	486,42±488,36	434,35±381,53	0,957
ALT (U/L)	22,50±6,87	23,63±21,63	0,348
AST (U/L)	25,25±15,46	21,43±14,74	0,333

SD: standard deviation, AST: aspartate aminotransferase, ALT: alanine aminotransferase, Anti-HBs: hepatitis B surface antibody.

Before the development of HBVr, only 1 patient received prophylactic antiviral therapy. Preemptive treatment was initiated in three patients who developed HBVr. In 2 of these 8 patients, the anti-HBs titer was negative at the time of reactivation. Two cases of HBVr were observed in 22 patients who had negative anti-HBs titers at baseline (9.1%), whereas five cases of HBVr were found in 238 patients who had positive anti-HBs titers (2.1%).

One patient experienced liver dysfunction; however, this patient did not have hepatitis, which is typically indicated by a threefold rise in ALT levels. During

reactivation, transaminase levels were: as follows AST, 69 U/L; ALT, 87 U/L.
All patients who experienced reactivation saw their HBV DNA values become negative in a brief period. Additionally, there was no notable progression in their liver function test results and none of the patients experienced fatal outcomes. In these cases, anti-TNF therapy was not interrupted. Three patients received preemptive treatment. In one of these patients, prophylactic antiviral therapy was altered.

DISCUSSION

The utilization of anti-TNF agents for the management of autoimmune diseases has become more prevalent in recent times. It is crucial to recognize that patients being treated with anti-TNF therapy are at risk of developing reactivation. HBVr can occur in patients with chronic hepatitis B, as well as in patients with resolved hepatitis B infection. However, there are currently insufficient and inconsistent data available on the frequency of HBVr and the appropriate use of antiviral medication in patients with resolved hepatitis B infection who are undergoing anti-TNF therapy. In our study, HBVr was detected in eight patients, with an incidence of 2.5%. Three patients received preemptive antiviral treatment, one patient's antiviral treatment was altered who was under prophylactic treatment. In four patients who did not start preemptive antiviral treatment, HBVr clinic regressed spontaneously. Eight patients did not display any liver-related adverse effects, including acute liver failure or decompensated liver disease, during the study period. Reactivation, characterized by an increase in HBV-DNA or HBsAg positivity, was not mortal. No progressive increase in HBV DNA or ALT levels was observed in these patients. After a brief period, both HBV DNA and HBsAg levels were negative. No cases of interrupted or discontinued anti-TNF treatment were observed among individuals with HBVr in our study. The consequences for individuals experiencing HBV reactivation were not unfavorable.
There have been numerous investigations conducted on the safety of anti-TNF therapies for individuals with resolved hepatitis B. These studies showed that the incidence of HBVr ranges from 0% to 5%. The earliest reported case of anti-TNF-α-induced HBVr was documented in 2003 (12). A retrospective cohort study was conducted in the USA, encompassing 8887 individuals who were under anti-TNF medications. Among these patients, 178 were HBsAg-negative and anti-HBc-positive, and none of them exhibited reactivation (13). In another study involving 87 patients who received anti-TNF therapy, no reactivation occurred in any of the 50 HBsAg (-)/anti-HBc (+) patients during the mean 12-month follow-up period (14). In a clinical trial involving 131 individuals with spondyloarthropathy who were treated with anti-TNF therapy, HBVr did not occur during a period of 75.50±33.37 months of follow-up (15). In a meta-analysis of 468 patients with resolved hepatitis B infection who were treated with anti-TNF, the HBVr rate was found to be 1.7% (16). In a different study that involved 360 individuals with resolved hepatitis B infection who were administered anti-TNF, it was discovered that 6 of them experienced reactivation, resulting in an HBVr rate of 1.7% (17). In another study, reactivation did not occur in 146 patients (18). The highest HBVr rate was found to be 5.3% in a meta-analysis of case reports with 168 HBsAg negative anti-HBc positive patients in 2011, and one of these patients died due to fulminant liver failure while receiving adalimumab. However, because the case reports of the studies included in this study were small retrospective studies the HBVr rate may have been found to be high (19). In a study including 1640 patients with resolved hepatitis b infection from 18 studies, the HBVr rate was found to be 1% and hepatitis b-related hepatitis was 0.07%, and and none of the patients experienced hepatic decompensation or death (20). According to the majority of research, the likelihood of HBVr in individuals with resolved hepatitis B infections who are being treated with anti-TNF drugs is low, and severe consequences, including liver failure, hepatic decompensation, and even death, are rare in those who experience HBVr. In our research, hepatitis B reactivation occurred in 8 (2.5%) of the 319 patients who received anti-TNF therapy. There were no reported instances of significant morbidity or mortality, adverse events, liver dysfunction, or hepatitis. Additionally, no cases of acute liver failure were observed. Anti-TNF treatments administered for the primary disease were not interrupted. The occurrence of HBVr-related hepatitis rather than the development of HBV reactivation is more clinically important, and clinicians' awareness of this issue should be increased. Our study did not find any instances of HBVr-related hepatitis, leading us to believe that anti-TNF agents may be safely administered using a preemptive treatment approach.
Although there is general agreement among international guidelines regarding the circumstances in which antiviral prophylaxis should be administered to patients with chronic hepatitis B who are also receiving immunosuppressive therapy, there is currently no consensus regarding the use of such prophylaxis in patients with anti-HBC-positive. The treatment of patients with resolved hepatitis B infection who are receiving anti-TNF remains a subject of debate, as guidelines do not offer a strong recommendation on the most effective approach. In a 2015 systematic review, the American Gastroenterological Association (AGA) determined that the risk of HBVr caused by anti-TNF agents in patients who were HBsAg (-) and anti-HBc (+) was moderate. As a result, AGA recommended antiviral prophylaxis for patients in this group (21). In APASL guideline from 2021, etanercept, a lower-potency anti-TNF agent, was classified as a low-risk for HBVr, with a risk percentage of less than 1%. On the other hand, higher-potency anti-TNF agents such as adalimumab,

golimumab, infliximab and certolizumab were assigned a moderate risk level for HBVr, with a risk percentage ranging between 1% and 10% (22). According to most guidelines, antiviral prophylaxis is not recommended in this patient group. The European Association for the Study of the Liver (EASL) suggests that careful monitoring may be conducted through the use of HBV-DNA and HBsAg and does not advise the implementation of routine antiviral prophylaxis for individuals who are receiving anti-TNF therapy (7). According to the European Crohn's and Colitis Organization, the probability of reactivation in this patient group is low, and close surveillance via HBV DNA testing is advocated instead of antiviral prophylaxis (22). Based on the guidelines established by The American Association for the Study of Liver Diseases (AASLD) and National Institutes of Health, antiviral prophylaxis is not recommended for patients with resolved hepatitis B infection who are receiving anti-TNF therapy, as HBVr is a rare occurrence in this patient population (23, 24). There are disparities in the recommendations regarding the likelihood of HBVr in individuals with resolved hepatitis B infection undergoing anti-TNF treatment. Currently, there is no consensus regarding the indications for antiviral prophylaxis for individuals in this group.

Screenings for hepatitis prior to the administration of immunosuppressive medications are essential to prevent reactivation. Most major community guidelines recommend HBV screening in all patients receiving immunosuppressive therapy. The recommendations made by AGA and AASLD for immunosuppressive treatment include testing for HBsAg and anti-HBc, whereas EASL and APASL suggest additionally testing for anti-HBs. It is also recommended to test for HBV DNA in HBsAg positive or HBsAg-negative anti-HBs positive patients (7, 11, 21, 23). In a study evaluating 3357 patients with inflammatory bowel disease receiving anti-TNF therapy, the screening rate was found to be 23.7% and increased over the years (25). In another study involving 4,008 patients who were receiving immunosuppressive therapy, the screening rate was 44.9% among 247 patients who were receiving anti-TNF therapy. The screening rates for hepatitis B were 28% for gastroenterologists, 64% for rheumatologists, and 61% for dermatologists (26). In a previous study, it was observed that the implementation of an alert system succeeded in elevating the screening rates for hepatitis B serology. Prior to the implementation of the alert system, the screening rates for HBsAg were less than 50%, whereas after the introduction of the system, the rates increased to 94%. Similarly, the screening rates for anti-HBc significantly increased from less than 30% to 85% following the implementation of the alert system (27). In our study, hepatitis serology screening rates by department were 92% for dermatology, 84% for physical therapy and rehabilitation, 80% for rheumatology, and 69% for gastroenterology. Our research has revealed an increase in the frequency of anti-HBC screening in recent years. (58.5% to 80.6%) ($p < .001$) Moreover, the number of patients tested for HBV-DNA has increased from 92 to 199. (28.8% to 62,3%) It is heartening to observe that the frequency of HBV-DNA and hepatitis serology testing has increased over the years. It is important to determine which serological tests should be performed to prevent HBVr. To diagnose HBV reactivation in HBsAg-negative, anti-Hbc-positive patients using anti-TNF agents, HBsAg, ALT and HBV-DNA levels should be carefully monitored, regardless of anti-HBs status. Collaborative meetings between clinicians should be arranged to enhance knowledge about hepatitis B reactivation in individuals receiving immunosuppressive treatment. Additionally, updating hospital information systems with software that alerts clinicians to patients whose serology or viral loads cannot be tested is an effective approach.

In multiple studies, it was observed that the incidence of HBVr was lower in individuals who were administered antiviral prophylaxis than in those who did not receive such treatment. In a study of 326 patients with resolved hepatitis B infection, HBVr occurred in 10.8% of 232 patients who did not use antiviral prophylaxis, whereas reactivation developed in only 2 of 92 patients who used antiviral prophylaxis, with a rate of 2.1% (28). In another study, reactivation was not observed in any of the 33 patients who received antiviral prophylaxis. In contrast, reactivation was identified in three of the 28 patients who did not receive antiviral prophylaxis (29). In our study, 88 of 319 patients received antiviral prophylaxis. Among the 88 patients who were administered prophylaxis, one individual experienced HBV reactivation, resulting in a 1.13% incidence rate. Conversely, among the 231 patients who did not receive prophylaxis, seven reactivations occurred, with an incidence rate of 3.03 %. A higher rate of HBVr development was observed in patients who did not receive antiviral prophylaxis. However, there was no statistically significant difference in the development of hepatitis B reactivation between the groups that received antiviral prophylaxis and those that did not. ($p=0,334$) Although there are many studies in which prophylactic treatment reduces the risk of HBVr, there is a need for studies comparing HBVr-related serious complications such as hepatitis and liver failure, and death.

Conclusions

Although a single-center study, our study is one of the largest cohort of HBsAg negative and anti-HBc IgG positive patients receiving anti-TNF therapy and it presents a real life data. In recent years, our knowledge of HBVr has grown significantly because of the extensive use of anti-TNF treatments and the increase in the number of research studies conducted on this topic. In our study, we observed that patients who developed HBVr did not experience any severe complications such as acute hepatitis, liver failure, or death. Based on these findings, we concluded that anti-TNF agents are safe for use in this patient population. Therefore, we believe that monitoring patients closely for HBVr, detecting early signs of viral reactivation, identifying

HBVr-associated hepatitis, and administering preemptive antiviral therapy when necessary is a more cost-effective approach than antiviral prophylaxis. Clinicians should recognize the significance of screening for HBV markers in patients receiving anti-TNF therapy and should be aware that these patients require careful monitoring. There is still a need for randomized controlled studies in patients with resolved hepatitis B infection receiving anti-TNF therapy, including large patient populations with long follow-up periods, to enable consensus on HBV screening tests, optimal monitoring frequencies, and indications for antiviral prophylaxis.

Conflicts of interest: None to declare.

Author contributions: M.M., M.A.Y. conceived and designed the study. A.S.Ş., H.D., G.C.S., Ş.G., M.B., M.A.Y., M.M. collected and analyzed the data. M.M., M.A.Y. analyzed and interpreted the data and drafted the manuscript. All authors played a crucial role in critically revising the manuscript and are fully accountable for its integrity and accuracy. They have read and approved the final version of the manuscript.

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