Rheumatology International (2023) 43:523–531
https://doi.org/10.1007/s00296-022-05169-2

Rheumatology
INTERNATIONAL

OBSERVATIONAL RESEARCH

Evaluation of hepatitis serology and frequency of viral reactivation in patients with inflammatory arthritis receiving biologic agents: a multicenter observational study

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Received: 1 June 2022 / Accepted: 1 July 2022 / Published online: 5 September 2022

Abstract

To evaluate of hepatitis serology and reactivation frequency in patients with rheumatic disease receiving biologic agents. Our study included patients with inflammatory rheumatic diseases from 23 centers, who were followed up with biological therapy. Demographic and clinical characteristics of the patients, duration of drug use and hepatitis serology and the state of viral reactivation were analyzed. A total of 4060 patients, 2095 being males, were included in our study. Of the patients, 2463 had Ankylosing Spondylitis (AS), 1154 had Rheumatoid Arthritis (RA), 325 had Psoriatic Arthritis (PsA), and 118 had other inflammatory rheumatic diseases. When the viral serology of the patients was evaluated, 79 patients (2%) who were identified as HBs Ag positive, 486 (12%) patients who were HBs Ag negative and anti-HBc IgG positive and 20 patients (0.5%) who were anti-HCV positive. When evaluated on a disease-by-disease basis, the rate of HBsAg was found to be 2.5% in RA, 2% in AS and 0.9% in PsA. Viral reactivation was detected in 13 patients while receiving biologic agents. HBs Ag was positive in nine patients with reactivation and negative in four patients. Anti-HBc IgG, however, was positive. Six of these patients had AS, four had RA, and three had PsA. The development of hepatitis reactivation in 11.4% of HBs Ag positive patients and 0.82% of anti-HBc IgG positive patients due to the use of biologic agents is an important problem for this group of patients. Antiviral prophylaxis is recommended to be started especially in patients who are HBs Ag positive and who are using biologic agents due to viral reactivation. Therefore, it is important to carry out hepatitis screenings before biologic agent treatment and to carefully evaluate the vaccination and prophylaxis requirements.

Keywords Hepatitis · Inflammatory arthritis · Biologic agents · Viral reactivation

Introduction

Hepatitis virus infection (hepatitis B and/or C), a global health problem, affects an estimated 325 million people worldwide. Hepatitis B is the most serious type of viral hepatitis. It is estimated that approximately one out of every three people in the world may have been exposed to hepatitis B virus infection (HBV) [1]. It is estimated that about 780,000 people die each year due to the consequences of hepatitis B, such as liver cirrhosis and liver cancer [2]. The estimated number of HBV carriers in Turkey is approximately 3.3 million and the overall prevalence of HBV is 4.57% [3]. In a study on inflammatory diseases in our country, the prevalence of hepatitis B surface antigen (HBsAg] was reported as 2.3% for rheumatoid arthritis (RA) and 3% for ankylosing spondylitis (AS) [4]. Immunosuppressive and biological therapies have been used in the treatment of

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inflammatory rheumatic diseases with increasing frequency in recent years. Hepatitis-B reactivation associated with immunosuppressive and biological therapies is an important cause of morbidity and mortality in patients exposed to hepatitis B virus infection [5]. Many international guidelines have made various recommendations on this issue, and patients should definitely have their hepatitis serology tested before starting treatment with these drugs. It should be kept in mind that in addition to HBs Ag positive patients, it is also important to manage individuals who are especially Hbs Ag negative and hepatitis B core antibody (anti-HBc) positive. Although the risk of hepatitis B virus (HBV) reactivation is lower in HBsAg-negative, anti-HBc-positive patients than in HBsAg-positive patients, the prevalence of anti-HBc is higher than in HBsAg. Co-morbidities of autoimmune diseases such as rheumatoid disease and hepatitis is not uncommon and one of the issue of this co-morbidities is their treatment may compromise each other. Thus, use of immune suppressive agents to treat rheumatic disease provide risk for reactivation hepatitis. Therefore, there are numerous cases of HBV inflammation in HBsAg-negative, anti-HBc positive patients receiving immunosuppressive regimens [5, 6]. Reported reactivation rates in this population range from 0.3% to 9% depending on the underlying disease and drug regimens used [7]. HBsAg-negative, anti-HBc-positive patients with detectable HBV DNA should be managed similarly to HBsAg-positive patients, and patients whose HBV DNA cannot be detected are recommended to be carefully monitored with aminotransferases and HBV DNA tests, and if necessary, to take biological agents under antiviral prophylaxis [8, 9].

In this study, we aimed to examine the hepatitis C and hepatitis B in particular, due their rate of occurrence and prognosis and viral reactivation status of individuals receiving biologic agents due to inflammatory rheumatic diseases in a large cohort and to determine the optimal strategies in the management of these patients.

Material and methods

Study design and patient population

This research was performed as a multicenter, non-interventional, retrospective analysis study. The study was conducted in the 23 rheumatology clinics located at different geographical regions of our country and the data of a total of 4060 patients with inflammatory rheumatic disease who were receiving biological agents at these centers were retrospectively analyzed. The study included cases between the period Jun 2010 and Jun 2020.

Demographic data, duration of drug use and hepatitis serology (Hbs Ag, anti-HBc and anti HCV) of the patients were recorded using an information form. Serum alanine aminotransferase (ALT), serum aspartate transaminase (AST), HBV DNA or HCV RNA data of patients with positive hepatitis serology were evaluated. HBV DNA, HBsAg, HBeAg, anti HBe, ALT, AST levels before and during reactivation were analyzed for patients with reactivation.

Inclusion Criteria

Each potential patient should comply with all the following criteria for registration to this research:

1. Having internationally defined criteria for inflammatory rheumatic diseases (RA, AS, psoriatic arthritis and other inflammatory rheumatic diseases)
2. Having initiated of biologic or synthetic, targeted disease-modifying anti-rheumatic drugs
3. Being older than 16 years
4. Patients with hepatitis serology test results (Hbs Ag, anti-HBc and anti HCV)

Exclusion criteria were as follows

Each potential patient having at least one of the following criteria were excluded from this research:

1. Any missing item among inclusion criteria
2. Not attending regular follow-ups and/or those not screened for hepatitis reactivation at least in one of the follow-ups

Definition of HBV reactivation

HBV reactivation has been defined as an increase of at least 2 logs in HBV DNA, HBV DNA turning positive, or HBV DNA being > 2000 IU/mL when the previous value is unknown [10].

Ethics statement

Local ethics committee approval was obtained from Karadeniz Technical University Faculty of Medicine (242,237,859–249/ 22.03.2020). All authors had access to the data and they approved the final version of the manuscript.

Statistical analysis

Descriptive statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS 23.0 for Windows; IBM, Armonk, NY, USA). The data were expressed as mean ± standard deviation (SD), percentage (%). $p < 0.05$

values were considered statistically significant. Categorical data were analyzed using the Chi-square and Fisher tests. Normal distribution measurements were performed using the Kolmogorov–Smirnov test. Continuous variables with normal distribution were compared using independent Student's t-test and continuous variables without normal distribution were compared using Mann–Whitney U test. Data are presented as mean ± standard deviations. Comparisons were performed using one way analysis of variance (ANOVA) followed by Bonferroni post-hoc test ($\alpha = 0.05$).

Results

A total of 4060 patients from 23 centers were included. The mean age of the patients was 45.7 ± 12.8 years, of which 2095 (51.6%) were male and 1965 (48.4%) were female. According to the diagnoses of the patients; there were 2463 Axial SpA (r-SpA and nx-SPA), 1154 Rheumatoid arthritis, 325 Psoriatic arthritis cases and 118 patients had other inflammatory diseases (Behcet's, Familial Mediterranean fever, Polymyalgia rheumatica, still disease's, Vasculitis). It was determined that 27.5% of the patients had concomitant systemic diseases. The most common concomitant disease was hypertension with 15.6%. See Fig. 1).

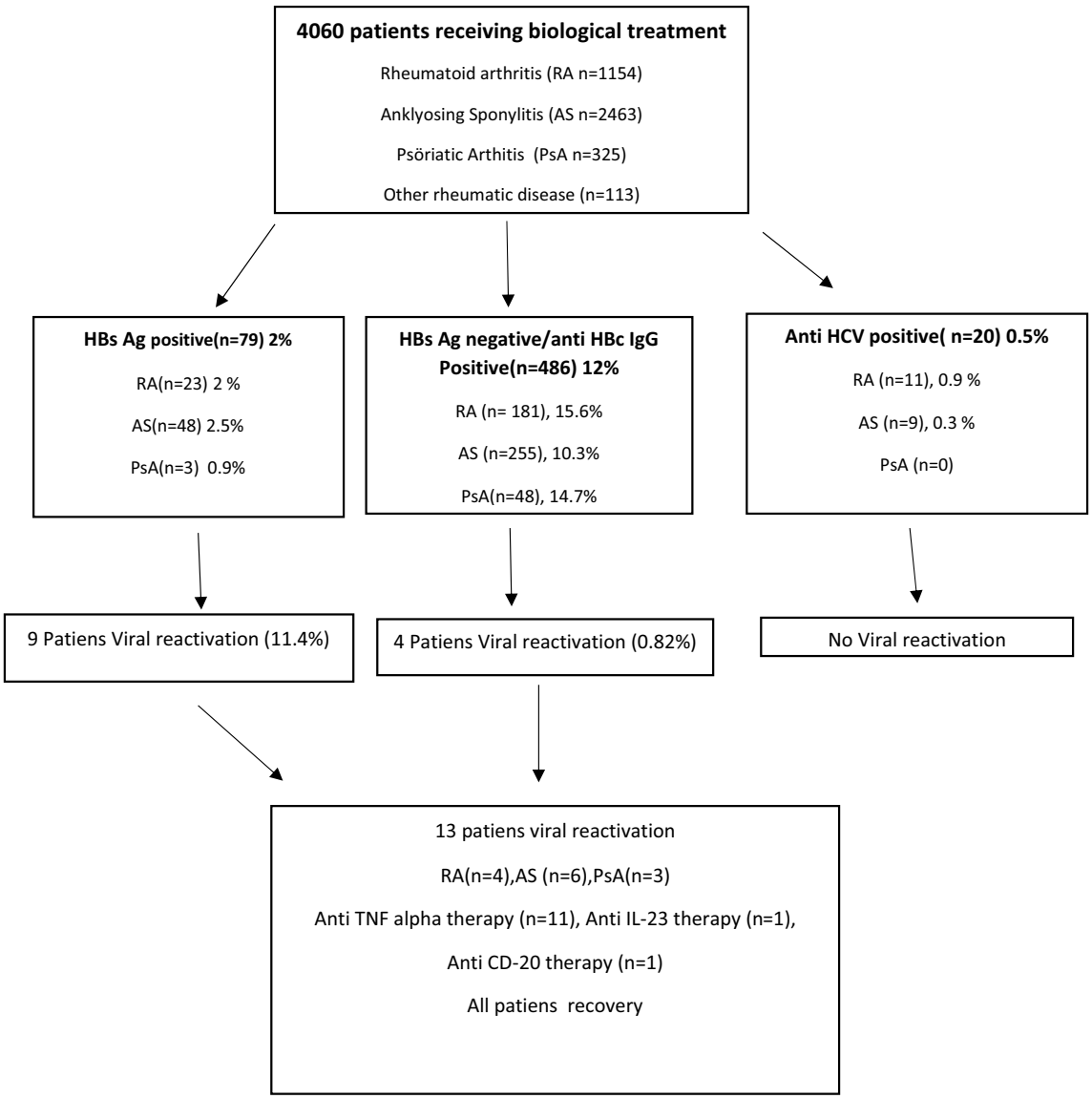

Fig. 1 Flow-charts of the patients enrolled in this analysis

Considering delayed diagnose as an important issue in rheumatic disease, the mean delay in diagnose was 10.3 ± 7.2 year (for AS: 9.4 ± 7.1, RA: 12.6 ± 8.2 and PsA: 9.2 ± 6.4 year).

According to the cases of drug use, it was observed that adalimumab was used by 1523 patients, etanercept by 1433, golimumab by 823, infliximab by 641, certolizumab by 388, sekukinimab by 230, rituximab by 213, tofacitinib by 202, tocilizumab by 176, inflixsimab biosimilar by 174, abatacept by 115, and ustekinumab by 20 patients. Among the total cases, 3163 (77.9%) patients used conventional drugs. Of the patients, 2372 had used Sulfasalazine, 1644 had used methotrexate, 715 had used leflunomide, and 687 had used hydroxychloroquine. In the study, 2907 (71.6%) patients were found to be using Non-steroidal anti-inflammatory drugs (NSAIDs). It was determined that 1600 (39.4%) of the patients used steroids, and 38.1% of these patients used steroids for more than 1 year, and 19.3% used it continuously.

When the viral serology of the patients was evaluated, 79 (2%) patients with HBs Ag positive, 486 (12%) patients with HBs Ag negative and anti-HBc IgG positive and 20 patients (0.5%) with anti-HCV positive were identified. Serological test results were analyzed according to the diagnostic subgroups. There was no difference between the groups in terms of HBs Ag positivity ($p = 0.133$). There was a statistically significant difference between the diagnostic subgroups in terms of anti-HBs positivity ($p = 0.042$). In post-hoc analyses, it was found that the anti-HBs positivity rate was significantly higher in AS patients rather than in RA patients ($p = 0.036$). There was a statistically significant difference between the diagnostic subgroups in terms of anti-HBc IgG positivity ($p < 0.001$). In post-hoc analyzes, it was found that the rate of anti-HBc IgG positivity in RA patients was significantly higher than in AS patients ($p < 0.001$). There was no significant difference between the diagnostic subgroups in terms of anti-HBe positivity ($p = 0.330$). In terms of anti-HCV positivity, statistical comparison could not be performed because the number of patients in group were too small (Table 1).

Table 1 Demographic characteristics of patients

Clinical characteristics	n (%)
Age, mean ± SD	45.7 ± 12.8
Gender	
Male	2095 (51.6%)
Female	1965 (48.4%)
Disease diagnosis	
Ankylosing Spondylitis	2463 (60.7%)
Rheumatoid Arthritis	1154 (28.4%)
Psoriatic Arthritis	325 (8%)
Other inflammatory rheumatic diseases	118 (2.9%)
Bıologic agent	
Adalimumab	1523 (37.5%)
Etanercept	1433 (35.3%)
Golimumab	823 (20.3%)
İnfliximab	641 (15.8%)
Certolizumab	388 (8.6%)
Sekukinimab	230 (5.7%)
Rituximab	213 (5.3%)
Tofacitinib	202 (5%)
Tocilizumab	176 (4.3%)
Infliximab biosimilar	174 (4.3%)
Abatacept	115(2.8%)
Ustekinumab	20 (0.5%)
Concomitant medications	3163 (77.9%)
Sulfasalazine	2372 (58.4%)
Methotrexate	1644 (40.5%)
Leflunomide	715 (17.6%)
Hydroxychloroquine	687 (16.9%)
Non-steroidal anti-inflammatory drugs	2907 (71.6%)
Corticosteroids more than 1 year	1600 (39.4%)
Corticosteroids continuously	309 (19.3%)
Viral serology	
Anti HBs Ag positive	1514 (37.8%)
HBs Ag positive Patients	79 (2%)
HBs Ag negative and anti-HBc IgG positive	486 (12%)
Anti-HCV positive	20 (0.5%)

In the study, the antiviral treatment status of a total of 565 patients was followed. It was determined that 49% (278 patients) of those evaluated had received antiviral treatment. Tenofovir was the most used in antiviral treatments with 58.6%, followed by entecavir with 26%, and lamivudine in 10% of our patients.

When the viral activation status of 565 patients with hepatitis follow-up was examined, a total of 13 patients had viral reactivation, which included six in the ankylosing spondylitis group, four in rheumatoid arthritis group and three in psoriatic arthritis group (Fig. 1). Not all of these patients had received antiviral prophylaxis. HBV reactivation was developed in 4.5% of patients who did not receive prophylaxis. Viral reactivation was observed in all of these patients during the use of biological agents. When gender was examined, it was seen that 9 of the 13 patients with viral reactivation were male ($p = 0.225$). 9 of the patients with reactivation were HBsAg positive and four others were anti-HBc IgG positive. In all patients with reactivation, the HBV-DNA value was increased by at least 2 $\log_{10}$ compared to the baseline value. The ALT value of 9 patients was 2 times higher than the normal value and there was a slight increase in 3 patients. There was no increase in the ALT value of one patient. The reactivation rate was 4 out of 1154 for (0.3%) RA, 6 out of 2463 (%0.3) for AS, 2 out of 325 (0.8%) for PsA. The rate of detected

Table 2 Characteristics of patients with viral reactivation

Case	Disease	Gender	Age	Disease duration(year)	Biologic Agent	Viral serology	Outcome
Case 1	RA	F	60	19	Etanercept	Hbs Ag (+)	Resolved
Case 2	PsA	F	40	6	Infliksimab	Hbs Ag (+)	Resolved
Case 3	AS	M	58	12	Golimumab	Hbs Ag (+)	Resolved
Case 4	AS	M	55	15	Adalimumab	Hbs Ag (+)	Resolved
Case 5	RA	M	63	10	Etanercept	Hbs Ag (+)	Resolved
Case 6	RA	F	67	3	Ritüksimab	Hbs Ag (−), Anti-HBc IgG(+)	Resolved
Case 7	AS	M	40	14	Adalimumab	Hbs Ag (+)	Resolved
Case 8	PsA	M	56	7	Ustekinumab	Hbs Ag (−), Anti-HBc IgG(+)	Resolved
Case 9	AS	M	50	11	Etanercept	Hbs Ag (+)	Resolved
Case 10	RA	M	76	8	Adalimumab	Hbs Ag (+)	Resolved
Case 11	AS	M	59	17	Golimumab	Hbs Ag (−), Anti-HBc IgG(+)	Resolved
Case 12	PsA	M	44	21	Infliksimab	Hbs Ag (+)	Resolved
Case 13	AS	F	44	9	Adalimumab	Hbs Ag (−), Anti-HBc IgG(+)	Resolved

reactivation was not significantly different between the diseases ($p = 0.615$). When comparison was made with respect to the different agents, there was reactivation in 2 out of 641 for infliximab, 3 out of 1453 for etanercept, 4 out of 1523 for adalimumab, 2out of 823 for golimumab, 1 out of 212 for rituxisimab and 1 out of 20 for ustekinumab. No reactivation was detected in patients who were under treatment with other agents (Table 2).

None of the patients with anti-HCV positivity developed reactivation. None of the cases who developed viral reactivation resulted in death.

Discussion

It is estimated that more than 250 million people worldwide are affected from the Hepatitis-B virus (HBV), but the actual number is much larger. The prevalence of hepatitis—B varies regionally and its frequency varies between < 2% and > 10% depending on different reasons such as vaccination policies, sociocultural characteristics [1, 11]. After the hepatitis B virus enters the body, it begins to multiply in liver hepatocytes. HBV covalent closed circular DNA, called cccDNA, continues to exist latently in hepatocytes and serves as a reservoir for reactivation. After the first period of the disease is over, it can end in different ways. These include cases with HBs Ag positivity, HBs Ag negativity and anti-HBs positivity, as well as cases with HBsAg negativity and anti-HBc positivity. Anti-HBc positivity has no clinical significance in HBs Ag negative cases unless an immunosuppressive condition is encountered. In cases where the immune system is suppressed, HBV reactivation may occur due to the presence of cccDNA in hepatocytes. Unfortunately, there is currently no treatment that can completely eliminate cccDNA from hepatocytes [12].

Although there is no definitive data on the prevalence of HBV in rheumatological diseases, it usually is parallel to the prevalence of HBV in regions where the patient lives. In our country, HBsAg prevalence is about 2.3% in RA and 3% in AS patients [4]. Similarly, in our cohort, RA was found to be 2.5%, AS was 2%, and Psoriatic Arthritis was 0.9%. It was observed that all of our cases were found in moderate endemic areas in terms of HBV and correspondingly, 14% of them were exposed to HBV. An important feature of these patients was that 90 > of these patients had HBsAg negative and anti-HBc positive serology. Significant number of these cases suggests that for patients who will receive immunosuppressive treatment, anti-HBc should be examined in pre-treatment screenings. However, it was also observed that there were disruptions in the screening of these patients. In studies on the screening rates of patients who will receive immunosuppressive treatment, it has been suggested that the most appropriate screening settings are transplant centers, followed by rheumatologists, oncologists and at the very least, by gastroenterologists [13]. The emergence of HBV reactivation with suppression of the immune system was first demonstrated by chemotherapies administered in patients with cancer. In the studies conducted on this subject in the literature, HBV reactivation rates were determined to be 0–24% [14]. In the retrospective review of the data of patients treated with anti-TNF-α treatment in a study conducted by Fidan et al., the overall HBV screening rate before starting anti-TNF-α therapy was found to be 82.3%. In this study, it was observed that the anti-HBc request rates were below 50%. When analyses are conducted by year, an increasing trend in HBV screening rates can be seen (64% in 2010, 87.4% in 2019). In the study, before initiation of

anti-TNF-α therapy, 272 patients were HBsAg negative and anti-HBc positive. Of these patients, HBV reactivation did not occur in 31 patients who received antiviral prophylaxis, while HBV reactivation was shown to occur in only 1 in 241 patients (0.4%) who did not receive antiviral prophylaxis [15].

In determining the virological risk, HBsAg positivity or negativity is important and the risk is greater in HBsAg-positive patients. Among our population, 2% of the patients were HBs Ag positive, 12% were HBs Ag negative and anti-HBc positive. Accordingly, a significant portion of our patients who had been exposed to HBV were in the low–to-moderate risk group. Reactivation was developed in 13 (2.3%) of our patients and oral antiviral prophylaxis was initiated in 49% of patients exposed to HBV. While HBV reactivation was not observed in any of the patients receiving prophylaxis, HBV reactivation was developed in 4.5% of the patients who did not receive prophylaxis. In the study conducted by Ryu et al., which included patients in the high-risk group in terms of reactivation, it was seen that the reactivation rates in patients who received prophylaxis were 5% and the rate in patients who did not receive prophylaxis was 6.9%. HBV reactivation may begin shortly after immunosuppressive therapy is initiated, or it may occur after treatment is discontinued [16]. All of the reactivation we have recorded had started during immunosuppressive therapy. The reactivation rate in HBsAg-positive patients was 11.5% and the reactivation rate in HBsAg negative/Anti-HBc positive patients was 0.8%.

Although HBV reactivation in patients undergoing chemotherapy for hematologic malignancy is well defined, there are fewer articles on HBV reactivation in rheumatological patients [18]. There are 3 factors that play a role in the risk of HBV reactivation. These include host factors, virological factors, and the type and duration of the drug used. Host factors include male gender, advanced age, presence of cirrhosis and type of disease. In our study, 9 of the 13 patients with viral reactivation were male. Among the virological factors, high initial HBV-DNA level, HBeAg positivity and chronic hepatitis B were evident. With regard to the type of drug, groups of low, medium and high-risk drugs were defined. Considering the agent to be applied in the treatment and the viral serological characteristics of the patient, the risk of reactivation is divided into low (< 1%), moderate (1–10%) and high (> 10%). Immunosuppressive agents are often used in our daily practice to treat rheumatic diseases. Viral reactivation states related to methotrexate, the biologic agents infliximab, etanercept, adalimumab and rituximab have been described in the literature [17–20]. All anti-TNF agents were defined as high risk (etanercept is medium risk) in HBs Ag positive patients, medium risk (etanercept is low risk) in HBsAg negative/anti-HBc positive group, and Rituximab as high risk in both groups. Steroids, on the other hand, have different risks depending on the dose and duration [18].

TNF-α and the cytokines involved are well-known as proinflammatory agents. Their widespread use has been associated with the reactivation of HBV. These cytokines were thought to affect the adaptive immune system responsible for HBV immune control, although the mechanism of action is not clearly known. However, recent advances in the understanding of HBV reactivation and the importance of cccDNA indicate that TNF-α and related cytokines exert this effect via cccDNA. These agents may block the endogenous antiviral pathway, leading to HBV replication and HBV reactivation [21]. Following the initial case report of HBV reactivation in patients treated with anti-TNF in 2003 [22], a number of case reports have shown an increased risk of HBV replication after anti-TNF therapy in patients with chronic HBV infection. In a review published in 2011, among 89 published cases of chronic HBV infection, HBV reactivation was observed in 39% of patients [19]. Over the past 10 years, case series on this issue have been published and antiviral prophylaxis has begun to be used. In our study, 11 of the 13 patients who were HBV activated were receiving anti-TNF-α therapy. Although etanercept was accepted as a relatively lower risk, only two of our patients were using etanercept. Rituximab is a monoclonal antibody against CD20, which is primarily expressed on the surface of B lymphocytes. It targets and destroys B cells, and this B cell marker is used to treat inflammatory rheumatic diseases and hematological cancers. B cells contribute to HBV clearance by producing neutralizing antibodies, preventing viral spread, and eliminating circulating viruses. Suppression of B cells can cause HBV reactivation [22]. One of our patients with viral reactivation was taking rituximab, which is considered high risk. This patient was treated at a time before awareness of the need to evaluate the serology of hepatitis in the use of Rituximab was established.

One of the limitations of our study is its retrospective nature. On the other hand, our study had several strengths including the relatively large number of cases, involvement of cases with variety of rheumatologic diseases and therapies with biological agents with different mechanism of action.

All in all, reactivation may occur in people who have encountered HBV if any treatment affecting the immune system is administered. The highest risk among these patients is HBsAg-positive patients, followed by patients who are HBsAg negative and anti-HBc and anti-HBc as well as anti-HBs positive. Therefore, HBsAg, anti-HBs and anti-HBc follow-up are required in all patients who will undergo any immunosuppressive therapy. HBV reactivation management should be planned by considering the drug regimens used and the risk factors of the patient.

As previously explained, all patients at high or medium risk for HBV reactivation should be considered candidates for prophylactic therapy. Prophylaxis should ideally begin 2–4 weeks before the start of immunosuppressive therapy and be continued for 6–12 months after the last dose of immunosuppressive therapy, according to the treatment administered. Differences in the frequency of reactivation and the introduction of new agents into our daily practice reveal the necessity of conducting comprehensive clinical studies on this subject.

Funding None of the authors of this paper has any financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

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