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Original Investigation

Current antiviral practice and course of Hepatitis B virus infection in inflammatory arthritis: a multicentric observational study (A + HBV study)

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Abstract

Objective: The reactivation of hepatitis B virus (HBV) infection is a well-known event in hepatitis B surface antigen (HbsAg)-positive patients receiving immunosuppressive therapy. The objective of this study was to assess the antiviral practice and course of HBV infection in inflammatory arthritis.

Material and Methods: Nineteen rheumatology centers participated in this retrospective study. HbsAg-positive patients who were taking disease-modifying antirheumatic drugs and who were being tested for HBV viral load at a minimum of two different time points were included. The case report form (CRF) consisted of demographic data, rheumatic diseases, treatment profiles, transaminase levels, viral hepatitis serological markers, and HBV viral load. The reactivation of HBV was defined as the abrupt rise in HBV replication by an increase in serum HBV DNA levels in a patient with a previously inactive HBV infection.

Results: In total, the data of 101 (female 50.5%) patients were included (76 patients with inactive HBV carriers and 25 patients with chronic HBV infection). The mean age of patients was 44±12 years, and the mean follow-up duration was 31±22 months. Of the 101 patients, 70 (69.3%) received antiviral treatment. HBV reactivation was detected in 13 of 76 (17.1%) patients with inactive HBV carriers. HBV reactivation was observed less frequently, not although significantly, in those patients receiving antiviral prophylaxis compared with those not receiving prophylaxis [5/41 (12.2%) vs. 8/33 (24.2%), p=0.17]. Forty-two patients (31 patients had inactive HBV carriers) were using anti-tumor necrosis factor agents. HBV reactivation was detected in 6 of the 31 (19.3%) patients. Twenty-five patients had chronic hepatitis, and five (20%) of them had not received antiviral prophylaxis. HBV viral loads were persistently elevated in 7 (28%) of 25 patients (three patients under and four patients not under antiviral treatment).

Conclusion: HBV reactivation was observed in approximately 17% of patients under immunosuppressive treatments. HBV reactivation was more frequently observed in those who did not receive antiviral prophylaxis.

Keywords: Rheumatoid arthritis, ankylosing spondylitis, hepatitis B infection, hepatitis B reactivation, hepatitis B viral load

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Introduction

Hepatitis B virus (HBV) infection is one of the major health problems worldwide (1). HBV prevalence was found to be around 4% in a recent population-based study in Turkey (2). HBV causes liver disease in humans, including acute hepatitis, chronic hepatitis, cirrhosis, and hepatocellular carcinoma (1). Chronic hepatitis B is defined as a positive hepatitis B surface antigen (HBsAg) with persistently or intermittently elevated alanine aminotransferase (ALT) values and detectable HBV-DNA (>10.000 copies/mL) with significant necroinflammation/fibrosis in liver biopsy (if performed). Inactive HBV carrier is defined as a positive HBsAg with undetectable HBV DNA (<10.000 copies/mL), persistently normal ALT values, negative HBeAg, and without significant necroinflammation or fibrosis in liver biopsy (if performed) (3).

The reactivation of HBV (defined as consecutive increases in the serum HBV DNA levels by more than 1 log in patients with previously inactive or resolved HBV infection) is a well-known event in HBsAg-positive patients receiving short-term chemotherapy for malignancies or long-term immunosuppressive therapy after bone marrow or solid organ transplantation and autoimmune diseases (4). Indeed, the current body of knowledge about HBV reactivation is mostly obtained from the oncology literature. The prevalence of clinically-evident HBV reactivation ranges from 38% to 53%, with a mortality rate of up to 40% in patients receiving chemotherapy for malignancies (4). From a rheumatology perspective, treatments with a high risk for HBV reactivation are methotrexate, leflunomide, high-dose glucocorticoids, and biological agents, including anti-tumor necrosis factor (TNF) alpha therapy and rituximab (4). Fortunately, in most instances, the flare of HBV infection is transient and clinically silent; however, acute hepatic failure and even death may occur (4). The European and American Association for the Study of the Liver recommends that every HBV inactive carrier undergoing chemotherapy or immunosuppressive therapy should receive preemptive administration of a nucleoside/nucleotide analog during therapy regardless of initial HBV-DNA levels (5, 6). On the other hand, data for patients having both HBV infection and rheumatic disease is scarce and limited to single case reports or small case series with a short follow-up. The American College of Rheumatology (ACR) stated that in the setting of treated chronic HBV, leflunomide and methotrexate were contraindicated for all Child–Pugh classifications, and biological agents were contraindicated in chronic HBV (whether treated or untreated) for those with significant liver injury, defined as chronic Child–Pugh classes B or C. There were no comments about patients with an inactive HBV carrier status in these recommendations (7). Furthermore, these ACR recommendations were mainly based on expert opinion.

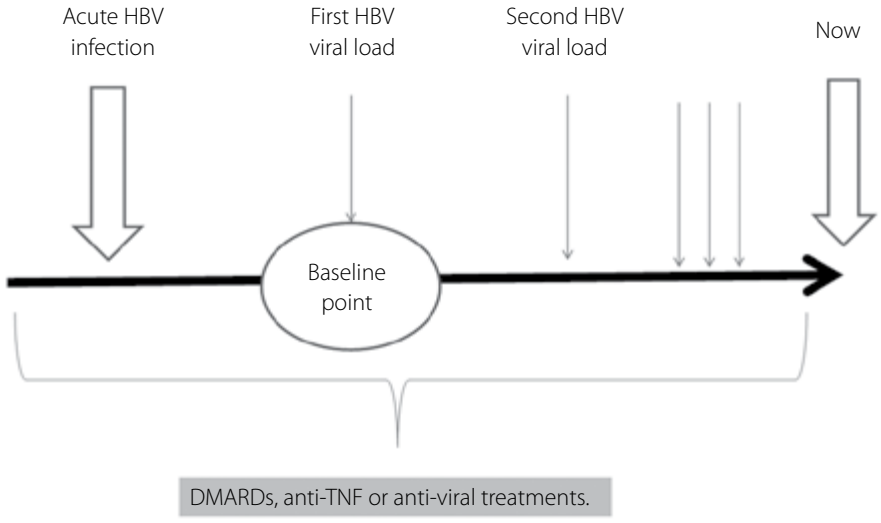

Figure 1. Time schedule of HBV infection and HBV viral loads
HBV: hepatits B virüs; DMARDS: disease-modifying anti-rheumatic drugs; TNF: tumor necrosis factor

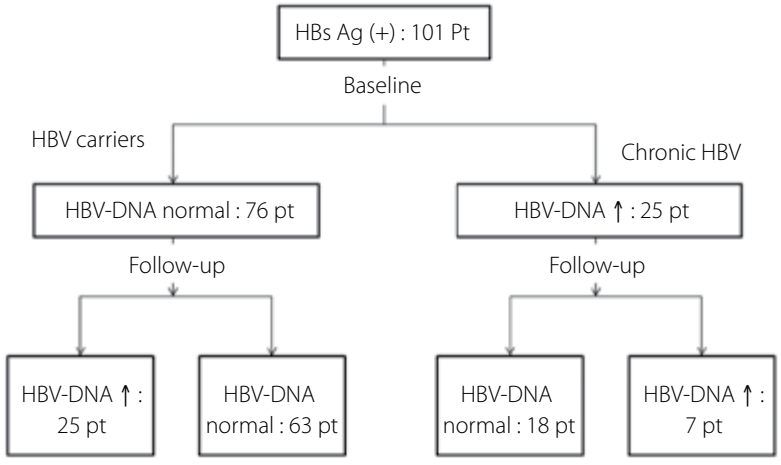

Figure 2. Flowchart of patients with HBV infection
HBs Ag: hepatitis B surfore antigen; hepatits B

The objective of this study was to assess the current antiviral practice and course of HBV infection in patients with inflammatory arthritis (A+HBV study) who took synthetic or biologic disease-modifying anti-rheumatic drugs (DMARDs).

Material and Methods

Study design and patients selection

Nineteen rheumatology centers from different regions of Turkey participated in this retrospective study. Data were collected by a case report form (CRF) from the medical records of patients. Ethical approval was obtained from the university local ethical committee. The files of all patients with an inflammatory arthritis such as rheumatoid arthritis (RA), spondyloarthritis (SpA), or juvenile chronic arthritis (JCA) were screened. HBsAg-positive patients who had been taking either synthetic or biologic DMARDs (i.e., methotrexate, sulphasalazine, leflunomide, infliximab, etanercept, adalimumab) and who were being tested for HBV viral load at a minimum of two different time points were included. HBsAg-positive inflammatory arthritis patients who had not been taking any DMARDs or were not tested for HBV viral load at a minimum of two different time points (followed with AST-ALT levels alone) were excluded.

Assessments

The study form consisted of demographic data, rheumatic disease features (RA, SpA,

Table 1. Demographic and laboratory features of all patients

	HBV carriers (n=76)	Chronic HBV infection (n=25)	p
Age (years); mean (SD)	45 (12)	41 (10)	>0.05
Female (n, %)	39 (52)	13 (52)	>0.05
Diseases (n, %)			
RA	40 (53)	13 (52)	>0.05
SpA	35 (46)	10 (40)	
JCA	1 (1)	2 (8)	
Disease duration (years); mean (±SD)	8.7 (6.9)	7.7 (6.5)	>0.05
DMARDs (n, %)			
Methotrexate	43 (56)	17 (68)	>0.05
Sulphasalazine	44 (58)	13 (52)	
Leflunomide	11 (14)	4 (16)	
Anti-TNF	31 (41)	11 (44)	
HBV viral loads (n, %) (baseline/follow-up)			
within normal/within normal	63 (83)	0 (0)	<0.001
within normal/elevated	13 (17)	0 (0)	
elevated /within normal	0 (0)	18 (72)	
elevated/elevated	0 (0)	7 (28)	
Transaminase levels (n, %) (Baseline/Follow-up)			
Within normal	69 (91)/65 (85)	18 (72)/21 (84)	0.015*
1–3 times elevated of upper normal	5 (6)/7 (9)	4 (16)/1 (4)	
>3 times elevated of upper normal	2 (3)/4 (6)	3 (12)/3 (12)	
Antiviral prophylaxis (n, %)			
No prophylaxis	26 (34)	5 (20)	>0.05
Concurrent prophylaxis	37 (49)	14 (56)	
Antivirals after DMARDs started	13 (17)	6 (24)	
Antiviral duration (months); mean (±SD)	26 (18)	27 (22)	>0.05

HBV: hepatitis B virus; RA: rheumatoid arthritis; SpA: spondyloarthritis; JCA: juvenile chronic arthritis; DMARDs: disease modifying anti-rheumatic drugs; SD: standard deviation

*At baseline, HBV carriers vs. chronic HBV infection

JCA), their treatment profiles (synthetic and biological DMARDs), duration of HBV infection, transaminase levels, viral hepatitis serological markers (HBsAg, HBeAg, Anti-HBs, Anti-HBc, Anti-HBe), HBV viral load (copy/mL), and liver biopsy features (histological activity index: HAI) (if available). The medical treatment histories of patients were collected carefully. The beginning and cessation (if present) time of all DMARDs (including methotrexate, leflunomide, and sulphasalazine) and anti-TNF alpha agents were noted. The status of antiviral treatments [lamivudine (Zeffix; Glaxo SmithKline, London, United Kingdom) and entecavir (Baraclude; Bristol-Myers Squibb, New Jersey, United States)] was defined according to the use and timing of synthetic and/or biological DMARDs, such as "no antiviral prophylaxis," "concurrent antiviral treatment," and "antiviral treatment after DMARDs started." All reported HBV viral loads and serial transaminase levels were collected for each visit.

Definition of baseline point and HBV reactivation

The timing of the initial HBV viral load assessment was defined as the baseline point of the study (Figure 1). Patients were classified according to the initial HBV viral load level. Inactive HBV carriers had HBsAg (+), undetectable HBV DNA (<10,000 copies/mL), and no necroinflammation or fibrosis in liver biopsy. Patients with chronic HBV had HBsAg (+), detectable HBV DNA (>10.000 copies/mL), and necroinflammation and/or fibrosis in liver biopsy (if performed). The reactivation of HBV was defined as the recurrence or abrupt rise in HBV replication by an increase in serum HBV DNA levels of at least 1 $\log_{10}$ (or >10.000 copies/mL) in a patient with a previously inactive HBV infection.

Statistical analysis

Descriptive statistics were used for patient characteristics that were compared using t-tests or chi-square tests, as applicable, with a level of significance set at 5% (two-sided). The following analyses were conducted using the Statistical Package for the Social Sciences (SPSS) (SPSS Inc., Chicago, Illinois, United States).

Results

Demographic features and anti-rheumatic treatment profiles

In total, the data of 101 (female 50.5%) patients were included in this study. Seventy-six patients were inactive HBV carriers, and the others had chronic HBV infection (Table 1 and Figure 2). The mean age of patients was 44±12 years, and the mean follow-up duration was 31±22 months. The diagnosis of patients was as follows: RA, 53 (52.5%); SpA, 45 (44.5%); and JCA, 3 (3.0%). Further, the distribution of treatment agents was as follows: methotrexate, 60 (59.4%); sulphasalazine, 57 (56.4%); leflunomide, 15 (14.9%); etanercept, 23 (22.8%) (four patients switched from infliximab and one patient switched from adalimumab); infliximab, 15 (14.9%); and adalimumab, 10 (9.9%).

HBV markers, HBV viral loads, and transaminases

All patients were positive for HBsAg and negative for anti-HBs. Other HBV markers were as follows: HbeAg, 8/96 (8.3%); anti-HBe, 57/97 (58.7%); and anti-HBc, 62/88 (70.5%). Transaminase levels and HBV viral loads at the baseline and during the follow-up period are shown in Table 1.

Antiviral treatment features

Of the 101 patients, 70 (69.3%) received antiviral prophylaxis/treatment (inactive HBV carriers: 50 patients; chronic HBV infection: 20 patients). Of the 70 patients, 51 (72.8%) received antivirals concurrently, and 19 (27.2%) received antivirals after synthetic or biologic DMARDs started. The mean antiviral treatment duration was 26±18 months (Table 1).

Table 2. Characteristics of HBV reactivation in inactive HBV carriers

	HBV reactivation (n=13) (n, %)	No HBV reactivation (n=63); (n, %)	p
Antiviral prophylaxis* (n, %)	5 (38.4)	36 (59.0)	0.176
Elevated transaminases			
Baseline	1 (7.7)	6 (9.5)	0.835
Follow-up	5 (38.4)	6 (9.5)	0.007
Methotrexate (n, %)	6 (46.1)	37 (58.7)	0.405
Sulphasalazine (n, %)	4 (30.8)	40 (63.5)	0.030
Leflunomide (n, %)	2 (15.4)	9 (14.3)	0.918
Anti-TNF agents (n, %)	6 (46.1)	25 (39.9)	0.666

HBV: hepatitis B virus; Anti-TNF: anti-tumor necrosis factor

*data were not available in three patients

Inactive HBV carriers and HBV reactivation

HBV reactivation was detected in 13 of the 76 (17.1%) inactive HBV carriers. HBV reactivation was observed less frequently in those patients receiving antiviral prophylaxis compared with those not receiving such prophylaxis, but it did not reach clinical significance [5/41 (12.2%) vs. 8/33 (24.2%), p=0.17] (Table 2). HBV viral load returned to normal in 9 (69.2%) of 13 patients with HBV reactivation during follow-up (lamivudine started in eight patients who did not receive prophylaxis before, one patient who was receiving lamivudine prophylaxis switched to entecavir, and the course of the remaining four patients receiving antiviral prophylaxis before was unknown).

Patients with chronic HBV infection

Twenty-five patients had chronic hepatitis according to HBV viral load. The duration of the mean follow-up duration was 30±22 months. Five of 25 (20%) patients had not received antiviral prophylaxis, whereas the remaining patients received antiviral treatment. HBV viral loads were persistently elevated in 7 of 25 (28%) patients (three patients under and four patients not under antiviral treatment). HBV viral load returned to the normal level in 18 patients (72%) (17 patients receiving antiviral treatment and one patient not receiving antiviral treatment). In one patient who was undergoing treatment with lamivudine and etanercept concurrently, the elevated HBV viral load (5×10^9 copy/mL) was normalized (7×10^2 copy/mL) within a year. However, HBV viral load (7×10^4 copy/mL) was again increased in the same patient 46 months later, in whom lamivudine was switched to entecavir, which resulted in the normalization of the viral load (6×10^2 copy/mL) 4 months following that switch.

HBV and anti-TNF agents

Forty-two patients were using anti-TNF agents. The mean age of patients was 43±10 years, and the mean follow-up duration was 33±19 months. Of the 42 patients, 31 (73.8%) were inactive HBV carriers. HBV reactivation was detected in 6 of the 31 (19.3%) patients who were inactive HBV carriers (Table 3). The duration of median HBV reactivation was 14 months (4–60). HBV reactivation was found less frequently in those who received antiviral prophylaxis [2/20 (10.0%)] compared with those who did not receive antiviral prophylaxis, although the difference was not significant [4/11 (36.4%), p=0.075].

Discussion

The A+HBV study disclosed that in patients with inflammatory arthritis who were also inactive HBV carriers, there was an HBV reactivation in around 17% of them under immunosuppressive treatments. HBV reactivation was more frequently observed in those who did not receive antiviral prophylaxis (24% vs. 12%). No difference was seen in the rate of HBV reactivation according to the type of immunosuppressive treatment (DMARDs vs. anti-TNF agents). Our findings also suggest that both DMARDs and anti-TNF agents can be safely used in patients with chronic HBV infection. In most patients, HBV reactivation was transient, and HBV viral load returned to normal. However, acute hepatic failure and even death may occur.

HBV viral load, transaminase levels, and/or repeated liver biopsy are tools to detect HBV reactivation (4) . Among these tools, HBV viral load is a sensitive and easily available tool for HBV reactivation. In fact, this study has shown that transaminases did not have sufficient sensitivity to screen HBV reactivation, and only 38% of patients with HBV reactivation had accompanying transaminase elevation. On the other hand, DMARDs and biological agents may cause an increase in transaminase levels during therapy and this itself may be a confounding factor for physicians. Consequently, HBV viral load was used in the A+HBV study. Interestingly, a questionnaire among US-based physicians demonstrated that the awareness of rheumatologists for the screening of HBV is not sufficient, and only 7% of the rheumatologists used HBV viral load as the follow-up assessment test for HBV screening (8).

It is obvious that most of the data and guidelines about HBV reactivation were transferred from the oncology literature to rheumatology practice. At the beginning of the 1980s, HBV reactivation has been shown to occur with chemotherapy for solid cancers and leukemia, particularly when using rituximab and prednisone. This condition frequently occurred after bone marrow and liver transplantation (4). A recent meta-analysis of 13 studies including 424 patients who did not receive antiviral prophylaxis demonstrated that the combined rate of HBV reactivation was around 50%, and the mortality rate of HBV reactivation was around 10% (9). The A+HBV study showed that HBV reactivation was found to be 24% without preemptive lamivudine therapy, and this rate increased to 36% under anti-TNF therapy. A number of recent meta-analyses have now confirmed that preemptive lamivudine therapy reduces the reactivation of HBV, with a risk reduction estimated to be between 79% and 89% (9-11). A major problem with its prolonged use is the possibility of resistant mutations in the tyrosine-methionine-aspartate-aspartate (YMDD) region of the HBV-DNA polymerase (4). In non-immunosuppressed patients with chronic HBV, the cumulative rate of drug resistance is 24% after 1 year and 65–70% after 5 years of lamivudine monotherapy (4). The A+HBV study was not planned to assess lamivudine resistance. In our study group, the mean follow-up duration of all patients was approximately 2.5 years, and the mean duration of using lamivudine was 2 years. Although lamivudine resistance was not investigated, the sign of lamivudine resistance (fluctuation of HBV viral load on follow-up period) was not detected in our inactive HBV carriers.

Alternative antiviral agents such as entecavir and tenofovir are more attractive candidates because of their high potency and extremely low resistance rates. However, they are significantly more expensive than lamivudine (4). Both the European and the American Associations of Liver Diseases have guidelines regarding the use of antiviral treatment for im-

Table 3. Features of patients with HBV reactivation under anti-TNF agents

Patient No	1	2	3	4	5	6
Age (years)/Sex	53/M	26/F	42/M	41/M	30/M	41/F
Disease	SpA	SpA	SpA	SpA	SpA	RA
Reactivation duration (months)	19	21	11	14	4	60
HBV viral load (copy/mL)	8.0×10^7	8.5×10^7	5.6×10^5	1.1×10^6	1.9×10^9	1.0×10^6
Transaminase levels	Within normal limits	1.5–3 times of NL	Within normal limits	Within normal limits	>5 times of normal limits	1.5–3 times of normal limits
Liver Biopsy (HAI score)	-	Activity 3/18 Fibrosis 1/6	-	-	Activity 8/18 Fibrosis 1/6	Activity 5/18 Fibrosis 0/6
Anti-TNF treatment	ADA	ADA	ADA	INF	INF	ETN+Mtx
Antivirals	Lamivudin started after reactivation	Lamivudin started concurrently with ADA, Lamivudin switched to entecavir after reactivation	Lamivudin started concurrently with ADA	Lamivudin started after reactivation	Lamivudin started after reactivation	Lamivudin started after reactivation
Follow-up Duration (months)	19	33	31	31	45	60
Course	Unknown	Viral load returned to normal value after entecavir treatment	Viral load returned to normal under lamivudin treatment	Viral load returned to normal value after lamivudine.	Viral load returned to normal value after lamivudin. INF switched to ETN 10 months later; No reactivation with ETN	Unknown

M/F: male/female; HBV: hepatitis B virus; RA: rheumatoid arthritis; SpA: spondyloarthritis; Anti-TNF: anti-tumor necrosis factor inhibitors; Mtx: methotrexate; HAI: histology activity index; ADA: adalimumab; INF: infliximab; ETN: etanercept

munosuppressive conditions (5, 6). Recently, Vassilopoulos and Manolakopoulos (3) have suggested a therapeutic algorithm regarding the choice and duration of antiviral therapy in patients with chronic HBV infection for an immunosuppressive therapy based on these guidelines. The choice of an antiviral agent and the duration of treatment depend on the duration of immunosuppressive therapy and the status of the underlying HBV disease (inactive carrier state vs. chronic hepatitis B) (3). According to these suggestions, patients with chronic hepatitis B should use entecavir or tenofovir. Some antiviral drugs such as adefovir, lamivudine, and telbivudine are only considered for patients receiving less than 12 months of immunosuppressive treatment, and entecavir or tenofovir are considered for long-term immunosuppressive therapy (3). On the other hand, almost all of the inactive HBV carriers in the A+HBV study, regardless of the duration of their immunosuppressive treatment, had used lamivudine. In fact, this observation results from an obligation of health insurance regulations in Turkey.

In general, patients with HBV infection and inflammatory arthritis are considered as "difficult case" in daily rheumatology practice. Although there is no controlled study, sulphasalazine and hyroxychloroquine are accepted as relatively safe drugs than steroids, methotrexate, leflunomide, and biological agents. Interestingly, in this study, methotrexate and sulphasalazine were used in similar rates. The uses of biological agents in HBV patients are still uncertain. TNF alpha level is increased in both serum and hepatocytes of patients with chronic HBV (12). In transgenic animal models, TNF alpha produced by HBV-specific cytotoxic T lymphocytes downregulated HBV replication in hepatocytes. Thus, TNF alpha is generally thought to be beneficial for viral clearance (12). More recently, a systematic literature review of HBV reactivation in patients receiving TNF-targeted therapy was published (13). According to this review, there were 3 prospective cohort studies, 9 retrospective studies, and 26 case reports, including 80 patients with chronic HBV infection [HBsAg (+) carriers]. Of the 80 patients, 35 (43.7%) had HBV reactivation. The frequency of HBV reactivation was lower in patients who received antiviral prophylaxis (23% vs. 62%). The A+HBV study included 42 new anti-TNF patients who were positive for HBsAg. The HBV reactivation rate of our study was 19%, and it is lower than the abovementioned study. Considering that the systematic literature review about this kind of a rare circumstance may exaggerate results because of the publication bias, the rate of HBV reactivation seems to be more realistic in the present study. The literature review also suggested that receiving antiviral prophylaxis is an important protective factor for HBV reactivation, which is also in line with the findings of the present study that shows a tendency of preventive effects with antiviral prophylaxis. The A+HBV study was evaluated in both inactive HBV carriers and patients with chronic HBV infection. The definition of chronic HBV infection was accepted according to HBV viral load. To the best of our knowledge, this type of a study was not present in the English literature. Twenty-five patients with chronic HBV infection were followed for approximately 2.5 years in the A+HBV study. Methotrexate and anti-TNF agents were used without major side

effects during this period, and lamivudine was also found to be an effective antiviral choice in these conditions.

The main limitation of the A+HBV study is its retrospective design. Recently, we have shown that the inactive HBV carrier rate in six rheumatology centers was found to be 2.2% among approximately 3000 patients with RA and SpA (14). In this respect, more than 5000 patients with inflammatory arthritis had to be screened and followed up to be included in our study population. This study was conducted in rheumatology divisions, and selection bias may be a possible confounding factor. In fact, the HBV reactivation rate (17%) found here should be considered as a "best case" scenario. Severe patients (e.g., cirrhosis, liver failure) and patients with HBV reactivation may have been followed in hepatology centers. The true rate of HBV reactivation could only be found in prospective studies, but these are difficult to obtain. The baseline point was another limitation of the A+HBV study. The accurate detection of the timing of acute HBV infection was not possible from retrospective data. Consequently, we decided to consider the first HBV viral load time as the baseline point, which may differ considerably among physicians and centers. Patients may have used DMARDs or biological agents before our baseline point. Therefore, an increased baseline HBV viral load may have been caused by previous treatments (Figure 1). Indeed, 5 of 25 patients (20%) with chronic HBV used DMARDs [methotrexate (5 patients), sulphasalazine (2 patients), and leflunomide (1 patient)] before our baseline point. Thus, it was unclear whether those five patients had HBV reactivation or chronic HBV infection. However, those patients were categorized as having chronic HBV infection.

In conclusion, this study showed that synthetic and biologic DMARDs have similar HBV reactivation rates. HBV viral load is an easy and sensitive method for the follow-up of patients with HBV. Rheumatologists should be aware of HBV infection before starting DMARD treatment in patients with inflammatory arthritis. Lamivudine seems to be effective against HBV reactivation.

Ethics Committee Approval: Ethics Committee approval was received for this study from Hacettepe University Local Ethics Committee.

Informed Consent: Informed consent was not received due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

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