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Rheumatologists' awareness of hepatitis B reactivation before immunosuppressive therapy

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Abstract

HBV reactivation (HBVr) is a well-known complication of immunosuppressive (IS) treatment. The aim of this study was to evaluate the awareness of rheumatologists about the risk of HBVr. A survey was sent via e-mail to 270 members of the Turkish Society for Rheumatology. It consisted of fourteen questions on their awareness of the major society guidelines, approach to hepatitis B virus (HBV) screening according to different IS regimens, decision process in screening patients for HBV, knowledge of antiviral treatments for HBV, follow-up strategies, experience and postgraduate training on HBVr. Forty-eight (17.8%) rheumatologists responded to the survey. Of the respondents, 93.8% reported that they screened all patients before IS treatment, while 6.2% screened patients with a high risk of HBV infection only. The screening rate was 95.8% (46/48) in patients undergoing high-risk IS treatment and 35.4% (17/48) in those undergoing low-risk treatment. All respondents screened for HBsAg, and 83.3% (40/48) screened for anti-HBc IgG and anti-HBs. Forty-four (91.7%) rheumatologists had previously initiated antiviral prophylaxis, and 14 (29.2%) had detected HBVr in at least one patient. Rheumatologists had a high awareness of the necessity for HBV screening before IS treatment. However, the screening rates were still lower than desired, especially in patients receiving IS treatments with moderate or low risk of reactivation.

Keywords Hepatitis B · Reactivation · Rheumatology · Immunosuppressive treatment

Abbreviations

AASLD	American association for the study of liver diseases
ACG	American College of Rheumatology
AGA	American gastroenterology association
APASL	Asian Pacific association for the study of the liver
DMARD	Disease-modifying antirheumatic drugs
EASL	The European association for the study of the liver
HBV	Hepatitis B virus
HBVr	Hepatitis B virus reactivation
SPSS	Statistical package for social sciences

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TRD Turkish society for rheumatology
USA United States of America

Introduction

Hepatitis B virus (HBV) reactivation (HBVr) is a well-known complication in patients receiving immunosuppressive (IS) therapy, resulting in increased serum aminotransferases, fulminant liver disease and/or mortality [1, 2]. Furthermore, IS treatment needs to be discontinued in patients with reactivation, often leading to primary disease progression.

IS agents are used in the treatment of rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, psoriatic arthritis and psoriasis. Among the biologics, B cell-depleting agents, such as rituximab and ofatumumab, are associated with a high risk of reactivation (> 10%), whereas TNF-alpha inhibitors and other cytokine and integrin inhibitors are associated with a moderate risk of reactivation (1–10%) [3].

The risk of HBVr is associated with the mechanism of action of the IS agent used, patient's HBV serology, and viral replication markers. HBsAg positive patients have an eight times higher risk of HBVr than HBsAg negative and anti-HBc IgG positive patients [4]. However, it has been shown that HBVr risk can be significantly reduced by screening patients for HBV and initiating prophylactic antiviral therapy in selected patients before IS treatment [3].

Major international organizations have published guidelines for HBV screening and prophylactic treatment [3, 5–9], but there are significant differences between their screening recommendations. The American Association for the Study of the Liver (AASLD) guideline published in 2009 recommended to screen only high-risk patients for HBV [4] whereas the latest one published in 2018 recommended screening all patients [7]. Other guidelines either recommend HBV screening in all patients [5–7] or in patients with moderate to high risk of HBVr [3, 8, 9]. American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis, published in 2015, referred to the 2009 AASLD guideline [10].

Despite the screening recommendations from major international societies, real-life data show that HBV screening rates are low. In a study of oncology clinics in Australia and the USA, HBV screening rates were less than 20% [11, 12]. Although there is no comprehensive study in rheumatology practice, the HBV screening rate was 34.7% in a 2017 USA study of 299 patients receiving methotrexate [13]. In another study, the rate of screening before starting biologic agents was 69%, but the screening rates were correlated to the potency of the IS drugs; for instance, it was only 7% prior to corticosteroid treatments [14].

The aim of this study was to evaluate rheumatologists' awareness of the risk of HBVr and their approach to screening and prophylactic treatment in patients receiving IS treatment.

Methods

A membership list of 343 rheumatologists was obtained from the Turkish Society for Rheumatology (TRD). The inclusion criteria were (a) being an expert physician in the field of rheumatology and (b) actively working as a clinician in Turkey. The survey was prepared by a commission consisting of two gastroenterologists, one infectious disease specialist and one rheumatologist, all of whom were academicians and experienced in their fields.

The current literature on HBVr in patients undergoing IS therapy was screened in detail, and current guidelines (ACG, AGA, EASL, APASL, AASLD, ACR, TGD) were reviewed by commission members. The suitability, comprehensibility and reliability of the questions and answers were evaluated by a second commission composed of one gastroenterologist, one infectious disease specialist and a TRD-member rheumatologist, all from Sakarya University School of Medicine.

The questionnaire consisted of 14 questions (Table 1). The first question asked whether clinicians followed any guideline on HBVr in patients receiving IS treatment and, if so, which guideline. In the next two questions, clinicians were presented with a list of drugs commonly used in rheumatology and were asked about their awareness of the necessity for HBV screening before using them and their clinical practice. The following two questions were about the reactivation risk groups and the viral serologic tests used for screening. In the next three questions, rheumatologists were asked to report on preferred prophylactic treatments and follow-up protocol in HBV serology positive patients. This was followed by four questions concerning their experience on HBV prophylaxis and reactivation. The final question inquired about their postgraduate training and professional experience.

The survey was adapted to the Google forms (http://www.google.com/forms) website. One or more answer choice could be marked according to the requirements of a particular question. Out of the 343 members of TRD, 270 met the inclusion criteria. Before starting the study, each participating physician was assigned a random 3-digit identification number that was used throughout the study. Rheumatologists who met our study criteria were invited to participate in the survey via an email from TRD. The e-mail comprised information on the survey and a 'single-response' link which could be accessed from 1 April to 30 June 2018. Identification of participants was not recorded, and data was collected

Table 1 The survey and responses

	Yes	No	Not sure
1 Do you follow a guideline on HBV screening in patients receiving immunosuppressive treatment (IS)?	28	20	–
2 Should a patient taking the following drugs be routinely screened for HBV serology before IS?			
Rituximab and ofatumumab	46		
Other biological treatments (TNF inhibitors, tocilizumab, abatacept, tofacitinib, anakinra)	45		
Cytokine and integrin inhibitors (ustekinumab, secukinumab, natalizumab, vedolizumab, etc.)	43		
Belimumab (B cell activator)	37		
Tyrosine kinase inhibitors (imatinib, nilotinib, etc.)	31		
Prednisolone equivalents of 10 mg and over for more than 4 weeks	42		
Less than 10 mg of prednisolone equivalents for more than 4 weeks	17		
Azathioprine, methotrexate, 6 mercaptopurine	36		
3. Do you routinely screen for HBV before IS in a patient taking the following drugs?			
Rituximab and ofatumumab	46		
Other biological treatments (TNF inhibitors, tocilizumab, abatacept, tofacitinib, anakinra)	45		
Cytokine and integrin inhibitors (ustekinumab, secukinumab, natalizumab, vedolizumab, etc.)	38		
Belimumab (B cell activator)	31		
Tyrosine kinase inhibitors (imatinib, nilotinib, etc.)	25		
Prednisolone equivalents of 10 mg and over for more than 4 weeks	38		
Less than 10 mg of prednisolone equivalents for more than 4 weeks	15		
Azathioprine, methotrexate, 6 mercaptopurine	33		
4 Which of the following conditions should be screened for HBV infection before IS?			
All patients	45		
High risk factors for HBV infection	33		
Elevated liver function tests	32		
Never vaccinated	24		
History of hepatitis	23		
Endemic area	27		
5 Which examinations do you routinely conduct for screening HBV and related infections?			
HBsAg	48		
Anti-HBs	40		
Anti-HBcIgG	40		
HBV DNA	4		
Anti-HCV	35		
Anti-HIV	17		
6 When should HBV prophylaxis be started?			
Before starting IS	37		
Concurrent with IS	10		
After initiation of IS	1		
7 How often do you follow up your patients with HBV prophylaxis?			
Once a month	6		
Every 3 months	30		
Every 6 months	–		
Every year	–		
According to the symptoms and findings	12		
No follow-up	–		
8 Do you follow up the patients who are positive for HBV serology and not prophylactic treatment?			
Once a month			
Every 3 months	30		
Every 6 months	9		
Every year	1		
According to the symptoms and findings	8		

Table 1 (continued)

	Yes	No	Not sure
No follow-up	–		
9 Has HBV prophylaxis been initiated in your patients receiving IS?	44	4	–
10 What treatment (s) were used if prophylaxis was initiated?			
Lamivudine	28		
Tenofovir	37		
Entecavir	33		
Adefovir	6		
Telbivudine	4		
11 Have you had any HBV reactivation in your patients who received IS?	14	31	3
12 If HBV reactivation was detected, how did the follow-up of your patient/patients end?			
No need to interrupt rheumatologic treatment	3		
Need to interrupt rheumatologic treatment	11		
Liver transplantation or exitus	–		
13 After graduation, have you received any training on hepatitis B reactivation in immunosuppressive patients?			
No	9		
Guidelines/Textbooks	25		
Conferences/Symposiums	30		
Pharmaceutical industry activities	4		
Online educational seminars	12		
Local meetings in the clinic	1		
14 How many years have you been working as a rheumatologist?			

using the previously assigned random numbers. Participants were allowed to withdraw from the study before the data was analyzed. However, answers could not be changed after submitting the survey.

The first link was sent by e-mail to each physician on April 1st 2018. If no response was received, TRD sent a new link on May 1st and June 1st. No incentives were given to clinicians to participate in the study. The study was reviewed and approved by Sakarya University School of Medicine Ethics Committee (Date: 01.22.2018, protocol number: 71522473/050.01.04/68).

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 24.0 software (SPSS Inc., Chicago, IL, USA). The results were expressed as mean ± standard deviation or median (minimum–maximum).

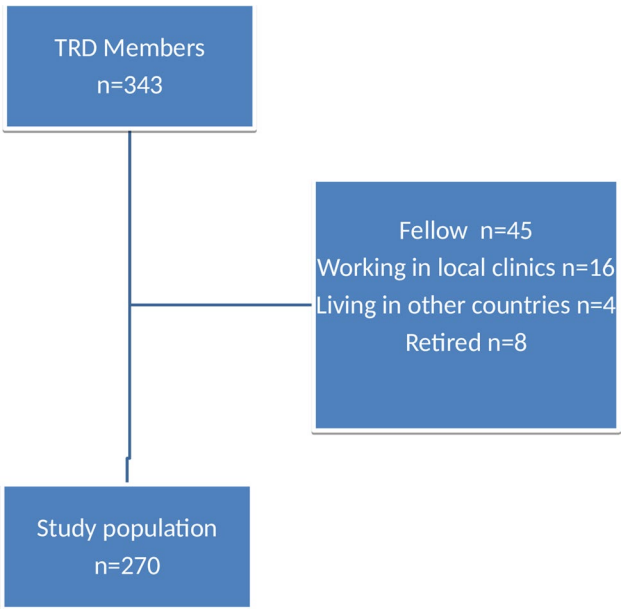

Fig. 1 The study population

Results

Study group

TRD e-mailed the survey to a total of 270 rheumatologists who met the inclusion criteria (Fig. 1). Of these, 48 rheumatologists (17.8%) completed the survey and were included in the study. 87.5% ($n=42$) of respondents were employed in university or education and research hospitals, while 12.5% ($n=6$) were employed in 2nd level

health institutions. Their average professional experience was 6.5 (1–25) years.

Screening and awareness of major guidelines

Of the rheumatologists participating in the study, 93.8% thought that HBV screening should be done in all patients to be treated with IS, while 6.2% thought this was only necessary for patients with a high risk of HBV infection. All participants considered that patients selected for screening should be tested for HBsAg, while 40 (83.3%) for anti-HBc IgG and 40 (83.3%) for anti-HBs. Only 4 (8.3%) rheumatologists considered HBV DNA necessary for screening. In addition, 35 (72.9%) rheumatologists reported that they routinely screened patients for anti-HCV and 17 (35.4) for anti-HIV (Table 1). Meanwhile, 28 (57.1%) rheumatologists reported that they followed specific guidelines: 20 followed TRD, 3 TRD and AGA, 4 AGA and 1 ACR guidelines.

HBV screening rates according to immunosuppressive drugs

Among the IS drugs, rheumatologists stated that HBV screening was most necessary in patients receiving rituximab ($n=46$, 95.8%) and least in patients receiving less than 10 mg prednisolone or equivalent for over 4 weeks ($n=17$, 35.4%) (Fig. 2). In practice, however, HBV screening was done in 52.1% of patients receiving tyrosine kinase inhibitors (imatinib, nilotinib etc.), 31.3% of patients receiving < 10 mg prednisolone or equivalent for over 4 weeks, and 68.8% of patients receiving azathioprine, methotrexate or 6-mercaptopurine (Table 1). On the other hand, the HBV screening rates were the same in theory and practice in patients receiving other IS drugs.

Approaches to prophylaxis and follow-up

The preferred timing of prophylactic treatment differed among the participants. While 37 (77.1%) rheumatologists thought that prophylaxis should be initiated before IS treatment, 10 (20.8%) preferred to start it simultaneously with IS treatment, and 1 (2.1%) after the start of IS treatment (Fig. 3). Thirty (62.5%) rheumatologists stated that follow-up was necessary every 3 months during prophylaxis, while 12 (25%) stated that follow-up duration should be determined according to signs and symptoms. Furthermore, 6 (12.5%) rheumatologists thought that a monthly follow-up was required. In patients with a positive HBV serology (HBsAg and/or anti-HBc IgG) who were not required to receive a prophylactic treatment, 30 (62.5%) rheumatologists considered to follow-up patients every 3 months, 9 considered (19.1%) every 6 months, and 1 (2.1%) considered once a year. Eight (17%) rheumatologists determined the frequency of follow-up according to signs and symptoms.

Clinical experience of prophylaxis and reactivation

Forty-four (91.7%) rheumatologists had at least one patient who received prophylaxis prior to IS treatment, while 4 (8.3%) had none. For prophylaxis, the most commonly used drug was tenofovir ($n=37$, 84.1%), while the least used was telbivudine ($n=4$, 9.1%).

Fourteen rheumatologists had at least one patient with HBVr, 31 (64.6%) had none, and 3 (6.3%) were unsure. Of

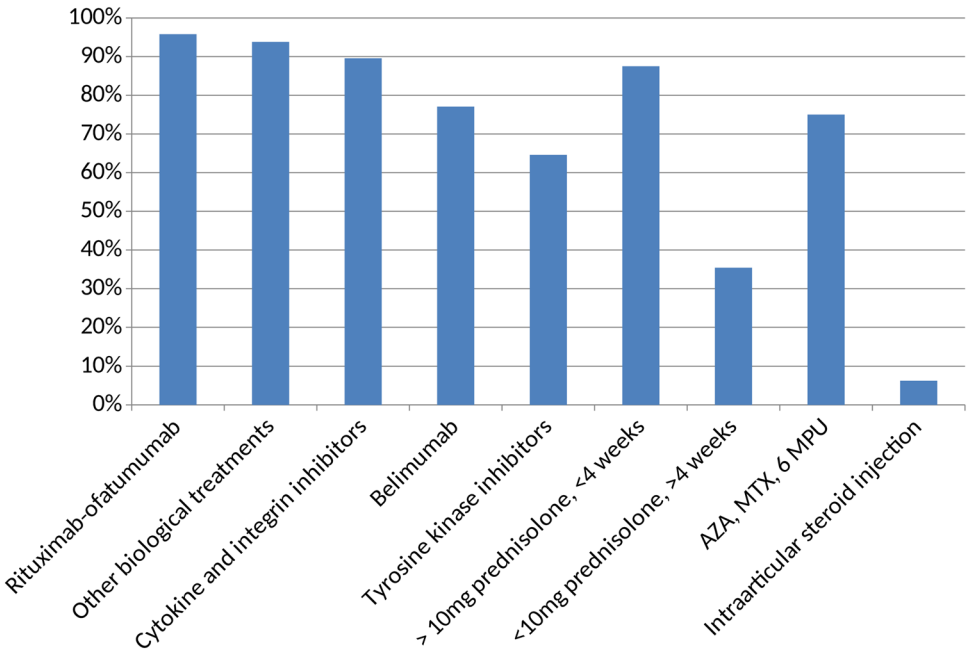

Fig. 2 HBV screening rates according to immunosuppressive drugs. *AZA* azathiopurine, *MTX* methotrexate, *6-MPU* 6 mercaptopurine

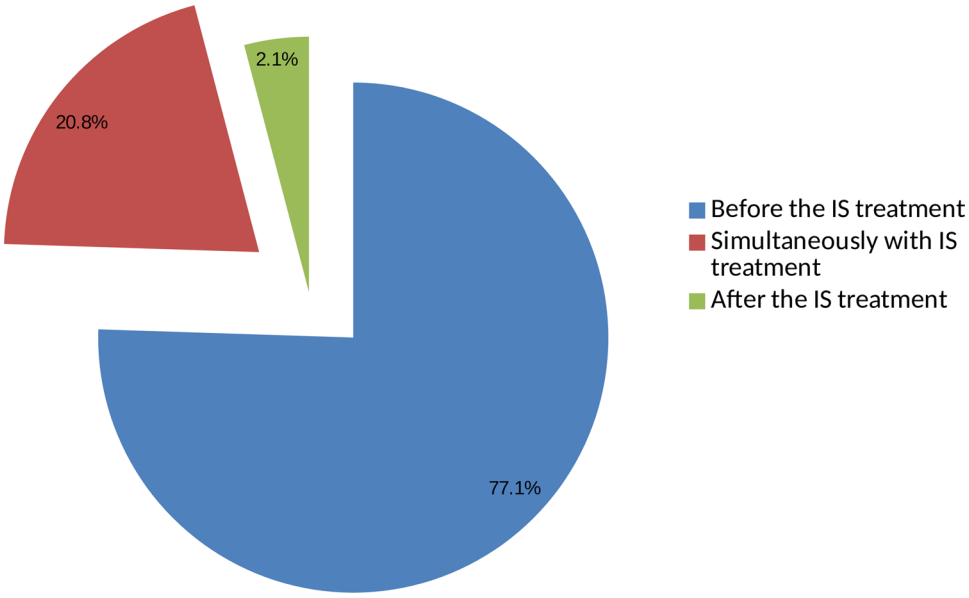

Fig. 3 Timing of antiviral prophylaxis in patients receiving immunosuppressive therapy

the 14 rheumatologists who had at least one patient with HBVr, 11 (78.6%) stopped the rheumatologic treatment during HBVr but 3 (21.4%) did not. None reported cases of exitus or liver transplantation due to HBVr.

Postgraduate training on HBVr

Thirty-nine (81.3%) rheumatologists had postgraduate training on HBVr. Training was most commonly received at conferences and symposiums ($n = 30$, 62.5%). In addition, 25 (52.1%) rheumatologists updated themselves from guidelines and textbooks, 12 (25%) from online educational seminars, 4 (8.3%) from various activities organized by the pharmaceutical industry and one (2.1%) in the clinic. Nine (18.8%) rheumatologists didn't receive any postgraduate training.

Discussion

In our study, we found that rheumatologists had a relatively high awareness of the necessity for HBV screening before IS treatments. Of the participants, 93.8% thought that screening should be performed in all patients before IS treatment, and the remaining 6.2% considered it necessary for only high-risk subjects.

There are only three questionnaire-based studies about physicians' awareness of HBVr before starting IS treatments [14–16]. Our study, compared to the previous ones, was novel with respect to its methodology. We classified IS agents according to their risk of reactivation based on AGA guideline [3] and evaluated some new parameters, such as awareness of the physicians about major society guidelines, their approach to HBV screening according to different IS regimens, their experience with HBVr and postgraduate training on HBVr.

TRD has 343 members. We excluded fellows, retired physicians, those working outside Turkey, and those working in private clinics and sent the survey to the remaining 270 members. Out of them, 48 (17.3%) responded to the survey. The members were contacted by e-mail only, and no additional way of contact, such as phone calls, was used. This may be one of the reasons behind the low participation rate. Similar studies conducted on rheumatology and dermatology physicians also reported low participation rates of 15.3% and 7.9%, respectively [14, 15]. Other factors that might have contributed to the low participation rate were the high number and specificity of the questions.

Of the participants, all considered that patients selected for screening should be tested for HBsAg, while 83.3% for anti-HBc IgG. In a 2014 study, out of 328 patients receiving IS treatment in rheumatology clinics, 187 (57%) were screened for HBsAg, while 95 (29%) were screened for anti-HBc IgG [17]. Since the DNA of the hepatitis B virus integrates with the host genome, a true virological cure cannot be achieved with the antiviral treatments currently available. In addition, in patients recovering from acute hepatitis B, viral cccDNA settles in the hepatocyte nucleus and serves as a pattern for the virus to replicate when IS therapy is given [18]. One meta-analysis reported that in patients who received chemotherapy for solid tumors, HBVr developed in 4-68% of HBsAg positive patients and 0.3-9% of patients with resolved infections (HBsAg negative, anti-HBc IgG positive and HBV DNA negative) [19]. A study on patients receiving anti-TNF or disease-modifying antirheumatic drugs (DMARD) treatment for rheumatoid arthritis reported

a HBVr rate of 12.3% in HBsAg positive patients ($n = 122$) [20], while HBVr rate was 5.2% in isolated anti-HBc IgG positive patients ($n = 135$) in another study [21]. Due to these high reactivation rates, guidelines recommend to test for HBsAg, anti-HBc IgG and anti-HBs during screening [3, 5, 7, 9].

Concerning the HBV screening rates according to IS regimens, there are few publications in the rheumatology practice. In a US survey conducted in 2010, rheumatologists reported that the frequency of HBV screening in all patients was 69% before biological DMARD, 42% before non-biological DMARD and 7% before corticosteroid treatments [14]. In our study, 95.8% of the rheumatologists stated that all patients should be screened before rituximab or ofatumumab and 93.8% before other biological treatments. The screening rate was correlated to the IS potency of the drugs. It is well known that the risk of reactivation should not be assessed by the potency of the agent alone but also by the viral serology. For example, in our study, we found that the screening rate decreased to 35.4% before the use of less than 10 mg prednisolone or its equivalents for more than 4 weeks. However, these patients might have a moderate (1–10%) risk of reactivation if they are HBsAg positive and, therefore, antiviral prophylaxis should have been initiated [3].

Another issue worth mentioning is the preferred timing of prophylactic antiviral treatment. In our study, 77.1% of rheumatologists thought that prophylactic antiviral treatment should be started before IS treatment and 20.8% simultaneously with IS treatment. Clinicians often want to initiate IS treatment without delay. The timing of prophylaxis and the choice of antiviral agent depend on the risk of reactivation, the duration of IS treatment, HBV DNA levels and previous antiviral therapy [22]. In randomized trials, prophylactic antiviral therapy was shown to be more effective than pre-emptive strategies. It may be more prudent to initiate prophylactic antiviral therapy 1–3 weeks before IS therapy in patients with HBV DNA levels greater than 10^4 IU/ml [5, 23, 24]. Prophylactic antiviral therapy can be initiated simultaneously with IS therapy in the remaining patients [5, 24]. We believe that informing primary physicians of patients starting IS treatment might remove concerns about delaying IS treatment, and increase the consultation rates of patients with a positive serology to specialists.

The ideal oral antiviral drugs for prophylaxis are the relatively fast-acting nucleos(t)ide analogues, tenofovir and entecavir, which are powerful in suppressing HBV DNA and have a high genetic barrier to the development of drug resistance [5, 7, 25]. 91.7% of rheumatologists had at least one patient who received prophylaxis prior to IS treatment, and in line with recommendations, tenofovir ($n = 37$, 84.1%) and entecavir ($n = 33$, 75%) were the most frequently used drugs.

Patients on prophylactic treatment should be monitored with liver function tests and HBV DNA every 3–6 months [5, 26, 27]. There are some differences between the international guidelines regarding the prophylaxis indications in HBsAg negative, anti-HBc IgG positive (anti-HBs positive or negative) and HBV DNA negative patients. If physicians do not initiate prophylaxis in these patients, they should follow them with liver tests every 1-3 months and HBV DNA tests every 3 months [3, 5]. However, in our study, 37.5% of the participants considered to follow-up such patients with an interval of more than 3 months. Therefore, it would be prudent to consult a specialist before making a decision about prophylaxis and determining follow-up intervals.

In our study, most of the participants (81.3%) had received postgraduate training on HBVr. In our opinion, several steps should be taken to raise awareness of HBVr in patients receiving IS treatment. Conferences and symposiums, web presentations, seminars and case meetings, training documents and brochures can all increase this awareness. Furthermore, increasing communication between the clinics will reduce obstacles to consultation and concerns about delays in IS therapies, and primary physicians will be able to consult their patients more easily to gastroenterology or infectious disease specialists. Computer alert programs have also been shown to increase awareness and screening rates [17, 28].

There are two questionnaire-based studies about rheumatologists' awareness of HBVr before starting IS treatment. Sixteen Canadian rheumatologists evaluated the hospital files of 140 patients and concluded that HBV screening was necessary in 81% of them before starting IS treatment [29]. A US study of 138 rheumatologists reported a universal screening rate of 70% before starting biologic DMARDs, 53% before non-biologic DMARDs and 12% before corticosteroids [14]. Turkey is in an endemic region for HBV (HBsAg positivity: 4%; anti-HBc IgG positivity: 30.6%) [30] and our study revealed a higher screening rate, which may be due to a growing literature on HBVr cases and publication of updated clinical practice guidelines in recent years. However, in all of these studies, the screening rates were markedly lower than desired, especially in patients receiving IS treatments with moderate or low risk of reactivation.

Our study had some limitations. Only 17.8% of rheumatologists completed the survey, which might be a source of bias. In addition, physicians who responded to our survey might be those more concerned about possible HBVr and this might have led to a high screening rate of 93.8%. Another reason for this high screening rate was that the study was a survey and not based on real-life data. However, as the study includes a large group of academicians and non-academic rheumatologists from all over the country, it is valuable in terms of demonstrating the general approach of all rheumatologists to HBVr. Additionally, the participation of rheumatologists with different professional experience ranging between 1 and 25 years was considered as a strength

of our study. Finally, our study was the first to evaluate the awareness of rheumatologists about HBVr in patients receiving IS therapy in endemic areas such as Turkey.

Conclusion

In conclusion, it seems likely that growing literature on HBVr-related morbidity and mortality combined with widespread in-service training opportunities have contributed to a high level of HBVr awareness among rheumatologists in Turkey. However, we believe that more effective communication between the clinics could help determine the reactivation risk due to IS drugs, prevent overlooking patients with isolated anti-HBc IgG positivity, and optimize the follow-up of patients.

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Compliance with ethical standards

Conflict of interest Author Toka B., Author Eminler A. T., Author Gönüllü E., Author Tozlu M., Author Uslan M. I., Author Parlak E., Author Karabay O. and Author Köksal A. Ş. have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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