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The evaluation of neurologists' awareness on hepatitis B virus reactivation before launching immunosuppressive treatment

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Abstract

Background: Individuals encountering hepatitis B virus (HBV) are at risk of hepatitis B virus reactivation (HBVr) when exposed to immunosuppressive (IS) therapy. Here, we aimed to evaluate neurologists' knowledge on HBVr in patients receiving IS treatment and draw attention to importance of the issue. *Methods:* Eighty-six physicians from neurology departments throughout Turkey between 1st March-30th April 2020 were enrolled. *Results:* Of 86 physicians (average age 37.2±7.6 years), 34 (39.5%) were affiliated with university hospitals, 23 (26.7%) in training and research hospitals, and 29 (33.6%) in secondary healthcare centers. While 28 (32.5%) stated following a guideline, 58 (67.4%) declared following no guidelines. Physicians receiving postgraduate training on HBVr administered prophylaxis before IS treatment at a higher rate (p=0.04), and 69 (80.2%) considered all patients receiving any IS treatment should be screened for HBVr. To all participants, patients selected for screening should be tested for HBsAg; 83 (96.6%) and 29 (33.3%) stated patients should be tested for anti-HBs and anti-HBc IgG, respectively.
Conclusion: Given our study findings, rate of screening performed by neurologists to give IS treatment for HBVr and their awareness level on the situation were not found to be sufficient. In addition, two more important factors required to be raised awareness were detected in our study: First, the rate of using anti-HBc in screening is low, and the awareness should be increased in this direction. Secondly, the risk of HBVr should be categorized in terms of IS treatment and host in our country where HBV infection is seen at a high rate, and determining the prophylactic approach is insufficient.

Keywords: Hepatitis B virus reactivation, immunosuppressive treatment, neurologist, prophylaxis

INTRODUCTION

The natural course of the hepatitis B virus (HBV) is determined by the interaction between virus replication and host immunity. HBV keeps on existing in the body even after acute hepatitis B infection serologically resolves. Therefore, if an individual is exposed to HBV, s/he is at the risk of hepatitis B virus reactivation (HBVr), characterized by the fluctuation of aminotransferase when the immunity is suppressed. The exacerbation of HBV is characterized by a sudden increase in serum levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in the presence of underlying liver disease, with or without clinical symptoms, and often manifests itself preceding the increase in hepatitis B virus deoxyribonucleic acid (HBV DNA).[1] Immunosuppressive (IS) therapy-associated HBVr is an important cause of morbidity and mortality in those currently infected with HBV or previously exposed to the virus. Since a curative treatment for HBV has yet to be available, there is a huge reservoir of individuals at risk for HBVr in the general population.[2] Almost every individual exposed to HBV infection faces the danger of reactivating the infection. The increase in viral replication may lead to the elevation of liver enzymes, liver failure, and even death. Additionally, HBVr may lead to the early discontinuation of IS therapy or some delay in the treatment program.[3] Major associations have published significant guidelines related to HBV screening and prophylactic

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treatment.[4-9] However, there are significant differences among the recommendations created by those associations on screening. While some guidelines recommend screening all individuals at risk for HBV before long-term IS therapy, others assert HBV screening in those with moderate-to-high HBVr risk.[4,8-10] The key to preventing HBVr is identifying patients with HBV infection before IS therapy, initiating prophylactic antiviral therapy in those with the moderate-or-high risk of HBVr, and monitoring other patients closely. Unfortunately, many patients infected with HBV are unaware of carrying the infection or the risk of IS treatment. Moreover, physicians cannot allocate enough time to systematically evaluate patients concerning HBV risk factors before launching IS therapy. Individuals having the risk factors should be screened in terms of HBV before IS therapy. Hepatitis B surface antigen (HBsAg) and antibody to hepatitis B core antigen (anti-HBc) should be screened in all patients planned for immunosuppressive therapy. If one or both of these are positive, HBV-DNA should be requested. Hepatitis B e-antigen (HBeAg), antibody to hepatitis B e-antigen (anti-HBe) and anti delta antibody (anti-HDV) should be requested in HBsAg positivity.[11,12] The HBV screening algorithm in patients planned for immunosuppressive treatment is summarized in Figure 1.[13]

Based on the literature, studies evaluating the clinical awareness and practices of physicians performing IS therapy regarding the prevention of HBVr are frequently composed of hematologists and oncologists as the study group.[14-17] With the recent developments, the utilization of steroids and biological drugs has increased in CNS inflammatory diseases treated by neurologists, especially in significantly in multiple sclerosis (MS) cases pacing with attacks.[10] MS is a neuroinflammatory, neurodegenerative, demyelinating disease leading to cognitive and neurological dysfunctions.[10] MS is a neuroinflammatory, neurodegenerative, demyelinating disease leading to cognitive and neurological dysfunctions.[18] The protocol of disease-modifying drugs (DMD) is determined by looking at the type of MS, course of the disease, and lesion load detected through neuroimaging methods. Such drugs as interferon beta (IFN-β), glatiramer acetate, natalizumab, fingolimod, teriflunomide, and dimethyl fumarate are widely used in the treatment of MS. However, the expected responses cannot be obtained in all patients receiving those treatments, or the condition keeps progressing in some patients. In a group of patients, MS may have a very aggressive or progressive course from the onset of the disease. In such cases, there are different treatment options

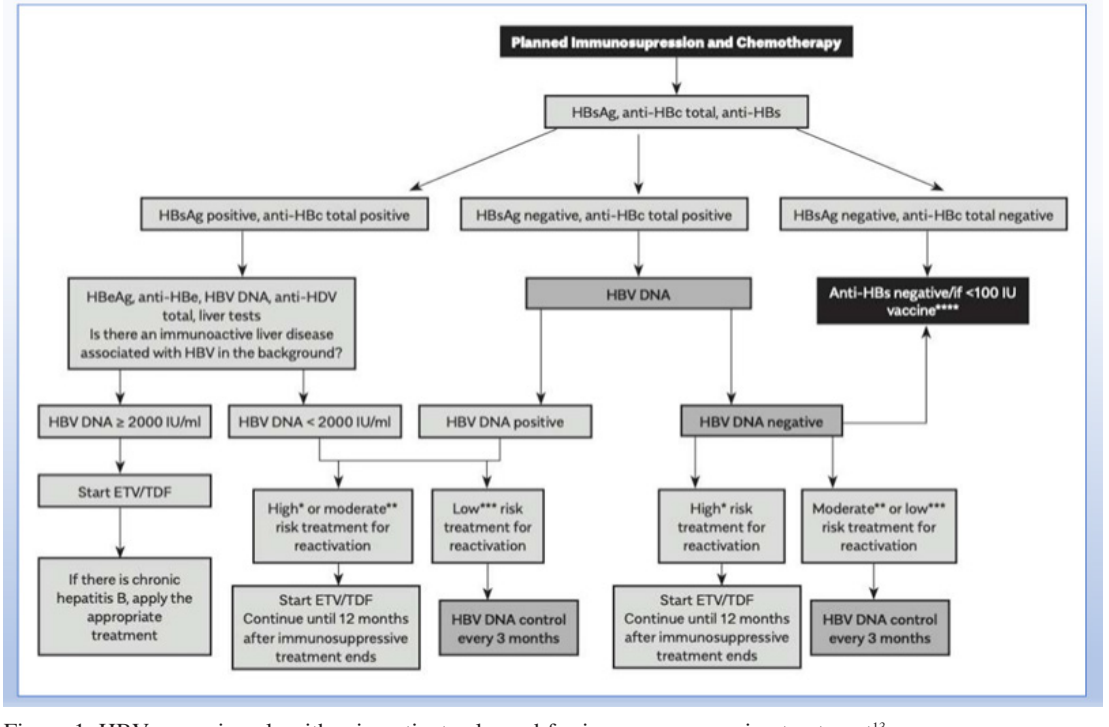

Figure 1. HBV screening algorithm in patients planned for immunosuppressive treatment[13]

as IS administered in the advanced stages of MS or in those who are unresponsive to first-line treatments.[19,20] Considering that a group of those diagnosed with MS are accompanied by hepatitis B, screening and follow-up are required for prophylaxis before IS DMD. Therefore, the presence of hepatitis B accompanying MS does not constitute a contraindication for DMD. To limit the progression of the disease and prevent seizures or exacerbations, the treatment of MS is of a priority, and it is recommended that patients be screened and followed-up only for HBVr, and prophylaxis be performed, when necessary. In our country, tenofovir and entecavir are chosen in case of the requirement for prophylaxis in MS patients receiving IS treatment.[7,20] In a study where 320 MS patients received the treatment of ocrelizumab, 10% of the patients were found to be positive for HBV core antigen, and entecavir was administered as prophylaxis for HBV reactivation in all cases, and HBVr was not observed in any of the patients.[21] When HBVr is witnessed during the close follow-up period both with and without prophylaxis, the treatment of treatment IS should be discontinued at once, and the reactivated chronic hepatitis B (CHB) should be treated.[20] However, it should not be ignored that ISTs given, especially steroids, may also cause AST/ALT elevation and cholestatic hepatitis. This condition must be distinguished from HBVr. In patients with active MS accompanied by CHB, optimal DMD should be selected to treat MS without seeking alternative strategies. Since a part of the patients has received anti-viral treatment due to the diagnosis of CHB independent of the MS treatment, there is no need for prophylaxis. In such patients, it is sufficient to increase the frequency of follow-up for HBVr in the process of disease-modifying IS treatment; and normal anti-viral treatment protocol is carried out in those with CHB but receiving no treatment. Even so, in the group with the diagnosis of CHB but no indications for antiviral treatment, pre-treatment prophylaxis or close follow-up, and prophylaxis are recommended, when necessary.[19,20] In the present study, it was aimed to evaluate the knowledge and awareness levels of neurologists administering IS therapy due to HBVr and draw attention to the significance of the issue through the evaluation.

METHODS

The study was approved by the Medical Specialization Training Board (MSTB) of Konya Training and Research Hospital in Health Sciences University on February 2, 2020 (Decision no: 35-29). Our study conforms to the Ethical Principles for Medical Research Involving Human Subjects of the 1964 Helsinki Declaration. The questionnaire investigating the knowledge and awareness levels of neurologists on IS treatment and HBVr was sent to the clinicians, and the responses were collected by the lead author between March 1 and April 30, 2020. Two hundred and seventy-eight neurologists, most were the members of the Turkish Neurological Society, were invited to the study through a questionnaire including informed consent. Of 278 individuals expected to participate in the study, 113 neurologists were considered to have accepted giving consent when responded. Respondents stating that they followed-up no MS patients and those responding to the survey questions incompletely were excluded from the study. As a result, a total of 86 (30.9%) neurologists were included in the study. In the selection process of neurologists participating in the survey, the criteria were that neurologists with different lengths of professional experience still work actively in various health facilities, such as university hospitals, secondary and tertiary centers. Thus, we considered that it was important to compare the knowledge and awareness levels of neurologists with different professional experiences on HBVr under IS treatment and working at different-level health centers. In designing the study, each clinician participating in the study was informed about the study. For protecting each participant's privacy, the credentials were kept confidential. The copies of the questionnaire investigating the neurologists' knowledge and awareness level concerning IS treatment and HBVr were sent to the clinicians by adapting to the website of www.google.com/forms, and the responses were accumulated and assessed by the lead author between March 1st and April 30th, 2020. In preparing the questionnaire, the existing guidelines created by such associations as The European Association for the Study of the Liver (EASL), The Asian Pacific Association for the Study of the Liver (APASL), The American Association for the Study of Liver Diseases (AASLD), and American Gastroenterological Association (AGA) related to HBVr in those receiving IS treatment were meticulously investigated by two infectious diseases specialists and a neurologist.[4-7] The questionnaire consists of 13 questions created to ensure the questions were understandable, valid, and reliable based

on the guidelines (Table 1). In the first question, clinicians were asked whether any guideline on HBVr was followed in evaluating IS treatment and if any, what guideline was followed. In the second and third questions, the clinicians were given a list of medications commonly used in neurology, especially in the treatment of MS, and asked about the necessity of HBV screening and the awareness level to the clinical practice before using such medications. The fourth and fifth questions were associated with HBVr risk groups and whether to test clinicians' background information on viral serological tests used for screening. The sixth, seventh and eighth questions were about determining the prophylaxis time and follow-up of those patients according to the clinicians' approaches to HBV serology. With the following four questions (questions 9-12), the clinicians' experience on HBV prophylaxis and the reactivation was aimed to be assessed. Even so, the last question was about whether or not clinicians received any training on such an important subject as HBVr after IS treatment. The questions were created as multiple-choice, including one or more options. As an alternative, the option of "other" was added to the last question.

Statistical analysis

All statistical analyzes were performed using the Statistical Package for the Social Sciences for Windows, version 24.0 software (SPSS Inc., Chicago, IL, USA). In describing the findings, the values were presented as mean±standard deviation (SD), or median (minimum-maximum).

RESULTS

A total of 86 neurologists participated in the study, and the clinicians' average age was measured as 37.2±7.6 years. The distributions of the respondents to the questionnaire in healthcare facilities were as follows: 34 (39.5%) in university-affiliated hospitals, 23 (26.7%) in training and research hospitals, 29 (33.6%) in secondary healthcare centers, 15 (17.4%) in state hospitals, and 14 (16.2%) in private hospitals. The average professional experience of the respondents was also found as 10.5±8.6 years (1-25).

The evaluation of physicians' awareness level on hepatitis B virus reactivation and following guidelines related to the issue

Of all neurologists participating in the study, while 28 (32.5%) stated to follow any guideline, 58 (67.4%) reported that they followed no guidelines. When the professional experience of clinicians was examined in four categories as <5 years, between 5-10 years and 10-20 years, and >20 years, it was observed that as the period of professional experience increases, the rate of following any guideline also increases (p=0.006). Additionally, the rate of following any guideline was found higher among the tertiary hospital-affiliated clinicians than those in secondary care hospitals (p=0.01). While 69 (80.2%) of the participants considered that all patients receiving any IS therapy should be screened for HBVr, 74 (86.05%) and 62 (72.09%) of the clinicians reported that screening tests were required for those having elevated findings of liver function tests and those with the familial history of hepatitis, respectively. Given that a participant could respond to more than one question, the distributions of the clinicians considering that screening tests should be performed for those with other characteristics were as follows: 60 (69.7%) clinicians were detected to choose screening tests for those with a history of jaundice, 51 (59.3%) for intravenous drug users, 59 (68.6%) for homosexual men, 66 (76.7%) for healthcare workers, 63 (73.2%) for those with a history of blood transfusion, 71 (82.5%) for hemodialysis patients, 66 (76.7%) for those not receiving HBV vaccine, and 45 (52.3%) for those living in an endemic region. While all the participants announced that those selected for HBVr screening should also be tested for HBsAg, 83 (96.6%) and 29 (33.3%) stated that patients should be tested for anti-HBs and anti-HBc IgG, respectively. Only 19 (22.09%) neurologists were found to consider that HBV DNA was necessary for screening due to HBVr. In addition, while 52 (60.4%) neurologists stated that patients were routinely screened with anti-HCV tests, 45 (52.3%) reported that patients were screened for anti-HIV (Table 1).

The evaluation of the rates of hepatitis B virus screening in terms of medications used in immunosuppressive treatment

Given the rates of HBV screening due to the medications used for IS treatment, neurologists declared that HBV screening was most required before the treatment with ocrelizumab (n=74, 85.05%), followed by rituximab (n=71, 82%) and natalizumab (n=70, 81%). However, the treatment required least for screening was considered to be glatiramer acetate (n=34, 39.5%) (Figure 1). Similarly, in the clinicians' practice, ocrelizumab came to the fore as the most common treatment

Table 1: The awareness questionnaire of neurologists on hepatitis B virus reactivation after immunosuppressive therapy

	Yes	No	Not convinced
1. Are there any guidelines/literature you follow about screening for HBV in patients receiving IS therapy?	28	58	-
2. Which of the following drugs would you consider asking for HBV serology before starting IS therapy?			
a Interferons	41		
b Glatiramer acetate	34		
c Azathioprine	58		
d Dimethyl fumarate	40		
e Teriflunomide	48		
f Fingolimod	58		
g Rituximab	71		
h Ocrelizumab	74		
i Natalizumab	70		
j Alemtuzumab	67		
k Prednisolone equivalents ≤20 mg for more than 4 weeks	46		
3. Which of the following medication/medications do you routinely use to screen all your patients for HBV before starting treatment?			
a Interferons	40		
b Glatiramer acetate	36		
c Azathioprine	52		
d Dimethyl fumarate	37		
e Teriflunomide	42		
f Fingolimod	54		
g Rituximab	69		
h Ocrelizumab	70		
i Natalizumab	62		
j Alemtuzumab	65		
k Prednisolone equivalents ≤20 mg for more than 4 weeks	39		
4. In which of the following situations do you think screening should be performed for HBV infection in patients IS therapy will be started for?			
All patients to receive any IS treatment	69		
Those with increased rates in liver function tests	74		
Those with familial history of hepatitis	62		
Those with a history of previous jaundice	60		
Those receiving iv medications	51		
Homosexual men	59		
Healthcare workers	66		
Those having a history of blood transfusion	63		
Patients on hemodialysis	71		
Those without HBV vaccination	66		
Those dwelling in an endemic area	45		
5. What tests do you conduct routinely for screening HBV and related infections?			
HBsAg	86		
Anti-HBs	83		
Anti-HBc IgG	29		

	Yes	No	Not convinced
HBV DNA	19		
Anti-HCV	52		
Anti-HIV	45		
6. When should HBV prophylaxis be launched?			
Before commencing IS treatment	64		
In combination with IS treatment	17		
After commencing IS treatment	4		
If the reactivation develops during the follow-up period	17		
7. How often do you follow-up your patients receiving HBV prophylaxis?			
Once a month	27		
Once every three months	31		
Once every six months	10		
Once per annum	1		
I define the frequency of follow-ups according to symptoms and findings.	12		
I do not follow-up.	-		
8. Do you follow-up your patients with the positivity of HBV serology, and for whom prophylactic treatment is not recommended in terms of reactivation?	17		
Once a month	28		
Once every three months	20		
Once every six months	2		
Once per annum	19		
I define the frequency of follow-ups according to symptoms and findings.	4		
I do not follow-up.	-		
9. Among those receiving IS treatment, did you have any patients treated with HBV prophylaxis?	19	42	25
10. If prophylaxis was launched, what treatment/treatments were utilized?			
Lamuvidin	8		
Entecavir	13		
Tenofovir disoproxil fumarate	10		
Adefovir	4		
Telbivudine	2		
11. Did any of your patients receiving IS therapy develop HBV reactivation?	4	46	31
12. If HBV reactivation was detected, how were the patient/patients' follow-ups stopped?			
No need to interrupt IS therapy	6		
Need for interrupting IS therapy	20		
A liver transplant was performed.	1		
Exitus	-		
13. Have you received any postgraduate training on hepatitis B reactivation in IS patients?	33	53	
Textbooks/Guides	17		
Congresses/Symposiums	14		
Training seminars organized by the pharmaceutical industry	-		
Resources on the internet	2		
Others	-		

Anti-HBc IgG: Antibody to hepatitis B core immunoglobulin G, Anti-HBs: Antibody to hepatitis B surface, Anti-HCV: Antibody to hepatitis C virus, Anti-HIV: Antibody to human immunodeficiency virus, HBsAg: Hepatitis B surface antigen, HBV: Hepatitis B virus, IS: Immunosuppressive, HBV DNA: Hepatitis B virus deoxyribonucleic acid

for HBV screening (n=70, 81.4%,). Used for screening due to the treatment modalities, other medications following ocrelizumab were detected to be rituximab (n=69, 80.2%) and alemtuzumab (n=65, 72.2%). Even so, the treatment for which screening was performed least was detected as glatiramer acetate (n=36, 41.8%). In terms of HBV, the rates of the medications the screening tests were performed for are presented in Figure 2.

The evaluation of prophylactic treatments administered for Hepatitis B virus reactivation, the principles of follow-ups of those with HBVr, and physicians clinical experience

For the patients' group requiring prophylaxis, the timing chosen for the treatment varied among the participants. While 64 (74.4%) neurologists considered that prophylaxis should be started before IS treatment, 17 (17.7%), 4 (4.6%) and 17 (19.7%) stated that prophylaxis should be commenced concurrently with IS treatment, after the initial of IS treatment, and in case of reactivation during follow-up, respectively. Although 31 (36.05%) neurologists stated that follow-up is required every 3 months during prophylaxis, 27 (31.4%) and 12 (13.9%) emphasized that follow-ups were necessary once a month, and that the follow-up period should be determined in light of the findings and symptoms, respectively. Moreover, while 10 neurologists (11.6%) stated that follow-ups were required every six months, and five neurologists (5.8%) considered that follow-ups were not essential, one neurologist (1.1%) declared that follow-ups would be sufficient once a year. For those with positive HBV serology not requiring prophylactic treatment, while 28 (32.5%) and 20 (23.2%) neurologists stated that follow-ups should be performed every 3 months and every 6 months respectively, 19 (22.09%) asserted that patients should be followed-up according to signs and symptoms. Additionally, 17 (19.7%) neurologists reported the follow-up rate as once a month, two (2.3%) followed-up the patients once a year, and four (4.6%) declared no follow-ups. Nineteen (22.09%) neurologists were also found out to state performing prophylaxis for at least one patient before IS treatment while 42 (48.8%) performed no prophylaxis. The physicians stating to follow any guideline were observed to administer prophylaxis before IS treatment at a higher rate (p=0.03). While entecavir (n=13, 15.1%) was declared as the most frequently preferred medication for prophylaxis, tenofovir (n=10, 11.6%) and lamivudine (n=8, 9.3%) ranked the second and third mediations most commonly used for prophylaxis. As the least used medication, telbivudine (n=2, 2.3%) was determined to be used for prophylaxis. While four neurologists stated that at least one of their patients had HBVr, 46 (56.7%) neurologists declared that no patients developed HBVr. Even so, 31 neurologists (38.2%) were not certain of whether the patients had HBVr. Four neurologists detecting HBVr during follow-up

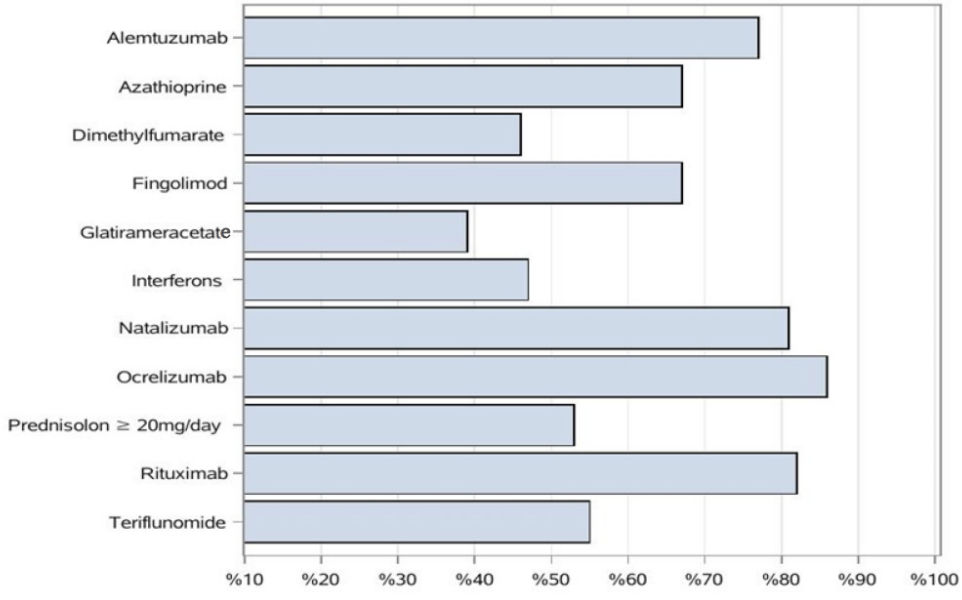

Figure 2. The screening rates for hepatitis B virus according to immunosuppressive medications

stated that IS treatment was interrupted in 20 (76.9%) of 26 patients with reactivation, and IS treatment was continued without interruption in six patients (23.08%). While one case was declared to undergo a liver transplant due to HBVr, no deaths were reported.

The evaluation of physicians' postgraduate training related to Hepatitis B virus reactivation

Among 33 (38.2%) neurologists detected to receive postgraduate training on HBVr, 17 (19.7%) were found to receive training from the guideline manuals and textbooks, 14 (16.2%) by attending congresses and symposiums, and two (2.3%) via the Internet. The clinicians stating to receive postgraduate training on HBVr were observed to perform prophylaxis at a higher rate before IS treatment (p=0.04).

DISCUSSION

Due to the increased number of departments giving IS therapy in recent years, and since there is the risk of HBVr in HBV contacts or those exposed to HBV previously and recovered, screening modalities are recommended for HBV serology before IS treatment in all current guidelines regarding reactivation. However, there are differences in the guidelines for screening created or recommended by different associations. Additionally, there is also no consensus among clinicians on the issue.[22-24] In recent years, the use of IS treatment, especially to treat MS cases, by neurologists, has increased. In MS patients with CHB, there is no harm in using DMD for IS treatment, which is indicated as long as follow-ups, and if necessary, antiviral prophylaxis procedures are performed for HBVr. As the treatment of the primary disease is a priority, the optimal treatment of MS should not be neglected or interrupted due to the additional diseases to be managed. However, if HBVr develops during the follow-ups, IS treatment should be interrupted or discontinued based on the clinician's decision.[19,20]

Since Turkey is located in a moderate endemicity region regarding HBV infection, the rates of reactivation may have been found higher, compared with the countries in low endemicity regions, where previous studies were conducted.[25] Based on the data released by the US Food and Drug Administration, many HBVr cases have been reported due to the use of rituximab and ofatumumab, and those drugs belong to the high-risk group. Therefore, a warning was issued in 2013, indicating that such drugs may lead to fulminant hepatitis, liver failure, and deaths.[26,27] Given the literature on rituximab, a drug used in the treatment of rheumatological diseases and hematological malignancies, the reactivation was observed at the rate of 24% in 46 lymphoma patients with HBsAg negativity and anti-HBc positivity in the follow-ups, and no reactivation was witnessed in the group receiving no rituximab.[28,29] Ocrelizumab is an anti-CD20 monoclonal antibody used for the treatment of advanced and recurrent MS.[30,31] Under the ocrelizumab treatment, considering the monoclonal antibody treatments (such as rituximab), it is considered that HBVr is likely to develop.[30-32] Current guidelines recommend the HBV prophylaxis or periodic follow-ups for those with HBsAg negativity, anti-HBs positivity, and HBV-DNA negativity patients at high risk (>10%) or intermediate-to-low risk (<10%) in terms of HBV reactivation.[5,7] Therefore, based on the literature, there are cases of HBVr following the use of ocrelizumab in the treatment of MS.[33] In a study conducted with 174 MS patients receiving DMD in Italy, HBVr was reported to be observed in two patients receiving ocrelizumab.[34] Further studies are needed to determine the risk of HBVr and the follow-up protocol during the treatment with ocrelizumab in MS patients. Under the guideline of MS in our country, screening for HBV serology is recommended before the use of IS effective DMD.[19] However, current studies are insufficient in providing a better approach in the case of HBVr, which can develop in the treatment of MS. Upon scanning the literature, no data were encountered on the development of new HBV infection under IS treatment in MS patients. During the screening against the risk of new HBV infection, HBV vaccination is recommended for seronegative individuals not encountered HBV and vaccinated yet before IS treatment. Higher doses or an accelerated vaccination schedule may be required to obtain an anti-HBs response in immunocompromised patients.[35]

A previous study reported that 88.5% of the physicians stating the patients were scanned in terms of HBVr risk before IS treatment wished all of the patients to be screened.[36] Although the rate was a bit lower in our study, 80.2% of neurologists reported that all patients to receive any IS treatment should be screened for HBVr. Although not a lower rate, the awareness rate for screening was seen to be insufficient with nearly 20% of loss; such a situation was also considered risky for HBVr due to the high rates of morbidity and mortality. In another study

where the serology of hepatitis B surface antigen (HBsAg) was evaluated, the serology rate was found to be 60% in neurology departments.[37] As well as the deficiency of theoretical knowledge, the rate demonstrates the flaw in reflecting current knowledge in clinical practice. In the guidelines concerning HBVr, it is also recommended to investigate antibodies of hepatitis B core (Anti-HBc) to screen for HBV patients, along with hepatitis B surface antigen (HBsAg).[4-9] If the patient is HBsAg-positive, it is recommended to investigate hepatitis B virus deoxyribonucleic acid (HBV DNA), in addition to Hepatitis B e-antigen (HBeAg) and anti-Hepatitis B e (anti-HBe). If the case is HBsAg-negative and anti-HBc-positive, the patient is recommended to be followed-up closely in terms of HBV DNA, and prophylactic antiviral treatment may be initiated according to IS treatment regimen given to the patient.[4] In the study conducted by Korkmaz et al., 63.3% of the physicians performing HBV screening before IS treatment were determined to order the anti-HBc test.[2] In parallel studies, the rate was reported to range between 22.6-91%.[14-16] The awareness level of our study participants on the use of anti-HBc in HBV screening was found to be quite low (33.3%). We consider that the low rate was related to the fact that physicians were out of internal diseases, infectious diseases, and gastroenterology departments with a specific approach to the issue, and regarded that the tests to be used for hepatitis B screening consist of HBsAg and anti-HBs. While it is accepted by most physicians that HBsAg negativity is sufficient to rule out the presence of HBV, anti-HBs positivity accompanied by HBsAg negativity is misinterpreted as if the patient were immune to HBV infection and certainly deprived of HBVr risk. However, if anti-HBs positivity is acquired by natural immunity, except for the vaccine-related formation, the virus keeps existing in hepatocytes and may lead to HBVr in case the host undergoes any IS treatment in future life. Whether accompanied by anti-HBs positivity or not, the positivity of antibody to hepatitis B core immunoglobulin G (Anti-HBc IgG) is a key test showing the existence of HBV in HBsAg negative cases. For this reason, training programs should be arranged to raise the awareness level about the requirement of anti-HBc IgG along with HBsAg during screening, and systemic warning mechanisms should be created in hospital settings to prevent HBVr from being ignored. Various studies also revealed that the rate of ordering anti-HBc test in screening was detected in a wide range between 22.6-91%; the reason for such a wide range may be related to the fact that the studies were conducted on different branches and at different times.[14-16] Even so, compared to the studies in previous years, the awareness of HBVr is seen to display positive trends to HBVr screening in recent studies. Also, it is not known by many physicians that HBV DNA should be requested in those with anti-HBc IgG positivity. In our study, the value of using HBV DNA in screening was found to be 22.09% as a quite low rate; the rate was found to vary between 6-11% in other studies and as 70% in a study conducted only with hematologists.[15,16] The reason why the awareness level on the issue was found higher among hematologists may have been that IS therapy has been utilized more frequently and chronologically earlier by hematologists than neurologists. Mounted experience from previous uses and encountering HBVrs in the follow-up of treatment regimes at earlier periods have led both theoretical and practical approaches to a positive evolution on the issue. Neurologists, starting to use novel generation IS treatments actively in recent years, appear to be more advantageous, compared with hematologists, oncologists, and rheumatologists since a certain awareness has been constituted for HBVr under IS treatment. Based on previous experiences, guidelines offering a professional approach have been developed over time. On the other hand, as the sub-specialties of internal diseases, such fields as hematology, oncology, and rheumatology are the departments including the notion of internal clinics. Neurologists seem to be disadvantageous, compared to those branches in terms of professional experience of approach to HBV infection. For this reason, neurologists are required to be informed on the issue before starting IS treatment. Increasing the awareness levels of the physicians, especially working in moderate and severe endemicity regions for HBV infection, may provide the use of accurate serological parameters for HBV screening through studies similar to ours.[36]

Among the medications assessed in our study for IS treatments, neurologists stated that HBV screening was mostly required before ocrelizumab treatment (85.05%), followed by rituximab (82%) and natalizumab (81%). Even so, glatiramer acetate (39.5%) was declared by neurologists as the least medication required for HBV screening. Likewise, in neurologists' clinical practice, ocrelizumab (81.4%) was seen to come to the fore as the most common treatment for HBV screening, followed by rituximab (80.2%) and alemtuzumab (72.2%) treatments, respectively.

The treatment regime for which screening was least performed was also detected as the glatiramer acetate (41.8%). In a study conducted on rheumatologists, it was found out that while 95.8% of the participants stated all patients should be screened before administering rituximab or ofatumumab, 93.8% reported that patients should primarily be screened before other biological treatments.[4] The strengths of the medications leading to IS treatment were also found to be high in our study. However, the risk of developing HBVr is not only related to the strength of the medication to be given but to HBV serology, as well. In our study, the screening rate after the use of glatiramer acetate was found to be very low (39.5%). Despite such a lower rate, however, if they are HBsAg positive, the patients may have a moderate risk of reactivation (1-10%), and therefore antiviral prophylaxis should be initiated.[4] Under the National Viral Hepatitis Guide released in our country, screening is recommended for HBV before all IS treatments. Under the National MS Diagnosis and Treatment Guidelines, HBV screening is also recommended for all DMDs with IS treatment[8,19]; however, no specific algorithm has been specified for the prophylaxis approach. In our country, the internationally-accepted guidelines released by the institutions such as EASL, APASL, AASLD, and AGA are followed. Although stated and recommended in the guidelines, the rate of neurologists' screening for HBVr was not found to be sufficient with a loss of nearly 20%, and such a situation was considered risky for HBVr with high morbidity and mortality. We consider that the inadequacy determined for hepatitis screening before IS treatment in our study is due to the low rate (32.5%) of physicians to follow the guidelines. In a previous study, 70% of the physicians stated that they followed-up the patients not receiving prophylaxis against the reactivation risk.[14] In another study conducted by Korkmaz *et al*., 78% of the study participants stated that the patients receiving no prophylaxis treatment were followed in terms of reactivation.[36] In our study, however, although the frequency of neurologists following-up the patients with positive HBV serology but not requiring prophylactic treatment was found to be different, 95.4% of the study participants was reported to follow-up their patients. Patients receiving prophylactic treatment should be monitored every three to six months through liver function tests and HBV DNA.[5,37-39] There are some differences between current international guidelines regarding the prophylactic indications in the patients with HBsAg negativity, anti-HBc IgG positivity (anti-HBs positivity or negativity), and HBV DNA negativity. If physicians start no prophylaxis, such patients should be followed-up with liver tests every one-to-three months and HBV DNA tests every three months. However, 32.5% of the participants stated that such patients were followed-up every 3 months in our study. Therefore, the consultation of multi-disciplinary specialists will be wise before deciding on prophylaxis and determining the follow-up intervals. Physicians receiving postgraduate training on HBVr were observed to give a higher rate of prophylaxis before IS treatment (p=0.04). Our study revealed that a very small proportion of neurologists (38.2%) stated to receive postgraduate training on HBVr. Such a low rate indicates that the training programs should be prioritized to increase the awareness of HBVr.

In conclusion, considering our study findings, the rate of screening ordered by neurologists performing IS treatment for HBVr, which can be fatal, was not found sufficient, and such a situation poses a risk for HBVr; thus, the awareness level on the issue needs to be increased. In addition, two more important factors requiring the awareness to be raised have come to the fore in our study. First, it is a must that the rate of using anti-HBc in screening is low, and the awareness should be increased to elevate the rate of anti-HBc screening. Another is that the risk of HBVr should be categorized in terms of IS treatment and host in our country where HBV infection is high, and the inadequacy in determining the prophylactic approach should be quelled. The optimal follow-up algorithm will be determined thanks to the further studies to be carried out on the detection and follow-up of CHB accompanying MS through screening before IS treatment. We consider that our study and similar studies on the issue will contribute to the literature in terms of drawing attention to the subject.

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