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The Awareness of Physicians Using Biological Agents in Treatment About Hepatitis B Virus Reactivation

Tedavide Biyolojik Ajanlar Kullanan Hekimlerin Hepatit B Virüs Reaktivasyonu Konusundaki Farkındalıkları

Şenel Yurtsever[1], Bilal Olcay Peker[2], Süreyya Gül Yurtsever[3], Kadriye Bahriye Payzın[4], Servet Akar[5], Yüksel Küçükzeybek[6], Firdevs Topal[7], Elif Sarıtaş Yüksel[7], Yeşim Beckmann[8]

[1]İzmir Bozyaka Training and Research Hospital, Dermatology Clinic, İzmir, Turkey, [2]İzmir Atatürk Training and Research Hospital, Medical Microbiology Laboratory, İzmir, Turkey, [3]İzmir Katip Çelebi University Department of Microbiology, İzmir, Turkey, [4]İzmir Katip Çelebi University Department of Hematology, İzmir, Turkey, [5]İzmir Katip Çelebi University Department of Rheumatology, İzmir, Turkey, [6]İzmir Katip Çelebi University Department of Medical Oncology, İzmir, Turkey, [7]İzmir Katip Çelebi University Department of Gastroenterology, İzmir, Turkey, [8]İzmir Katip Çelebi University Department of Neurology, İzmir, Turkey

ORCID ID: Şenel Yurtsever: https://orcid.org/0000-0003-3705-0135, Bilal Olcay Peker: https://orcid.org/0000-0001-8735-2962
Süreyya Gül Yurtsever: https://orcid.org/0000-0002-4421-230X, Kadriye Bahriye Payzın: https://orcid.org/0000-0001-7471-5453
Servet Akar: https://orcid.org/0000-0002-3734-1242

***Sorumlu Yazar / Corresponding Author:** Süreyya Gül Yurtsever, **e-posta / e-mail:** sgul71@yahoo.com

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Abstract

Aim As long as immunosuppressive treatments are widely used, careful monitoring of HBVr is essential. We aimed to measure the awareness of Turkish physicians of certain specialties about the risk of hepatitis B virus reactivation (HBVr), HBV screening methods, prophylactic treatment practices and personal experiences in treating patients with biological agents.

Material and Method An electronic questionnaire link containing 21 questions about demographics and their applications to HBVr was sent to participants working in the various specialties across the country.

Results 227 participants took our survey (Female: 52.4%, n:119, Male: 47.6%, n:108), and consisted of 70 Hematologists, 65 Rheumatologists, 38 Gastroenterologists, 33 Oncologists, and 21 Dermatologists. We obtained extremely different results. It was found that all specialties are aware that the use of biological agents can cause HBVr (97.8%, n:222/227). Biological agents were used in 96% of the participants and HBVr was detected in 53.7% (Hematologist: 74.3%, Rheumatologist: 53.8%, Oncologist: 45.5%, Gastroenterologist: 44.7%, Dermatologist: 14.3%, p< 0.001). The general opinion was that, screening tests should be used (Gastroenterologist: 47.4%, p< 0.001) and 55.1% awared of how to monitor HBVr (Gastroenterologist: 65.8%, p = 0.06). The duration of antiviral prophylaxis was answered correctly in 70.4% (Hematologist: 82.6%, p = 0.01), the parameters of screening tests in 95.2% (Gastroenterologist: 97.4%, p = 0.52) and the highest risk of reactivation in 93% (Rheumatologist: 96.9%, p = 0.15) and the agent with the highest risk of reactivation in 82.8% of participants (Hematologist: 94.3%, p< 0.001).

Conclusion The opinions of different the clinical disciplines vary according to the profile of patients. Gastroenterologists' perspective on HBVr follow-up and treatment differs markedly from that of other clinical disciplines. However, to create general awareness and manage HBVr, guidelines for specific patient groups are definitely needed.

Keywords Hepatitis B virus reactivation, prophylaxis, clinical practice, clinical awareness, online forum, biological agents

Özet

Amaç *İmmünsupresif tedaviler yaygın olarak kullanıldığı sürece, HBVr'nin dikkatle izlenmesi esastır. Belirli uzmanlık dallarındaki Türk hekimlerinin, hepatit B virüsü reaktivasyonu (HBVr) riski, HBV tarama yöntemleri, profilaktik tedavi uygulamaları ve biyolojik ajanlarla hasta tedavisindeki kişisel deneyimleri hakkındaki farkındalıklarını ölçmeyi amaçladık.*

Gereç ve Yöntem *Ülke genelinde çeşitli uzmanlık alanlarında çalışan katılımcılara, demografik bilgiler ve bunların HBVr uygulamaları hakkında 21 soru içeren bir elektronik anket bağlantısı gönderildi.*

Bulgular *Anketimize 70 Hematolog, 65 Romatolog, 38 Gastroenterolog, 33 Onkolog ve 21 Dermatolog olmak üzere toplam 227 kişi (Kadın: %52,4, n:119, Erkek: %47,6, n:108) katılmıştır. Son derece farklı sonuçlar elde ettik. Biyolojik ajan kullanımının HBVr'ye neden olabileceğinin tüm uzmanlık dallarınca bilindiği görüldü (%97,8, n:222/227). Katılımcıların %96'sı tedavide biyolojik ajan kullanılmış ve %53,7'si hastalarında HBVr saptanmıştır (Hematolog: %74,3, Romatolog: %53,8, Onkolog: %45,5, Gastroenterolog: %44,7, Dermatolog: %14,3, p<0,001). Genel kanı tarama testlerinin kullanılması gerektiği (Gastroenterolog: %47,4, p<0,001) ve %55,1'inin HBVr'nin nasıl izleneceğini bildiği (Gastroenterolog: %65,8, p= 0,06) yönündeydi. Katılımcılar tarafından, antiviral profilaksi süresi %70,4 (Hematolog: %82,6, p=0,01), tarama testlerinin parametreleri %95,2 (Gastroenterolog: %97,4, p=0,52), en yüksek reaktivasyon riski %93 (Romatolog: %96,9, p=0,15) ve katılımcıların %82,8'inde reaktivasyon riski en yüksek ajan (Hematolog: %94,3, p< 0,001) doğru olarak yanıtlandı.*

Sonuç *Farklı klinik disiplinlerin görüşleri hasta profiline göre değişmektedir. Gastroenterologların HBVr takibi ve tedavisine bakış açısı, diğer klinik disiplinlerden belirgin şekilde farklıdır. Bununla birlikte, genel farkındalık yaratmak ve HBVr'yi yönetmek için, belirli hasta gruplarına yönelik kılavuzlara kesinlikle ihtiyaç vardır.*

Anahtar Kelimeler *Hepatit B virüs reaktivasyonu, profilaksi, klinik uygulama, klinik farkındalık, online forum, biyolojik ajanlar*

INTRODUCTION

Chronic hepatitis B virus (CHBV) infection is a global public health problem. Approximately 2 billion people are exposed to hepatitis B virus (HBV), 350 million of them are CHBV carriers worldwide, and there are 887,000 HBV-related deaths each year[1,2]. The prevalence of hepatitis B surface antigen (HBsAg) positivity is reported to be 4.57%, and an estimated 3.3 million HBV carriers have been reported[3].

The seropositivity rate for total anti-HBc is still over 30%[4]. This large number of anti-HBc-positive / HBsAg-negative patients is important for those who need immunosuppressive (IS) treatment with regard to the development of HBV reactivation (HBVr)[4]. Although Turkey has included HBV vaccine in its routine immunization program since 1998, it is still one of the countries with intermediate endemicity for HBV[5].

In the past, only chemotherapeutic agents caused immunosuppression, but currently many immunomodulatory agents such as tumor necrosis factor (TNF) inhibitors and drugs that reduce B cells are included in treatment protocols and are widely used in Rheumatology, Dermatology, Neurology, Gastroenterology, Nephrology clinics and transplantation units. Currently, rituximab is used as an immunomodulator in several cases for the treatment of autoimmune diseases inflammatory diseases, graft-versus-host disease, transplant rejection, and post-transplant lymphoproliferative disorders[6]. Among biologic drugs, rituximab and ofatumumab are associated with a high risk of reactivation (> 10%), whereas TNF-alpha inhibitors and other cytokines, as well as integrin inhibitors, are associated with a moderate risk of reactivation (1 – 10%)[7]. HBVr risk is related to the mechanism of action of the IS agent used, the patient's HBV serology, and viral replication markers. Patient serology was categorized into very high-risk (HBsAg-positive, HBeAg-positive / negative, HBV-DNA> 2000 IU/mL) medium-risk (HBsAg-negative, anti-HBc IgG-positive, anti-HBsAg-negative), and low-risk (HBsAg-negative, anti-HBc IgG-positive anti-HBs-positive) groups[8]. When treating high and medium-risk patients, antiviral therapy is recommended before IS therapy. However, HBVr risk can be significantly reduced between 84% and 87% by HBV screening and initiation of prophylactic antiviral therapy in selected patients prior to treatment with IS agent[7,9]. Several studies have shown that reactivation rates ranged from 30% to 80% in patients treated for cancer chemotherapy, transplantation, inflammatory diseases, and autoimmune diseases[10].

According to the World Health Organization's Global Hepatitis Programme and Asian-Pacific clinical practice guidelines recommend screening of all patients undergoing IS therapy. In the most recent consensus guidelines, the various scientific societies recommend prophylactic antiviral therapy for HBV carriers 2 – 3 weeks before the start of chemotherapy and its continuation for at least six months after the end of chemotherapy[1,5-7,11-13].

In the literature, studies evaluated clinical awareness and physician practice regarding prevention of HBVr during IS therapy generally involve hematologists and oncologists. There are few studies conducted on physicians using biological drugs which are widely used in Rheumatology, Gastroenterology, and Dermatology[5,15-22]. When reviewing the literature, it was found that there are not enough studies on this topic in Turkey. In our study, we aimed to measure the awareness of Turkish physicians of certain specialties about the risk of HBVr, HBV screening methods, prophylactic treatment practices, and personal experiences in treating patients with biological agents.

MATERIALS and METHODS

Study population and survey modalities

An electronic questionnaire survey was designed by Dermatologist, Infecitous Disease and Microbiology specialist on the internet portal (with Google Forms) and sent to Gastroenterologists, Rheumatologists, Dermatologists, Hematologists, and Oncologists with 227 participants in

April 2019. The survey link was e-mailed to the specialist working in universities, training and state hospitals and private hospitals in different cities and was active for one month. The survey included 21 questions about participant demographics (gender, age, job title, specialty, length of practice, and institution), knowledge, and awareness about HBVr. It also asked about attitudes toward HBV screening during treatment with biological agents. The physicians who participated in the survey were working in academic and government institutions. All questions had to be answered in order to proceed with the survey, with the exception of the questions regarding demographic information. Survey questions were categorized and included participants' HBVr awareness and experience regarding the value of screening tests prophylaxis application, level of knowledge about HBVr, general opinion and suggestions.
The demographic variables were age (25 – 35; 36 – 45; 46 – 55; 56 – 65 and >65 years), gender, job title (Professor doctor, associate professor, assistant professor, specialist, and resident), length of practice (0 – 1; 2 – 5; 6 – 10, and >10 years) and institution (university hospital, training and research hospital, private hospital, and public hospital).

Statistical analysis

The statistical analysis of the data was calculated using the program IBM SPSS version 23 (IBM Corp., Armonk, NY, US) with the significance level set at $p < 0.05$. Qualitative results were recorded in categorical variables. The categorical variables were analyzed using the calculated theoretical frequencies for the Pearson's chi-square test and Fisher's exact test. The frequencies of responses to all questionnaire items were determined and overall scores per questionnaire item were calculated. This overall score was the sum of correct respones and unselected incorrect responses. The rates were given in comparison between the groups to show the value within the group.

RESULTS

The study included 227 participants (female; 52.4%, n:119, male; 47.6%, n:108) and consisted of 70 Hematologists, 65 Rheumatologists, 38 Gastroenterologists, 33 Oncologists, and 21 Dermatologists. In 84.6% (n:192) of the participants work in academic settings and 15.4% (n:35) in other settings (private and public hospitals). In 32.6% (n:74) of the participants were experienced physicians who have been working in their specialty for more than ten years. The demographic data of the participants and the number of patients followed-up are shown in Table 1.

Table 1. The demographics of the participants and the number of patients in follow

Demographic features	**n (%)**
Female	119 (52.4)
Age	
25 – 35	65 (28.6)
36 – 45	108 (47.6)
46 – 55	43 (19)
56 – 65	10 (4.4)
>65	1 (0.4)
Professional title	
Professor	34 (15)
Associate professor	47 (20.7)
Assistant professor	20 (8.8)
Specialist	109 (48)
Resident	17 (7.5)
Working period years	
0 – 1	15 (6.6)
2 – 5	71 (31.3)
6 – 10	67 (29.5)
>10	74 (32.6)
Institution	
University hospital	116 (51.1)
Training and research hospital	76 (33.5)
Public hospital	17 (7.5)
Private hospital	18 (7.9)
Patient follow-up numbers	
1 – 10	28 (12.3)
11 – 50	66 (29.1)
51 – 100	36 (15.8)
>100	88 (38.8)

In line with the participants' responses, different results were collected. In 56.8% of the participants indicated that they had a good level of knowledge regarding the use of biological agents. The data on the use of biological agents by physicians in IS patients are presented in Table 2.

Table 2. Data on physicians' application of biological agents in IS patients

Status	**n**	**%**	**p-value**	**Status**	**n**	**%**	**p-value**
Do you use biological agents in your center?			NA	Have you seen in your daily pracitice that HBV is reactivated after using biological agents?			NA
Yes	218/227	96		Yes	122/227	53.7	
No	9/227	4		No	105/227	46.3	
Number of patients using biological agents followed by centers				Does chemotherapy or IS therapy cause HBVr?			
0 – 10	28/218	12.3		Yes	222/227	97.8	
10 – 50	66/218	29.1		No	5/227	2.2	
50 – 100	36/218	15.8					
>100	88/218	38.8					
How would you evaluate your personal knowladge about HBV prophylaxis before treatment in patient with HBsAg-positive for use biological agents?			NA	Which routine tests do you screen for HBV infection before IS therapy?			NA
I have no idea	21/227	9.2		HBsAg	3/227	1.3	
Little	-	-		HBsAg and anti-HBs	7/227	3.1	
Good	129/227	56.8		HBsAg, anti-HBc IgG and anti-HBs	217/227	95.6	
Very good	77/227	34		I am not screening	-	-	
Which patients using biological agents should receive HBV prophylaxis? (multiple choice)			0.152	Which is the riskiest serological profile in HBV screening before chemotherapy or IS therapy?			0.521
Chronic HBsAg carriers	202/227	88.9		HBsAg (+) HBeAg(+)/(-), HBV-DNA> 2000 IU/mL	211/227	93	
anti-HBs and anti-HBc (+) patients with previous infections	133/227	58.5		HBsAg (-) anti-HBc IgG (+) anti-HBsAg (-)	13/227	5.7	
Only anti-HBc (+) patients	151/227	66.5		HBsAg (-) anti-HBc IgG (+) anti-HBsAg (+)	3/227	1.3	
anti-HBs (+) patients	36/227	15.8		I have no idea	-	-	
All of them	36/227	15.8					

Table 2. Data on physicians' application of biological agents in IS patients

Status	n	%	p-value	Status	n	%	p-value
How do you monitor HBVr? (multipel choice)			0.069	If there is no vaccine record before treatment / If the history is not reliable, which serological tests should be done? (multiple choice)			<0.001
Liver function tests	191/227	84.1		Measles, Mumps, Rubella	65/227	28.6	
Viral serology	162/227	71.3		Varicella	66/227	29	
Quantitative detection of HBV-DNA	210/227	92.5		Viral hepatitis (HAV, HBV, HCV)	219/227	96.4	
Clinical symptoms	136/227	59.9		Tuberculosis	154/227	67.8	
All of them	111/227	48.8		All of them	52/227	22.9	
I have no idea	-	-		I have no idea	8/227	3.6	
When is the best time to start HBV prophylaxis? (multiple choice)			0.576	How long should prophylactic antiviral therapy be continued after IS therapy is discontinued?			**0.014**
Concurrent with IS therapy	39/227	17.1		1 month	28/227	12.4	
1 week before IS therapy	100/227	44		2 months	36/227	15.8	
1 month before IS therapy	134/227	59		12 months	152/227	67	
Anytime	9/227	4		I have no idea	11/227	4.8	
I have no idea	4/227	1.7					
Which application has a high risk of HBVr (over 10%) according to drug groups?			**<0.001**	Would it be useful to have a central warning system from the hospital computer system for patients at risk of HBVr during the IS therapy?			NA
Rituximab	187/227	82.4		Yes	218/227	96	
Infliximab	24/227	10.6		No	8/227	3.6	
Adalimumab	2/227	0.9		I have no idea	1/227	0.4	
Methotrexate	6/227	2.6					
Azathioprine	8/227	3.5					

HAV: Hepatitis A virus, HBV: Hepatitis B virus, HBVr: Hepatitis B virus reactivation, HCV: Hepatitis C virus, NA: Not applicable, IS: Immunosuppressive.

HBVr awareness and experience

It was observed that the use of biological agents that can cause HBVr is known in all fields (97.8%, n:222/227). Biological agents are used in 96% of participants and 53.7% have been encountered HBVr (Hematologist: 74.3%, Rheumatologist: 53.8%, Oncologist: 45.5%, Gastroenterologist: 44.7%, and Dermatologist: 14.3%). The HBVr rate in patients followed-up in Dermatology is the lowest and statistically significant ($p < 0.001$, Pearson chi-square)

The value of screening tests

The question about screening test for IS patients before using biological agents was answered correctly by 95.2% of the participants. The distributions according to the fields are as follows: 97.4% in Gastroenterologist, 90.5% in Dermatologist, 87.9% in Oncologist, 97.1% in Hematologist, and 96.9% in Rheumatologist ($p = 0.17$, Fisher's exact test). Approaches of the participants, to patients without vacci-

nation records, and/or when a reliable history could not be obtained were answered correctly by a rate of 22.4%. Gastroenterologists' awareness of this condition was statistically significant ($p < 0.001$, Pearson chi-square).

Prophylaxis application

In 14.5% of the participants answered correctly to the question in which patients prophylaxis should be applied. The distribution by specialty is as follows: 26.3% in Gastroenterologist, 14.3% in Dermatologist, 15.2% in Oncologist, 14.3% in Hematologist, and 7.7% in Rheumatologist ($p = 0.15$, Pearson chi-square).

Participants answered the question about the ideal time to use prophylaxis correctly at a rate of 5.8%. The distributions by specialty were as follows: 7.9% in Rheumatologist, 7.9% in Gastroenterologist, 5.3% in Dermatologist, 5.7% in Hematologist and 0% in Oncologist, and there is no statistically significant difference between the highest and lowest rates among specialties except for Oncologist ($p = 0.53$ Fisher's exact test).

Participants answered the question about duration of use of antiviral prophylaxis correctly at a rate of 70.4%. The distributions by specialty were as follows: 82.6% in Hematologist, 66.7% in Rheumatologist, 73.7% in Gastroenterologist, 44.4% in Dermatologist, and 61.3% in Oncologist. The awareness level of Hematologists is statistically significant compared to other the other specialties ($p = 0.01$, Pearson chi-square).

Level of knowledge about HBVr

In 93% of the participants correctly answered the situation with the highest risk of reactivation in the given serological profiles. The distributions by specialty were as follows: 96.9% in Rheumatologist, 89.5% in Gastroenterologist, 95.2% in Dermatologist, 90.9% in Oncologist, and 91.4% in Hematologist ($p = 0.52$, Fisher's exact test).

The question about reactivation monitoring was answered correctly by 55.1% of the participants. The distributions by specialty were as follows: 65.8% in Gastroenterologist, 33.3% in Dermatologist, 42.4% in Oncologist, 60.0% in Hematologist, and 56.9% in Rheumatologist ($p = 0.06$, Pearson chi-square).

The question about the agent with the highest potential risk of reactivation was answered correctly by 82.8% of the participants. Hematologists' awareness of this topic was highest (94.3%) and statistically significant ($p < 0.001$, Pearson chi-square).

General opinion and suggestions

The awareness of HBVr risk in patients using biological agents varies widely among Turkish physicians. Although current guidelines and recommendations are not fully known by physicians, the vast majority of physicians are able to perform and practice general screening. In 96.5% of the participants requested a warning in the automation systems and 99.6% of them suggested that a national regulation should be made.

DISCUSSION

Due to the increasing use of IS therapies and the emerging risk of liver failure associated with these treatments in patients with HBV, screening for HBV prior to IS therapies is recommended in all current guidelines. However, there is no consensus on screening recommendations, and physicians are not sufficiently aware of the importance of this issue[21-26]. Among physicians who perform IS therapies and use biological agents, the rate of patients screened for HBV before treatment varies from 14% to 93% in the literature. The physician group with the lowest rate was oncologists; hematologists had the highest rate[15,16,19,21-23]. Our study showed that oncologists screen for HBV less than other specialties. While hematologists were more aware than other specialties in setting the ideal prophylaxis time point, it was observed that this rate was lower among oncologists. Currently, there are some recommendations in the literature on screening, monitoring, and treatment of

HBVr in Oncology.

However, there are few formal recommendations for screening, monitor and treatment of HBVr in the oncology literature. As a result, numerous oncologists report not having observed this complication and many are unaware of current gastroenterology-hepatology recommendations for CHBV prophylaxis. Despite these recommendations for HBV screening, screening rates have been shown to be suboptimal in high-risk populations[11].

In our study, the use of biological agents that can cause HBVr is known in all settings (97.8%). In 96% of the participants use biological agents and 53.7% of them have encountered HBVr. In the literature, the HBVr encounter rates of Oncologists, Rheumatologists, and Dermatologists are 22 – 30%, 7%, and 0%, respectively[15,19,21]. In our study, these rates are Hematologist: 74.3%, Rheumatologist: 53.8%, Oncologist: 45.5%, Gastroenterologist: 44.7%, and Dermatologist: 14.3%, which is quite high compared to the literature. Turkey is located in a region of intermediate endemicity for HBV infection[26]. Higher reactivation rates may have been found than in regions of low endemicity where studies on this topic have been conducted[15,19,21]. In countries located in regions of middle or high endemicity for HBV infection, IS therapy may increase the likelihood of HBVr exposure. Therefore, physicians need to take this into consideration. Our study shows that most physicians using IS therapy have already been encountered HBVr. For this reason, it is necessary to increase the awareness of all physicians using IS therapy about the importance of the issue before encountering HBVr[19]. Each country should form a common consensus in a working group. For this purpose, a consensus report on HBV screening, pretreatment and prophylaxis if necessary, due to the risk of HBVr in patients receiving IS treatment was released in our country in 2018[8].

Relevant guidelines for HBVr, recommend testing the anti-HBc antibody along with HBsAg to screen the patient for HBV[13-17,24,25,27]. If the patient is HBsAg-positive, it is recommended that HBV-DNA be tested in addition to other hepatitis markers. If the patient is HBsAg negative and anti-HBc-positive, HBV-DNA monitoring is recommended, and even prophylactic antiviral treatment may be required depending on IS teratment regimes. In our study, 95.6% of physicians who performed HBV screening before IS treatment screened HBsAg, anti-HBc IgG, and anti-HBs parameters. In similar studies, this rate varies from 22.6% to 91%[16,19,21,22]. In a study conducted in USA[11], the HBV screening rates among Gastroenterologist, Dermatologist, Oncologist, Hematologist and Rheumatologist were 66.5%, 38.4%, 67.2%, 58.7%, and 46.4%, respectively, whereas in our study they were 97.4%, 90.5%, 87.9%, 97.1%, and 96.9%. This shows that HBV screening rates are high and our physicians have high awareness about HBVr. The risk of reactivation is calculated based on the combination of the patient's serological status (HBsAg-positive or negative) and the IS therapy given to the patient. Although data are limited, they show that physicians initiated antiviral therapy for HBVr primarily in patients with active HBV infection (52 – 82%) or chronic HBsAg carrier (46 – 60%)[15,16]. In our study, 88.9% of physicians initiated treatment in patients with chronic HBsAg carriers, and 66.5% in patients with pure anti-HBcIgG-positive. If reactivation occurs during follow-up of low-risk patients, treatment can be started early with close monitoring of the patient[27]. The rate of initiation of prophylactic antiviral therapy for HBVr in patients with previous HBV infection was reported to be 8.3% and 52% in two studies[15,22]. In our study, it was found that 58.5% of physicians initiated treatment for anti-HBc IgG-positive and anti-HBs-positive patients. Our data show that physicians started prophylactic antiviral treatment in all risk groups, especially in the group of HBsAg-positive patients and who often belong to the medium and high-risk group for HBVr.

Action tests is recommended in patients in whom antiviral treatment is not initiated for HBVr[7,12]. In a study conducted, 70% of physicians reported that they followed up the

group of patients in whom they did not initiate prophylaxis for reactivation risk and they most commonly used HBV-DNA and liver enzymes during follow-up[16]. Also, in our study, participants reported following quantitative measurement of HBV-DNA in 92.5%, liver function tests in 84.1%, viral serology in 71.3%, and clinical symptoms in 59.9%. In 82.4% (Hematologist 94.3%, $p< 0.05$) of respondents chose rituximab (anti-CD20) as the most potent agent to cause reactivation. Statistically, there was a significant difference between the departments when answering in the question about the scheme of serological screening (Tuberculosis, measles, mumps, varicella, etc.) before starting treatment with biological agent.

HBV prophylaxis should be initiated 1-3 weeks before IS therapy[8,27]. Prophylactic therapy should be continued for an additional 12 months after discontinuation of IS therapies8. In our study, physicians were undecided about the timing of antiviral therapy. More participants felt that prophylactic antiviral therapy should be started before biological therapy than those who considered concurrent treatment. Most participants reported that they continued antiviral medication for 12 months after discontinuing biological agents.

According to our study, it was observed that physicians who initiated IS treatment had higher rates and awareness of HBVr screening compared with similar studies, and that screening tests were appropriate. Physicians with more than 10 years and 5-10 years of professional experience had higher participation in the study. These data suggest that the professional experience of the participants in the application of HBVr treatment is advanced. It is encouraging that the physicians included in the study in our country, where HBV infection is endemic, are aware of the risk of HBVr in individuals who have already had HBV infection and know that prophylaxis may be needed. It can be seen that the recommendations of the guidelines are followed in the clinical practice on HBVr. Another finding of our study is that physicians with more clinical experience of HBVr perform more screening regarding HBVr. However, to avoid the negative consequences of HBVr, physicians who perform IS therapy should be aware of this complication. Our study is important to drawing attention to this issue. The limitation of our study is that the survey was restricted to one-month. Therefore, it may not reach most of the physicians using biological agents in our country. However, since our study presents multidisciplinary data, it will contribute to the literature in a general perspective.

In conclusion, reactivation is a serious and fatal condition, and the response to antiviral treatment after HBVr is inadequate. Moreover, the discontinuation of IS drugs that cause reactivation may leat to progression of the primary disease. Therefore, initiation of antiviral prophylaxis prior to IS therapy or chemotherapy may be life-saving. Given the increasing numbers on studies in the literature and guidelines on prevention for HBVr, training in congresses and symposiums will gain experience and awareness of physicians on this topic. In addition, computer alert software could increase interest and awareness in this regard.

Conflicts of Interest

The authors have none to declare

Author Contributions:

Yurtsever Ş, Peker BO and Gül Yurtsever S: Conceptualization, methodology, writing - original draft preparation and reviewing, software, data collection. Beckmann Y: Reviewing and editing. Sarıtaş Yüksel E, Payzın B, Topal F, Küçükzeybek Y, Akar S: Data curation, collection and reviewing

Ethical Approval

This study was approved by İzmir Katip Çelebi University ethics committee of clinical research (Jan 10, 2019, Approval Number 6) and was conducted according to the guidelines of 1964 Declaration of Helsinki.

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None

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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