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Evaluation of Hepatitis Serology Screening Frequency and Viral Reactivation in Patients Followed with Biological Therapy or Cytotoxic Chemotherapy

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Abstract

Objective
Our study aimed to evaluate the results of hepatitis B and C serology screening before biological therapy and chemotherapeutic treatments in internal medicine clinics (rheumatology, medical oncology, and gastroenterology) by comparing between departments and investigating the virus reactivation status.

Material and Method
The study included 1147 patients aged 18 and over who were admitted to the medical oncology, rheumatology, and gastroenterology departments between 2019 and 2021 and received cytotoxic chemotherapy and biological treatment. HBsAg, Anti-HBs, Anti-HBc, and Anti-HCV data were used to screen for hepatitis. The departments were compared and evaluated based on the frequency of screening and reactivation.

Results
Before undergoing chemotherapy or biological therapy, 77% of patients in oncology, 40% in rheumatology, and 43% in gastroenterology were fully screened for hepatitis. The rates of incomplete screening were 16%, 48%, and 52%, respectively, while 3%, 10%, and 4% were never screened. In total, reactivation was observed in twelve patients (1.0%), while no reactivation was observed in 1135 patients (99.0%). A statistically significant correlation was found between the departments and the presence of reactivation ($p<0.001$). Reactivation was detected in 1 oncology patient and 11 rheumatology patients, while no reactivation was seen in all gastroenterology patients.

Conclusion
Although complete screening for viral hepatitis was recommended by the guidelines, it was observed that it was not implemented in clinical practice. It is important to note the need to improve screening rates, especially in populations receiving chemotherapy or biological therapy, where the risk of reactivation is high. Raising awareness about HBV and reminder practices about hepatitis B and C serology screening before chemotherapy and biological therapies for clinical applications may help to increase screening rates.

Keywords: Biological therapy, chemotherapy, hepatitis B, hepatitis C, reactivation

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Introduction

Hepatitis B virus (HBV) is the cause of active fulminant hepatitis, chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC). Turkey is located in an endemic region for hepatitis B virus. The prevalence of HBsAg positivity in Turkey is 4%, and anti-HBc IgG positivity is 30.6% (1). Even if the HBsAg test result of patients who have had HBV infection is negative, the virus continues its genetic structure as a carrier in the patient (2). The frequency of HBV reactivation increases as a result of immunosuppression (3).

The use of chemotherapeutic and immunosuppressive agents is increasing due to developments in the treatment of malignant and inflammatory diseases. Therefore, HBV reactivation is frequently observed in susceptible individuals. To prevent severe exacerbations that may be life-threatening, it is important to determine which patients will receive prophylactic antiviral treatment before initiating immunosuppressive treatment, in terms of HBV reactivation (4). Therefore, it is crucial to diagnose and treat HBV reactivation promptly. HBV reactivation can range from an asymptomatic stage to fulminant hepatitis (5).

The risk of HBV reactivation is classified according to the guidelines of the American Gastroenterological Association (AGA) and the American Association for the Study of Liver Diseases (AASLD). According to the AGA guidelines, the risk of reactivation is above 10% when using anthracycline derivatives and high-dose corticosteroids. The risk of reactivation when using cytokine, integrin, TNF-α, and tyrosine kinase inhibitors, as well as medium-dose corticosteroids, is between 1-10%, depending on the patient's HBV serology. The risk of reactivation when using low-dose or intra-articular corticosteroids and traditional immunosuppressive drugs such as azathioprine, 6-mercaptopurine, and methotrexate is less than 1% (6).

Immunosuppression caused by chemotherapy may lead to HBV reactivation, resulting in discontinuation of anti-cancer treatment and liver failure. To prevent this, guidelines recommend HBV screening in high-risk patients with HBV infection and the use of antiviral drugs as prophylaxis in cancer patients receiving chemotherapy (7, 8). Additional doses of vaccine or high doses of vaccine may be necessary to induce an immune response in these patients. Preemptive treatment is recommended for patients who test positive for HBsAg, regardless of their HBV DNA levels and genotype. Nucleoside analogues are potent agents used to treat patients with high viral load. It is recommended that patients who are seropositive for hepatitis B virus receive prophylactic antiviral treatment, even if they are positive for both anti-HBs and anti-HBc IgG. Patients who are positive for anti-HBc IgG should be monitored and treated similarly to those who are positive for HBsAg and have a high level of HBV DNA. To monitor patients with low HBV DNA and natural immunity, it is recommended to monitor both HBV DNA and alanine aminotransferase (ALT) levels every 1-3 months. If a patient is HBV DNA positive but HBsAg negative and Anti-HBc IgG positive, preemptive treatment may be necessary before immunosuppressive treatment. Treatment should be continued for at least 12 months after the end of immunosuppressive treatment (9). In cases of active liver disease related to hepatitis B, treatment should be administered following general hepatitis B treatment principles (10, 11). It is important to implement preventive medicine principles at an optimal level and direct individuals who have encountered hepatitis B to appropriate treatment, especially considering the obstacles in accessing healthcare services and patient follow-up, as outlined in the guidelines. The demand for antiviral treatment is rising due to the growing number of patients undergoing cytotoxic chemotherapy, the widespread use of organ transplantation, and the use of biological drugs to treat autoimmune diseases. Due to Turkey's location in the middle endemic region for HBV, patient screening is crucial. Studies conducted in our country have revealed deficiencies in viral hepatitis serology screening and follow-up (9, 12).

Hepatitis C virüs (HCV) is an RNA virus that can cause chronic liver disease, hepatocellular cancer (HCC) and cirrhosis. There are six genotypes of HCV, designated 1, 2, 3, 4, 5 and 6. The most common genotype in Turkey is 1b. HCV reactivation after immunosuppressive treatment is observed rarely. It has been observed that drug-induced hepatotoxicity occurs more frequently in chronic HCV patients receiving chemotherapeutic and immunosuppressive agents. Consequently, an increase of more than 1 log 10 IU/ml in HCV RNA level is indicative of HCV reactivation. In patients who do not have liver malignancy, do not have a recent history of blood transfusion, do not receive hepatotoxic drugs and do not have a history of systemic diseases other than HCV, at least a three-fold increase in ALT level may be considered as exacerbation (13, 14).

Our study aimed to evaluate the results of hepatitis B and C serology screening before biological therapy and chemotherapeutic treatments in internal medicine clinics (rheumatology, medical oncology, and gastroenterology) by comparing between departments

and investigating the virus reactivation status.

Material and Method

Patients aged 18 years and over who applied to the medical oncology, rheumatology and gastroenterology departments of the University Faculty of Medicine Hospital between January 2019 and January 2021 and received cytotoxic chemotherapy and biological treatment were included in the study. A total of 1147 patients received treatment in the rheumatology, gastroenterology, and medical oncology departments.

Inclusion criteria:

1. Patients over 18 years of age receiving cytotoxic chemotherapy and biological agent treatment

2. Being followed up in the departments of Rheumatology, Gastroenterology and Medical Oncology

3. Patients whose socio-demographic data, and clinical and laboratory findings before and after treatment were obtained.

Exclusion Criteria:

1. Those who have not completed at least 1 cycle of chemotherapy

2. Patients who do not take the biological treatment started to the patient at the planned dose and duration

3. Patients with positive markers of human immunodeficiency virus (HIV)

4. Patients with secondary liver disease such as haemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency severe cardiopulmonary disease, hepatocellular carcinoma causing chronic liver damage,

5. Patients whose treatment is terminated due to death due to primary disease during biological treatment or chemotherapy

6. Patients who were followed up in the COVID intensive care ward during treatment or within 6 months after treatment

HBsAg, Anti-HBs, Anti-HBc, and Anti-HCV data were used to screen for hepatitis. The frequency of screening was compared and evaluated in the rheumatology, gastroenterology, and medical oncology departments. The initiation status of prophylactic antiviral treatment and the antiviral agents (adefovir, entecavir, lamivudine, and tenofovir) given to patients before planned chemotherapy and biological treatment were also evaluated. The study evaluated the frequency of antiviral treatment based on the patients' HBsAg and Anti-HBc test results.

The recorded data included demographic characteristics, diagnosis, hepatitis B and C serology screening, and prophylactic antiviral treatment of patients who received cytotoxic chemotherapy in the medical oncology department, and biological treatment in the rheumatology and gastroenterology department. The study also evaluated cytotoxic chemotherapies and biological treatment administered according to the American Gastroenterological Association (AGA) guidelines. The guideline categorised the grouping as high, medium, or low risk (15).

In the rheumatology department, the study included various drugs such as abatacept, adalimumab, etanercept, golimumab, infliximab, sertolizumab, rituximab, secukinumab, tocilizumab, and ustekinumab. These drugs are cytokine and integrin inhibitors, TNF-α inhibitors, anti-CD20 monoclonal antibodies, interleukin 17 receptor inhibitors, interleukin 6 receptor inhibitors, and interleukin 12 and interleukin 23 inhibitors. The reactivation status of each patient was assessed based on their diagnosis and the biological treatment they received. Patients who received biological treatment (adalimumab, infliximab, and vedolizumab) in the gastroenterology department were recorded, along with information on prophylactic antiviral treatment. Patients were grouped by ulcerative colitis and Crohn's disease.

HBV reactivation is defined as a positive HBV DNA level in patients who had negative HBV DNA at baseline and an increase in HBV DNA of more than 2 log10 IU/mL in patients who had positive HBV DNA at baseline. The term 'reverse seroconversion' refers to the presence of HBsAg in patients who were previously HBsAg negative and anti-HBc positive (15, 16). Clinical and laboratory information of patients who developed reactivation were recorded.

The electrochemiluminescence immunoassay (ECLIA) method with Roche Diagnostic cobas E411 automatic immunoassay uniassay chemistry analyser was used to perform HBsAg, anti-HBc, anti-HBs, and anti-HCV tests (Elecsys, Diagnostic cobas E411, Roche, Sandhofer straße, Mannheim, Germany). The PCR (real-time polymerase chain reaction) method using COBAS (Roche Molecular Diagnostics) devices

was used to analyse HBV DNA. The biochemical parameters AST and ALT were studied using the AU 5800 series AU model biochemistry analyser. Normal values for AST and ALT are 0-35 IU/L.

Statistical Analysis

The data were analysed using IBM SPSS 23 software (IBM Inc., Chicago, IL, USA). Before statistical analysis, we checked for data entry errors and ensured that the parameters were within the expected range. Descriptive statistics of continuous variables were presented using mean and standard deviation, while categorical variables were presented using the number of people (n) and percentage (%) values. The relationships between categorical variables were analysed using chi-square test analysis. Shapiro-Wilk's normality test and Levene's test were used to check the homogeneity of variance in continuous variables. If normal distribution was not observed, three-level comparisons were performed using the Kruskal-Wallis H-test. Post-hoc tests were used to determine correlation. A significance level of $p<0.05$ was used for all analyses.

Results

The study included 1147 patients followed up in rheumatology, gastroenterology and medical oncology clinics. The mean age of the patients included in the study was 53.66±14.50 years. The mean age of the patients in the oncology department was 58.72±11.90 years, in the rheumatology department 46.15±14.76 years and in the gastroenterology department 47.31±15.08 years. There was a statistically significant difference between the mean age and the departments ($p<0.001$). Of the patients, 556 (48.5%) were male and 591 (51.5%) were female. Of the patients, 681 (59.4%) were followed up in oncology, 418 (36.4%) in rheumatology and 48 (4.2%) in gastroenterology (Table 1).

Before treatment, patients with oncological conditions were not screened for HBsAg (3.4%), Anti-HBs (3.7%), Anti-HBc (22%), or Anti-HCV (3.2%). Among patients with rheumatological conditions, 10.3% were not screened for HBsAg, 14.4% for anti-HBs, and 59.1% for anti-HBc tests before treatment. Conversely, 4.2% of gastroenterology patients had not undergone screening for HBsAg, 4.2% for anti-HBs, 56.3% for anti-HBc, and 2% for anti-HCV tests before treatment. A statistically significant relationship was detected between the departments and HBsAg, Anti-HBs, Anti-HBc, and Anti-HCV test groups ($p<0.001$). In six patients (2 with a diagnosis of oncology and 4 with a diagnosis of rheumatology), the presence of HCV RNA was investigated following a positive anti-HCV test. However, all six patients had negative results. (Table 2). Antiviral treatment was initiated before treatment in 60 (8.8%) patients in the oncology group, 23 (5.5%) in the rheumatology group, and 4 (8.4%) in the gastroenterology group (Table 3).

Reactivation of HBV was detected in 1 oncology patient and 11 rheumatology patients, while no reactivation was seen in all gastroenterology patients. In total, reactivation was observed in twelve patients (1.0%), while no reactivation was observed in 1135 patients (99.0%). A statistically significant correlation was found between the departments and the presence of reactivation ($p<0.001$) (Table 4). It was noted that 3 of the patients with reactivation did not receive antiviral treatment. In the study, 60 (8.8%) oncology, 23 (5.5%) rheumatology and 4 (8.4%) gastroenterology patients received antiviral treatment. It was found that entecavir treatment was preferred most frequently. When the frequency of antiviral treatment was evaluated

Table 1 Sociodemographic characteristics

	Oncology (n= 681)	Rheumatology (n=418)	Gastroenterology (n=48)	p
Age, years	58,72±11,90	46,15±14,76	47,31 ± 15,08	**<0,001***
Woman, (n, %)	311 (45,7)	256 (61,2)	24 (50,0)	**<0,001***
Common diagnosis (%)	1. Lung Ca (25.5%) 2. Breast Ca (17.3%)	1. SpA (51%) 2. RA (41.1%)	1.UC (58.3%) 2.CD (41.7%)	

*: Significant at 0.05 level according to paired Student's t-test,

Table 2 Distribution of hepatitis serology by departments

		Oncology (n= 681)	Rheumatology (n=418)	Gastroenterology (n=48)	
		n (%)			p
HBsAg	Negative	642 (94,3)	363 (86,8)	43 (89,6)	**<0,001***
	Positive	16 (2,3)	12 (2,9)	3 (6,3)	
	Not tested	23 (3,4)	43 (10,3)	2 (4,2)	
Anti HBs	Negative	450 (66,1)	239 (57,2)	31 (64,6)	**<0,001***
	Positive	206 (30,2)	119 (28,5)	15 (31,3)	
	Not tested	25 (3,7)	60 (14,4)	2 (4,2)	
Anti HBc	Negative	366 (53,7)	132 (31,6)	18 (37,5)	**<0,001***
	Positive	165 (24,2)	39 (9,3)	3 (6,3)	
	Not tested	150 (22,0)	247 (59,1)	27 (56,3)	
Anti HCV	Negative	657 (96,5)	369 (88,3)	46 (95,8)	**<0,001***
	Positive	2 (0,3)	4 (1,0)	0 (0,0)	
	Not tested	22 (3,2)	45 (10,8)	2 (4,2)	

*: Significant at 0.05 level according to paired Student's t-test, HBsAg: Hepatitis B surface antigen, Anti-HBs: Hepatitis B surface antibody, Anti-HBc: Hepatitis B core antibody, Anti-HCV: Hepatitis C virus antibody

Table 3 Antiviral treatment status of patients according to departments

		Oncology	Rheumatology	Gastroenterology	
		n (%)			p
		60 (8,8)	**23(5,5)**	**4(8,4)**	
Antiviral Treatment	**Entecavir**	42 (6,2)	15 (3,6)	1 (2,1)	0,072
	Tenofovir	17 (2,5)	7 (1,7)	2 (4,2)	
	Lamuvidine	1 (0,1)	1 (0,2)	1 (2,1)	

*: Significant at 0.05 level according to paired Student's t-test,

according to HBsAg and Anti-HBc test results in the rheumatology department, it was seen that 19 patients in the anti-HBc positive patient group were given antiviral treatment. In the rheumatology department, 51 (43%) of the patients who received rituximab treatment, a high-risk drug, were not screened for anti-HBc. Of the 15 patients who tested positive for anti-HBc, 9 received antiviral treatment. Only 1 patient receiving rituximab showed reactivation. In the oncology group, 654 (57.0%) patients were in the low-risk group, while 16 (1.4%) and 11 (1.0%) were in the high and intermediate-risk groups, respectively.

Table 4 Reactivation status of patients according to departments

		Oncology	Rheumatology	Gastroenterology	p
		n (%)			
Reactivation	**Yes**	1 (0,1)	11 (2,6)	0 (0,0)	**<0,001***
	No	680 (99,9)	407 (97,4)	48 (100,0)	

*: Significant at 0.05 level according to paired Student's t-test,

Discussion

In our study, the frequency of hepatitis B and C serology screening before biological therapy and chemotherapy treatment in internal medicine (rheumatology, medical oncology and gastroenterology) clinics was found to be low, similar to the literature. Upon examination of the departments, we observed that viral hepatitis screening before chemotherapy was more common in the medical oncology department than in the rheumatology and gastroenterology departments. In rheumatology and gastroenterology departments, the AntiHBc test was performed less frequently on low and medium-risk patients due to their lower risk of reactivation. The increasing use of biological and chemotherapeutic treatments has led to a higher frequency of hepatitis B reactivation. Despite frequent updates to hepatitis B and C serology screening recommendations, our study shows that it has not been fully implemented in clinical practice.

In a retrospective study by Hwang et al, 1,787 (16.7%) of 10,729 newly diagnosed cancer patients receiving chemotherapy were screened for HBV serology (17). Engin et al. found that 47.8% of 445 patients receiving immunosuppressive treatment were not screened for hepatitis, 28.9% were incompletely screened (HBsAg or Anti-HBc IgG was not checked), and 23.3% were fully screened before receiving treatment (18). Bozkurt et al. conducted a study to determine the rate of HBV screening and reactivation frequency in patients receiving anti-TNF. The study retrospectively evaluated 644 patients using anti-TNF for different indications. Before treatment, hepatitis B indicators (HBsAg, Anti-HBc IgG, Anti-HBs) and viral load were analysed. Only 410 (63.7%) of the patients were screened for hepatitis B before treatment (19). The study found that before receiving chemotherapy in the oncology department, 77.7% of patients were fully screened for hepatitis B, 16.6% were incompletely screened, and 3.4% were not screened at all. In the rheumatology department, 40.9% of patients were fully screened for hepatitis, 48.8% were incompletely screened, and 10.3% were not screened at all. In the gastroenterology department, 43.8% of patients were fully screened for hepatitis, 52% were incompletely screened, and 4.2% were not screened at all. High rates of viral hepatitis screening before chemotherapy were observed in the medical oncology department. The study found that screening for viral hepatitis tests was more frequent in rheumatology and gastroenterology departments compared to the literature. The reason for incomplete screening in rheumatology and gastroenterology departments is that 72% of the biological treatments given in rheumatology and all of them in gastroenterology departments were classified as low-medium risk according to AGA guidelines. Therefore, it is believed that in patients at low to intermediate risk, HBsAg and Anti-HBs were tested without checking for the Anti-HBc total.

According to the AGA guideline classification of hepatitis reactivation, prophylactic antiviral treatment is not recommended if the patient is HBsAg-negative, Anti-HBc-positive, and in the low or medium-risk group. However, some studies do recommend prophylactic antiviral treatment. Risk factors for hepatitis reactivation include young age, male gender, and high ALT levels in patients before immunosuppressive treatment (20). In the clinical approach, elevated ALT and AST levels in patients who are planned to receive biological treatment other than rituximab (in the intermediate risk group according to AGA risk classification) indicate the need for prophylactic antiviral treatment. According to a study conducted by Bessone et al., a high baseline ALT level was found to be significant in terms of HBV reactivation (21). Conversely, in the study conducted by Cheng et al., no such association was found between ALT levels before treatment (22). There is still uncertainty regarding the evaluation of AST and ALT levels as a criterion for initiating prophylactic antiviral treatment before biological treatment. Our study found

no statistically significant difference between the group that received antiviral treatment before biological treatment and the group that did not receive antiviral treatment, both of which were in the intermediate risk group according to AGA risk classification. Regarding reactivation, refraining from initiating antiviral treatment before biological treatment did not show any association with AST and ALT values. Due to the limited number of patients experiencing reactivation, it is challenging to establish a correlation between AST and ALT values and reactivation. Therefore, a more extensive study is required in this area.

Reactivation of the HBV was observed in one patient in the oncology department and eleven patients in the rheumatology department. No viral reactivation was observed in the gastroenterology department. The patient in the oncology follow-up who experienced reactivation had received anthracycline-containing chemotherapy, and antiviral treatment was initiated before chemotherapy. Reactivation occurred in one out of 16 high-risk patients according to AGA guidelines in the oncology department. No viral reactivation was observed in the low and medium-risk groups. It was observed that 10 of the rheumatology patients with reactivation used etanercept, while one used rituximab treatment. The high incidence of reactivation in patients using etanercept treatment is not due to the drug being inherently more risky, but rather to the fact that it is more commonly used in patients who are at a higher risk of developing reactivation. In the case of hepatitis B carriers, anti-TNF therapy is recommended as a first-line treatment option, with etanercept being the preferred agent. Consequently, this treatment was selected more frequently. Two patients in the oncology department and four patients in the rheumatology department were found to have negative HCV RNA results, despite positive anti-HCV results. No evidence of HCV reactivation was observed in this group.

In their systematic review, Cholongitas et al. found that although reactivation was higher in patients receiving rituximab-containing combination therapy compared to those receiving rituximab-free combination therapy in the general population, the difference was not statistically significant. However, in HBsAg(-)/Anti-HBc(+) patients, reactivation was significantly higher in those receiving rituximab treatment (23). Koskinas et al. (24) found no significant difference between patients who received rituximab and those who did not. In our study, only one out of 117 patients who received rituximab treatment in the rheumatology department experienced reactivation. The patient had a positive HBsAg test, and as per the literature, none of the patients with a negative anti-HBc test who received rituximab treatment developed viral reactivation.

Although the retrospective nature of our study is a limitation, extremely valuable data were obtained. Prospective screening and follow-up programmes and studies including a large number of patients will be more enlightening in this regard. The limitations of our study include the fact that it included patients admitted between the specified dates, the insufficient number of patients with reactivation, the inability to follow up AST, ALT and reactivation for a longer period, and the insufficient number of patients in the high-risk group according to AGA risk assessment. Since the chemotherapy treatment initiated by patients in the oncology department is very diverse and includes different types of treatments, more comprehensive studies are needed because obtaining accurate data is limited.

Conclusion

In conclusion, although complete screening for viral hepatitis was recommended by the guidelines, it was observed that it was not implemented in clinical practice. Even in patients who were fully screened for hepatitis, prophylaxis or referral to vaccination was found to be incomplete. Failure to initiate prophylactic antiviral treatment results in viral reactivation. In patients with viral reactivation, treatment of the primary disease is delayed. This results in an increase in primary disease and hepatitis-related mortality. The organisation of joint educational meetings by the centres dealing with HBV education and treatment in cooperation with the centres applying chemotherapy and biological treatment and raising awareness about HBV through these programmes are among the recommended solutions.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
The study was approved by the ethics committee of Süleyman Demirel University (Ethics committee approval number (2022-4/56). The study was conducted according to the "Declaration of Helsinki".

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Availability of Data and Materials
Data are available on request due to privacy or other restrictions.

Authors Contributions

AK: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft

AD: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Supervision; Visualization; Writing-original draft; Writing-review & editing.

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