Research Article

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The Importance of Antiviral Prophylaxis against Hepatitis B Virus in Patients under Immunosuppressive Therapy

İmmünosupresif Tedavi Alan Hastalarda Hepatit B Virus Profilaksisinin Önemi

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ABSTRACT

Objectives: Immunosuppressive (IS) therapies present a risk of reactivation in patients with previous or known hepatitis B virus (HBV) infection and may cause mortality and morbidity. Before starting these therapies, patients should be tested for HBV serology and evaluated for antiviral therapy.

Materials and Methods: hepatitis B surface antigen (HBsAg)-positive or HBsAg-negative and Anti-HBs and/or anti-HBc immunoglobulin-positive patients aged over 18 years old who were scheduled to undergo or who were already on IS therapy due to underlying diseases were evaluated retrospectively. The study included patients who had monthly transaminase levels during the first six months of antiviral prophylaxis, and then who had transaminase and HBV-DNA levels every three months during subsequent follow-ups.

Results: Sixty-three patients were included in the study. Forty-eight patients (76%) received prophylaxis with IS therapy and 15 patients (24%) did not receive prophylaxis at the appropriate time. HBV reactivation (HBVr) was observed in three patients who did not receive prophylaxis at the appropriate time. The incidence of HBVr in all our patients was 4.8%, but was 20% in patients with delayed prophylaxis.

Conclusion: IS therapies represent a major risk in terms of HBVr. Before starting these therapies, patients should be evaluated for antiviral prophylaxis by testing their HBV serology.

Keywords: Hepatitis B virus, prophylaxis, immunosuppressive therapy

ÖZ

Amaç: İmmünosupresif tedaviler, önceki veya bilinen hepatit B virüsü (HBV) enfeksiyonu olan hastalarda reaktivasyon açısından bir risk oluşturur ve mortalite ve morbiditeye neden olabilir. Bu tedavilere başlamadan önce, hastalar HBV serolojileri test edilerek antiviral tedavi açısından değerlendirilmelidir.

Gereç ve Yöntemler: Altta yatan hastalıklar nedeniyle immünosupresif tedavi planlanan veya daha önce başlanan 18 yaş üstü hepatit B yüzey antijeni (HBsAg)-pozitif veya HBsAg-negatif ve anti-HBs ve/veya anti-HBc immünoglobulin-pozitif hastalar retrospektif olarak değerlendirildi. Çalışmaya antiviral proflaksi başlanan hastalardan ilk 6 ay boyunca aylık transaminaz, sonraki takiplerinde her üç ayda bir transaminaz ve HBV-DNA seviyeleri bakılan hastalar dahil edildi.

Bulgular: Altmış üç hasta çalışmaya alındı. Kırk sekiz (%76) hastaya immünosupresif tedavi ile birlikte profilaksi başlandı, 15 (%24) hastada profilaksi uygun zamanda başlanmadı. Uygun zamanda profilaksi alamayan hastaların üçünde HBV reaktivasyonu (HBVr) görüldü. Tüm hastalarımızda HBVr insidansı %4,8 idi, ancak gecikmiş profilaksi olan hastalarda %20 idi.

Sonuç: İmmünsupresif tedaviler HBV reaktivasyonu açısından önemli bir risk oluşturmaktadır. Bu tedavilere başlamadan önce, hastalar HBV serolojilerini test ederek antiviral profilaksi açısından değerlendirilmelidir.

Anahtar Kelimeler: Hepatit B virüs, profilaksi, immünosupresif tedavi

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Introduction

Hepatitis B virus (HBV) infection is one of the world's most important health problems. Immunosuppressive (IS) therapies constitute a risk in terms of HBV reactivation (HBVr) and can cause mortality and morbidity in patients with previous or known HBV infection (1,2). Patients receiving these must therefore first be tested in terms of HBV serology (1,2). Cancer chemotherapy, autoimmune diseases, IS therapies in patients receiving solid organ and stem cell transplantation, glucocorticoids, and biological agents frequently used in recent years are all risk factors for reactivation (1,2,3,4,5,6). HBVr is characterized by a symptomatic or asymptomatic increase in serum aminotransferase (alanine aminotransferase or aspartate aminotransferase) levels. An increase in HBV-DNA frequently accompanies that manifestation (1,2,3,7). HBVr is defined by the European Association for the Study of the Liver and the Asian Pacific Association for the Study of the Liver as hepatitis B surface antigen (HBsAg) seroreversion and an increase in HBV-DNA levels (2,8). According to the American Association for the Study of Liver Diseases, active necroinflammatory disease of the liver in inactive HBsAg carriers or subjects with histories of HBV infection is defined as reactivation (4). HBVr can be prevented in subjects receiving IS therapy with antiviral prophylaxis. HBV prophylaxis should be initiated 1-3 weeks before the IS therapy, if possible, or at least concomitantly with the IS therapy (1,2,4,7,8,9,10,11). However, this is known to be less effective on liver damage when given after IS therapies have already been started (1,2,4,7,8,9,10,11). According to the American Gastroenterological Association (AGA) guideline, the risk of reactivation in continuing or previous HBV infection varies depending on serology and/or immunosuppression (1). Subjects such as the prevention of reactivation, the most appropriate population for screening, who should use prophylaxis, the best specific agent, duration of prophylaxis, and monitoring when prophylaxis is not employed are still unclear (1,2). However, the consensus in all guidelines is that it is essential for patients to be evaluated in terms of antiviral therapy before IS therapy begins in order to prevent progression of HBVr and underlying disease (since IS therapy may be discontinued when HBVr develops) (1,2,7,8,9,10,11).

The purpose of this study was to assess the effect on HBVr development of prophylactic antiviral therapy in patients receiving IS therapy. While there have been previous case reports from Turkey, we encountered no studies concerning HBVr, and our study is thus the first of its kind from Turkey.

Materials and Methods

This study was conducted at our clinic between 01.01.2010 and 30.10.2016. The data were analyzed retrospectively. We evaluated patients diagnosed with chronic hepatitis B that received IS therapy or planned. HBsAg-positive or HBsAg-negative and anti-HBs and/or anti-HBc Immunoglobulin G (IgG)-positive patients aged over 18 age scheduled to be or already started on IS therapy due to underlying diseases (patients with solid or hematological malignity receiving chemotherapy, with autoimmune and/or rheumatological diseases, patients undergoing solid organ or stem cell transplantation, or patients using IS therapy, glucocorticoids, or biological agents for any reason) were enrolled in the study. Patients with known transaminase and HBV-DNA levels were included. Patients with human immunodeficiency virus (HIV), HCV, Delta co-infection were not included. Antiviral prophylaxis has started according to the guidelines of the period (1,4,7). Risk assessment performed according to AGA guidelines (1). No additional examination was requested except for the recommendations of the guidelines in the follow-up of the patients. Data of patients were obtained from electronic records. The study included patients who had received antiviral prophylaxis for the first 6 months of transaminase monthly, followed by transaminase and HBV-DNA levels every three months. One of lamivudine, tenofovir and entecavir was used as antiviral. Patients were divided into two groups. Group 1: Patients had been started on prophylaxis together with IS therapy (appropriate time), Group 2: Patients had not been started on prophylaxis timely (patients who did not receive prophylaxis at the appropriate time.). Data analysis was performed by using frequencies for the descriptive statistics.

Statistical Analysis

Data analysis was performed by using frequencies for the descriptive statistics.

Results

Sixty-three patients were included in the study, 33 men (52.3%) and 30 women (47.6%). Patients' mean age was 52.2±14.2 years (24-86). HBsAg, anti-HBc IgG was positive and anti-HBs-negative in 54 patients (85.7%). Forty-eight patients (76%) had been started on prophylaxis together with IS therapy (group 1), while 15 (24%) had not been started on prophylaxis timely (group 2). Patients' characteristics are shown in Table 1. In terms of IS drugs, 29 (46.1%) patients received anti-TNF, 24 (38.1%) chemotherapy, 5 (%7.9) took steroids, and 5 (7.9%) received chemotherapy combined with steroids. Based on the AGA guideline (1). In all groups, prophylaxis was evaluated by considering IS risk group, HBV serology and underlying diseases (1).

27 (42.9%) of the patients were in the high risk group, 31 (49.2%) were in the moderate risk group and 5 (7.9%) were in the low risk group. Of the high-risk patients, 18 (66.7%) received chemotherapy, 3 (11.1%) received anti-TNF, 3 (11.1%) received steroid and 3 (11.1%) received steroid and chemotherapy. In twenty-seven (100%) patients were HBsAg positive/anti-HBc IgG positive of these 26 (96.3%) were HBeAg negative and 1 (3.7%) was HBeAg positive. Eighteen (66.7%) lamivudine, 7 (25.9%) tenofovir and 2 (7.4%) entecavir were used as antiviral prophylaxis in high risk patients. HBV-DNA levels were <2000 IU/mL in 15 (55.6%) patients and HBV-DNA >2000 IU/mL in 12 (44.45) patients. 86.2% of the patients receiving anti- tumor necrosis factor (TNF) were moderate risk, 10.3% were high risk, and 3.5% were low risk.

Lamivudine, tenofovir and entecavir were used as prophylactic therapy by 46 (73%), 11 (17.4%) and 6 (9.5%) patients, respectively. Eight patients (72.7%) receiving tenofovir had experience of lamivudine.

The underlying diseases of HBeAg negative patients were rheumatological disease (n=38), hematological malignity (n=14), solid tumor (n=2), renal transplantation (n=1) and bone marrow transplantation (n=1). The prophylactic therapies of HBeAg

Table 1. The characteristics of the patients who take prophylaxis timely or not		
	Group 1, n=48	**Group 2, n=15**
Gender (Male/Female)	25/23	8/7
Underlying diseases		
- Rheumatological disease	31	7
- Hematological malignity	14	4
- Solid tumor	2	1
- Bone marrow transplantation	-	3
- Renal transplantation	1	-
HBV infection history, (HBsAg positivity)		
<1 year	6	3
1-5 year	13	4
>5 year	20	8
HBV serology		
- HBsAg positivity/anti-HBc IgG positivity	n=39	n=15
- HBsAg negativity/anti-HBs positivity/anti-HBc IgG positivity	3	-
- Isolated anti-HBc IgG positivity	6	-
HBV infection definitions		
HBeAg positivity	4	3
- HBV-DNA >20000 IU/mL, ALT: normal or elevated	3	3
- HBV-DNA < 20000 IU/mL, ALT: normal or elevated	1	-
HBeAg negativity	35	12
- HBV-DNA <2000 IU/mL, ALT: normal or elevated	18	3
- HBV-DNA >2000 IU/ml, ALT: normal or elevated	17	9
Risk group		
- High	20	7
- Moderate	25	6
- Low	3	2
Immunosuppressive drugs		
- Anti-TNF	24	5
- Steroid	4	1
- Chemotherapy	17	7
- Steroid and Chemotherapy	3	2
Antiviral prophylaxis		
- Lamivudine	40	6
- Tenofovir	5	6
- Entecavir	3	3
Reactivation	-	3
HBV: Hepatitis B virus, HBsAg: Hepatitis B surface antigen, Ig: Immunoglobulin, ALT: Alanine aminotransferase, TNF: Tumor necrosis factor		

negative patients were lamivudine (n=42), tenofovir (n=8) and entecavir (n=6). The underlying diseases of HBeAg positive patients were hematological malignity (n=4), solid tumor (n=1) and bone marrow transplantation (n=2). The prophylactic therapies of HBeAg positive patients were lamivudine (n=4) and tenofovir (n=3). The underlying diseases of isolated anti-HBc IgG positive patients were hematological malignity (n=3), rheumatological disease (n=2) and bone marrow transplantation (n=1). The prophylactic therapies of isolated anti-HBc IgG positive patients were lamivudine (n=4), entecavir (n=1) and tenofovir (n=1).

The HBVr rate among all our patients was 4.8%, but the figure was 20% among patients in whom prophylaxis was delayed. The rate among the 54 HBsAg-positive patients was 5.6%. Delay time of prophylaxis was 9.5±9.2/month. The time of referral of the patients in group 2 from the clinics treating the underlying disease to our clinic was long. It was thought that this was due to the lack of awareness of the relevant clinics about HBVr. Three of the patients (4.8%) not receiving prophylaxis after being started on IS therapy presented with a manifestation of HBVr. All three patients who developed HBVr were male. IS treatment and underlying disease of

Table 2. The characteristics of the patients who developed hepatitis B virus reactivation

	Patient 1	Patient 2	Patient 3 (Exitus)
Age	25	36	76
Gender	Male	Male	Male
Underlying diseases	Rheumatological disease	Rheumatological disease	Hematological malignity
HBV infection history (HBsAg positivity)	<1 year	<1 year	>5 year
HBV serology	HBsAg positivity	HBsAg positivity	HBsAg positivity
	Anti-HBs negative	Anti-HBs negative	Anti-HBs negative
	HBeAg negative	HBeAg negative	HBeAg negative
	Anti-HBc IgG positivity	Anti-HBc IgG positivity	Anti-HBc IgG positivity
HBV-DNA level (when admitted to hospital)	$1.07x10^3$ IU/mL	$1.07x10^5$ IU/mL	$3.89x10^7$ IU/mL
HBV-DNA level (6. month)	Negative	Negative	-
HBV-DNA level (12. month)	Negative	Negative	-
Immunosuppressive treatment	Infliximab	Rituximab	Azathioprine
Risk group (AGA guideline)	Moderate	High	Low
Prophylactic agents	Lamivudine	Entecavir	Lamivudine
Delay time of prophylaxis (HBVr time)	10/ month	4/ month	30/ month

HBVr: Hepatitis B Virus reactivation, HBsAg: Hepatitis B surface antigen, Ig: Immunoglobulin, AGA: American Gastroenterological Association, HBV: Hepatitis B Virus

the patients were showed in the Table 2. Patient 3 did not receive antiviral prophylaxis during previous IS therapy. The patient received chemotherapy one month before he came to us. When the patient was admitted to the service, Lamivudine prophylaxis was started (because the patient developed respiratory distress and the patient started high-dose steroid therapy). Transaminase levels and HBV-DNA level were increased. HBVr was considered in the patient. Patient 3 died in intensive care unit on the 50th day of hospitalization from fulminant hepatitis (50th Day of Antiviral Prophylaxis). The characteristics of the patients who developed HBVr were shown in the Table 2.

Fifty (79.3%) continued with prophylactic therapy at six-month follow-up. HBV-DNA exceeded 2000 IU/mL in three patients at the end of six months. IS therapy was continuing in two of these patients. Patients had non-compliance to prophylactic therapy. When prophylactic therapy compliance is achieved, the three patients' HBV-DNA became negative at the end of the 12th month. Two of the patients had used lamivudine and one had tenofovir.

The HBV-DNA levels of two patients with negative HBV-DNA at six months rose above 2000 IU/mL at the end of 12 months. Both patients were taking lamivudine. Flare-up occurred at the end of 12 months in one patient not using treatment regularly. While no concrete cause could be identified in the other patient, resistance tests could not be performed in the patients. All the other patients were persisted with HBV-DNA negativity.

Conclusion

Individuals encountering HBV infection are at risk of HBVr when their immunity is suppressed. HBVr may appear with differing clinical manifestations, from asymptomatic disease to a severe and fatal course. This also affects the morbidity and mortality of the underlying disease as a cause of discontinuation of immunosuppression and chemotherapy (11).

Determining serological status and type and duration of immunosuppression by screening patients at risk of reactivation is very important in the management of the antiviral therapy process (1,2,4,7,8,9,10). Patients receiving IS therapy must be scanned in terms of HBsAg, anti-HBs and anti-HBc markers before treatment. In terms of our patients' serological parameters, HBsAg, Anti-HBs and anti-HBc IgG positivity rates were 89.4%, 1.8%, and 100%, respectively. HBVr is more common in patients with HBsAg positivity (1,2,3,4,5,6,7,8,9). Tavakolpour et al. (3) reported a high risk of reactivation in HBsAg- and HbeAg-positive patients. Our three patients with reactivation were HBsAg-positive and HBeAg-negative. Lee et al. (12) reported a 12.3% level of HBVr in 122 HBsAg-positive patients receiving IS therapy due to rheumatological diseases, compared to 5.6% in our study. No previous studies from Turkey, including case reports, have reported this rate.

The type of IS employed and length of use also constitute a risk for reactivation (1,2,3,4,5,6,7,8,9). When drugs that suppress B cells, antracycline derivatives and high-dose corticosteroids are used, the risk of reactivation is above 10%. The risk of reactivation with the use of TNF-alpha, cytokine, integrin, tyrosine kinase inhibitors and low-dose corticosteroids ranges between 1% and 10%. The reactivation risk associated with low-dose or intra-articular corticosteroid or conventional IS drug (azathioprine, 6-merkaptopurin, and methotrexate) use is less than 1% (1,11). In our study, 46.1% (n=29) of patients had received anti-TNF, 38.1% chemotherapy, 7.9% steroids, and 7.9% chemotherapy and steroid therapy. According to the AGA guideline (1), 86.2% of our patients receiving anti-TNF were at moderate risk, and the most commonly used agent was infliximab (n=13). An additional 10.3%

were at high risk, and all had used rituximab, while 3.5% were in the low-risk group. Two of the patients with HBVr had used anti-TNF (infliximab, and rituximab), and the other patient, azathioprine. The IS therapies used by our patients were in the low-, moderate-, and high-risk groups. Although azathioprine involves a low risk (<1% risk of HBVr), HBVr occurred in one of our patients, and that patient died. One previous study reported that a risk of HBVr with azathioprine, but that this was lower compared to other chemotherapeutic agents (13).

The current antivirals of choice in patients receiving IS therapy are tenofovir and entecavir (11,14). Lamivudine therapy was administered to patients with HBVr receiving anti-TNF, and entecavir therapy to a patient using azathioprine.

IS therapies, steroids, and biological agents that have become intensively used in several diseases in recent years constitute a major risk in terms of HBVr, and these cases may be missed in clinical practice. These patients must be evaluated in terms of prophylaxis requirement by means of serological screening before treatment. Prophylactic antiviral therapy prevents HBVr in patients receiving IS therapy, but as seen in our study, delayed treatment can result in morbidity and mortality. HBVr was present in one patient in our low-risk group, and it is impossible to say whether this was associated with the natural course of the disease or else incidental, and further studies involving larger patient numbers on this subject are now needed. It should be remembered that HBVr can also be seen in low-risk patients, and we think that these patients also require close and careful follow-up.

Ethics

Ethics Committee Approval: Retrospective study.
Informed Consent: Retrospective study.
Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.A., S.K., Concept: F.A., Design: F.A., S.K., Data Collection or Processing: F.A., H.N.K., S.A., İ.K., G.Y., Analysis or Interpretation: F.A., G.Y., Literature Search: S.K., H.N.K., Writing F.A.

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