Overuse of prophylaxis in HBsAg and/or anti-HBc positive patients after increasing awareness to prevent reactivation in patients receiving immunosuppressive therapies: How rational are our prophylaxis decisions according to the literature?

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SUMMARY

Screening prior to initiation of immunosuppressive therapy, and decision making between the initiation of hepatitis B virus (HBV) prophylaxis and monitoring with the intent of on-demand anti-HBV therapy initiation are the key determinants to prevent reactivation of HBV. Patients over 18 years of age with HBsAg and/or anti-HBc positivity, who received HBV prophylaxis due to immunosuppressive treatments between 2013 and 2019, enrolled in this retrospective descriptive study. We tried to create awareness about the reactivation of hepatitis among clinicians in our hospital from the beginning of 2017, via warnings at the hospital data management system and via in-service training activities. Changes or differences between two-time period groups (first group between 2013 and 2016, the second between 2017 and 2018) and between four reactivation risk groups (low, moderate, high and very high) were analyzed. Of 125 patients who received immunosuppressive therapies and HBV prophylaxis, 52 (41.6%) were HBsAg positive while 73 (58.4%) were anti-HBc positive/HBsAg negative. Eighteen of the patients were in the 1st-period-years and 107 were in the second. The ratio of anti-HBc positive/HBsAg negative patients increased from 22.22% (n: 4) to 64.49% (n: 69) in the 2nd period (p: 0.001). In the 1st period, 16.67% of the patients had hepatitis B surface antibodies (anti-HBs), which increased to 46.73% during the 2nd period. The ratio of patients with HBV DNA positivity was found to be 55.56% in the first period and 33.87% in the second. Patients in the moderate (1-10%) and high (10-30%) reactivation risk groups were predominant, with rates of 38.89% and 33.33% of all the patients during the 1st period, respectively. However, the number of patients with a low reactivation risk increased 19-fold (from 2 to 38) and reached a proportion of 35.51% of all patients during the 2nd period. There was also a 6.33-fold increase (from 6 to 38) in the number of patients with high reactivation risk, reaching a rate of 35.51% during the 2nd period. None of the patients developed HBV reactivation when HBV prophylaxis was initiated before (n:11), concurrently (n:81) with or after (n:33) the immunosuppressive therapy.

Awareness of HBV reactivation among clinicians has significantly increased in recent years mainly due to in-service training activities in our hospital. This rapid progress in awareness resulted in increased rates of screening for HBV and therefore increased the number of anti-HBc positive/HBsAg negative patients. However, it also led to the overuse of HBV prophylaxis even in low-risk patients.

Keywords: HBV reactivation, prophylaxis, immunosuppressive treatment, resolved infection, anti-HBc positive.

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INTRODUCTION

Hepatitis B virus (HBV) infection is one of the major health problems in the world, especially considering its course leading to cirrhosis and hepatocellular carcinoma. Despite achievements in decreasing the number of new cases through vaccination policies, Turkey is still one of the countries with intermediate endemicity for HBV. The prevalence of hepatitis B surface antigen (HBsAg) positivity is said to be 4.57%, and an estimated 3.3 million HBV carriers have been reported. Furthermore, the seropositivity rate for anti-HBc total is still over 30% [1, 2]. This large number of anti-HBc positive/HBsAg negative patients is important for patients who need to receive immunosuppressive treatments with regard to the development of hepatitis reactivation. Recently, new immunosuppressive treatment modalities like B-cell-depleting agents, besides the traditional ones, have raised awareness of reactivation of HBV among clinicians. On the other hand, the risk of reactivation and the severe consequences of the condition might have caused overuse of oral nucleoside analogues (NAs) in terms of prophylactic approach.

According to guidelines for the management of HBV infections, all persons with high reactivation and exacerbation risk like immunosuppressed patients should be screened for HBV infection, especially in regions with a moderate or high prevalence of HBV [3-5]. The risk of reactivation varies according to HBV status and the immunosuppressive regimen. Although there are no strict recommendations as to which cases require initiation of antiviral prophylaxis, the clearest risk classification, and management recommendations are reported in two publications, a technical review and a guideline, by the American Gastroenterological Association Institute, concerning the management of HBV in patients with immunosuppressive treatment [6, 7]. In 2018, a consensus report about the management of HBV in patients using immunosuppressive therapy was published by a Turkish group of experts [8].

In this study, our first aim is to reveal awareness of clinicians about HBV reactivation and the importance of HBV screening in patients receiving immunosuppressive treatments. The second is to question our decisions on HBV prophylaxis in anti-HBc positive/HBsAg negative patients receiving immunosuppressive treatments in our hospital and to discuss the rationality of the clinical management of these patients within the scope of literature.

MATERIALS AND METHODS

This retrospective descriptive study was conducted in a tertiary training and research hospital. The data were gathered and analyzed retrospectively through the patient data management system of the hospital. The study was approved by the Hamidiye Clinical Research Ethics Committee of University of Health Sciences on March 29th, 2019 (SBU-HGOAEK 19/40).

Population and groups

All the patients over 18 years of age, who received HBV prophylaxis due to immunosuppressive treatments between 2013 and 2018 were enrolled in the study. Patients received HBV prophylaxis and were followed up until 6 to 12 months after completion of the immunosuppressive treatment. There were no exclusion criteria in the study. The study consisted of two periods; the first between 2013 and 2016, the second between 2017 and 2018. We tried to create awareness about the reactivation of hepatitis among the clinicians in our hospital from the beginning of 2017, via warnings at hospital data management system and via in-service training activities.

Patients were divided into six groups according to the clinical units where they were being followed-up; haematology, oncology, neurology, physical therapy, dermatology clinical units and others (pulmonary diseases, endocrinology, nephrology, gastroenterology clinical units). Diseases that necessitated the use of immunosuppressive therapies consisted of six groups as leukemia, lymphoma, solid malignancies, rheumatologic diseases, multiple sclerosis, and the other immunosuppressive conditions. Immunosuppressive drugs were separated into seven groups as B-cell depleting agents, TNF-α inhibitors, tyrosine kinase inhibitors, anthracyclines, purine analogues, corticosteroids, and other traditional immunosuppressants. Only systemic corticosteroid treatments over four weeks were considered in the study classification. Doses of corticosteroids were determined as moderate-dose (10-20 mg prednisone daily or equivalent) and high-dose (≥20

mg prednisone daily or equivalent). Since the risk of reactivation varied according to HBV status and the immunosuppressive regimen, HBsAg, anti-HBc total, anti-HBs, HBV DNA results were recorded.

Risk groups for reactivation of HBV were determined in accordance with recommendations of the American Gastroenterological Association Institute Guideline published as "American Gastroenterological Association Institute Guideline on the Prevention and Treatment of Hepatitis B Virus Reactivation during Immunosuppressive Drug Therapy" [7]. Risk groups for reactivation in our study consisted of four groups as low-risk (<1%), moderate-risk (1-10%), high-risk (10-30%) and very high-risk (≥30%) (Table 1). When determining risk groups in patients receiving a combination of immunosuppressive treatments, the drug with the highest rate of reactivation in the combination was considered.

The study group consisted of three-patient subgroups in terms of prophylaxis time; in the first group HBV prophylaxis was initiated before the immunosuppressive treatment, in the second group HBV prophylaxis was initiated concurrently with the immunosuppressive treatment. Whereas the third group consisted of patients who had already been receiving immunosuppressive treatments, and in whom HBsAg and/or anti-HBc positivity were detected during the follow-up period after at least four weeks after the initiation of immunosuppressive treatments. The reason in the third group was that the clinicians had not screened the patients for HBV at the first visit before initiating immunosuppressive treatment because of the lack of awareness of hepatitis B reactivation.

Laboratory tests

HBsAg, anti-HBc total, anti-HBs tests were performed using chemiluminescence microparticle immunoassay (Abbot, Architect System). HBV DNA was quantitatively determined by HBV QNP 2.0 Real Time PCR Assay (Iontek, Turkey) with the lowest detection limit of 10 IU/mL (80 copies/mL) and a limit of quantification between $2x10^9$ and $2x10^1$ IU/mL.

Statistical analysis

The baseline characteristics were presented as means and standard deviation for ages in years and as frequencies and percentages for categorical variables. Statistical computation was conducted using the e-picos online calculator (www.e-picos.com).

RESULTS

A total of 125 immunocompromised patients who received HBV prophylaxis during the study period due to HBsAg and/or anti-HBc total positivi-

Table 1 - Classification of reactivation risk groups in the study.

	Class of immunosuppressive drug	*HBV status*
Very high (>30%)	B-cell depleting agents	HBsAg (+)
High (10-30%)	B-cell depleting agents	HBsAg (-) / anti-HBc (+)
	Anthracyclines	HBsAg (+)
	Moderate or high dose plus ≥4 weeks steroid	HBsAg (+)
Moderate (1-10%)	TNF-alpha inhibitors	HBsAg (+)
	Tyrosine kinase inhibitors	HBsAg (+)
	Moderate or high dose plus ≥4 weeks steroid	HBsAg (-) / anti-HBc (+)
	Low dose plus ≥4 weeks steroid	HBsAg (+)
	Anthracyclines	HBsAg (-) / anti-HBc (+)
Low (≤1%)	TNF-alpha inhibitors	HBsAg (-) / anti-HBc (+)
	Tyrosine kinase inhibitors	HBsAg (-) / anti-HBc (+)
	Low dose plus ≥4 weeks steroid	HBsAg (-) / anti-HBc (+)
	Other traditional chemotherapies	Anti-HBc (+) / HBsAg (+) or (-)

Adapted from reference [7].

ty were included in the study. Of the patients, 18 were in the 1st-period-years (2013-2016) while 107 were in the 2nd-period-years (2017-2018) (Table 2). The mean age of patients was 56.90±16.09, and 56 (44.8%) of the patients were male.

Majority of the study group consisted of patients from the haematology and oncology clinical unit with the diagnosis of leukemia, lymphoma and solid malignancies. Increase both in the numbers and proportion of patients from the hematology clinical unit, and who were diagnosed with leukemia and lymphoma, was found to be remarkable in the 2nd period years (Table 2). Haematology patients increased 16.3 fold, while the increase in the number of neurology patients was 9 fold. Changes in the number of patients diagnosed with rheumatologic diseases and multiple sklerosis in the 2nd period years were more significant, with 8.5- and 7.5-fold increase. As a result, with regards to both the numbers and distribution of patients, patient distribution was found to be more homogenous with regard to their diagnosis in the 2nd period than the 1st period (Table 2).

Concerning patients with HBV prophylaxis, 52 (41.6%) had HBsAg positivity while 73 (58.4%) were anti-HBc positive/HBsAg negative. The ratio of patients with HBsAg positivity decreased from 77.78% (n: 14) in the 1st period to 35.51% (n: 38) in the 2nd period, whereas the ratio of anti-HBc positive/HBsAg negative patients increased from 22.22% (n: 4) to 64.49% (n: 69) in the 2nd period (p: 0.001) (Table 2). In the 1st period, 16.67% of the patients had hepatitis B surface antibody (anti-HBs), which increased to

Table 2 - Baseline characteristics of immunosuppressed patients (n: 125).

	Total	*1st period (2013-2016)*	*2nd period (2017-2018)*	*Increase in numbers (fold)*
Number of patients	125	18	107	5.9
Age (mean±sd)	56.90±16.09	52.56±18.17	57.64±15.69	1.1
Sex				
Male	56 (44.8%)	10 (55.56%)	46 (42.99%)	4.6
Female	69 (55.2%)	8 (44.44%)	61 (57.01%)	7.6
Clinics				
Hematology	52 (41.6%)	3 (16.67%)	49 (45.8%)	16.3
Oncology	29 (23.2%)	8 (44.44%)	21 (19.62%)	2.6
Neurology	20 (16%)	2 (11.11%)	18 (16.82%)	9
Physical therapy	10 (8%)	2 (11.11%)	8 (7.48%)	4
Others	14 (11.2%)	3 (16.67%)	11 (10.28%)	3.66
Disease				
Leukemia	19 (15.2%)	0 (0%)	19 (17.76%)	NA
Lymphoma	26 (20.8%)	5 (27.78%)	21 (19.63%)	4.2
Solid Organ Tm	19 (15.2%)	3 (16.67%)	16 (14.94%)	5.33
Rheumatologic	19 (15.2%)	2 (11.11%)	17 (15.89%)	8.5
Multiple Sclerosis	17 (13.6%)	2 (11.11%)	15 (14.02%)	7.5
Others	25 (20%)	6 (33.33%)	19 (17.76%)	3.16
HBsAg				
(+) (n; %)	52 (41.6%)	14 (77.78%)	38 (35.51%)	2.7
(-) (n; %)	73 (58.4%)	4 (22.22%)	69 (64.49%)	17.25
Isolated anti-HBc positivity				
(+) (n; %)	73 (58.4%)	4 (22.22%)	69 (64.49%)	17.25
(-) (n; %)	52 (41.6%)	14 (77.78%)	38 (35.51%)	2.7
Anti-HBs				
(+) (n; %)	53 (42.4%)	3 (16.67%)	50 (46.73%)	16.66
(-) (n; %)	72 (57.6%)	15 (83.33%)	57 (53.27%)	3.8
HBV DNA	n: 80	n: 18	n: 62	
(+) (n; %)	31 (38.75%)	10 (55.56%)	21 (33.87%)	2.1
(-) (n; %)	49 (61.25%)	8 (44.44%)	41 (66.13%)	5.1

46.73% in the 2nd period (p: 0.017). The ratio of patients with HBV DNA positivity was found to be 55.56% and 33.87% in the 1st and 2nd periods, respectively (p: 0.096).

The number of immunosuppressive drugs per patient varied between 1 and 6, and the majority of the patients (44.44% and 55.14% in the 1st and 2nd periods, respectively) received just one drug (Table 3). Between the two periods, a 13.33-fold-increase in the number of B-cell depleting agents, most of which was rituximab, was reported to be significant, and the proportion also increased from 16.67% in the 1st period to 37.38% in the 2nd period. Patients in the moderate (1-10%) and high (10-30%) reactivation risk groups were found to be predominant with rates of 38.89% and 33.33% of all patients in the 1st period, respectively. The ratio of the patients with a low risk of reactivation increased from 11.11% in the 1st period to 35.51% of all patients during the 2nd period. And there was only a slight increase in the ratio of patients with a high risk of reactivation in the 2nd period; from 33.33% in the 1st period to 35.51% in the 2nd period (Table 3).

Of all the patients, 11 (8.8%) were started on HBV prophylaxis at least two weeks before the immunosuppressive treatment was administered. HBV prophylaxis was initiated on 81 (64.8%) patients concurrently with immunosuppressive treatment, whereas 33 (26.4%) of the patients were administered HBV prophylaxis at any time after initiating immunosuppressive treatment (Table 3). The proportion of patients who were administered HBV prophylaxis concurrently with immunosuppres-

Table 3 - Immunosuppressive treatments, and subgroups according to risk groups, HBV prophylaxis time and anti-HBV agents.

	Total	*1st period (2013-2016)*	*2nd period (2017-2018)*	*Increase in numbers (fold)*
Number of immunosuppressive agents used on each patient				
1	67 (53.6%)	8 (44.44%)	59 (55.14%)	7.37
2	18 (14.4%)	1 (5.56%)	17 (15.89%)	17
3	15 (12%)	4 (22.22%)	11 (10.28%)	2.75
4	5 (4%)	2 (11.11%)	3 (2.8%)	1.5
5	17 (13.6%)	2 (11.11%)	15 (14.02%)	7.5
6	3 (2.4%)	1 (5.56%)	2 (1.87%)	2
Class of immunosuppressive treatment				
B-cell depleting agents	43 (34.4%)	3 (16.67%)	40 (37.38%)	13.33
TNF-alpha inhibitors	7 (5.6%)	0 (0%)	7 (6.54%)	NA
Tyrosine kinase inhibitors	5 (4%)	3 (16.67%)	2 (1.87%)	0.66
Anthracyclines	32 (25.6%)	6 (33.33%)	26 (24.3%)	4.33
Purine analogues	39 (31.2%)	4 (22.22%)	35 (32.71%)	8.75
Corticosteroids	52 (41.6%)	15(83.33%)	37 (34.58%)	2.46
Traditional immunosuppressants	93 (74.4%)	15(83.33%)	78 (72.89%)	5.2
Groups according to reactivation risk				
Low (<1%)	40 (32%)	2 (11.11%)	38 (35.51%)	19
Moderate (1-10%)	28 (22.4%)	7 (38.89%)	21 (19.63%)	3
High (10-30%)	44 (35.2%)	6 (33.33%)	38 (35.51%)	6.33
Very high (≥30%)	13 (10.4%)	3 (16.67%)	10 (9.35%)	3.33
*Prophylaxis time**				
Before	11 (8.8%)	4 (22.22%)	7 (6.54%)	1.75
Concurrently	81 (64.8%)	8 (44.45%)	73 (68.22%)	9.12
After	33 (26.4%)	6 (33.33%)	27 (25.24%)	4.5
Anti-HBV agent				
Lamivudine	16 (12.8%)	16(88.88%)	0 (0%)	NA
Entecavir	94 (75.2%)	1 (5.56%)	93 (86.92%)	93
Tenofovir	15 (12%)	1 (5.56%)	14 (13.08%)	14

* Temporal relationship between hepatitis prophylaxis and immunosuppressive treatment.

sive treatment increased from 44.45% in the 1st period to 68.22% in the 2nd period. Majority of the patients (88.88%) were administered lamivudine (LAM) as HBV prophylaxis during the 1st period, whereas the majority of them (86.92%) were administered entecavir (ETV) during the 2nd period.

DISCUSSION

Reactivation of hepatitis B and hepatitis flares is a common complication of HBV infection with the incidence reaching up to 70% in patients receiving chemotherapy or other immunosuppressive treatments [3]. HBV reactivation is associated with a high mortality and morbidity rate when it occurs and may also cause interruption of chemotherapy or other immunosuppressive therapies; however, it is a preventable consequence of HBV infection [6].

Several issues about HBV reactivation and prevention of manifestations in patients under immunosuppressive therapy remain unclear including those who are to be screened for HBV, those who should be initiated on, and the duration HBV prophylaxis, and management of patients when HBV prophylaxis has not been started [7]. According to study results conducted in different patients receiving various types of immunosuppressive treatments in literature; it is concluded that higher rates of reactivation occurred in patients who did not receive HBV prophylaxis, than in patients receiving prophylaxis [9-11].

Screening is the first and the main stage of preventing consequences related to HBV reactivation in a patient receiving immunosuppressive treatments. Although some studies revealed that universal HBV screening is cost-effective and cheaper only for patients receiving anticancer therapy associated with a high reactivation risk, universal HBV testing before the initiation of immunosuppressive therapy is recommended in regions where HBV prevalence is moderate to high according to guidelines [3, 4, 12]. Hence, screening of HBV has a critical role among immunosuppressive patients, especially in endemic countries like Turkey where HBV prevalence is 4.5% and moreover where one-third of the people were anti-HBc positive/HBsAg negative. However, clinicians prescribing immunosuppressive treatments in Turkey were not aware of the importance of the condition until recent years, in terms of HBV reactivation; as a result, adequate screening of patients for HBV was not performed. In a large multicenter study in Turkey including 8322 patients with lymphoma or solid malignancies between the years 2000 and 2014, we can conclude that only 47% of the patients were screened for HBV. Moreover, the screening was performed only by testing for HBsAg, whereas anti-HBc was neglected [13]. Although the authors revealed a high risk of reactivation, they did not refer the importance of anti-HBc in such a country in which almost one-third of people with exposed to HBV, because of the lack of awareness; and this may be considered as a flaw of the study. According to the results of a study in the United States, it is revealed that HBV testing rates prior to anti-CD20 antibody (Ab) treatment increased more than two-fold between 2004 and 2014, however only 49% of the patients for HBsAg positivity and only 43% of patients for anti-HBc positivity had pretreatment screening within 6 months of anti-CD20 Ab initiation. Moreover, ≤37% of the patients with chronic infection received HBV antiviral treatment during the high-risk period, while 21% to 23% of those with anti-HBc positivity/HBsAg negativity, respectively, received HBV antiviral treatment during the follow-up period. So, the awareness about screening and prophylaxis to prevent HBV reactivation is also said to be low in the United States [14]. In our hospital, an almost six times increase in the number of the patients in the last-two-year-period than the period between 2013 and 2016, supports results for an increase in awareness of the importance of screening of HBV in immunosuppressed patients. Anti-HBc positive/HBsAg negative patients may have a more critical role in Turkey due to the fact that one-third of people have been exposed to HBV virus. Hence, HBV screening should always include an anti-HBc total test. In our study, the increase in the number of patients given HBV prophylaxis was mainly based on those with anti-HBc positivity/HBsAg negativity. In the 2nd period, not only the number of anti-HBc positive/HBsAg negative patients increased more than 17 folds, but also the ratio of them increased from about one-fifth to two-thirds of the patients. These findings indicate that a significant awareness arose about the importance of anti-HBc positivity among clinicians who give immunosuppressive therapies and began to screen for anti-HBc in recent years, in addi-

tion to HBsAg. In-service training activities from the beginning of 2017 to create awareness about immunosuppressive agents and reactivation of hepatitis in our hospital concluded as the main reason for progress in the screening. In particular, the wide use of rituximab raised the interest in reactivation of hepatitis, and this interest continued increasingly as various immunosuppressive antibodies which could be classified as B-cell depleting agents, TNF-alpha inhibitors, tyrosine kinase inhibitors became available. These new agents not only led to an increase in the number of patients receiving HBV prophylaxis but also led to diversity in patient types. After 2017, a significant increase in the numbers of patients with leukemia from hematology clinic, multiple sclerosis from neurology clinic, and patients with rheumatologic diseases from physical therapy and dermatology clinics is noticeable in our study. However, the awareness led by the efforts through the training activities in our hospital also brought about concerns among clinicians on the severe consequences of HBV reactivation. So that clinicians began to give HBV prophylaxis to all patients, regardless of the HBV status and class of immunosuppressive treatment; which was not a rational approach not cost effective at the very least [6, 7].

In our study, 42.4% of all patients, in other words, more than two-thirds of the patients with anti-HBc positivity also had anti-HBs positivity. In a large multicenter prospective study, negative or low titers of anti-HBs were reported to be a risk factor for reactivation in patients with rheumatologic diseases, who were using various immunosuppressive therapies [15]. According to a meta-analysis including studies on anti-HBc positive/HBsAg negative patients receiving chemotherapy for haematological malignancies, anti-HBs positivity was found to be associated with a decreased risk of reactivation; it was concluded that HBV screening in this patient population should have included routine anti-HBs testing, and those who were anti-HBs-negative should have received antiviral prophylaxis [16]. However, AGA guideline concluded according to various studies in literature with more than two-thirds of them having anti-HBc positivity and also detectable anti-HBs, demonstrated that only 11 (4.3%) of cases in such studies developed HBV reactivation [7]. Although this rate is slightly lower among such cases than the total group of anti-HBc positive patients, the data and the evidence are lacking in concluding on the protective role of anti-HBs due to the small numbers of such cases. Thus, the AGA guideline does not recommend using anti-HBs status to guide antiviral prophylaxis in all risk groups [7]. According to our results, the HBV DNA positivity rate was 38.75%; however, only 80 of all the patients were screened for HBV DNA meaning that HBV DNA testing rates were still relatively low in our hospital. Baseline HBV DNA level has been shown to be the best predictor for reactivation, and HBV reactivation is 5 to 8 times less likely to occur in anti-HBc positive/HBsAg negative patients than in HBsAg positive patients [17, 18]. Despite the low risk in anti-HBc positive/HBsAg negative patients, this may be substantial in immunosuppressive patients who have to receive new classes of immunosuppressive agents, long term corticosteroids or some of the classical chemotherapies [4]. In a meta-analysis study among patients receiving chemotherapy for solid tumors, it was demonstrated that the reactivation risk ranged between 4% to 68% in chronic HBV infection and 0.3% to 9% in anti-HBc positive/HBsAg negative patients, and that antiviral prophylaxis significantly reduced the risk for HBV reactivation and chemotherapy interruption in patients with chronic infection [19]. These studies in the meta-analysis mainly included HBsAg positive patients, and not anti-HBc positive/HBsAg negative patients who usually do not require prophylactic antiviral treatment according to literature [20]. Furthermore, a significant proportion of patients in our study receiving classical chemotherapies for solid tumors were anti-HBc positive/HBsAg negative patients. However, in another meta-analysis no association was found between the use of antiviral prophylaxis and risk of HBV reactivation in anti-HBc positive/HBsAg negative patients who underwent immunosuppressive therapy; the antiviral prophylaxis in anti-HBc positive/HBsAg negative patients was concluded to be beneficial only in patients receiving B-cell depleting agents-based therapies like rituximab [21]. In a recent study which reported the outcome of immunosuppression-driven HBV reactivation in 70 patients who were presented with reactivation without receiving prophylaxis, 72.9% of the patients were HBsAg negative at baseline screening. Three-quarters of the patients in the study were receiving treatments with very

high or high risks of reactivation like rituximab (66.2%) and corticosteroids (10%) [22].
In brief, risk groups are determined by the HBV status and the reactivation risk related to the immunosuppressive treatment. In patients with negative HBsAg and positive anti-HBc, it is clear that the risk of reactivation is still high if the patient receives anti-CD20 monoclonal antibody therapies like rituximab, and it is reasonable to give anti-HBV prophylaxis in these patients [3]. Anti-HBc positive/HBsAg negative patients receiving high dose steroids for a prolonged duration or anthracycline derivatives make the patient have a moderate risk for reactivation, and it may also be reasonable to initiate anti-HBV prophylaxis instead of on-demand therapy if the clinician has restrictions about close monitoring of the patients. However, it is clear that anti-HBc positive/HBsAg negative patients who receive biological therapies, TNF inhibitors and traditional immunosuppressive therapies have a low risk for developing reactivation. Hence, they are suggested to be monitored with the intent of on-demand anti-HBV therapy initiation at the first sign of HBV reactivation [4]. However, one-third of the patients with HBV prophylaxis in our study were in the low-risk group in which using antiviral prophylaxis routinely is not recommended by guidelines. The rational monitoring in this high proportion of patients who did not receive HBV prophylaxis should include HBV DNA testing at least every 1-3 months because reactivation emerges first with a sudden increase in HBV DNA levels, and this increase might be accompanied by increased levels of ALT at least a few weeks later [4, 8, 23]. In some high-risk patients like those with haematologic malignancy and/or haematopoietic stem cell transplantation who are normally recommended to receive anti-HBV prophylaxis, monitoring of HBV-DNA levels every month is suggested among HBV positive patients when prophylaxis is not received [24].
In summary, awareness of HBV reactivation among clinicians significantly increased in recent years mainly after wide use of new classes of immunosuppressive drugs and due to in-service training activities in our hospital. This rapid progress in the awareness resulted in increased rates of screening for HBV and as a consequence an increased number of patients with HBV. On the other hand, it also led to overuse of HBV prophylaxis, because clinicians did not want to take the risk of reactivation even if it was very low.
We have some limitations in the study. First, we did not have the data for HBV screening rate in patients under immunosuppressive treatments. Second, the number of patients in any risk groups without HBV prophylaxis was lacking. Therefore, we could not conclude on the change in the incidence of HBV among immunosuppressed patients in two study periods in our hospital. Also due to the same reasons, we could not perform further statistical assessments of the data in addition to descriptive evaluation.

CONCLUSIONS

The prophylactic approach may be reasonable for patients with a high and moderate risk of reactivation; however, clinicians should be encouraged to monitor patients with low risk of reactivation at least with the intent of on-demand anti-HBV therapy initiation at the first sign of HBV reactivation. Further in-service training programs should be formed to create rational management and prophylactic approach based on risk stratification of reactivation, for clinicians who prescribe immunosuppressive and anti-HBV therapies. It is hard to conduct randomized controlled prospective studies with regards to ethical concerns in such patients with higher mortality risk. However, at least, there is a strong need for further randomized controlled prospective studies in patients with low reactivaction risk.

Author contributions
EY conceived, designed, collected data, and drafted the manuscript.
RAC collected data, and edited and reviewed the manuscript.

Conflict of Interest
The authors declare no conflict of interest.

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