What Is the Risk of Reactivation in Patients with Resolved and Past HBV Infection During Immunosuppressive Therapy If HBV-DNA Negative before Treatment?

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Cite this article as: Tokmak S, Gümürdülü Y, Taş DA, Kara İ, Güzel AB. What is the risk of reactivation in patients with resolved and past HBV infection during immunosuppressive therapy if HBV-DNA negative before treatment? *Turk J Gastroenterol.* 2021; 32(3): 294-301.

ABSTRACT

Background: *Reactivation of Hepatitis B (HBVr) related to immunosuppressive drug therapy (ISDT) in patients with resolved and past infection is a challenging entity. The number of prospective long-term studies is limited.*

Methods: *Two groups of patients with resolved and past HBV infection were analyzed prospectively. The patients were further categorized as 266 patients receiving ISDT (group 1) and 246 patients receiving antineoplastic therapy (group 2).*

Results: *We did not detect any cases of HBVr among 108 patients receiving rituximab (71 of which were anti-HBc positive only), 111 patients receiving tumor necrosis factor inhibitors (66 of which were anti-HBc positive only), and 42 patients receiving high-dose glucocorticoids for more than 4 weeks (24 of which were anti-HBc positive only) during a mean follow-up time of more than 24 months. Subgroup analysis of the anti-HBs (+) patients showed that in group A (anti-HBs >1000 mIU/mL) the antibody levels did not change; in group B (anti-HBs between 100 and 1000 mIU/mL) the antibody levels changed non-significantly (P = .25), and in Group C (anti-HBs between 0 and 100 mIU/mL) the antibody levels declined significantly (P = .002). Furthermore, 16 patients in Group C had an anti-HBs loss during follow-up, but no HBVr was detected.*

Conclusion: *The risk of HBVr by immunosuppressive therapy in this group may be lower than that suspected in the literature and anti-HBs levels may not seem to correlate with the risk of reactivation.*

Keywords: *Hepatitis B antigens, rituximab, prophylaxis, immunosuppressants, antineoplastic agents*

INTRODUCTION

Hepatitis B virus reactivation (HBVr) is described as an abrupt increase in HBV replication in an inactive carrier or in patients with a resolved state. It is an important cause of morbidity and mortality. Covalently closed circular DNA (cccDNA) enables reactivation because it persists in the hepatocyte nucleus for years.[1] Reactivation almost always develops during immunosuppressive drug therapy (ISDT) to treat autoimmune diseases and cancer.[2]

Almost one-third of the world's population will develop cancer during their lifetime, and most of these patients will receive chemotherapy.[3] Additionally, immunosuppressive drugs are increasingly used to treat rheumatic diseases. Thus, TNF inhibitors have been prescribed for more than 3 million patients in the US alone. HBVr in these immunocompromised patients is a growing concern considering the high prevalence of HBV surface antigen (HBsAg) and past HBV infection rates, which are 0.4 and 3%, respectively, in the US alone.[4] If we extrapolate these rates to the world population, millions of HBVr cases could occur globally.

Continuous expansion of the implementation of ISDT has resulted in an increased number of HBVr cases reported in the literature in the last decade. However, despite these statistics, few prospective studies have been conducted; therefore, a pressing need exists for specifications regarding definitions and monitoring. This study aimed to determine HBVr rates in patients receiving ISDT, analyze the associated factors, and define the need for prophylactic antiviral treatment.

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Received: ***December 25, 2020*** *Accepted:* ***February 12, 2021*** *Available Online Date:* ***XX XX, 2021***

DOI: ***10.5152/tjg.2021.201131***

MATERIALS AND METHODS

Patient Selection

According to our hospital policy, all candidates for ISDT are routinely subjected to HBV serology. Therapy-naive patients aged between 18 and 85 years old were candidates for antineoplastic and immunosuppressive therapy of any type in the oncology, hematology, rheumatology, and gastroenterology clinics of our tertiary care center January 2016 and May 2018 were included in the study.

Serum samples obtained in the initial assessment; HBsAg, anti-HBs, anti-HBclgG, HBV-DNA, ALT, and INR measurements were recorded and repeated monthly during follow-up. According to the national healthcare policy, the HBV-DNA levels were measured by PCR every 3 months. The HBsAg levels were determined by an Elecsys® HBsAg II assay (Roche Diagnostics, Mannheim, Germany; lower limit of detection 0.9 COI). The hepatitis B core antibody (anti-HBc) levels were measured by an Elecsys® anti-HBc kit (Roche Diagnostics, Mannheim, Germany; lower limit of detection >1 COI). The hepatitis B surface antibody (anti-HBs) levels were measured by an Elecsys® anti-HBs kit (Roche Diagnostics, Mannheim, Germany; lower limit of detection 10 mIU/mL). The HBV-DNA levels were quantified by a COBAS® AmpliPrep/COBAS® TaqMan® HBV Test, v2.0 (Roche Diagnostics, Mannheim, Germany; lower limit of detection 0 IU/mL).

Exclusion Criteria

- Patients who were anti-HBc (–) or HBsAg (+) or HBV-DNA (+) or anti-HCV (+) or anti-HDV (+) were excluded.
- Patients who discontinued treatment because of HBV-unrelated reasons (intolerance, complications, death., etc..) were excluded.
- Patients with a history of treatment with interferon (IFN) or antiviral drugs were excluded.

HBVr criteria defined as; any detectable HBV-DNA or seroreversion.[5]

MAIN POINTS

- *Hepatitis B virus reactivation during immunosuppressive drug therapy in patients with resolved and past infection is a growing concern; however, prospective long-term follow-up studies are rare.*
- *If pre-treatment HBV-DNA levels are negative, reactivation may not occur in this population.*
- *Anti-HBs levels may not correlate with reactivation risk.*

Subgroup Definition

The study population was divided into 2 groups: group 1 included patients receiving immunosuppressive therapy, and group 2 included patients receiving antineoplastic therapy. The baseline characteristics and treatment regimens were recorded.

Some studies have suggested that high anti-HBs titers indicate protection against HBVr, and 100 mIU/mL was determined as a cut-off level; changes in anti-HBs titers have been suggested to predict HBVr.[6-8] Based on this information, we divided the anti-HBs (+) patients into 3 subgroups to identify the effect of anti-HBs titers on HBVr:

i. anti-HBs>1000 mIU/mL (group A);
ii. anti-HBs between 100 and 1000 mIU/mL (group B); and
iii. anti-HBs between 0 and 100 mIU/mL (group C).

Informed consent was obtained from all subjects or from the legal guardian in accordance with the principles of Good Clinical Practice, the principles of the Declaration of Helsinki and national laws. The study was reviewed and approved by the institutional ethical review board.

Statistical Analysis

The statistical analysis was performed with IBM SPSS Statistics for Windows, version 21.0 (SPSS Inc., Chicago, IL, USA). Student's *t*-test was used as a parametric test, and the Mann–Whitney *U* test was used as a nonparametric test to calculate 95% CI.

RESULTS

Among the 676 patients recruited for this study, 164 were excluded according to the aforementioned criteria (84 patients did not meet the criteria, and 80 patients were lost to follow-up, discontinued the treatment or died before the 6-month threshold); thus, 512 patients were included (shown in Figure 1). In total, 266 patients were in group 1, and 246 were patients in group 2. The patients in group 1 were significantly younger (52.4 vs. 65.6 years) and female dominant (59.7% in group 1 vs. 41% in group 2). The mean follow-up time was 25.3 months and 24.1 months respectively. The baseline INR and ALT levels were normal (Table 1).

We did not detect any case of HBVr that corresponded to our criteria, including the 80 patients who discontinued treatment because of HBV-unrelated reasons and/or

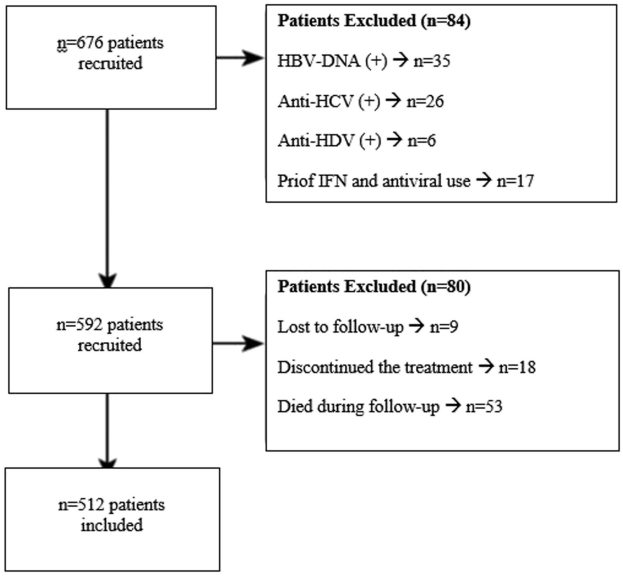

Figure 1. Overview of patients included.

died during the follow-up. The changes in the mean ALT and INR levels were not significant ($P = .41$ and $P = .62$, respectively). Among the 205 anti-HBs positive patients, the subgroup analysis showed that in group A the antibody levels did not change. In group B, the antibody levels declined but the difference was statistically not significant ($P = .25$). In group C, antibody levels declined significantly ($P = .002$); however, we did not detect any case of HBVr (Table 2). Anti-HBs loss (defined as anti-HBs titers becoming negative during follow-up) developed in 16 of the patients in group C during follow-up. Among these patients, 11 had rituximab (7 of for treatment of lymphoma, 2 for treatment of chronic myeloid leukemia and 2 for lupus), 2 had high-dose (x > 20 mg) glucocorticoids (used more than 4 weeks), 2 had infliximab (combined with AZA), and the last one had tocilizumab; however, despite these changes, we did not detect any HBVr cases (Table 1). The changes in anti-HBs titers in the subgroups are presented in Figure 2.

The treatment regimens for each group are presented in Table 3. They included 108 patients receiving rituximab, 111 patients receiving tumor necrosis factor inhibitors, 42 patients receiving high-dose glucocorticoids for more than 4 weeks and 71 patients receiving anthracycline containing regimens for antineoplastic therapy.

The characteristics of the anti-HBc (+) and anti-HBs (–) patients are presented in Table 4. Despite the high risk of HBVr estimated for these populations in previous studies,[9-11] we did not detect any HBVr cases, even among the 71, 66, 24, and 42 patients who received rituximab, TNF inhibitors, high-dose glucocorticoids and doxorubicin, respectively

DISCUSSION

The results of our prospective study indicate that the HBVr incidence may be overestimated in this study population. Treatment with high doses of glucocorticoids, rituximab and with TNF inhibitors increases the risk of HBVr.[9,10] Among antineoplastic agents, anthracyclines have been associated with the greatest increase in HBVr risk as they enhance HBV-DNA secretion.[11] However, we did not detect any HBVr, even in 108 patients receiving rituximab and 111 patient receiving TNF inhibitors in patients with resolved and past infection.

One explanation for our results may be the exclusion of HBV-DNA (+) patients. In previously reported HBVr case studies, the patients may have already carried mutant HBV variants before treatment initiation

Table 1. Patient Baseline Characteristics

	All Patients	Immunosuppressive Therapy (Group 1)	Antineoplastic Therapy (Group 2)	*P*
Patients (n)	512	266	246	.231
Age, years, median (range)	59.9 (20-76)	52.4 (20-76)	65.6 (36-73)	.035
Sex (male/female), n (%)	252 (49)/260 (51)	107 (40)/159 (60)	145 (58)/101 (42)	.041
Mean follow-up time, months, median (range)	24,8 (19-30)	25.3 (19-30)	24.1 (22-27)	.256
ALT, IU/L, mean ± SD	23 ± 3	22 ± 7	24 ± 10	.783
INR, mean ± SD	0.6 ± 0.1	0.6 ± 0.1	0.8 ± 0.2	.811
Anti-HBs (+) patients, n (%)	205 (40)	93 (45)	112 (55)	.246
Anti-HBs loss*, n (%)	16 ([7])	7 ([7])	13 ([11])	.005

Table 2. Analysis of Laboratory Results

	Initial Result	Third month	Sixth month	Ninth month	Twelfth month	Fifteenth month	*P*
ALT (IU/l), mean (SD)	23 (±9)	27 (±8)	28 (±9)	30 (±7)	30 (±8)	29 (±6)	.41
INR, mean (SD)	1 (±0.1)	0.96 (±0.3)	0.93 (±0.2)	0.88 (±0.4)	1 (±0.2)	1.1 (±0.3)	.62
Anti-HBs (mIU/mL), median (range)							
Group A (n = 37 patients)	>1000	>1000	>1000	>1000	>1000	>1000	Ø
Group B (n = 91 patients)	208 (110-957)	232 (102-939)	244 (105-991)	241 (108-964)	215 (102-928)	213 (124-952)	.25
Group C (n = 77 patients)	66 (11-94)	39 (12-79)	31 (0-78)	26 (0-72)	14 (0-68)	16 (0-53)	.002

because the pre-treatment levels of HBV-DNA were not examined in retrospective studies and case reports. Huang et al.[12] reported 7 cases of HBVr in 39 patients with lymphoma who received rituximab and cytotoxic chemotherapy during a mean follow-up of 18.5 months, but all of the patients had detectable HBV-DNA levels at baseline (median: 41.9 IU/mL, range 18-1140 IU/mL). Hsu et al.[13] prospectively studied 150 patients with resolved hepatitis B infection with lymphoma who received rituximab and cytotoxic chemotherapy. The authors measured the baseline HBV-DNA levels; despite undetectable HBV-DNA levels at baseline, 17 patients had HBVr. Notably, the assay used for HBV quantification had a low limit of detection (1000 copies/mL), and the second assay used for confirmation retrospectively had a lower limit of detection (300 copies/mL). The present study results revealed that the choice of an HBV-PCR test with a lower limit of detection (0 IU/mL) and the exclusion of all HBV-DNA (+) patients is very important to preventing HBVr. Therefore, we suggest that if we had used a test with a higher limit of detection, we would misdiagnose several patients as HBVr.

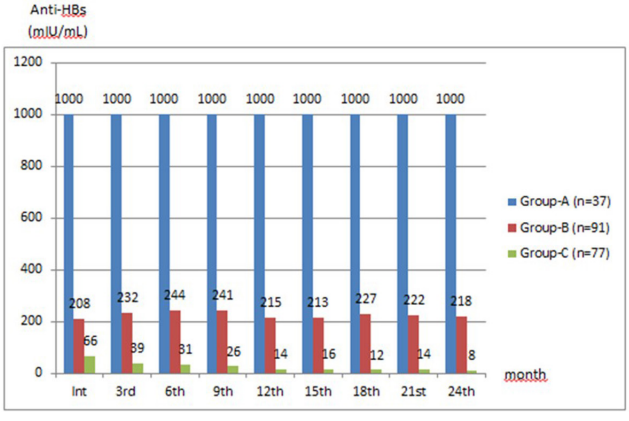

Figure 2. Changes in anti-HBs titers.

Another explanation is that the reported cases may have anti-HBc false positivity. Two reasons can explain the overestimation of the actual rate of anti-HBc positivity in clinical settings. First, anti-HBc tests can produce false-positive results. Despite the use of modern specific immunoassays, sampling and preparation errors may occur. Cross-reactivity with serum proteins and immunoglobulins secreted by HBV-sensitive T lymphocytes can also cause false positivity.[14] In a study comparing 2 different commercial kits, the false-positive rate was 66%, and the kit used for verification repeatedly detected 32% of samples as false positives.[15] Second, passive transfer of antibodies by blood transfusion can occur in clinical settings. In patients receiving antineoplastic therapy, especially in those with hematological malignancies, transfusion is almost always a routine part of the treatment. For example, in Europe, almost 30% of blood transfusions are performed in patients with hematological malignancies.[16] Furthermore, blood transfusion from anti-HBc (+) donors can also cause *de novo* HBV infection.[17]

As mentioned above, anti-HBc levels alone may not be a reliable marker for HBV exposure as the test can produce both false-positive and false-negative results. The initiation of antiviral prophylaxis based only on anti-HBc measurements may result in the unnecessary use of antiviral drugs and can increase the cost of treatment and the risk of emergence of mutant HBV variants. Therefore, we suggest routine pre-treatment testing for HBV-DNA in all candidates for ISDT regardless of anti-HBc status, especially in endemic areas.

Initiation of prophylactic antiviral treatment is an important issue because YMDD mutation is a major cause of HBVr, and one of the main reasons for the YMDD mutation is the use of nucleoside/nucleotide analogs.[18] Longer courses of prophylactic therapy increase

Table 3. Treatment Regimens

Drugs and Regimens	No. of Patients	Treatment Duration (Months, Mean)
Immunosuppressant		
Methotrexate	47	25.6
High-dose (x>20 mg) glucocorticoids (used more than 4 weeks)	42	18.2
Infliximab	55	24.4
Adalimumab	30	23.8
Abatacept	11	24.7
Azathiopurine	15	20.1
Rituximab	33	25.4
Etanercept	26	28.7
Tofacitinib	4	26.1
Omalizumab	3	21.1
Antineoplastic		
Paclitaxel + carboplatin	19	18.5
Rituximab + cyclophosphamide + doxorubicin + vincristine	51	25.7
Gemcitabine + cisplatin	8	24.5
Cyclophosphamide + doxorubicin	40	23.1
Fluorouracil + doxorubicin + cyclophosphamide	31	26.4
Rituximab + cyclophosphamide + fludarabine	24	24.3
Cisplatin + vinorelbine	3	24.8
Cisplatin + etoposide	3	20.5
5-Fluorouracil	35	26
Cetuximab	11	24
Bevacizumab	8	19,7
Others (temozolomide, sorafenib, dabrafenib, decitabine ...)	13	N/A

the risk of mutant HBV variants.[19] Furthermore, the occurrence of the YMDD mutation in HBV during lamivudine prophylaxis is also a major cause of HBVr in patients receiving TNF inhibitors.[20] Recently, Shirvani-Dastgerdi et al.[21] showed that during long-term application, antiviral drugs with a high genetic barrier to resistance can cause mutations in HBV polymerase and consequent resistance to antivirals.

Another explanation for our results can be the genotype of the virus. HBV genotypes differ ethno-geographically and determine the immune response of the patient as well as disease progression.[22] One can also speculate that there are no or very low levels of cccDNA in the liver of these patients or that this cccDNA is transcriptionally inactive.[23] It would be very interesting to examine cccDNA in these livers, but we did not perform liver biopsies. Finally, there may be some effective immunological control (antibodies and T-cell responses), regardless of the immunosuppressive therapies.[24]

There are some limitations to this study. First of all, the study is monocentric and observational. Second, compared with the cancer types in previous prospective studies (mostly lymphoma), those in this study are heterogeneous, and a relatively low number of patients received high-risk treatment regimens. Another limitation of the study is the relatively short follow-up period. Seto et al.[25] reported 19 cases of HBVr in a prospective study of lymphoma patients who received rituximab and cytotoxic chemotherapy and included 63 resolved hepatitis B infection cases over a 2-year period. Our median follow-up time was 24.3 months, but 21 patients had a follow-up of 19 months (range 19-30 months). It should be noted that none of these patients had rituximab. Another limitation is the interval for HBV-DNA

Table 4. Characteristics of Anti-HBc (+) and Anti-HBs (–) Patients

Disease	Treatment (No. of Patients)	Follow-Up (Months/Mean)
Inflammatory bowel disease		
Crohn's disease	Infliximab (13)	26.9
	Adalimumab (12)	28.1
	High-dose steroid (9)	20.3
	Azathioprine (8)	
Ulcerative colitis	Infliximab (13)	26.5
	Adalimumab (10)	24.8
	High-dose steroid (17)	25.5
	Azathioprine (4)	23.1
Rheumatic diseases		
Ankylosing spondylitis	Etanercept (20)	27.3
Rheumatoid arthritis	Rituximab (14)	26.3
	Methotrexate (35)	21.4
MCTD	Azathioprine (3)	23.3
Colon cancer	5-Fluorouracil (18)	24.7
Breast cancer	Fluorouracil + doxorubicin + cyclophosphamide (25)	21.4
	Doxorubicin + cyclophosphamide (34)	23.2
Lung cancer	Paclitaxel + carboplatin (7)	25.9
Ovarian cancer	Paclitaxel + carboplatin (5)	26.2
Endometrium cancer	Paclitaxel + carboplatin (3)	25.9
Hematologic malignancies		
NHL	R-CHOP (34)	24.8
CLL	Rituximab + cyclophosphamide + fludarabine (23)	25.1

MCTD, mixed connective tissue disease, NHL, non-Hodgkin lymphoma; CLL, chronic lymphoid leukemia.

measurements. In the studies as mentioned earlier, HBV-DNA measurements were performed each month, but we could only perform measurements trimonthly because of the national healthcare policy.

The HBVr incidence among anti-HBc (+)/anti-HBs (+) patients is reported to be approximately 4.3%,[4,] which is significantly lower than that in patients who are only anti-HBc (+). Several studies have suggested that anti-HBs may protect against reactivation and that changes in anti-HBs titers can be used to predict HBVr, even in patients receiving rituximab and TNF inhibitors.[6-8,18,26] In our subgroup analysis of anti-HBs (+) sera, the titers in group A and group B changed non-significantly, whereas those in group C showed a significant decrease. We also found that in group C, 16 of the patients had an anti-HBs loss. Among these patients, 11 had rituximab (7 of for treatment of lymphoma, 2 for treatment of chronic myeloid leukemia, and 2 for lupus), 2 had high-dose (x>20 mg) glucocorticoids (used more than 4 weeks), 2 had infliximab (combined with AZA), and the last one had tocilizumab; however, despite these changes, we did not detect any HBVr cases. Thus, we did not find an association between anti-HBs changes and HBVr even though a role for anti-HBs in HBVr has previously been suggested. The explanation for this result may be the low number of patients or the exclusion of HBV-DNA (+) patients.

Of note, the anti-HBs titers of 128 patients (62%) were moderate (>100 mIU/ml) or high (>1,000 mIU/ml). Thus, as many as 62% or more of the total population of anti-HBc patients could be presumed to be anti-HBs-positive overall. The seroprevalence of anti-HBs positivity was reported to be as high as 31.9% in Turkey. This apparent discrepancy is also another limitation of this study. Notably, none of these patients had been hyperimmunized

with a vaccine, and none of them had been given hepatitis B immunoglobulin preceding the initiation of ISDT. This might be due to the location of our center, in the southeastern region of Turkey, a highly endemic area that has also been cited as a risk factor for HBV infection by Tozun et al.[27] Most recently, the findings of Su et al.[28] support our suggestion. They found 76.6% anti-HBs seroprevalence in a large cohort of 1000 patients from Taiwan, another highly endemic area.

In conclusion, we did not detect any HBVr cases in this prospective study. The key points of this study are the following: (i) HBV-DNA should be assayed before the initiation of immunosuppressive therapy and antineoplastic therapy, (ii) monitoring should be performed every 3 months to discourage antiviral prophylaxis without evidence of HBVr due to the risk of developing mutant HBV variants and the increased cost. Finally, we suggest that changes in anti-HBs titers should not be a reason for the initiation of prophylactic antiviral therapy. Further comprehensive studies involving a larger number of patients are needed to confirm these suggestions.

Ethics Committee Approval: The study was reviewed and approved by the institutional review board of Cukurova University Medical Board and Ethics committee (Date: 13.01.2017 – Number: 60/69).

Informed Consent: All study participants, or their legal guardian, provided written consent prior to study enrollment.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Y.G.; Design – Y.G.; Supervision – Y.G.; Materials – Y.G., S.t.; Data Collection and/or Processing – S.T., D.A.T., İ.O.K., A.B.G.; Analysis and/or Interpretation – S.T.; Writing – Y.G., S.T.; Critical Reviews – Y.G.

Acknowledgments: We thank Macit Ilkit for providing invaluable comments on the manuscript.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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