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RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS WITH NEUROLOGICAL DISEASES RECEIVING ANTI-CD20 THERAPIES

NÖROLOJİK HASTALIĞI BULUNAN VE ANTİ-CD20 TEDAVİSİ ALAN HASTALARDA HEPATİT B VİRÜSÜ REAKTİVASYON RİSKİ

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ABSTRACT

Objective: Anti-CD20 therapies may increase the risk of hepatitis B virus (HBV) reactivation, particularly in patients with prior HBV exposure. Despite the recognized preventive measures for managing HBV reactivation, specific data regarding the safety of anti-CD20 therapies in this context remain limited. This retrospective study aims to evaluate the risk of HBV reactivation with prior HBV exposure among patients with neurological disorders treated with anti-CD20 therapies in a single-center cohort from Türkiye.

Methods: We reviewed the records of 580 patients who received at least one dose of anti-CD20 therapies between July 2018 and March 2024. Patients were stratified according to their HBV serostatus, with particular emphasis on anti-HBc positive individuals, who are considered at risk for HBV reactivation. Quantitative anti-HBs titers and rates of antiviral prophylaxis were also documented.

Results: Among the 71 patients who were anti-HBc positive (12.24% of the total cohort), anti-HBs positivity was detected in 50 patients (70.42%). The majority of patients received antiviral prophylaxis (78%), while 22% did not, reflecting some physicians' preference to withhold prophylaxis based on high anti-HBs titers. In contrast, all anti-HBs negative patients (n=21) were administered prophylaxis (100%). Importantly, no cases of HBV seroconversion or clinically meaningful HBV DNA elevation were observed in any subgroup, including anti-HBs positive patients who did not receive prophylaxis.

Conclusion: Our findings suggest that anti-CD20 therapy does not confer a detectable risk of HBV reactivation in anti-HBc positive patients, including those who are anti-HBs positive and did not receive prophylaxis.

Keywords: Anti-CD20 Therapies, HBV Reactivation, Multiple Sclerosis, Ocrelizumab, Antiviral Prophylaxis

ÖZ

Amaç: Anti-CD20 tedaviler, immün aracılı nörolojik hastalıkların tedavisinde yaygın olarak kullanılmaktadır. Ancak bu tedaviler, özellikle daha önce hepatit B virüsü (HBV) ile karşılaşmış hastalarda HBV reaktivasyon riskini artırabilir. HBV reaktivasyonunun önlenmesine yönelik çeşitli stratejiler mevcut olsa da, anti-CD20 tedavilerinin bu bağlamdaki güvenliğiyle ilgili özgül veriler sınırlıdır. Bu retrospektif çalışmada, Türkiye'de tek merkezde izlenen bir hasta kohortunda, nörolojik hastalıklar nedeniyle anti-CD20 tedavisi alan ve daha önce hepatit B virüsü ile karşılaşmış bireylerde HBV reaktivasyon riskini değerlendirmeyi amaçladık.

Yöntem: Temmuz 2018 ile Mart 2024 tarihleri arasında en az bir doz anti-CD20 tedavisi almış 580 hastanın verileri retrospektif olarak incelendi. Hastalar HBV serolojik durumlarına göre sınıflandırıldı; özellikle HBV reaktivasyon riski taşıyan anti-HBc pozitif bireyler değerlendirmeye alındı. Kantitatif anti-HBs titreleri ve antiviral profilaksi oranları belgelendi.

Bulgular: Anti-HBc pozitif olan 71 hastanın (toplam kohortun %12,24'ü) 50'sinde (%70,42) aynı zamanda anti-HBs pozitifliği mevcuttu. Hastaların çoğuna antiviral profilaksi uygulanmıştı (%78), ancak %22'lik bir gruba uygulanmamıştı; bu durum, bazı hekimlerin yüksek anti-HBs titresi temelinde profilaksiyi vermeme yönündeki tercihlerini yansıttı. Öte yandan, anti-HBs negatif olan tüm hastalara (n=21) profilaksi verilmişti (%100). Takip süresince, profilaksi almayan anti-HBs pozitif hastalar da dahil olmak üzere hiçbir alt grupta HBV serokonversiyonu veya klinik olarak anlamlı HBV DNA artışı gözlemlenmedi.

Sonuç: Bulgularımız, anti-CD20 tedavisinin anti-HBc pozitif hastalarda, anti-HBs pozitifliğinde profilaksi almayan bireylerde dahi belirgin bir HBV reaktivasyon riski oluşturmadığını göstermektedir.

Anahtar Kelimeler: Anti-CD20 tedavileri, HBV reaktivasyonu, Multiple Skleroz, Okrelizumab, Antiviral Profilaksi

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Introduction

Hepatitis B virus (HBV) reactivation can occur in patients treated with immunosuppressive medications. Fundamentally, risk stratification for HBV reactivation depends on HBV serology indicating past or chronic HBV infection, the host immune response, and the type of immunosuppression.[1–3] Although it is well-recognized that this is a preventable consequence of hepatic decompensation or acute liver failure, there are still unclear aspects of preventive care.[2]

Recent advances in understanding the pathophysiology of immune-mediated neurological disorders have led to an increased use of B cell strategies, particularly through anti-CD20 therapies. These therapies, such as ocrelizumab, ofatumumab, and rituximab are commercially available in Türkiye and play a considerable role in our practice for immune-mediated neurological disorders. Current guidelines from major societies recommend screening for HBV in all patients planning to receive anti-CD20 therapies. Given the potentially serious outcomes of HBV reactivation, patients who are supposed to be treated with anti-CD20 therapies with either HBsAg positivity or anti-HBc positivity (regardless of HBsAg status) are considered at elevated risk.[2–4]

However, due to limited real-world data—particularly concerning ocrelizumab—existing guidelines primarily base their recommendations on rituximab and, to a lesser extent, ofatumumab.

Based on the 2010 epidemiological study, which revealed a high frequency of HBV infection in Türkiye[5], this article is specifically tailored to explore the impact of anti-CD20 therapy on HBV courses in neurology practice. We focus specifically on patients who are anti-HBc positive to explore the relationship between anti-HBs status, quantitative antibody titers, prophylaxis implementation, and the occurrence of seroconversion. Our findings will be considered within the context of existing literature to provide clinically relevant insights.

Methods

Sample collection

We conducted a retrospective study to analyze the data from patients (n=580) who received at least one dose of anti-CD20 therapies (ocrelizumab, n=469; ofatumumab, n=12; rituximab, n=99) at our neuroimmunology clinic of Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital between July 2018 and March 2024. The study includes baseline and six-month follow-up serological patterns for HBsAg, Anti-HBs, Anti-HBc IgM, Anti-HBc Ig G, HBV DNA (if available), liver enzymes, and antiviral prophylaxis. Basic demography for age, sex, and indications for anti-CD20 therapy are also recorded. Data was obtained from the hospital information management system and the personal health record system of the Turkish Ministry of Health.

Since the risk of HBV reactivation primarily affects HBsAg carriers and anti-HBc positive individuals undergoing immunosuppressive therapy, seroconversion analyses were specifically limited to these subgroups, which represent the population at virological risk.[2] Baseline HBV status was categorized into three groups: anti-HBc positive, anti-HBs positive, HbsAg negative; anti-HBc positive, anti-HBs negative, HBsAg negative, and anti-HBc positive, anti-HBs negative, and HbsAg positive for each treatment arm. This classification was created in accordance with the recommended guidelines for a risk-based approach. Use of prophylaxis and antiviral medication preference were also recorded for each category and treatment arm.

Serological follow-up data, repeated every 3-6 months, were reviewed for seroconversion*.

*Seroconversion analysis is based on the definition of the American Association for the Study of Liver Diseases (AASLD).[3]

The criteria for HBV reactivation are defined as the following:

- For HBsAg positive and anti-HBc positive patients: HBV DNA level that increases 100-fold (2-log) or greater compared to the baseline level; HBV DNA level of 1,000 IU/mL or greater in a person with a previously undetectable level (given that HBV-DNA levels fluctuate); or HBV DNA level of 10,000 IU/mL or greater if the baseline level is not available.
- For HBsAg negative and anti-HBc positive patients: detectable HBV DNA or reappearance of HBsAg.

Data Analysis

All statistical analyses were performed using GraphPad Software. Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. Continuous variables were presented as mean ± standard deviation (SD) for normally distributed data or as median with interquartile range (IQR) for non-normally distributed data. Categorical variables were expressed as counts and percentages. Comparisons of anti-HBs titers between patients who received antiviral prophylaxis and those who did not were made using the Mann–Whitney U test due to the non-normal distribution of the data. Chi-square or Fisher's exact test was used to compare categorical variables. A two-tailed p-value of <0.05 was considered statistically significant.

Results

A total of 580 patients treated with anti-CD20 therapies (ocrelizumab n=469; rituximab, n=99; ofatumumab, n=12) are retrospectively analyzed. HBV screening results according to methodological category at baseline are given in Table 1. At baseline, anti-HBc positivity was identified in 71 out of 580 patients (12.24%). Specifically, 63 patients (15.57%) in the ocrelizumab group and 8 patients (8.08%) in the rituximab group tested positive for anti-HBc. However, this difference was not statistically significant (p=0.195), indicating a comparable

distribution of prior HBV exposure between the two treatment arms. As shown in Table 1, anti-HBc positive patients—particularly those with or without anti-HBs or with HBsAg positivity—represent the virologically at-risk population for HBV reactivation. Accordingly, analyses related to seroconversion and antiviral prophylaxis were primarily concentrated on these subgroups. Since none of the 12 patients receiving ofatumumab were anti-HBc positive, this arm was excluded from HBV risk analysis.

HBsAg positivity was 1.21% (n=7) across all treatment arms, with a rate of 9.86% in the anti-HBc positive population. The mean age of the 71 patients showing anti-HBc positivity was 50.05 +/- 9.13 years, with 40 (56.4%) of them being female. The median duration of diagnosis that necessitates anti-CD20 therapy was 12 years (0.75-42 years). The patients were receiving a median of 4 (1-13) cycles of anti-CD20 therapy. Table 2 provides a detailed summary of the basic demographic data of patients with anti-HBc positivity, along with the treatment arms of ocrelizumab and rituximab. Patients in the ocrelizumab group were older on average (50.72 ± 8.93 years) compared to the rituximab group (44.75 ± 9.56 years). Both groups had a female predominance, consistent with the gender distribution typically seen in immune-mediated neurological diseases such as Multiple Sclerosis (MS). Ocrelizumab was used exclusively in MS patients (100%). In comparison, the rituximab group included a heterogeneous mix: relapsing optic neuritis (ON) (12.5%), MS (25%), Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD) (25%), and Neuromyelitis Optica (NMO) (37.5%) reflecting a broader off-label use of rituximab in various neuroimmunological conditions.

When all the groups were evaluated, the prophylaxis rate was 84.51%. Among the anti-HBs positive group, the prophylaxis rate was 78%, while it was 100% in the anti-HBs negative side. Prophylaxis rates and preferred treatments according to serological status are shown in Table 3. All patients who were anti-HBs positive and did not receive prophylaxis (n=11; 22%) were those who received ocrelizumab (Anti-CD20 therapy cycles, median (IQR) 3 (2-6). The median antibody titer of patients who did not receive prophylaxis was 1000 IU/L (IQR: 340–1000), which was higher than that of patients who received prophylaxis (462 IU/L; IQR: 88–758.5), although the difference did not reach statistical significance (p= 0.064).

Two patients who were HBsAg and anti-HBc positive and were under prophylaxis showed detectable HBV DNA levels during follow-up (18 and 40 IU/mL, respectively). However, these levels did not meet the AASLD seroconversion criteria, and there was no deterioration in liver functions. No other patients were showing detectable HBV DNA levels, suggesting seroconversion.

Table 1. HBV screening results according to methodological category at baseline

HBV screening	**Anti-HBc positive**			**Anti-HBc negative**
	Anti-HBs positive HBsAg negative	**Anti-HBs negative HBsAg negative**	**Anti-HBs negative HBsAg positive**	
Rituximab **(n=99)**	5	2	1	91
Ocrelizumab **(n=469)**	45	12	6	406
Ofatumumab* **(n=12)**	0	0	0	12
Total (n)	50	14	7	509

*Ofatumumab-treated patients were included for cohort representation but not analyzed for HBV reactivation risk due to absence of anti-HBc positivity in this group.

Table 2. Detailed summary of the basic demographic data of patients with anti-Hbc positivity, along with the treatment arms of ocrelizumab and rituximab

Patient characteristics	**Anti-HBc positive patients in ocrelizumab arm (n=63)**	**Anti-HBc positive patients in rituximab arm (n=8)**
Age, mean SD	50.72 +/-8.93	44.75+/-9.56
Sex %	55.55% female 44.45% male	62.5% female 37.5% male
Duration of diseases (years), median (IQR)	12 (1-42)	2 (0.75-26)
Disease distribution	MS 100%	Relapsing ON: 12.5% MS: 25% MOGAD: 25% NMO: 37.5%
Anti-CD20 therapy cycles, median (IQR)	4 (1-13)	2 (1-11)

MS; Multiple Sclerosis, ON; Optik Neuritis, MOGAD; Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease, NMO; Neuromiyelitis Optica

Three patients under prophylaxis with initial serum anti-HBs positivity tested negative after receiving ocrelizumab infusions during follow-up. Their antibody titers were low at baseline (13, 14, and 17 IU/L, respectively). The total number of anti-CD20 therapy cycles leading to anti-HBs loss was 4, 1, and 1 cycles, respectively.

After the infusions, it's worth noting that one patient in the ocrelizumab group experienced a loss of anti-HBc after the second infusion, while three patients in the rituximab group experienced anti-HBc loss after their first infusions.

Considering all sera, seroconversion to HBsAg positivity was not observed in any patient, regardless of whether they were under prophylaxis or not.

Table 3. Prophylaxis rates and preferred treatments according to serological status

		Anti-HBc positive	
	Anti-HBs positive HBsAg negative (n=50)	**Anti-HBs negative HBsAg negative (n=14)**	**Anti-HBs negative HBsAg positive (n=7)**
Prophylaxis in rituximab (100%)	5 of 5 (1T* 4E**)	2 of 2 (2E*)	1 of 1 (1E*)
Prophylaxis in ocrelizumab (82.54%)	34 of 45 (9T** 25E*)	12 of 12 (2T** 10E*)	6 of 6 (6E*)
Total prophylaxis (84.51%)	39 (78%)	14 (100%)	7 (%100)
Seroconversion	0	0	0

*(E): Entecavir; **(T): Tenofovir

Discussion

This study provides real-world data on the management of patients with prior HBV exposure (anti-HBc positive) undergoing anti-CD20 therapies for neurological diseases, focusing on prophylaxis decisions, anti-HBs antibody levels, and seroconversion outcomes. The scarcity of data on HBV reactivation risk, particularly with ocrelizumab treatment, highlights the potential of our study to inform future research in this field.

In a study conducted by the Turkish Association for the Study of the Liver between 2009 and 2010, 4% of adults tested positive for HBsAg, and 30.6% tested positive for anti-HBc, indicating a high prevalence of hepatitis in Turkey.[5] Our anti-HBc positivity was 12.24%, while the HBsAg positivity was 1.21% across all treatment arms. The decrease in positivity rates may be attributed to the implementation of more comprehensive vaccination policies over the years.

Our results demonstrate that none of the patients experienced seroconversion to HBsAg positivity while previously negative or showing significant HBV DNA levels that met the reactivation criteria across all serological subgroups. Additionally, among patients treated with ocrelizumab, those who did not receive prophylaxis (22%) due to their anti-HBs positivity also did not show seroconversion. Generally, a person remains antibody-positive for life following HBV infection. However, under immunosuppressive conditions, both anti-HBc and anti-HBs antibodies may become negative.[6,7] In our sera, we observed a loss of anti-HBs in three out of 50 patients (6%), particularly those with low baseline antibody titers. This finding aligns with data indicating that low antibody levels are a risk factor for anti-HBs loss in individuals undergoing immunosuppression.[8] Additionally, four out of 71 patients (5.63%) experienced a loss of anti-HBc. However, it's important to note that neither of these losses appeared to be a risk factor for HBV reactivation.

To emphasize, the prophylaxis rate was 78% in the anti-HBs positive group and 100% in the anti-HBs negative group. The 22% loss of prophylaxis rate in the anti-HBs positive group can be attributed to the physician's discretion. In real-world clinical practice, the administration of prophylaxis to patients who are anti-HBs positive is inconsistent due to a lack of definitive, universally accepted guidelines. In our study, prophylaxis was not given according to a standardized protocol; instead, it was determined at the physician's discretion. Notably, some clinicians chose to start prophylaxis even for patients with high anti-HBs titers, while others decided against it in similar cases. This variability in clinical practice may have introduced a selection bias, potentially affecting the distribution of antibody titers between the prophylaxis and non-prophylaxis groups. Although the median anti-HBs titer was numerically higher in the non-prophylaxis group, the difference was not statistically significant. These findings highlight the need for more specific guidelines for this subgroup.[7,9] Although current evidence is insufficient to recommend anti-HBs titers as a standalone criterion for prophylaxis decisions, our findings suggest that the decision to administer or withhold prophylaxis did not affect clinical outcomes in our cohort.

Our findings are in line with those of a Spanish prospective study, which demonstrated that anti-CD20 monotherapy (rituximab, n = 22; ocrelizumab, n = 6) did not pose a detectable risk of HBV reactivation in HBsAg-negative/anti-HBc-positive patients with NMOSD and MS, even in the absence of antiviral prophylaxis.[10] Similarly, data from an Italian cohort reported no cases of HBV reactivation, despite the fact that 53% of patients with anti-HBs levels below 100 mIU/mL and 30% with levels above 100 mIU/mL did not receive either prophylaxis or active monitoring.[11] A recent study from our region presents findings that contrast with previous results, including our own. Among three patients undergoing ocrelizumab therapy who experienced HBV reactivation, two out of seven (28.6%) had not received

antiviral prophylaxis, while one patient failed to adhere to the prescribed prophylaxis regimen.[12]

We achieved significant results in our study, though it is important to recognize some limitations. First, as a retrospective observational study, it has certain constraints. While this research represents the largest cohort of patients treated with ocrelizumab in the available literature concerning hepatitis seroconversion, the sample size in the rituximab treatment group was comparatively small. Additionally, we lacked data on vaccine-induced HBV immunity. Addressing these limitations in future research could provide even more comprehensive insights.

In conclusion, our research suggests that monotherapy with anti-CD20 is not associated with a detectable risk of HBV reactivation in our neuroimmunological practice. Moreover, the absence of antiviral prophylaxis in patients with anti-HBs positivity in the ocrelizumab group was also not linked to a detectable risk of HBV reactivation. However, prospective studies involving a larger number of patients and extended follow-up periods are needed to confirm these findings and clarify the existing literature.

Ethical Approval

The study has received ethical committee approval with the number E-46059653-050.99-225242407 (25.09.2023) from the Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital ethical committee.

Conflict of Interest

The author declares no conflicts interests.

Author Contributions

SD, IGD: Concept-Design; IGD, FD, DCT: Data Collection and/or Processing; SD, IGD: Analysis and/or Interpretation; IGD, FY, DCT: Literature Review; IGD: Writer; SD, DCT: Critical Review

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None

Data Availability:

The datasets that support the findings of this study are available from the corresponding author upon reasonable request.

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