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Risk of HBV reactivation and loss of anti-HBc in anti-CD20 treated multiple sclerosis patients: a six-year observational cohort study

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Introduction

- Hepatitis B virus (HBV) reactivation during immunosuppressive/immunomodulatory therapy is still a hot topic worldwide [1].
- HBsAg-positive pwMS and pwMS with serological evidence of previous exposure to resolved HBV (HBsAg negative/HBcAb positive) are at risk of reactivation which may lead to transient or persistent discontinuation of disease-modifying therapy (DMTs), and thus having a negative impact on the overall survival rate of patients [2].
- The aim of our study was initially to stratify and monitor HBV reactivation risk in people with multiple sclerosis (pwMS) treated with anti-CD20.

Methods

- At the Neuroinfectious Unit, pwMS were longitudinally evaluated for infectious risk before starting, switching, or during disease-modifying therapies (DMT). HBsAg, anti-HBs, and anti-HBc (IgM and IgG) were periodically assayed.
- In pwMS with serostatus suggestive of previous HBV exposure, a watch-and-wait approach by periodic HBV-DNA assessment each six-months (Figure 1).
- Liver function tests, complete blood count were also monitored during the follow-up.

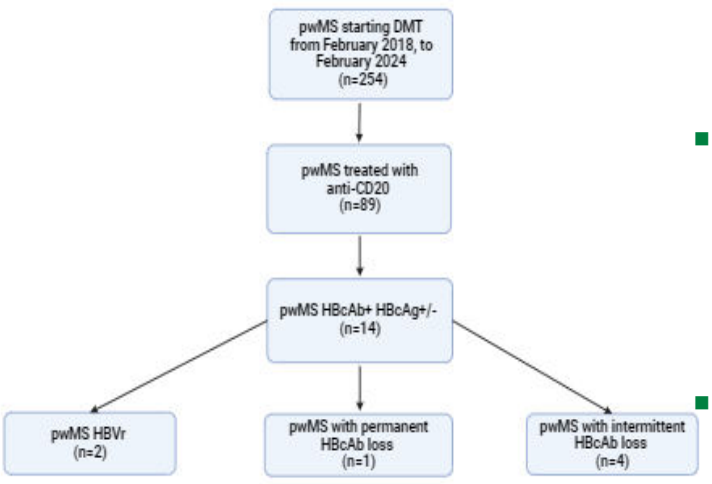

Figure 1. Study population.
pwMS-HBVr: patient with multiple sclerosis who showed HBV reactivation.

Results

- A six-year observational study was carried out and 254 pwMS (154 females/100 males, median age [IQR] 51 [42-60] years) were enrolled.
- Overall, 89/254 (35%) pwMS were treated with anti-CD20 and among them, 14/89 (16%) (7 females/7 males, median age [IQR] 55 [51-65] years) were HBcAb+ HBsAg+/- (Table 1, Figure1).

	pwMS HBcAb+/HBsAg+/- (n=14)
female/male	7/7
Age, median [IQR] years	55 [51-65]
EDSS score, median [IQR]	6 [4-6]
years of disease, median [IQR]	11 [7-22]
Previous treatment	
Alemtuzumab	0
Azathioprine	1
Cladribine	0
Daclizumab	0
dimethyl fumarate	5
Fingolimod	1
glatiramer acetate	0
IFN-β	1
Mycophenolate	0
Natalizumab	0
Ocrelizumab	0
Ozanimod	0
Rituximab	1
Siponimod	0
Teriflunomide	0
None	5
Clinical findings at baseline	
AST (UI/mL)	18 [13.8 - 23.8]
ALT (UI/mL)	16.5 [11 - 27.3]
Total bilirubin (mg/dL)	0.4 [0,3-0.7]
Direct Bilirubin (mg/dL)	0.15 [0.098 - 0.24]
HBsAb title (mUI/ml)	13.5 [2.57 - 930.5]
Leucocytes (x10^9/L)	5.4 [5.3 - 7.8]
Lymphocytes (x10^9/L)	1.4 [1.2 - 3.2]
Neutrophils (x10^9/L)	3.5 [3.2 - 4]
Monocytes (x10^9/L)	0.4 [0.34 - 0.7]

Table 1. Baseline characteristics of pwMS HBcAb+/HBsAg+/- treated with anto-CD20

- Through the initial assessment of infectious status, 2/14 (14%) HBcAb+ HBsAg+ pwMS (2 males, median age [IQR] of 63 [60-66] years) with detectable HBV-DNA were identified and were therefore treated with antiviral before the start of anti-CD20 treatment.
- On the other hand, during the follow-up, two patients under anti-CD20 treatment, showed an HBV-DNA detection in blood samples.
- Patient 1 showed for three times HBV-DNA detection in blood samples: at 12 months (HBV-DNA: 40,8 UI/mL), at 54 months (HBV-DNA: 61.2 UI/mL) and at 60 months after starting DMT (HBV-DNA: 2881 IU/mL9 (Figure 2).
- Patient 2 who initially had undetectable HBV-DNA levels, showed an HBV reactivation one month after starting anti-CD20 treatment. Serological tests showed increased HBV-DNA levels (41 UI/mL), the presence of anti-HBs and anti-HBc respectively, while HBsAg was negative (Figure 2).

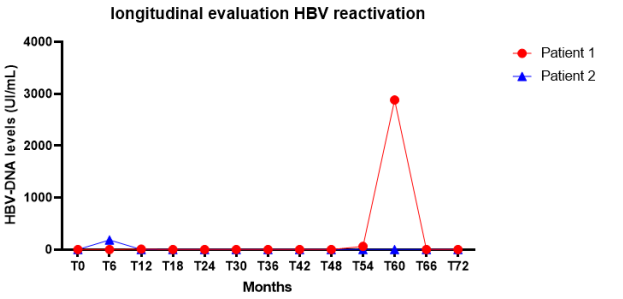

Figure 2. Longitudinal evaluation HBV reactivation in two pwMS under anti-CD20 treatment.

- On the other hand, during anti-CD20 therapy, 4/14 (29%) pwMS (1 female / 3 males, median age [IQR] of 64 [45-69] years) showed a transient loss of HBcAb after a median (IQR) of 6 (5-6) years. Conversely, one pwMS showed a permanent loss of the anti-HBc antibodies positivity, 36 months after starting DMT and to date the following serological profile: HBsAg-, HBsAb-, and undetectable HBV-DNA levels.
- Besides that, no correlation was found between anti-HBc antibody titers and the assessment of liver enzymes (AST, ALT, total and direct bilirubin).

Conclusion

- Although there is no doubt, that anti-HBc is an important and excellent screening marker to identify patients with ongoing or previous HBV infection [3], our data showed that during the anti-CD20 therapy, it is possible to observe a loss of HBcAb probably due to the immunomodulatory action of these drugs.
- Infectious disease screening in pwMS candidates for DMT helps to mitigate infectious risk. During DMT, a regular assessment of infectious risk allows to avoid discontinuing MS therapy and guarantees a higher degree of safety. Preventive prophylaxis and monitoring strategies in selected pwMS allowed anti-CD20 treatment to continue safely.

References

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