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Effect of the Number of Vaccine Doses Before Starting Anti-CD20 Therapy on Seroprotection Rates Against Hepatitis B Virus in People With MS

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Abstract

Background and Objectives

Hepatitis B vaccination (HBV) requires 6 months to complete and is recommended for patients with multiple sclerosis (PWMS), particularly those who are candidates for anti-CD20 therapy. However, limited data exist on HBV immunogenicity in PWMS receiving disease-modifying therapies (DMTs) and the impact of starting anti-CD20 therapy during immunization. We aimed to evaluate HBV immunogenicity in PWMS starting anti-CD20 therapy during vaccination, focusing on the number of doses received before anti-CD20 initiation.

Methods

We conducted a retrospective analysis of a prospective cohort of adult PWMS at a single center in Spain, from April 2015 to May 2023. Eligible participants completed a 4-dose HBV course and underwent postvaccination serologic testing. We assess seroprotection rates (SRs), defined as the percentage of patients achieving anti-hepatitis B surface antibody titers ≥10 IU/L, focusing on those who switched to anti-CD20 therapy during vaccination, based on doses received before starting anti-CD20 and type of DMT at vaccination start. A multivariate generalized linear model (GLM) was used to identify factors associated with higher seroconversion.

Results

A total of 289 PWMS (median [interquartile range (IQR)] age, 47.7 [42.8–54.4] years; 65.7% female; median [IQR] disease duration, 14.8 [6.7–21.2] years) were included. SRs progressively declined with fewer doses before anti-CD20 initiation, from 92.8% (95% CI 87.1–96.5) for 4 doses to 24.0% (95% CI 9.4–45.1) for 1 dose. Patients transitioning from sphingosine 1-phosphate (S1P) modulators showed the lowest SR at 25.0% (95% CI 7.3–52.4). The multivariate GLM confirmed these findings, with 3 doses (SR ratio 3.23 [95% CI 1.68–6.23]; $p = 0.0005$) or 4 doses (SR ratio 3.76 [95% CI 1.96–7.24]; $p < 0.0001$) before anti-CD20 therapy significantly associated with higher SRs, while starting S1P modulators at vaccination onset was significantly associated with lower SRs (SR ratio 0.42 [95% CI 0.23–0.78]; $p = 0.0058$). Female sex (SR ratio 1.15 [95% CI 1.01–1.32]; $p = 0.0389$) and younger age (SR ratio 0.90 [95% CI 0.83–0.97]; $p = 0.0036$) were also significantly associated with higher SRs.

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Glossary

anti-HBs = anti-hepatitis B surface antibodies; **COVID-19** = coronavirus disease 2019; **DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **GLM** = generalized linear regression model; **IQR** = interquartile range; **OCR** = ocrelizumab; **OMB** = ofatumumab; **PWMS** = patients with multiple sclerosis; **RTX** = rituximab; **S1P** = sphingosine 1-phosphate; **HUVH** = Vall d'Hebron University Hospital.

Discussion

Initiating anti-CD20 therapy during HBV negatively affects SRs, with a direct correlation with the number of doses received before anti-CD20 initiation. Early planning and execution of required vaccinations are crucial in managing PWMS.

Classification of Evidence

This study provides Class III evidence that HBV during initiation of anti-CD20 therapy is less effective in establishing seroprotection to hepatitis B than in patients in whom HBV is completed before initiation of anti-CD20 therapy.

Introduction

Immunization is a pivotal component of the risk management strategies in patients with multiple sclerosis (PWMS).[1-3] Yet, its effectiveness may be compromised because of exposure to disease-modifying therapies (DMTs) that can potentially blunt vaccine responses. Highly effective DMTs, notably sphingosine 1-phosphate (S1P) modulators and anti-CD20 therapies, have demonstrated a reduction in immune responses to commonly administered vaccines, including influenza,[4] pneumococcal,[5] and, more recently, coronavirus disease 2019 (COVID-19).[6] However, limited data are available for vaccines with longer schedules, such as hepatitis B.[7]

The hepatitis B vaccination (HBV) is a recombinant non-infectious subunit viral vaccine recommended for PWMS who do not have immunity against hepatitis B, especially those with risk factors,[8] such as patients undergoing anti-CD20 therapy.[9-12] This is particularly important because there have been reports of severe and fatal fulminant hepatitis in patients with de novo hepatitis B infection while receiving anti-CD20 therapies.[13]

Recommended HBV regimens involve 4 doses over an usual 6-month period (administered at 0, 1, 2, and 6–12 months).[14] HBV has an accepted protection correlate based on the level of anti-hepatitis B surface antibodies (anti-HBs), and patients are considered seroprotected if postvaccination titers are over 10 IU/L a threshold[15] because they strongly correlate with the effective prevention of both acute hepatitis B infection and chronic liver disease.[14,15]

Current guidelines recommend completing vaccination with inactivated vaccines at least 2 weeks before initiating treatment to ensure a protective response.[9,10,16] However, this recommendation poses challenges, particularly for highly active patients, because it may entail a prolonged delay in treatment onset in the case of vaccines with multiple-dose schedules, such as HBV.

This study evaluated the effectiveness of HBV immunization in PWMS who initiate anti-CD20 therapy during the vaccination series, specifically assessing how the number of HBV doses received before anti-CD20 initiation influences seroprotection rates (SRs).

Methods

Design and Study Population

This study was conducted within the ongoing prospective cohort established in 1995 at the Multiple Sclerosis Centre of Catalonia (Cemcat), as detailed in previous publications.[17-19] Starting in 2015, PWMS at Cemcat underwent routine referral to the Preventive Medicine Department at Vall d'Hebron University Hospital (HUVH) for baseline serostatus evaluation and immunization in accordance with official guidelines.

For the purposes of this study, we included adult MS candidates for HBV because of risk factors[8] and/or anticipated initiation of anti-CD20 treatment who met the following criteria: (1) completion of a 4-dose vaccination schedule for HBV (administered at 0, 1, 2, and 6–12 months), within a maximum span of 14 months between the first and last dose, using either of the 2 recommended formulations (VHB 20 μg adjuvanted or VHB 40 μg)[20]; (2) availability of a postvaccination serologic test measuring anti-HBs, performed between 1 and 3 months after vaccination; and (3) not receiving anti-CD20 therapy before the beginning of the vaccination. The first vaccine dose was administered between April 30, 2015, and April 30, 2022. Patients were followed up until May 2023 to confirm the completion of the vaccination course and postvaccination serology.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the clinical research ethics committee at HUVH and followed the Strengthening the

Reporting of Observational Studies in Epidemiology reporting guideline. Databases have been developed according to national and international standards on ethical aspects (Declaration of Helsinki[21] and Declaration of Tokyo[22]). All patients signed written informed consent according to the Declaration of Helsinki.[21]

Study Variables, Sources of Information, and Outcomes

We collected data on demographics, clinical information, vaccination history, and serologic test results. Demographic data (such as sex and age) and clinical information had been prospectively recorded in the Cemcat cohort database. We extracted the date of the first clinical demyelinating episode, disability status according to the Expanded Disability Status Scale (EDSS) at the time of vaccination, and information about the treatment received at the beginning and throughout the vaccination course (including DMT start and stop dates) from the Cemcat cohort database. Vaccination and serology information was retrospectively collected from electronic health records, including vaccine type, date, and dose, as well as the date of serology and anti-HB titers. Serologic tests were performed using the Atellica IM anti-hepatitis B surface antigen 2.[23]

Statistical Analysis

To assess the effect of DMTs on vaccine responses, we established drug exposure for each DMT at the time of each vaccination dose according to the drugs' mechanism of actions.[10] Next, treatments were reclassified into 2 types based on anticipated interference with vaccination responses, according to current evidence: (1) high vaccine interference (anti-CD20 monoclonal antibodies and S1P modulators) and (2) low vaccine interference (first-line injectables [interferon-β and glatiramer acetate], first-line orals [dimethyl fumarate and teriflunomide], and natalizumab). In addition, we defined 2 groups of patients based on whether there was a change to "anti-CD20" therapy during the course of vaccination.

A descriptive analysis was conducted, assessing absolute frequencies and percentages for qualitative variables and medians and interquartile ranges (IQRs) for quantitative variables, because of the non-normal distribution of data. To compare demographic and clinical characteristics at the time of vaccination between groups, χ^2 tests were used for qualitative variables and Student t or Mann-Whitney U tests were applied for quantitative variables, as appropriate.

We assessed the global SR, including 95% CIs calculated using the exact Clopper-Pearson method. SR was defined as the percentage of patients achieving an adequate humoral response in the postvaccination serostatus evaluation, based on the accepted cutoff levels for HBV (anti-HBs, 10 IU/L).[15] SRs were calculated according to (1) type of DMT at the start course of vaccination, (2) start of anti-CD20 therapy during the course of vaccination, and (3) the number of vaccine doses received before the start of anti-CD20. Furthermore, postvaccination anti-HB median titers in seroprotected patients were evaluated according to the number of vaccine doses before anti-CD20 therapy.

A bivariate analysis was conducted to study the association between anti-HB seropositivity and the rest of the demographic, clinical, treatment, and vaccination variables. The strength of association of the bivariate analysis was measured through proportion ratios, whose 95% CIs were estimated using Poisson regression models with robust variance and the null hypothesis was tested bilaterally using the Wald test. A multivariate generalized linear regression model (GLM) was explored, using methodology analogous to that described previously. For the inclusion of variables in the adjusted model, those with marginal statistical significance in the bivariate analysis were considered ($p < 0.10$), as well as their possible association with the outcome variable, according to the literature. Nested models and interactions were evaluated using the Wald test with sandwich covariance, applying a type I error threshold of 5%. The statistical analysis was conducted using version 4.3.2 of the R statistical software.

Data Availability

Anonymized patient data that support the findings of this study are available on reasonable request from the corresponding author. These data are not publicly available because of privacy and ethical restrictions but can be shared with qualified investigators for research purposes.

Results

A total of 977 PWMS were referred for vaccination evaluation to the Preventive Medicine Department in the inclusion period. Among them, 648 were identified as not having immunity against hepatitis B and 348 completed a full immunization schedule in our center using adjuvanted or high-load vaccines during the study period. Of these, 59 were excluded because of not fulfilling inclusion criteria (eFigure 1). A final cohort of 289 PWMS (median [IQR] age, 47.7 [42.8–54.4] years; 65.7% female; median [IQR] disease duration; 14.8 [6.4–21.2] years; median [IQR] EDSS score 3.5 [2.0–5.5]) met our inclusion criteria and were included in the analysis. At the onset of vaccination, 140 (48.4%) were not receiving any DMT. The remaining patients were on DMT, with most (19.4%) using first-line injectables, followed by natalizumab (12.8%) (Table 1). During the vaccination course, 151 PWMS (52.2%) switched to anti-CD20 therapy while 138 (47.8%) did not. Figure 1 illustrates the dynamic changes in DMT types throughout the vaccination period. Of the 138 patients who did not switch to anti-CD20 during vaccination, 47 (34%) ultimately changed after completing the full 4-dose vaccination scheme, with a median (IQR) time of 321 (102.5–723.0) days.

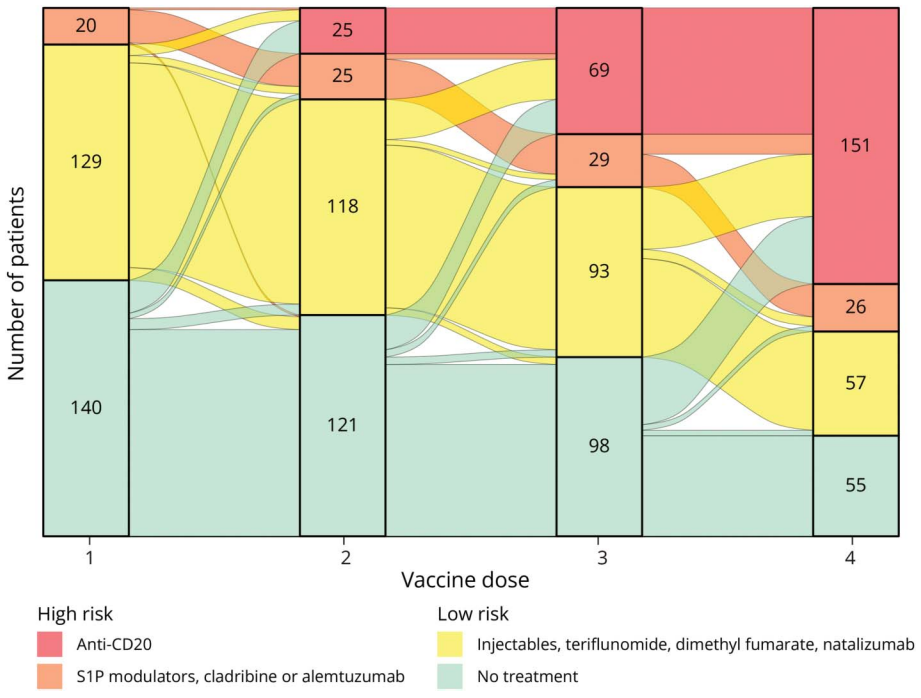
Patients who started anti-CD20 therapy during the vaccination course, compared with those who did not, were older (median [IQR] age, 49.0 [43.5–55.1] vs 46.5 [41.4–54.0]

Table 1 Demographic and Clinical Characteristics at the Time of First Dose of the Hepatitis B Vaccine According to Change to Anti-CD20 During the Vaccination

Characteristics	Overall (N = 289)	No change to anti-CD20 (N = 138)	Change to anti-CD20 (N = 151)	*p* Value[a]
Sex, women, n (%)	190 (65.7)	95 (68.8)	95 (62.9)	0.3
Age, y, median (IQR)	47.7 (42.8–54.4)	46.5 (41.4–54.0)	49.0 (43.5–55.1)	0.032
Disease duration, y, median (IQR)	14.8 (6.4–21.2)	13.3 (4.6–20.7)	15.7 (8.1–22.1)	0.028
EDSS score, median (IQR)	3.5 (2.0–5.5)	2.5 (1.5–4.0)	4.0 (3.0–6.0)	<0.001
DMT, n (%)				0.002
No treatment	140 (48.4)	69 (50.0)	71 (47.0)	
First-line injectables	56 (19.4)	26 (18.8)	30 (19.9)	
First-line orals	36 (12.5)	26 (18.8)	10 (6.6)	
Natalizumab	37 (12.8)	13 (9.4)	24 (15.9)	
S1P modulators	20 (6.9)	4 (2.9)	16 (10.6)	
Vaccination formulation, n (%)				<0.001
HBV 20 µg adjuvanted	108 (37.4)	66 (47.8)	42 (27.8)	
HBV 40 µg	128 (44.3)	55 (39.9)	73 (48.3)	
Mixed	53 (18.3)	17 (12.3)	36 (23.8)	

Abbreviations: DMT = disease modifying therapy; EDSS = Expanded Disability Status Scale; HBV = hepatitis B vaccine; IQR = interquartile range; S1P = sphingosine-1-phosphate.
[a] Pearson χ^2 test; Wilcoxon rank-sum test; Fisher exact test.

Figure 1 Dynamic Changes in Disease-Modifying Therapies Throughout the Vaccination Period According to Type of Disease-Modifying Therapy and Their Impact in Vaccination



S1P = sphingosine-1-phosphate.

years; $p = 0.032$); exhibited a longer disease duration (median [IQR] 15.7 [8.1–22.1] vs 13.2 [4.6–20.7] years; $p = 0.028$); had higher disability as measured using EDSS scores (median [IQR] 4.0 [3.0–6.0] vs 2.5 [1.5–4.0]; $p < 0.001$); and were more frequently treated with highly effective therapies before switching to anti-CD20 (S1P modulators, 16 [10.6%] vs 4 [2.9%]; natalizumab, 24 [15.9%] vs 13 [9.4%]; $p < 0.001$) (Table 1).

Seroprotection Rate

After a full 4-dose immunization course with the HBV, 206 of 289 patients developed a protective antibody response, yielding an overall SR of 71.3% (95% CI 65.7–76.4).

Among the 138 PWMS who did not change to anti-CD20 therapy during the vaccination course, a SR of 92.8% (95% CI 87.1–96.5) was achieved, except for those vaccinated while on S1P modulators, where the SR was 50.0% (95% CI 6.8–93.2) (Table 2).

Conversely, among the 151 PWMS who transitioned to anti-CD20 therapy (rituximab [RTX; n = 121], ocrelizumab [OCR; n = 28], ofatumumab [OMB; n = 1], or ublituximab [n = 1]) during the vaccination course, only 78 exhibited successful antibody responses, resulting in a SR of 51.7% (95% CI 43.4–59.9). A reduction in the postvaccination humoral responses was observed for all patients, independent of the therapy used before switching to anti-CD20 at the beginning of vaccination. However, the most significant reduction in vaccine response was observed in patients previously treated with S1P modulators, with a final SR of 25.0% (95% CI 7.3–52.4) (Table 2). These patients received a median (IQR) of 3 (2–3) doses of the HBV while on S1P before the switch to anti-CD20.

We observed a progressive decrease in SR depending on the number of vaccine doses received before the introduction of anti-CD20 therapy. When the complete vaccination schedule was administered before starting anti-CD20, the SR was 92.8% (95% CI 87.1–96.5). However, when only 1 dose was given before initiating anti-CD20 therapy, the SR dropped to 24.0% (95% CI 9.4–45.1) (Figure 2, eTable 1).

Postvaccination Anti-HB Median Titers

In the group of 208 PWMS who achieved a protective antibody response (anti-HBs ≥10 IU/L) in their postvaccination serology, median titers exceeded the cutoff level by more than 4-fold (median [IQR] titers 617.81 [97.25–1,000.00]). However, there was a significant difference in median depending on the number of HBV doses administered before the initiation of anti-CD20 therapy. The median (IQR) titer for those who received 4 doses before starting anti-CD20 therapy was 1,000.00 (386.72–1,000.00), compared with those who received only 1 dose before anti-CD20, with a median (IQR) titer of 14.88 (12.92–30.02). This difference was statistically significant ($p < 0.01$) (Figure 3).

Multivariate GLM

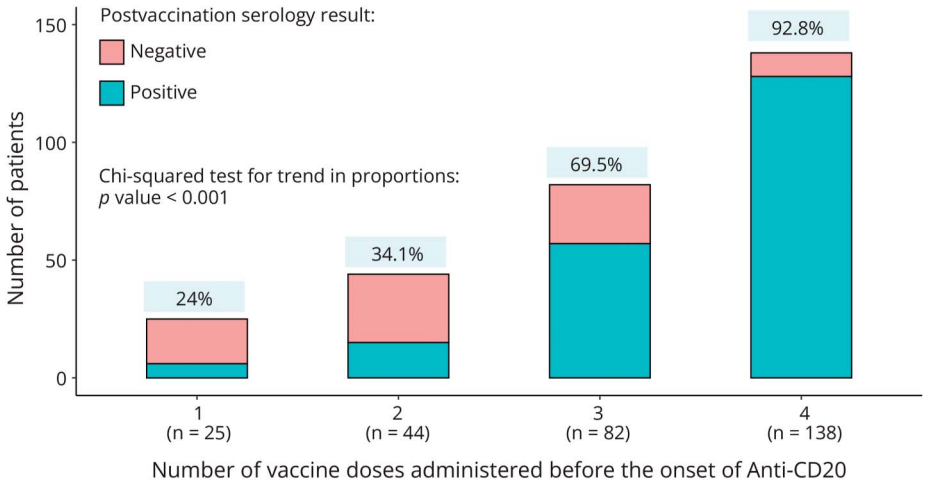
After implementing a multivariate GLM, we found that with each decade increase in age, the likelihood of achieving seroprotection decreases by 10% (SR ratio of 0.90 [95% CI 0.83–0.97; $p = 0.0036$]). In addition, starting vaccination while on S1P modulators was significantly associated with lower SR (SR ratio of 0.42 [95% CI 0.23–0.78; $p = 0.0058$]). Conversely, female sex and higher number of vaccine doses administered before starting anti-CD20 therapy were associated with a higher seroconversion rate. Specifically, women were 15% more likely to achieve seroprotection compared with men (SR ratio of 1.15 [95% CI 1.01–1.32; $p = 0.0389$]). Receiving 3 doses of HBV before anti-CD20 therapy resulted in a SR that was 3 times higher (SR ratio of 3.23 [95% CI 1.68–6.23; $p = 0.0005$]) while 4 doses of HBV led to a SR that was almost 4 times higher (SR ratio of 3.76 [95% CI 1.96–7.24; $p < 0.0001$]) compared with those who received 1 dose before anti-CD20 therapy (Figure 4).

Table 2 SRs According to Change to Anti-CD20 During the Course of Vaccination and Treatment at the Beginning of Vaccination

	No change to anti-CD20		Change to anti-CD20	
Disease-modifying therapy	**N1/N2**	**SR (95% CI)**	**N1/N2**	**SR (95% CI)**
No treatment	64/69	92.8 (83.9–97.6)	38/71	53.5 (41.3–65.5)
First-line injectables[a]	26/26	100 (86.8–100)	17/30	56.7 (37.4–74.5)
First-line orals[b]	23/26	88.5 (69.8–97.6)	5/10	50 (18.7–81.3)
Natalizumab	13/13	100 (75.3–100)	14/24	58.3 (36.6–77.9)
S1P modulators	2/4	50 (6.8–93.2)	4/16	25 (7.3–52.4)
Total	128/138	92.8 (87.1–96.5)	78/151	51.7 (43.4–59.9)

Abbreviations: anti-HBs = anti-hepatitis B surface antibodies; N1 = patients who achieved a protective antibody response (anti-HBs ≥10 IU/L); N2 = total patients who receive vaccination; S1P = sphingosine-1-phosphate; SR = seroprotection rate.
[a] Interferon β and glatiramer acetate.
[b] Dimethyl fumarate and teriflunomide.

Figure 2 Seroprotection Rates According to the Number of Doses Before the Start of Anti-CD20 Therapy

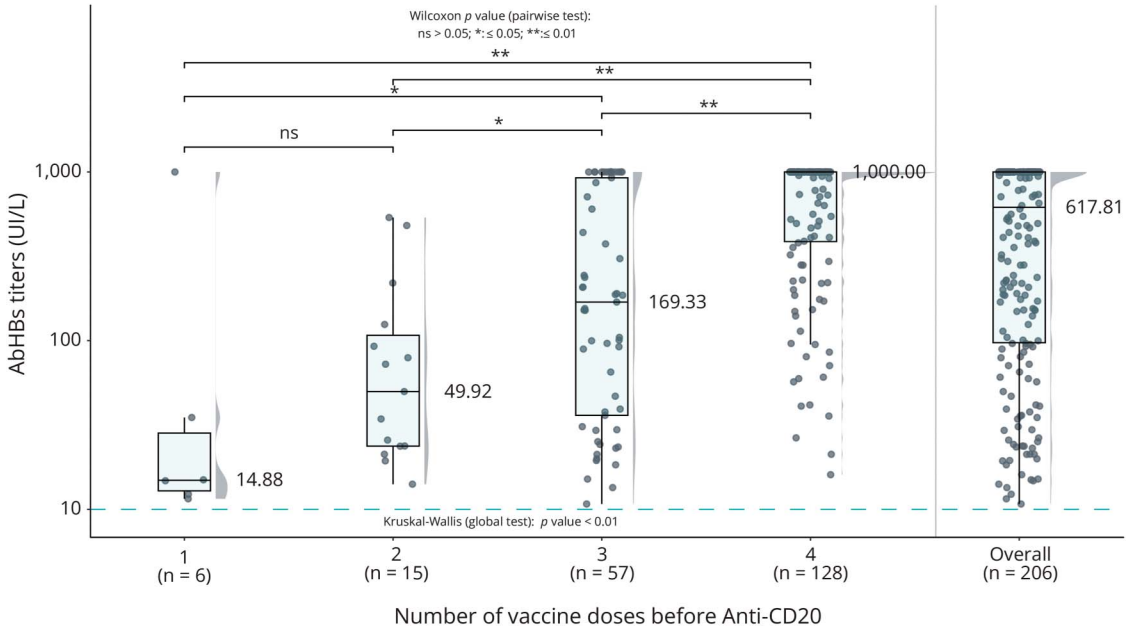


This study provides Class III evidence that HBV during initiation of anti-CD20 therapy is less effective in establishing seroprotection to hepatitis B than in patients in whom HBV is completed before initiation of anti-CD20 therapy.

Discussion

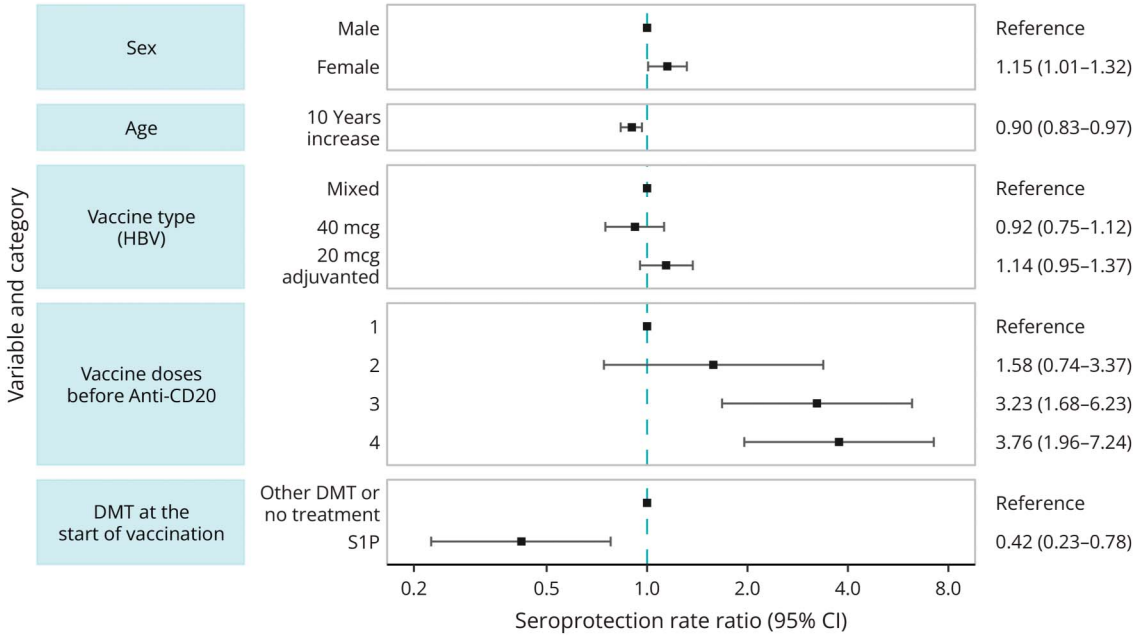
In this cohort study examining the immunogenicity of the HBV within a large group of MS candidates for anti-CD20 therapy, we observed that initiating anti-CD20 therapy during the course of vaccination was associated with a reduction in postvaccination humoral responses, regardless of the therapy used at the start of vaccination. A critical finding is that the number of HBV doses administered before anti-CD20 exposure positively correlated with both the SR and the achieved anti-HB levels. Patients who completed the entire vaccine schedule before starting anti-CD20 therapy achieved a SR exceeding 90%, in contrast to those who received only 1 dose before anti-CD20 therapy initiation, of whom only 1 in 5 developed protective humoral responses. This observation underscores the vital role of vaccine timing in relation to the

Figure 3 Box Plot Showing IgG Titers in Seroprotected Patients According to the Number of Doses Before Anti-CD20 Therapy Initiation



AbHBs = total antibody to hepatitis B surface antigen; IgG = immunoglobulin G.

Figure 4 Forest Plot Illustrating the Multivariate Generalized Linear Regression Model to Identify Factors Associated With an Increased Likelihood of Seroconversion



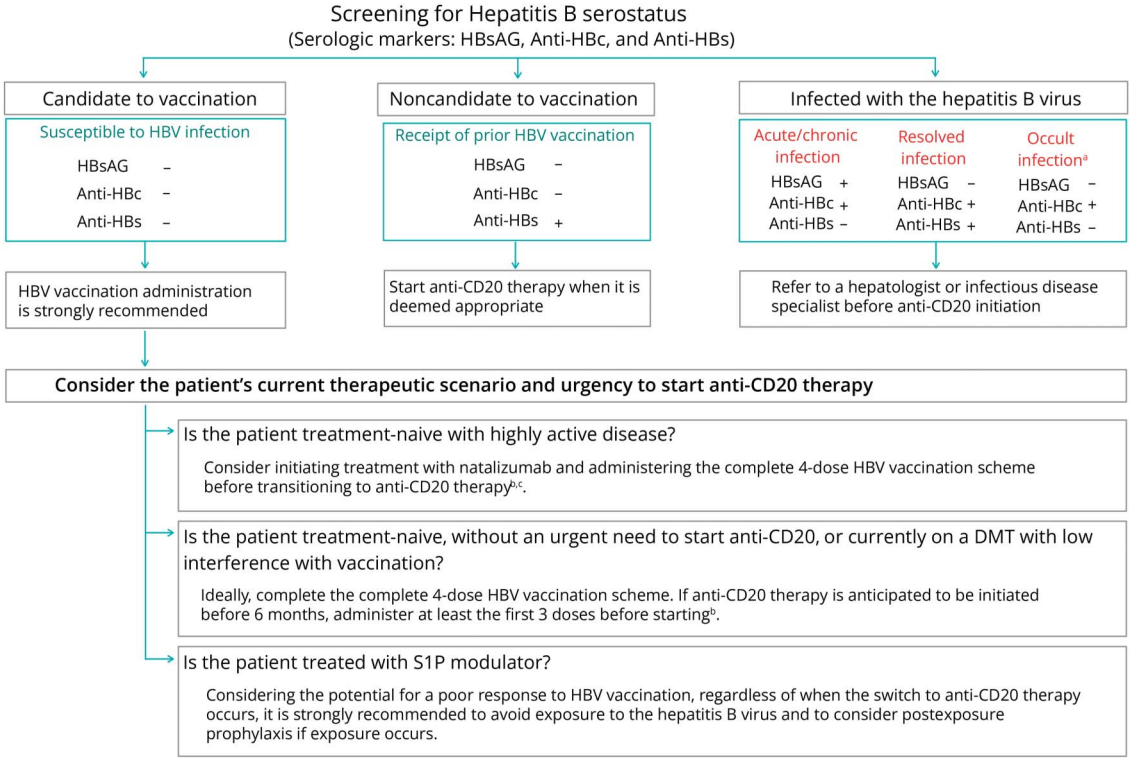
DMT = disease modifying therapy; HBV = hepatitis B vaccine; S1P = sphingosine-1-phosphate.

introduction of anti-CD20 therapy for achieving optimal immune responses, as advocated by existing guidelines,[9,10] especially in highly active patients where vaccination has proven to be safe.[25] Our results align with previous studies showing that patients on anti-CD20 therapies often experience significantly reduced postvaccination humoral responses across various vaccines, including those for influenza, pneumococcal, tetanus, and COVID-19.[5,26] This study contributes valuable information regarding the HBV, an highly recommended immunization for patients undergoing anti-CD20 therapy.[10,11,16,27]

Despite low hepatitis B incidence in countries such as the United States because of effective vaccination programs,[14] it remains a significant global health threat, affecting 257 million people and causing 820,000 deaths annually,[28] particularly in regions such as South America, Asia, and Africa. Given these disparities, it is essential to adopt a broader, more inclusive vaccination approach, especially for vulnerable groups on immunosuppressive therapies such as anti-CD20. Hepatitis B is a major cause of liver disease, with B cells and humoral immunity playing critical roles in its progression.[29] While it is mandatory to screen for latent hepatitis B (total antibody to hepatitis B core antigen positive) before starting anti-CD20 therapy,[30-33] the risk of exposure and primary infection in PWMS receiving anti-CD20 treatment without immunity against hepatitis B remains unclear. However, a study from Taiwan[13] involving patients with B-cell lymphoma who received rituximab indicated that 4 (4.2%) of 95 nonimmune (hepatitis B surface antigen-negative) patients developed de novo hepatitis B virus–related hepatitis during rituximab therapy, with 2 cases resulting in fatal fulminant hepatitis. Experts agree that anti-CD20 monoclonal antibodies pose a uniquely high risk of hepatitis B virus–related hepatitis and liver failure, sometimes leading to death, highlighting the need for immunization against the hepatitis B virus in this population.[11] After vaccination, achieving anti-HB titers of ≥10 IU/L is widely recognized as an effective threshold for preventing both acute and chronic hepatitis B in both healthy individuals and immunosuppressed populations.[34,35] Cellular immune response monitoring is not typically recommended for assessing protection against hepatitis B.[15]

Other authors have explored alternative HBV schemes, such as an accelerated schedule (0, 7, and 21 days and 12 months), in PWMS before initiating anti-CD20 therapies, aiming to achieve faster immune responses.[7] However, as observed in a prospective single-center study conducted in France, this accelerated schedule seems to be less immunogenic in this population.[36] The authors found that in 17 patients vaccinated with the accelerated HBV schedule, the SR was 58.8% after the first 3 doses (0, 7, 21 days) administered before the initiation of anti-CD20 therapy.[36] Additionally the accelerated vaccination schedule is only authorized for the regular antigenic-load HBV (10 or 20 μg depending on the vaccine brand), which is not recommended for immunosuppressed populations.[37] Our study used the adjuvanted or high antigenic-load vaccine in its standard scheme (0, 1, 2, 6–12 months), which is recommended for immunosuppressed individuals or those at risk of future immunosuppression.[20,37]

Figure 5 Proposed Algorithm for Immunizations Against Hepatitis B Virus in Patients With MS Who Are Potential Candidates to Anti-CD20 Therapies



(A) The presence of total anti-HBc indicates previous or ongoing infection with HBV in an undefined time frame. People who have immunity to hepatitis B from a vaccine do not develop anti-HBc.[50] (B) Consider vaccinating with adjuvanted or high-load HBV (0, 1, 2, and 6–12 months) if short-term immunosuppression is anticipated. (C) Consider maintaining or switching depending on JC virus serology.[25] Anti-HBc = total antibody to hepatitis B core antigen; anti-HBs = total antibody to hepatitis B surface antigen; DMT = disease-modifying therapy; HBsAG = hepatitis B surface antigen; HBV = hepatitis B vaccine; MAbs = monoclonal antibodies; MS = multiple sclerosis; S1P = sphingosine-1-phosphate.

The Centers for Disease Control and Prevention recommends the accelerated schedule for specific situations, such as individuals traveling on short notice who might face imminent hepatitis B virus exposure.[37] The main advantage of the standard HBV schedule is its established efficacy and long-term immunity.[38] The gradual administration of doses over several months allows for sustained stimulation of the immune system, leading to a robust and durable immune response. This is particularly crucial in the context of our study involving PWMS who are considering anti-CD20 therapy, which is likely to lead to long-term immunosuppression. Another important aspect is that although our study did not find a statistically significant difference, there seems to be a trend toward better SR with the adjuvanted HBV over high-load HBV. Further studies are needed to assess the effectiveness of adjuvanted vs high-load HBV in PWMS.

It is important to highlight that about one-third of our vaccinated patients had not started anti-CD20 therapy by the study's conclusion. This may be due to some transitioning to anti-CD20 therapy after the study ended in May 2023. It is important to note that our cohort follows an early immunization approach to ensure protection before initiating immunosuppressive treatments such as S1P modulators or anti-CD20. This strategy anticipates the potential reduction in vaccine response in immunosuppressed patients. Regarding HBV, we advocate for a broad vaccination strategy, supported by the 2022 Advisory Committee on Immunization Practices guidelines recommending universal HBV for all adults aged 19–59 years, which is particularly relevant for the population we studied.[14] However, we emphasize that these recommendations should not replace individualized clinical decisions. Physicians should carefully consider each patient's specific treatment context, risk factors, and local disease prevalence when determining vaccination needs.

Our study underscores several key aspects. First is the reduced SR observed in older patients. It is well established that immunosenescence—the gradual decline in immune function with age—results in diminished vaccine responses.[39] Moreover, older age is a well-documented risk factor of increased vulnerability to various types of infections.[40,41] Given this, older PWMS who are treated with anti-CD20 require special consideration. They face heightened risks of severe and opportunistic infections, malignancies, and reduced vaccine response due to both age-related immunosenescence and the immunosuppressive effects of anti-CD20 therapy.[42] We also observed that female sex was associated with a higher

likelihood of achieving protective seroconversion, which can be explained by well-established biological differences in immune responses between men and women.[43] Genetic and hormonal influences contribute to greater immunoglobulin production and stronger vaccine responses in women, as demonstrated in numerous studies with different type of vaccines.[43] In addition, we observed a possible additive effect of immunosuppression in PWMS. Patients who began vaccination under S1P modulator treatment and then transitioned to anti-CD20 therapy showed the most impaired vaccination response. It is well documented that S1P modulators, especially the nonselective ones, affect postvaccination immune responses, both humoral and cellular.[4,24,44-46] These patients and those on anti-CD20 therapy require a detailed and planned strategy to minimize infection risks, such as optimizing vaccination timing.

This study has multiple strengths. First, it is based on patients belonging to a high-quality and deeply phenotyped prospective ongoing cohort at Cemcat, which has provided numerous outstanding publications.[18,19,25,47] In addition, the close collaboration with the Department of Epidemiology and Preventive Medicine at HUVH enabled to enroll a substantial number of patients immunized with HBV, ensuring consistent evaluations with a wealth of clinical, vaccine-related, and serologic data. Second, although evidence has consistently shown a significant impact on postvaccination humoral immune responses with anti-CD20 therapies,[5,24] this study attempts to demonstrate vaccine responses in relation to the number of doses received. This information will enable us to develop better strategies for those vaccines that require multiple doses, not only for HBV but also for other important vaccines such as the human papillomavirus vaccine or the recombinant zoster vaccine, recommended for PWMS.[10,12]

However, we also acknowledge some limitations. Although we have a large number of patients who started vaccination with another DMT and transitioned to anti-CD20 therapies during the course of vaccination, none of them began with immune reconstitution therapies such as alemtuzumab or cladribine, limiting conclusions for this subset of patients. In addition, although the number of patients who started vaccination while on S1P modulators was low, 80% of them transitioned to anti-CD20 therapy during vaccination. This group consistently showed the lowest SR, as confirmed by the multivariate GLM, aligning with previous knowledge about the impairment of vaccine responses during S1P therapy. The potential additive immunosuppressive effects of these drugs in PWMS require further study. Finally, most of our cohort received RTX or OCR, limiting our conclusions regarding other anti-CD20 therapies such as OMB, because of its more recent approval. While available data suggest that OMB also impairs humoral immune responses after severe acute respiratory syndrome coronavirus 2 vaccination,[48] it seems to do so to a lesser extent compared with RTX or OCR.[49] However, the current evidence is limited, and larger studies are required to better understand the potential differences in vaccine responses among the various anti-CD20 therapies.

This study indicates that starting anti-CD20 therapy during the HBV course impairs the development of a protective humoral response. The likelihood of achieving seroconversion is closely linked to the number of vaccine doses received before initiating anti-CD20 therapy. Given the widespread use of anti-CD20 treatments across the MS phenotypes, many PWMS are likely to require these therapies at some point in their disease. According to our results, it is crucial to advance vaccination as much as possible, ideally administering at least 3 doses before starting anti-CD20 therapy, or to find alternative strategies to achieve adequate vaccine responses, such as implementing bridging therapy approaches and/or using enhance immunogenicity vaccines. Consequently, we propose an algorithm focused on hepatitis B risk prevention in PWMS, emphasizing the importance of early planning and completion of the HBV course (Figure 5). Our results could have a broader impact because of the extensive use of anti-CD20 therapies in various autoimmune conditions, beyond inflammatory demyelinating diseases of the CNS.

Author Contributions

R. Carvajal: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. D. Guananga-Álvarez: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. C. Tur: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. J. Esperalba: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Rodríguez-Barranco: major role in the acquisition of data. A. Rando-Segura: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. B. Borras-Bermejo: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Cobo-Calvo: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. P. Carbonell-Mirabent: study concept or design. R. Zules-Oña: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J.A. Rodrigo-Pendas: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. X. Martínez-Gómez: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. X. Montalban: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. M. Tintore: drafting/revision of the manuscript for content, including medical writing for

content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. S. Otero-Romero: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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