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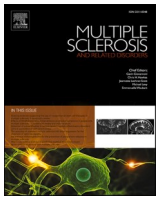

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Seroconversion rate following HBV vaccination in clinical practice: The role of age and DMT treatment

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ABSTRACT

HBV screening and immunization is recommended in all MS patients and is mandatory before the start of some DMT. However, studies evaluating the immune response to HBV vaccine in MS patients are scarce. We aimed to evaluate the seroprotection rate following HBV immunization in MS patients and to assess if older age and DMT-treatment influenced seroprotection.

We conducted a cohort study between 2016 and 2020 and compared the immune response to HBV vaccine in MS patients under different DMTs and in patients 50 years old or younger and older than 50.

We found that patients under non-injectable DMT presented lower rates of seroprotection comparing to patients under injectable DMT's or without treatment. In patients older than 50, although the seroprotection rate was similar to the remaining patients, the antibody anti-HBV surface antigen titers following HBV immunization were lower and patients were more likely to require a 4th dose of the vaccine to achieve seroprotection.

Our findings highlight to need to consider HBV immunization in MS patients early in the disease course, in order to ensure a proper immune response to the vaccine.

1. Introduction

The use of progressively more immunosuppressive disease-modifying therapies (DMTs) in multiple sclerosis (MS) has increased the risk of severe infection of vaccine-preventable diseases, such as hepatitis B (HBV).

Due to the higher risk of HBV infection in MS patients under DMTs, every patient should be screened for HBV with antigen and antibody testing (Epstein et al., 2018; Moiola et al., 2020). Considering the low risk of HBV immunization and the potential complication of acute infection, the HBV vaccine is recommended in seronegative patients. (Pourcher, 2020; Riva et al., 2020).

DMTs might compromise the immune response to other vaccines, such as influenza, tetanus-diphtheria-toxoid, pneumococcal, or meningococcal vaccine (Ciotti et al., 2020; Bar-Or et al., 2020; Loebermann et al., 2012). However, data regarding the HBV vaccine are scarce.

In this study, we aimed to evaluate the seroprotection rate following HBV immunization in MS patients and to assess if older age and DMT-treatment influenced seroprotection.

2. Materials and methods

A cohort study was conducted, including all MS patients followed in our outpatient clinic between 2016 and June 2020 submitted to HBV immunization. Since 2016, an infectious disease evaluation including HBV serology was performed in all patients at the time of diagnosis or when starting or switching DMTs. HBV immunization was recommended to all seronegative patients, with the single-antigen vaccine "Engerix". The immunization consisted of an accelerated HBV regimen comprising a first course of 3 doses administered on days 0, 7 and 21. The antibody anti-HBV surface antigen (HbS) titers were reevaluated 4 weeks after the last dose. A fourth dose was administrated in seronegative patients following 3 doses of HBV vaccine and the antibody evaluation was repeated after another 4 weeks.

All patients completing the immunization regimen with available serologic testing evaluating immune response to the vaccine were included.

Baseline variables (at the time of the first HBV vaccine) were collected from patients' records, including age, gender, number of vaccine doses administered, MS type, disease duration, and the DMT used at the time of immunization.

The seroprotection rate was the primary outcome. In patients achieving seroprotection 2 additional outcomes were analyzed: the antibody titer following HBV immunization and the need for a 4th dose of HBV vaccine to achieve seroprotection.

Comparisons between patients under injectable, non-injectable, and without treatment were conducted, to evaluate the immunization response in different treatment groups

Comparisons between patients 50-years-old or younger and older than 50 were performed to evaluate the immunization response according to age.

Comparisons between groups were conducted using Fisher's exact test or qui-square test, two-tailed *t*-test or Mann-Whitney test and median comparison test as appropriate.

The study was approved by the local Ethics Committee and informed consent was obtained from all participants.

3. Results

During the study period, 1270 patients were evaluated in our MS outpatient clinic, 826 had MS, 140 presented a negative HBV serology, and were proposed to HBV immunization. Nineteen patients were

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Table 1
Study population characteristics.

	Total (n = 121)
Female, (%; 95% confidence interval for percentage)	77 (63.6; 54.9–72.3)
Age, mean (SD)	46.1 (13.9)
Disease duration in years, mean (SD)	10.0 (8.3)
MS-type, n (%; 95% confidence interval for percentage)	
Relapsing-remitting	73 (60.3; 51.5–69.2)
Secondary progressive	11 (9.1; 3.9–14.3)
Primary progressive	37 (30.6; 22.3–38.9)
DMT, n (%; 95% confidence interval for percentage)	
Without DMT	50 (41.3; 32.4–50.2)
Injectable DMT	25 (20.7; 13.3–28.0)
Non-injectable DMT	46 (38.0; 29.2–46.8)
Teriflunomide	12 (9.9; 4.5–15.3)
Dimethyl fumarate	17 (14.0; 7.7–20.3)
Fingolimod	6 (5.0; 1.0–9.0)
Natalizumab	11 (9.1; 3.9–14.3)

excluded: in 11 the immunization regimen was incomplete, in 8 the post-vaccine serology was unavailable.

The final analysis included 121 patients. The majority were women (n = 77, 63.6%) with a mean age of 46.1 ± 13.9 years and a mean disease duration of 10.0 ± 12.0 years. The most frequent MS type was relapsing-remitting (n = 73, 60.3%), followed by primary progressive (n = 37, 30.6%) and secondary progressive (n = 11, 9.1%).

At the time of the immunization the majority (n = 72, 60.0%) of patients was under treatment: 20.7% under injectable DMTs, 38.0% under non-injectable DMTs (table 1).

The seroprotection rate was 80.2% (n = 97). Among patients who achieved seroprotection, a 4th dose of HBV vaccine was required in 24 (24.7%) patients and the median antibody titer following immunization was 384.0 (IQR 963.5).

3.1. Response to immunization according to treatment

In patients under a non-injectable DMT, the seroprotection rate was 66.0% (95%CI 52,3–80,0%), which was lower than observed in patients under an injectable DMT (92.0%, 95% CI 80,6–100%; p = 0.021) or without any treatment (87.8%, 95%CI 78.2–97.3%; p = 0.015) Figure 1. The seroprotection rate was similar in patients under an injectable DMT and without DMT (p = 0.709). Among patients who achieved seroprotection, the use of a non-injectable DMT did not impact on the median antibody titer following immunization (107.3 vs 152.6, p = 0.471) or in the need for a 4th dose to achieve seroprotection (21.2%, 95% CI 11.1–31.3% vs 32.3%, 95%CI 14.8–49.7%; p = 0.313) which were similar to that observed in the remaining patients.

3.2. Response to immunization according to age

We found similar seroprotection rates in patients 50 years old or younger (82.2%; 95% CI 73.2–91.2%) and older than 50 (77.1%; 95%CI 64.8–89.4% p = 0.495). However, among patients older than 50 years old who achieve seroprotection, the antibody titers following immunization were lower (66.3 vs 276.9, p = 0.04), and the proportion of patients requiring a 4th dose of HBV vaccine was higher (45.9%, 95%CI 29.1–62.8% vs 11.7%, 95%CI 3.3–20.0%; p <0.001).

4. Discussion

With the increasing number and efficacy of DMT, the need for infection surveillance and prevention is required, including HBV serology and immunization[2], (Riva et al., 2020). Available data suggest that some DMTs might decrease the immune response to influenza, pneumococcus, meningococcus, or tetanus-diphtheria-toxoid vaccine

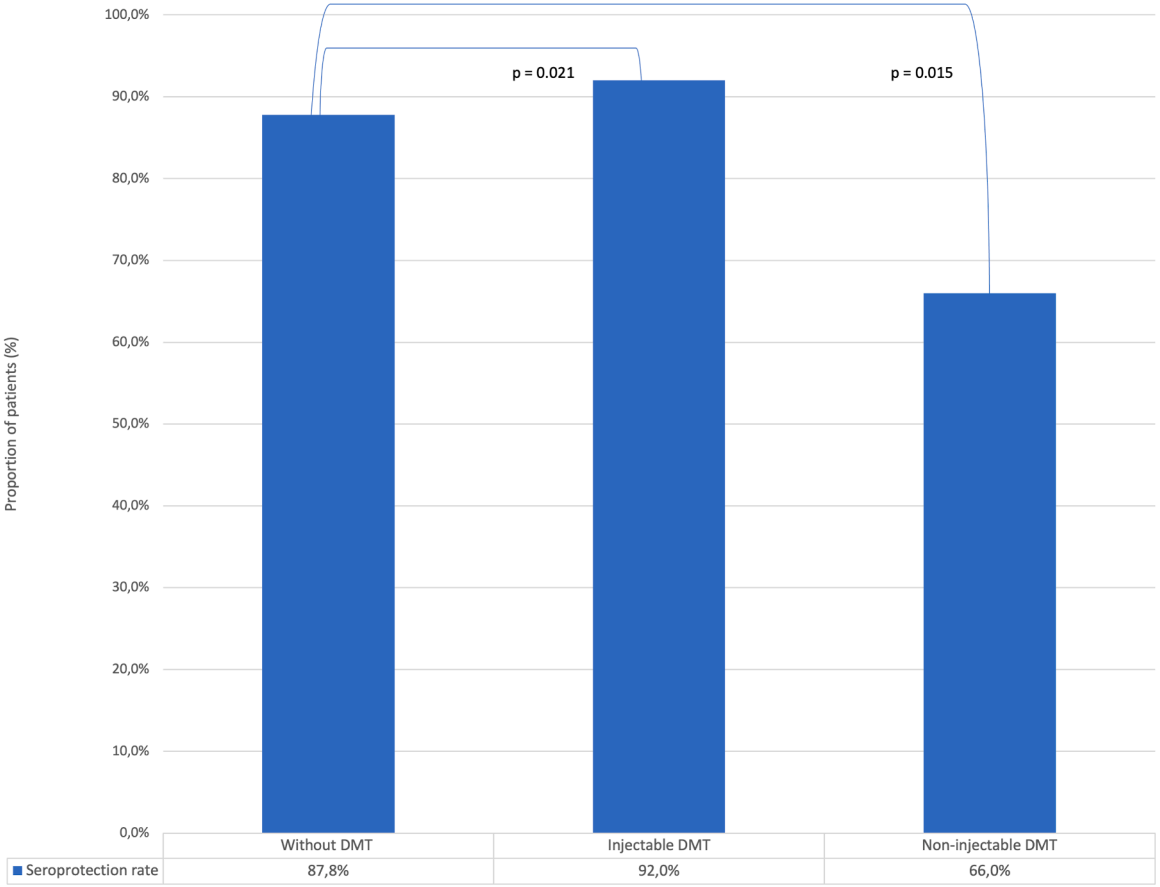

Fig. 1. Seroprotection rate according to treatment.

(Ciotti et al., 2020), (Bar-Or et al., 2020). On the other hand, increasing age has been associated with a reduction in the competence of the immune system, which might also decrease responses to vaccines (Goronzy and Weyand, 2013). However, the response to HBV immunization in MS patients under DMT or with increasing age has been seldom assessed and might be relevant deciding when to propose patients to immunization to ensure a higher probability of seroprotection.

We hypothesized that the use of immunosuppressants and increasing age in MS patients could compromise the immune response to the HBV vaccine. We found that patients under non-injectable DMTs present a lower seroprotection rate compared with patients without DMT or under injectable DMTs. Patients older than 50 had similar seroprotection rates compared to younger patients, however, the anti-HbS antibody titers following immunization were lower and there was a higher need for a 4th dose of the vaccine to achieve seroprotection.

Our findings support the need to propose patients to HBV vaccine early in their disease course, while patients are younger and under no treatment or injectable DMTs, in order to achieve a proper immune response.

Limitations of our study include the single-center design which might limit extrapolation to other centers using different HBV vaccines and regimens. Also, due to the low number of patients under non-injectable DMT, we couldn't assess differences in seroprotection rate between DMT included in this group. Finally, the differences in the seroprotection rate between different treatments groups might also be influenced by different baseline characteristics, since they influence treatment choices, and not the treatment itself. Future studies with larger samples should evaluate both the effect of the patient's characteristics and DMT treatment.

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Declarations of Competing Interest

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References

Epstein, D.J., Dunn, J., Deresinski, S, 2018. Infectious complications of multiple sclerosis therapies: implications for screening, prophylaxis, and management. Open Forum Infect. Dis.

Moiola, L., Barcella, V., Benatti, S., et al., 2020. The risk of infection in patients with multiple sclerosis treated with disease-modifying therapies: a Delphi consensus statement. Mult. Scler. J. 1–16.

Pourcher, V, 2020. What are the infectious risks with disease-modifying drugs for multiple sclerosis and how to reduce them? A review of literature. Rev. Neurol. (Paris).

Riva, A., Barcella, V., Benatti, S.V., et al., 2020. Vaccinations in patients with multiple sclerosis: a Delphi consensus statement. Mult. Scler. J. 1–13.

Ciotti, J.R., Valtcheva, M.V., Cross, A.H, 2020. Effects of MS disease-modifying therapies on responses to vaccinations: a review. Mult. Scler. Relat. Disord.

Bar-Or, A., Calkwood, J.C., Chognot, C., et al., 2020. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis: the VELOCE study. Neurology.

Loebermann, M., Winkelmann, A., Hartung, H.P., et al., 2012. Vaccination against infection in patients with multiple sclerosis. Nat. Rev. Neurol.

Goronzy, J.J., Weyand, C.M, 2013. Understanding immune senescence to improve vaccine responses. Nat. Immunol. 14 (5), 428–436. Available at. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4183346/.

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