Original Article

Efficacy of Accelerated Vaccination against Hbv to Achieve Antibody formation in Multiple Sclerosis Patients Receiving Anti-Cd20 Therapy

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Abstract

Aim: Ocrelizumab is a monoclonal antibody that has been approved for use in both relapsing–remitting multiple sclerosis (RRMS) and primary progressive multiple sclerosis (PPMS). Since ocrelizumab acts on B cells, it also affects humoral immunity, thus reducing the vaccine response. In this study, we aimed to elucidate the relationship between the antibody response following rapid vaccination against hepatitis B virus (HBV) in multiple sclerosis (MS) patients receiving ocrelizumab treatment, and the time of vaccination. **Materials and Methods:** A total of 220 MS patients were included in this retrospective analysis. The patients' baseline HBV serostatuses (HbsAg, Anti-HbsAb, Anti-HbcAb), previous drug history for MS, whether they were vaccinated against HBV in the past, vaccination status before or after ocrelizumab treatment, and protective antibody titers according to vaccination times, occult HBV incidence and initiation of antiviral treatment were evaluated. **Results:** Forty-nine percent of MS patients using ocrelizumab were not vaccinated against HBV. The patients were divided into three groups according to their vaccination status as: individuals vaccinated in the past (7.3%, n = 16), vaccinated before treatment (4.5%, n = 10), and vaccinated after treatment (22.3%, n = 49). The antibody titers of the patients in the 6th month after ocrelizumab treatment were measured as 78 mIU/ml, 193 mIU/ml, and 0, respectively. The number of patients with occult HBV infection was 38. **Conclusion:** In patients with a suspected diagnosis of MS, HBV serostatus should be evaluated at the beginning and if necessary, patients should be vaccinated in the early period. Vaccinating patients at least 1 month before initiating multiple sclerosis treatment is more effective in terms of protective antibody formation.

Keywords: Accelerated vaccination, anti-CD-20 therapy, antibody response, HBV serostatus, multiple sclerosis

Introduction

Multiple sclerosis (*MS*) is an autoimmune disease of the central nervous system with immune-mediated demyelination, axon loss, and degeneration. It is the most common cause of nontraumatic disability in young adults worldwide.[1] Early research demonstrated the role of T cells in the development of inflammation and demyelination in MS. With the understanding of the role of B cells in the pathogenesis of MS treatments that deplete B cells have been introduced. However, treatments that deplete B cells are associated with potential risks of viral infection, and hepatitis B virus (*HBV*) infection is the most common chronic viral infection in the community.[2,3]

Vaccination is the most effective method of protection against HBV. The Hepatitis B vaccine was included in the childhood vaccination calendar in Turkey in 1998 and has been administered in three doses since then. In our country, the hepatitis B vaccine is administered in 3 doses at 0, 1, and 6 months in some risk groups other than childhood.[4] In some special cases, vaccination according to the accelerated vaccination schedule may be recommended for individuals who need the vaccine within a certain period of time. According to this program, four doses of vaccine are required to achieve long-term immunity. The first three doses can be administered within 21 days (*days 0, 7, and 21*), while the 4th dose can be administered one year later on an accelerated Schedule.[5]

Disease-modifying treatments (*DMTs*) affect the immune system by modulating or suppressing the immune system, which may affect the patient's immune response to the vaccine. It has been shown that some of the DMTs affect the cellular and some on the humoral vaccine response. This effect is mainly related to the timing between treatment and vaccination. Humoral vaccine responses are significantly impaired, particularly by anti-CD20 monoclonal antibody treatments that deplete B cells.[6,7] Limited data indicate the HBV seroprevalence and the vaccine response to the HBV vaccine in the MS population.[8,9]

Occult HBV infection (*OBI*) is defined as the long-term presence of persistent HBV genome in the liver of individuals

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who were serologically HBsAg negative, regardless of HBV DNA status.[10] Although anti-HBV antibodies are positive in most OBI cases (*Anti-HBs and Anti-HBc or only Anti-HBc*), anti-HBV antibodies can be negative in more than 20% of the cases. Therefore, OBI can be serologically classified as seropositive (*Anti-HBc and Anti-HBs positive or only Anti-HBc positive*) and seronegative (*Anti-HBc and Anti-HBs negative*). Treatments that deplete B cells (*rituximab, ocrelizumab*) potentially carry a risk (>10%) of HBV infection reactivation.[11,12] Ocrelizumab is a humanized monoclonal antibody used to treat MS that selectively targets CD20-expressing B cells.[13] Due to the risk of hepatitis B reactivation and fulminant hepatitis that may occur following B-cell depletion during ocrelizumab treatment, current guidelines recommend periodic monitoring of HBV serostatus.[14,15]

In this study, we aimed to evaluate the HBV screening results of 220 patients using ocrelizumab with the diagnosis of multiple sclerosis in our institution. We have investigated the vaccination status against HBV in the past, the rates of vaccination before/after treatment, the rates of initiation of prophylactic treatment, and vaccine/antibody responses.

Materials and Method

This retrospective analysis was conducted in our institution's MS outpatient clinic between *August 2017 and January 2022*. The data from 220 patients have been interpreted within the scope of this research. Although it was planned to complete the analysis with 274 individuals due to clinical deterioration/lack of data, some cases were excluded (*8 deceased and 46 clinically ill*). All procedures followed were by the ethical standards of the responsible committee on human experimentation (*institutional and national*) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution with protocol number *2022-18/25.* Informed consent has not been obtained as this was retrospective research.

Basal HBV serostatus (*HbsAg, Anti-HbsAb, Anti-HbcAb*), previous MS treatment, lifetime HBV vaccination history, HBV vaccination before ocrelizumab treatment, HBV vaccination history after ocrelizumab treatment, baseline and HBV vaccination, and subsequent HBV antibody titers were recorded.

Patients ≥18 years old with a diagnosis of relapsing–remitting multiple sclerosis (*RRMS*), active secondary progressive multiple sclerosis (*aSPMS*), or primary progressive multiple sclerosis (*PPMS*), currently receiving ocrelizumab treatment and received at least one dose of ocrelizumab in the last 6 months have been enrolled.

In recommended patients, HBV vaccination was performed as an accelerated program (*3 doses of HBV vaccine were given to the patients on day 0, day 7, and day 21, and a booster was recommended at 12 months*). Patients were vaccinated either before the initiation of ocrelizumab 1 month before treatment, or after ocrelizumab treatment at 4th month (*vaccinated according to the accelerated schedule 3 months before the next dose*). Although the research planned to enroll 274 patients, eight individuals were deceased and 46 were clinically ill and those were excluded due to lack of laboratory data, and a total of 220 patients were included in the study.

Statistical analysis

Statistical analysis of the data was performed in the statistical package program IBM SPSS 28.0 (*IBM Corp. Released 2021. IBM SPSS Statistics for Windows, version 28.0. Armonk, NY: IBM Corp*.). The *Shapiro–Wilk test* was utilized to examine whether the data showed normal distribution. *Descriptive statistics* are expressed as mean, standard deviation, or median (IQR) for quantitative data *and frequency and percentage for qualitative data*. *Mann–Whitney U and Kruskal–Wallis tests* were used for non-normally distributed variables. *Pearson Chi-square, Fisher–Freeman–Halton, and Fisher's exact Chi-square tests* were used to analyze *categorical data*. In case of statistical significance, the *Bonferroni test* or *multiple comparison* tests were used. The significance level was determined as $\alpha = 0.05$.

Results

The mean age of patients included in the study was 45.19 ± 10.6 years (n = 220). The gender distribution was; 69% (n = 152) were female, and 31% (n = 68) were male. The mean follow-up period of the patients under ocrelizumab treatment was 15.19 ± 8.76 months, median IQR: 13 (8–19); the mean number of infusions was 3.07 ± 1.58, median IQR: 3 (1–8). When the patients were evaluated according to the number of drugs they used before ocrelizumab treatment, the patients using ≤1 drug were 40.5% (n = 89), and patients using more than 1 drug were 59.5% (n = 131). The demographic and clinical characteristics of the patients are summarized in Table 1.

HBV screening was performed in all 220 patients who have initiated ocrelizumab treatment. According to this, HBsAg positivity was not detected in any of the patients,

Table 1: The demographic and clinical characteristics of the study population

Features	*n* (%)
Age (years), mean±SD	45.19±10.6
Sex, *n* (%)	
Female	152 (69)
Male	68 (31)
Previous DMT, *n* (%)	
≤1	89 (40.5)
>1	131 (59.5)
Follow-up duration, months±SD	15.19±8.76
Ocrelizumab infusion,	
Mean (SD)	3.07±1.58
Median (IQR)	3 (1–8)

49% (n = 107) of the patients had not been exposed to or vaccinated against HBV (*HBsAg, Anti-HBsAb, and Anti-HBcAb negative*). The vaccination status of the individuals could be elaborated as: immunized in the past (7.3%, *n* = 16), patients vaccinated before treatment (4.5%, *n* = 10), and patients vaccinated after therapy (22.3%, *n* = 49). Accordingly, the antibody titers of the patients in the 6th month after ocrelizumab treatment were measured as 78 mIU/ml, 193 mIU/ml, and 0, respectively.

According to the HBV screening values before ocrelizumab treatment, 22% (*n* = 48) of the patients were positive for HBsAb, while 77% (*n* = 172) had negative HBsAb. HBsAb was positive (*HBcAb negative*) in 19 (9%) patients, and both HbsAb and HBcAb-IgG were positive in 29 (13%) patients as an indicator of previous infection. Of 19 patients positive for HBsAb and negative for HBcAb-IgG, 16 had a vaccination history against HBV. While HBsAb was negative in 6 of the patients, HbcAb was positive. Patients with potential for occult HBV infection were; HBsAb+/HBcAb+ (*n* = 29, 13%), HBsAb+/HBcAb− (*n* = 3, 1%; unvaccinated), and HBsAb−/HBcAb+ (*n* = 6, 3%) serology [Table 2].

HBV vaccine was recommended for patients (49%, *n* = 107) who were not exposed to the HBV virus. Of the patients, 10 (4.5%) were vaccinated 1 month before ocrelizumab therapy and 49 (22%) after ocrelizumab therapy. After starting ocrelizumab treatment, the mean time of the first dose vaccination was the end of the 3rd month and the beginning of the 4th month. Anti-HBsAb titers were measured 1 month before the next dose of ocrelizumab in each of the three groups according to the vaccination times. Accordingly, the antibody titer formed in those vaccinated according to the accelerated vaccination schedule 1 month before the initiation of ocrelizumab treatment was significantly higher than in the other two groups (p: 0.003), [Table 3 and Figure 1]. Antiviral treatment was administered in 35 of 38 patients with occult HBV infection, regardless of the level of HBsAb titer. Three of the patients refused to use antiviral therapy.

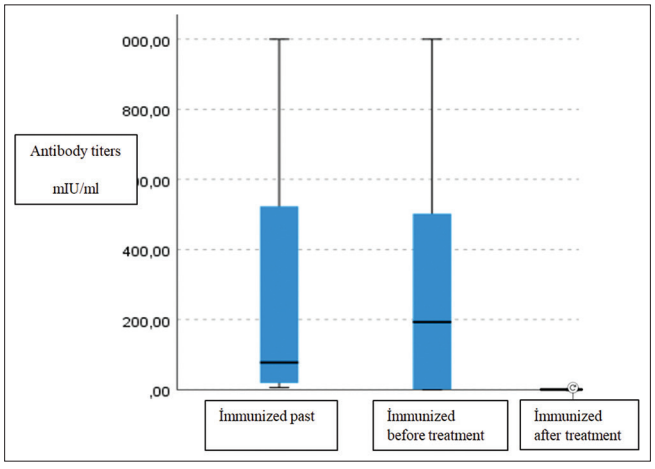

Figure 1: Vaccination time and antibody titers

No correlation was observed between the number of DMTs previously used by MS patients and the resulting HBsAb titer and patient age and antibody titer. Before initiating ocrelizumab treatment, one patient who was negative for HBsAg, HBsAb, and HBcAb refused to receive HBV vaccination, and she had an acute HBV infection after the third application of ocrelizumab treatment.

Discussion

In this study, all MS patients treated with ocrelizumab were screened for HBV before treatment. As a result of this screening, most of the patients (49%, *n* = 107) were not vaccinated against HBV, and the HBsAb titers measured in these patients before starting the treatment were primarily negative. The risk of catching and severe HBV infection increased in these patients who do not have a protective level of HBsAb titer and received immuno-suppressive therapy. Screening patients for HBV status before treatment and recommending vaccination, if necessary, is of great importance in protecting the MS population and the whole society against HBV infection and the chronic diseases it may cause.

In patients using ocrelizumab to treat MS, there is a risk of reactivation of latent HBV infection due to B cell depletion of the drug. In particular, if HBsAg-negative/HBcAb-positive/HBV-DNA-negative is detected, the risk of HBV reactivation is high. It has been reported that the risk of reactivation was increased in patients with HBsAb negative occult HBV infection followed up with the diagnosis of rheumatoid arthritis and using rituximab. In addition, HBsAg-negative, HBcAb-positive, and HBsAb-positive HBV reactivation was observed after the decrease of HBsAb titer with rituximab

Table 2: Patients with complete baseline screening of HBV serology

HBV serology	*n* (%)
HBsAg positive, *n* (%)	0 (0)
HBsAb positive, *n* (%)	48 (22)
HBsAb (+), HBcAb (−)	19 (9)
*HBsAb (+), HBcAb (+)	29 (13)
HBsAb negative, *n* (%)	172 (78)
Potential for occult HBV infection, *n* (%)	38 (17)
HBsAb+/HBcAb+	29 (13)
HBsAb+/HBcAb−	3 (1)
HBsAb−/HBcAb+	6 (3)
**(HBsAg, Anti-HBsAb, and Anti-HBcAb negative) *n* (%)	107 (49)

*HBsAb (+), HBcAb (+): Previous infection. **The patients had not been exposed to or vaccinated against HBV

Table 3: Patients' vaccination time and antibody titers

Vaccination time	*n* (%)	Antibody titer# mIU/ml
Immunized in the past	16 (7.3)	78
Immunized before treatment	10 (4.5)	193
Immunized after treatment	49 (22.3)	0

#Antibody titer normal range between 0 and 10 mIU/ml

treatment. It should be underlined that detecting HBsAb titer >100 mIU/mL in this patient group was a protective factor against HBV reactivation.[16] For this reason, it was stated that if the HBsAb titer is >100 mIU/ml during the use of B-cell-depleting treatment in occult HBV patients, and if healthy communication can be established with the patient, regular check-ups for HBV DNA can be followed even before antiviral treatment is initiated.[8]

In our institution, prophylaxis treatment with an antiviral agent was used in 16% of MS patients with HBcAb positive, HBsAb negative, or HBsAb titer <100 mIU/mL who were given B-cell depletion therapy to prevent the risk of HBV reactivation. It was also recommended to continue antiviral treatment for at least 12 months after discontinuing the B-lymphocyte-targeted drug.[15,17] We did not detect any HBV reactivation in patients during the follow-up period under ocrelizumab treatment. This may be because patients were regularly screened for HBV every 6 months by a multidisciplinary medical team, and treatment with a potent antiviral agent might be initiated for patients at risk for HBV reactivation.

Today, we know that vaccinating the person at the appropriate time and dose is the most effective method to protect against HBV infection. In our study, the accelerated vaccination program included both patients vaccinated 1 month before the treatment and those vaccinated at least 3 months after receiving ocrelizumab treatment. The protective level of antibody titer did not occur significantly compared to patients vaccinated before treatment. This may be related to the fact that ocrelizumab also depletes the B cells responsible for antibody production, and its effect on these cells continues for a long time. In previous literature, there were different data regarding the protective antibody titer formed as a result of vaccination against HBV before starting ocrelizumab treatment and the protective antibody titer formed as a result of vaccination after treatment. Buonomo *et al.* reported a trend toward a decrease in HBsAb titers in MS patients receiving ocrelizumab who were vaccinated before treatment compared to those vaccinated after treatment, but this difference was not statistically significant. This situation may be related to the time of vaccine administration, the number of doses administered, and the method of determining the antibody titer formed.

In our country, screening patients for HBV infection is obligatory before each application of DMTs that act on B cell depletion. This approach allows the initiation of antiviral prophylaxis at the appropriate time to prevent HBV reactivation in case the antibody titer decreases over time in an occult HBV-infected patient with initial HBcAb positive and HBsAb titer >100 mIU/mL. In studies conducted in rheumatology, screening method and treatment approaches have been adopted with a similar frequency.[18]

The main limitations of this study could be attributed to its retrospective nature and the relatively low number of patients vaccinated before initiating ocrelizumab. The second limitation is; the serial antibody level screening test could have given us more information about vaccine response. However, with this study, whether there is a difference in the formation of protective antibodies between the patients vaccinated with the accelerated vaccination protocol before the anti-CD20 monoclonal antibody treatments and the patients vaccinated with the routine vaccination program has also been raised.

In conclusion, HBV serostatus should be evaluated before initiating ocrelizumab, a B-cell suppressor DMT used in the treatment of MS. It has been revealed that most MS patients need vaccination against HBV. If MS patients are to be treated with drugs that act on B cells, and if the patient needs a vaccine against HBV, the initiation of MS treatment may be delayed. After starting anti-CD20 therapy, adequate antibody response does not occur; for this reason, HBV serostatus should be evaluated at the diagnostic stage in patients who are thought to be diagnosed with MS, and if necessary, patients should be vaccinated in the early period.

Vaccinating patients at least 1 month before starting with ant-CD20 treatment (e.g., ocrelizumab, rituximab) with the accelerated vaccination program is more effective in terms of protective antibody titers. Thus, we recommend an accelerated vaccination program against HBV before treatment to achieve antibody formation. There is a specific risk associated with the use of biological therapies for patients with HBV infection, patients that were planned to receive these therapies should be accurately classified as active or inactive carriers. Patients with active HBV should undergo antiviral therapy before initiating immunosuppressive therapy, and occult HBV carriers should be monitored or prophylactic antiviral therapy initiated based on the risk of reactivation associated with the therapy administered. This approach will contribute to protecting not only MS patients but also the health of the entire community in the long run.

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Ethical declaration

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 1975 Declaration of Helsinki, as revised in 2008. Ethics committee approval has been granted from our institution.

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Conflicts of interest

There are no conflicts of interest.

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