*Research Article (Araştırma Makalesi)*

# Status of Hepatitis B Virus Serological In Patients With Multipl Sclerosis Using Ocrelizumab

## *Ocrelizumab Kullanan Multipl Skleroz Hastalarında Hepatit B Virüsü Serolojisi*

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**Özet**

**Amaç:** B-hücresi tüketen tedaviler, potansiyel viral enfeksiyon riskleri ile ilişkilidir. Hepatit B virüsü (HBV) enfeksiyonu en yaygın kronik viral enfeksiyondur ve dünya nüfusunun tahminen %30'unun mevcut veya geçmiş enfeksiyona ilişkin serolojik kanıtlara sahip olduğu tahmin edilmektedir.

**Gereç ve Yöntemler:** Çalışmamız tek merkezli, retrospektif, kesitsel bir çalışmadır. ocrelizumab alan Multiple Skleroz (MS) hastalarının klinik kayıtlarını geriye dönük olarak inceledik. Hastaların demografik ve klinik özellikleri, Ortalama Expanded Disability Status Scale (EDSS), MS için ocrelizumab öncesi ilaç geçmişi; ortalama ocrelizumab alma süreleri, sigara kullanım durumu, Hepatit C virüs, HIV serolojik durumları, HBV serolojik durumu, HBV tedavi durumu kaydedildi.

**Bulgular:** Çalışmaya ocrelizumab ile tedavi edilen 64 MS hastası dahil edildi. Ortalama yaş 41.6±9.8 yıl (min-max: 21-62 yıl) idi. Olguların %75'i kadın (n:48), %25'i erkek (n:16) idi. Olguların tümünde HIV, Hepatit C virüs serolojik testleri negatif idi. HBsAg %1.6 (n:1), Anti HBcIgG %12.5 (n:8) oranında pozitif saptandı. Hepatit B tedavisi başlanan hasta sayısı %12.5 (n:8) olup, 2 hastaya (%25) tenofovir disoproksil, 5 hastaya (%62.5) entekavir, 1 hastaya (12.5) tenofovir alafenamid tedavisi başlanmıştır. Hastaların ortalama ocrelizumab alma süreleri 28.5±13.1 ay (min-max:6-46 ay) olarak saptandı.

**Sonuç:** Sonuç olarak, ocrelizumab tedavisine başlamadan önce tüm hastalarda HBV taraması yapılmalıdır. Hem HBsAg hem de Anti-HBcIg testleri kullanılmalıdır. Anti-HBcIg G'nin varlığı HBV reaktivasyonunu engellemez, bu nedenle immünosupresif tedaviden önce Anti-HBcIg açısından mutlaka taranmalıdır.

**Anahtar kelimeler:** Multipl Skleroz, Hepatit B virüs, Ocrelizumab

**Abstract**

**Objective:** B-cell depleting treatments are associated with potential risks of viral infections. Hepatitis B virus (HBV) infection is the most common chronic viral infection and it is estimated that 30% of the world population has serological evidence of current or past infection.

**Material and Methods:** Our study is a single-center, cross-sectional study. We retrospectively reviewed the clinical records of MS patients receiving ocrelizumab. Demographic and clinical characteristics of patients, Expanded Disability Status Scale (EDSS), drug history before ocrelizumab for MS; Mean ocrelizumab intake times, smoking status, hepatitis C virus, HIV serological status, HBV serological status, HBV treatment status were recorded.

**Results:** The study included 64 MS patients treated with Ocrelizumab. The mean age was 41.6±9.8 years (min-max: 21-62 years). 75% of the cases were female (n:48), 25% were male (n:16). HIV and hepatitis C virus serological tests were negative in all cases. HBsAg was found to be positive in 1.6% (n:1) and Anti-HBcIgG in 12.5% (n:8). The number of patients who were started on hepatitis B treatment was 12.5% (n:8), and tenofovir disoproxil was started in 2 patients (25%), entecavir in 5 patients (62.5%), and tenofovir alafenamide in 1 patient (12.5). The mean duration of taking ocrelizumab for the patients was 28.5±13.1 months (min-max: 6-46 months).

**Conclusion:** In conclusion, all patients should be screened for HBV before starting ocrelizumab therapy. Both HBsAg and Anti-HBcIg G tests should be used. The isolated presence of Anti-HBcIg G may cause HBV reactivation. Therefore, Anti-HBcIg G should be screened before immunosuppressive therapy.

**Keywords:** Multiple Sclerosis, Hepatitis B virüs, Ocrelizumab

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## INTRODUCTION

Multiple Sclerosis (MS) is an autoimmune chronic inflammatory and neurodegenerative disease of the central nervous system that typically affects young adults, with most cases beginning between the ages of 20 and 40. Most patients have a relapsing form characterized by relapsing-remitting MS, but over time, it can develop a progressive course in the clinical process and turn into a secondary progressive multiple sclerosis form. Approximately 15% of patients have progressive disease from onset. The pathological feature of the disease in the acute phase is the accumulation of focal demyelinating lesions in the white and gray matter of the brain and spinal cord. Multiple Sclerosis has traditionally been considered a T-cell-mediated autoimmune disease, but in recent years, evidence for the influence of B cells in the pathophysiology of MS has accumulated both at the early stage and with disease progression. A more selective depletion of B cells is achieved with anti-CD20 monoclonal antibodies such as ocrelizumab used in the treatment of MS. B-cell depleting treatments are associated with potential risks of viral infections. Hepatitis B virus (HBV) infection is the most common chronic viral infection and it is estimated that 30% of the world population has serological evidence of current or past infection (1-4).

In this study, we aimed to present the HBV serology status, whether there is reactivation and our clinical experience with prophylaxis in MS patients who will be started on ocrelizumab.

## MATERIAL AND METHODS

Our study is a single-center, cross-sectional study. We retrospectively reviewed the clinical records of MS patients receiving ocrelizumab. The clinical files of the patients were reviewed from January 2018 to May 2022. Inclusion criteria were patients older than 18 years of age with relapsing-remitting MS, secondary progressive MS, primary progressive MS, currently using ocrelizumab and have received at least one dose of ocrelizumab in the past six months. Exclusion criteria were high-dose steroids (>20mg/day prednisone or equivalent), taking methyl prednisolone 1000mg/day monthly for the last 6 months, patients receiving intravenous immunoglobulin within the past six months, patients receiving additional immunosuppressive therapy in addition to ocrelizumab.

Demographic and clinical characteristics of patients, Expanded Disability Status Scale (EDSS), drug history before ocrelizumab for MS; Mean ocrelizumab intake times, smoking status, hepatitis C virus, HIV serological status, HBV serological status, HBV treatment status were recorded. The screening rates for hepatitis B surface antigen (HbsAg), hepatitis B surface antibody (AntiHBs) and hepatitis B core protein antibody (Anti-HBcIgG) before the start of treatment and prophylaxis given according to the screening results were retrospectively analyzed. In addition, antivirals started in eligible patients were recorded.

### Statistical analysis

SPSS 25 package program was used in the statistical evaluation of the data obtained in the study (SPSS Inc, Chicago, Illinois, USA). Continuous data were summarized as mean and standard deviation, while categorical data were summarized as numbers and percentages. The suitability of the data for normal distribution was evaluated by Kolmogorov Smirnov and Shapiro Wilk tests. Normally distributed data were given as mean + standard deviation. Data that were not normally distributed were given as median (minimum/maximum).

Approval for the study was obtained from the Ethics Committee of KSU Faculty of Medicine (Session: 2022/20 Decision no: 05, Date: 14.06.2022). The study was planned in accordance with the Declaration of Helsinki.

## RESULTS

The study included 64 MS patients treated with ocrelizumab. The mean age was 41.6±9.8 years (min-max: 21-62 years). 75% of the cases were female (n:48), 25% were male (n:16). In our study, there was 40.6% (n:26) relapsing remitting MS, 46.9% (n:30) secondary progressive MS, and 12.5% (n:8) primary progressive MS.

The status of taking medication before ocrelizumab was found to be fingolimod 26.6% (n:17), dimethyl fumarate 21.9% (n:14), interferon beta 1a 17.2% (n:11), naive patient group 4.7% (n:3) (**Table 1**).

The mean EDSS was 5.1±1.5 (min-max:1-6.5). The mean disease duration was 9.6±4.8 years (min-max:2-27 years). Smoking status was 87.5% (n:56) never smoked, current users or smoked less than 1 pack in the last 1 year, 7.8% (n:5), current smokers more than 1 pack 4.7% (n:3).

HIV and hepatitis C virus serological tests were negative in all cases. HBsAg was found to be positive in 1.6% (n:1) and Anti-HBcIgG in 12.5% (n:8). The number of patients who were started on hepatitis B treatment was 12.5% (n:8), and tenofovir disoproxil was started in 2 patients (25%), entecavir in 5 patients (62.5%), and tenofovir alafenamide in 1 patient (12.5). The mean duration of taking ocrelizumab for the patients was 28.5±13.1 months (min-max: 6-46 months).

**Table 1. Drugs used before ocrelizumab**

| | n | % |
|---|---|---|
| **Naive** | 3 | 4.7 |
| **Interferon beta-1b subcutan** | 5 | 7.8 |
| **Interferon beta-1a subcutan** | 11 | 17.2 |
| **glatiramer asetat** | 3 | 4.7 |
| **Fingolimod** | 17 | 26.6 |
| **Teriflunomide** | 1 | 1.6 |
| **Dimetiyl fumarate** | 14 | 21.9 |
| **Interferon beta-1a intramusculer** | 3 | 4.7 |
| **Other** | 7 | 10.9 |
| **Total** | 64 | 100.0 |

## DISCUSSION

Anti-CD20 agents (rituximab, ofatumumab, ocrelizumab) are monoclonal antibodies that target CD20, a surface cell antigen of B lymphocytes. The immune complexes formed after their binding are recognized and destroyed by phagocytes, thus leading to B-cell depletion. B-cell depleting treatments are associated with potential risks of viral infections. HBV infection is the most common chronic viral infection and an estimated 30% of the world's population is estimated to have serological evidence of current or past infection.

The observation that anti-CD20 monoclonal antibodies can cause HBV reactivation depends more than 20 years. So far, 183 cases of rituximab-associated HBV reactivation have been identified in a medical literature review between 1997 and 2009. Most studies of HBV reactivation in HBsAg-positive patients originate from the hematology and oncology literature. In the meta-analysis of Evens AM et al., regarding the anti-CD20 monoclonal antibody ritixumab treatment in lymphoproliferative diseases, it was emphasized that there was a significant increase in hepatitis B virus reactivation (6).

There are limited studies and case reports on HBV after ocrelizumab in MS patients. Phase III studies excluded HBsAg-positive patients, but allowed HBsAg-negative/anti-HBc-positive patients with undetectable HBV DNA. No cases of HBV infection were reported in MS studies. In phase III studies in rheumatoid arthritis, ocrelizumab and methotrexate combined therapy was associated with a single case of HBV reactivation, with an incidence of 1/300 HBsAg-negative/HBcAb-positive patients (without prophylaxis) (7,8).

A single case report of a 60-year-old diagnosis of primary progressive MS was described by Ciardi et al. (9). The patient was subsequently shown to have an immune carry immune-escape involving a defective HBsAg production and continued treatment with entacavir (10).

In our study, most of our patients had a history of previous use of dimethyl fumarate and fingolimod. Again, in a significant part of our patients, the advanced stage of the disease was found to be EDSS 5.1. This situation cause general infections due to disability. HCV and HIV tests were negative in all of our cases. HBsAg was found to be positive in 1.6% (n:1) and Anti-HBcIgG in 12.5% (n:8). The number of patients who were started on hepatitis B treatment was 12.5% (n:8), tenofovir disoproxil was started in 2 patients (25%), entecavir treatment was started in 5 patients (62.5%), tenofovir alafenamide treatment was started in 1 patient (12.5%). The follow-up of the patients continues with the joint follow-up of the infection clinic and the neurology clinic.

The limitation of our study is its retrospective nature and the relatively low number of cases. Further prospective, multicenter studies with large number of cases are needed to define the best follow-up strategy for MS patients.

In conclusion, all patients should be screened for HBV before starting ocrelizumab therapy. Both HBsAg and Anti-HBcIg G tests should be used. The isolated presence of Anti-HBcIg G may cause HBV reactivation. Therefore, Anti-HBcIg G should be screened before immunosuppressive therapy. Patients with positive HBV screening should be followed closely with infectious diseases. Considering the possible necessity of using immunomodulatory treatment such as ocrelizumab in the course of the disease, our study will contribute to the literature about awareness of hepatitis serological status of patients with MS, at the beginning of the disease and vaccination when necessary.

**Ethical approval:** Approval for the study was obtained from the Ethics Committee of KSU Faculty of Medicine (Session: 2022/20 Decision no: 05, Date: 14.06.2022). The study was planned in accordance with the Declaration of Helsinki.

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