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ID CASE

# Reactivation of Hepatitis B Virus With Immune-Escape Mutations After Ocrelizumab Treatment for Multiple Sclerosis

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Ocrelizumab is an anti-CD20 monoclonal antibody for the treatment of multiple sclerosis (MS) that is closely related to rituximab. We describe a case of hepatitis B virus (HBV) reactivation in an MS patient with resolved HBV infection receiving ocrelizumab. HBV reactivation was monitored with HBV-DNA and HBV surface antigen periodic assessment. Anti-HBV treatment with entecavir was started after HBV-DNA detection. Ocrelizumab can reactivate viral replication in patients with resolved HBV infection. HBV reactivation monitoring seems an effective and safe option for the management of these patients. More studies are needed to assess the optimal management of HBV reactivation in MS patients on ocrelizumab treatment.

**Keywords.** HBV; CD20; liver; biologics; entecavir; prophylaxis.

Ocrelizumab is an anti-CD20 monoclonal antibody for the treatment of primary progressive (PP) and relapsing (R) multiple sclerosis (MS) [1, 2]. Given the homology of ocrelizumab with other B-cell-targeting disease-modifying therapies (DMTs; such as rituximab), hepatitis B virus (HBV) reactivation is considered possible [1–3]. Current guidelines recommend either HBV prophylaxis or periodic monitoring for HBV surface antigen (HBsAg)–negative, anti-HBV core antigen antibody (HBcAb)–positive, HBV-DNA-negative subjects at high risk (>10%) or moderate to low risk (<10%) of HBV reactivation, respectively [4, 5]. Here we describe a case of HBV reactivation in an HBsAg-negative/HBcAb-positive patient on ocrelizumab treatment for MS.

## CASE REPORT

A 60-year-old Caucasian man affected by primary progressive multiple sclerosis (PPMS) since 2012, with an expanded disability status scale of 6.5 and previous treatment with azathioprine, was started on ocrelizumab in February 2018. Pre-ocrelizumab serologic tests showed the presence of antibodies to HBV surface (10.02 mUI/mL; lower detection limit, 2.5 mUI/mL) and core antigens (HBsAb and HBcAb, respectively), whereas HBV surface and e antigens (HBsAg and HBeAg, respectively) and antibodies to HBV e antigen (HBeAb) were negative. HBV-DNA was undetectable (<20 IU/mL), white blood cell (WBC) counts, lymphocyte percentages, and liver enzymes were within normal ranges. HBV reactivation was monitored, with monthly assessment of liver enzymes, HBsAg, and HBV-DNA. Six week after first ocrelizumab administration, HBV-DNA became detectable (41 IU/mL) and increased to 132 and 184 IU/mL at 10 and 13 weeks, respectively. The patient remained asymptomatic, and liver enzymes and WBC counts were unchanged (Figure 1), HBsAg remained undetectable. HBV phylogenetic analysis revealed a viral genotype D (subgenotype D3). No known drug resistance mutations were found in the reverse transcriptase gene (RT). Conversely, preS/S gene (encoding for HBsAg) was characterized by the mutation S117N, introducing a new N-linked glycosylation site on HBsAg, and P120T, C124Y, and G145A were localized in the major hydrophilic HBsAg region and known to act as immune-escape mutations. Furthermore, a stop codon was found at position 223, causing the production of a defective HBsAg. Treatment for HBV reactivation with entecavir 0.5 mg once daily was started, and HBV-DNA rapidly decreased to 100 IU/mL after 2 days of treatment, and below 20 IU/mL (detectable under the lower limit of quantification) at 2 and 4 weeks after first entecavir administration. Twenty-four weeks after ocrelizumab initiation, HBV-DNA was undetectable, and the patient received the scheduled dose of ocrelizumab. The patient remained asymptomatic, and liver enzymes and WBC counts were within normal ranges (Figure 1). HBsAg was persistently undetectable. The patient is currently under follow-up.

## DISCUSSION

Ocrelizumab can reactivate latent HBV infection in PPMS patients. In a previous report, ocrelizumab and methotrexate combined therapy was linked to HBV reactivation in a patient with rheumatoid arthritis [6]. Furthermore, rituximab-based

Received 11 November 2018; editorial decision 18 December 2018; accepted 21 December 2018; published online December 26, 2018

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DOI: 10.1093/ofid/ofy356

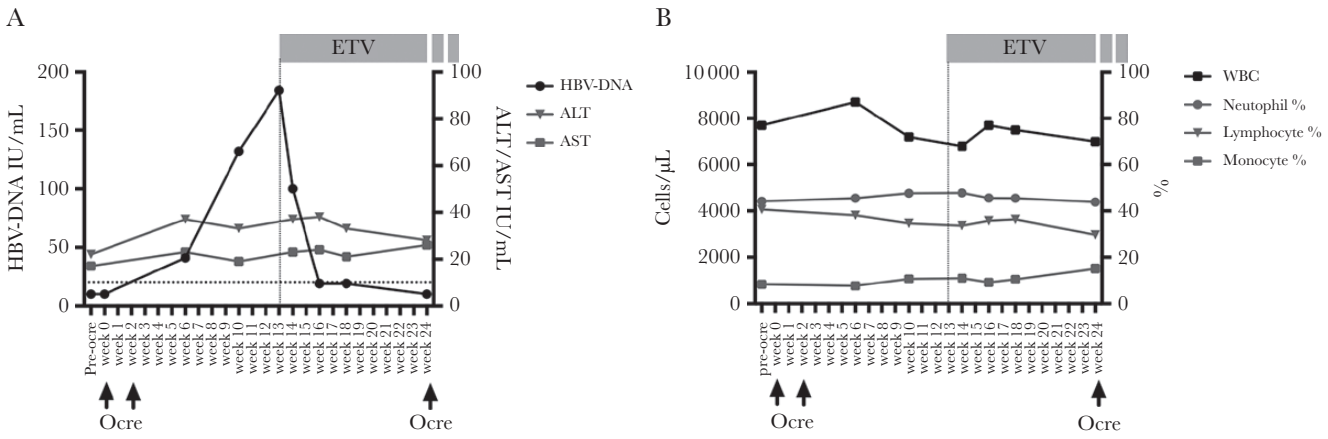


**Figure 1.** Longitudinal evaluation of hepatitis B virus (HBV)–DNA, liver enzymes, and white blood cell counts before and after ocrelizumab treatment. A, HBV-DNA, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) modifications over time during ocrelizumab treatment. B, White blood cell absolute counts and neutrophil, lymphocyte, and monocyte percentages over time during natalizumab treatment. Arrows represent ocrelizumab infusions. Horizontal dotted line: HBV-DNA lower limit of quantification (20 IU/mL). HBV-DNA was detected and quantified using the Cobas AmpliPrep/CobasTaqman HBV Test (Roche Molecular Diagnostic, Pleasanton, CA). Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ETV, entecavir; Ocre, ocrelizumab; WBC, white blood cells.

therapy for rheumatologic diseases has been associated with HBV reactivation in HBsAg-negative/HBcAb-positive subjects, with an increased risk for HBsAb-negative subjects [7].

In our case, the enrichment of immune-escape mutations in the preS/S gene encoding for HBsAg could have promoted the restoration of viral replication in the setting of suboptimal humoral immune response. The complex HBsAg mutational profile identified in this patient, together with the presence of a stop codon, which is associated with intracellular HBsAg retention, could have impaired HBsAg recognition by diagnostic antibodies, thus explaining the undetectability of HBsAg [8–10].

Current guidelines suggest starting prophylaxis for HBV reactivation for those subjects initiating an immune-suppressing treatment at high risk for HBV reactivation (>10%), and HBV reactivation monitoring can be adopted for patients at moderate (1%–10%) and low risk (<1%). Universal prophylaxis is generally recommended in selected clinical settings, such as long duration of immunosuppression, limited compliance to monitoring, or unknown risk of viral reactivation for new DMTs [4, 5]. HBV reactivation monitoring with HBV-DNA periodic assessment may not be cost-effective in special health care settings where low-cost entecavir is available.

Considering the absence of onco-hematological diseases, the experience derived from rituximab use in rheumatologic diseases [7, 11] and the positivity for HBsAb (despite a low titer) before ocrelizumab administration, in our patient HBV reactivation was managed with periodic monitoring instead of prophylaxis. HBV reactivation treatment with a potent antiviral agent seems to be an effective and safe option for HBsAg-negative/HBcAb-positive/HBV-DNA-negative patients starting ocrelizumab. HBV prophylaxis or reactivation monitoring can prevent ocrelizumab discontinuation. Moreover, compared with universal prophylaxis, periodic monitoring could spare HBV treatment in unnecessary cases. When starting prophylaxis or a therapy for HBV in the setting of immune-suppressing treatments, a long-term course of anti-HBV therapy should be considered and a high–genetic barrier antiviral is advisable in order to reduce the risk of drug resistance strain emergence. For this reason, entecavir is preferred over lamivudine in our patients, whereas tenofovir was spared for use in case of further HBV reactivation during entecavir treatment [12, 13].

Of note, HBV treatment should be continued for at least 12 months after B-lymphocyte-targeting drug discontinuation [13].

More studies are needed to define HBV reactivation risk during ocrelizumab treatment and the best approach for its management.

## Acknowledgments

***Financial support.*** This work was supported by Sapienza Università di Roma.

***Potential conflicts of interest.*** M.I. has received a grant from Società Italiana di Malattie Infettive (SIMIT) and honoraria for lectures from AIM Education s.r.l. M.A.Z. has received travel compensation for attending conferences for ViiV Healthcare. C.M.M. has received a research grant from Jansen-Cilag and honoraria for lectures from Gilead, MSD, Abbvie, and ViiV Healthcare. The other authors declare no conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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