Ocrevus and Coronavirus Disease (COVID-19) in Multiple Sclerosis

This document responds to your request for information on the Coronavirus Disease 2019 (COVID-19) and the use of Ocrevus® (ocrelizumab) in patients with multiple sclerosis.

In-Brief

- Clinical Experience
  - We are aware of multiple reports of Ocrevus-treated patients who have tested positive for COVID-19. Further details are provided below.

Abbreviations

AAN=American Academy of Neurology
ACTRIMS=Americas Committee for Treatment and Research in Multiple Sclerosis
CDC=Centers for Control of Disease and Prevention
COVID-19=coronavirus disease of 2019
CPAP=continuous positive airway pressure
CRP=C-reactive protein
DMT=disease-modifying treatment
ECTRIMS=European Committee for Treatment and Research in Multiple Sclerosis
IgA=immunoglobulin A
ICU=intensive care unit
IgG=immunoglobulin G
IgM=immunoglobulin M
IL-6=interleukin-6
MS=multiple sclerosis
PCR=polymerase chain reaction
PPMS=primary progressive multiple sclerosis
RMS=relapsing forms of multiple sclerosis
SARS-CoV-2=severe acute respiratory syndrome coronavirus 2
WHO=World Health Organization

Background Information

The current outbreak of the novel coronavirus (SARS-CoV-2) was first reported from Wuhan, China, on December 31, 2019, and is currently being studied by various health organizations. COVID-19 is caused by a new strain of coronavirus, so knowledge about how it may affect people with multiple sclerosis (MS) and those treated with Ocrevus is currently limited.

Patients receiving Ocrevus that are either exposed to the coronavirus or confirmed to have the COVID-19 infection, should contact their neurologist or other medical professional right away. Note that the incubation period for COVID-19 is commonly around 5 days, but has been estimated to range from 1-14 days, and some case reports suggest that it may be up to 24 days.[1]

Patients should speak with their neurologist or other medical professional before discontinuing their medications.

In addition to local Public Health guidance, or local guidance specifically issued by medical or patient associations, more information about COVID-19 can be found on the Centers for Control of Disease and Prevention (CDC) or the World Health Organization (WHO) websites:

- CDC: https://www.cdc.gov/coronavirus/2019-ncov/index.html
- WHO: https://www.who.int/emergencies/diseases/novel-coronavirus-2019

Considerations for Use of Ocrevus

Infections

In the Phase 3 clinical studies, Ocrevus has been shown to be associated with an increased risk of certain infections, including upper respiratory tract infections that were predominantly mild to moderate (classified as non-serious).[2] A higher proportion of Ocrevus-treated patients experienced non-serious

infections compared with patients taking interferon beta-1a (58% vs. 52%, respectively, in the OPERA I and II studies) or placebo (70% vs. 68%, respectively, in the ORATORIO study). These infections were predominantly mild to moderate, were equally likely to be bacterial or viral, and resolved with standard of care treatment, and in most cases patients remained on treatment with Ocrevus.

For further information on the topic of Ocrevus and infections, the interested reader may request the following Medical Letter: *Ocrevus and Infections in MS*

Adaptive Immune Response

Data from our Phase 3 OPERA I and II studies show that pre-existing adaptive immunity was not affected by Ocrevus treatment.[3] Additionally, in the VELOCE study (which evaluated the immune response to vaccines in patients with RMS), although reduced in comparison to placebo-treated patients, results show that patients treated with Ocrevus were able to mount immune responses to vaccines and new antigens.[4]

For further information on the topic of Ocrevus and adaptive immune response, the interested reader may request the following Medical Letter: *Ocrevus and Vaccinations in MS*

Clinical Experience in Use of Ocrevus in Patients with COVID-19

We are aware of multiple reports of Ocrevus-treated patients who have tested positive for COVID-19.[2] With the worldwide situation in relation to COVID-19 evolving, it is anticipated that the number of COVID-19 cases will increase, and as a result, it is likely that the number of COVID-19 cases in people with MS that are being treated with DMTs, will also rise.

Patient safety is Roche's highest priority, and consistent with our safety reporting processes we report to health authorities in accordance with standard pharmacovigilance processes.

There are no data currently available to inform specific recommendations or changes to treatment protocols for people treated with Ocrevus.

Reported Cases

As of April 30, 2020, there have been 100 validated reports received through standard pharmacovigilance activities relating to Ocrevus-treated patients with a confirmed or suspected SARS-Cov-2 infection and/or COVID-19.[5] Of these reports, 26 cases were considered suspected cases (defined as having signs and symptoms consistent with COVID-19, but not confirmed by laboratory testing; none of the suspected cases were hospitalized) and 74 cases were confirmed (reported as either testing positive for SARS-CoV-2 with symptoms of COVID-19 or clinically diagnosed with COVID-19).

Out of the 100 cases, 26 patients had either been previously hospitalized and discharged (n=13) or were still hospitalized at the time of the report (n=13). Of these 26 patients:

- 19 were reported as recovered or recovering
- 7 did not report an outcome

Of the 13 patients that were still hospitalized at the time of report:

- 5 were classified as critical (defined as requiring intensive care and/or mechanical ventilation)
    - 1 was in an ICU
    - 1 was on a ventilator
    - 1 had been in an ICU on a ventilator, but was weaned off after 5 days, and recovering with supplemental oxygen in the hospital

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- 1 required non-invasive ventilation for 4 days, and was reported as stable
- 1 required non-invasive ventilation, and was discharged from the hospital on supplemental oxygen

- 8 were severe (defined as pneumonia and/or hospitalization):
  - 4 were recovering
  - 4 did not report an outcome

In the 77 cases where COVID-19 symptom severity was provided, 64% (n=49), 30% (n=23), and 6% (n=5) were assessed to be asymptomatic/mild/moderate, severe, or critical, respectively.[5] For the 40 cases in which it could be calculated, the time from last Ocrevus dose to mean time of onset of COVID-19 was 12.5 weeks (median: 8.7 weeks; range: 3 days to 7.5 months). For the 46 cases in which it could be calculated, the mean exposure to Ocrevus at the time of onset of COVID-19 was 84.2 weeks (median: 67 weeks; range: 1 week to 8.3 years).

Additional Case Report

Novi et al. reported on a 58-year-old male with PPMS who developed COVID-19 while on Ocrevus treatment.[6] The patient initiated treatment with Ocrevus in January 2018, with his last dose received in August 2019 (a subsequent dose was scheduled for February 2020, but was delayed to March 2020 for patient convenience). At the time of his last infusion, the patient exhibited moderately low IgG levels (6.5 g/L [reference range: 8-17 g/L]) with normal IgM and IgA levels, and peripheral B-cell depletion (8 CD19+ cells/mm^3). On March 6, 2020, the patient developed a fever and cough, and was subsequently admitted to the hospital on March 10 due to persistent high fevers and a severe cough. The patient exhibited normal leukocyte and lymphocyte counts, an elevated CRP level (63.1 mg/L [reference range: 0-5 mg/L]), a mild increase in IL-6 levels (6 pg/mL [reference range: 0-3.4 pg/mL]), and moderate IgG hypogammaglobulinemia (6.5 g/L). COVID-19 was confirmed with two positive nasal swabs for SARS-CoV-2 on PCR. The patient's arterial blood gas test showed normal blood oxygenation, and the patient was treated with acetaminophen for fevers, which resolved after 2 days. The patient was discharged to home quarantine on March 13, with normal leukocyte and lymphocyte counts, a reduced CRP level (16.4 mg/L), and complete peripheral B-cell depletion (1 CD19+ cells/mm^3). As of March 28, the patient continued to be on home quarantine with no occurrence of new symptoms.

Ocrevus and Coronavirus Disease (COVID-19) in Multiple Sclerosis Reference List

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