Ocrelizumab and COVID-19

Patient safety is Roche/Genentech's highest priority and we are closely monitoring the evolving coronavirus disease (COVID-19) situation. We believe that treatment decisions should be made between a patient and their treating neurologist/healthcare professional based on a benefit/risk assessment specific to the individual patient.

COVID-19 is caused by a new strain of coronavirus called SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), and although new findings and case studies around the impact of this virus continue to emerge, knowledge of the effect of SARS-CoV-2 on the general population and multiple sclerosis (MS) community remains limited.

Like many other disease-modifying therapies for MS, ocrelizumab works by making changes to the immune system.

Per the Ocrevus Summary of Product Characteristics (SmPC; Section 4.8 Infection):

In the active-controlled studies in RMS, infections occurred in 58.5% of patients receiving Ocrevus vs 52.5% of patients receiving interferon beta 1a. Serious infections occurred in 1.3% of patients receiving Ocrevus vs 2.9% of patients receiving interferon beta 1a. In the placebo-controlled study in PPMS, infections occurred in 72.2% of patients receiving Ocrevus vs 69.9% of patients receiving placebo. Serious infections occurred in 6.2% of patients receiving Ocrevus vs 6.7% of patients receiving placebo. An increase in the rate of serious infections was observed in RMS between Years 2 and 3, but not in subsequent years. No increase was observed in PPMS.

In patients with active infections, treatment with ocrelizumab should be delayed until the infection is resolved.

Frequently Asked Questions

1. **Do you believe that patients on ocrelizumab are at a higher risk of contracting SARS-CoV-2 infection and/or having a more severe course of COVID-19?**
    - We are closely assessing emerging data, both our own pharmacovigilance data and real-world data (RWD).
        - Our pharmacovigilance data suggest that COVID-19 follows a similar course in ocrelizumab-treated patients with MS as in the general population.
        - Risk factors for severe COVID-19 in the general population include old age and presence of comorbidities, including hypertension, diabetes, obesity, smoking, and cardiovascular and lung diseases, which are likely to be similar in the MS population and those treated with ocrelizumab.
        - Major risk factors identified for fatal COVID-19 in the general MS population are advanced age (>50 years old), high levels of disability, a progressive form of MS, and comorbidities (eg, cardiovascular).
        - We are aware that emerging RWD from registries show varying findings on the impact of ocrelizumab treatment on the severity of COVID-19 in people with MS.

The differences in these findings are to be expected because of the challenges of collecting, analyzing, and interpreting RWD, and how healthcare systems in different counties are being impacted by the pandemic.
    - There has been no association between ocrelizumab and fatal COVID-19 outcomes reported to date.
    - From the limited RWD available globally, the general MS population does not seem to be at higher risk of contracting SARS-CoV-2.
    - The emerging RWD have not changed our position and assessment of the benefit/risk of ocrelizumab in patients with MS.
- We believe we need to continue to gather as much data as we can to help address limitations in RWD and get a clearer understanding of the impact of COVID-19 on patients treated with ocrelizumab in the absence of randomised, controlled trials to inform future recommendations.
- We believe that treatment decisions should be made between a patient and their treating neurologist or other medical professional based on a benefit/risk assessment specific to the individual patient.
- Physicians and patients should consult the Ocrevus SmPC for relevant information regarding the safety of ocrelizumab. For additional information and context surrounding the risk of infections, including COVID-19, with ocrelizumab, please consult the "Additional Information on Topics of Interest" section of www.ocrelizumabinfo.global.

2. Do you recommend any change to patients' treatment with ocrelizumab because of COVID-19?

- We are actively discussing insights and perspectives related to MS and COVID-19 with the neurology community. Currently, there are only limited data available to inform specific recommendations or changes to treatment protocols for people treated with ocrelizumab.
- From our pharmacovigilance data, the risk factors for severe/fatal COVID-19 outcomes do not indicate a difference between ocrelizumab-treated patients and the general population.
- We appreciate how difficult it may be for physicians and people with MS to make treatment decisions at this time, and we understand that some neurological and patient societies recommend the delay of treatment initiation or re-treatment. We believe that patients should speak with their neurologist or other medical professional before discontinuing or delaying treatment, so that decisions can be made based on a benefit/risk assessment specific to the individual patient.

3. What guidance can you provide for the treatment with ocrelizumab following a delay of a scheduled dose?

- The current clinical situation may necessitate to delay a scheduled dose of ocrelizumab due to logistical reasons or based on an individual benefit/risk decision.
- Per the Ocrevus SmPC (Section 4.1 Posology and method of administration; Subsequent Doses):

  Subsequent doses of Ocrevus thereafter are administered as a single 600 mg intravenous infusion every 6 months. The first subsequent dose of 600 mg should be administered six months after the first infusion of the initial dose.

- Per the Ocrevus SmPC (Section 4.1 Posology and method of administration; Delayed or Missed Doses):

  If an infusion of Ocrevus is missed, it should be administered as soon as possible; do not wait until the next planned dose. The treatment interval of 6 months (with a minimum of 5 months) for Ocrevus should be maintained between doses (see Table 1).

- Based on limited data available from the OPERA I and II studies, a delay in ocrelizumab dosing did not appear to increase the rate of infusion-related reactions with the next 600-mg dose administered as a single infusion. Patients who missed more than one ocrelizumab dose may have a higher risk of IRRs; however, there are currently no data on whether re-initiation of treatment with 2x300mg dual infusions is needed to mitigate this risk.

OPERA I/II – IRRs/Infusions Based on Time Between Doses (ITT Population)*											
Time from Last Dose (weeks)	≤24	24-28	28-32	32-36	36-40	40-44	44-48	48-52	52-56	56-60	>60
IRRs/ Infusions (%)	338/6,851 (4.7%)	138/2,145 (6%)	23/164 (12.3%)	1/28 (3.4%)	0/11 (0%)	0/9 (0%)	2/13 (13.3%)	3/11 (21.4%)	0/4 (0%)	1/2 (50%)	1/6 (14.3%)

*Cut-off date: January 2020
Abbreviations: IRR=infusion-related reactions; ITT=intention to treat.

4. Clinical trial data shows that patients on ocrelizumab have an increased risk of developing infections. How are you assessing the potential risk to ocrelizumab patients?

- COVID-19 is caused by a new strain of coronavirus called SARS-CoV-2, so knowledge about how it may affect people with MS and those treated with ocrelizumab is currently unavailable.
- Like many other disease-modifying therapies for MS, ocrelizumab works by making changes to the immune system.
- Per the Ocrevus SmPC (Section 4.8 Infection):

  In the active-controlled studies in RMS, infections occurred in 58.5% of patients receiving Ocrevus vs 52.5% of patients receiving interferon beta 1a. Serious infections occurred in 1.3% of patients receiving Ocrevus vs 2.9% of patients receiving interferon beta 1a. In the placebo-controlled study in PPMS, infections occurred in 72.2% of patients receiving Ocrevus vs 69.9% of patients receiving placebo. Serious infections occurred in 6.2% of patients receiving Ocrevus vs 6.7% of patients receiving placebo. An increase in the rate of serious infections was observed in RMS between Years 2 and 3, but not in subsequent years. No increase was observed in PPMS.

- Patient safety is Roche/Genentech's highest priority. As a company we are closely following developments regarding COVID-19 and we are committed to keeping the MS community updated with any new information to help inform health decisions related to ocrelizumab.

5. **Can you provide more detail about the upper and lower respiratory tract infections from Pivotal Clinical Trials?**
    - The upper and lower respiratory tract infections reported in patients treated with ocrelizumab were predominantly mild to moderate (80–90%).
    - The proportion of respiratory tract infections was higher in ocrelizumab-treated patients compared with those taking interferon beta-1a or placebo.
        - In the RMS clinical trials, 40% of ocrelizumab-treated patients and 33% of interferon beta-1-a-treated patients experienced an upper respiratory tract infection, and 8% of ocrelizumab-treated patients and 5% of interferon beta-1-a-treated patients experienced a lower respiratory tract infection.
        - In the PPMS clinical trial, 49% of ocrelizumab-treated patients and 43% of patients who received placebo experienced an upper respiratory tract infection, and 10% of ocrelizumab-treated patients and 9% of patients who received placebo experienced a lower respiratory tract infection.

6. **Which type of infections were generally observed during treatment with ocrelizumab?**
    - Rates of serious infection in all patients exposed to ocrelizumab in clinical trials remain consistent with rates of infection-related hospitalisation in real-world MS cohorts.
        - Ocrelizumab was not associated with an increased risk of serious infections in patients with MS, as shown in our phase 3 clinical studies vs comparators (interferon beta-1a or placebo). Of those serious infections that occurred, the vast majority were bacterial, and the patients responded to standard of care treatment. Longer-term data through continued observation in our open-label extension studies have revealed no new or particular pattern of serious infections in patients with MS treated with ocrelizumab.
    - Ocrelizumab has been shown to have an increased risk of contracting certain infections, including upper respiratory tract infections that were predominantly mild to moderate (classified as non-serious).
        - A higher proportion of ocrelizumab-treated patients experienced non-serious infections compared with patients taking Rebif (interferon beta-1a) (58.5% vs 52.5%) or placebo (72.2% vs 69.9%). 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 ocrelizumab.

7. **Are there data that show how treatment with ocrelizumab affects the body's ability to create an adaptive immune response?**
    - Per the Ocrevus SmPC (Section 4.4 - Vaccinations):

      The safety of immunisation with live or live-attenuated vaccines, following Ocrevus therapy has not been studied and vaccination with live-attenuated or live vaccines is not recommended during treatment and not until B-cell repletion (in clinical trials, the median time for B-cell repletion was 72 weeks). See section 5.1.

      In a randomized open-label study, RMS patients were able to mount humoral responses, although decreased, to tetanus toxoid, 23-valent pneumococcal polysaccharide with or without a booster vaccine, keyhole limpet hemocyanin neoantigen, and seasonal influenza vaccines.

- For more information, please go to the most recent ocrelizumab safety data (link here).