Prescribing information*

Progressive Multifocal Leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the John Cunningham (JC) virus that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability.

Although no cases of PML were identified in ocrelizumab clinical trials, a risk of PML cannot be ruled out since JC virus infection resulting in PML has been observed in patients treated with anti-CD20 antibodies and other MS therapies and associated with risk factors (e.g., patient population, polytherapy with immunosuppressants). Physicians should be vigilant for the early signs and symptoms of PML, which can include any new onset, or worsening of neurological signs or symptoms, as these can be similar to MS disease.

If PML is suspected, dosing with ocrelizumab must be withheld. Evaluation including MRI scan, preferably with contrast (compared with pre-treatment MRI), confirmatory CSF testing for JC viral DNA and repeat neurological assessments should be considered. If PML is confirmed, treatment must be discontinued permanently.

When switching from drugs with prolonged immune effects, such as fingolimod, natalizumab, teriflunomide, cladribine or mitoxantrone, consider the duration and mode of action of these drugs because of additive immunosuppressive effects when initiating ocrelizumab.[1,2]

**Indications vary in different countries. The local prescribing information for your country is the primary source of information on the known and potential risks associated with ocrelizumab.*

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Ocrelizumab and PML

As of December 2020, no unconfounded[a] PML cases associated with ocrelizumab therapy have been reported. Out of more than 200,000 patients treated globally (clinical trials and post-marketing experience) there have been 10 confirmed, confounded cases of PML in patients treated with ocrelizumab, of which 9 were carry-over[b] cases from a prior DMT.[3,4]

Narratives of confirmed, confounded PML cases in patients treated with ocrelizumab

Report Date	Case Description
	Carry-over cases
May 2017	Case was from a compassionate-use program in a JCV+ patient who switched to ocrelizumab after 36 infusions of natalizumab. Assessment of the case resulted in it being reported to regulators as related to natalizumab and not ocrelizumab.[3]
April 2018	The patient had increasingly worsening neurological symptoms and MRI changes prior to discontinuing treatment with fingolimod in December 2017. The patient started treatment with ocrelizumab in March/April 2018. In April 2018, MRI changes, worsening clinical presentation and JCV DNA in the CSF confirmed the diagnosis of PML. The case was reported to regulators as a carry-over PML from fingolimod as assessed by the physician.[3]
April 2018	A JCV+ patient was previously treated with natalizumab for 7 years. Due to MRI changes and worsening clinical symptoms, natalizumab was discontinued in February 2018. The patient received a single infusion of ocrelizumab in April 2018. The case was reported by the physician as a carry-over PML from natalizumab.[3]
June 2018	A JCV+ patient was previously treated with natalizumab for a total of over 6 years, with the last infusion in March 2018. The patient had new and progressive symptoms since February 2018 prior to commencing treatment with ocrelizumab (first 2 infusions) in April/May 2018. In late May, brain MRI was consistent with PML, supported by a subsequent brain biopsy. The physician assessed the PML as related to natalizumab.[3]
July 2018	A JCV+ patient was previously treated with natalizumab for a total of 2 years, with the last infusion in March 2018. The patient had new and progressive symptoms since the beginning of June 2018, prior to commencing treatment with ocrelizumab (first 2 infusions) in the middle and end of June 2018. In the beginning of July 2018, the brain MRI showed lesions consistent with the diagnosis of PML, which was subsequently supported by detection of JCV in the CSF by PCR.[3]
September 2018	The patient was previously treated with natalizumab for a total of 4 years, with the last infusion in March 2018. The patient had had increasingly worsening neurological symptoms and MRI changes in February 2018 (reported as "exacerbation of MS"), prior to discontinuing treatment with natalizumab. Ocrelizumab treatment was started in May/June 2018 following a further MRI in May described as showing "further deterioration", and a lumbar puncture that was reported as negative. In August 2018, MRI changes and a positive lumbar puncture confirmed a diagnosis of PML. The case was reported to regulators as a carry-over PML from natalizumab as assessed by the physician.[3]
February 2019	The patient was previously treated with natalizumab for approximately 2 years with a high anti-JCV antibody index in serum (>1.5) prior to initiation of natalizumab treatment. The last infusion of natalizumab occurred in September 2018. The patient had increasingly worsening neurological symptoms and MRI changes in October 2018. Ocrelizumab treatment was started in November 2018 (full first dose). At the end of December 2018, the patient experienced further clinical deterioration. An MRI performed mid-January 2019 showed further changes and a CSF analysis positive for JCV DNA confirmed the diagnosis of PML. We have since been informed that the patient passed away.[3]
January 2020	A JCV+ patient, with worsening RMS following the birth of her first child, began therapy with natalizumab in October 2017. After approximately 2 years, and due to a positive JCV titre, natalizumab therapy was discontinued. The last dose of natalizumab was received on 27 August 2019. Ocrelizumab therapy was initiated on 17 November 2019. Two weeks later, at the beginning of December 2019, the patient's speech suddenly deteriorated and before Christmas, she developed worsening motor symptoms. Initially, these symptoms were considered to be related to the underlying disease; however, MRI scans conducted in January 2020 revealed signs of PML, and this was supported by detection of JCV DNA in the CSF by PCR. The case was reported by the physician as carry-over PML from natalizumab.[3]
October 2020	A JCV+ patient was treated with natalizumab for approximately 10 years (for the last 2 years the patient received extended interval dosing). The last natalizumab dose was administered in April 2019 and 55 days later, therapy with ocrelizumab was initiated. In early July, CSF analysis was positive for JCV DNA and there were signs of PML on MRI (in retrospect, subtle signs of PML were present on MRI from April 2019). Two weeks later, PML-IRIS was suspected based on MRI findings and the patient experienced mild symptoms. Clinical symptoms and MRI lesions stabilised following treatment and ocrelizumab was restarted in March 2020. The case was reported as mild carry-over PML from natalizumab.[3]
	Non-carry-over case
September 2019	A 78-year-old patient treated with ocrelizumab for approximately 2 years (last infusion in February 2019), diagnosed as a result of clinical and MRI findings compatible with PML and subsequent detection of a high number of JCV DNA copies in the CSF, with ocrelizumab as a probable contributor. The patient had a long-standing history of MS but had not been previously treated with a DMT. However, other confounding factors were reported by the physician, namely the patient's age with potential immunosenescence, low ALC prior to treatment with ocrelizumab (max CTCAE Grade 1, no subtypes available), as well as low ALC (max Grade 2), low CD4+ (max Grade 2) and low CD8+ counts during treatment. Following the PML diagnosis, the patient was monitored and supported. However, we have since been informed that the patient passed away.[3]

Footnotes: [a]Confounding of adverse event reporting occurs when the assessment of association between exposure to a drug and an adverse event is distorted by the effect of one or several other variables that are also risk factors for the outcome of interest;[5,6] in the cases detailed above, confounders included such factors as serum anti-JCV antibodies, prior treatment with another DMT (carry-over PML), age-related immunosenescence and lymphopenia. [b]Carry-over PML: PML that develops a few months after stopping one DMT known to increase the risk of PML and starting a different DMT. In these cases, PML could have developed without causing symptoms while the patient was still on the previous DMT, or shortly after stopping the previous DMT.[7]

Abbreviations: ALC=absolute lymphocyte count; CD=cluster of differentiation; CSF=cerebrospinal fluid; CTCAE=Common Terminology Criteria for Adverse Events; DMT=disease-modifying therapy; JCV=John Cunningham virus; MRI=magnetic resonance imaging; MS=multiple sclerosis; PCR=polymerase chain reaction; PML=progressive multifocal leukoencephalopathy; PML-IRIS=PML immune reconstitution inflammatory syndrome; RMS=relapsing MS.

References: 1. OCREVUS® (ocrelizumab) Summary of Product Characteristics (SmPC): https://www.ema.europa.eu/en/documents/product-information/ocrevus-epar-product-information_en.pdf (Last accessed January 2020); 2. OCREVUS® (ocrelizumab) Prescribing Information (PI): https://www.gene.com/download/pdf/ocrevus_prescribing.pdf (Last accessed January 2020); 3. Roche data on file; 4. Clifford DB, et al. Presented at ECTRIMS 2019 (Poster; 970); 5. Varallo FR, et al. *Clin Ther.* 2017;39:686–696; 6. Mills EA and Mao-Draayer Y, *Mult Scler.* 2018;24:1014–1022; 7. Giovannoni G, et al. *Pract Neurol.* 2016;16:389–393.