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, JC virus infection resulting in PML has been observed in patients treated with other anti-CD20 antibodies and other MS therapies and has been associated with some risk factors (eg, immunocompromised patients, polytherapy with immunosuppressants).

At the first sign or symptom suggestive of PML, withhold ocrelizumab and perform an appropriate diagnostic evaluation. MRI findings may be apparent before clinical signs or symptoms. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

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

Ocrelizumab & PML

As of July 31, 2019, no unconfounded PML cases[a] associated with ocrelizumab therapy have been reported; there have been 7 confirmed cases of carry-over PML[b] in MS patients treated with ocrelizumab, out of more than 120,000 MS patients treated globally (clinical trials and post-marketing experience):[2]

Report Date	Case Description
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.[2]
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.[2]
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.[2]
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 in June 2018. The physician assessed the PML as related to natalizumab.[2]
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.[2]
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 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 which 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.[2]
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.[2]

There have been five unconfirmed carry-over cases reported as PML, or suspicion of PML,[3] that do not meet AAN PML diagnostic criteria[4] for definite PML; all reports were in patients previously treated with natalizumab and already at higher risk for a natalizumab-associated PML.

Note: All of the above PML cases were non-fatal as of the time of each respective report.

[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] in the cases detailed above the confounding variable is the prior treatment with another DMT.

[b]Carry-over PML: PML that develops a few months after stopping one disease modifying therapy (DMT) 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.[6]

CSF=cerebrospinal fluid; DNA=deoxyribonucleic acid; JCV=John Cunningham virus; MRI=magnetic resonance imaging; MS=multiple sclerosis; PCR=polymerase chain reaction.

References:
1. https://www.gene.com/download/pdf/ocrevus_prescribing.pdf; 2. Genentech data on file;
3. Clifford DB, et al. Presented at: ECTRIMS 2019 (Poster 970); 4. Berger JR, et al. Neurology. 2013;80:1430–1438;
5. Varallo FR, et al. Clin Ther. 2017;39:686–96; 6. Giovannoni G, et al. Pract Neurol. 2016;16:389–393.

Information current as of July 31, 2019.

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OCR/032218/0083a(10)

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