Ocrelizumab and PML

Overview

As of June 2024 there have been 16 confirmed cases of PML in more than 350,000 patients treated with ocrelizumab globally, amounting to a total of more than 1,000,000 patient years. Of these, 12 were carry-over* cases attributed to a prior DMT[1,2]

Narratives of confirmed PML cases in patients treated with ocrelizumab

Report date	Previous DMT	Case description
Carry-over cases		
May 2017	**NTZ**	Case was from a compassionate-use programme 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.[1]
Apr 2018	**FTY**	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.[1]
Apr 2018	**NTZ**	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.[1]
Jun 2018	**NTZ**	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.[1]
Jul 2018	**NTZ**	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.[1]
Sep 2018	**NTZ**	The patient was previously treated with natalizumab for a total of 4 years, with the last infusion in March 2018. The patient had experienced 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.[1]
Feb 2019	**NTZ**	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.[1]
Jan 2020	**NTZ**	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.[1]

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Report date	Previous DMT	Case description
		Carry-over cases
Oct 2020	**NTZ**	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.[1]
Oct 2021	**NTZ**	A 41-year-old was diagnosed with PML <1 month after starting ocrelizumab. Signs and symptoms suggestive of PML predated initiation of ocrelizumab treatment. The patient previously received natalizumab for approximately 3 years. The patient fully recovered and was discharged from hospital. **Please note that this case has not been independently verified** as the reporting physician refused consent to follow up.[1]
Dec 2022	**NTZ**	A 49-year-old male patient was diagnosed with PML in December 2022. The patient received natalizumab from 2019 to September 2022 and discontinued due to concerns of PML (JCV index values ranged from 3.11 to 4.47). Ocrelizumab therapy was initiated on Nov 2022 and the patient developed symptoms of PML just under one week later (left face and arm weakness). In retrospect there were MRI changes consistent with PML in April and August 2022. PML diagnosis was confirmed in December 2022 by JCV DNA in the CSF and further MRI changes. The patient died from PML on 12 January 2023. The case was reported as carry-over PML from natalizumab.[1] **Please note that this case was not independently verified as copies of MRIs were not provided**.
Mar 2024	**DMF**	Case with scant details and unclear chronology received via a regulatory health authority from the MAH for dimethyl fumarate (DMF). A 65-year-old female patient was treated with DMF from 2016 to 21 Aug 2023. The narrative states: she was diagnosed with PML on 11 Aug 2023, developed lymphopenia on 22 Aug 2023, CSF was negative for JCV DNA in August and October 2023. She started therapy with ocrelizumab on an unknown date in September 2023. On an unknown date in 2024 it is reported that MRI confirmed lesions related to PML. On 28 Feb 2024, JCV DNA was detected in her CSF. No further event details were available.[1] **Please note that independent verification of the case is not possible** and it has been conservatively assessed as confirmed carry-over PML.

Non-carry-over cases	
Sep 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. 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. The patient decided to receive palliative care and died 1 month following diagnosis of PML.[1]
Dec 2021	A 57-year-old patient treated with ocrelizumab for approximately 4.5 years (last infusion in August 2021), began to develop symptoms suggestive of PML whilst hospitalised for acute infectious ileitis in November 2021. MRI findings were consistent with PML and the diagnosis was confirmed in December 2021 after JCV DNA copies were detected in the CSF. Transient lymphopenia (max CTCAE Grade 2) of unknown aetiology was detected in the 20 months preceding the onset of PML; external expert committee review determined that there was a potential causal association with ocrelizumab. The patient received treatment for PML and pancolitis and had begun intensive rehabilitation; however, her condition worsened and she chose to receive palliative care, passing away due to PML complications in February 2022.[1]
May 2023	A 56-year-old male patient treated with ocrelizumab for ~4 years, after switching from glatiramer acetate, presented with an episode of aphasia which worsened after two months. Subsequent MRI scans showed lesions compatible with PML, and JC virus DNA was confirmed in the CSF. No relevant comorbidities or history of other immunosuppressive drugs were reported. Laboratory findings were unremarkable with normal lymphocyte and neutrophil counts, and immunoglobulin levels at the time of the PML diagnosis. In the absence of established risk factors for PML, a potential association with ocrelizumab therapy could not be excluded by the external expert committee. The patient was hospitalized upon laboratory confirmation of PML, while appearing to be in a stable condition. Patient showed gradual clinical improvement and was discharged two weeks later. The patient attended therapy and rehabilitation twice a week, showed some improvement and initially remained stable. However, his condition later deteriorated and he was readmitted to hospital with limb weakness and worsening aphasia. We were informed on 26 July 2023 that the patient had died from PML.
Feb 2024	A 49-year-old male patient with a history of epilepsy, presented with suspected PML (cognitive impairment and MRI changes) approximately 2 years after starting treatment with ocrelizumab for PPMS. Based on the presence of haemophilus influenzae DNA and the absence of JCV DNA in the CSF, a diagnosis of PML was initially discounted and the patient was diagnosed with haemophilus encephalitis. Over the following months, the patient's condition worsened and when a repeat lumbar puncture was positive for JCV DNA, the patient was diagnosed with PML. At the last report, the patient was in hospital receiving treatment with mefloquine and mirtazapine and his condition was stable.

Footnotes

*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;[3]

†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;[4,5]
in the cases detailed above, confounders included factors such prior treatment with another DMT (carry-over PML), age-related immunosenescence and lymphopenia.

Abbreviations
ALC, absolute lymphocyte count; COVID-19, coronavirus disease 2019; CSF, cerebrospinal fluid; CTCAE, Common Terminology Criteria for Adverse Events; DMF, dimethyl fumarate; DMT, disease-modifying therapy; DNA, deoxyribonucleic acid; FTY, fingolimod; JCV, John Cunningham virus; MAH, marketing authorisation holder; NTZ, natalizumab; PCR, polymerase chain reaction; PML, progressive multifocal leukoencephalopathy; PML-IRIS, PML immune reconstitution inflammatory syndrome; PPMS, primary progressive MS; RMS, relapsing MS.

References

1. Roche data on file;
2. Clifford DB, *et al.* Presented at ECTRIMS 2019 (Poster P970);
3. Giovannoni G, *et al. Pract Neurol* 2016;16:389–93;
4. Varallo FR, *et al. Clin Ther* 2017;39:686–96;
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