Mild progressive multifocal leukoencephalopathy after switching from natalizumab to ocrelizumab

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Neurol Neuroimmunol Neuroinflamm 2021;8:e904. doi:10.1212/NXI.0000000000000904

Abstract

Objective
To describe the disease course of carryover progressive multifocal leukoencephalopathy (PML) after switching from natalizumab to ocrelizumab in 2 patients with relapsing-remitting MS.

Methods
Two case reports with 1 year of follow-up and retrospective longitudinal measurements of serum neurofilament light (NfL) levels and B-cells.

Results
PML was diagnosed 78 days (case 1) and 97 days (case 2) after discontinuation of natalizumab. Both patients developed mild immune reconstitution inflammatory syndrome (IRIS) despite B-cell depletion caused by ocrelizumab. NfL levels increased in both patients during PML-IRIS. PML-IRIS lesions stabilized after treatment with mefloquine and mirtazapine, followed by methylprednisolone, and both patients continued therapy with ocrelizumab when B-cells started to repopulate.

Conclusions
The clinical course of carryover PML was mild in both patients, suggesting that B-cell depletion possibly did not aggravate PML-IRIS in these 2 patients.
Natalizumab is an effective drug approved for the treatment of relapsing-remitting MS (RRMS). A rare but dangerous complication is progressive multifocal leukoencephalopathy (PML), an opportunistic infection of the brain caused by the John-Cunningham virus (JCV). After PML diagnosis, discontinuation of natalizumab often leads to immune reconstitution inflammatory syndrome (IRIS).1

Ocrelizumab is another effective disease-modifying therapy in MS. Nine confirmed cases of PML have been reported in patients using ocrelizumab, although not yet published (Clifford et al. ECTRIMS 2020; Roche data on file 2020). In 8 cases, patients previously used natalizumab or fingolimod, likely causing PML. This phenomenon has been described as carryover PML.2

Neurofilament light (NfL) is a promising biomarker of neuronal damage and could potentially support early radiologic findings of PML.3,4 We report 2 cases of carryover PML-IRIS after switching from natalizumab to ocrelizumab with a relatively mild clinical disease course in whom longitudinal serum NfL (sNfL) was measured in retrospect.

**Data availability**
Anonymized data will be shared by request from any qualified investigator.

**Standard protocol approvals, registrations and patient consents**
Both patients provided informed consent for publishing of this article.

**Case 1**
A 34-year-old man with RRMS started treatment with natalizumab in 2012. JCV serostatus was positive (index 2.22–3.23 between 2012 and 2018) as measured by the STRATIFY-2 test (Unilabs, Copenhagen, Denmark). The patient wished to continue treatment despite PML risk. Consequently, every 3 months, MRI brain scans were performed as per local protocol approvals, registrations, and patient consents. In late March 2019, a fast-growing juxtacortical white matter lesion in the right frontal lobe suspect for PML was detected. Follow-up scans showed progression of enhancement suspect for PML-IRIS (C, D, G, H). The amount of days indicates the time from the first infusion with ocrelizumab. Natalizumab was discontinued in January 2019, and PML was diagnosed after 78 days. Blue arrow indicates subtle signs suggestive of PML in retrospect before diagnosis (B). White arrows indicate the lesions suggestive of PML-IRIS. FLAIR = fluid-attenuated inversion recovery; IRIS = immune reconstitution inflammatory syndrome; PML = progressive multifocal leukoencephalopathy.

**Glossary**

EDSS = expanded disability status scale; EID = extended interval dosing; IRIS = immune reconstitution inflammatory syndrome; IVMP = IV methylprednisolone; JCV = John-Cunningham virus; NfL = neurofilament light; PML = progressive multifocal leukoencephalopathy; RRMS = relapsing-remitting MS; sNfL = serum NfL.
pharmacovigilance scan protocol. The follow-up showed no disease activity under natalizumab treatment. In January 2019, because of the patient’s desire for a treatment switch to ocrelizumab, natalizumab was discontinued. Per local pharmacovigilance scan protocol to exclude PML before ocrelizumab, 2 MRI brain scans showed no new or enlarging T2 lesions and CSF was negative for JCV DNA with CSF NfL levels of 396 pg/mL. The expanded disability status scale (EDSS) score was 4.0. The patient received 300 mg of ocrelizumab 43 days after the last natalizumab infusion. A third MRI was performed per local pharmacovigilance protocol before the second 300 mg ocrelizumab infusion. A white matter lesion suspect for PML was detected (figure 1). No lesions suspect for MS disease activity were present. In retrospect, subtle signs suggestive of PML were
already present on MRI in October 2018 under natalizumab treatment. CSF was positive for JCV DNA (11.0 copies/mL). CSF NfL levels increased to 844 pg/mL, and sNfL levels were 9.9 pg/mL (figure 2A). Based on limited evidence, the patient started mefloquine 250 mg for 3 days, continued at a dose of 250 mg weekly, and mirtazapine 30 mg daily. MRI brain scans with gadolinium showed progression of enhancement suspect for PML-IRIS. The patient received 1 g IV methylprednisolone (IVMP) for 3 days. Over the next 2 months, MRI scans showed a decrease of the inflammatory component of PML-IRIS and treatment for PML was discontinued. CSF was negative for JCV DNA. The neurologist felt comfortable to continue treatment with 300 mg of ocrelizumab after the first signs of B-cell repopulation. The patient reported no clinical symptoms during the disease course of PML-IRIS with a stable EDSS score of 4.0.

Case 2
A 37-year-old man with RRMS started treatment with natalizumab in 2009. JCV serostatus was positive (index 0.37–0.84 between 2014 and 2019). The patient wished to continue natalizumab treatment; consequently, every 3 months, MRI brain scans were performed. Regular follow-up showed no disease activity under natalizumab treatment. In January 2017, the patient switched to personalized extended interval dosing (EID) based on trough concentrations (6 week interval). In April 2019, because of the patient’s desire for treatment switch, natalizumab was discontinued. Two MRI brain scans showed no new or enlarging T2 lesions, and CSF was negative for JCV DNA with CSF NfL levels of 211 pg/mL. The EDSS score was 2.5. The patient received 300 mg of ocrelizumab 55 days after the last natalizumab infusion. A third MRI scan showed new focal areas with elevated signal on the diffusion-weighted imaging setting (figure 3). No lesions suspect for MS disease activity were present. In retrospect, subtle signs suggestive of PML were already present on MRI in May 2019 under natalizumab treatment. CSF was positive for JCV DNA (copy number not quantified). CSF NfL levels increased to 466 pg/mL, and sNfL levels were 16.7 pg/mL (figure 2B). The patient started mefloquine 250 mg for 3 days, continued at a dose of 250 mg weekly, and mirtazapine 60 mg daily. Two weeks later, an MRI with gadolinium showed multiple foci of elevated signal suspect for PML-IRIS. By then, the patient became symptomatic with a mild left upper limb paresis. There was worsening of his gait because of instability of the left leg and new numbness of the right arm. The patient received 1 g IVMP twice, and the progression of clinical symptoms and lesions on MRI stabilized. Treatment for PML was discontinued in October 2019. Clinical symptoms improved, and the neurologist felt comfortable to continue treatment with 300 mg of ocrelizumab after the first signs of B-cell repopulation. The patient reported only mild clinical symptoms during the disease course of PML-IRIS with an EDSS score of 2.5 after recovery.

Discussion
We report 2 patients with RRMS with a relatively mild disease course of carryover PML after switching from natalizumab to
ocrelizumab. Interestingly, both patients developed IRIS despite complete B-cell depletion for several months after a single infusion of 300 mg ocrelizumab. One patient developed PML despite EID of natalizumab. PML is described in patients on EID, implicating EID does not obliterate the risk of PML. However, a recent case series suggests a possible less severe disease course of PML in 4 patients on EID.7 Furthermore, 7 confirmed cases of carryover PML in patients with MS switching from natalizumab to ocrelizumab have been reported (Clifford et al. ECTRIMS 2020; Roche data on file 2020). Although not described in detail, 6 cases were nonfatal. In a previous case report in a patient with MS, complete B-cell depletion by rituximab did not aggravate PML and did not prevent development of IRIS.8 A histologic study showed that IRIS is predominantly initiated by CD8+ T cells in natalizumab-associated PML.9 However, high numbers of B-cells were present in lesions from patients with PML-IRIS, whereas no B-cells were present in low-inflammatory PML not related to natalizumab therapy. Because ocrelizumab caused total depletion of CD20+ B-cells in both patients, it might be possible that ocrelizumab allowed immune reconstitution by T-lymphocytes with reduction of the inflammatory component of IRIS by depletion of B-cells.

Both patients were asymptomatic at the time of PML diagnosis. Subtle radiologic signs of PML were initially missed despite an extensive protocol for radiologic detection of PML in our tertiary MS center. It has been previously described that MRI diagnosis of PML remains difficult because of heterogeneous lesions.10 We measured longitudinal sNfL levels before and during PML-IRIS in retrospect in one batch (figure 2). sNfL levels increased during development of PML-IRIS. After PML-IRIS stabilized, sNfL values started to decline. A recent cohort study showed elevation of sNfL at PML onset compared with sNfL levels before PML onset.3 Another study found a correlation between PML lesion volume and sNfL.4 sNfL was not elevated before radiologic diagnosis of PML. However, individual relative change of sNfL might be helpful to support early radiologic findings suspect for PML.

We present 2 cases of carryover PML-IRIS with a relatively mild disease course after switching from natalizumab to ocrelizumab. Depletion of B-cells by ocrelizumab possibly contributed to reduction of the inflammatory component of IRIS in these 2 patients.

Study funding
No targeted funding reported.

Disclosure
C.E. Teunissen has served on advisory boards for Roche, has received nonfinancial support in the form of research consumables from ADx NeuroSciences and Euroimmmun, and has performed contract research or received grants from Probiopharm, Biogen, Esai, Toyama, Janssen Prevention Center, Boehringer, Axon Neuroscience, EIP Pharma, PeopleBio, and Roche. M.P. Wattjes has received consultancy or speaking fees from Biogen, Novartis, Roche, Celgene, IXICO, Sanofi Genzyme, Bayer Healthcare, Biologix, Genilac, and Merck Serono. F. Barkhof is supported by the NIHR biomedical research centre at UCLH. J. Killestein has accepted speaker and consulting fees from Merck Serono, Biogen, Roche, Teva Pharmaceutical Industries, Genzyme, and Novartis. A.A. Toorop, Z.Y.G. van Lierop, E.E.M. Strijbis, A. Petzold, B.A. de Jong and Z.L.E. van Kempen report no disclosures. Go to Neurology.org/NN for full disclosures.

Publication history
Received by Neurology: Neuroimmunology & Neuroinflammation June 17, 2020. Accepted in final form September 3, 2020.

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| Name                  | Location                                                                 | Contribution                                                                 |
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| Brigit A. de Jong, MD, PhD | Department of Neurology, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam | Interpreted the data and revised the manuscript for intellectual content. |
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### Appendix (continued)

| Name                     | Location                                                                 | Contribution                                                                 |
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DOI 10.1212/NXI.0000000000000904

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