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Severe rebound after cessation of fingolimod treated with ocrelizumab with coincidental transient aggravation: report of two cases

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Abstract

Background: Fingolimod (FTY), an oral treatment for patients with relapsing-remitting multiple sclerosis (RRMS), has been associated with a significant rebound of disease activity after cessation of therapy.

Methods: We present the clinical and radiological findings of two patients with severe rebound after FTY withdrawal, which was further aggravated by the initiation of treatment with the B cell-depleting monoclonal antibody, ocrelizumab.

Results: Both patients exhibited significant Expanded Disability Status Scale progression after administration of ocrelizumab despite immune reconstitution more than 3 months after FTY withdrawal.

Conclusions: Although the observed effect may be coincidental, ocrelizumab may complicate recovery of rebound after cessation of FTY. Further studies are warranted to better understand and predict the clinical and immunological consequences of sequential immunosuppressive and immunomodulatory treatments in patients with highly active RRMS.

Keywords: disease-modifying therapy, fingolimod, multiple sclerosis, ocrelizumab, rebound

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Introduction

Fingolimod (FTY), an oral treatment for patients with relapsing-remitting multiple sclerosis (RRMS), has been shown to exert its therapeutic effect by preventing lymphocyte egress from secondary lymphoid tissues *via* down-regulation of the sphingosine-1-phosphate receptor.[1] While discontinuation of FTY has not been associated with a significant rebound of disease activity in large phase III clinical trials such as FREEDOMS and FREEDOMS2,[2] several cases of clinical rebounds after cessation of FTY treatment have been described.[3–7] Here, we report another two cases of severe rebound after FTY discontinuation, which was transiently aggravated by the initiation of treatment with the B cell-depleting monoclonal antibody, ocrelizumab (OCR). These case reports further highlight the potential pitfalls and consequences of sequential application of potent immunomodulatory and immunosuppressive drugs. Both patients gave written consent to use their medical history and magnetic resonance imaging (MRI) images for publication.

Case 1

A 44-year-old white woman with RRMS was diagnosed in 2000 (age of onset 26 years) and treatment with interferon beta-1a intramuscularly was initiated. This treatment was withdrawn in 2011 after two relapses in 2010 and 2011 (Expanded Disability Status Scale (EDSS) 2.5) and therapy was switched to natalizumab (NTZ), which was discontinued in 2013 due to recurrent infections. After a therapy-free interval of 8 weeks she was started on FTY and remained free of clinical and radiological signs of disease activity until 2017 when two relapses resulted in incomplete

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remission with disability progression (EDSS 4.0). FTY was discontinued in December 2017 in order to switch to OCR. She rapidly developed tetraparesis (EDSS 6.5) 4 weeks after discontinuation of FTY. At this point peripheral lymphocyte counts had almost returned to the lower normal range (900/µl). MRI showed multiple gadolinium (Gd)-enhanced T1 lesions supratentorially and infratentorially (Figures 1 and 2) and two enhancing spinal cord lesions at the C5 and D4 level. After two courses of intravenous steroid treatment with 5 × 1 g methylprednisolone (MP) and 5 × 2 g MP, respectively, there was only partial recovery (EDSS 6.0). In January 2018, she developed severe tetraparesis with further EDSS progression (7.5). MRI revealed multiple new Gd-enhanced T1 lesions in the cervical and thoracic cord (Figure 3). After a course of 5 × 2 g MP and eight cycles of plasma exchange (PLEX), she resumed the ability to walk with a walker (EDSS 6.5). OCR was started on 22 February 2018. The patient deteriorated again 1 week after the first dose of 300 mg OCR, due to a bilateral weakness of the hip flexors (EDSS 7.0). MRI revealed five new spinal Gd-enhanced lesions and she received another cycle of 5 × 2 g MP. After the second dose of OCR on 21 March 2018 and 6 weeks of rehabilitation, the patient partially improved with an EDSS of 6.0. In August 2018 cranial and spinal MRI revealed no new T2 lesions and no Gd-enhanced T1 lesions. Clinically, there was no further EDSS improvement. The clinical events and measures after FTY cessation are summarized in Figure 4.

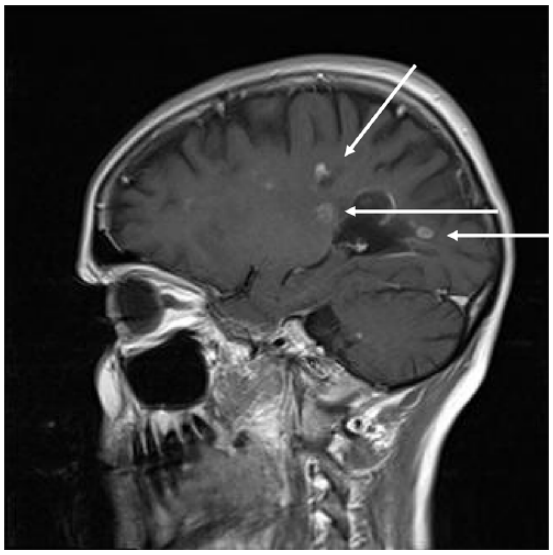

Figure 1. Gd-EDTA enhanced T1-weighted sagittal cranial MRI demonstrates multiple supratentorial contrast-enhanced lesions.

Case 2

The second patient was a 37-year-old white woman. RRMS was diagnosed in 2006 (age of onset 25 years) and treatment with interferon beta-1b subcutaneously was initiated. After a series of relapses in 2009 and 2010 with incomplete remission (EDSS 4.5) she was switched to NTZ in 2011 after a therapy-free interval of 4 weeks. She remained free of clinical and MRI activity and even improved clinically (EDSS 3.5). In April 2015 she was switched to FTY after a therapy-free interval of 6 weeks due to the presence

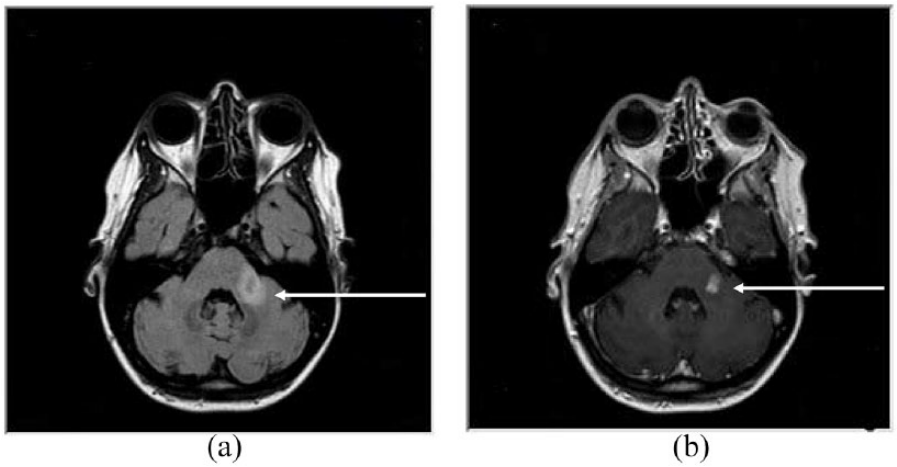

Figure 2. Axial FLAIR (a) and Gd-EDTA enhanced T1-weighted sequences (b) on cranial MRI demonstrate a large lesion in the left cerebellar peduncle.

of JC virus antibodies. She remained clinically stable despite recurrent subclinical MRI activity in March 2016, November 2016 and April 2017. Due to lymphopaenia (107/µl) FTY was reduced to an every-other-day regime in April 2017. In November 2017 a relapse occurred with incomplete remission and disability progression (EDSS 5.5). FTY was withdrawn in December in order to switch to OCR. At 6 weeks following discontinuation of FTY neurological examination revealed bilateral INO, paraparesis of the legs and ataxia (EDSS 6.5). At this point peripheral lymphocyte counts had almost returned to the lower normal range (923/µl). Cranial MRI showed four Gd-enhanced lesions supratentorially. After two courses of steroid treatment with 5 × 1 g MP intravenously, there was only partial recovery (EDSS 6.0). OCR was started on 15 February 2018. At 1 week after the first dose of 300 mg OCR, neurological examination revealed severe tetraparesis and dysphagia as well as an absent gag reflex (EDSS 8.0). MRI revealed a large Gd-enhanced lesion extending from the pons to the medulla (Figure 5). She received another cycle of 5 × 2 g MP intravenously. After the second dose of OCR on 5 April 2018 the patient's condition slowly improved (EDSS 5.5). In August 2018 cranial and spinal MRI revealed no new T2 lesions and no Gd-enhancing T1 lesions. Clinically, there was further EDSS improvement (EDSS 4.5). The clinical events and measures after FTY cessation are summarized in Figure 6.

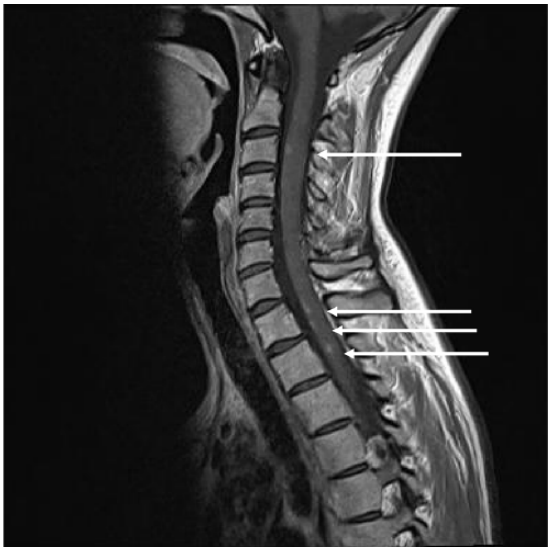

Figure 3. Sagittal Gd-EDTA enhanced T1-weighted sequences on spinal MRI demonstrate multiple contrast-enhanced lesions at the C2, C7 and D1 level.

Discussion

Both patients with highly active RRMS showed breakthrough disease under treatment with FTY, necessitating treatment optimization, and subsequently developed clinical and MRI features of severe rebound after cessation of FTY as previously described.[3–7] Rebound in both patients occurred as early as 4–6 weeks after discontinuation of FTY, which is also in line with other case reports[3–7] and

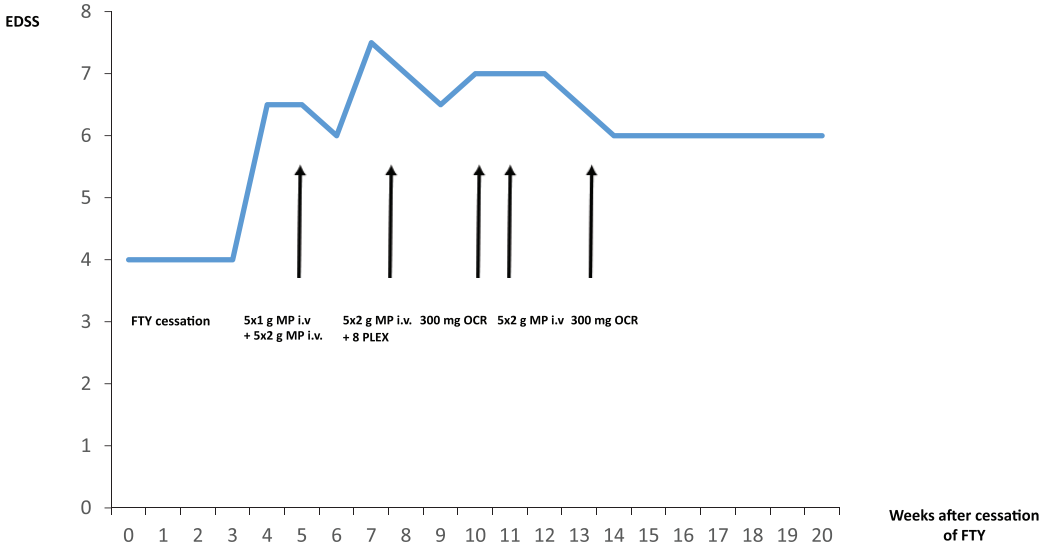

Figure 4. Clinical evolution after cessation of fingolimod (FTY) in case 1. iv, intravenous; MP, methylprednisolone; OCR, ocrelizumab; PLEX, plasma exchange.

most likely explained by the release of TH17 T cells trapped in the secondary lymphoid organs invading the central nervous system.[1,8] Pharmacodynamic data show rapid recovery of lymphocyte counts starting several days after treatment cessation.[9] Recent studies suggest that FTY also modulates the composition of circulating B cells, promoting regulatory subsets and increasing the proportion of transitional B cells.[10] In line with this finding, rebound activity after cessation of FTY only partially responds to steroid pulse therapy, sometimes necessitating PLEX.[11] This scenario applies well to the patient in case 1 who did not fully respond to repeated high-dose steroid pulses and was only stabilized after PLEX. The massive inflammatory activity affecting the spinal cord is also in line with a B cell-mediated inflammation as observed in neuromyelitis optica and opticospinal variants of MS.[12]

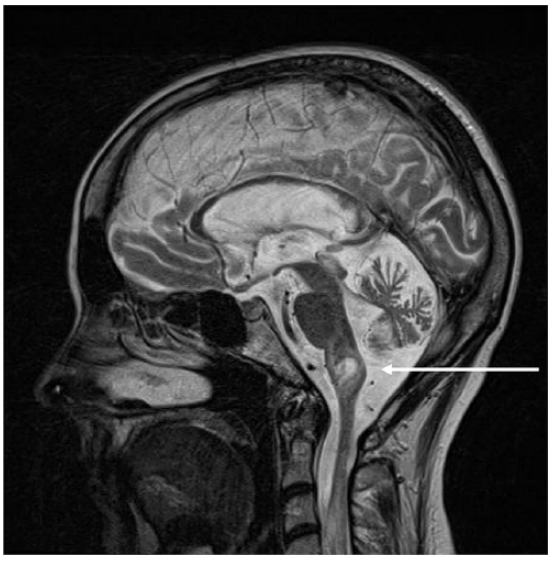

Figure 5. Sagittal T2-weighted sequences on cranial MRI demonstrate a large brainstem lesion extending into the medulla.

Of note, initiation of OCR treatment further aggravated the course of rebound in both patients. At the time of OCR administration, FTY had been discontinued for more than 8 weeks in both patients, suggesting that peripheral immune reconstitution had been completed.[9] While both patients significantly deteriorated after the first dose of OCR, case 1 who had responded to PLEX did not deteriorate as significantly as case 2 whose rebound had responded better to steroid pulse therapy. Notably, the tumefactive brainstem lesion in case 2 did not occur within the first 2 months of FTY withdrawal, but developed a few days after administration of OCR. Tumefactive brainstem lesions as observed in case 2 may also be seen in neuromyelitis optica spectrum disorders (NMOSD). However, the clinical course of disease in case 2 was typical of highly active RRMS not raising the question of a possible differential diagnosis of NMOSD so that we assumed the atypical brainstem lesion was related to FTY withdrawal and the consecutive administration of OCR.

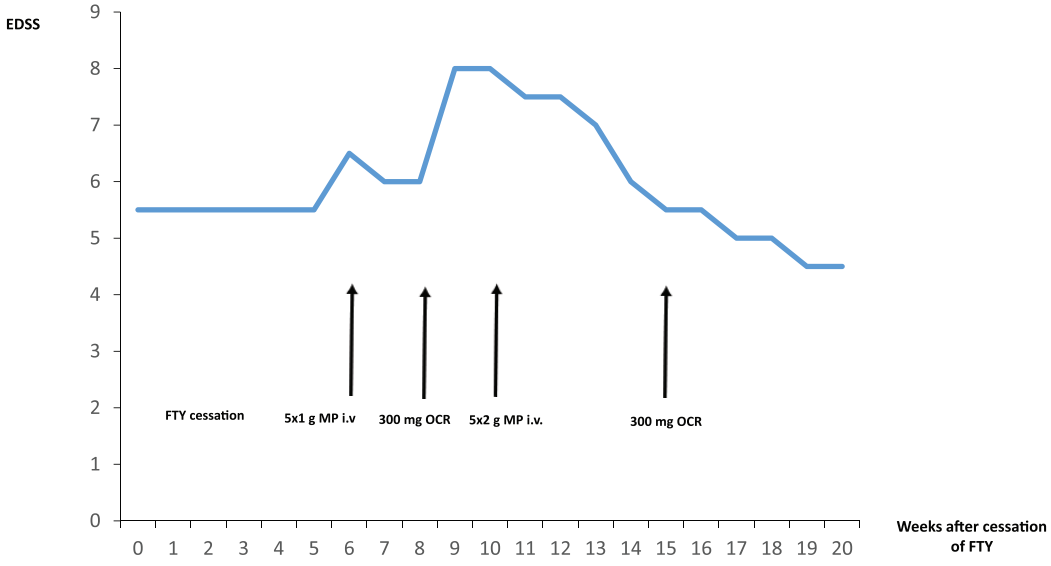

Figure 6. Clinical evolution after cessation of fingolimod (FTY) in case 2. iv, intravenous; MP, methylprednisolone; OCR, ocrelizumab.

OCR is a monoclonal antibody directed against the CD20 transmembrane cellular protein-depleting pre-B cells and mature and memory B cells.[13] B cells produce regulatory IL-10 inhibiting differentiation of pathogenic Th1 and Th17 cells and secrete IL-35,[14,15] a recently discovered regulatory cytokine of critical importance during autoimmune attacks. Regulatory B cells also secrete TGF-β.[16] Given the regulatory function of certain B-cell subsets, it appears plausible that the removal of these B cells from the peripheral immune system even several weeks after cessation of FTY treatment might have contributed to the secondary deterioration in both patients. On the other hand, the rapid deterioration within a few days of administration of 300 mg OCR might also be explained by a still lingering rebound activity after FTY cessation, so that the recurrent disease activity was not causally related to OCR administration. Moreover, since both patients stabilized or even improved after continuation of OCR treatment, it can be assumed that B-cell depletion was not detrimental in the long run and that the therapeutic effect might have only been delayed in halting rebound activity.

Both case reports highlight the difficulties of managing rebound activity after cessation of FTY in individual patients. Moreover, initiation of sequential immune therapies such as OCR might result in transient, but severe deterioration of a still lingering rebound. Further studies are needed to better understand and predict the clinical and immunological consequences of sequential immunosuppressive and immunomodulatory treatments in patients with highly active RRMS.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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