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Letter to the editor

Disease reactivation in a patient with secondary progressive multiple sclerosis after switching treatment from fingolimod to siponimod

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Dear Editor,

Multiple sclerosis (MS) is an autoimmune, chronic inflammatory demyelinating disease of the central nervous system (CNS). With a growing number of available disease-modifying drugs (DMDs), the transition between different drugs has become an increasingly complex challenge. Some DMDs such as natalizumab and fingolimod have been associated with disease reactivation or even rebound of disease activity after cessation [1–3].There is no consensus regarding how the choice and timing of the next drug after fingolimod affects the risk of disease reactivation. Furthermore, although disease reactivation after fingolimod discontinuation have been nearly exclusively observed in patients with relapsing-remitting MS, it can occur even in patients with secondary progressive MS (SPMS) [4].

Siponimd, a selective sphingosine-1-phosphate (S1P) receptor 1 and 5 modulator, is the only approved DMD for the treatment of SPMS in Japan. Similar to fingolimod, siponimod reduces inflammatory activity by inhibiting the egress of S1P-sensitive subsets of lymphocytes out of lymph nodes [5]. We report an unusual case of disease reactivation in a patient with SPMS who was switched treatment from fingolimod to siponimod.

A 49-year-old female patient was diagnosed with relapsing-remitting MS at the age of 42. She was started on disease-modifying therapy with fingolimod due to high disease activity; three relapses in the previous year and the presence of gadolinium-enhancing brain lesions before fingolimod. During the first two years after initiation of fingolimod, she experienced several relapses with incomplete recovery and progressive increase in brain magnetic resonance imaging (MRI) lesion load, and her score on the Expanded Disability Status Scale (EDSS) deteriorated from 3.5 to 5.5. In the next five years, she was relapse-free without MRI activity; however, her disability gradually worsened to EDSS score of 7.0 and she was diagnosed with SPMS. Fingolimod was considered to be insufficient to prevent disease progression independent of relapse activity and treatment switching was decided. Because she was positive for anti-John Cunningham virus antibody and none of B-cell-depleting drugs was approved for the treatment of MS in Japan, fingolimod was switched to siponimod without wash-out period. Peripheral lymphocyte count at initiation of siponimod (day 1) was 376/μL, and 433/μL at day 7. She developed double vision at day 11 and visited to our hospital at day 14 because her symptom persisted. Neurological examination revealed no new additional findings except for right internuclear ophthalmoplegia. Brain MRI showed multiple hyperintense infra- and supratentorial lesions on fluid-attenuated inversion-recovery images, some of which were enhanced with gadolinium (Fig. 1). Her peripheral lymphocyte count remained depressed (380/μL) while taking siponimod. A work-up for infectious causes was negative. Standard cerebrospinal fluid (CSF) analysis showed slightly elevated protein level (59 mg/dL) and normal cell count (8 lymphocytes/μL). Elevated levels of IgG index (1.07) and myelin basic protein (613 pg/mL) were found in the CSF. A diagnosis of disease reactivation associated with fingolimod discontinuation was made and siponimod was switched to fingolimod immediately. She also received two cycles of pulse therapy with intravenous 1000 mg of methylprednisolone for three days, which led to a marked improvement of her clinical symptom and MRI findings.

To our knowledge, this is the first case of disease reactivation immediately after switching treatment from fingolimod to siponimod in a patient with SPMS. Increases in clinical and MRI activity have been widely reported in relation to fingolimod discontinuation [1,2]. In some patients, disease activity can exceed pre-treatment baseline; thus, it is referred to as a rebound syndrome. Given the mild symptom and high disease activity at pre-fingolimod baseline, a disease reactivation rather than true rebound would be expected in this case.

It is noteworthy that disease reactivation occurred despite treatment with siponimod following fingolimod discontinuation. Both fingolimod and siponimod are S1P receptor modulators; fingolimod binds to four (S1P1, S1P3, S1P4 and S1P5) of the five S1P receptors, whereas siponimod binds only S1P1 and S1P5 receptors. S1P1 plays an essential role in lymphocyte egress from secondary lymphoid organs and an overexpression of S1P1 receptor on lymph node-entrapped lymphocytes was observed before clinical rebound in an animal model of MS [6].This supports mechanism for disease reactivation due to a rapid lymphocyte reconstitution following fingolimod discontinuation, but this mechanism would not be expected in this lymphopenic patient continuously treated with S1P1 receptor modulator.

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Astrocyte expresses S1P receptors, particularly S1P1 and S1P3 receptors. Because both S1P1 and S1P3 receptors are upregulated on activated astrocytes in the CNS inflammation [7], astrocyte is considered to be a target of fingolimod. In the neuropathological study of the autopsy case of rebound syndrome following fingolimod discontinuation, an overexpression of S1P receptors was observed on reactive astrocytes [8]. Because siponimod does not bind to S1P3 receptor, it is hypothesized that dysregulated S1P receptor-mediated signaling in astrocyte triggered *via* S1P3 receptor after switching from fingolimod to siponimod leads to the activation of nuclear factor-κB and release of inflammatory cytokines and nitric oxide [8], which could in part explain the mechanism of disease reactivation in this case. This hypothesis is

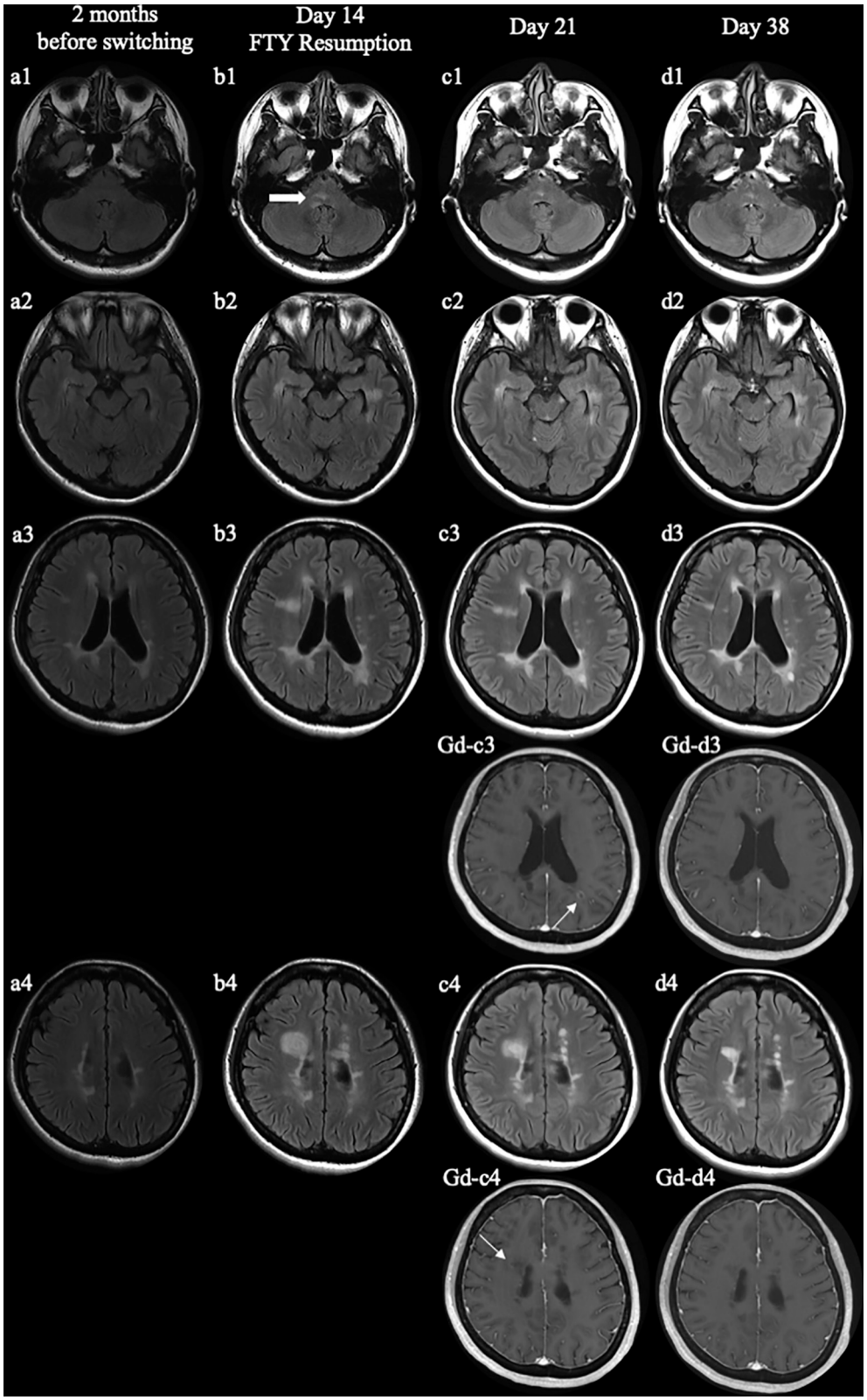

Fig. 1. Brain MRI before and after switching treatment from fingolimod to siponimod.
Axial views of fluid-attenuated inversion-recovery (FLAIR) images at different time points are displayed. Gadolinium-enhanced imaging was not performed at disease reactivation (day 14), but there were several new and enlarging FLAIR hyperintense lesions (b1–4). The thick white arrow indicates right pontine dorsomedial tegmentum lesions (b1). After resumption of fingolimod and one cycle of intravenous methylprednisolone pulse therapy (days 21), an improvement of MRI findings was observed but there were gadolinium-enhancing lesions on T1-weighted images (thin white arrow in Gd-c3 and c4). After additional one cycle of intravenous methylprednisolone pulse therapy (day 38), gadolinium enhancement was disappeared (Gd-d3 and d4) and there was no evidence of new or enlarging FLAIR hyperintense lesions thereafter.
FTY: fingolimod, Gd: gadolinium.

supported by the observation that new lesions did not continued to form after resumption of fingolimod, although *in vitro* assay showed that siponimod inhibits astrocyte inflammatory activity as sufficiently as fingolimod [9].

Another characteristic point of this case is the timing of disease reactivation. Disease reactivation or rebound syndrome often occur 4–16 weeks after fingolimod discontinuation [1,2]. This timeline is consistent with the long half-time of fingolimod of 6–9 days. However, in this case, disease reactivation occurred only 11 days after fingolimod discontinuation. Similarly, Ashtari et al. reported the case of severe rebound developed 12 days after fingolimod discontinuation [10]. This suggests that the mechanism underlying disease reactivation after fingolimod discontinuation may be heterogenous.

In conclusion, this case highlights that disease reactivation may occur immediately after switching treatment from fingolimod to siponimod irrespective of the disease course. A careful monitoring of disease activity is therefore recommended after fingolimod discontinuation. Further studies are needed to elucidate the underlying mechanisms as well as risk factors of disease reactivation after fingolimod discontinuation, which will help establish a strategy for the safe switching of fingolimod to another DMD.

Disclosures

Hirofumi Ochi is on the scientific advisory board for Biogen Japan Ltd., Novartis Pharma K.K., and Alexion Pharmaceuticals Inc.; received speaker honoraria from Bayer Yakuhin Ltd., Novartis Pharma K.K., Mitsubishi Tanabe Pharma Corp., Alexion Pharmaceuticals Inc., Chugai Pharmaceutical Co., Ltd., Nihon Pharmaceutical Co., Ltd., and Takeda Pharmaceutical Co., Ltd. Kensuke Senzaki, Masayuki Ochi, Yoko Okada, Shiroh Miura, and Yasumasa Ohyagi report no disclosures.

Author contribution statement

Kensuke Senzaki designed and conceptualized the study, analyzed clinical data, acquired and interpreted clinical data, and drafted the manuscript for intellectual content.

Hirofumi Ochi designed and conceptualized the study, analyzed clinical data, acquired and interpreted clinical data, and drafted the manuscript for intellectual content.

Masayuki Ochi acquired and interpreted clinical data.

Yoko Okada acquired and interpreted clinical data.

Shiroh Miura revised the manuscript for intellectual content.

Yasumasa Ohyagi revised the manuscript for intellectual content.

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Patient consent

Written consent has been obtained from the patient.

References

[1] B. Barry, A.A. Erwin, J. Stevens, C. Tornatore, Fingolimod rebound: a review of the clinical experience and management considerations, Neurol. Ther. 8 (2) (2019) 241–250.

[2] S.E. Hatcher, E. Waubant, B. Nourbakhsh, E. Crabtree-Hartman, J.S. Graves, Rebound syndrome in patients with multiple sclerosis after cessation of fingolimod treatment, JAMA Neurol. 73 (7) (2016) 790–794.

[3] L. Prosperini, R.P. Kinkel, A.A. Miravalle, P. Iaffaldano, S. Fantaccini, Post-natalizumab disease reactivation in multiple sclerosis: systematic review and meta-analysis, Ther. Adv. Neurol. Disord. 12 (2019), 1756286419837809.

[4] A. Czlonkowska, L. Smolinski, T. Litwin, Severe disease exacerbations in patients with multiple sclerosis after discontinuing fingolimod, Neurol. Neurochir. Pol. 51 (2) (2017) 156–162.

[5] J. Chun, G. Giovannoni, S.F. Hunter, Sphingosine 1-phosphate receptor modulator therapy for multiple sclerosis: differential downstream receptor Signalling and clinical profile effects, Drugs. 81 (2) (2020) 207–231, https://doi.org/10.1007/s40265-020-01431-8.

[6] L. Cavone, R. Felici, A. Lapucci, D. Buonvicino, S. Pratesi, M. Muzzi, et al., Dysregulation of sphingosine 1 phosphate receptor-1 (S1P1) signaling and regulatory lymphocyte-dependent immunosuppression in a model of post-fingolimod MS rebound, Brain Behav. Immun. 50 (2015) 78–86.

[7] R. Van Doorn, J. Van Horssen, D. Verzijl, M. Witte, E. Ronken, B. Van Het Hof, et al., Sphingosine 1-phosphate receptor 1 and 3 are upregulated in multiple sclerosis lesions, Glia. 58 (12) (2010) 1465–1476.

[8] M.T. Giordana, P. Cavalla, A. Uccelli, A. Laroni, F. Bandini, M. Vercellino, et al., Overexpression of sphingosine-1-phosphate receptors on reactive astrocytes drives neuropathology of multiple sclerosis rebound after fingolimod discontinuation, Mult. Scler. 24 (8) (2018) 1133–1137.

[9] E. Colombo, C. Bassani, A. De Angelis, F. Ruffini, L. Ottoboni, G. Comi, et al., Siponimod (BAF312) activates Nrf2 while hampering NFkappaB in human astrocytes, and protects from astrocyte-induced neurodegeneration, Front. Immunol. 11 (2020) 635.

[10] F. Ashtari, M.A. Sahraian, M. Oustad, Y. Nilipour, Tumefactive rebound of multiple sclerosis after the short-term cessation of fingolimod: a case report, Mult. Scler. Relat. Disord. 39 (2019) 101883.

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