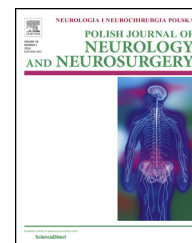


Available online at www.sciencedirect.com

ScienceDirect

journal homepage: <http://www.elsevier.com/locate/pjnns>

Case report

Substantial disease exacerbation in a patient with relapsing-remitting multiple sclerosis after withdrawal from siponimod

Tomasz Litwin^a, Łukasz Smoliński^a, Anna Członkowska^{a,b,*}^a Second Department of Neurology, Institute of Psychiatry and Neurology, ul. Sobieskiego 9, 02-957 Warsaw, Poland^b Department of Clinical and Experimental Pharmacology, Medical University of Warsaw, ul. Banacha 1b, 02-097 Warsaw, Poland

ARTICLE INFO

Article history:

Received 3 July 2017

Accepted 3 October 2017

Available online 13 October 2017

Keywords:

Multiple sclerosis

Siponimod

Withdrawal

Rebound

Fingolimod

ABSTRACT

Among patients with multiple sclerosis, discontinuing highly effective disease-modifying treatments can potentially lead to severe disease recurrence, especially cessation of natalizumab and fingolimod. Similar to fingolimod, siponimod is a sphingosine-1-phosphate receptor modulator that inhibits the egress of a lymphocyte subpopulation from lymph nodes. In the present case report, we describe a patient with MS who experienced substantial disease exacerbation after withdrawal from siponimod.

© 2017 Polish Neurological Society. Published by Elsevier Sp. z o.o. All rights reserved.

1. Introduction

Among patients with multiple sclerosis (MS), discontinuing highly effective disease-modifying treatments can potentially lead to severe disease recurrence, especially cessation of natalizumab and fingolimod [1]. Siponimod is a drug that has been investigated in patients with relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS) [2]. It is a sphingosine-1-phosphate (S1P) receptor modulator that inhibits the egress of a lymphocyte subpopulation from lymph nodes. In contrast to fingolimod, siponimod selectively binds to only two S1P receptors (S1P1 and S1P5), does not require

in vivo phosphorylation, and has a shorter half-life and elimination time. In the present case report, we describe a patient with MS who experienced substantial disease exacerbation after withdrawal from siponimod.

2. Case report

A 24-year-old woman was diagnosed with RRMS after experiencing two relapses over a period of four years [annualized relapse rate (ARR) = 0.5, Expanded Disability Status Scale (EDSS) = 2.5]. Following the second relapse (December 2009), the patient was enrolled in a clinical trial with siponimod [2].

* Corresponding author at: Second Department of Neurology, Institute of Psychiatry and Neurology, ul. Sobieskiego 9, 02-957 Warsaw, Poland.

E-mail address: czlonkow@ipin.edu.pl (A. Członkowska).

<http://dx.doi.org/10.1016/j.pjnns.2017.10.001>

0028-3843/© 2017 Polish Neurological Society. Published by Elsevier Sp. z o.o. All rights reserved.

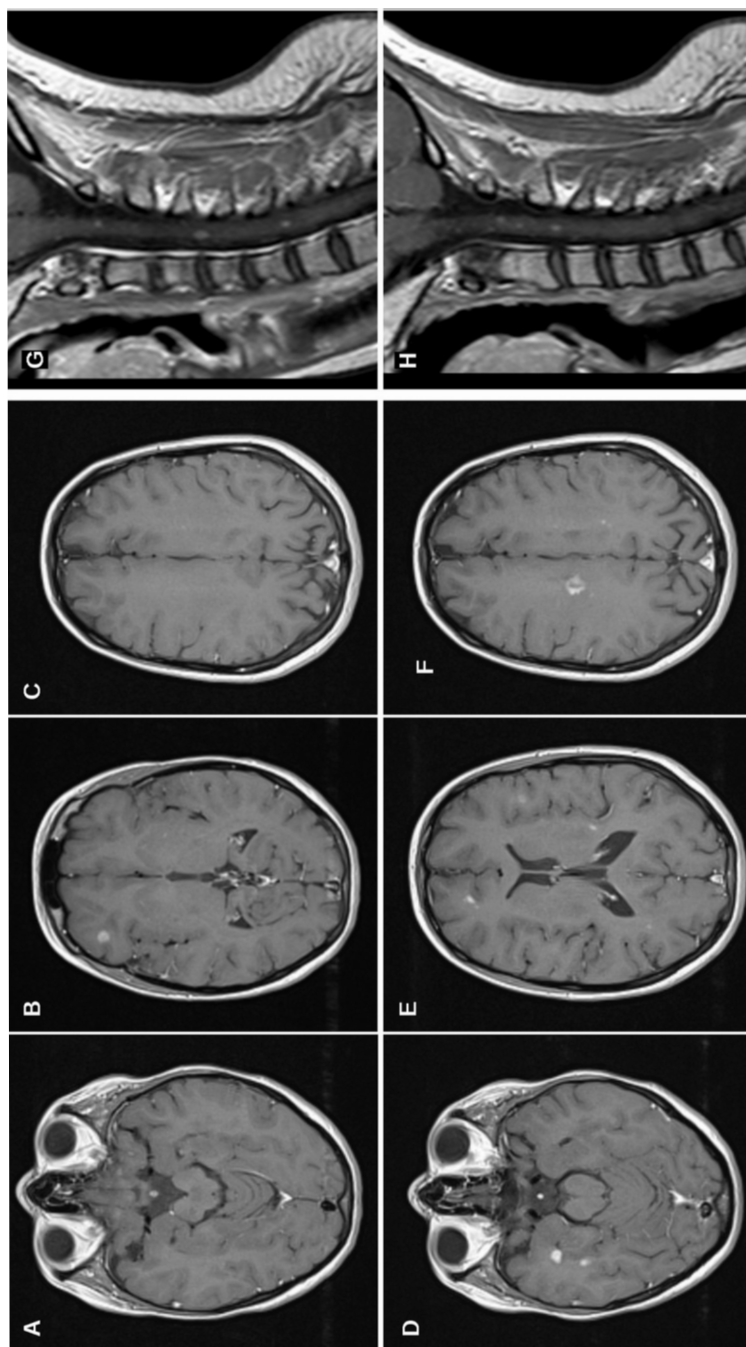


Fig. 1 – Brain MRI of a 31-year-old female patient with RRMS treated with siponimod. Corresponding FLAIR images on siponimod initiation (A–D) and on siponimod withdrawal, 6 years later, (E–H) show comparable lesion counts. Twelve weeks after siponimod withdrawal, during a relapse with left-sided hypoesthesia and left-sided pyramidal signs, FLAIR images (I–L) revealed multiple new lesions, and T1 images after gadolinium administration displayed multiple (over 10) gadolinium-enhancing lesions in the brain (M–S) and in the cervical spinal cord (T–U). Arrows indicate gadolinium-enhancing [Gd(+)] lesions.

On trial initiation, the patient had a gadolinium-enhancing lesion in the left frontal lobe (Fig. 1A–D). She remained in this trial until its completion in July 2016. During the last four years of the trial, she received siponimod at a daily dose of 2 mg. Upon trial completion, the patient was in clinical remission (EDSS = 1.5, on treatment ARR = 0.28). Brain MRI revealed a gadolinium-enhancing lesion in the right frontal lobe; however, the lesion count on FLAIR images was comparable to that on siponimod initiation (Fig. 1E–H).

After 10 weeks without any disease-modifying treatment, we started dimethyl fumarate as the patient preferred oral treatment and other oral agents were not available under reimbursement arrangements. However, two weeks later, she was admitted due to a relapse with left-sided hypoesthesia and left-sided pyramidal signs (EDSS = 2.5). MRI revealed multiple (over 10) gadolinium-enhancing lesions in both brain hemispheres and in the cervical spinal cord (Fig. 1I–U). The lymphocyte count had returned to a normal level (1.81 K/ μ l) compared to a level of 0.42 K/ μ l on siponimod. The patient received intravenous methylprednisolone (1 g for 5 days) and improved (EDSS = 2.0). Despite further treatment with dimethyl fumarate, 6 weeks later, the patient presented with gait worsening, paresthesia in the lower extremities, and hypoesthesia in the anogenital area (EDSS = 3.0). Repeated treatment with intravenous methylprednisolone was administered on an outpatient basis, which led to reversal of relapse symptoms (EDSS = 2.0). Because second-line treatments (e.g., natalizumab, fingolimod) were not available under reimbursement arrangements, the patient stayed on dimethyl fumarate.

3. Discussion

In patients with MS, discontinuation of highly effective disease-modifying treatments can lead to substantial disease recurrence. Prior reports of such recurrence have most often followed withdrawal of natalizumab and fingolimod. Notably, siponimod and fingolimod are both S1P receptor modulators and, thus, it could be suspected that discontinuation of siponimod may also lead to disease exacerbation. Additionally, siponimod will likely be indicated for use in patients with SPMS who also experience increased disease activity after withdrawal from S1P receptor modulators [3].

To our knowledge, this is the first case report to describe disease exacerbation in a patient with MS following siponimod discontinuation. Our patient exhibited disease reactivation three months after siponimod treatment cessation, which is similar to prior reports involving fingolimod cessation [4]. Our patient's first relapse after treatment withdrawal did not lead to severe neurological impairment; however, MRI revealed multiple gadolinium-enhancing lesions in both brain hemispheres and the cervical spinal cord. Despite further treatment with dimethyl fumarate, six weeks later, the patient experienced another relapse with a more significant deficit.

Notably, the disease reactivation in our patient occurred upon reconstitution of the lymphocyte count, which has also been reported in patients with MS who experienced disease reactivation after fingolimod discontinuation. This observation, along with the similar temporal relationship between treatment discontinuation and disease reactivation, may

indicate that analogous processes lead to disease recurrence after withdrawal of siponimod and fingolimod. Cessation of siponimod or fingolimod likely leads to an egress of lymphocytes from lymph nodes, restoration of the lymphocyte count, and immune infiltration of the central nervous system. This process can be interpreted in the context of immune reconstitution inflammatory syndrome (IRIS), in which neurological symptoms develop due to an exaggerated immune system response, particularly towards previously silent infections [5]. However, without specific criteria, it is difficult to differentiate between IRIS and the return of spontaneous disease activity when dealing with a primary immune-mediated disease, such as MS.

No factors have yet been identified as predicting the occurrence of substantial disease reactivation after discontinuation of treatment with S1P receptor modulators. However, it is notable that the presently described patient had a gadolinium-enhancing lesion in her brain at the time of treatment termination, despite being in clinical remission. In future studies, it would be informative to investigate whether the presence of gadolinium-enhancing lesions is associated with a higher risk of significant exacerbation in patients with MS who discontinue S1P receptor modulators. Moreover, it may be noteworthy that the exacerbation observed in our patient occurred despite treatment with dimethyl fumarate. Similar findings have been reported in patients who discontinued fingolimod and were later switched to dimethyl fumarate; however, rescue treatment with rituximab also failed to prevent disease recurrence in a patient with MS after fingolimod cessation [1,4].

4. Conclusion

In conclusion, discontinuation of siponimod treatment can provoke substantial disease reactivation in patients with MS. This observation underscores the need to identify risk factors of substantial disease recurrence in patients with MS who discontinue S1P receptor modulators. Moreover, it is important to develop effective disease-modifying treatments or alternative management strategies that can be used after discontinuation of S1P receptor modulators in patients with RRMS or SPMS.

Conflict of interest

None declared.

Acknowledgement and financial support

None declared.

REFERENCES

- [1] Członkowska A, Smoliński Ł, Litwin T. Severe disease exacerbations in patients with multiple sclerosis after

- discontinuing fingolimod. *Neurol Neurochir Pol* 2017;51:156-62. <http://dx.doi.org/10.1016/j.pjnns.2017.01.006>
- [2] Kappos L, Li DKB, Stüve O, Hartung HP, Freedman MS, Hemmer B, et al. Safety and efficacy of siponimod (BAF312) in patients with relapsing-remitting multiple sclerosis. *JAMA Neurol* 2016;73:1089. <http://dx.doi.org/10.1001/jamaneurol.2016.1451>
- [3] Ghezzi A, Rocca MA, Baroncini D, Annovazzi P, Zaffaroni M, Minonzio G, et al. Disease reactivation after fingolimod discontinuation in two multiple sclerosis patients. *J Neurol* 2013;260:327-9. <http://dx.doi.org/10.1007/s00415-012-6744-7>
- [4] Hatcher SE, Waubant E, Nourbakhsh B, Crabtree-Hartman E, Graves JS. Rebound syndrome in patients with multiple sclerosis after cessation of fingolimod treatment. *JAMA Neurol* 2016. <http://dx.doi.org/10.1001/jamaneurol.2016.0826>
- [5] McCarthy M, Nath A. Neurologic consequences of the immune reconstitution inflammatory syndrome (IRIS). *Curr Neurol Neurosci Rep* 2010;10:467-75. <http://dx.doi.org/10.1007/s11910-010-0138-y>