Case report / Praca kazuistyczna

Farmakoterapia w Psychiatrii i Neurologii 2018, 34 (2), 139–142

DOI: http://dx.medra.org/10.17393/fpn.2018.07.002

Rebound effect after S1P receptor modulator treatment in a patient with relapsing-remitting multiple sclerosis

Efekt odbicia po leczeniu modulatorem receptora S1P u pacjentki z rzutowo-remisyjną postacią stwardnienia rozsianego

Maciej Świat[1, 2], Magdalena Targosz-Gajniak[1], Małgorzata Szymańska[3], Olga Rezner[1]

Received 8.06.2018
Accepted 6.08.2018

AFFILIATIONS / AFILIACJE

1 Department of Neurology, Regional Hospital Rybnik, Poland
2 Jan Dlugosz University in Czestochowa, Poland
3 Centrum Terapii SM i Chorób Zwyrodnieniowych

KEYWORDS

- multiple sclerosis
- sphingosine--phosphate receptor modulator
- amiselimod

SŁOWA KLUCZOWE

- stwardnienie rozsiane
- modulator receptora fosforanu sfingozyny
- amiselimod

CORRESPONDENCE ADDRESS / ADRES DO KORESPONDENCJI

Małgorzata Szymańska
Centrum Terapii SM i Chorób Zwyrodnieniowych
ul. Załęska 9, 40-571 Katowice, Poland
email: mklecha@wp.pl

ABSTRACT

We present a case report of severe steroid-refractory rebound disease activity after cessation of MT-1303 (amiselimod) treatment in a patient with relapsing-remitting multiple sclerosis (RRMS), which has not been described in the literature previously. MT-1303 is a novel selective sphingosine-phosphate receptor (S1P1) modulator that was discovered by the chemical modification of fingolimod with the aim of avoiding its heart rate-reducing effect.

STRESZCZENIE

Przedstawiono opis przypadku ciężkiego, opornego na steroidy, rzutu z odbicia po zaprzestaniu leczenia MT-1303 (amiselimod) u pacjenta z rzutowo-remisyjnym stwardnieniem rozsianym (RRMS), który nie został wcześniej opisany w literaturze. MT-1303 to nowy selektywny modulator receptora sfingozyno-fosforanowego (S1P1), który został wykryty przez chemiczną modyfikację fingolimodu w celu uniknięcia jego efektu obniżania rytmu serca.

Introduction

Sphingosine 1-phosphate (S1P) receptor modulators are the new compounds used for disease-modifying therapy for RRMS, acting by inhibiting the lymphocyte S1P receptor. As a result lymphocytes are kept sequestered in the lymph nodes and prevented from contributing to autoimmune reactions (Subei and Cohen 2015). The first oral non-selective sphingosine-1-phosphate receptor ($S1P_{1\text{-}5}$) modulator to demonstrate superior efficacy compared with placebo and interferon β-1a in phase III studies was FTY720 (Fingolimod), approved

for the treatment of relapsing-remitting multiple sclerosis (Członkowska *et al.* 2017). The risk of side effects with Fingolimod is partially related to its non-selective mechanism of action on all of the S1P receptor subtypes ($S1P_{1-5}$).To avoid side effects arising from this non-selective mechanism of action many novel compounds with high selectivity – especially for $S1P_1R$ – are intensively explored. MT-1303 (amiselimod) is a selective $S1P_1$ receptor modulator expected to present a lower risk of bradycardia (Sugahara *et al.* 2015). The safety and efficacy of three doses of MT-1303 in patients with RRMS were assessed in a phase II clinical trial (MOMENTUM study) (24-weeks treatment period), and its extension phase (18 months). We present a case report of severe disease activity rebound three months after cessation of MT-1303 treatment in an RRMS patient.

Case report

A 33-year-old female with RRMS diagnosed in 2009 arrived at our hospital in September 2015 with a history of five days of lower limbs weakness and dysarthria. She was started with interferon beta 1b (Betaferon) in April 2009, which was changed to glatiramer acetate (Copaxone) due to in lack of efficacy in August 2011. As she was still experiencing moderate to severe relapses in 2012 and the beginning of 2013 she was offered participation in the MOMENTUM trial outside the hospital. She was enrolled in May 2013 and after a blinded 24-week phase she received active treatment with MT-1303 for 18 months until June 2015, when the trial was terminated. On admission she scored 6.5 on the Expanded Disability Status Scale (EDSS), a method of quantifying disability and monitoring changes in the level of disability over time in MS patients. A brain magnetic resonance imaging (MRI) scan showed additional T2 lesions with several new gadolinium enhancing lesions. There were no signs or symptoms of infection. Routine blood tests were unremarkable (including white blood cells and lymphocytes that were low but within normal limits, clotting, thyroid function tests and inflammation markers). The test for blood JCV (John Cunningham Virus) was positive. A relapse of the multiple sclerosis (MS) was diagnosed and the patient received treatment with intravenous methylprednisolone in a total dose of 5.0 grams, with a mild improvement of neurological symptoms on the day of discharge (EDSS – 6.0). One month later, in October 2015, the patient developed rapidly progressive tetraplegia with severe dysarthria and bowel and bladder dysfunction, with diffuse neuropathic pain. Her EDSS was 9.5. The MRI scan of the brain and cervical spine showed multifocal contrast enhanced lesions (Fig. 1). Routine blood tests were normal. Cerebrospinal fluid (CSF) for JCV and viral PCR (polymerase chain reaction) testing were negative, as was the aquaporin-4 antibody. During her stay in the hospital she developed a urinary tract infection, which was treated with antibiotics. She was treated with cyclophosphamide iv in a total dose of 1.0 g, followed by a course of methylprednisolone (5.0 g *i.v.*), producing a slight improvement of upper limb weakness. Her EDSS at discharge was 8.5. She was transferred to the Rehabilitation Department for further treatment, where she stayed for 6 weeks. Unfortunately she did not improve significantly and her EDSS remains at 8.5.

Discussion

The safety and efficacy of three doses of MT- 1303 in patients with RRMS were assessed in a phase II clinical trial (MOMENTUM) (Kappos *et al*. 2015). The trial compared 3 doses of MT-1303 with a placebo in 415 participants over a 24 week period and found that the drug dose-dependently reduced the number of lesions in the brain. It also decreased the annualized relapse rate and grey matter loss at higher doses. The number of white blood cells in the blood test was also reduced. Overall there were no adverse effects reported and cardiac events, which were of particular interest, were similar across treatment arms and in the placebo group (Kappos *et al*. 2015). In study of up to 2 years of treatment, amiselimod was well tolerated and dose-dependently effective in controlling disease activity (Kappos *et al.* 2017).

The presented patient completed the MOMENTUM trial (24 weeks) and its extension phase (18 months), which evaluated the long-term safety and efficacy of MT-1303 in subjects with relapsing-remitting multiple sclerosis receiving one of three doses of amiselimod (total length of study 24 months). The primary endpoint was the total number of gadolinium-enhanced T1-weighted lesions on monthly brain MRI scans from weeks 8 to 24 (Kappos *et al*. 2016). This investigational product was well tolerated, the most common treatment-emergent adverse events being headache and nasopharyngitis. Amiselimod at doses of 0.2 mg and 0.4 mg was effective in reducing the total number of new gadolinium-enhanced T1 lesions in MRI (Kappos *et al.* 2016).

Within 3 months of completing the extension phase our patient suffered from a severe neurological deterioration due to refractory MS rebound. This is the first case reported in the literature to show severe steroid refractory rebound disease activity after cessation of MT-1303 treatment in an RRMS patient.

The etiology of the rebound in our case remains putative, however MT-1303 and fingolimod share the same mechanism of action on $S1P_1$, and the consequence of their cessation may be similar.

The steroid-refractory rebound after fingolimod discontinuation in multiple sclerosis has already been described in recent years (Havla *et al*. 2012, De Masi *et al.*

2015) and its pathogenesis is inferred from knowledge of the drug's mechanism of action. There is the possibility of a returning to pretreatment disease activity (Havla *et al.* 2012, Hakiki *et al.* 2012); however most authors attribute the rebound to an immune reconstitution-like mechanism supported by increased numbers of lymphocytes in the CSF and brain following cessation of the fingolimod therapy (De Masi *et al.* 2015). This theory has been studied in iv vitro and in vivo models showing that rebound is preceded by a burst of $S1P_1$ over-expression in lymph node-entrapped lymphocytes which correlates with subsequent massive lymphocyte egress and widespread CNS immune infiltration. Also, consistent with the ability of $S1P_1$ to counteract polarization and the function of T regulatory lymphocytes, the number and suppression of effector T cells is reduced by fingolimod suspension (Cavone *et al*. 2015).

All of the rebound syndromes described in literature took place during the 120 day wash out period after termination of the S1P modulator treatment, which would support the theory of the rebound after withdrawal of fingolimod being connected to an immune reconstitution inflammatory syndrome mechanism in the central nervous system (Alroughani *et al.* 2014), as was described previously in many MS patients after termination of natalizumab therapy (Sugahara *et al*. 2015, N'gbo *et al*. 2016).

A long-term, post-marketing evaluation of the safety profile and functionality of FTY was made after marketing the drug in Japan. It found, among other things, edema of the white matter, rebound syndrome after drug discontinuation, association with progressive multifocal leukoencephalopathy (PML) and progressive multifocal leukoencephalopathy-related immune reconstitution inflammatory syndrome (IRIS), optic neuritis and leukoencephalopathy (Yoshii *et al.* 2017).

A case of severe exacerbation was described by a Russian author, in their report on a woman with multiple sclerosis treated with fingolimod who experienced a severe relapse when her treatment ended (Belova *et al.* 2017). The author draws attention to the fact that diagnostic criteria and prognostic factors for IRIS and rebound are needed in patients with multiple sclerosis who discontinue the new disease modification therapy (Belova *et al.* 2017).

Severe clinical and radiological worsening has been described after cessation of fingolimod treatment in three cases MS patients treated in Poland (Członkowska *et al.* 2017). Severe disease exacerbation after withdrawal of another novel S1P receptor modulator, siponimod, has also been reported (Litwin *et al.* 2018).

Natalizumab (NTZ) is an effective treatment for relapsing-remitting multiple sclerosis, but the complication of this treatment may be PML. In patients developing PML, NTZ cessation causes a reconstruction of cellular immunity, a rapid transition of cells through the blood-brain barrier, and significant inflammation in the central nervous system, leading to IRIS (N'gbo *et al.* 2016, O'Connor *et al*. 2011). IRIS can also occur after cessation of NTZ in the absence of PML and in MS patients treated with Fingolimod after the discontinuation of NTZ treatment (Killestein *et al*. 2014, Calic *et al*. 2015).

Sometimes there is a need to switch between immunotherapies due to lack of efficacy or treatment side effects. Patients who discontinued fingolimod might be at risk of developing IRIS, resulting in disease reactivation in the washout period (Alroughani *et al.* 2014). Because we have now a variety of therapeutic agents for MS patients, we should evaluate the balance between the benefits and potential risks of treatment cessation when it is needed.

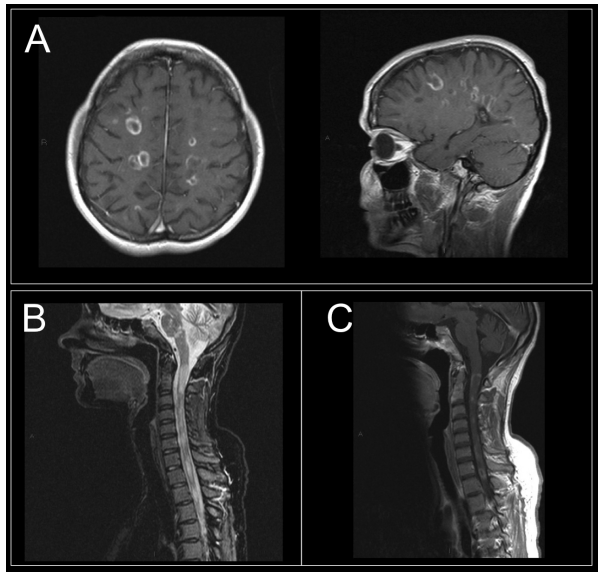

Figure 1 MRI findings: A – multiple gadolinium enhanced lesions in both hemispheres, B – T2 lesions in cervical spinal cord, C – gadolinium enhanced lesions in cervical spinal cord

Conflict of interest and financial support was not declared. / Nie zgłoszono konfliktu interesów oraz dofinansowania.

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans, EU Directive 2010/63/EU for animal experiments, and Uniform Requirements for manuscripts submitted to biomedical journals. / Treści przedstawione w artykule są zgodne z zasadami Deklaracji Helsińskiej, dyrektywami EU oraz ujednoliconymi wymaganiami dla czasopism biomedycznych.

Authors' contributions / Wkład autorów: MŚ – substantial input in the concept and draft of the paper, review, acceptance of the final draft to be published / zasadniczy wkład w koncepcję i projekt pracy, recenzowanie, akceptacja ostatecznej wersji do opublikowania. Współautorzy: MTG, OR, MSz – data collection and interpretation, analysis of study results, collection of references / zbieranie danych i ich interpretacja, analiza wyników, zebranie piśmiennictwa.

References

1. Alroughani R, Almulla A, Lamdhade S, Thussu A. Multiple sclerosis reactivation post fingolimod cessation: is it IRIS? BMJ Case Rep. Published online: 2014 Oct 15, doi: 10.1136/bcr-2014-206314.
2. Alroughani R, Almulla A, Lamdhade S, Thussu A. Severe reactivation of multiple sclerosis after discontinuation of fingolimod: An IRIS-associated phenomenon. Mult Scler Nov 2014; 6: 748.
3. Belova AN, Rasteryaeva MV, Zhulina NI, Belova EM, Boyko AN. Immune reconstitution inflammatory syndrome and rebound syndrome in multiple sclerosis patients who stopped disease modification therapy: current understanding and a case report. Zh Nevrol Psikhiatr Im S S Korsakova 2017; 117: 74–84.
4. Calic Z, Cappelen-Smith C, Hodgkinson SJ, McDougall A, Cuganesan R, Brew BJ. Treatment of progressive multifocal leukoencephalopathy-immune reconstitution inflammatory syndrome with intravenous immunoglobulin in a patient with multiple sclerosis treated with fingolimod after discontinuation of natalizumab. J Clin Neurosci 2015; 22: 598–600.
5. Cavone L, Felici R, Lapucci A, Buonvicino D, Pratesi S, Muzzi M *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 2015; 50: 78–86.
6. Członkowska A, Smoliński Ł, Litwin T. Severe disease exacerbations in patients with multiple sclerosis after discontinuing fingolimod. Neurol Neurochir Pol 2017; 51: 156–162.
7. De Masi R, Accoto S, Orlando S, De Blasi V, Pasca S, Scarpello R *et al*. Dramatic recovery of steroid-refractory relapsed multiple sclerosis following Fingolimod discontinuation using selective immune adsorption. BMC Neurol 2015; 31: 15–125.
8. Gasperini C, Ruggieri S, Mancinelli CR, Pozzilli C. Advances in the treatment of relapsing-remitting multiple sclerosis – critical appraisal of fingolimod. Ther Clin Risk Manag 2013; 9: 73–85.
9. Hakiki B, Portaccio E, Giannini M, Razzolini L, Pastò L, Amato MP. Withdrawal of fingolimod treatment for relapsing-remitting multiple sclerosis: report of six cases. Mult Scler 2012; 18: 1636–1639.
10. Havla JB, Pellkofer HL, Meinl I, Gerdes LA, Hohlfeld R, Kumpfel T. Rebound of disease activity after withdrawal of fingolimod (FTY720) treatment. Arch Neurol 2012; 69: 262–264.
11. Kappos L, Arnold DL, Bar-Or A, Camm J, Derfuss T, Sprenger T *et al*. Two-year results from a phase 2 extension study of oral amiselimod in relapsing multiple sclerosis. Mult Scler. Published online 2017 Sep 15; doi.org/10.1177/1352458517728343.
12. Kappos L, Arnold DL, Bar-Or A, Camm J, Derfuss T, Kieseier BC. Safety and efficacy of amiselimod in relapsing multiple sclerosis (MOMENTUM): a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol 2016; 11: 1148–1159.
13. Kappos L, Arnold D, Bar-Or A, Camm J, Derfuss T, Kieseier B *et al*. MT-1303, a novel selective s1p1 receptor modulator in RRMS – results of a placebo controlled, double blind phase II trial (momentum) Journal of the Neurological Sciences 2015; 357: 430–431.
14. Killestein J, Vennegoor A, van Golde AE, Bourez RL, Wijlens ML. Wattjes MP. PML-IRIS during Fingolimod Diagnosed after Natalizumab Discontinuation. Case Rep Neurol Med. Published online 2014; Nov 23: dx. doi.org/10.1155/2014/307872.
15. Litwin T, Smoliński Ł, Członkowka A. Substantial disease exacerbation in a patient with relapsing-remitting multiple sclerosis after withdrawal from siponimod. Neur Neurochir Pol 2018; 52: 98–101.
16. N'gbo N'gbo Ikazabo R, Mostosi C, Quivron B, Delberghe X, El Hafsi K. Lysandropoulos AP. Immune-reconstitution Inflammatory Syndrome in Multiple Sclerosis Patients Treated With Natalizumab: A Series of 4 Cases. Clin Ther 2016; 38: 670–675.
17. O'Connor PW, Goodman A, Kappos L, Lublin FD, Miller DH, Polman C *et al*. Disease activity return during natalizumab treatment interruption in patients with multiple sclerosis. Neurology 2011; 76: 1858–1865.
18. Subei AM, Cohen JA. Sphingosine 1-phosphate receptor modulators in multiple sclerosis. CNS Drugs 2015; 29: 565–575.
19. Sugahara K, Maeda Y, Shimano K, Ogawa K, Kumagai H, Yamamoto T *et al*. MT-1303, a novel sphingosine 1-phosphate (S1P) receptor modulator, has less potential for bradycardia than fingolimod. 31ST ECTRIMS 2015 Barcelona; ECTRIMS Online Library. 2015 Oct 8; 115480.
20. Yoshii F, Moriya Y, Ohnuki T, Ryo M, Takahashi W. Neurological safety of fingolimod: An updated review. Clin Exp Neuroimmunol 2017; 8: 233–243.