Clinical Case Report

Medicine®

OPEN

Improvement of macular edema without discontinuation of fingolimod in a patient with multiple sclerosis

A case report

Hisanao Akiyama, MD, PhD*, Yu Suzuki, MD, Daisuke Hara, MD, Kensuke Shinohara, MD, Hana Ogura, MD, Masashi Akamatsu, MD, Yasuhiro Hasegawa, MD, PhD

Abstract

Introduction: Generally, fingolimod administration is simply discontinued when fingolimod-associated macular edema (ME) appears, and the majority of cases are said to recover spontaneously. However, to the best of our knowledge, this is the 1st report regarding improvement of ME without discontinuation of fingolimod administration.

Case presentation: The patient was a 66-year-old woman with relapsing-remitting multiple sclerosis. She was started on treatment with fingolimod to prevent recurrence, after which she developed ME that was probably due to fingolimod. The patient expressed a strong fear of recurrence if fingolimod was discontinued, so we continued fingolimod therapy and followed up the patient frequently. The ME improved after approximately 1 year without any need for concomitant treatment.

Conclusion: We believe that the continuation of fingolimod therapy with strict follow-up examination is one option for treatment, though strategies for managing rapid deterioration of ME should be borne in mind.

Abbreviations: ADR = adverse drug reaction, DME = diabetic macular edema, FAME = fingolimod-associated macular edema, ME = macular edema, MRI = magnetic resonance imaging, MS = multiple sclerosis, OCT = optical coherence tomography, RRMS = relapsing-remitting multiple sclerosis, VEGF = vascular endothelial growth factor.

Keywords: fingolimod, macular edema, multiple sclerosis, optical coherence tomography, spontaneous recovery

1. Introduction

Fingolimod-associated macular edema (FAME) is well known as an adverse drug reaction (ADR) during fingolimod therapy for multiple sclerosis (MS), although its incidence is low.[1–6] Generally, fingolimod is simply discontinued when FAME appears, and the majority of FAME cases improve without the concomitant use of other drugs.[1–4,6] Here, we report a case of MS in which the ophthalmologist and patient strongly desired continuation of fingolimod despite the appearance of macular edema (ME) soon after starting fingolimod therapy, and the ME improved with no other concomitant treatment.

Editor: Fadi Khasawneh.

The authors have no funding and conflicts of interest to disclose.

Department of Neurology, St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan.

** Correspondence: Hisanao Akiyama, Department of Neurology, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan (e-mail: h2akiyama@marianna-u.ac.jp).*

Medicine (2016) 95:29(e4180)

Received: 21 February 2016 / Received in final form: 16 June 2016 / Accepted: 16 June 2016

http://dx.doi.org/10.1097/MD.0000000000004180

2. Case presentation

The patient was a 66-year-old woman. She was being treated with oral amlodipine besylate and sitagliptin phosphate hydrate for hypertension, and steroid-induced diabetes mellitus. Her lifestyle history revealed no history of smoking or alcohol consumption. In terms of the history of the present illness, the patient became aware of a mild weakness in the right lower limb around 1991 (aged 42 years), which was left untreated. The symptoms worsened (details unknown) in 1994 (aged 46 years). The patient was then examined at hospital A and diagnosed with MS. Thereafter, the symptoms (details unknown) followed a remitting and relapsing course, but around 2009 (aged 61 years), motor paralysis of the right lower limb developed and she was admitted to hospital B. The patient was administered steroid pulse therapy for relapsing-remitting MS (RRMS) at this hospital and was discharged walking with a cane. Since that time, the patient had been treated with oral prednisolone and self-administered interferon β-1b injections, but noticed that the symptoms persisted and followed the same remitting and relapsing course. Her activities of daily living decreased to the point that she required a wheelchair, and commuting to hospital became difficult, so the patient was referred to a new doctor at the outpatients' department at hospital C. When the patient was referred, she was noted to have hyperglycemia due to long-term oral prednisolone intake, so the dose was gradually reduced until prednisolone was discontinued, and interferon β-1b injections were also discontinued. On June 17, 2014, the patient was referred to our hospital for the introduction of fingolimod therapy to prevent relapse in RRMS.

At the time of admission, the blood pressure was 143/84 mm Hg, the pulse rate was 78 beats/minute and regular, and the body temperature was 36.2 °C. The general internal medical examination revealed no abnormalities, while the positive neurological findings included the already-known isolated right lower limb paralysis, hyperreflexia in the right upper limb, a disorder of deep sensation affecting the lower limbs bilaterally, and an autonomic nervous system disorder. The patient was evaluated as having an Expanded Disability Status Scale score of 7.5. Cerebrospinal fluid testing revealed a cell count of 1 monocyte/μL (normal range <5), protein level of 57 mg/dL (normal range 10–50), IgG index of 0.7 (normal range <0.7), myelin basic protein levels of <31.3 pg/mL (normal range <102), and positive oligoclonal IgG bands. The patient was negative for serum anti-AQP4 antibodies. The electrocardiogram showed that the patient was in sinus rhythm with a pulse rate of 75 beats/minute, with no ischemic changes. The cardiothoracic ratio on the chest X-ray was 47.0%, with no abnormalities observed in the lung fields. Bilateral paraventricular and juxtacortical focal demyelination on cranial double inversion recovery and T2-weighted magnetic resonance imaging (MRI), T1 black hole on T1-weighted MRI, and spinal cord demyelination on cervical T2-weighted MRI at high cervical levels were observed. Dawson fingers were also observed on the sagittal views (Fig. 1). The patient was given a definitive diagnosis of RRMS after the tests were performed during admission, and was started on oral fingolimod at a dose of 0.5 mg per day on June 27, 2014 (day 11 of the hospital stay). She experienced no issues after introduction, such as bradycardia, and was discharged home on day 13. Since her discharge, 1.5 years have elapsed to date, and during that time, no clinical MS recurrence has been observed.

Meanwhile, we noted the appearance of ME in the left eye from the middle of July, which was approximately 2 weeks since the start of fingolimod therapy, while following up the findings in the fundus using optical coherence tomography (OCT). Thereafter, until around March 2015, the ME observed in the left eye gradually worsened and took on a cystoid appearance. However, the patient herself did not complain of decreased visual acuity and there was no worsening of the HbA1c on the blood test results, and it was difficult for the ophthalmology department to differentiate between FAME and diabetic macular edema (DME). The patient also strongly desired continuation of treatment as she considered prevention of clinical relapse to be paramount, so the oral fingolimod therapy was continued. Thereafter, she received fingolimod without interruption, and the ME in the left eye disappeared spontaneously approximately 1 year after introduction without the use of concomitant drugs, such as corticosteroids, or laser therapy (Fig. 2).

3. Discussion

Fingolimod has been approved for use for "the prevention of both MS recurrence and progression of somatic injuries" in Japan since 2011. ADRs include bradyarrhythmia when therapy is initiated, decreased peripheral blood lymphocyte counts, infection, and liver dysfunction in addition to ME. Among these ADRs, ME has a low incidence at 0% to 1.6%,[1–5] and 3 to 4 months commonly elapse from the time of fingolimod introduction to the appearance of ME,[1–2,4,6] though there have also been reports of onset from 1 to 2 weeks up to 2 years after starting treatment.[3] In addition, it occurs more readily in patients with diabetic retinopathy, uveitis, retinal vascular occlusion, and age-related macular degeneration as an underlying disease.

ME disappears after fingolimod is discontinued in the majority of patients who experience ME,[1–4,6] so early detection is important for the treatment. For this reason, periodic ophthalmology tests such as visual acuity tests, examinations of intraocular pressure and fundus, slit lamp microscopy, and OCT are recorded at 1, 3, and 6 months after starting treatment

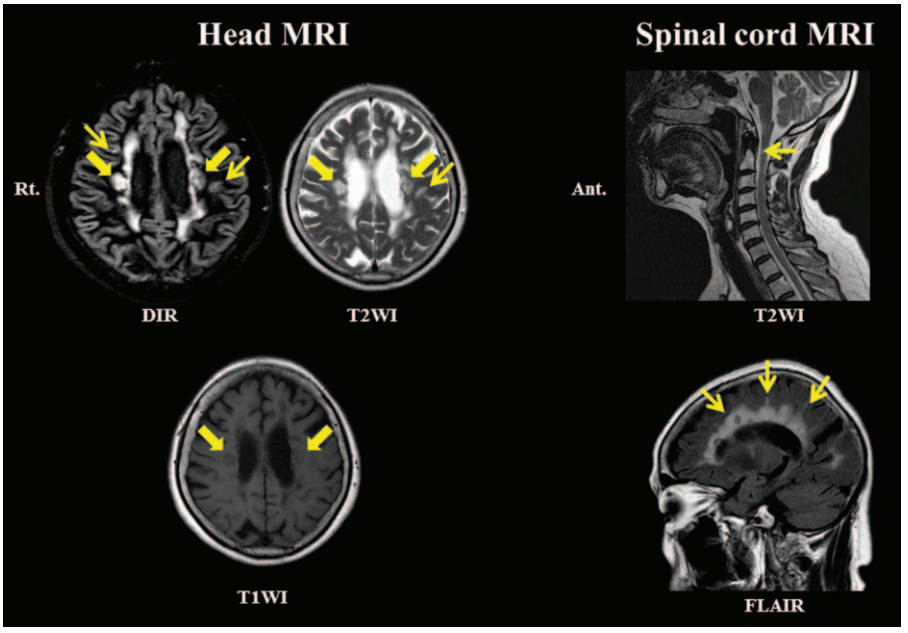

Figure 1. Head and spinal cord MRI on admission. Bilateral paraventricular (⇒) and juxtacortical (→) focal demyelination on cranial double inversion recovery and T2-weighted MRI, T1 black hole (⇒) on T1-weighted MRI, and spinal cord (→) demyelination on cervical T2-weighted MRI at high cervical levels were observed. Dawson fingers (→) were also observed on the sagittal views. Ant = anterior, DIR = double inversion recovery, FLAIR = fluid attenuated inversion recovery, MRI = magnetic resonance imaging, Rt = right, T1WI = T1-weighted image, T2WI = T2-weighted image.

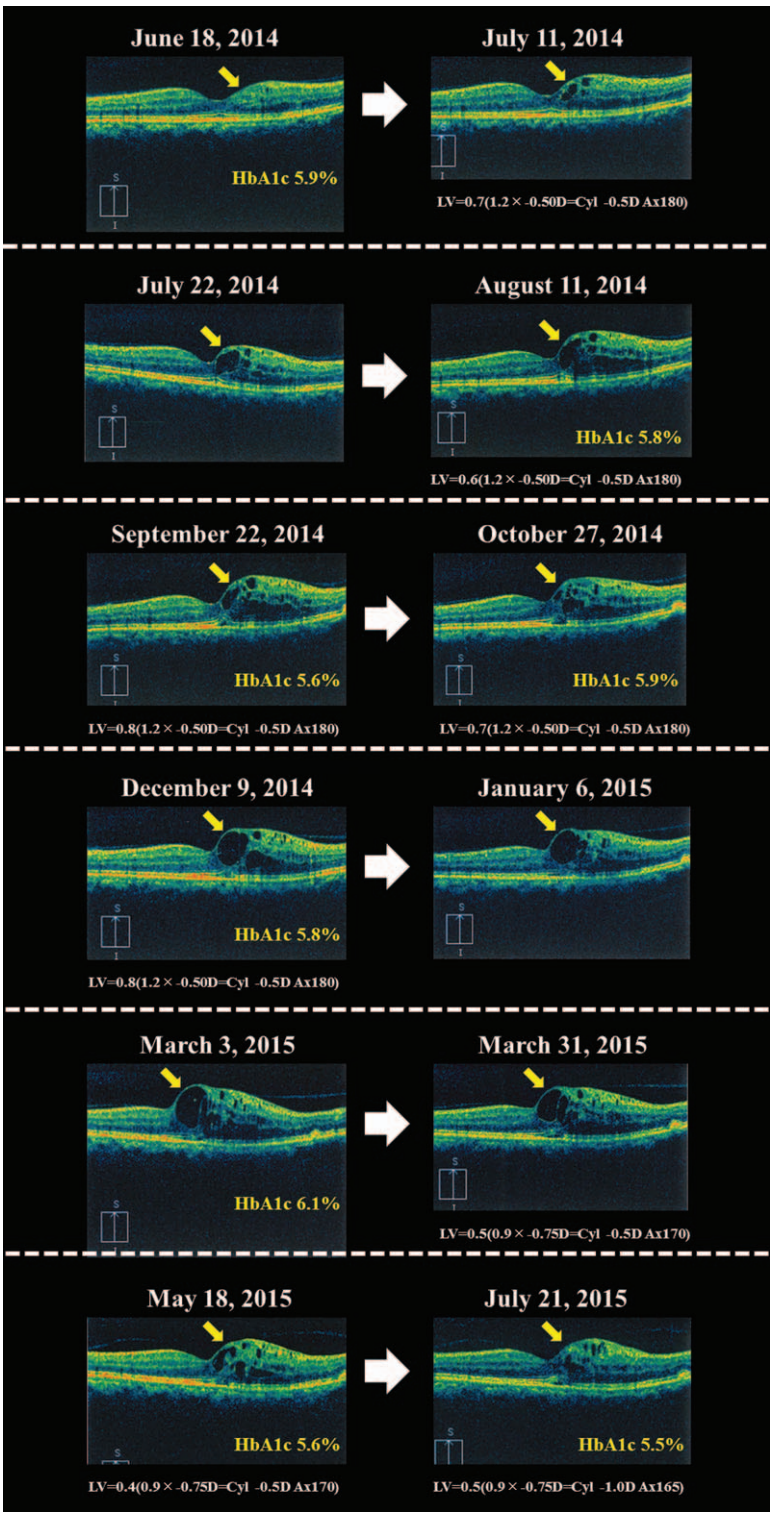

Figure 2. Change of fundus optical coherence tomography images after introducing fingolimod. ME appeared approximately 2 weeks after fingolimod was introduced. Approximately 8 months thereafter, we noted gradual cystoid deterioration of the ME, but the patient did not complain of decreased visual acuity and there was no worsening of HbA1c levels, so oral fingolimod was continued. The ME disappeared spontaneously after approximately 1 year after introduction of fingolimod therapy without the use of any concomitant drugs. Cyl = cylindrical, D = diopter, LV = left vision, ME = macular edema.

with fingolimod, and then every 6 months thereafter. There have also been reports of patients who required concomitant administration of intraocular triamcinolone injections when improvement did not occur after discontinuing fingolimod,[7] but to the best of our knowledge, there have been no reports of remission occurring after fingolimod was continued in the absence of concomitant treatment.

In the present case, we started frequent ophthalmological examinations early, because she had well-controlled, steroid-induced impaired glucose tolerance before fingolimod therapy was introduced. This allowed us to detect the appearance of ME after the short period of 2 weeks after fingolimod introduction, and we considered discontinuing fingolimod therapy. However, we discussed this with both the ophthalmologist and the patient herself, and it was not possible to conclusively state that the ME was caused by fingolimod, so we decided to continue without changing the treatment and scheduled strict follow-up examinations. As a result, we noted spontaneous improvement of the ME approximately 1 year later without the use of concomitant drugs and reported this case for its clinical significance.

The details regarding the mechanism of FAME are unknown, but similar to DME, vascular permeability increases in a fingolimod-dependent fashion and is mediated by S1P1 receptors. This causes a breakdown of the blood-retinal barrier and extravasation occurs.[4] As previously mentioned, discontinuation of oral fingolimod therapy is considered appropriate for stopping this extravasation, but it may become necessary to consider reintroduction of fingolimod therapy when 2 or more weeks have elapsed, and apprehension regarding the possibility of bradyarrhythmia at the time of introduction and recurrence of MS when oral intake is discontinued must be considered.

We were unable to make a definitive diagnosis regarding whether ME was due to FAME or DME in the present case. During the 1st year of treatment, the HbA1c was well-controlled,[8] there were originally no diabetic findings, such as fundal hemorrhage, cotton-wool spots or macroaneurysms,[9] and the patient presented with cystoid ME,[9] and the ocular changes were unilateral. We considered this condition to be FAME, but we could not state this definitively as the interval until FAME onset was short, at approximately 2 weeks after fingolimod introduction.

Although worsening of ME was observed when examined using OCT from the time fingolimod was started until approximately 8 months later, the patient did not complain of decreased visual acuity and wanted to continue treatment with fingolimod. After 1 year had elapsed, we noted that the ME was disappearing and that the ME had improved without the need for concomitant therapy, such as triamcinolone intraocular injections, laser therapy, or vascular endothelial growth factor antibody therapy.

Based on the above, although the contemporary belief is that fingolimod should be discontinued immediately after the appearance of ME, we believe it is necessary to acknowledge cases like the present case, in which administration of fingolimod was continued. Our patient has not required treatment for ME, experienced no recurrence of MS, and is under frequent ophthalmology follow-up, but the clinical course did take some time. The accumulation of further cases will be required.

4. Conclusion

We observed gradually worsening ME for 8 months on OCT from approximately 2 weeks after starting fingolimod therapy, but the patient did not complain of decreased visual acuity and we observed spontaneous disappearance of ME after approximately 1 year. Although the general belief is that fingolimod should be discontinued immediately after the appearance of ME, the present case showed that spontaneous improvement could be observed despite continuation of fingolimod therapy, though improvement does take some time. We believe that the continuation of fingolimod therapy with strict follow-up examination is one option for the treatment, though strategies for managing rapid deterioration of ME should be borne in mind. We will need to accumulate more FAME cases.

5. Consent

The study was approved by St. Marianna university hospital's Human Research Ethics Committee (No. 2879). The patient or their next of kin gave written informed consent for publication of this report.

References

[1] Kappos L, Radue E, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010;362:387–401.
[2] Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med 2010;362:402–15.
[3] Khatri B, Barkhof F, Comi G, et al. Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: a randomized extension of the TRANSFORMS study. Lancet Neurol 2011;10:520–9.
[4] Jain N, Bhatti MT. Fingolimod-associated macular edema. Incidence, detection, and management. Neurology 2012;78:672–80.
[5] Saida T, Kikuchi S, Itoyama Y, et al. A randomized, controlled trial of fingolimod (FTY720) in Japanese patients with multiple sclerosis. Mult Scler 2012;18:1269–77.
[6] Turaka K, Bryan JS. Does fingolimod in multiple sclerosis patients cause macular edema? J Neurol 2012;259:386–8.
[7] Thoo S, Cugati S, Lee A, et al. Successful treatment of fingolimod-associated macular edema with intravitreal triamcinolone with continued fingolimod use. Mult Scler 2015;21:249–51.
[8] Varma R, Bressler NM, Doan QV, et al. Prevalence of and risk factors for diabetic macular edema in the United States. JAMA Opthalmol 2014;132:1334–40.
[9] Afshar AR, Fernandes JK, Patel RD, et al. Cystoid macular edema associated with fingolimod use for multiple sclerosis. JAMA Opthalmol 2013;131:103–7.