Cystoid Macular Edema Associated With Fingolimod Use for Multiple Sclerosis

Fingolimod is the first oral drug approved by the US Food and Drug Administration for multiple sclerosis (MS). It is a sphingosine-1-phosphate–receptor modulator that prevents lymphocyte egress from lymph nodes and enhances astrocyte function.1,2 In this retrospective case series, 4 eyes from 3 patients developed cystoid macular edema (CME) after initiating fingolimod therapy. The study was approved by the University of Chicago Institutional Review Board.

Report of Cases. Case 1. A 52-year-old man with primary progressive MS had progressively blurred vision in the left eye for 3 weeks. He was not diabetic. The patient started treatment with oral fingolimod, 0.5 mg/d, 4 weeks prior for MS refractory to mycophenolate mofetil and intravenous steroids. Best-corrected visual acuity was 20/20 OD and 20/40 OS, from 20/20 OD and 20/25 OS 2 months prior. Retinal examination showed new CME in the left eye. One week prior to starting fingolimod, at the request of his 1 neurologist, the patient had spectral-domain optical coherence tomography (SD-OCT) of the optic nerves and maculas (Figure 1A), which were normal in each eye. Findings on SD-OCT 4 weeks after starting fingolimod treatment confirmed CME in the left eye with central foveal thickness of 573 μm (Figure 1B). The neurologist continued fingolimod therapy owing to improvement in the patient’s MS, so the patient began treatment with topical nepafenac 3 times daily and difluprednate twice daily in the left eye. Four weeks later, visual acuity was 20/20 OD and 20/30 OS. Dilated examination showed retinal pigment epithelial changes but no CME in the left eye. Findings on SD-OCT showed resolution of CME with central foveal thickness of 301 μm (Figure 1C).

Case 2. A 60-year-old woman with relapsing-remitting MS had progressively blurred vision in each eye for 2 weeks. She had optic neuritis in the right eye 15 years prior and diabetes without retinopathy. Her glycated hemoglobin level was 6.1% of total hemoglobin (to convert to proportion of total hemoglobin, multiply by 0.01) 1 month prior. The patient started treatment with oral fingolimod, 0.5 mg/d, 1 month prior for MS refractory to azathioprine sodium, interferon beta-1b, and natalizumab. At the request of her neurologist, she had an eye examination and SD-OCT of her optic nerves and maculas 2 weeks prior to starting fingolimod treatment; they were normal in each eye (Figure 2A and D). Visual symptoms began 10 days after starting the drug. Best-corrected visual acuity was 20/60 OD and 20/40 OS, from 20/25 OU prior to starting the drug. Dilated examination showed CME in each eye, with central foveal thickness of 477 μm OD (Figure 2B) and 389 μm OS (Figure 2E) on SD-OCT. Fundus photographs and fluorescein angiography confirmed CME in each eye (Figure 3). The neurologist discontinued fingolimod treatment. Four weeks later, visual acuity was 20/30 OU. Dilated examination findings were normal in each eye and central foveal thickness was 210 μm OD (Figure 2C) and 212 μm OS (Figure 2F) on SD-OCT.

Case 3. A 57-year-old man with relapsing-remitting MS had blurred vision in the left eye for 1 week. Four weeks prior, he started treatment with oral fingolimod, 0.5 mg/d, 1 week prior for MS refractory to azathioprine sodium, interferon beta-1b, and natalizumab. At the request of his neurologist, he had an eye examination and SD-OCT of his optic nerves and maculas 2 weeks prior to starting fingolimod treatment; they were normal in each eye (Figure 2A and D). Visual symptoms began 10 days after starting the drug. Best-corrected visual acuity was 20/60 OD and 20/40 OS, from 20/25 OU prior to starting the drug. Dilated examination showed CME in each eye, with central foveal thickness of 477 μm OD (Figure 2B) and 389 μm OS (Figure 2E) on SD-OCT. Fundus photographs and fluorescein angiography confirmed CME in each eye (Figure 3). The neurologist discontinued fingolimod treatment. Four weeks later, visual acuity was 20/30 OU. Dilated examination findings were normal in each eye and central foveal thickness was 210 μm OD (Figure 2C) and 212 μm OS (Figure 2F) on SD-OCT.

Figure 1. Case 1. Spectral-domain optical coherence tomographic images of the left eye 1 week prior to starting fingolimod (A), 4 weeks after starting fingolimod (B), and 8 weeks after starting fingolimod, after 4 weeks of topical nepafenac and difluprednate (C). I indicates inferior; N, nasal; S, superior; and T, temporal.
for progressive MS refractory to interferon beta-1b, intramuscular interferon beta-1a, and glatiramer acetate. At the request of his neurologist, 5 days prior to initiating fingolimod treatment, he had an eye examination and time-domain OCT of his optic nerves and maculas (Figure 4A), which were normal in each eye. One month after starting fingolimod, visual acuity was 20/20 OD and 20/30 OS, from 20/20 OU prior. Dilated examination showed CME in the left eye (the right eye was normal). Time-domain OCT confirmed CME in the left eye with central foveal thickness of 452 μm and an incidental new epiretinal membrane (Figure 4B). The neurologist stopped fingolimod treatment and the patient began treatment with topical bromfenac twice daily in the left eye. One month after discontinuing fingolimod treatment, visual acuity was 20/25 OS. This visit was at a different office, where SD-OCT showed epiretinal membrane and central foveal thickness of 341 μm in the left eye (Figure 4C). Three months after discontinuing fingolimod treatment, visual acuity was 20/25 OS and the blurred vision had resolved. Findings on SD-OCT showed epiretinal membrane and central foveal thickness of 348 μm in the left eye (Figure 4D).

Comment. This first case series reporting CME associated with fingolimod in patients with MS includes the first case of bilateral fingolimod-associated CME. There are 2 case reports documenting fingolimod-associated CME. Saab et al described a patient receiving 5 mg/d of fingolimod after a renal allograft. Turaka and Bryan described a patient with MS who developed CME 3 months after starting treatment with fingolimod, 0.5 mg/d. All patients in our series developed CME within 1 month of starting treatment with fingolimod, 0.5 mg/d.

The phase 3 TRANSFORMS (n=1123) and FREEDOMS (n=946)
studies investigating fingolimod for MS showed CME in 6 and 7 patients, respectively. In the TRANSFORMS study, 4 of the 6 patients were taking 1.25 mg/d and 2 were taking 0.5 mg/d. All 7 patients in the FREEDOMS study were taking 1.25 mg/d. Only a dosage of 0.5 mg/d is approved by the US Food and Drug Administration for MS. A limitation of these studies was the use of time-domain OCT, which is less sensitive than SD-OCT at illuminating subtle macular pathology. Owing to CME in these trials, many neurologists request eye examinations and OCT prior to starting fingolimod treatment.

Treatment of fingolimod-associated CME with a newer-generation nonsteroidal anti-inflammatory drug and a steroid may hasten resolution of CME. In the 2 patients treated with topical nonsteroidal anti-inflammatory drugs, CME resolved within 4 weeks; this is in contrast to the TRANSFORMS and FREEDOMS studies, in which CME took up to 6 months to resolve without treatment. In case 1, suppression of CME by a retina specialist allowed the patient to continue treatment with fingolimod.

The patient with bilateral fingolimod-associated CME was diabetic. Although she had no retinopathy, diabetic microvascular changes likely increased susceptibility to developing CME. Owing to its mechanism of action, fingolimod may increase vascular permeability and cause breakdown of the blood-retinal barrier.

With increasing use of fingolimod for MS, reports of associated CME will likely increase. The 0.5% incidence in the TRANSFORMS and FREEDOMS studies in patients taking 0.5 mg/d is likely an underrepresentation of this adverse effect. The patients in this study were not consecutively screened; they were isolated referrals from a neurologist during a 4-month span. A study screening all patients starting fingolimod at 1 institution would more accurately depict the prevalence of fingolimod-associated CME and warrants further investigation.

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Figure 3. Case 2. Fundus photographs (A) and fluorescein angiograms (B) of the right and left eyes 4 weeks after starting fingolimod.
Figure 4. Case 3. Time-domain optical coherence tomographic images of the left eye 5 days prior to starting fingolimod (A) and 4 weeks after starting fingolimod (B), and spectral-domain optical coherence tomographic images of the left eye 4 weeks after discontinuing fingolimod (C) and 3 months after discontinuing fingolimod (D). I indicates inferior; N, nasal; S, superior; and T, temporal.
Athena Neurosciences, Avanir, Aventis, Bayer Pharma AG, Berlex Laboratories, Biogen and Biogen/Idec, BioMS Medical, Boehringer Ingelheim Pharmaceuticals, Caremark Rx, Centocor, Cephalon, Connectics/Connective Therapeutics, CroMedica Global, Elan Pharmaceuticals, Eli Lilly & Co, Ezoce Sciences, Genentech, Genzyme Corp, GlaxoSmithKline, Hoechst Marion Roussel Canada Research, Hoffman-La Roche, Idec. Immunex, Johnson & Johnson, Kalebios, Neurocrine Biosciences, Novartis, Parke-Davis, Pfizer, Pharmacia & Upjohn, Protein Design Labs, Quantum Biotechnologies, Quintiles, Serono, Sention, Shering AG, SmithKline Beecham, Berilpharm, Takeda Pharmaceuticals, Teva-Maron, and Triton Biosciences. Dr Hariprasad has been a consultant for Alcon, Allergan, Genentech, Bayer, OD-OS, Optos, and Regeneron.


Myelinated retinal nerve fiber layers (RNFLs) are relatively common and generally benign. They appear as white, sharply demarcated patches on the surface of the retina that obscure the underlying retinal vessels. They have frayed or feathered borders that correspond in shape and distribution to ganglion cell axons. Myelination of the RNFL is often congenital but can be acquired or even progress in childhood or adolescence.1 Also, partial or total regression of the myelinated RNFL has been observed after injury to the optic nerve.2

Curiosity about the etiology of this superfluous myelination abounds, but the pathophysiology remains largely unknown. Normal myelination typically progresses from the chiasm to the optic nerve from the eighth month of gestation until birth and then stops at the lamina cribrosa. Proposed factors for normal inhibition of myelination in the human retina include the structure of the lamina cribrosa itself, plasma proteins leaking from the choroidal circulation that may stimulate the differentiation of oligodendrocytes, and factors released by type 1 astrocytes that inhibit oligodendrocyte migration.3

Many of the imaging characteristics of RNFL myelination have not yet been described. One report of optical coherence tomographic (OCT) images of myelinated RNFL in 2 patients with high myopia and small optic nerves showed reduced retinal thickness in the same distribution of the myelination.4 To our knowledge, there are no published reports of OCT findings in eyes without high myopia and abnormal optic nerves (based on an English-language PubMed search including “myelinated nerve fiber layer AND OCT,” “retina nerve fiber layer myelination,” “myelinated retina nerve fiber layer,” “optical coherence tomography AND myelin,” and “autofluorescence AND nerve fiber layer”). Herein, we describe the retrospectively obtained red-free, fluorescein, OCT, infrared, and autofluorescence characteristics of these structures in 4 eyes.

Report of Cases. A 14-year-old girl was referred to the neuro-ophthalmology service because of an abnormal appearance of her left optic disc. She was otherwise healthy and asymptomatic. A color fundus photograph (Zeiss FF-4; Carl Zeiss Meditec) of the left eye was taken in 2011 (at age 14 years) (Figure, A).

A red-free image (Zeiss FF-4) highlights the white appearance of the myelinated RNFL (Figure, B). Infrared imaging (Spectralis; Heidelberg Engineering) highlights the white appearance of the myelinated RNFL (Figure, C). Autofluorescence imaging (Spectralis) reveals a dark area in the region of the myelinated RNFL (Figure, D). An OCT image (Spectralis) shows a thickened RNFL in areas of the myelination (Figure, E). A color fundus photograph of the left eye from 2007 (at age 10 years) indicates that development of the peripapillary myelinated RNFL occurred sometime between ages 10 and 14 years and also reveals that the pigmented spot was unchanged (Figure, F).

Color fundus, red-free, infrared, autofluorescence, and OCT images are shown for an 83-year-old man (eFigure 1, http://www.jamaophthalmology.com), a 55-year-old woman (eFigure 2), and a 55-year-old man (eFigure 3).

Administrative review by the University of Utah Institutional Review Board was obtained. The project was determined to not meet the definition of human subjects research and therefore did not require further institutional review board oversight.

Comment. The imaging characteristics of these patients’ myelinated RNFLs are similar in almost all respects.

On infrared and red-free imaging, the myelinated RNFL stands out as white. Myelin consists largely of lipid, so this suggests that red-free imaging (488 nm) and infrared imaging (820 nm) are sensitive to structures with high lipid content. The high lipid content of myelin is also most likely responsible for the blocking effect created on fluorescein angiography.

Fundus autofluorescence (488 nm) works by detecting the natural fluorescence occurring from lipofuscin, a toxic product of photoreceptor cells that accumulates in lysosomes of unhealthy retinal pigment epithelial cells. Myelinated RNFL appears dark on autofluorescence, most likely because it blocks detection of underlying fluorescent material such as lipofuscin.