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## CONTINUING FINGOLIMOD AFTER DEVELOPMENT OF MACULAR EDEMA: A CASE REPORT

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Fingolimod is the first effective oral agent in widespread use for relapsing-remitting multiple sclerosis (MS), but it can cause macular edema (ME) as an uncommon complication. ME may be mild and asymptomatic, but it can also produce visual impairment. The mechanism of fingolimod-associated ME (FAME) is thought to be through sphingosine-1-phosphate receptor antagonism, affecting endothelial integrity and increasing the risk of microvascular leaks.<sup>1</sup>

Analysis of phase 2 and 3 fingolimod studies found 19 cases of ME out of 2,615 patients (0.7%).<sup>1</sup> Thirteen had onset within 4 months of fingolimod commencement, 4 had onset between 4 and 12 months, and 2 had onset after 12 months. Fingolimod was ceased in all cases, with complete resolution of ME in 16 and partial resolution in the remainder. Eleven required treatment with topical anti-inflammatory drugs. Risk factors for FAME include previous uveitis and diabetes.

The most sensitive technique for detecting ME is optical coherence tomography (OCT). Treatments include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, vascular endothelial growth factor antagonists, laser photocoagulation, and vitreoretinal surgery.<sup>1</sup> However, all have side effects, including delayed healing, increased bleeding and infection risk, and elevated intraocular pressure.

**Case report.** A 37-year-old woman with an 18-year history of relapsing-remitting MS began fingolimod in May 2011. She had previously used interferon  $\beta$ -1a and mitoxantrone, but she experienced severe relapses after mitoxantrone cessation when the maximum cumulative dose was reached. She was anti-JC virus positive in serum. She has had one episode of right optic neuritis but no history of uveitis or diabetes.

When fingolimod was commenced, she was wheelchair-bound with an Expanded Disability Status Scale (EDSS) score of 7.5. Best corrected visual acuity was 6/18 (left eye [LE]) and 6/18<sup>-2</sup> (right eye). Baseline ophthalmologic examination was otherwise unremarkable. After 4 months' treatment, she could walk short distances with assistance (EDSS 7). Visual acuity was

unchanged. However, OCT (using Stratus OCT [Carl Zeiss Meditec, Inc., Dublin, CA] fast macula thickness protocol) revealed a new left foveal cyst with central foveal thickness of  $213 \pm 47 \mu\text{m}$  (LE) (normal:  $182 \pm 23 \mu\text{m}$ ) (figure). Fundal examination demonstrated altered foveal light reflexes bilaterally, confirming ME.

Because the patient was neurologically improved and natalizumab was relatively contraindicated, she continued fingolimod with regular ophthalmology reviews. She has not had any treatment for ME and visual acuity remains unchanged. The degree of ME has fluctuated but has not worsened 25 months after diagnosis. Her current EDSS is 6.5 and she is able to walk 20 meters aided.

**Discussion.** It is recommended that patients undergo baseline ophthalmologic assessment prior to commencing fingolimod and at 3–4 months. Those with a history of diabetes or uveitis should have more frequent examinations.<sup>1</sup>

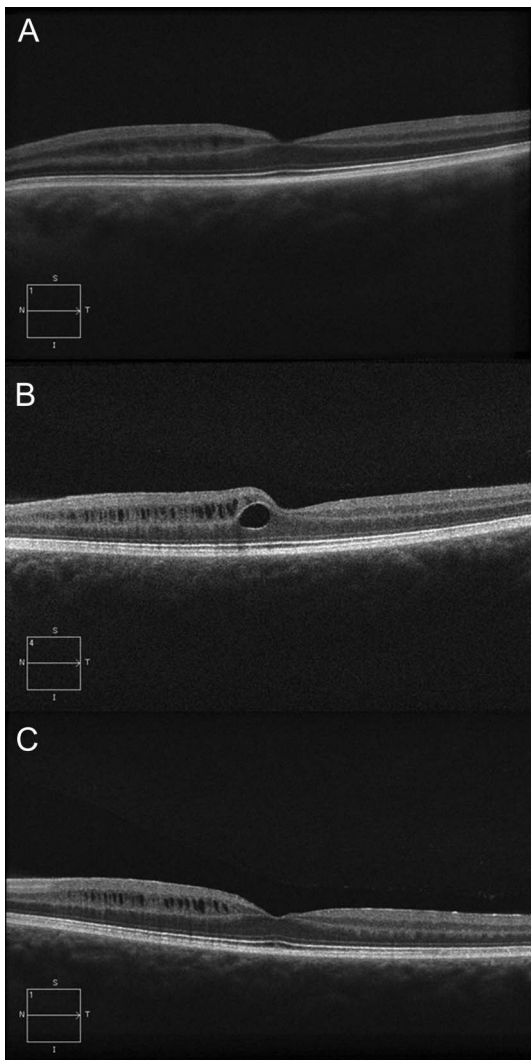
There are a small number of case reports of FAME in MS, encompassing 11 eyes in 8 patients.<sup>2–6</sup> Time to onset of visual symptoms or diagnosis of ME ranged from 5 days to 6 months after starting fingolimod.

Management of FAME varied. Fingolimod was discontinued in 6 of 11 eyes; 4 of these were treated with NSAID eye drops and 2 were untreated. In the other 5 eyes, fingolimod was continued with NSAID eye drops in 4 cases and observation only in 1 case. In all 4 treated eyes in which fingolimod was continued, ME and visual acuity improved or resolved. Attempts were made, unsuccessfully, to wean therapy in 2 eyes and fingolimod was ultimately ceased.<sup>3</sup> Anti-inflammatory eye drops were followed by sub-tenon triamcinolone injection in 1 case with resolution of ME, but the patient developed acute intraocular hypertension. ME worsened over 1 month in the 1 eye in which fingolimod was continued without treatment, requiring eventual sub-tenon triamcinolone injection.<sup>5</sup>

In 9 of 11 eyes, macular changes disappeared after 3–32 weeks. However, visual recovery was incomplete in 4 of 9 eyes. In 2 of 11 eyes, some ME was still present at time of report.

Increases in macular volume on OCT have been observed more widely in patients on fingolimod over 5–6 months' follow-up.<sup>7</sup> Whether this represents a neuroprotective effect or rather a subclinical form of

**Figure** Serial optical coherence tomographies (OCTs) of left eye (LE) over time with corresponding central foveal thickness (CFT) measurements of both eyes



Serial OCTs of LE on (A) October 7, 2011; (B) February 3, 2012; and (C) April 26, 2013. The CFT measurements of both eyes on these dates were (A) 272  $\mu\text{m}$  (LE), 262  $\mu\text{m}$  (right eye [RE]); (B) 308  $\mu\text{m}$  (LE), 258  $\mu\text{m}$  (RE); and (C) 259  $\mu\text{m}$  (LE), 259  $\mu\text{m}$  (RE).

cystoid ME requires further research. This also has implications for interpreting OCT findings in patients treated with fingolimod.

This case describes a patient continuing fingolimod long-term without additional treatment after FAME onset. Macular changes were first detected after 4 months of treatment, consistent with the time course reported in earlier studies. This report provides Class IV evidence that it may be possible to continue fingolimod in patients with FAME with stable vision and macular changes with very close monitoring, potentially allowing highly selected patients with MS to continue an effective treatment.

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