CASE REPORT

Severe early bilateral macular edema following fingolimod therapy

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Abstract
We report a case of bilateral macular edema (ME) within 10 days of starting fingolimod 0.5 mg therapy in a patient with Multiple Sclerosis (MS). The complication resolved without treatment as demonstrated by sequential Optical Coherence Tomography (OCT). Fingolimod is a sphingosine-1-phosphate receptor modulator that reduces lymphocyte presence in the CNS. In pivotal trials, ME, a known complication of fingolimod, typically occurred unilaterally with onset at approximately 3 months. A 60 y/o AA female, diagnosed with MS in 1977, started oral fingolimod treatment on 05/31/2011. Baseline screening with OCT and ophthalmology evaluation showed no ME. On 06/10, she developed bilateral blurry vision and discontinued fingolimod. On 06/27, OCT revealed severe bilateral ME. Later OCT exams showed a progressive decrease in Central Foveal Thickness (CFT) and Macular Volume (MV), without specific treatment other than discontinuation of fingolimod. On 07/27, OCT revealed severe bilateral ME. Later OCT exams showed a progressive decrease in Central Foveal Thickness (CFT) and Macular Volume (MV), without specific treatment other than discontinuation of fingolimod. On 07/27, CFT, MV, and Visual Acuity (VA) were similar to baseline. This is the first reported case of bilateral, early onset ME following fingolimod treatment at the current FDA-approved dose of 0.5 mg. Diabetes, a known risk factor for ME, may have contributed to her early, bilateral involvement. Our case provides further support for earlier OCT, in conjunction with ophthalmic examinations, for at-risk patients on fingolimod, and suggests that cessation of fingolimod may be associated with resolution of ME.

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1. Introduction
Multiple sclerosis (MS) is a disease characterized by myelin-specific T cells, antibodies, and B cells, which attack the central nervous system (CNS) and promote demyelination, leading to...
Fig. 1  Sequential OCT scans showing bilateral Macular Edema and subsequent resolution. OD-right eye and OS-left eye. 
(A) Bilateral baseline scans showing no macular edema. (B) Scans from 6/27/2011 showing marked macular edema bilaterally. Arrows depict swelling of macula. Numerical values reveal increase in macular volume and Central Foveal Thickness (CFT) in center circle. (C) Follow-up scan from 7/27/2011 shows resolution of macular edema with values near baseline.

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lesions and neurodegeneration (Zamvil and Steinman, 2003). Oral fingolimod was approved in September of 2010 for treatment of relapsing-remitting MS, following clinical trials that demonstrated that it reduced relapses and magnetic resonance imaging (MRI) lesions. Fingolimod is a sphingosine-1-phosphate receptor (S1PR) modulator that inhibits lymphocyte egress from the lymph nodes and reduces their presence in the CNS (Brinkmann et al., 2002).

In clinical trials, macular edema (ME) occurred in 0.4% of patients treated with 0.5 mg of fingolimod, and in 1.0% of patients treated with 1.25 mg (Jain and Bhatti, 2012). The macular edema appeared at approximately 3 months following initiation of treatment, and most cases improved over weeks following discontinuation of therapy.

2. Case report

A 60 y/o African American woman was diagnosed with MS in 1977. Her previous MS treatment included interferon-beta, natalizumab, and azathioprine. She had diabetes, hypertension, and migraines, and was taking metformin [500 mg BID], verapamil [80 mg BID] Toprol XL [100 mg BID] and aspirin [81 mg QD]. The patient also had bilateral cataracts, and baseline VA was 20/25 and 20/25 R/L. Of note, the patient had papillor in her left eye, due to two episodes of prior optic neuritis. She was started on oral fingolimod treatment [0.5 mg QD] on 05/31/2011. Baseline screening Optical Coherence Tomography (OCT) using a Heidelberg Spectralis revealed no macular edema [CFT: 202 μm, 207 μm R/L, normal range 219–322 μm] *(CFT: Central Foveal Thickness). There were no first-dose related symptoms.

On 06/06, she developed severe headaches accompanied by bilateral upper and lower extremity weakness and numbness. On 06/10, she woke up with bilateral blurred vision, more severe in the right eye. The patient’s vision loss was painless, and she reported no pain with eye movements. She discontinued fingolimod and all other medications, except for aspirin.

The patient presented to the neurology department on 6/27, and she was referred for an OCT in order to evaluate for possible macular edema. OCT revealed severe bilateral macular edema [CFT: 449 μm, 586 μm R/L VA: 20:60 and 20:30 R/L] confirmed by full ophthalmic examination on 6/28. No other medications were initiated at that time.

An OCT on 7/01 showed a bilateral decrease in CFT and macular volume. OCT scans from 7/13 confirmed a continuous decrease in both CFT and macular volume, and a rapid improvement toward the patient’s normal baseline. Visual acuity on 7/13 was 20/30 and 20/30 R/L. On 7/20, the patient resumed taking metformin, verapamil, and metoprolol succinate, and was started on azathioprine therapy for her MS. OCT scans on 7/27 revealed CFT and macular values similar to baseline, and visual acuity of 20/25 and 20/25 R/L (Fig. 1). On 8/10, ophthalmology examination showed no pars planitis and visual acuity of 20/20 and 20/25 R/L, and concluded that no further treatment was warranted.

3. Discussion

Macular edema is an accumulation of intraretinal fluid in cystic spaces between the internal nuclear layer and the outer plexiform layer. Diabetes, vein occlusions, uveitis, and eye surgery are all known causes (Tranos et al., 2004). Ophthalmologic examinations are recommended at 3-4 months after the first dose of fingolimod, according to FDA guidelines. There are rare cases of unilateral macular edema prior to this recommended time point (FDA and CDER 2010). Our case suggests that earlier OCT, in conjunction with ophthalmologic examinations, should be considered for at-risk patients on fingolimod. Here, 10 days of fingolimod treatment resulted in severe symptomatic bilateral ME. This is the first reported case of bilateral, early onset ME following fingolimod treatment at the current FDA-approved dose of 0.5 mg. Diabetes, a known risk factor for ME when on fingolimod, may have contributed to her early and bilateral involvement. Of note, the patient had no history of uveitis, another possible risk factor. Our case demonstrates the value of immediate OCT, in conjunction with ophthalmologic examinations, for diabetics on fingolimod, and suggests that cessation of fingolimod is associated with resolution of ME.

Conflict of interest

Dr. Bernard has served as a Consultant for Biogen, Bayer and Novartis. Oscar Michael Coppes reports no disclosures. Ismael Gutierrez reports no disclosures. Dr. Susan Ksiazek reports no disclosures. Dr. Reder’s disclosures are on file with AAN.

References

FDA and CDER. Peripheral and central nervous system drugs advisory committee meeting: Fingolimod (NDA 22-527) background package; 2010.


