CASE REPORTS

Late Onset Macular Oedema in a Patient with Multiple Sclerosis Treated with Fingolimod

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ABSTRACT

Macular oedema is a rare complication of fingolimod treatment. It usually presents within 3–4 months, but occasionally presents later. It can resolve without treatment despite continuation of fingolimod treatment. Herein we report a case of very late onset macular oedema in a 49-year-old woman with multiple sclerosis treated with fingolimod for 7 years. The patient presented with blurred vision in both eyes with visual acuities of 20/32 in her right eye and 20/25 in her left eye. She had macular oedema, that without discontinuing fingolimod treatment, resolved after 1 month.

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Introduction

Fingolimod, an immunomodulatory agent, is used for the treatment of relapsing–remitting multiple sclerosis (RRMS). Fingolimod-associated macular oedema (FAME) is a known complication with an incidence of 0.4%.¹ The current recommendation for treatment of FAME is cessation of fingolimod, which typically reverses its macular effects.

Case report

A 49-year-old Caucasian female with a history of RRMS started fingolimod treatment (0.5 mg per day) after experiencing significant disease progression whilst on glatiramer acetate. As part of her treatment protocol, she was referred to the neuro-ophthalmology unit for a baseline screen that was completely normal. She had no other systemic diseases. Seven years after commencing fingolimod, she developed decreased vision in the right eye. The neurologist performed an optical coherence tomography (OCT) examination that revealed moderate macular oedema (ME) and cystic changes in the macula of both eyes (OU) (Figure 1). The patient was referred 1 week later to neuro-ophthalmology for consultation. Her best corrected visual acuity (BCVA) measured 20/32 in her right eye (OD) and 20/25 in her left eye (OS). Dilated fundal

examination showed mild ME in OU. Repeat OCT revealed an improvement in her ME compared with the previous examination (Figure 1). There were no other causes for ME identified on full slit-lamp examination. She was diagnosed with FAME.

Management options for FAME were discussed with the patient, including cessation of fingolimod, observation or non-steroidal anti-inflammatory drops. Since her multiple sclerosis was well controlled with fingolimod, she was reluctant to discontinue this medication. As an improvement of the FAME had been seen it was decided to continue fingolimod with close observation and without any topical treatment. The patient returned for follow-up after 4 weeks. Her BCVA improved to 20/20 in OU. Ophthalmologic examination and OCT showed that the FAME had resolved (see Figure 1).

Discussion

Fingolimod was the first oral agent approved by the US Food and Drug Administration (FDA) in 2010 for the treatment of RRMS. Active metabolites of fingolimod bind to the sphingosine-1-phosphate (S1P) receptor on T-lymphocytes' surface resulting in internalisation and degradation of the receptor. This action prevents lymphocytes from leaving secondary lymphoid organs, thus reducing the number of circulating

Figure 1. Optical coherence tomography (OCT) at diagnosis of macular oedema (ME), right eye (a) and left eye (b), both with moderate cystoid ME. OCT 1 week after diagnosis showing a decrease in ME in both eyes; complete resolution in the right eye with restoration of the normal foveal contour (c) and residual intraretinal cysts in the left eye (d). OCT 5 weeks after diagnosis with resolution of ME in both eyes; right eye (e) and left eye (f).

lymphocytes available to participate in central nervous system autoimmune demyelination. In addition to modulating lymphocytes, the S1P receptor is responsible for regulating vascular permeability via

interaction with the cytoskeleton and intracellular junctions. Disruption of the endothelial barrier in the retina may be implicated in the development of ME with the use of fingolimod.²

Table 1. Cases of FAME published with onset 5 months or more after starting fingolimod treatment.

Authors	Delay from the start of fingolimod treatment to the onset of FAME (months)	Daily dose	Visual acuity	OCT changes	Treatment	Outcome
Zarbin et al. ⁴	27	0.5 mg	Not reported	Increase of foveal thickness in OS	Topical anti-inflammatory drugs and steroids with discontinuation of fingolimod	ME resolved in 6 weeks
	43	1.25 mg	20/20 OD 20/32 OS	ME in OS	Systemic prednisone (tapered) and acetazolamide with discontinuation of fingolimod	ME fully resolved after 35 days
Husmann et al. ⁷	12 6	1.25 mg 0.5 mg	20/20 OU 20/25 OD 20/20 OS	Increase of foveal thickness OU Moderate ME in the right macula	Discontinuation of fingolimod Nonsteroidal anti-inflammatory drops without discontinuation of fingolimod	ME resolved after 2 months 20/20 OD and ME improved after 1 month
Chui et al. ⁵	6	0.5 mg	20/25 OD 20/20 OS	Macular cystic changes in OD	Topical ketorolac and dexamethasone with discontinuation of fingolimod	20/20 OU and ME improved after 2 months
Thoo et al. ⁸	12 21	0.5 mg	20/40 OD	OCT confirmed ME	Intravitreal triamcinolone with continuation of fingolimod	Vision improved to 20/25 OD in 5 weeks
Goh et al. ⁹	21	Not reported	20/125 OU	Increase of central foveal thickness OU	Discontinuation of fingolimod	20/125 OD and 20/200 OS after 10 months *Bilateral optic nerve damage

FAME = fingolimod-associated macular oedema; OD = right eye; OS = left eye; OCT = optical coherence tomography; OU = both eyes.

FAME is dose dependent with incidence ranging from 0.40% to 1%, occurring predominantly in the first 3–4 months of therapy.³ The FDA recommends baseline ophthalmologic examination with repeated studies at 3–4 months. More frequent examinations are recommended for patients with diabetes mellitus or uveitis due to their increased risk of having cystoid ME.⁴

It has been published that resolution occurs spontaneously in most patients after cessation of treatment but in resistant cases, topical corticosteroids and non-steroidal anti-inflammatory drops are used with improvement seen over 4–6 weeks.^{5,6} Refractory FAME may require more invasive interventions such as subconjunctival or intravitreal administration of corticosteroids or antivascular endothelial growth factor.

There have been seven cases published of FAME occurring more than 5 months after initiation of fingolimod treatment for RRMS. They are listed in Table 1. Note that one patient had a history of uveitis, one had cataract surgery 4 days after the ME had been noticed and one had optic neuritis before the development of ME and possibly a further episode of optic neuritis during the time with ME. Some of the case resolved with discontinuation of fingolimod, others with topical treatment and one with intravitreal injections.

A limitation of this case report is the possibility that the use of fingolimod was unrelated to the development of ME, even though no obvious cause was found. Multiple sclerosis can be associated with intraretinal changes that can mimic ME, but the changes shown in this case do not look typical of that and the prompt resolution is also not suggestive. Spontaneous resolution of ME in this case could be due to a minimum disruption of the endothelial barrier in the retina that resolved due to its own regulatory mechanisms.

Conclusions

FAME can present late and close observation without any topical treatment could be an option for patients who do not want to discontinue fingolimod.

Patient consent and ethics statement

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Declaration of interest statement

The authors declare that there are no conflicts of interest. The authors alone are responsible for the writing and content of the article.

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