Fingolimod and macular edema

Pathophysiology, diagnosis, and management

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Summary

Fingolimod causes macular edema (ME) by acting via the S1P3 receptor agonism, thereby reducing the tight junction between the endothelial cells of the retinal capillaries. This results in the breakdown of the inner blood retinal barrier, causing ME. Ophthalmologic evaluation including optical coherence tomography is recommended at baseline and then at 3 months, 6 months, and annually thereafter in all patients on fingolimod. The risk of ME increases in patients who are diabetic, have had uveitis, or who undergo intraocular procedures such as cataract surgery, and hence these patients need close monitoring. Cessation of the drug results in resolution of the ME. However, ME can also be treated using anti-inflammatory medication (steroids) in patients who opt to remain on fingolimod.

Fingolimod is the first oral disease-modifying therapy approved for the treatment of multiple sclerosis (MS). The efficacy of fingolimod has been demonstrated in 2 large, phase III, double-blind, randomized trials.^{1,2} Practical aspects related to the use of fingolimod and its systemic side effects have been described.³

Fingolimod was used initially as an immunomodulator to augment the immunosuppressive effect of other drugs in renal transplant rejection. The dosage for renal transplant ranged between 2.5 and 5 mg, 5 and 10 times that approved for treatment of MS. Fingolimod failed to show a benefit for the prevention of renal allograft rejection over the conventional treatment in large phase III studies and hence further development in renal transplantation was stopped. In these studies, fingolimod was associated with the development of macular edema (ME).⁴ As

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Figure 1 Optical coherence topography of normal macula

Optical coherence topography of macula shows a foveal pit (arrow) and the intraretinal layers: retinal pigment epithelium (RPE), inner plexiform layer (IPL), outer plexiform layer (OPL), inner nuclear layer (INL), outer nuclear layer (ONL).

a result of this important incidental finding, monitoring of ME was implemented in subsequent trials involving fingolimod in MS.^{1,2}

The Food and Drug Administration recommends ophthalmologic screening before and while a patient is taking fingolimod.⁵ In this article, we describe the pathophysiology, clinical features, and diagnosis of ME in patients with MS on fingolimod and discuss the possible treatment options in patients who develop ME as a complication of fingolimod.

Pathophysiology of ME

ME results due to accumulation of fluid in the outer plexiform layer and the inner nuclear layer and the swelling of the Müller cells of the retina (figure 1). It is a nonspecific sign, which represents the final pathway of a number of ocular and systemic diseases involving the retinal vasculature.

In physiologic state, the interstitial spaces of the retina are kept dry due to the blood–retinal barrier (BRB). The BRB consists of 2 parts. The outer BRB is formed by the tight junctional complexes between the retinal pigment epithelium (RPE) cells, which separate the choroidal circulation from the neural retina, and the inner BRB is formed by the tight junction of the endothelium of the retinal capillaries in the inner retinal circulation.

The BRB prevents the passage of macromolecules and circulating cells from the vascular compartment to the extracellular space, i.e., from the blood to the neural tissue.⁶ A breakdown of the BRB results in retention of proteins within the retinal tissues, which causes water retention through osmosis. The initial event that causes increased vascular permeability is controversial. While the perivascular supporting cells like pericytes and glial cells may play a role, endothelial cell dysfunction and injury is likely to be the first step towards the breakdown of the BRB early in the disease. Inflammation within the vessel wall, as in uveitis (e.g., pars planitis associated with MS) and diabetes, results in leukocyte infiltration of the retinal tissue, which in turn results in endothelial cell apoptosis causing vascular leakage.⁷ Inflammatory mediators like prostaglandins and vascular endothelial growth factor (VEGF) have been implicated in the breakdown of the BRB.⁸ Other inflammatory mediators that have been associated with ME are angiotensin II, cytokines, chemokines, matrix metalloproteinases, interleukins, P selectin, E selectin, vascular adhesion molecule–1, intercellular adhesion molecule–1, and inflammatory cells (macrophages, neutrophils).^{7,8} Various systemic and ocular drugs are also reported to be associated with ME. Systemic drugs reported to be associated with ME include

In patients who develop fingolimod-associated ME, cessation of the drug results in the resolution of symptoms.

thiazolidinediones (rosiglitazones, pioglitazones), taxanes (docetaxel and paclitaxel), tamoxifen, niacin, and interferons. Ophthalmic drugs associated with ME include prostaglandin analogue (latanoprost, bimatoprost, travoprost), epinephrine, and β -blockers (timolol, betaxolol). Mechanical factors such as in vitreomacular traction may also contribute to ME.⁸

The exact mechanism by which fingolimod results in the breakdown of BRB is unclear. An important mediator in fingolimod-associated ME is sphingosine 1 phosphate (SIP), a platelet-derived bioactive lipid, and its receptors (mainly S1P1 and S1P3). These receptors play an important role in the regulation of endothelial and epithelial barriers^{9–11} and have been shown to increase vascular permeability.¹² Fingolimod is an S1P receptor analogue, which acts via the S1P1 receptor agonism to protect the adherence junction between the cells; it also acts via the S1P3 receptor agonism to reduce the tight junction between the endothelial cells. This reduction in the tight junctions results in the breakdown of the inner BRB, resulting in ME.^{5,13–15} In conditions like diabetes and uveitis, there is preexisting inflammation of the vessel wall. It is likely that the exposure to fingolimod causes the S1P receptor to degrade further, thereby increasing the risk of breakdown of the BRB, which leads to ME.

In a recent cross-sectional analysis, spectral-domain optical coherence tomography (OCT) was performed in patients with MS.⁵ Microcystic edema was noted in 4.7% (15/318) of the patients assessed. None of these patients were on fingolimod and none of these patients had retinal periphlebitis. These patients had reduced visual acuity and significantly worse disability vs those without ME. ME occurred more commonly in patients who had history of previous optic neuritis. The proposed mechanisms of the edema suggested by the authors were (1) focal intraretinal microglial activation and inflammation resulting in retinal neuronal and axonal injury; and (2) breakdown of the BRB, which may occur concurrently with breakdown of the blood–brain barrier.

Limitations of the study include the fact that fundus fluorescein angiogram (FFA) was not performed in these patients and a leak on FFA would be able to identify a breakdown in the BRB. In this cohort, a history of previous uveitis was noted and retinal periphlebitis was excluded, but the patients did not have ophthalmologic examination to rule out coincident anterior uveitis or other ocular morbidity that might contribute to ME. While assessing fingolimod-associated ME, it was determined that a baseline OCT assessment before starting fingolimod is essential. Patients with pre-existing microcystic ME who are treated with fingolimod may be at increased risk of developing ME.

Risk factors associated with the development of ME in patients on fingolimod

Various factors may predispose to risk of ME in patients taking fingolimod.

Dose of fingolimod The risk of ME was dose-dependent and occurred more commonly in patients on 1.25 mg vs those on 0.5 mg.^{1,2} The risk varied from 1% to 1.6% in those on 1.25 mg ME vs 0% to 0.5% in the 0.5 mg dose in these studies. In the pooled data of patients from the core and extension studies of FREEDOMS and TRANSFORMS, the risk of ME was 0.3% and 1.2% in the 0.5 mg and 1.25 mg group.¹⁶ The risk of ME in doses of 2.5–5 mg was much higher in renal transplant patients.^{4,17}

Duration of treatment ME most commonly occurred within 3–4 months of starting the treatment; however, late onset of ME (>12 months) has been reported.¹⁶

Age The risk of ME increases in patients ≥ 41 years (58%).¹⁶ Coexisting disease like diabetes, diabetic retinopathy, retinal vascular disease, past ocular surgery, and uveitis increase the risk of ME.^{16,17}

Figure 2 Fundus fluorescein angiogram of macular edema

(A) Fundus photograph, (B) red-free photograph, and (C, D) fundus fluorescein angiogram of the left eye. Fundus photograph shows yellow reflex area capillary dilation and late fluorescein leakage to the macula (arrowhead). ON = optic nerve; M = macula.

Clinical features of ME

Clinically, patients with ME can present with reduced vision, contrast sensitivity, and altered color vision. Patients may also complain of metamorphopsia or micropsia. Some patients describe symptoms that result from a reduction in the central retinal sensitivity with either a relative or absolute scotoma. ME can be diagnosed on a dilated fundus examination using a slit-lamp and either a contact lens (e.g., Goldmann lens) or a handheld noncontact lens (e.g., +78 D or +60 D lens). Fundus examination shows an elevation of the retina or intraretinal cysts seen as an altered light reflex. These changes may be better visualized using green light. However, clinical examination for the detection of mild ME (foveal thickness 201–300 μm) is relatively insensitive.

Imaging of ME

OCT is a noninvasive method to visualize retinal structure, and allows a precise, reproducible assessment of ME.¹⁸ It is based on the principle of low-coherence interferometry, where a low beam of light is split into 2 beams, one directed to the retina and the other to a reference mirror. The light reflected back from the retina is combined with the light from the reference mirror and is used to construct an axial A scan. Moving the beam of light along the tissue in a line results in a compilation of A scans with which a 2-dimensional cross-sectional image of the retina is reconstructed (figure 1). In ME, there is retinal thickening with intraretinal cavities of reduced reflectivity on OCT. The OCT can also measure the macular thickness and is an important tool used to monitor the clinical course of ME and treatment efficacy.

FFA is also a useful test in diagnosing ME. In the early phase of FFA, capillary dilation can be detected in the perifoveal region. In the late phase of the FFA, a petalloid pattern of vascular leak is seen (figure 2). The amount of fluorescein leak depends on the retinal vascular dysfunction.¹⁹ In longstanding ME, the intraretinal cysts may become impermeable to the fluorescein dye and as a result leakage is not seen.

Table Medical treatment options for macular edema by etiology

Treatment option	Mechanism of action	Etiology	
Carbonic anhydrase inhibitors ²⁰	CAI improve the ability of the RPE to pump fluid out of the retina by inducing acidification in the subretinal space	Postsurgical ME	
		ME in retinitis pigmentosa	
		Uveitic ME	
Nonsteroidal anti-inflammatory drugs	NSAIDs inhibit cyclo-oxygenase COX and thus reduce leucocyte adhesion and breakdown of the BRB	Postsurgical ME	
		Uveitic ME	
		Diabetic ME	
Corticosteroids	Inhibit the release of arachidonic acid by blocking COX 2 enzyme and hence reduce prostaglandin synthesis	Diabetic ME and other ME of vascular origin	
		Reduce vascular permeability	Uveitic ME
		Stabilize endothelial tight junctions	ME postcataract surgery
		Downregulate the production of VEGF	
Anti-VEGF agents, e.g., ranibizumab, bevacizumab	Reduce VEGF mediator to reduce vascular growth	All forms of ME	
Steroid-sparing immunosuppressants like interferon-α, cyclosporine A, anti-TNF, octreotide	Anti-inflammatory effect	Uveitic ME	
		Interferon-α is beneficial in MS-related uveitis	
Abbreviations: BRB = blood-retinal barrier; CAI = carbonic anhydrase inhibitors; ME = macular edema; NSAID = nonsteroidal anti-inflammatory drugs; RPE = retinal pigment epithelium; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor.			

Treatment of ME

There are several treatment options for ME and the choice is dependent on the mechanism of ME. The treatment options for ME can be classified as laser treatment, medical treatment, or surgery. Laser photocoagulation is indicated in ME secondary to diabetes. The mechanism of action includes thermal destruction of retinal photoreceptors, which results in cell death, enabling oxygen to diffuse through the laser scar to the inner retina and hence restore hypoxia. Laser also helps in proliferation of the RPE and endothelial cells, leading to repair and restoration of the BRB. Medications used to treat ME include carbonic anhydrase inhibitors, nonsteroidal anti-inflammatory drugs, corticosteroids, anti-VEGF (e.g., ranibizumab and bevacizumab), and systemic steroid-sparing immunosuppressants (interferon- α , cyclosporine A, anti-tumor necrosis factor, octreotide). The mechanisms by which each of these treatment options help to reduce ME and the specific ocular conditions in which they are used are detailed in the table. Surgical treatment of ME includes vitrectomy with or without peeling of the internal limiting membrane, which is indicated in ME from tractional or vascular cause. Releasing tractional forces at the vitreomacular interface improves the oxygen tension in the inner retina and removes the excess VEGF and interleukin-6. It should be noted that it is essential to treat the underlying

Figure 3 Serial optical coherence topography of patient 2 shows macular edema development and resolution

(A) Normal optical coherence topography (OCT) of the right eye at baseline. (B) OCT of the right eye 4 days post-cataract surgery shows macular edema. (C) OCT of the right eye shows persistent macular edema and failure of response to topical nonsteroidal anti-inflammatory drugs and steroids. (D) OCT of the right eye shows resolution of macular edema post intravitreal triamcinolone injection. ILM = internal limiting membrane; RPE = retinal pigment epithelium.

disease responsible for causing ME, e.g., diabetes, hypertension, and inflammatory conditions. In many cases, ME may respond poorly to treatment or not at all.

In patients who develop fingolimod-associated ME, cessation of the drug results in resolution of symptoms. We present 2 cases and highlight successful treatment of ME in patients taking fingolimod. Case 2 highlights that it may be possible to treat ME while continuing to use fingolimod.

Case 1

A 41-year-old otherwise healthy woman diagnosed with relapsing-remitting MS had bilateral recurrent intermediate uveitis and had been under the care of an ophthalmologist for 6 years. She had had previous episodes of ME in the left eye, which had been treated with sub-Tenon injection of triamcinolone. The right eye had not experienced any previous inflammation. The patient previously had been on glatiramer acetate for 3 years, but was concerned regarding ongoing subcutaneous injection and hence changed to fingolimod 0.5 mg/day. At the scheduled 3-month eye review after starting fingolimod, she developed ME and fingolimod was ceased. The patient was clinically asymptomatic. After cessation of fingolimod, ME resolved within a month.

Case 2

A 66-year-old woman had stable controlled relapsing-remitting MS and had been on oral fingolimod 0.5 mg/day for 9 months duration. She did not have any fingolimod-associated ME at baseline or at the 3-month and 6-month reviews (figure 3A). She developed a progressive cataract in the right eye and underwent a cataract extraction with intraocular lens implantation. She had an uncomplicated surgery and achieved an unaided visual acuity of 6/6 on day 1. She noted an acute decrease in vision on day 4 postsurgery and the vision was reduced to 6/12; OCT confirmed ME (figure 3B). She was treated with topical nonsteroidal anti-inflammatory and steroid therapy for 1 month, which failed to resolve the ME (figure 3C). She was then treated with intravitreal triamcinolone 2 mg/0.05 mL to the right eye and

Patients with history of diabetes, previous uveitis, or on concurrent medications associated with ME who have been started on fingolimod need to be monitored more closely.

within 1 week the ME had settled (figure 3D) and the vision improved to 6/7.5. She subsequently underwent left cataract surgery with intraocular lens implantation, which was treated with intravitreal triamcinolone prophylactically intraoperatively. The left eye did not develop postoperative ME. The patient remained on oral fingolimod without any ophthalmic or systemic complications.

It is difficult to ascertain whether the cause of ME in this patient was secondary to cataract surgery or whether it was an accentuation of fingolimod-associated ME in the event of intraocular inflammation secondary to cataract surgery. This case also demonstrates that it is possible to treat ME if fingolimod is deemed the most appropriate treatment for MS by the neurologist.

DISCUSSION

ME is a known complication of fingolimod use. All patients on fingolimod need a baseline ophthalmologic evaluation including an OCT followed by repeat OCT at 3 months. The long-term ophthalmic evaluation of patients on fingolimod is not known, but follow-up eye examination at regular intervals 6 months after and then annually is recommended.^{15,16} Patients with history of diabetes, previous uveitis, or on concurrent medications associated with ME who have been started on fingolimod need to be monitored more closely. Conversely, patients on fingolimod undergoing ophthalmologic procedures such as cataract surgery may be at increased risk of ME and may benefit from increased surveillance or prophylactic treatment for ME.

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