Conflict of Interest Disclosures: The data in the study and takes responsibility for the in-
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Fingolimod is the first orally active drug approved for the management of relapsing-remitting multiple sclerosis (MS). Its immunosuppressive action is related to downregulation of sphingosine 1–phosphate receptor 1 on lymphocytes, which inhibits their egress from lymphoid tissues. Macular edema (ME) is an infrequent adverse effect of fingolimod, usually occurring within 3 months of initiation of treatment and resolving on cessation of fingolimod. We report a case of ME in a patient with MS receiving fingolimod and its successful management by topical anti-inflammatory drugs.

Management of Fingolimod-Associated Macular Edema

Fingolimod is the first orally active drug approved for the management of relapsing-remitting multiple sclerosis (MS). Its immunosuppressive action is related to downregulation of sphingosine 1–phosphate receptor 1 on lymphocytes, which inhibits their egress from lymphoid tissues. Macular edema (ME) is an infrequent adverse effect of fingolimod, usually occurring within 3 months of initiation of treatment and resolving on cessation of fingolimod. We report a case of ME in a patient with MS receiving fingolimod and its successful management by topical anti-inflammatory drugs.

Report of a Case. A 67-year-old woman had decreased vision in her right eye. She began treatment with fingolimod, 0.5 mg/d, 6 months earlier for chronic relapsing-remitting MS. She denied history of other systemic illness or previous ocular disease and was taking no concurrent medications.

On examination, her best-corrected visual acuity (BCVA) was 6/7.5 OD and 6/6 OS. Intraocular pressure was 14 mm Hg OU. Anterior segment examination findings were normal. Funduscopy and optical coherence tomography showed macular cystic changes in her right eye (Figure 1, week 0). A provisional diagnosis of fingolimod-associated ME (FAME) was made.

Because the patient wished to continue treatment with fingolimod, she began topical treatment with ketorolac tromethamine, 0.5%, and dexamethasone suspension, 0.1%, both 4 times daily in her right eye. After 1 month, BCVA remained at 6/7.5 OD but worsened to 6/9 OS, corresponding to optical coherence tomographic findings of resolving ME in her right eye with progression in her left untreated eye (Figure 1, week 4). To exclude other causes of ME, fluorescein angiography was performed, demon-

Figure 2. Mean choroidal thickness over all locations measured in 500-µm intervals, 2500 µm temporal (T) and nasal (N) to the fovea before treatment and 3, 6, and 12 months after the first treatment. Note that the N measurements are thinnest where the T measurements are thickest. The numbers next to the T and N locations indicate millimeters.

Essary to determine whether there is a dose response. Another limitation to this prospective investigation was that there was no standard protocol for the initiation of therapy or the timing and number of injections. The use of anti-VEGF for the treatment of neovascular AMD has been shown to improve visual acuity and is currently being used extensively for this purpose. In our study, there was significant thinning of the choroid in patients with neovascular AMD treated with anti-VEGF. This may have implications for long-term choroidal function.

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strating late-phase leakage of dye in the left central macula (Figure 2). At this stage, topical ketorolac and dexamethasone were prescribed for both eyes twice daily with temporary improvement of BCVA to 6/7.5 OU after 3 weeks. Increased instillation frequency of topical anti-inflammatory eyedrops (initially 4 times daily, then every 2 hours) led to resolution of ME (Figure 1, week 23) with improvement of BCVA to 6/6 OU. Unfortunately, attempts at weaning topical anti-inflammatory drugs failed while the patient continued to use fingolimod. After consultation with her neurologist, a decision was made to cease fingolimod use, resulting in resolution of her ME 5 weeks later (Figure 1, week 35).

Comment. Fingolimod-associated ME is observed in up to 0.5% of patients with MS receiving fingolimod. The proposed pathophysiological mechanism behind FAME is loss of sphingosine 1–phosphate receptor 1 signaling in endothelial cells, subsequent downregulation of adhesion complexes, and enhanced vascular permeability.

In previous reports, FAME resolved after cessation of fingolimod use. Because our patient’s neurological symptoms were well controlled and she wished to continue treatment with fingolimod, we elected to manage her FAME with topical medications. Our patient was partially responsive to topical nonsteroidal anti-inflammatory drugs and glucocorticoids since attempts at dose reduction led to exacerbation of FAME. The mechanism behind this responsiveness is unclear, but we speculate that an inflammatory component may have contributed in this case. Topical nonsteroidal anti-inflammatory drugs have been successfully used to manage cystoid ME. More recently, Afshar et al successfully managed FAME with topical nonsteroidal anti-inflammatory drugs. Further clinical trials may assist in optimizing management of FAME without cessation of fingolimod use.

Although not present in our case, optic neuritis is a diagnostic consideration in patients with MS who have visual disturbance. This may be differentiated from ME by the presence of a relative afferent pupillary defect, dyschromatopsia, and ocular pain on eye movements. Another possibility is that the ME may be unrelated to fingolimod use. Microcystic ME, predominantly affecting the inner nuclear layer, is reported in 4.7% of patients with MS and is more common in eyes with a history of optic neuritis. We cannot exclude preexisting microcystic ME because our patient was receiving fingolimod prior to her first clinic attendance and she did not have pretreatment optical coherence tomographic investigations, even though ophthalmological evaluation is recommended by the manufacturer prior to commencement of fingolimod treatment. Additionally, the frequency
in measuring intraocular pressure. We performed a similar experiment in 1 enucleated human eye but increased the IOP stepwise by 5 mm Hg using a pump for much longer periods (30 minutes). We reported excellent results.

In addition, the authors studied the reproducibility of the measurements by repeating their examinations 1 week apart. The Pearson correlation showed an overall correlation of $r=0.59$, determined as fair to good. We studied the reproducibility in only 5 subjects (young, healthy eyes; not for 24 hours, but for 2 hours) and found the same results.3

Besides safety, tolerability, and reproducibility, one very important quality is yet missing: the validity of the results gained by the CLS in young subjects as well as in elderly patients with and without glaucoma. Leonardi et al, the “inventors” of this CLS, (only) performed measurements in juvenile porcine eyes by inducing very short-acting spikes of intraocular pressure (IOP) (injection and release within 5 seconds) and reported excellent results.2

We performed a similar experiment in 1 enucleated human eye but increased the IOP stepwise by 5 mm Hg using a pump for much longer periods (30 minutes). We could not obtain the expected stepwise profile by means of the CLS.6

No further experimental studies have been published on the validity of the results of the CLS so far. We therefore built a setup of 5 young subjects with healthy eyes in whom we measured the IOP in one eye with ap-