

1 Title

2 Fingolimod: therapeutic mechanisms and ocular adverse effects.

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Abstract

Fingolimod is an oral immunomodulating drug used in the management of relapsing-remitting multiple sclerosis (RRMS). We aim to review the published literature on ocular manifestations of fingolimod therapy and their possible underlying mechanisms.

The therapeutic effects of fingolimod are mediated via sphingosine receptors, which are found ubiquitously in various organs including lymphoid cells, central nervous system, cardiac myocytes and smooth muscle cells. Fingolimod associated macular oedema (FAME) is the most common ocular side effect but retinal haemorrhages and retinal vein occlusion can occur. The visual consequences appear to be mild and, in cases of FAME, resolution is often attained with discontinuation of therapy. However, in cases of retinal vein occlusion, discontinuation of fingolimod alone may not be sufficient and intra-vitreous therapy may be required. We also propose a pragmatic service pathway for monitoring patients on fingolimod therapy, which includes stratifying them by risk and visual acuity.

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64 Introduction

65

66 Fingolimod is the first orally administered agent to be licensed by the Food and Drug Administration  
67 (FDA), and also approved by the National Institute for Health and Care Excellence (NICE), for use in  
68 patients with highly active relapsing remitting multiple sclerosis (RRMS) after recent clinical trials  
69 demonstrated its efficacy in reducing the frequency of relapses and disability progression on long  
70 term follow-up of patients with multiple sclerosis when compared with placebo (1,2). These  
71 therapeutic effects in multiple sclerosis therapy are thought to be due to the action of fingolimod on  
72 preventing the egression of lymphocytes from lymphoid tissue into the circulation thereby sparing the  
73 central nervous system from attack by myelin-reactive lymphocytes (3, 4). In vivo, fingolimod exerts  
74 this immunomodulating effect through a novel mechanism by binding sphingosine-1-phosphate (S1P)  
75 receptors on lymphocytes. Although S1P receptors are found with the highest density in leucocytes  
76 and lymphoid tissue, they are also widely expressed in many cell types in other organs systems  
77 including the heart, brain, liver, stomach and probably also in the retina. This ubiquitous nature of the  
78 target receptor for fingolimod accounts for the wide range of adverse effects including hypertension,  
79 heart block, bradycardia and macular oedema.

80

81 In the original pivotal FREEDOMS study all seven patients with macular oedema had been  
82 randomized to, and received, fingolimod (1). Since its launch in 2010, numerous reports of a variety  
83 of adverse events associated with fingolimod therapy have been published. This has led to the  
84 recommendation that patients should have cardiac and ophthalmic evaluation prior to commencing  
85 fingolimod and at every 3-4 months during therapy (5).

86

87 Given the recent anecdotal reports of Fingolimod Associated Macular oEdema (FAME) and other  
88 retinal complications, coupled with the paucity of data on the putative pathogenic mechanisms  
89 responsible for the effect of fingolimod in the eye, we have reviewed the relevant published literature  
90 with the aim of summarising the current concepts on the mode of action of fingolimod, collating the  
91 available body of clinical experience on diagnosis, treatment and outcomes of ophthalmic

92 complications presumed to be associated with fingolimod therapy. This article should provide  
93 ophthalmologists with an initial current reference base for the management of patients on fingolimod  
94 therapy in clinical practice and should also provide some insight into the possible pathogenic  
95 mechanisms responsible, which could serve to focus our thoughts on the development of more  
96 specifically targeted therapy for these novel retinal problems. With this information, we then go on to  
97 suggest a pragmatic care pathway for the ophthalmic monitoring of patients on fingolimod therapy.

98

#### 99 *Fingolimod's mode of action and its cardiovascular side effects*

100 In vivo, fingolimod is phosphorylated to fingolimod-phosphate and becomes structurally similar to a  
101 sphingolipid called sphingosine-1-phosphate (S1P), an extracellular mediator, preventing it from  
102 binding normally to the five types of S1P receptors (S1PR<sub>1-5</sub>). At the cellular level, it leads to  
103 internalisation and eventual degradation of these cell surface receptors and abnormal cellular function  
104 and communication (4,6). S1P receptors are found on lymphocytes and other organs and whilst in  
105 MS it has the desired therapeutic effect of reducing the up-regulation of lymphocytes and their  
106 migration from lymphoid tissue into the circulation and the central nervous system, the destruction of  
107 S1P receptors in other organs is responsible for its cardiovascular and probably also retinal side  
108 effects.

109 The location of S1P receptors on cardiac myocytes and smooth muscle cells is probably responsible  
110 for the adverse cardiovascular effects of fingolimod, which include bradycardia, atrioventricular nodal  
111 block and systemic hypertension. Bradycardia occurs in 0.6% of patients treated with fingolimod. It is  
112 typically observed 4-5 hours after the first dose, with a mean maximum heart rate reduction of 8bpm.  
113 S1PR<sub>1</sub> activation with fingolimod activates G-protein coupled inwardly-rectifying potassium channels  
114 (GIRKs) on myocytes. This leads to an efflux of potassium, thereby hyperpolarising the cell  
115 membrane and temporarily reducing excitability. This effect is transient but leads to internalisation of  
116 S1PR<sub>1</sub>. This same mechanism is responsible for Mobitz type 1 second-degree AV nodal block  
117 observed in 0.2% of those patients treated with fingolimod (6,7). An increase in blood pressure is  
118 observed in patients treated with fingolimod. This increase is, on average, +2mmHg systolic and  
119 +1mmHg diastolic. This effect is believed to be via the presence of S1PR<sub>1</sub>, S1PR<sub>2</sub> and S1PR<sub>3</sub>  
120 receptors in arterial smooth muscle cells. Activation of S1PR<sub>1</sub> in arterial smooth muscle cells causes  
121 increased nitric oxide production (therefore vasodilation) as well as an intracellular increase in

122 calcium. This rise in calcium causes an increase in smooth muscle contraction; therefore these  
123 opposing effects initially offset one another. However, once S1PR<sub>1</sub> internalises, binding shifts to  
124 S1PR<sub>2</sub> and S1PR<sub>3</sub> that are also found on arterial smooth muscle cells, thus smooth muscle  
125 contraction is the over-riding force. This effect on blood pressure is prolonged longer than first-dose  
126 related bradycardia and AV nodal block, with a peak at 6 months after which it stabilises (6).

127

### 128 *Fingolimod and the eye*

129 In the retina the effects of fingolimod on the actions of the sphingolipid, sphingosine-1-phosphate and  
130 its S1P receptors are less well understood. Sphingolipids are the third most abundant lipid in the  
131 retina (8). It is well recognised that sphingolipid metabolism plays important roles in retinal cell death  
132 and survival. This balance is referred to as the “sphingolipid rheostat.” Ceramide (Cer) is the key  
133 metabolite for sphingolipid production. There are two major pathways for Cer production - *de novo*  
134 synthesis for higher-order sphingolipids and the recycling/degradation of higher order sphingolipids.  
135 Aberrant sphingolipid metabolism is known to cause various metabolic storage diseases such as Tay-  
136 Sachs, Fabry's disease and Niemann-Pick disease (9). Although fingolimod can potentially affect  
137 sphingolipid metabolism globally in the whole retina by inhibiting Cer enzymes, thereby reducing the  
138 formation of *de novo* Cer (9) it seems that this is unlikely to be pathogenic mechanism behind the  
139 causation of macular oedema that have been reported in the recent literature as all the cases have  
140 reported very localised distribution of oedema to the macular area only and not globally across the  
141 whole retina (10-21).

142 There are a number of ocular conditions that have been linked to fingolimod. The most common is  
143 fingolimod associated macular oedema (FAME), the only ocular condition to have been mentioned in  
144 the original FREEDOMS and TRANSFORMS trials as well as in the drug marketing literature.  
145 However since 2010, when fingolimod has been used outside of these clinical trials, several other  
146 ocular side effects have been reported including retinal haemorrhages and retinal vein occlusion (22-  
147 24).

148

### 149 *Pathophysiology of FAME*

150 The proposed pathophysiological mechanism of FAME is based upon the interaction between  
151 fingolimod and S1PR<sub>1</sub> present on endothelial cells in retinal vessels. S1PR<sub>1</sub> signalling is responsible

152 for maintaining cell-to-cell and cell-to-matrix adhesion complexes. The use of fingolimod is thought to  
153 down regulate this receptor, thus leading to down regulation of adhesion complexes and subsequent  
154 increased retinal vascular permeability resulting in oedema (25, 26).

155

#### 156 *Incidence of FAME*

157 Macula oedema has been a well-documented side effect of fingolimod since it was originally  
158 evaluated as an anti-rejection agent for renal transplantation (27, 28). FAME was therefore monitored  
159 for and reported in the initial clinical trials investigating the efficacy of fingolimod for RRMS. The  
160 FREEDOMS study was a phase III multicentre, 24-month, double blind randomised study comparing  
161 0.5mg (n=425) and 1.25mg (n=429) fingolimod daily treatment with placebo (n=418) in patients with  
162 RRMS (1). None of the 425 patients receiving 0.5mg fingolimod developed macular oedema. Seven  
163 out of 429 (1.6%) patients receiving 1.25mg fingolimod developed macular oedema and three of  
164 these were reported as serious. In 5 out of those 7 patients, macular oedema occurred within 3  
165 months of starting treatment. In 6 out of those 7 patients the macular oedema had resolved within 6  
166 months of discontinuing therapy. The past ophthalmic history was not reported in any of these cases  
167 in the FREEDOMS study.

168 The TRANSFORMS study was a phase III multicentre, 12 month, double blind randomised study  
169 comparing fingolimod 0.5mg (n=429) and 1.25mg (n=420) to IFN $\beta$ -1a intramuscularly (n=431) in  
170 patients with RRMS (29). Two out of 429 patients receiving 0.5mg treatment (0.5%) and 4 out of 420  
171 (1%) patients receiving 1.25mg treatment developed macular oedema. Three of those 6 patients  
172 were visually asymptomatic and macular oedema was diagnosed only on macular examination. Five  
173 out of those 6 patients developed macular oedema within 4 months of treatment initiation. In 4 out of  
174 those 6 patients, macular oedema had resolved within 3 months of treatment discontinuation. In the  
175 remaining 2 patients one was unchanged 1 month after treatment discontinuation and one had  
176 reduction of macula oedema 8 months after treatment discontinuation. It is not known whether these  
177 patients had ocular co-morbidities prior to entering the FREEDOMS and TRANSFORMS studies. The  
178 FREEDOMS II study (30) was a separate phase III clinical trial to the original FREEDOMS study and  
179 the TRANSFORMS study. It was conducted as the FDA had stipulated the need for additional  
180 monitoring, such as Holter monitoring, which was not performed in the original FREEDOMS and  
181 TRANSFORMS studies. FREEDOMS II was a phase III multicentre 24-month double-blind

182 randomised control trial comparing fingolimod 0.5mg vs. fingolimod 1.25mg vs. placebo in the  
183 treatment for RRMS. Macular oedema was reported in 4 out of 370 (1%) in the 1.25mg group, 3 out  
184 of 358 (0.8%) in 0.5mg group and, interestingly, 2 out of 355 (0.6%) in the placebo group. All those  
185 cases of FAME in this study resolved with the discontinuation of therapy except one in the 1.25mg  
186 group and one in the placebo group. To our knowledge, none of the patients with resolution of  
187 macular oedema after fingolimod discontinuation were re-challenged by recommencing fingolimod in  
188 the prospective studies.

189 Both the FREEDOMS and TRANSFORMS studies had parallel extension studies to assess the long-  
190 term effects of fingolimod therapy. These studies found no further increased risk of FAME over a  
191 period of up to 4.5 years (2, 31). In a retrospective study by Ontaneda et al a similar incidence  
192 (3/317, 0.9%) of macular oedema at 3 months after therapy initiation was reported (32).

193 Regarding the onset of FAME Zarbin et al, using pooled analysis of data from the phase II core and  
194 extension study with the phase III core and extension studies of FREEDOMS and TRANSFORMS,  
195 reported that FAME developed within 3-4 months of commencing fingolimod in 68% of affected cases  
196 (33).

197 From the analysis of the 15 patients (24 eyes) we found from published case reports (Table 1), the  
198 time of onset of FAME after commencement of fingolimod was within 6 months for all but two cases.  
199 In these two cases, both had been on fingolimod for an extended period (1 year in one case, 2 years  
200 in the other) and macular oedema only occurred after cataract surgery, suggesting that these may not  
201 be directly related to FAME per se. The majority of cases (12 out of 15) developed FAME within 4  
202 months of initiation of therapy and 7 out of 15 occurred within 1 month. This was in keeping with the  
203 experience from the FREEDOMS and TRANSFORMS clinical trials. In summary, FAME can occur  
204 within the first six months of commencing fingolimod therapy. The incidence appears to be dose-  
205 dependent, occurring in 0.4% of patients treated with 0.5mg, and in 1% of those treated with 1.25mg  
206 (10-21).

207

### 208 *Symptoms of FAME*

209 Although the cases identified in the FREEDOMS and TRANSFORMS trials were not reported in  
210 sufficient detail to review their symptomatology, the case reports were a very useful source of this  
211 information. Of the 15 patients (24 eyes) with FAME reported as case reports in the literature (Table

212 1), the majority were symptomatic; the most common presenting complaint being painless blurred  
213 vision. One patient had metamorphopsia and another patient was asymptomatic but actually had  
214 reduced vision of 6/18. Presenting vision was mildly reduced (20/30 or better) in 8 of 24 eyes and  
215 moderately reduced (20/30 – 20/80) in the remainder (16 of 24 eyes). The worst visual acuity  
216 reported in an eye with FAME was 6/24 or, approximately, 20/80.

217

#### 218 *Diagnosis of FAME*

219 In all of the 15 cases of retinal problems thought to be attributed to fingolimod therapy, all of them had  
220 abnormal signs on OCT scanning or fluorescein angiography of either macular thickening, foveal or  
221 perifoveal cysts, subretinal fluid, venous tortuosity or dye leakage. These findings are easily visible  
222 on biomicroscopy and OCT scanning. Fluorescein angiography can be used to rule out other  
223 causes of macular oedema such as posterior uveitis or retinal vein occlusion or diabetic retinopathy.  
224 In making the diagnosis of FAME, it is important to be aware that neuronal loss and retinal thinning  
225 can result in the presence of degenerative microcysts in about 4-5% of patients with MS, typically  
226 seen in the inner nuclear layer on OCT scanning. Although these cysts have been termed microcystic  
227 macular oedema secondary to multiple sclerosis, they are probably not due to transudation or  
228 exudation as they are not known to be associated with reduced visual acuity or dye leakage on  
229 fluorescein angiography and are more often associated with reduced macular volume and overall  
230 retinal thinning particularly in patients with long standing or severe MS (34, 35).

231

#### 232 *Management of FAME*

233 Although Zarbin et al reported that 84% of patients had macular oedema resolution after fingolimod  
234 cessation in the All Studies group, there are numerous reports of cases in which discontinuation did  
235 not lead to resolution and needed topical prednisolone and ketorolac (18). There are also reports on  
236 cases in which fingolimod was not discontinued and this led to persistence of MO (11), and variable  
237 resolution with topical nepafenac and difluprednate (17), topical ketorolac and dexamethasone (13),  
238 oral acetazolamide (19), sub-tenon triamcinolone (20) and intravitreal triamcinolone (21). From these  
239 reports, it appears that the current steps for managing FAME is to firstly to confirm the diagnosis with  
240 OCT scan and fluorescein angiography to rule out other causes of MO and then discontinue  
241 fingolimod if possible. Persistent MO on early follow-up can then be treated with topical steroidal or



242 non-steroidal agents initially before introducing subtenon or intravitreal triamcinolone. There is no  
243 evidence base available at present for the use of intravitreal ozurdex, intravitreal anti-VEGF or oral  
244 corticosteroids in the management of FAME.

245

#### 246 *FAME and its association with uveitis*

247 Zarbin et al suggested a higher risk of developing FAME in patients with a history of uveitis than those  
248 without (33). Using pooled analysis of data from the phase II core and extension study with the phase  
249 III core and extension studies of FREEDOMS and TRANSFORMS (N=2615), a total of 19 cases had  
250 reported macular oedema. The prevalence of patients with a history of uveitis in this dataset was 1%  
251 (26 out of 2615), but interestingly amongst those who developed macular oedema the prevalence of a  
252 history of uveitis was 26% (5 out of 19). Thus the incidence of macular oedema amongst those with a  
253 history of uveitis was 19% (5/26) compared with the overall incidence of macular oedema in the  
254 dataset being 0.7% (19 out of 2615). All 5 patients with uveitis who developed macular oedema were  
255 taking 1.25mg fingolimod. It is difficult to comment on the link between FAME and uveitis from the  
256 case reports detailed in Table 1, as there is no control for comparison but it can be noted that out of  
257 the 14 case reports containing sufficient detail on past ocular history, there were only two patients  
258 with a history of uveitis prior to commencing fingolimod. The findings from the analysis of these  
259 anecdotal case reports therefore support the suggestion by Zarbin et al that although patients without  
260 any history of uveitis can develop FAME, those with a past history of uveitis probably have an  
261 increased risk of developing FAME.

262

#### 263 *FAME and its association with diabetes*

264 Patients with diabetes mellitus were excluded from the FREEDOMS and TRANSFORMS clinical  
265 trials. The clinical trials assessing the use of fingolimod as an anti-rejection agent in renal transplant  
266 patients was reported by Salvadori et al and Tedesco-Silva et al. Both these clinical trials evaluated  
267 higher dose fingolimod (5mg and 2.5mg) in association with cyclosporine and both reported higher  
268 rates of macular oedema (Salvadori et al: 2.2% at 5mg dose, 1.3% at 2.5mg dose) (27), (Tedesco-  
269 Silva et al: 3.4% at 5mg dose and 1.7% at 2.5mg) (28). Tedesco-Silva and Salvadori did not exclude  
270 patients with diabetes in the sample population. However, as doses used were up to 10 times higher  
271 than the licensed dose today, it is difficult to state whether this increase in rate of FAME is due to the

272 higher dosage or the fact that diabetic patients were included in the sample. In addition, as diabetic  
273 patients were not excluded from the study, it is difficult to conclude whether the macular oedema was  
274 caused by fingolimod or related to diabetic maculopathy. Furthermore, in the case reports we  
275 reviewed, only 2 out of 14 patients had diabetes and one with no diabetic retinopathy, there is  
276 insufficient evidence to suggest that patients with diabetes or diabetic retinopathy without  
277 maculopathy are at an increased risk of developing FAME with fingolimod.  
278 It is reasonable; however, to suspect that diabetic patients are more likely to be prone to macular  
279 oedema than non-diabetic patients, due to an already compromised blood-retinal barrier, thus  
280 fingolimod must be used with caution in this cohort of patients

281

### 282 *Fingolimod and Retinal Haemorrhages*

283 To date, there have been two cases of retinal haemorrhage in patients treated with fingolimod  
284 therapy. Bhatti et al report a 54-year-old female, with no history of diabetes mellitus or hypertension,  
285 who had been treated with 0.5mg of fingolimod for 11 months for RRMS. She presented with a grey  
286 opaque spot in her visual field and LVA of 20/80. A unilateral, dense retinal haemorrhage involving  
287 the fovea with an adjacent hard exudate and macular thickening were confirmed on OCT in her left  
288 eye. FFA of the affected eye revealed fluorescein blockage due to blood and lipid exudates and  
289 hyperfluorescence adjacent due to areas of blockage, but without overt angiographic signs of retinal  
290 vein occlusion. Fingolimod was promptly discontinued and one month later the macular haemorrhage  
291 had completely resolved. By three months, visual acuity had recovered to baseline of 20/30 and OCT  
292 was normal (22). Ueda and Saida reported a case of a 31-year-old male with RRMS and pre-existing  
293 poor visual acuity (OD 20/600, OS 20/400), who developed both macular oedema and retinal  
294 haemorrhages in all four quadrants unilaterally in his left eye one month after commencing fingolimod  
295 therapy. Treatment was discontinued but due to persisting FAME 13 weeks after cessation of therapy  
296 topical betamethasone 0.1% was commenced. The macular oedema resolved 4 weeks after this  
297 addition of topical steroid (17 weeks after cessation of fingolimod), and the haemorrhages resolved 11  
298 weeks after the addition of topical steroid (24 weeks after cessation of fingolimod) (23). The  
299 mechanism by which fingolimod may cause retinal haemorrhages has not yet been fully elucidated,  
300 though it may also be linked with the S1PR1 mechanism of FAME, rendering retinal blood vessels  
301 increasingly permeable (25, 26).

302

303 *Fingolimod and its association with retinal vein occlusion*

304 As retinal vein occlusion (RVO) is a common condition, it is uncertain whether a link exists between  
305 RVO and fingolimod therapy. To date, only one previous report of branch retinal vein occlusion has  
306 been published in the literature. Gallego-Pinazo et al. described a case of a 47-year-old female  
307 patient with a 9-year history of MS. She had been treated with fingolimod for 6 years prior to  
308 developing unilateral sudden visual reduction in her left eye to 20/40 due to a superotemporal BRVO  
309 associated with macular oedema and central foveal thickness of 396µm. FFA typically revealed an  
310 area of delayed venous filling and blockage of fluorescence by the intraretinal haemorrhages.  
311 Fingolimod was discontinued and the patient was treated with one intravitreal ranibizumab injection.  
312 The patient had neither cardiovascular risk factors, nor any coagulation abnormality suggestive of an  
313 alternative cause for RVO. Three weeks later, visual acuity had improved to 20/20 in the patient's left  
314 eye and there was almost complete resolution of retinal oedema (24). It is uncertain whether  
315 fingolimod has a thrombogenic effect in veins but Nealon et al describe a case of a patient who  
316 developed a thrombus in a developmental venous angioma two months after commencing fingolimod  
317 therapy (36). Similar to the patient described by Gallego-Pinazo, this patient also did not have any  
318 recognised cardiovascular risk factors or coagulation abnormality. Thus, the authors concluded that  
319 fingolimod could be thrombogenic. Schwarz et al reported a patient who developed critical arterial  
320 vasospasm of the left arm within 7 days of commencing fingolimod therapy. Considering the half-life  
321 of fingolimod is 9 days and the maximum vasospasm occurred at 13 days post-discontinuation, they  
322 argued that this chronological sequence is suggestive of a causal relationship between fingolimod and  
323 vasospasm (37). If vasospasm were to occur at the point of an AV crossing, a retinal vein occlusion  
324 would ensue. Lastly, as fingolimod causes a rise in blood pressure, one could argue that this could  
325 have facilitated retinal vein occlusion. However, due to the transient and also rather modest (+2mmHg  
326 systolic) rise in blood pressure, this mechanism seems unlikely (6, 7).

327

328 *Ophthalmic monitoring in patients on fingolimod therapy*

329 The time of onset of FAME after commencement of fingolimod was within 6 months for all but two  
330 cases. Both of these cases had been on fingolimod for an extended period (1 year in one case, 2  
331 years in the other) and CMO developed in both these cases only after cataract surgery, a known

332 trigger for developing CMO. The majority of cases (12/15) developed FAME within 4 months of  
333 initiation of therapy, keeping in line with the original FREEDOMS and TRANSFORMS clinical trials.  
334 Therefore, screening patients on fingolimod after 3-4 months as per NICE guidelines seems  
335 appropriate. Moosavi et al performed a retrospective study to assess the adherence to these NICE  
336 guidelines and to measure the impact of delivery of these guidelines on clinical service. In a 9-month  
337 period, 38 referrals for fingolimod screening were made, contributing to a significant 9% of new  
338 referrals. Only 1 patient had FAME, who had in fact developed blurred vision soon after fingolimod  
339 initiation and was seen in the eye clinic at 5 weeks post commencement where OCT confirmed  
340 FAME; shorter than the 3-4 month recommendation. Moosavi et al concluded that reviewing  
341 fingolimod patients at 3-4 months is a huge burden to eye services for a rare side effect. They  
342 recommend that near and distance acuity is measured by the physician prescribing fingolimod, and  
343 referrals to an ophthalmologist should only be made if there is a reduction in acuity or a change in  
344 visual symptoms (38). As with Moosavi's study, we also found from most of the case reports  
345 published that the majority of patients had symptoms of visual blurring. This is in contrast to the  
346 original FREEDOMS and TRANSFORMS trials that reported fingolimod ocular effects to be  
347 asymptomatic. This perception from the FREEDOMS and TRANSFORMS trials that fingolimod  
348 effects on the eye is often asymptomatic may be the reason for the stipulation by NICE for routine  
349 ophthalmic screening at 3-4 months in all patients commencing fingolimod therapy. Given the low  
350 incidence of ocular effects and the higher likelihood that such effects are associated with visual  
351 symptoms, we would like to propose a pragmatic pathway for implementing the NICE guidelines on  
352 screening. Figure 1 shows the proposed pathway based on previous ocular history and a simple  
353 visual acuity measurement prior to discontinuation of fingolimod or referral to hospital ophthalmology  
354 departments. If there is a past history of uveitis or diabetic retinopathy, patients could be screened  
355 before commencement of fingolimod to rule out active maculopathy, as the addition of fingolimod may  
356 exacerbate pre existing disease. In those patients with a history of ocular comorbidities but no active  
357 disease, review in eye clinic within the most likely time window for the development of FAME (3-4  
358 months) is suggested. However in those with no significant ophthalmic history, we propose that a  
359 baseline visual acuity measurement are performed by the physician prescribing fingolimod followed  
360 by a further visual acuity test and OCT 3-4 months later in a virtual eye clinic. In the unlikely event  
361 that a patient with FAME is asymptomatic, there will still be an opportunity for such a patient to be

362 detected in this screening pathway at the second contact in the virtual eye clinic. As the risk of FAME  
363 is low after 4 months, screening beyond this time is probably unnecessary. However, as patients on  
364 fingolimod therapy, regardless of duration, who undergo intraocular surgery are at an increased risk of  
365 FAME, it is suggested that this cohort of patients have a routine OCT at the pre and postoperative  
366 check.

367

### 368 *Conclusion*

369 In summary, there is a significant association of macular oedema (FAME) and other retinal vascular  
370 problems in patients who are on treatment with fingolimod for MS. Fortunately the visual  
371 consequences appear to be mild and often resolve on discontinuation of fingolimod therapy. The  
372 pathophysiologic mechanism responsible for FAME is thought to be due to an increased permeability  
373 of the retinal vessels due to the effect of fingolimod on retinal sphingolipid receptors. However, in  
374 rarer cases where there is retinal vein occlusion, discontinuation of fingolimod alone may not lead to  
375 resolution and intra-vitreous therapy may be required. Due to its efficacy in treating multiple sclerosis  
376 symptoms, fingolimod may become more widely used. Thus, we suggest that ophthalmic monitoring  
377 of patients should be based upon their visual acuity, OCT findings and co-morbidities, enabling close  
378 monitoring of those at-risk whilst ensuring the burden is manageable. Continued reporting of other  
379 cases in the scientific literature and via the yellow card system should further our knowledge and  
380 experience of this new cause of macular oedema.

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