Reviewer’s report

Title: Retinal hemorrhages following fingolimod treatment for multiple sclerosis; a case report

Version: 0 Date: 04 Aug 2015

Reviewer: Kimberly Winges

Reviewer's report:

The authors detail a case report of retinal hemorrhages after fingolimod treatment in a 31-year-old male with relapsing-remitting multiple sclerosis. The information presented is generally clear and the authors make the acceptable conclusion that fingolimod is causative of the retinal hemorrhages, based on the appearance of retinal hemorrhages starting 4 weeks after treatment and stopping after cessation of treatment, as well as being concurrent with macular edema. I would suggest the following major changes in order to consider this for publication:

1) Presentation of case: should include prior treatment, specifically time between prior treatment and initiation of fingolimod (i.e. plasmapheresis was how long prior to initiation of fingolimod?). If pt had previously been on IFN Beta-1a, see the following reference: "Asymptomatic Peripheral Retinal Hemorrhages as a Manifestation of Interferon Beta 1a Retinopathy* January 2015, Vol. 30, No. 1 , Pages 56-57

Present initial exam with visual acuity and explanation why it is so poor (There is mention of nystagmus and inability to sit for fluorescein thus I am assuming pt has significant nystagmus and severe MS as suggested by EDSS score). Post-treatment exam at time of the photos should detail visual acuity and exam at that time point. There should be mention of no other signs of vasculitis or uveitis (including intermediate uveitis or other vitreous cell). The absence of fluorescein angiogram is a limitation of this case report as the authors are concluding mechanism for retinal hemorrhages is increased vascular permeability.

2) Right eye should also be included with a discussion of why retinal hemorrhages were not found in the right eye.

3) Authors state in the Case Presentation section that the retinal hemorrhages were around arteries and veins (p.5 line 1-2), and later state that they were preferentially around arteries. I see both arterioles and venules affected in RNFL, but also deeper dot-blot hemorrhages. Please correct text to reflect both artery and vein involvement. This may be important as MS-associated uveitis generally affects veins.

4) would change "macula edema" to "macular edema" and grammar and punctuation should be rechecked throughout the article (using "that" for "which" for example). Also, the term "immunological inflammation of MS" could be changed to "uveitis associated with MS"
or "MS-associated uveitis" or simply "pathophysiology inherent in MS" or "Multiple sclerosis inflammatory disease"

5) Discussion, p.7 lines 9-14 (bottom of page). Please reword. Line 12 "Not only fingolimod, but also the immunologic inflammation of MS, may lead to..." suggest possibly switching order of statements: "Our case report suggests that not only Multiple sclerosis inflammatory disease, but also MS treatment with fingolimod, may lead to an increase in vascular permeability in some patients." The macular hemorrhage in Fingolimod article that authors reference (2) is useful and includes a brief discussion worth considering. Would rephrase the discussion to state that the authors' case report suggests that fingolimod may play a role in disrupting vascular integrity because hemorrhages are not routinely seen in MS patients without other signs of uveitis. Also, Consider Including a discussion of blood-retinal barrier disruption and the authors may want to address the following reference, part of a group of literature that would suggest that fingolimod helps, not hurts, the blood-retinal barrier: Copland DA1, Liu J, Schewitz-Bowers LP, Brinkmann V, Anderson K, Nicholson LB, Dick AD. Therapeutic dosing of fingolimod (FTY720) prevents cell infiltration, rapidly suppresses ocular inflammation, and maintains the blood-ocular barrier. Am J Pathol. 2012 Feb;180(2):672-81.

6) Discussion: retinal hemorrhages were in temporal periphery along the distal arcade vessels, but there is one disc hemorrhage at the superior disc margin, and authors state they were only in periphery. Please correct

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

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