Author’s response to reviews

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

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Version: 1 Date: 30 Aug 2015

Author’s response to reviews:

Dr. Eleni Papageorgiou
Executive Editor
BMC Ophthalmology
30 August 2015

Dear Dr. Papageorgiou:

Thank you for your helpful review of our manuscript “Retinal hemorrhages following fingolimod treatment for multiple sclerosis; a case report” (BOPH-D-15-00016).

We corrected all points as suggested by the reviewers and have outlined each in the following point-by-point discussion. All changes are in red font in the revised manuscript.

We hope our revised manuscript is improved and in now acceptable for publication in BMC Ophthalmology.

Please note that written informed consent was obtained from the patient’s mother for publication of this case report and accompanying images. Because the patient and his mother could not understand English, we have translated your English consent form into Japanese, and then obtained written consent in Japanese. This can be provided to the journal.

Thank you for your consideration of our manuscript.

Sincerely,

Naoko Ueda
Naoko Ueda
Response to Reviewers

Reviewer #2:

Is there any history of pars planitis or uveitis in this patient? ;
There is no history of pars planitis or uveitis in this patient (p.5 lines 2—3)
Write a sentence commenting on whether the slit lamp ---in both eyes. ;
The anterior segment was normal (p.6 lines 2—3).
What were the fundus findings in the right eye especially in mid-peripheral retina? ;
The retinal hemorrhages and macular edema were not seen in the right eye (p.6 lines 9—10);
Was there any evidence of cystoid macular edema in the right eye on OCT? To compare with CME in left eye, include at least one image of the right eye in figure2. ;
CME was not seen in the right eye (p.5 lines 5—7). We added the OCT images of both eyes before the treatment with fingolimod (Fig. 1).
Page 6 line1 states no hemorrhages----- infero-temporal retinal arterial branches. ;
There were a hemorrhage on the optic disc and more hemorrhages at the retina, so we corrected the sentence (p.5 lines 12—14 and p.6 line 1).
Did anyone check blood pressure, even though it was mentioned that patient had no hypertension? ;
The patient’s blood pressure was around 90—105/50—75mmHg, so he had no history of hypertension (p4. lines 13—14).
Was the patient no concomitant interferon- therapy along with fingolimod? As interferon------939-40.;
Interferon-β was only used for half a year, six years prior (p.4 lines 7—8).
Though authors mentioned that no hematological abnormalities, it will be good to mention the hemoglobin level and platelet count in this patient.

When retinal hemorrhages were recognized, hemoglobin level was 15.0g/dL and platelet count was 210,000/μL, within the normal range (p.5. lines 1—3).

Was PPD test done—literature.

We have discussed Eales disease, PPD, and tuberculous vasculitis (p.7. lines 7—12).

Reviewer #3:

Presentation of cases: should include prior treatment.---;

We present prior treatment data on p.4. lines 5—9.

Present initial exam with visual acuity and explanation why it is poor.

At the first ophthalmological examination before taking fingolimod, SD-OCT showed a thinner retina, particularly in the nerve fiber layer in both eyes (Figure 1 was added). The patient’s past history revealed that the onset of MS was accompanied by a visual disorder. The loss of the nerve fiber layer due to his past optic neuritis may be regarded as the cause of poor visual acuity (p.4. lines 4—5 and p.5. lines 4—8.).

In all directions, he showed gaze-related nystagmus (p.5. line 8).

There should be mention of no other signs of vasculitis or uveitis—;

There were no signs of vasculitis or uveitis (p.5. lines 2—3 and p.6. lines 2—3).

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

During progression, neither the retinal hemorrhages nor ME developed in the right eye (p.6. lines 9—10). We discussed the reasons for this finding on p.9 lines 5—10.

According to retinal hemorrhages;

We changed to p. 5 lines 12—14 and p.6 line 1.

We changed “macula edema” to “macular edema” throughout the text. The grammar and punctuation were rechecked by Edanz Group Japan. In addition, “immunological inflammation of MS…” was changed to “MS-associated uveitis” (p.9. line 3).
“Not only fingolimod, but also the immunologic inflammation of MS, may lead to…” was changed to “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.” (p.9. lines 11—13)

The macular hemorrhage in Fingolimod article that authors reference (2) is useful and-------;

On page 8 lines 1–3, we rephrased the discussion to state that “This care report suggests that fingolimod may play a role in disrupting vascular integrity, because hemorrhages are not routinely seen in MS patients without other sign of uveitis”.

Paper of “Therapeutic dosing of fingolimod(FTY720) prevents cell infiltration, rapidly suppress ocular inflammation, and maintains the blood-ocular barrier” is very interesting. But at present, we could not adopt this article to discussion in this paper, because it may produce some confusion.

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

We corrected this on p. 5. lines 12—14 and p.6 line 1.

Specific Request by the Editor:

Ethics Committee Approval:

The Ethics Committee of Hakuaikai Hospital approved this research. This was added to the Consent section of the manuscript on p.10 line 10.

Consent Section:

Concerning patient consent, written informed consent was obtained from the patient’s mother for publication of this case report and accompanying images. Because the patient and his mother could not understand English, we translated your English consent form into Japanese, and obtained the patient’s consent in Japanese.

Authors’ contributions:

This information is now included on p. 11 lines 7—10