Author’s response to reviews

Title: Hyperreflective foci in OCT image as a biomarker of poor prognosis in diabetic macular edema patients treating with Conbercept in China

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Author’s response to reviews:

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Hyperreflective foci in OCT image as a biomarker of poor prognosis in diabetic macular edema patients treating with Conbercept in China” (ID: BOPH-D-19-00048_R2). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in color in the paper. The main corrections in the paper and the responds to the reviewer’s comments are as following:

David Antonetti (Reviewer 1)

1. In this manuscript, the investigative team attempts to address whether hyperreflective foci (HF) correlate with changes in edema after anti-VEGF treatment. HF have recently been assessed in OCT scans of patients with diabetes as a potential clinical correlate likely relating to inflammation. The authors claim the HF may act as a biomarker for poor visual outcomes, although this was clearly not demonstrated. The authors do attempt to provide data for HF as a clinical correlate to edema and visual acuity in diabetes. However, even here, there is a limited study size and only a moderate correlation r values of baseline HF as compared to final BCVA (~.4, ~.5). Further, the baseline HF to final BCVA does not really make sense. What is needed is
a correlation between the change in HF and change in BCVA after treatment. Importantly, the HF changes over drug treatment are not plotted.

We appreciate the reviewer’s comments. In addition to the correlation analysis between baseline HFs and final BCVA, we also did the analysis between the changes of HFs and the changes of BCVA: “There was also a significant positive correlation between outer retinal HFs reduction, total retinal HFs reduction and increase of BCVA (r=0.40, p=0.043 and r=0.393, p=0.04 respectively)” (In the result section). Furthermore, the changes of HFs after Conbercept treatment were listed in the result section: “4. Changes of HFs before and after anti-vascular endothelial growth factor treatment”. We also added Figure 4 to plot the HF changes over drug treatment according to the reviewer’s suggestion.

2. In addition, the authors fail to mention significant selection biases associated with their study design, sex biased patient demographics, and the out of pocket cost associated with this medication influencing selection of which Anti VEGF medication to use.

We appreciate the reviewer’s comments. As this was a retrospective study, selection bias, sex bias could not be avoided. We added the limitation of this study in the discussion section. The cost of anti-VEGF medication can influence the choice of the patients, however, as this was not a prospective controlled study, and we did not compare the efficacy of different anti-VEGF medication, it would not influence the result of this study.

Honghua Yu (Reviewer 3)

The authors present a study of analyzing the dynamic changes of HFs in DME patients treated with Conbercept, and investigating the relationship between HFs and the BCVA of DME patients. Overall several similar studies regarding HFs and the BCVA prognosis of DME patients after anti-VEGF had been reported, so the idea and design are not novel.

We appreciate the reviewer’s comments. Previous studies has demonstrated the changes of HFs in the treatment of DME, however, it was not assessed when using Conbercept, which was the first choice of treating DME at our clinic. Therefore, we analyzed the changes of HFs in DME patients treated with Conbercept to find out if HFs can also act as a biomarker of the prognosis when using this medication.

1. The study contained a small sample size and selection bias could not be avoided, which could result in an inaccurate conclusion.
We appreciate the reviewer’s comments. As this was a retrospective study, selection bias could not be avoided. Furthermore, it contained a relatively small sample size and short follow-up period. These limitations were listed in the discussion section.

2. It would be better to have them analyze the relationship between the baseline HFs and the baseline BCVA of DME patients to make sure whether baseline HFs is a biomarker of poor final visual outcome after treatment or it is just a biomarker of poor vision of DME patients. The scientific logic flow needs to be clear.

We appreciate the reviewer’s comments. According to the reviewer’s suggestion, we further analyzed the relationship between the baseline HFs and the baseline BCVA of DME patients. The results showed that the baseline HFs in the outer retina was positively correlated with baseline BCVA (r=0.42, p=0.034). Moreover, there was a positive significant correlation between the baseline number of HFs in the inner retina, outer retina, subretina and final BCVA. These results suggested that the baseline HFs in the outer retina may be a biomarker of poor vision of DME patients, however, the number of baseline HFs in the inner retina and subretina can be a biomarker of poor final visual outcome after treatment. We added these information in the result section.

3. Page 8 line 40-46 "...although this kind of treatment strategy was not assessed in previous published works." This statement is incorrect, since many published studies used 3 monthly Conbercept injection +PRN regiment to treat DME.

We are sorry for the unclear description. Although some previous published studies used 3 monthly Conbercept injection +PRN regiment to treat DME, the changes of HFs during the treatment were not studied before. Therefore, we changed the sentence on line 35-40 in the first page of introduction section: “In previous published papers, Conbercept has also been demonstrated to be effective in treating DME.” (We also add two references, which are BMC Ophthalmol 2019, 19(1):123. BMC Ophthalmol 2017, 17(1):158.). On line 55-58 in the first page of introduction section and line 1 in the second page of introduction section, we added the sentence: “In our clinic, we usually use 3 monthly Conbercept injection + PRN regiment to treat DME, however, the changes of HFs was not assessed in previous published works using this treatment strategy.”

4. The quality of figures 3A and 3B is not good enough to show what they have stated in the figure legends. Also, the HFs should be indicated by arrows.

We appreciate the reviewer’s comments and changed the figures according to the suggestion.