Author’s response to reviews

Title: The relationship between foveal outer nuclear layer thickness in the active and resolved phases of central serous chorioretinopathy treated with half-dose photodynamic therapy

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Version: 1 Date: 01 Dec 2018

Author’s response to reviews:

Guangde Tu
Editor-in-Chief
BMC Ophthalmology

Dear Tu,

We appreciate the comments of the reviewers on the manuscript BOPH-D-18-00698, entitled “The relationship between foveal outer nuclear layer thickness in the active and resolved phases of central serous chorioretinopathy”.

We are pleased to submit herewith the revised manuscript, which addresses the points that have been raised by the reviewers. Each of the co-authors has seen and agreed to each of the changes made to this manuscript and the way his or her name is listed. We believe the reviewers’ recommendations have allowed us to improve the quality of our paper.

We address all the comments below.

Technical Comments:
None.

Editor Comments:

Please revise the manuscript according to the reviewer's comments.

Response: Thank you. We are pleased to submit herewith the revised manuscript, which addresses the points that have been raised by the reviewers.

Reviewer 1: This manuscript requires significant revision in order to make it useful to readers.

1 The inclusion criteria need to be clear. There seems to be patients included who had acute CSR (see under symptoms ranging 13-784 days). Eyes with acute CSR should be excluded, and the definition of chronic CSR needs to be clearly stated in the manuscript. The duration of CSR before treatment should be stated (line 83 on Page 5).

Response: Thank you for your comment. Half-dose photodynamic therapy (PDT) has been shown to be effective in promoting the resolution of the subretinal fluid in both acute and chronic CSC and in preventing recurrence.1-6 Some CSC patients have shown a significant reduction in their best corrected visual acuity (BCVA) within 3 months as a result of subretinal exudation.7 CSC is also associated with the type A personality.8 Therefore, at our hospital, treatment with half-dose PDT is recommended for CSC patients who have been symptomatic for more than 3 months, have suffered frequent recurrence, have BCVA lower than 8/20 (Snellen), or who were anxious to recover quickly. Therefore, in the previous version of this manuscript, the median symptom duration before half-dose PDT was 58 days and some enrollees had even shorter symptomatic periods before half-dose PDT was administered. However, the designation of chronicity in CSC remains somewhat arbitrary.9 In order to retain as much data as possible, we chose the shortest definition of chronic CSC (6 weeks).10,11 Following the requirement, we excluded patients with acute CSC whose symptom duration before half-dose PDT was less than 6 weeks. However, because the number of remaining patients decreased to only 52, we supplemented qualified chronic CSC patients, whose symptom duration was more than 6 weeks and who received half-dose PDT between July 2016 and Oct 2017. Thus, the final number of enrollees increased to 62. Therefore, all the data in the Results section have been altered and the Figure 2(A, B and C) has been replaced by a qualified patient’s OCT. The following statements have been added to the Methods section:” The subjects included were those with clear and detailed medical records; symptom duration of 6 weeks or more; …. The exclusion criteria were: fragmentary medical records; symptom duration of less than 6 weeks;…." [Methods: pg. 4, lines 68 and line 73]. The median symptom duration before half-dose PDT was 69.5 days (range, 42-784 days).[Table 1]


The relevant sentence is shown below.


The relevant sentence is shown below.

2 Visudyne infusion was over 8 minutes. This, to the best of my knowledge, is not standard. The authors need to explain that or reference that time choice.
Response: Thank you for your comment. The PDT protocol in this study was half-dose, according to references 19-21, cited below. We have cited these references in the Methods section [Methods: pg. 5, lines 84]. We have also replaced “PDT” with “half-dose PDT” throughout the text.


The relevant sentence is shown below.


The relevant sentence is shown below.


The relevant sentence is shown below.

3 The statement in lines 168-170 regarding ‘retinal stretch’ needs more evidence rather than speculation. It has always been known, and it is intuitive that the retina is stretched in CSR.

Response: Thank you for your comment. We are so sorry that we cannot provide any other firm evidence with OCT. Basic research with a proper animal model may provide further firm evidence. We have added this suggestion to the study limitations:” This study had several limitations: 1) the inference of retinal stretch within the detached area still requires firm evidence. ….Basic research with a proper animal model may provide further firm evidence.” [Discussion: pg. 9, lines 166-167, and line 169-170].

Reviewer 2: I wish to thank the Associated Editor for the invitation in this review.

The authors are presenting a manuscript dealing with the calculation of the relationship between the foveal ONL thickness before photodynamic therapy and 1 year after PDT treatment.

1- The title should be changed in accordance to the aim of the paper (adding half fluence PDT).

Response: Thank you for your comment. In this study, the PDT protocol for CSC was performed with half the normal dose of verteporfin (3 mg/m2 verteporfin) based on the rationale that a
lower dose has less-severe collateral damage effects to the retina and choroid. Therefore, we have added the following phrases to the title “treated with half-dose photodynamic therapy”.


The relevant sentence is shown below.

2- Was computer based calliper measurement tool employed in order to measure the ONL on the OCT scans? please specify in the text

Response: Thank you for your comment. All the measurements in this study, including the ONL thickness at the fovea, the height of retinal detachment, and the width of the subretinal space, were made manually with the supplied caliper measurement tool. We have specified this in the Methods section of the revised manuscript. These measurements were made manually with the supplied caliper measurement tool. [Methods: pg. 5, line 101 to pg.6,line 102].

3 The figures shown by the authors are not clear, they need symbols and numbers in order to specify the anatomic features and quantitative measurements of the fovea respectively.

Response: Thank you for your comment. We have added a figure to the revised manuscript to illustrate the anatomical features of each parameter, including the ONL thickness at the fovea, the width of the subretinal space, and the height of the detached retina. [Figure 1 A, B and C] We have also included the values for these measurements in Figure 2.

4- A demographic table is necessary (age, gender, bcva, crt and PDT details such as spot size).

Response: Thank you for your comment. We have added a table to the revised manuscript that includes both the clinical characteristics of the patients and their OCT parameters (age, gender, symptom duration before half-dose PDT, BCVA before half-dose PDT, BCVA after half-dose PDT, CRT, the half-dose PDT spot size, height of the retinal detachment, width of the subretinal space on horizontal and vertical scans, H/W on both horizontal and vertical scans, and the difference in foveal ONL thickness). [Table 1]

5- Why did the authors employ the median and not the mean? please specify in the text

Response: Thank you for your comment. All the data in this study were subjected to the one-sample Kolmogorov–Smirnov test for normality. In the original version of the manuscript, the normally distributed data were presented as means ± standard deviations, and those not normally distributed were presented as medians and ranges. To simplify the results, we have combined the demographic data for the patients and the values for their OCT parameters in Table 1. Both the
means and medians, and the results of the Kolmogorov–Smirnov test are presented. Either the mean or median values are specified in bold according to the Kolmogorov–Smirnov test results: P \geq 0.05 indicates that the data are normally distributed, and the mean value is shown in bold. P < 0.05 indicates that the data are not normally distributed, and the median value is shown in bold.

We have added this information as a footnote to Table 1: *The Kolmogorov–Smirnov test was used to confirm the normality of the data. P \geq 0.05 indicates that the data are normally distributed, and the mean value is shown in bold. P < 0.05 indicates that the data are not normally distributed, and the median value is shown in bold.*[Table 1: footnote].

6- Which was the mean number of PDT sessions and did PDT treatment result in SRF absorption in all patients in the first attempt? please specify in the text

Response: Thank you for your comment. All the patients included had only one session of half-dose PDT. Those with persistent subretinal fluid more than 2 months after half-dose PDT or recurrence within 1 year were excluded. We have specified this in the Methods section: *The subjects included were those with …; subretinal fluid resolution within 2 months of half-dose PDT; no recurrence within 12 months of half-dose PDT; ….. The exclusion criteria were: … any residual subretinal fluid for up to 2 months after half-dose PDT; any recurrence within 12 months of half-dose PDT.* [Methods: pg. 4, line 70 and line 76-77].

7- What was the mean disease duration? please specify in the text

Response: Thank you for your comment. The mean disease duration before half-dose PDT was 132.05±156.17 days (Table1). Because these data were not normally distributed (Kolmogorov–Smirnov test, P=0.000), we have presented both the mean and median symptom durations in Table 1, with the median values shown in bold.[Table 1]

8- Did the authors notice a correlation between disease duration and ONL thickness at the end of the 12 months? please specify in the text

Response: Thank you for your constructive comment. In the revised paper, we have analyzed the correlation between the symptom duration and ONL thickness 1 year after half-dose PDT. The disease duration correlated negatively with the foveal ONL thickness after 12 months(R= -0.545, P = 0.000). The following statements have been added to the Methods and Results sections: *Either Pearson’s correlation coefficient or Spearman’s correlation coefficient was used to examine the correlation between the symptom duration and the foveal ONL thickness 12 months after half-dose PDT.* [Methods: pg. 6, line 112-114]. “Symptom duration before half-dose PDT and foveal ONL thickness 12 months after half-dose PDT were negatively correlated (R= -0.545, P = 0.000).” [Results: pg. 7, line 126-127].
9- In the discussion section the authors should mention the study limitations such as absence of a normal control group/ standard fluence control group, small sample group, absence of a second blind examiner measuring the ONL.

Response: Thank you for your comment. We apologize for our carelessness. We have discussed the limitations of the study in the revised Discussion:” This study had several limitations: 1) the inference of retinal stretch within the detached area still requires firm evidence; 2) the lack of a normal control group, a standard dose control group, and the measurement of ONL by a second blinded examiner; and 3) the sample group was small. Basic research with a proper animal model may provide further firm evidence. Further prospective studies with large populations and control groups may tell us more. ” [Discussion: pg. 9, line 166-170].

10- In their conclusions the authors are claiming that in their study the majority of eyes with resolved CSC showed some increase in the foveal ONL thickness (without specifying if this increase is statistically significant) due to the ratio of the retinal detachment height to the subretinal space width in the active phase. However there are a number of studies, including the employment of PDT in cCSC patients, claiming that short disease duration (<18 months) does not show to influence ONL thickness.


Study 2 R. M. Silva, J. M. Ruiz-Moreno, F. Gomez-Ulla et al., "Photodynamic therapy for chronic central serous chorioretinopathy: a 4-year follow-up study,"

Study 3 H. Vasconcelos, I. Marques, A. R. Santos et al., "Long-term chorioretinal changes after photodynamic therapy for chronic central serous chorioretinopathy."]

Moreover in attendance to Ozdemir I. et al, the patients affected by cCSC and not treated by PDT or Anti-VEGF showed a thinner ONL only in the 4th month of the disease as the SRF was increasing.

Study 4 [Outer nuclear layer thickness at the central fovea relation with symptom duration in central serous chorioretinopathy. Ozdemir I, Eren A, Ersöz G. Int Ophthalmol.]

Response: Thank you for your constructive comment. In the revised manuscript, we used a paired t-test to compare the foveal ONL thickness 12 months after half-dose PDT with that before PDT. [Methods: pg. 6, line 114-115] The increase was significant (t = 8.83, P = 0.000).[Results: pg. 7, line 129]

In study 1, the foveal ONL thickness was 81.43 ± 17.26 μm at baseline and 83.68 ± 20.87μm at 12 months after full standard dose of PDT. The difference was not significant, probably because the ratio of the retinal detachment height to the subretinal space width was low. This ratio was
not considered in their study. Some patients in our study also showed little change in their foveal ONL thickness (Figure 2, only 4μm).

In studies 2 and 3, stratus OCT was used, which is a time-domain OCT with low resolution. Therefore, the slight difference between the OCT parameter values can be ignored. Furthermore, they studied the neural retinal thickness rather than the foveal ONL thickness. In their studies, the neural retinal thickness was defined as the distance between the internal limiting membrane and the anterior limit of the subretinal fluid. Therefore, it included both the ONL thickness and the thickness of the photoreceptor layer (PRL). In active CSC, the morphology of the PRL changes continuously, 1-4 and these changes include elongation, granulation, and defect. 1-4 These PRL changes were quite different in thickness.1-4 Therefore, the neural retinal thickness dose not reflect the foveal ONL thickness because there is wide variation in the PRL thickness.


We fully agree with the reviewer and Ozdemir I (study 4) that the foveal ONL thickness in eyes with active CSC continues decrease as the symptom duration increase. It is speculated that continuous ONL thinning results from the continuation of photoreceptor cell death after retinal detachment, through apoptosis, necroptosis, autophagy, and macrophage or microglial infiltration.5 However, the ONL thickness in the eyes with resolved CSC showed no significant change for at least 6 months after subretinal fluid resolution.5 This indicates that the loss of photoreceptors does not continue after the resolution of the subretinal fluid.5 All the subjects in our study received half-dose PDT, leading to the rapid resolution of their subretinal fluid. Therefore, the photoreceptor death ceased and the ONL thickness was retained. The slight increase in the foveal ONL thickness (9.15μm) was probably attributable to the recovery of retinal stretch in their active phase.

And we have added the study 4 into reference.[ Reference 13]

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Response: Thank you. There is no request for improvements to the English language within this manuscript.

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Response: Thank you. We included a Declarations section as required.