Author's response to reviews

Title: Changes in Macular Sensitivity after Half-Dose Photodynamic Therapy for Chronic Central Serous Chorioretinopathy

Authors:

Alp Atik (ala374@mail.harvard.edu)

Yijun Hu (huyijun2014@163.com)

Honghua Yu (yhhgtm@126.com)

Chun Yang (602757305@qq.com)

Bin Cai (105455762@qq.com)

Yijing Tao (taotao2212@hotmail.com)

Dongli Li (kyxiaoyi51@163.com)

Yan Chen (3206512935@qq.com)

Li Lu (872898493@qq.com)

Guodong Li (daliguodong@sina.com)

Ling Yuan (yuanling8061@163.com)

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Reviewer reports:

Tomas S. Aleman (Reviewer 1): Atik et al. present a well-conceived study where changes in visual sensitivity are explored following half-dose photodynamic therapy (PDT) as a treatment of persistent or chronic central serous chorioretinopahy (CSCR). They used automatic static perimetry before and after PDT and conclude there were significant changes in sensitivity following this type of treatment. The results are indeed interesting specially since there are only rare occasions were treatments for CSCR have been scrutinized in this detail. The manuscript is thus relevant to the understanding of this condition and on the impact that treatments have on vision, not only visual acuity (VA). My main concern has to do with the interpretation of the findings. That is, without measurements (or reference to) the range of intervisit variability

expected for the sensitivity or retinal thickness measures it is hard to estimate if the changes observed are clinically significant, although it is obvious that they are statistically significant. This is perhaps less important for central foveal thickness (CFT) measurements as the changes are without doubt beyond variability. If such estimates are not available, then the authors should use estimates from the literature and emphasize other features that support a change in sensitivity that could only be explained by the treatment. For example, use of interocular comparisons and/or the relationship between each of the parameters (VA, CFT, 4deg 10 deg MS), time-course of changes.

Also unless I am reading this wrong, I would strongly disagree with the use of dilated choroidal vasculature in itself or a thickened choroid should be an inclusion criteria If there is no clinical, OCT or angiographic evidence of CSCR. If the cohort was limited to patients with CSRC and pachychoroid then this should be clearly stated and discussed, since this would be a specific subtype of CSCR. The same applies for sub-RPE or RPE separations. There are multiple instances in the manuscript where 'and/or serous RPE detachment' is used. Serous RPE detachment is not CSCR unless they are sequelae. That is, CSCR should occur at least at some point as a separation of the retina and RPE.

Response: We feel that the improvements in MS, MD and PSD seen in our study are both statistically and clinically significant. In a previous study Squirrell et al. has demonstrate that a change of >1.5dB in MS detected by microperimetry can be regarded as a significant change in visual function in wet AMD patients. The mean change of 10 degree MS in our study was 1.98dB at 1 month, 1.75dB at 3 months and 1.43dB at 6 months. The mean change of 10 degree MS in our study was 3.45dB at 1 month, 3.5dB at 3 months and 2.94dB at 6 months. Most of the changes were more than 1.5dB. In a study by Frennesson et al. the mean improvement of MD in wet AMD patients successfully treated with ranibizumab was at least 27% from the baseline MD. In our study, the mean improvement of MD from baseline was 42.2% at 1 month, 42.8% at 3 months and 27.7% at 6 months. All of the improvement was more than 27%. Moreover, a less extent of change in MS and MD would be expected in CSCR patients. This is because patients with better central vision usually have smaller variation in MS and MD and CSCR patients usually have better central vision than wet AMD patients (line 386-420).

About the dilated choroidal vasculature and serous RPE detachment in CSCR patients, we have amended the diagnostic criteria in the manuscript. A CSCR patient needed to meet all of the 5 criteria to be included in the study (line 136-149).

Other comments:

Abstract: please mention what type of perimetry was used.

Response: This has been amended in the manuscript (line 33-34).

Methods: How did you determine the mean defect, PSD and sensitivity for the central 4 deg. It is my understanding this is not a standard parameter output of the 10-2 protocol.

Response: The MD and PSD were automatically calculated by the Humphrey Field Analyzer II-750. The 10 degree MS was calculated as the mean of the 68 point sensitivity within the central 10 degree area on the print-out of the 10-2 program. The 4 degree MS was calculated as the mean of the 16 point sensitivity within the central 4 degree area on the print-out of the 10-2 program. We have added the information in Methods (line 177-181).

Methods: Please specify what type of visual acuity notation is being listed (logMAR, decimal fraction).

Response: The visual acuity is decimal fraction (line 160).

Results:I would emphasize on the differences between your findings at 4 deg and 10 deg as well as on the relationship between each of the parameters, namely, VA, CFT.

Response: We have added the information in Results (line 271-290 and line 315-316).

Results: Please realize that P values should not be quoted as zeros.

Response: This has been amended in the manuscript. Since some of the actual P values were very low (<0.001) and it was very inconvenient to list the actual P values, therefore we used the "P<0.001" to quote these P values.

Results: Sensitivity and md are saying the same thing Why is it significant here?

Response: The MS and MD values are related but do not demonstrate exactly the same thing. The MS is a logarithmic unit in dB that reflects macular sensitivity to a light stimulus. It does not

take into account patient age or other factors such as generalized reduction in sensitivity (e.g. cataract).

In contrast, the MD values are an average reduction in sensitivity per point compared with age-matched controls. We have used both values to show that both holistically and when matched with controls, half-dose PDT improves macular function.

Results: Interesting that the fovea improved more than the entire macular

Response: We agree that this is an interesting but consistent finding with other studies. Sekine et al. have shown a lower MS at the fovea compared to that at the outer macular area in CSCR. Consistently, Ehrlich et al. have shown that improvement of 6 degree MS is more profound than 12 degree MS at 3 months and 6 months after PDT treatment for CSCR (line 445-450). We would thus also expect the foveal recovery to be more significant than the entire macula.

Catherine Meyerle (Reviewer 2): The authors evaluate macular sensitivity with automated static perimetry in chronic central serous chorioretinopathy patients treated with half dose PDT. Following are some comments on the manuscript.

1) Methods, Study participants, page 5: Please expand on the definition of chronic central serous chorioretinopathy and add to the inclusion criteria. Was there fluid documented by OCT for greater than 3 months? Or was the definition based on symptoms greater than 3 months per patient report?

Response: This has been amended in the manuscript (line 136-138).

2) Methods, page 6: How was the spot size for PDT determined - based on FFA leakage or based on choroidal hyperpermeability on ICGA or OCT guided in the area of fluid or multimodal based?

Response: PDT was applied to cover the area of leakage on FFA and choroidal hyperpermeability on ICGA (line 191-193).

3) Results, Basic Characteristics, page 8: It would be helpful to elaborate on the baseline characteristics of the study participants. For example, how many had signs of diffuse retinal pigment epitheliopathy vs how many had relatively well preserved RPE. This is important as one would expect less improvement in patients with advanced RPE damage.

Response: Most of our patients had relatively well preserved RPE (line 214). Severe and diffuse retinal pigment epitheliopathy was not seen in our patients.

4) Results, FFA and ICGA, page 9: Description of baseline fluorescein leakage patterns is important. How many had foveal leakage vs extrafoveal leakage? One would be more concerned about treating over the fovea as opposed to extafoveal leakage.

Response: All of the eyes had leakage within the foveal avascular zone (line 236). That was why we chose PDT treatment and therefore all of the PDT treatment was over the fovea.

5) Results, general comment: How many required PDT treatment directly over the fovea? What was the spot size range for all participants? Was there any correlation between these parameters and outcome - i.e. did direct foveal treatment result in less improvement?

Response: Since all of the PDT treatment was over the foveal avascular zone because all of the eyes had leakage within this area, direct comparison of outcome between foveal treatment and extafoveal treatment was not possible in our study.

6) Discussion, page 12, line 211: The authors write " Our results demonstrate that PDT with half dose verteporfin is effective for chronic CSCR." Since this has already been reported, I would change this statement to "Our results demonstrate that macular sensitivity as assessed with automated static perimetry can be improved after half dose verteporfin. This is clinically important as visual acuity often does not capture the visual disturbances of central serous chorioretinopathy patients."

Response: This has been amended in the manuscript (line 348-351).

7) Discussion, page 15, line 277: The authors write "The results are generalizable only to patients with idiopathic CSCR and not to patients with secondary CSCR". I would revise this to say "Our results are not generalizable to all CSCR patients given the small and short term nature of this study, but they do indicate that automated static perimetry may play a useful role in evaluating treatment response in this patient population."

Response: This has been amended in the manuscript (line 508-511).

8) Conclusion, page 15, line 281: Change "macular sensitivity could be improved" to "may be improved."

Response: This has been amended in the manuscript (line 514).

9)Conclusion, page 15, line 283-285: The authors write "Considering the safety of half-dose PDT, we recommend that patients receive half-dose PDT in cases of chronic CSCR." It is difficult to make safety comments given the small short term nature of this study. Instead, I recommend saying "Our results showing improvement in macular sensitivity in the chronic CSCR patients treated with half dose PDT provide further evidence supporting the role of half dose PDT treatment in this patient population."

Response: This has been amended in the manuscript (line 516-519).

10) Typo: When the authors write "one section of half dose PDT", I think they mean "one session of half dose PDT." Please change throughout the manuscript.

Response: This has been amended throughout the manuscript. Apologies for this typing error (line 29 and line 189).