Author’s response to reviews

Title: Predictive multi-imaging biomarkers relevant for visual acuity in idiopathic macular telangiectasis type 1

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Author’s response to reviews:

Dear Editor:

Thank you for considering the revised version of our manuscript entitled “Predictive multi-imaging biomarkers relevant for visual acuity in idiopathic macular telangiectasis type 1” for publication in BMC ophthalmology. We are thankful to the referees and the Editor for pointing out some important modifications needed in the report. We have thoughtfully taken into account these comments. The explanation of what we have changed in response to the reviewers’ concerns is given point by point in the following pages.

Reviewer Comments:

Reviewer #1:

Key words: please expand (eg DRIL, EZ….)

Response: Thank you so much for your reminding. We revised all key words according to format requirement.
It would be useful if the authors briefly reported on the current classification of MT types 1 and 2.

Response: Thank you so much for your suggestion. We revised the introduction and added the current classification of macular telangiectasia type 1 and type 2. (Page 3, line 5-10)

The authors briefly state the utility of OCTA but it would be useful to also describe the utility of SD-OCT and mention that thickness of vascularized layers can be evaluated by automatic segmentation (Demirkaya N et al. Effect of age on individual retinal layer thickness in normal eyes as measured with spectral-domain optical coherence tomography. Invest Ophthalmol and Vis Sci 2013; 54:4934-4940 and Abdolrahimzadeh et al. Optical coherence tomography evidence on the correlation of choroidal thickness and age with vascularized retinal layers in normal eyes. Retina 2016; 36(12): 2329-2338) but that OCT A can provide further details on the vascular networks …

Response: Thank you so much for your suggestion. Because this main purpose of this article was to explore the correlation between baseline VA and the SD-OCT and OCTA-derived anatomic factors, so it would be useful to describe the utility of SD-OCT. We fulfilled in the background of the utility of SD-OCT firstly and then stated the preponderance of OCTA. Moreover, we cited the recommended two references (Page 3, line 20)

The authors report "In previous research, visual acuity (VA) of MT type 1 was assessed the correlation with IS/OS and cystoid spaces" and put reference 2 for this (Sugiura Y et al) who, however, do not mention IS/OS in their paper. Please amend this.

Response: Thank you so much for your reminding. We revised the accurate reference (Takayama K et al, Retina. 2012;32(9):1973-1980) (Page 3, line 17)

Please confirm absence of retinal changes in fellow and normal eyes.

Response: Thank you so much for your reminding. All patients included in this research had comprehensive ocular examinations in both eyes. But the normal groups (the right eye of ten people) underwent SD-OCT and OCTA. We explain the specific eyes of the normal group and the retinal changes of the fellow eye in MT patients. (Page 4, line 14-15)

Please mention time range when OCT examinations were carried out, if possible.
Response: Thank you so much for your suggestion. Because we mainly explore the SD-OCT and OCTA-derived anatomic factors at baseline. All patients underwent SD-OCT at the first visit.

The authors report that the vascular layers assessed were divided into 4 layers SCP, DCP, outer layer, and choroidal layers by OCT A. However, they do not report their results on the choroidal layers. Neither do they discuss this interesting aspect. Please explain or add relevant data to this respect.

Response: Thank you so much for your reminding. Firstly, although vascular retinal layers were divided into the following four layers: SCP, DCP, outer retina and choroidal layers by OCTA, The flow density map software Angio-Analytics can only assess the foveal avascular zone and density of the macula in SCP and DCP. Secondly, the pathologic change of MT lied in the inner retina, therefore we do not discuss the alteration of choroid and no alteration in the choroidal layer was detecte in this case series.

The phrase "all patients had blurred vision of the diseased eyes at the first visit" can be deleted.

Response: Thank you so much for your reminding. We had deleted tis sentence.

Please state vision of contralateral eyes; and vision and CMT in normal eyes.

Response: Thank you so much for your reminding. We added the vision and CMT of contralateral and normal eyes.(Page 6, line 3-6)

Which eyes of the healthy controls were used? Were these 10 eyes or ten patients? Both eyes? or one eye of each patient? Table states "normal eyes -10" but in the abstract the authors state "10 healthy people as age matched controls"

Response: Thank you so much for your reminding. We revised it and indicated the right eye of normal people included in our study.(Page 4, line 14)

Furthermore, the results seem to be based on comparison of eyes with MT and contralateral eyes and there is no mention of "normal eyes" in the analysis of data.

Response: Thank you so much for your reminding. We added the comparison of MT eyes with normal eyes (Page 6, line 2-6)
In table 1 the values for SCP in the contralateral eyes and normal eyes are not shown.

Response: Thank you so much for your reminding. We revised the specific data in Table 1.

The authors should discuss their results with comparison to the existing literature. In the introduction, the authors do state "However, there was few SD-OCT and OCTA derived parameters associated with VA", therefore, it would be useful to better discuss these papers in the discussion section with appropriate references. As an example they should compare their results with those of Matet et al in AJO as regarding the correlation of VA with the superficial and deep capillary plexus.

Response: Thank you so much for your suggestion. We revised the first paragraph according to the comments and cited the accurate references.(Page 8, 9)

The authors state that "It has been proven that the deep capillary bed is conductive to the oxygen requirements of the photoreceptor layer " and have cited reference 22. The authors should expand on this concept as it can be misleading. First, they should mention that the study they cite has been on an animal model. Second, Birol et al reported that "… photoreceptors …are supplied primarily by the choroidal circulation, with only 10-15% of the supply coming from the retinal circulation." This should be clearly mentioned. Furthermore, Birol et al conclude that "oxygenation of the fovea is somewhat different from that of the perifovea….." thus, it would be useful to mention this and discuss any correlations that might be relevant as regarding the foveal and perifoveal areas.

Response: Thank you so much for your suggestion. MT is generally characterized by abnormally dilated and tortuous capillaries around the fovea. We further discussed the difference of the deep capillary bed in the foveal and perifoveal areas.(Page 9, line 11-16)

The authors should delete " And from patients 4, we predicted that the vascular changes of DCP scaled by OCT A were a earlier sign of MT type 1" from the first paragraph of the discussion. The first paragraph should include the most significant results. The authors extensively describe the alterations in patient 4; although this is interesting, it confuses the reader and interrupts the train of thought for the major results they obtained; therefore, the discussion should be focused on these.
(Also the last sentence of the results is a conclusion and not a result … and can be deleted: "From patient 4 we discovered…")

Response: Thank you so much for your suggestion. We deleted the contents of the patient 4 at the first paragraph of the discussion and at the sentence of the results.

The sentence "These OCT and OCTA derived anatomic parameters could act as better alternatives for evaluating VA to select the therapeutic regimen and participant counselling " should be modified to not be an "alternative" to VA but to provide "further" information. The sentence should be more of a conclusive sentence and perhaps the authors could briefly mention the "therapeutic regimens" that could be selected.

Response: Thank you so much for your suggestion. We revised the sentence to be “These SD-OCT and OCTA-derived anatomic parameters could act as further information for evaluating VA to select the therapeutic regimen and participant counseling”. (Page 5, line 36-38)

The conclusions should be more completely presented eg the authors do not mention telangiectasia

Response: Thank you so much for your suggestion. We have add the alteration of telangiectasia in the conclusion.

Table headings: there are misused capital letters.

Figure legends: abbreviations should be first written in full and then abbreviated, improve legend presentation eg do not use "stands for" etc.

Response: Thank you so much for your reminding. We revised the format of table and figure.

Reviewer #2:

1. The authors have failed to enroll an adequate number of eyes in each group.

Response: Thank you so much for your suggestion. Our limitations are the retrospective design and a small sample size due to the low prevalence of MT type 1.
2. There are numerous grammatical errors in the manuscript, which made it difficult to follow.

Response: Thank you so much for your reminding. We revised this manuscript by reputable English language editing service. (Stallard Scientific Editing)

3. As CMT was increased in eyes with macular telangiectasia, the eyes may have intraretinal cysts, which may lead to errors in the calculation of FAZ or microvascular density of SCP or DCP. Hard exudates may also significantly affect the calculation and also that of photoreceptor defects (due to posterior shadowing). The authors did not mention the possible sources of image artifacts in their OCTA images, which are very important for interpreting the results.

Response: Thank you so much for your reminding. Two independent observers (GJL, TWY) assessed the OCTA in the 3 × 3-mm scan of best quality and averaged both data. The signal strength index of all images was greater than 60. The data of the whole image was chosen as the microvascular density in the SCP and DCP layer. (Page 5, line 14-19)

4. How can the authors ensure that there were no segmentation errors in eyes with MT (pathologic eyes)?

Response: Thank you so much for your reminding. The superficial plexus is defined as 3µm below the inner limiting membrane to 16µm below the outer border of the inner plexiform layer and deep plexus is defined as 16-69µm below the outer border of the inner plexiform layer. We controlled the corrected segmentation for 14 patients before reporting the data. (Page 4, line 17)

5. Mann-Whitney test is used for comparing mean between two independent groups. As the eyes with MT and contralateral eyes were paired, non-parametric version of paired t-test (Wilcoxon) may be more appropriate.

Response: Thank you so much for your reminding. We re-compute statistics. (Page 5, line 24)