Author's response to reviews

Title: Indocyanine green angiography findings in patients with long-standing Vogt-Koyanagi-Harada disease: a cross-sectional study

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Author's response to reviews: see over
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Emilie Aime, MD
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RE: BMC Ophthalmol Ms ID1874182104697943 – Manuscript Review
“Indocyanine green angiography findings in patients with long-standing
Vogt-Koyanagi-Harada disease: A cross-sectional study”

Dear Editors,

Thank you very much for the Journal’s careful appraisal of our manuscript. We are very pleased to know that it has received some favorable reviews and, as requested, we have considered and carefully addressed each of the Reviewers’ recommendations for revision, as detailed below.

We greatly appreciate all comments regarding our paper, and thank you very much for your time and effort in considering our manuscript for publication.

Yours sincerely,

Joyce H. Yamamoto
Rogerio A. Costa

Reviewer:
FENG WEN

Comment #1: “The results of the article may be better to add the table to show the ICGA findings in detail.”
Authors’ Reply #1: As requested by the Reviewer, a table containing detailed information about the ICGA findings in patients with VKH and long-standing disease was prepared and included as supplementary material (Table 3).

Comment #2: “The figures of ICGA showed in the article is not enough to reveal the finds of VKH, please add more figures of ICGA or typical cases.”
Authors’ Reply #2: As requested by the Reviewer, a new figure to illustrate the ICGA findings of patients with VKH and long-standing disease was prepared and included in the revised version of the manuscript as new Figure 1 (Page 7, paragraph3, line 6).

Comment #3: “The article not to reveal the choroidal folds and Dalen-Fuchs nodules
changes in VKH. How about the choroidal folds and Dalen-Fuchs nodules play a role in the paper?”

Authors’ Reply #3: Choroidal folds associated with VKH disease have been observed in the acute phase of the disease, and correlated to serious ocular manifestations and/or severe choroidal inflammation at the acute uveitic stage of the disease (Wu et al. Choroidal folds in Vogt-Koyanagi-Harada disease. *Am J Ophthalmol.* 2007;143:900-901; Fardeau et al. Retinal fluorescein and indocyanine green angiography and optical coherence tomography in successive stages of Vogt-Koyanagi-Harada disease. *Int Ophthalmol.* 2007;27:163-172; Zhao et al. Choroidal folds in acute Vogt-Koyanagi-Harada disease. *Ocul Immunol Inflamm.* 2009;17:282-288; and, Tanigawa et al. Choroidal folds in acute-stage Vogt-Koyanagi-Harada disease patients with relatively short axial length. *Case Report Ophthalmol.* 2012;3:38-45). In the study by Wu et al., in which choroidal folds were observed in 12% of the patients with VKH, the disease course was between 40 days and one year (Figures and online supplementary figures provided in the paper illustrate patients with VKH for 40 and 45 days, respectively). In the present study we were not able to identify choroidal folds in the patients with VKH and long-standing disease. The absence of this finding in our study might be related to the fact that the median duration of the disease in our patients was 91.5 months (ranging from 9 to 348 months).

Dalen-Fuchs nodules, depigmented small atrophic nummular lesions located usually in the fundus periphery of patients with VKH (Inomata and Rao. Depigmented atrophic lesions in sunset glow fundi of Vogt-Koyanagi-Harada disease. *Am J Ophthalmol.* 2001;131:607-614), were observed in 10 patients of the current study. However, given their somewhat variable angiographic features (these areas occasionally corresponded to dark spots on ICGA that remained hypofluorescent in later phases), they were not included as a sign of disease activity (Herbort et al. Indocyanine green angiography in Vogt-Koyanagi-Harada disease: Angiographic signs and utility in patients’ follow-up. *Int Ophthalmol.* 2007;27:173-182). Moreover, the design (cross sectional) of the current study precludes the appreciation of the changes in Dalen-Fuchs nodules over time.

In order to address the Reviewer’s comments, the following changes were performed in the revised manuscript:

Page 10, paragraph 1, line 8, the following statement was added to the text:
“Additional findings identifiable on angiographic studies that have been correlated to serious ocular manifestations and/or severe choroidal inflammation at the acute uveitic stage of VKH disease [18-21], such as the presence of choroidal folds as reported by Wu et al. [18], were not identified in the current study”.

We greatly appreciate all the comments made by Dr. Wen and hope that each of the issues raised in the review have been resolved with the revision.

Yours sincerely,
Joyce H. Yamamoto
Rogerio A. Costa

Reviewer:
General Comment: “Overall this is a well written paper by Silva et al. that demonstrates that monitoring of disease activity by clinical examination and fluorescein angiography are not adequate and reinforces the importance of indocyanine green angiography in monitoring disease activity and in better conducting treatment.”
Authors’ Reply: We thank the reviewer for the nice words about our work.

Comment #1: “I have the following criticism: Figures – incomplete description in the manuscript and legends. I find only figure 1 description in the manuscript.”
Authors’ Reply #1: We truly apologize for this error. Figures were revised and the legends included in the main manuscript text file at the end of the document. For each figure, the following information was provided: Figure number (in sequence, using Arabic numerals - i.e. Figure 1, 2, 3 etc); short title of figure (maximum 15 words), and; detailed legend (up to 300 words).

Comment #2: “It is already reported in ref. 5 that ICGA is useful for monitoring late stage of VKH. Please emphasize in the manuscript how your paper is different from previous reports.”
Authors’ Reply #2: This was a cross-sectional study focusing on ICGA findings in a non-European nor Asian population whose treatment were high-dose oral prednisone tapered according to clinical and fluorescein findings. First, we believe our study confirm European and Asian-based studies that ICGA can detect ongoing choroidal inflammation even in clinically silent (quiescent) eyes. Second, and most importantly, we could demonstrate that these ICGA findings, which could be also observed in patients with central serous chorioretinopathy due to corticosteroid use, were observed independent of systemic corticosteroid treatment in the current study, thus providing additional and relevant data to support its correlation with actual ongoing disease-related choroidal inflammation.

In order to address the Reviewer comment, the following changes were performed in the revised manuscript:

Page 4, paragraph 2, line 5, the following words were added to the text: “…been investigated [4-7], mainly in European and Asian countries. Its relevance has…”

Page 8, paragraph 3, line 6, the following words were added to the text: “…detectable disease activity, thus confirming previous studies in European and Asian population and reinforcing the usefulness of ICGA to assist monitoring disease activity to better tailor treatment strategies.”

Page 11, paragraph 2, line 3, the following statement: “In the current study a considerable proportion of patients with long-standing VKH disease whose treatment was tapered based only on clinical and FA findings demonstrated subclinical ongoing disease (choroidal inflammation) on ICGA” was changed to “In the current study a considerable proportion of patients with long-standing VKH disease whose treatment was tapered based only on clinical and FA findings demonstrated ICGA findings suggestive of disease-related choroidal inflammation. Importantly, we have also demonstrated that these ICGA findings, which share some angiographic features with those associated with corticosteroid treatment, were observed independent of the use of systemic corticosteroid.”
Comment #3: “Please indicate which criteria among ICGA findings were frequently observed in the manuscript.”

Authors’ Reply #3: The ICGA findings observed in the current study had been described in the methods section of the original manuscript (Page 6, paragraph 3, line 2), as follows: “The following ICGA findings were categorically analyzed: 1) diffusely leaking choroidal vessels in the intermediate phase (“fuzzy vessels”), 2) diffuse choroidal hyperfluorescence in the late phase, and 3) hypofluorescent dark dots in the intermediate phase with later iso-fluorescence [5, 6, 15]. Those eyes presenting at least 2 of these findings were considered to have disease-related choroidal inflammation on ICGA.” This information was maintained in the revised manuscript.

Comment #4: “Please describe the reason that the number of eyes with systemic treatment, in Table 1 [13] eyes with systemic medication, however in Table 2 [23] eyes with systemic medication.”

Authors’ Reply #4: A total of 13 patients (23 eyes) were under systemic treatment (i.e., 13 patients (not eyes) in Table 1; 23 eyes in Table 2 [now Table 3]).

Comment #5: “Discussion: line 25-26 in page 9, in the absence of melanocyte, is it easier for observing the choroidal status?”

Authors’ Reply #5: Severe VKH disease implies in loss of melanocytes (Inomata H, Sakamoto T. Immunohistochemical studies of Vogt-Koyanagi-Harada disease with sunset sky fundus. Curr Eye Res 1990;9 Suppl 35) and this situation implies in stromal scarring that means lack of diffusion of ICG molecules within these cicatricial areas as a result of the stromal shrunk (Herbort CP, Mantovani A. Indocyanine green angiography in Vogt-Koyanagi-Harada disease: angiographic signs and utility in patients follow-up. Int Ophthalmol 2007;27:173). In order to address the Reviewer comment, the following changes were performed in the revised manuscript:

Page 10, paragraph 2, line 7, the following statement:
“…to identify ICGA signs of choroidal inflammation in a severely altered fundus and the destruction of a considerable proportion of choroidal melanocytes [1]” was changed to “…to identify ICGA signs of choroidal inflammation in a severely altered fundus with destruction and scarring of a considerable proportion of the choroidal stroma…”

Comment #6: “What about the status of all patients fundus? (All sunset glow funds?) There is a correlation between the inflammation stage and funds status?”

Authors’ Reply #6: We evaluated the possible correlation between the ICGA findings and a fundus-based VKH disease severity (da Silva FT, Hirata CE, Olivalves E, Oyamada MK, Yamamoto JH: Fundus-based and electoretinographic strategies for stratification of late-stage Vogt-Koyanagi-Harada disease patients. Am J Ophthalmol 2009,148:939-945). This analysis suggested that ICGA findings were more easily identified in eyes with mild disease than in those with severe disease. In order to address the Reviewer comment, this analysis was included in the revised manuscript as a supplementary material (Additional material 1).

We greatly appreciate all the comments made by Dr. Nakai and hope that each of the issues raised in the review have been resolved with the revision.
Comment #1: “This manuscript investigated indocyanine green angiography (ICGA) findings in patients with Vogt-Koyanagi-Harada (VKH) disease at the chronic phases. The authors concluded that there was persistent choroidal inflammation detected only on ICGA in the majority of the cases, independent of the clinical findings or the treatment status. This manuscript provides some new information, however, and to be quite honest, I am unable to perceive how important the choroidal findings seen at the chronic phases are from this manuscript. Was there any relationship between the choroidal findings and the sunset glow fundus? How was the relationship with the visual function? Is it necessary to treat the patients intensively until the choroidal findings completely disappear? For example, we never abolish the choroidal neovascular membrane itself in the treatment of neovascular age-related macular degeneration. The authors should at least provide some information on the relationship between the presence or absence of the ICGA findings and the other morphologic or functional aspects.”

Authors’ Reply #1: As mentioned in the introduction section of the original manuscript, some patients with VKH present slowly vision loss associated with progressive fundus depigmentation over time in spite of aggressive treatment during the acute phase of the disease. This observation has been reported even in the absence of detectable clinical signs of disease activity. It is currently unknown whether this slowly progressive fundus depigmentation is related to some disease activity undetected on regular clinical examination or occurs as part of the natural history of VKH disease. Considering the former hypothesis, as well as peculiarities related to the disease in question, the evaluation of the choroid in patients with VKH and long-standing disease seems a fairly logical approach.

The ANCHOR and MARINA trials have demonstrated the relative efficacy of ranibizumab in controlling [choroidal] neovascular activity and preventing moderate visual acuity loss in nearly 95% of patients for 2 years. However, the HORIZON trial demonstrated an incremental decline of the visual acuity within the subsequent 2 years of treatment (Singer et al. HORIZON: An Open-Label Extension Trial of Ranibizumab for Choroidal Neovascularization Secondary to Age-Related Macular Degeneration. Ophthalmology 2012 Feb 4. [Epub ahead of print]). Therefore, and bearing in mind the pathogenesis of each entity, the parallel between VKH disease and neovascular age-related macular degeneration seems quite inappropriate in this context.

As requested by the Reviewer, information about the relationship between the presence or absence of the ICGA findings and other morphologic aspect has been provided in the revised manuscript (Please refer to Authors’ Reply #6 to Reviewer 2 [Dr. Nakai]).
Comment #2: “Discussion; Page 5, Paragraph 1: The authors stated, “In the current study disease-related choroidal inflammation on ICGA was apparently more easily observed among those patients with milder fundus changes than in those with more severe fundus changes [17, 18].” However, there was no such information in the Results section.”
Authors’ Reply #2: Please refer to Authors’ Reply #6 to Reviewer 2 (Dr. Nakai).

Comment #3: “There were no figure legends. They should be provided.”
Authors’ Reply #3: We truly apologize for this error. Figures were revised and the legends included in the main manuscript text file at the end of the document. For each figure, the following information was provided: Figure number (in sequence, using Arabic numerals - i.e. Figure 1, 2, 3 etc); short title of figure (maximum 15 words), and; detailed legend (up to 300 words).

Comment #4: “There were no limitations of the study in the manuscript.”
Authors’ Reply #4: In order to address the Reviewer suggestion, the following changes were performed in the revised manuscript:
Page 10, paragraph 2, line 10, the following statement was added to the text: “It should be noted that this study has limitations due to the relatively small number of patients and its cross sectional design. In addition, the misinterpretation of the ICGA findings should always be considered in studies of this nature. Future studies, combining ICGA with other fundus imaging modalities such as fundus autofluorescence and enhanced depth imaging optical coherence tomography may facilitate our understanding of the choroidal involvement in patients with VKH disease [24,25], independent of the degree of disease associated fundus alterations.”

Comment #5: Did the IRB approve the study?
Authors’ Reply #5: The information about IRB approval (and protocol number) was described in the methods section of the original manuscript (Page 5, paragraph 2, line 1): “The study protocol followed the statements of the Declaration of Helsinki and was approved by local Institutional Review Board (#10121/2008).”

We greatly appreciate all the comments made by Dr. Koizumi and hope that each of the issues raised in the review have been resolved with the revision.

Yours sincerely,
Joyce H. Yamamoto
Rogerio A. Costa

Reviewer: CARL HERBORT

Comment #1: “This is a paper that perfectly understands and depicts the disease mechanism of VKH. It is very well known by now that smoldering disease is going on in
non-treated or under-treatment of VKH and this is once more well shown in this study. It is therefore an important study that will contribute to a very much needed change of attitude in the management of VKH disease.”

Authors’ Reply #1: We thank very much the Reviewer for the kindest words about our study.

Comment #2: “Abstract, conclusion: “Therefore, the current study reinforces a possible role…” should be changed to “Therefore, the current study reinforces the crucial role…”

Authors’ Reply #2: As requested by the Reviewer, the following changes were performed in the revised manuscript:

Page 3, paragraph 1, line 1, the following statement:
“…reinforces a possible role…” was changed to “…reinforces the crucial role…”

Comment #3: “Background, first paragraph, last sentence (Whether this slowly..) should be changed to: There is increasing evidence that this slowly progressive fundus pigmentation is related to some disease activity undetected on regular clinical examination, is due to insufficient therapy and does most probably not occur as part of the natural history of VKH disease. (Ref 3 + add new reference: Bouchenaki N, Herbort CP. Indocyanine Green Angiography Guided Management of Vogt-Koyanagi-Harada Disease. J Ophthalmic Vis Res 2011;6:241-248). This new publication and what it says should also be included in the discussion.”

Authors’ Reply #3: In order to address the Reviewer suggestion, the following changes were performed in the revised manuscript:

Page 4, paragraph 1, line 7, the following statement: “Whether this slowly… … remains to be determined” was changed to “There is increasing evidence that this slowly progressive fundus depigmentation is related to some disease activity undetected on regular clinical examination and is due to insufficient therapy; it does most probably not occur as part of the natural history of VKH disease [3].”

Page 9, paragraph 1, line 22, the following statement was added to the text: “The importance of ICGA guided management of VKH disease to meaningfully assess choroidal inflammation has been recently reinforced by Bouchenaki and Herbort [3]. These authors proposed that zero tolerance to subclinical choroidal inflammation could avoid irremediable evolution towards sunset glow fundus [3];”

We greatly appreciate all the comments made by Dr. Herbort and hope that each of the issues raised in the review have been resolved with the revision.

Yours sincerely,

Joyce H. Yamamoto
Rogerio A. Costa