Author's response to reviews

Title: Funduscopic Results after 4-Year Follow-Up Treatment with Ranibizumab for Age-Related Macular Degeneration in a Region of Spain

Authors:

Rosa M. Coco MD, PhD (rosa@ioba.med.uva.es)
M. Rosa Sanabria MD, PhD (rsanabria@ioba.med.uva.es)
Melissa Castrejon MD (melcastrejon@gmail.com)
M. Isabel Lopez-Galvez MD, PhD (maribel@ioba.med.uva.es)
Laura Monje-Fernandez MD (lauriya58@hotmail.com)
Marta Fernandez-Munoz MD (mfernandezmunoz@gmail.com)
Alejandro Anton MD (alexaben78@yahoo.es)
Lourdes de Juan-Marcos MD, PhD (mloujm@hotmail.com)
Sonia Villaron-Alvarez MD (s.villaron@hotmail.com)
Itziar Fernandez PhD (itziar.fernandez@ioba.med.uva.es)

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From the author of Manuscript:

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**Revision requested**

Dear Ms Cruz

Thank you for considering our manuscript to be published in the BMC Ophthalmology and for your comments from August 15th and 28th, 2014.

We appreciate your kind’s suggestions. The manuscript has been modified according to your request.

**Answer to Editorial request**

(1) Requesting name of ethics committee: Please update your ethics statement to include the name of the ethics committee that approved your study.

Done, page 3, lines 26-27.

(2) Requesting for Line Numbering: Please revise your manuscript to include line and page numbers. Authors are asked to ensure that line numbering is included in the main text file of their manuscript at the time of submission to facilitate peer-review. Once a manuscript has been accepted, line numbering should be removed from the manuscript before publication. For authors submitting their manuscript in Microsoft Word please do not insert page breaks in your manuscript to ensure page numbering is consistent between your text file and the PDF generated from your submission and used in the review process.

Done.

(3) An summary of the treatment protocol needs to be included in the paper as many international readers will not be familiar with the publications cited.

Done, another 2 references [13 and 14] have been added too. Page 4, lines 3-6.

(4) The results are confusingly written and it is difficult to determine the important messages here. It might help to clarify the outcome measures in the methods, as there appears to be little structure to the results section at present.
The Results section is organized this way:

- n + demographic data
- Follow-up and VA evolution along it + what you asked about evolution according to the initial VA
- Causes of treatment discontinuation and evolution of this particular group of patient stopping treatment
- Causes to change treatment drug and complications
- Influence of cataract surgery
- Results of different variables according to final VA
- Results in retinal thickness change
- Results according to the type of CNV seen on FA
- Differences related to the associated lesions at base line
- Results on number of visits and injections, and what you asked about more aggressive treatment.
- Results about fellow eyes
- Different variables results according to final macular anatomy and its different subgroups.

But I am happy to change the order if you think that should be done.

The major questions which remain are-
(a) what are the long-term outcomes of treatment. For (a), it would be useful to stratify patients into different groups at presentation - for example recent papers have looked at different outcomes for patients with initial visual acuities of 0 - 0.3, 0.3 - 1.0 and over 1.0 (rather than just dividing them by final visual acuity). This gives a better indication of the prognosis for particular groups of patients, rather than putting them all together.

We added table 2 and referred that table in the text in page 6, line 18. We also added a paragraph at page 8 lines 12-14 giving the final macular state differences according to that grading in initial VA.

(b) what factors predict particular outcomes. I would prefer the authors to address these questions more directly. For (b) it would be good to see an analysis of factors that predict good or bad outcomes at a particular timepoint, e.g. 3 years, and their relative importance. This would also assist with the bias that is introduced in studies such as this which otherwise have variable follow-up durations.

The results on predictive models at different time points would give us an entire paper, so we thought to publish a second paper. We think the present article is long enough as it is, to include this kind of analysis. Also, you have several tables with results on different time points that may help to understand the influence of time. Nevertheless if you think this is necessary, I may add some results on that, but as I told you, I would prefer to write it a different paper.

and (c) how do different treatment regimes affect outcomes. For (c) it may be possible to identify patients treated more aggressively and see if these
outcomes differ (although there may be insuperable biases in this type of retrospective analysis).

Done. Treatment regime is only one that is described in page 4, lines 1-6. There are not different treatment regimes within patients included in this study to avoid biases due to this reason. Nevertheless, with respect to patients receiving more aggressive treatment, remember we had performed an analysis of patients receiving more that 5 injections a year and we have added the only results being statistically significant that we found. Page 7 lines 28-30 and page 8 lines 1-3.

(5) Reviewer 2's comments about the diagnosis of IPCV need to be addressed

I added an statement about cases in which ICG was performed, page 4, lines 26-28, stating that ICG was always performed on suspicious cases of IPCV and in patients with initial poor response to treatment and. In fact diagnosis was confirmed in 4 eyes before starting treatment and 10 eyes confirmed throughout the study as we had already addressed in our paper (page 7, line 16 and lines 22-23).

(6) As a retrospective study, potential sources of bias are important and need to be discussed in more detail - e.g. patients not responding to treatment may be more likely to drop out than patients responding well, improving observed long-term outcomes, etc. etc. This is not really addressed at all in the manuscript.

We already had addressed the retrospective nature of the study as well as the initial number of dropouts as two main limitations of the study, but we have expanded the comment. Page 12 lines 19-24.

Answer to Reviewer 1


Reference added: page 9 lines 21-22.

(2) The limitations of the work are stated, but they said that the VA estimates were recorded as Snellen acuity and converted to the ETDRS equivalent, but in the work they talking about logMar not about ETDRS. That must be clarified.

Done, we corrected the only confusing statement, page 12, line 25.

(3) The title convey what has been found, However the number of injections, visits and visual acuity change should be mentioned in the abstarct.
Answer to Reviewer 2

(1) How can you classify disease activity based on fundoscopic appearance alone? If this was a retrospective notes review and/or OCT was not available or not utilised then this should be stated as so.

We already gave data on that in the paper. As you may see FA was almost always performed before first treatment (we had those data in 206 eyes) -page 7 line 14-, which gave us fundus photographs to be addressed in most patients for the initial visit and to address the initial associated lesions and the fundus status of the contralateral eye.

But mainly, we also had fundus photographs on most OCTs, and this was performed in each visit and each patient –page 4 line 14-, which also gave us data on fundus aspects to be reviewed.

Finally we had fundus photographs available on 287 eyes adding both –page 8 line 8-.

Nevertheless if you think this is not clear enough and we should change the data localization or organization, please let me know, I will be happy to change it according to your criteria.

You list ‘others’ for the side effects not listed – these reasons need to be stated in full either in the appendix or in a table.

I do not quite understand well this concern. I suppose you speak about the list in methods that adds others when we retrieved the causes for treatment discontinuation (page 5, line 12). I eliminated it, because in fact we did not use this item As you can see at the results, we found secondary effects in 5 patients: (2 eyes had a RPE tears; two patients had a stroke, and one had thrombosis), so I think all the secondary effects had already been listed (page 6 lines 25-27).

Secondary effects – you didn’t mention what these were exactly

Yes, we did, as I already said and as you can see at the results, we found secondary effects in 5 patients: (2 eyes had a RPE tears; two patients had a stroke, and one had thrombosis (page 6 lines 25-27).

Did any of your patients have an ICG to visualise the polypoid lesions?

I added an statement about cases in which ICG was performed, page 4, lines 26-28, stating that ICG was always performed on suspicious cases of IPCV and in patients with initial poor response to treatment and.

In fact diagnosis was confirmed in 4 eyes before starting treatment and 10 eyes confirmed throughout the study as we had already addressed in our paper (page 7, line 16 and lines 22-23).

The OCT machines used throughout the study were different – was any attempt made to standardise the readings between the various devices to adjust for
Furthermore, technology exists on modern OCT to calculate a change in CRT from successive OCTs performed.

This has already been widely explained in the methods and discussion of the paper.
Because of this problem, we used the change in retinal thickness with a formula developed by us—page 4, lines 14-25-. This formula gives us a percentage of change in thickness, it does not give us any absolute value of thickness and the obtained data does not have any unit. Because of that results obtained with different machines would be comparable.
Besides, as you may also see in the discussion, we think this is an important contribution of this paper, because our results show a good correlation with the macular morphology on OCT (i.e.: presence of subretinal fluid), and allows uniform results avoiding the bias that could result from the use of different OCT tools, page 11, lines 20-25.
We decided not to use the existing technology of each OCT, because we used different tools, so in either those results would not be comparable. We think the solution we found is probably the best we can apply to our study and we demonstrate that it works well.

It is not clear what this study adds to the current published literature on this topic.

As we said in the covering letter, this is one of the published series with longer follow-up on the use of anti-VEGF treatment in ARMD in clinical practice to date, with an acceptable number of patients included.
It provides data on VA worsening in long follow-up and shows how appearance of atrophy and/or fibrosis preclude vision remaining stable in long follow-up.
Macular Status had never been taken into account in previous studies.
It also adds a new method to compare the retinal thickness measured by OCT different machines (something that may be useful for other multicentre studies), and provides new data on final fundoscopic appearance of these patients for the first time to our knowledge.

Quality of written English: Needs some language corrections before being Published

The paper had been revised by an English speaker professional editor.