Author's response to reviews

**Title:** Effectiveness of intravitreal ranibizumab in exudative age-related macular degeneration (AMD): comparison between typical neovascular AMD and polypoidal choroidal vasculopathy over a 1 year follow-up.

**Authors:**

Wataru Matsumiya (ytkmatsu@hotmail.com)
Shigeru Honda (sighonda@med.kobe-u.ac.jp)
Sentaro Kusuhara (kusu@med.kobe-u.ac.jp)
Yasutomo Tsukahara (tsuka@med.kobe-u.ac.jp)
Akira Negi (negi@med.kobe-u.ac.jp)

**Version: 4 Date: 22 February 2013**

**Author's response to reviews:**

We greatly appreciate the reviewers for many valuable comments on our manuscript. Here, we have provided point-by-point responses to the reviewers’ essential concerns and have revised the manuscript in accordance with their advices.

For Reviewer # Dr..Michael Stewart,

1. What do the authors mean by "typical AMD"? I assume that it refers to occult, classic and RAP lesions. Please specify. Also please provide information about the relative frequencies of each of these lesions in the tAMD group.

   #In this manuscript, we use the term “typical AMD” as neovascular AMD including classic and occult CNV according to the previous report (Maruko I, Iida T, Saito M, Nagayama D, Saito K. Am J Ophthalmol. 2007;144(1):15-22). Therefore RAP lesions were not included. We have mentioned about it in the Method section. In addition, the number of classic CNV and occult CNV has been indicated in the text. (Page 9, Line 111-112)

2. Abstract, Results: rather than saying "repeated measures ANOVA over 12 months" please say that the difference was significant at each time point, or give the p-values for each time point during the year.

   #In our study, we used repeated measures ANOVA to compare the transition in the mean BCVA between subtypes over 1 year of follow-up. The results showed a significant difference in the amplitude of visual improvement between two subtypes (P=0.04). However, as pointed by the reviewer, we have compared the BCVA change between tAMD and PCV at each time point measured. In this analysis, tAMD showed a significantly greater visual improvement than PCV at 3M after the initial treatment (P=0.43 at 1M, P=0.036 at 3M, P=0.066 at 6M and P=0.11 at 12M). We have added this description in our revised manuscript. (Page 12, Line 167-171)
3. Abstract, Conclusion: I don’t know what the authors mean by the first sentence. Please re-write
#We have revised the sentence to make the conclusion clear. (Page 3, Line 45-46)

4. Introduction, first sentence: actually bevacizumab is the drug of first choice for most retina surgeons - according to US Medicare utilization and ASRS PAT survey. Please amend this sentence.
#Actually bevacizumab was used at a higher rate than ranibizumab for the treatment of neovascular AMD in 2008. (Brechner RJ, Rosenfeld PJ, Babish JD, Caplan S. Am J Ophthalmol. 2011;151(5):887-895.) Therefore we have amended the sentence. (Page 5, Line 53)

5. Introduction: the MARINA and ANCHOR treated patients monthly. They did not provide any evidence regarding the importance of 3 loading doses.
#As pointed, the MARINA and ANCHOR did not show any evidence regarding the importance of 3 loading doses. However, the VA improvements observed with ranibizumab in the first 3 months were sustained and some additional improvement was seen over the trial period in those study. (ref. #7). We have amended the corresponding sentence. (Page 5, Line 59-62).

6. How were the 54 patients identified? Were these ALL the patients seen during the time period that satisfied the entry criteria?
#This is a consecutive case series of tAMD and PCV who received IVR between April 2009 and April 2011 and satisfied the entry criteria. (Page 8, Line 91-92)

7. Page 8: should read "...3 consecutive monthly injections..."
#We thank the reviewer for this comment. We have amended corresponding sentence. (Page 9, Line 120).

8. Was visual improvement in the tAMD group statistically better than the PCV group at each time point?
#Please check our answer to the question #2 and the additional sentences in our revised manuscript. (Page 12, Line 167-171)

9. The number of retreatments (0.9, 1.2) is very small compared to trials such as CATT. How do the authors explain this?
#The number of retreatment in our study was smaller than CATT probably because the retreatment criterion in CATT was more strict than that in the present study. However, it is unknown why the number of retreatment in our study was smaller than PrONT0 and SUSTAIN whose retreatment criteria are comparable to the present study. In the clinical practice, there might be an extended interval between a decision of retreatment and the actual treatment in our study. (Muether PS et al. Graefes Arch Clin Exp Ophthalmol. 2013 Feb;251)
We have mentioned about this limitation in our revised manuscript (Page 18, Line 247-250).

10. The authors need to take care when comparing visual improvements between the 2 groups. Though the improvements were statistically greater in tAMD patients, these patients started and finished with worse visions than those with PCV. Though the groups were not statistically different at baseline (p=0.09) they were very close. Therefore, one could argue that tAMD patients improved more because they started with worse vision. Poorer vision is known to correlate with greater improvement. The authors need to address this in their Discussion and state that further studies with more patients and better matched groups are important.

#As pointed by the reviewer, the Ceiling effects may affect our results (ref. #37). On the other hand, we showed that baseline visual acuity was not a prognostic factor for an improvement in the BCVA at 12months by logistic regression analysis. Therefore we believe that the lesion phenotype (tAMD vs. PCV) was a significant prognostic factor for an improvement in the BCVA after the treatment with IVR. We have discussed about this issue in our revised manuscript (Page 18-19, Line 263-269).

For Reviewer # Dr. Timothy Lai,
1. OCT measurement. The OCT measurements might not be accurate as it was unclear how PED were measured.

#The state of PED was not count in our retreatment criteria according to PrONTO study. Hence we did not measure the height or volume of PED.

2. Methods. Were ICGA performed to assess for change in polyp? This is an important issue to decide retreatment.

#We agree that the change in polyp lesions is an important issue to estimate the effectiveness of IVR in the PCV cases. However, the state of polyp lesions was not count in our retreatment criteria according to PrONTO study. Therefore we repeated FA and ICGA as needed at the discretion of the investigators. We have described about this issue in our revised manuscript (Page 9-10, Line 124-126).

3. The number of prior PDT should be stated and included in the analysis. This might influence the treatment outcome.

#We have indicated the number of PDT as 1) no history of PDT, 2) a single session of PDT 3) repeated performance of PDT in the tAMD and PCV groups in Table 1. Furthermore, we have performed a multivariate logistic regression analysis including the number of PDT as an explanatory variable, which did not show the number of previous PDT as a significant prognostic factor. (Page 10, Line 141)
4. The duration of symptoms is another important confounding variable and should be included in the analysis.

We agree with the reviewer’s concern, but it was difficult to determine the duration of symptoms accurately in each patient from the medical records. Therefore we could not evaluate the influence of this factor on the treatment outcome. We have mentioned about this limitation in the text.

Minor revision:
1. Introduction. The EXTEND-I study has previously evaluated the use of ranibizumab for Japanese AMD patients and should be added.

As pointed by the reviewer, we have added the EXTEND-I study in the revised manuscript. (Page 5, Line 61-62).

For Reviewer # Dr. Takashi Ueta,
1. Page 2. In the method section, the design of the study, retrospective cohort, should be explained.

We have added in the Method section. (Page 2, Line 31).

2 Page 6. “no comparative studies have not been published on the effectiveness of IVR associated with these different phenotypes of AMD” should be corrected because of the previous report in AJO as well as the author’s previous report (J Ophthalmol 2011;2011:742020).

We have corrected corresponding sentence. (Page 6, Line 77-80).

3. In the discussion section, several limitations such as relatively small sample size or retrospective design should be mentioned.

As pointed by the reviewer, there were some limitations in our study. Thus, we have added them in our revised manuscript (Page 18-19, Line 263-269).

The revised parts are indicated in red. We hope that this improved manuscript is suitable for publication in “BMC Ophthalmology”.

Sincerely yours,
Shigeru Honda