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30th January, 2019

Dear Prof Kaye,

**RE: Submission of revised paper - Manuscript ID bmjophth-2018-00024**

Title: 5 year outcomes of retinal vein occlusion treated with vascular endothelial derived growth factor inhibitors.

By: Dr Andrew Chang et al

Thank you for your email dated 23rd December 2018 enclosing the reviewers’ comments. We have carefully reviewed the comments and have revised the manuscript accordingly. Our responses are given in a point-by-point manner below. Changes in the manuscript are shown in red.

We hope the revised version is now suitable for publication and look forward to hearing from you in due course.

Sincerely,

A/Prof Andrew Chang

**FORMATTING AMENDMENTS (if any)**

**Required amendments will be listed here; please include these changes in your revised version:**

**1. The abstract should be followed by a key messages box which outlines the significance of the study. This should address the following questions:**

**What is already known about this subject?**

The efficacy and safety of anti-VEGF therapies for the treatment of macular oedema secondary to retinal vein occlusions has long been established, however, clinical trials only present up to 2 years of outcomes.

**What are the new findings?**

The present study assesses the long-term efficacy of anti-VEGF therapy over 5 years in a real world clinical study. We have demonstrated that the number of anti-VEGF injections did not decrease from 2 to 5 years in contrast to eyes with diabetic macular oedema.

**How might these results change the focus of research or clinical practice?**

Long-term gains demonstrated in this study reassure all to the substantial gains that can be achieved albeit with ongoing anti-VEGF therapy.

**2. Figure file format**

**Please note that we do not accept figures in Word document, PowerPoint.**

**All figures and images should be supplied as high quality image files, we recommend TIFF, JPG/JPEG or PDF format. Please ensure images are a minimum of 300dpi and a maximum of 600dpi (resolution).**

We will upload amended figures in required format.

**3. Statements**

**Please include the following statements in the main document file, which should match the details given in the submission pages:**

**a. Contributorship Statement**

**b. funding**

**c. competing interests**

**d. acknowledgement**

Updated thank you

**Response to Reviewer 1:**

**Thank you for your review of our paper. We have answered each of your points below.**

**1. It was a retrospective study. It is well known that retrospective studies have many confounding factors which can result in less reliable information than a planned, prospective study.**

We understand the limitations of retrospective studies and have amended the limitations section accordingly to give a more thorough explanation of confounding variables.

**2. This is not the first study on the subject. There is already a 5 year follow-up, cross‐sectional study of consecutive patients with macular oedema due to RVO. (see Acta Ophthalmol. 2015;93:719-25.). Spooner and colleagues’ comment that that study “raises doubt as to the representability of the data” is not valid.**

Thank you for your comments. We have adjusted this conclusion to be “This may not be representative of the initial cohort”.

**3. Question: what criteria were used to diagnose “Ischaemic type”?**

Ischaemic type was defined as more than 10 disc areas of retinal capillary non-perfusion based on FFA, which has been added to the methodology (Page 6).

**4. The authors state: “Treated with bevacizumab only, 11 eyes (16%) were switched from bevacizumab to ranibizumab, 4 eyes (6%) were switched from to aflibercept, 2 eyes (3%) were treated with ranibizumab only, and 8 (12%) patients were treated with all 3 agents during the course of their treatment…………………. Of the 1,970 anti-VEGF injections administered in the study eyes during the study period, 355 (18%) were ranibizumab, 1,498 (76%) were bevacizumab, and 117 (5.9%) were aflibercept. Most patients received repeated injections of a single anti-VEGF agent, but in 33.8% of patients, the type of anti-VEGF therapy used was switched at least once during the study period……… Six patients (9%) required additional focal/ grid laser treatment……”**

**This shows that the patients were a “mixed bag” of cases.**

**(a) It has been shown that although bevacizumab, ranibizumab and aflibercept are all anti-VEGF agents, the response of macular oedema to them varies. The authors themselves stated: “In our study, switching to ranibizumab or aflibercept, was associated with a significant improvement in VA”.**

**(b) Macular laser treatment had been applied to 19% of the eyes prior to initiation of anti-VEGF therapy. That is an important confounding factor in the study.**

**Therefore, it is not a clean study. It contains patients treated not only with three different anti-VEGF drugs but also using panretinal photocoagulation. In view of that, the authors need to present results of different groups separately, instead of lumping them all together. The application of photocoagulation, especially, vitiates the results.**

We have amended the results to separate BRVO and CRVO as well as those which received laser and where anti-VEGF agent was switched.

**5. The effect of a treatment on a disease must be compared with the natural history of the disease before it can be determined to be valid. The authors have not done that. A paper published in the journal Retina (Retina 2015;35:1016-1027.) describes the natural history in 214 consecutive RVO patients.**

Thank you for your comments. We have included comparison to the natural history within the discussion.

**6. Branch RVO is of two types: major and macular BRVO, with different characteristics and degrees of macular oedema. The authors have combined those into one category. Similarly, CRVO is either ischaemic or non-ischaemic, and macular oedema and visual outcome is very different between the two types. The authors once again grouped those into one category. This is misleading.**

We were not able to separate major and macular BRVO as this information was not collected. However, we have reported the outcomes for ischaemic and non-ischaemic CRVO separately.

**7. It is well-known that long lasting macular oedema usually produces secondary retinal pigment epithelial changes, which themselves result by in poor visual acuity. There is no mention of that.**

Thank you for your comments. We have now addressed this in the manuscript. (Introduction, page 2)

Data on RPE changes secondary to chronic CMO were not collected in our study and hence we have not been able to include this information in the manuscript.

**8. There are several reports that repeated injections of anti-VEGF drugs result in ocular hypertension and glaucoma. The author state that “twenty eyes were treated for IOP rise with topical medications (increase in IOP of >10mmHg from baseline)”. They do not mention whether that was a complication of repeated intravitreal injection of anti-VEGF drugs, or the well-known association of ocular hypertension/glaucoma with CRVO, or both.**

Thank you. We have clarified in the results that this was due to ocular hypertension associated with CRVO. (results, page 11)

**9. The authors state: “One eye developed rubeosis, receiving laser PRP. Five eyes (7%) underwent phacoemulsification during the course of follow-up. One patient was diagnosed with myelofibrosis”. Iris neovascularisation is a complication of ischaemic CRVO and is often associated with angle neovascularisation as well, which results in raised IOP. All these factors act as confounding factors in such a study; therefore, all these patients need to be deleted.**

Being a real world retrospective clinical study we feel that eliminating these variables may not be representative of a true patient population and the inclusion of these safety outcomes was intentional to reduce bias. Cataract development/extraction is not an uncommon occurrence in eye with ocular disease undergoing treatment and hence we believe these eyes should be included.

**10. The study included 68 eyes from 66 patients. Table 1 gives information about “Demographic and Clinical Characteristics of Included Patients”. But this table includes mixed information about eyes and patients, which is not correct.**

Thank you for your comments. We have removed the data pertaining to the whole cohort for clarification.

**11. In Fig. 1 graph, to give information about “All” is not valid, for the following reasons.**

**(a). The extent of retinal involvement in CRVO and BRVO is not identical, although both do have macular oedema. Moreover, as mentioned above, BRVO is of two types, macular or major BRVO, with different findings of macular oedema and visual outcome. Similarly, CRVO is of two types, ischaemic and non-ischaemic, with very different fundus findings and visual outcomes.**

**(b). The authors state: “The vision at the end of 1-year was a predictor for the final VA at year-5 (R2==0.66, p<0.001).”; but this is based on “All” eyes combining CRVO + BRVO eyes; that is highly misleading and completely invalid because it is combining 4 different diseases (with different visual outcomes) into one group. Moreover, the graph does not support that, because in CRVO VA is poorer after one year, while in BRVO it is better after one year.**

**(c). As for changes in central foveal thickness, in CRVO the one-year and five-year findings are similar, but in BRVO it is worse at 5 years than at one year.**

**This shows that their findings from “All eyes” are misleading.**

Thank you for your comments. We have removed the data pertaining to the whole cohort, and have amended results accordingly to better differentiate between RVO subtypes.

**12. They had only two eyes with hemi-RVO; it is quite wrong to compare findings in only 2 eyes with 34 eyes with CRVO. In view of that, the findings of the hemi-RVO cases should be deleted. Similarly in Table 2, giving visual acuity information on “All eyes” is misleading; it should be categorized according to the type of RVO.**

We did not compare HRVO to CRVO in our study. Instead we included HRVO with CRVO sub-type, as HRVO is commonly referred to as a variant of CRVO and generally has similar outcomes to CRVO. We have subdivided Table 2 by RVO subtype as suggested, thank you.

**13. In their study, 32 eyes were classified as BRVO; 34 CRVO and 2 hemi-RVO. However, Table 1 states 31 BRVO and 37 CRVO/HCRVO.**

Thank you for your comments. The typo in the tables have been adjusted to the correct numbers.

**14. In the third paragraph on page 8, the authors first state: “Two eyes from 2 patients were excluded from the measurement of FAZ due to a high quantity of motion artefacts.” And then they go on to state: “FAZ measurements were obtained for both patients with macular ischemia and non-ischemic patients”. Then they write: “Mean VA was negatively associated with macular ischemia (R2=-0.63, P=0.05); those eyes with no macular ischemia had better visual acuity.” It is well-established that the level of VA depends upon the integrity of the macular retina. All this information is supposed to apply to 2 patients who were excluded. All this description is highly confusing.**

The description relates to all patients, except the 2 that were excluded.

**15. The authors imply that the results from clinical trials do not reflect real world population. This is not true, because the latter group is heterogeneous, with multiple confounding factors to muddle the results, while in clinical trials the data are collected prospectively and carefully, to provide scientifically reliable information. Their argument that “Participants in clinical trials tend to be healthier on average” is not correct at all; clinical trials select patients with retinal vein occlusion (or whatever the condition under study may be), regardless of their general health. In clinical trials, funding agencies, ethics committees, and medical journals scrutinize the scientific rationale and validity of findings, which is not the case in a study dealing with the “real world population”.**

Thank you for your comments. Prospective randomised clinical trials do indeed offer stringent criteria to exclude confounding variables. However, many patients with the disease to be studied are excluded because of this. One such example, is the ability to reliably meet the study visit schedule. Patients with multiple comorbidities cannot always meet this requirement. Similarly, if too many visits are missed in a clinical trial, then, those patients are often excluded from the trial. For this reason, it is important to report real world data as well as clinical trial data.

We wanted to describe a true clinical patient population, hence confounders to treatment were included. We were not perhaps clear in our original manuscript, so with your suggestions we have stated confounders in our limitations. (page 15)

**16. The authors state: “Macula oedema was absent on SD-OCT imaging at 5-years in the majority of patients (65%). In the RETAIN, whilst 50% of BRVO eyes had resolution of macular oedema at 4 years, just 44% of CRVO eyes had resolution of macular oedema.” The pattern of resolution of macular oedema in CRVO and BRVO is not similar; it tends to resolve earlier in BRVO than in CRVO. The study by Spooner and colleagues was not only retrospective but also consisted of a mixture of CRVO and BRVO. It is a mistake to make comparison with those studies.**

We have removed this comparison from the paper.

**Reviewer: 2**

**Comments to the Author**

**appreciate the opportunity to review the work of Dr. Chang et al, ''5 years outcomes of retinal vein occlusion treated with vascular endothelial derived growth factor inhibitors.''**

**The paper is well written and provides a welcome addition to the literature providing long-term data on patients with anti-VEGF for RVO related CME.**

**I have the following comments:**

1. **The study includes a small number of eyes. This needs to be acknowledged in the limitation section.**

Thank you for your comments. We will include as a limitation.

1. **Figure 3 is not very useful in my view. I suggest removing it.**

Thank you for your comments. We are unsure whether to respond to this reviewer and remove it or respond to reviewer one who preferred greater differentiation between BRVO and CRVO outcomes. We have thus kept the figure but if the editor feels otherwise, will remove it.