Author’s response to reviews

Title: Repeated intravitreal injections of antivascular endothelial growth factor in patients with neovascular age-related macular degeneration may increase the risk of ischemic optic neuropathy

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Author’s response to reviews:
Dear Editors and Reviewers,

Thank you for your comments. The point-by-point response was listed below.

Sincerely,
Dr. Yu-Yen Chen

Comments from the editor:
Editor Comments:

1. Please include a 'Conclusions' section in the main text.
   Answer: Thank you for your comment. I have added the ‘Conclusions’ section. Please see Line 316-325:

   “Conclusions
   Currently, intravitreal injection of anti-VEGF has become the mainstay of treatment in neovascular AMD. Our study, revealed the possible complication of ION after repeated injections. Our recommendation is not to oppose treatment or change the protocols, which require more time and additional studies. At present, our study is simply a reminder for ophthalmologists to check optic nerve
changes following anti-VEGF injections among neovascular AMD patients, especially those who receive a high number of injections. The risk of ION should also be considered when determining the use of anti-VEGF injections for the treatment of neovascular AMD.”

2. Please rename the section 'Ethical approval' to 'Ethics approval and consent to participate'. If consent was not required, please provide details of why this was waived and the institution/committee who approved this. Please provide details in the Ethics and Consent to Participate section.
   \ Answer: Thank you for your comment. I have revised the section according to your comment. Please see Line 337-341:
   “Ethics approval and consent to participate
This study was approved by the ethical committee of Yang-Ming University Hospital (2015A018). The informed consent was exempt according to the Institutional Review Board because each patient record was anonymized and de-identified prior to analysis.”

3. Please include a point-by-point response to the editor's and the reviewers' comments, describing any additional experiments that were carried out. Please also ensure that all changes to the manuscript are indicated in the text by highlighting or using track changes.

   \ Answer: Thank you for your comment. The point-by-point response was listed below. All the changes to the manuscript are indicated using track changes. The manuscript with track changes has been uploaded (file name: revision_with track changes).

Reviewer reports:
Reviewer 2 (Reviewer 1): GENERAL COMMENTS:
I read and reviewed the manuscript entitled "Repeated intravitreal injections of antivascular endothelial growth factor in patients with neovascular age-related macular degeneration may increase the risk of ischemic optic neuropathy".

The topic is interest and the work is well done.
I have some suggestions on the present study as below.
REQUESTED REVISIONS:

1. First, the lack of ocular demographics such as visual acuity, intraocular pressure values may strengthen the study.
   If these can not be done, it should be mentioned in the limitations of the study.
   \ Answer: Thank you for your comment. We have mentioned it in the limitations of the study. Please see Line 273 and line 276-277:
   “One limitation of our study is the lack of visual acuity and IOP values in our NHIRD.”
   “Further clinical studies are necessary in order to include these information.”

2. Secondly, the association of the metabolic vascular disease particularly hypertension and diabetes mellitus affect the ION incidence. Although authors mentioned this association, I suggest to add a few discussion about this issue.
   Besides, also they mentioned that group III had higher incidence of ION, older patients (even reported no difference between groups) tend to have more morbidities including DM, HT, ischemic cardiac disease etc that may exist with ION.
Answer: Thank you for your comment. I have added a paragraph in the Discussion Section according to your comment. Please see Line 283-293:

“Patients in the groups with higher numbers of intravitreal anti-VEGF injections were significantly older and had a significantly higher prevalence in hypertension, hyperlipidemia, and ischemic heart disease. These systemic factors may have affected the incidence of ION. Additionally, older people tend to have more comorbidities including diabetes, hypertension, and ischemic heart disease, which may coexist with ION. These confounding effects potentially complicated our analyses. We tried as possible as we could to adjust these factors in the Cox regression. However, from the perspective of epidemiology, not all confounders were measurable and could be adjusted with statistical methods. Therefore, randomized control trials are still needed to address this issue.”

3. Thirdly, I agree with the authors that mentioned a potential mechanism may be the transient IOP elevation after intravitreal injection of anti-VEGF. Moreover, I think that the mechanism of the Anti-VEGFs needed to be evaluate with respect to their prevention of new vessels as well as collateral vessels as in heart. One may think that to prevent the new vessel formation in the retina or choroid, it may result with inadvertent regression of the collateral vessels of the optic nerve head. This may cause an increased risk of ischemic optic neuropathy particularly in patients who received multiple doses of AntiVEGFs

Answer: Thank you. I have emphasized this point of view according to your comment. Please see Line 97-102:

“One potential mechanism may be transient IOP elevation after intravitreal injection of anti-VEGF. Another possible explanation may be due to the properties of anti-VEGF. Anti-VEGF not only inhibits the formation of the neovasulature from the choroid, but also might result in inadvertent regression of the collateral vessels of the optic nerve head. Thus, increasing the number of injections may increase the risk of developing ION.”

4. Fourthly, The Anti-VEGFs used in their study was not mentioned. An off-label drug, bevacizumab and other licensed drugs such as aflibercept, ranibizumab, etc. If possible to compare their effect on ION, what are the difference? this may be strengthen their study

Answer: Thank you. I have addressed the limitation in the Discussion Section according to your comment. Please see Line 274-277:

“In addition, we retrieved patients receiving anti-VEGF injections through the procedure codes, but we could not differentiate what kind of anti-VEGF the patients received. These are the inherent drawbacks of our database. Further clinical studies are necessary in order to include these information.”

5. Finally the question is " Do we observe higher incidence of ION in patients receive higher number of intravitreal injections? or The patients need is higher in these patient population who tend to develop ION?" These may be discussed.

Answer: Thank you. I have added this in the Discussion Section according to your comment. Please see Line 306-314:

“We cannot conclude a causal relationship between repeated anti-VEGF injections and ION. Most likely, the observation that a higher incidence of ION in patients receiving more anti-VEGF injections only reflects a greater need for anti-VEGF in those patients who tend to have ION. At present, all analyses were based on our database, and we derived a positive association between repeated anti-VEGF injections and ION. The underlying mechanism of the association is still not fully understood. Further basic research, animal models, and possibly large-scale prospective cohort studies are needed to unravel the pathogenesis.”
6. The lack of control subjects with similar demographics may be discussed at least in the limitations paragraph.

Answer: Thank you for your comment. We have added this limitation in the Discussion Section. Please see Line 278-293:

“Another limitation of our study is that we lacked controls with similar demographics. More studies regarding the comparison of ION risk between those with anti-VEGF and matched controls (without anti-VEGF) are warranted. In our study, patients who underwent fewer than 10 injections (the first-level group) were regarded as the reference group. However, the first-level, second-level, and third-level groups did not have similar baseline characteristics. Patients in the groups with higher numbers of intravitreal anti-VEGF injections were significantly older and had a significantly higher prevalence in hypertension, hyperlipidemia, and ischemic heart disease. These systemic factors may have affected the incidence of ION. Additionally, older people tend to have more comorbidities including diabetes, hypertension, and ischemic heart disease, which may coexist with ION. These confounding effects potentially complicated our analyses. We tried as possible as we could to adjust these factors in the Cox regression. However, from the perspective of epidemiology, not all confounders were measurable and could be adjusted with statistical methods. Therefore, randomized control trials are still needed to address this issue.”

7. A minor comment: "Neovascular age-related macular degeneration (AMD) is characterized by the proliferation of abnormal blood vessels (neovasculatures) in the choroid and can cause severe vision loss." "in the choroid" or "from the choroid"???

Answer: Thank you. I have changed the sentence “in the choroid” to “from the choroid”. Please see Line 75-77:

“Neovascular age-related macular degeneration (AMD) is characterized by the proliferation of abnormal blood vessels (neovasculature) from the choroid and can cause macular edema and severe vision loss.”

Prof. Matias Iglicki (Reviewer 2):

1. please add on the keywords this does not match with the manuscript

Answer: Thank you. We have added the keywords. Please see Line 68-70:

“Keywords: intravitreal injection, antivascular endothelial growth factor, neovascular age-related macular degeneration, ischemic optic neuropathy, cohort study, risk factor, National Health Insurance Research Database”

2. The authors should express why is relevant for AMD patient to stop using ANTI VEGF early en the current algorithm

Answer: Thank you. We have added the explanation in the Method Section according to your comment. Please see Line 143-146:

“During the follow-up period, fundoscopy, FA, and OCT were performed regularly. If the neovasculature and fluid resolved and if no relapse occurred, the treatment with injections was ended.”

3. The authors should explain why their findings make a different for ophthalmologist around the world and for the readers of BMC Ophthalmology.

Answer: Thank you. We have added this in the Conclusion Section. Please see Line 315-325:

“Conclusions
Currently, intravitreal injection of anti-VEGF has become the mainstay of treatment in neovascular
AMD. Our study, revealed the possible complication of ION after repeated injections. Our recommendation is not to oppose treatment or change the protocols, which require more time and additional studies. At present, our study is simply a reminder for ophthalmologists to check optic nerve changes following anti-VEGF injections among neovascular AMD patients, especially those who receive a high number of injections. The risk of ION should also be considered when determining the use of anti-VEGF injections for the treatment of neovascular AMD.”

4. The authors should explain the source of the information and what were the criteria they used for adding to the paper. Were the assessors masked? What was the ICC between them in order to analyze the data? Was the randomization digitalized?

Answer: Thank you. We have added the explanations according to your comments. Please see Line 120-124:

“Datasource
The NHIRD was derived from the Taiwan National Health Insurance Program, which covers more than 99% of Taiwan’s 23 million residents. The NHIRD contains all the original claims data from the program and is released annually by the National Health Research Institute in an electronically encrypted form.”

Please see Line 131-135:

“Study subjects
We conducted a retrospective cohort study from January 1, 2007, to December 31, 2013. First, we selected patients from the NHIRD who were diagnosed with neovascular AMD (ICD-9-CM code 362.52) during the study period, which required confirmation by fundoscopy, fluorescein angiography (FA), and/or optical coherence tomography (OCT).”

Please see Line 140-143:

“If patients were found to have an obvious choroidal neovascuclature and fluid in fundoscopy/FA/OCT, they were treated with intravitreal anti-VEGF. Those who received intravitreal anti-VEGF injections for the treatment of neovascular AMD were included in the study cohort.”

Please see Line 295-299:

“In our health care system, the National Health Administration (NHA) frequently checks the cross-consistency of claims and chart data. The NHA also confirmed diagnoses that have been approved by a standard protocol of examinations. Therefore, the diagnoses in our database have a high degree of accuracy.”

5. Please add references and rephrase the sentence. English grammar should be applied in the whole introduction section

Answer: Thank you for your comment. The whole manuscript has been edited by American Journal Expert (AJE).

6. Please add in the introduction that papers have been published showing use of injections in the current treatment of macular diseases (add a sentence in the introduction part and also add this in the reference section. This 7 papers should be add in the manuscript and in the reference section. You refer LASER and anti-VEGF agent but not corticosteroids. If you don't add a sentence of this papers this could be bias.

DEXAMETHASONE IMPLANT FOR DIABETIC MACULAR EDEMA IN NAIVE COMPARED WITH REFRACTORY
EYES: The International Retina Group Real-Life 24-Month Multicenter Study. The IRGREL-DEX Study.
Iglicki M1, Busch C2, Zur D3,4, Okada M5, Mariussi M6, Chhablani JK7, Cebeci Z8, Fraser-Bell S9, Chaikitmongkol V10, Couturier A11, Giancipoli E12, Lupidi M13, Rodríguez-Valdés PJ14, Rehak M2, Fung AT15,16,17, Goldstein M3,4, Loewenstein A3,4,17.


Answer: Thank you for your comment. We have added these information in the Introduction Section and these literature in the Reference Section. Thank you.
Intravitreal injection of steroids has the effect of decreasing macular edema [1-6].”

Please also see Line 369-393 in the Reference Section (reference 1-6):


7. please add how, and how long takes for a retina specialist to switch in their mind the mandatory use of Anti VEGF in AMD thinking on Ischemic of the ON
   Answer: Thank you for your comment. We have added these in the Conclusion Section. Please see Line 318-325:
   “Our recommendation is not to oppose treatment or change the protocols, which require more time and additional studies. At present, our study is simply a reminder for ophthalmologists to check optic nerve changes following anti-VEGF injections among neovascular AMD patients, especially those who receive a high number of injections. The risk of ION should also be considered when determining the use of anti-VEGF injections for the treatment of neovascular AMD.”

8. Results could be misinterpreted add a short summary of the similarities in different OCT devices and
also add different OCT modalities SD, swept source EDI etc and what can be improved in the process of detecting AMD is mandatory in the discussion section.

Answer: Thank you for your comment. We have added these information according to your comment.

Thank you.

Please see Line 135-138:
“In cases of neovascular AMD cases, FA can detect the presence of lesion and determine the size and location of the choroidal neovascularization. OCT can define the cross-sectional architecture of the retina and can reveal the presence of subretinal and intraretinal fluid.”

Please see Line 299-305:

“It is noteworthy that in the diagnosis of neovascular AMD, OCT plays an important role. Although the brand or type of OCT machine is not exactly the same in every hospital or clinic, these machines are all useful for detecting the neovascularure and fluid. Some newer modalities, such as spectrum domain OCT, swept source OCT, enhanced depth OCT, and OCT angiography can provide earlier detection of the choroidal neovascularure and can be applied in additional research.”

9. Please apply correction for misspelling and English grammar

Answer: Thank you. We have corrected the misspelling and English grammar with the editing service of the American Journal Expert (AJE).

10. This paper should be corrected by an English redactor

Answer: Thank you. The American Journal Expert (AJE) has corrected the whole manuscript. Thank you very much.