Author’s response to reviews

Title: A Single-Center Retrospective Study of Factors Related to the Effects of Intravenous Glucocorticoid Therapy in Moderate-To-Severe and Active Thyroid-associated Ophthalmopathy.

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Author’s response to reviews:

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Dear Editor,

Thank you very much for your letter and advice on our manuscript. We have resubmitted new version of manuscript in accordance with the style of BMC Endocrine Disorders. We have addressed the comments raised by reviewers, and the amendments are highlighted in red in the revised manuscript. We hope that the revision is acceptable and look forward to hearing from you soon.

Our specific comments to reviewers are as follows:
Christine May (Reviewer 2)

1. The statistics still require a review by a statistician.

Response: Thank you very much for the advice. Our manuscript has been reviewed by a statistician Dr. Tienan Feng in Clinical Research Center, Shanghai Jiao Tong University Medicine School. And the other reviewer also stated that he could assess the statistics.

2. Your choice of patient has limited your results. Because of the retrospective nature you could have included all patients with TAO, including those who did not have ivGC (including those graded as severe and who were excluded). This biases your results and limits the conclusions you can draw from this.

Response: Thank you very much for the advice. In EUGOGO 2016, 4.5 g ivGC (0.5 g per week for 6 weeks, followed by 0.25 g per week for 6 weeks) is the first line of treatment for moderate-to-severe TAO. Higher doses ivGC can be used for severe TAO. Actually, for severe TAO, we used 0.5 g glucocorticoids per day for 3 days and then performed orbital decompression surgeries. In our study, we hope to find possible factors related to the effects of 4.5 g ivGC in moderate-to-severe TAO. So we did not include severe TAO in our study. Other studies (Shen 2014, Sisti 2015, Xing 2015 and Leo 2016) which focused on the possible factors related to the effects of 4.5 g ivGC in TAO also only included moderate-to-severe TAO. We are sorry because we should have made it more clear in the title and abstract. (Page 1 Line 2 and Page 1 Line 21)

EUGOGO 2016: “High-dose glucocorticoids (GCs), preferably via the intravenous route, are the first line of treatment for moderate-to-severe GO. The optimal cumulative dose appears to be 4.5–5 g of methylprednisolone, but higher doses (up to 8 g) can be used for more severe forms.”

Shen 2014: Circulating microRNA predicts insensitivity to glucocorticoid therapy in Graves' ophthalmopathy. Endocrine.

Sisti 2015: Age and Dose Are Major Risk Factors for Liver Damage Associated with Intravenous Glucocorticoid Pulse Therapy for Graves' Orbitopathy. Thyroid.

Xing 2015: Smoking was associated with poor response to intravenous steroids therapy in Graves' ophthalmopathy. Br J Ophthalmol.

Leo 2016: Variables affecting the long term outcome of Graves' orbitopathy following high dose intravenous glucocorticoid pulse therapy in patients not treated with orbital radiotherapy. Endocr Pract.

3. Roc curves and discussions on diagnostic accuracy have no place in this retrospective audit.

Response: Thank you very much for the advice. We are sorry for the missing of ROC curves and discussions on diagnostic accuracy. In our revised manuscript, we added four ROC curves
including three single-variable prediction models and one multivariable prediction model (Page 11 Line 5, Figure 1). As significant interactions were observed between the pretreatment CAS and both the duration of eye symptoms and restoration of euthyroidism according to the interaction analysis (Table 5), we excluded the pretreatment CAS and used the duration of eye symptoms and restoration of euthyroidism to establish the multivariable prediction model. Due to the analysis of area under curve (AUC), the multivariable prediction model was better than the single ones with an AUC of 0.784 (95% CI, 0.685–0.882, p=0.000) (Page 10 Line 13).

As to diagnostic accuracy, we found the cut-off of duration of eye symptoms was 13 months and the cut-off of pretreatment CAS was 2.5 points which were presented in results part (Page 10 Line 13). We believed prompt diagnosis and treatment (within 13 months) is important (Page 13 Line 9). After literature review, we found that the cut-off of pretreatment CAS was different with previous studies. The possible reasons might be the relatively small sample size and the different orbital anatomy between Caucasians and Asians, which were presented in discussion part (Page 12 Line 11). Besides, we hope to verify the multivariable prediction model in larger cohorts. Hope it can be used to predict ivGC efficacy and facilitate the selection of suitable patients (Page14 Line 2).

4. I am afraid I still don't understand where an ex-smoker falls and what a passive smoker is.

Response: We discussed the different outcomes of three different studies including Xing 2015, Leo 2016 and our study. In Leo 2016 and our study, we found smoking status was not a factor that was significantly associated with the effects of ivGC therapy. But in Xing 2015, smoking is reportedly associated with a poor response to glucocorticoid therapy. One possible reason for this difference might be the different definitions of smoking status. In Xing 2015, patients were divided into three groups: Never smokers, Passive smokers and Active smokers. Patients who had never smoked throughout their lives and had never breathed in the smoke from other people’s cigarettes throughout their lives were considered as never smokers. Patients who had never smoked themselves but breathed in the smoke from other people’s cigarettes were considered as passive smokers. The others were considered as active smokers. They compared active smokers and never smokers. In Leo 2016 and our study, we compared active smokers and never smokers plus passive smokers. (Page 14 Line 15)

Xing 2015: active smokers vs. never smokers

Leo 2016 and us: active smokers vs. (never smokers + passive smokers)

5. Did you have all data points for all 90 patients? How complete is your data e.g. do you have smoking status for all 90, if not how many are you missing data this helps with reliability of your data.

Response: Thank you very much for the advice. We have smoking status for all 90 patients. We have all data points for all 90 patients except 4 patients’ data of “Restoration of euthyroidism”.
6. Do you have comorbidities of your patients? This may impact on your outcomes.

Response: Thank you very much for the advice. We excluded patients with abnormal heart, liver and kidney function before ivGC therapy, because we feared for their intolerance to high-dose glucocorticoids. For these patients, we usually recommended orbital radiation therapy or steroid-sparing immunosuppressive therapy. So we thought there was no comorbidity which may impact patients’ response to ivGC therapy in our study. So we did not include comorbidities information in our manuscript. To make it more clear, we added “abnormal heart, liver and kidney function” in exclusion criteria (Page 6 Line 8).

7. On table for inclusion exclusion criteria- number 5 is exclusion. This sold be in a separate row, maybe just split table into 2.

Response: Thank you very much for the advice. We followed the suggestion. (Page 6 Line 8)

8. In your non responder group they have an average CAS of 2. Your definition of response is a drop in 3 factors. So you have artificially created a non-responder group.

Response: Thank you very much for the advice. Definition of pretreatment CAS and definition of response are two different things. We did not artificially created a non-responder group.

Definition of pretreatment CAS included the following 7 items:

1 Spontaneous retrobulbar pain

2 Pain on attempted upward or downward gaze

3 Redness of eyelids

4 Redness of conjunctiva

5 Swelling of caruncle or plica

6 Swelling of eyelids

7 Swelling of conjunctiva (chemosis)

Definition of response included the following 7 items:

1 Reduction in lid width by at least 3 mm

2 Reduction in any of the class 2 NO SPECS signs by at least two grades
3 Reduction in intraocular pressure by at least 2 mm Hg
4 Reduction in proptosis by at least 2 mm
5 Improvement in CAS by at least two points
6 Improvement in diplopia (disappearance or lessening of the degree)
7 Improvement in visual acuity by 1 Snellen score

9. Your results and methods section have overlap. Please keep each section separately.

Response: Thank you very much for the advice. We followed the suggestion and deleted those tedious repetitions in result part. (Page 8 Line 15)

Thank you again for your consideration. I look forward to hearing from you.

Sincerely,

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