April 29, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 16791-review.doc).

Title: Pharmacologic vitreolysis: New strategy for treatment of anomalous vitreo-macular adhesion.

Author: Desislava Koleva-Georgieva

Name of Journal: *World Journal of Ophthalmology*

ESPS Manuscript NO: 16791

The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated. The core tip was reduced to 98 words.

2. Revision has been made according to the suggestions of the reviewer

1) Why is this a challenging new approach? Intravitreal injection is much simpler than vitrectomy.
   - "Challenging" has been erased.
2) A third factor promoting PVD is weakening of the vitreoretinal adhesion.
   - The weakening of vitreo-retinal adhesions is thought to be a process following liquefaction and fibrillar meshwork collapse. In a normal vitreous this age-related process gives rise to normal PVD without any pathology. In eyes with firm vitreo-retinal adhesions this vitreo-retinal separation (weakening of the adhesion) cannot happen, or is hampered, and untoward effects happen – macular hole, viteromacular traction syndromes, persistent macular edema, retinal tears, ect. We tried to explain this better in the revised manuscript by adding "With time areas of liquefaction increase, the collagen fibrillar meshwork undergoes collapse and forms thick fibers (synergetic debris). These large areas of liquefaction with subsequent collapse appear to drive vitreoretinal separation following attenuation of the adhesion between the cortical vitreous and the ILM." [1-5, 13-15].
3) Why is vitrectomy for V-M traction accompanied by compulsory post-op positioning?
   - Vitrectomy for macular hole with gas tamponade requires postoperative compulsory positioning. To the revised manuscript "compulsory postoperative positioning for macular hole cases" is added.
4) Page 8: should be coronary not coronal.
   - In the manuscript on p. 8, in row 18 stays: "symptomatic coronary artery".
5) When did Jetrea receive FDA approval.
   - On 17. October 2012 FDA approved Jetrea (ocriplasmin) for treatment of symptomatic VMA.
6) Expand on the potential for lens subluxation. Because of findings on animal models, Jetrea should not be administered a second tome to the same eye.
   - The potential for lens subluxation is listed in the safety information of Jetrea. Ocriplasmin acts as human plasmin and lyses fibrin, laminin, and fibronectin, and increases levels of other

proteases that disrupt extracellular matrix structures. Although its effects are specific for vitreous and less active on other ocular structures, such as lens, ciliary body, and vessels, the pothential for lens subluxation should be kept in mind.

- In MIVI IIt trial the investigators have repeated injection of ocriplasmin in eyes with unreleased VMA after day 28 in the 125 µg cohort, and their own study results showed that this did not increase the chance of successful PVD induction. So, conclusion is that injection of Jetrea should not be repeated if unsuccessful. [Stalmans P, Delaey C, de Smet MD, et al. Intravitreal injection of microplasmin for treatment of vitreomacular adhesion: results of a prospective, randomized, sham-controlled phase II trial (the MIVI-IIT trial). *Retina.* 2010;30(7):1122–1127]

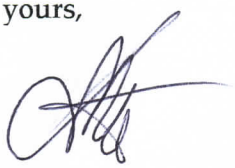
7) VMA adhesion of ?1500 um? Or of ?400?
   - The citation "focal VMA <1500microm" is correct – it is an observation of the MIVI-TRUST study group, published by Haller, Stalmans, Benz and coauthors in: Haller JA, Stalmans P, Benz MS, et al. MIVI-TRUST Study Group. Efficacy of intravitreal ocriplasmin for treatment of vitreomacular adhesion: subgroup analyses from two randomized trials. *Ophthalmology* 2015;122(1):117-22. PMID 25240630/ doi: 10.1016/j.ophtha.2014.07.045.
8) Surgery within 1-2 weeks of Jetrea injection? I think that waiting 28 days, like in the MIVI-Trust trials is a more reasonable approach.
   - The period 1-2 weeks in the revised manuscript has been changed to 28 days, although in a personal communication with the investigators (Stalmans, Eckardt, Gandorfer) we have been stressed that if VMA release happens, it will be in the first 7 to 14 days. If no VMA release is noted until 14 day and with view of possible adverse events (as described in the manuscript) surgery may be undertaken without delay. So, investigators advise that candidates for ocriplasmin injection should be scheduled for surgery (if necessary – to be able to perform it without waiting in the queue list).
9) The final sentence on the Conclusions highly speculative. Do the authors have any data to back up this assertion?
   - Some in-vivo pre-clinical studies on animal models have shown higher success rates with a combination of hyalorunidase and plasmin/microplasmin, compared with lower rates in eyes treated with individual agents alone. The statement in the Conclusions section is not based on our own data or experience; it is rather a notion of the investigators devoted in this field of ophthalmology. (Sebag J. Is pharmacologic vitreolysis brewing? *Retina* 2002;22(1):1-3).

3. References and typesetting were corrected. The citation numbers with PMID and DOI (if available, were added.

4. We do not have a video-file for the manuscript. We were not informed before submitting the manuscript and have not prepared it.

Thank you again for publishing our manuscript in the *World Journal of Ophthalmology*.

Sincerely yours,



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