Published in final edited form as:

Retina. 2017 November ; 37(11): e141–e143. doi:10.1097/IAE.0000000000001887.

Reply to Editor: High dose high frequency aflibercept for recalcitrant neovascular age-related macular degeneration

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Keywords

age-related macular degeneration; treatment; aflibercept; vascular endothelial growth factor

The authors would like to thank Drs. C lug ru¹ for their interest in our study “High dose high frequency aflibercept for recalcitrant neovascular age-related macular degeneration”.² We addressed the points raised as following.

1. The retrospective nature of the study design has been clearly stated in the methods section. The relatively small sample size has been discussed as one of the limitations of our study. However, considering that the study is addressing the relatively rare, highly resistant wet age related macular degeneration (AMD) cases, a group of 33 recalcitrant eyes is a clinically meaningful size.
2. Due to the limited sample size, we pooled the vitrectomized and non-vitrectomized eyes into the analysis. We realized the differences between these two groups of patients and performed a subgroup analysis. The results of the analysis were presented in the paper and did not change our conclusion.
3. The baseline characteristics of the two groups of patients have been presented clearly in Table 1. As we pointed out earlier, we noted the differences between these two groups of patients, carried out a subgroup analysis and presented the results in the results section.
4. From comment 4 to comment 8, Drs. C lug ru raised questions about the predictors of treatment response, such as the baseline lesion type (polypoidal choroidal vasculopathy, occult/minimally classic/predominant classic choroidal vasculopathy); the presence of intraretinal fluid, subretinal fluid or hemorrhage, subretinal and sub- retinal pigment epithelium (RPE) fibrovascular proliferation, choroidal thickness, vitreo-macular interface status, the status of external

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Proprietary interest: no proprietary interest exists for any author.

limiting membrane band, the ellipsoid zone, the interdigitation zone, and the RPE band as well as presence of reticular pseudodrusen and other baseline factors. All these potential predictors of progression and treatment response have been studied extensively in previous studies, including studies from our group^{3,4,5}, but not in the current study as these predictors can be sorted out only with a very large study. On the other hand, as we pointed out in our paper, the primary purpose of the study was to evaluate the efficacy of monthly 4mg (high dose high frequency, 4Q4W) aflibercept intravitreal injections in wet AMD patients who were resistant to other anti-vascular endothelial growth factor (VEGF) treatments. Furthermore, due to the limited sample size, further analysis of predictors on treatment response would not result in definitive conclusions. To answer these interesting questions about treatment response predictors, a much larger sample size with a control group is warranted in the future.

5. Drs. C lug ru suggested that a washout period to evaluate the treatment effect of 4Q4W aflibercept would be needed. This would be a nice idea in an experimental environment. However, in the real world, it would be unethical to wait for the washout period and not to treat patients in a timely manner. As Drs. C lug ru stated in their conclusion, promptness of the treatment would strongly affect treatment outcome.
6. Drs. C lug ru stated the 16-month results of our patients were not good in terms of visual acuity and anatomical outcomes. When interpreting the data, the readers need to bear in mind that these patients were refractory cases who had been treated with a substantial number of previous anti-VEGF injections for a long-time. For these difficult cases in our study, the mean visual acuity was maintained, although not improved. It is also noteworthy that fifteen eyes(45%) showed vision improvement of one line or more, and four eyes (12%) improved three or more lines at the last visit. Anatomically, the improvement was more significant. The mean central foveal thickness decreased significantly after initiating 4Q4W aflibercept injections, from 292.4 μm at baseline to 241.9 μm at 1month ($P=0.02$), and this therapeutic effect remained significant at 12 months (302.7 μm vs. 251.3 μm , $n=22$, $P=0.008$). Similarly, the mean foveal thickness decreased significantly from 399.2 μm at baseline to 360.5 μm ($P=0.01$) at 1 month and to 334.7 μm ($P=0.001$) at 12 months. Both intraretinal fluid (IRF) and subretinal fluid (SRF) significantly decreased at 1-month and at 12 months (all $P<0.05$). Interestingly, sub-RPE fluid also decreased, but responded more slowly than IRF and SRF. The RPE detachment height decreased from 134.6 μm at baseline to 120.6 μm ($P=0.11$) at 1 month after injection, 126.3 μm at 3months ($P=0.39$), 114.4 μm at 6 months ($P=0.047$), and 107.3 μm at 12months ($P=0.037$). At the final visit, 39% of eyes were completely dry, and the mean CFT was 260.4 μm , significantly thinner than that of baseline visit ($P=0.05$). Considering the long-term and refractory nature of these cases, these results suggest that such dose escalation may be useful, particularly if performed earlier in the course of disease.

7. Drs. C lug ru suggest changing to monthly 2mg aflibercept injections immediately after the resistance to monthly ranibizumab/bevacizumab injections was found. This has been discussed in the introduction section in our paper. In our practice, patients with wet AMD were treated according to a stepwise algorithm. Considering the aflibercept was officially recommended for injections every two patients initially treated with monthly (Q4W) ranibizumab or bevacizumab were switched to 2 mg aflibercept every 8 weeks (2Q8W) when resistance occurred, then escalated to Q4W2mg (2Q4W) aflibercept when resistant to 2Q8W aflibercept, then escalated to double dose at Q4W4mg (4Q4W) aflibercept when resistance to 2Q4W aflibercept developed. We previously reported 60% of eyes with resistant AMD while on Q4W ranibizumab or bevacizumab responded well to 2Q8W aflibercept,⁶ and the macula was dry for up to 2 years after switching to 2Q8W aflibercept.⁷ Recently, we also reported the results of 2Q4W aflibercept treatment.⁸ Drs. C lug ru are encouraged to read these series of publications to better understand our stepwise algorithm.

In summary, our systematic dose escalation algorithm with aflibercept in patients with recalcitrant wet AMD can provide better anatomical outcomes and improve vision in some patients.

Acknowledgments

Supported in part by UCSD Vision Research Center Core Grant P30EY022589, an unrestricted grant from Research to Prevent Blindness, NY (WRF), National Natural Science Foundation of China and (No. 81400422) and 2015 Outstanding Young Scholar of Beijing (2015000021223ZK22). The sponsor or funding organization had no role in the design or conduct of this research.

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