

Comment on “Predictors of short-term outcomes related to central subfield foveal thickness after intravitreal bevacizumab for macular edema due to central retinal vein occlusion”

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Dear Editor,

We read with great interest the article by Wang *et al*^[1] which investigated the predictive factors for short-term outcomes related to central subfield foveal thickness (CSFT) after intravitreal bevacizumab (IVB; Avastin, Genentech Inc., South Francisco, CA, USA) injections in 60 patients with macular edema (ME) secondary to central retinal vein occlusion (CRVO). The authors concluded that IVB significantly improved visual acuity and CSFT after 3mo. Older age and lower baseline CSFT were associated with a good 3mo prognosis and were good predictors of short-term CSFT outcomes. There are some issues related to this article, that we would like to address and that can be summarized as follows: 1) The conclusion of the study that patients >60-year-old achieved better cystoid macular edema (CME) resolution and lower CSFT at 3mo compared with patients aged ≤60y is valid only for patients with CME at baseline and a duration of CRVO >3mo (intermediate phase of disease^[2]) since onset *i.e.* an average of 4.63mo for responders and an average of 3.01mo for incomplete responders. However, this assertion of the authors does not match the early, acute phase of CRVO patients. 2) There were a significant difference regarding the response to treatment between patients with CME alone (36/60) and those presenting CME with associated subretinal retinal fluid (SRF) (24/60) at baseline. The fact that 58.3% of

CME cases and 98.3% of CME cases with SRF responded to treatment with a complete resolution at 3mo brings into discussion two issues *i.e.* the greater effect of bevacizumab in patients with CME and associated SRF (compared with patients without SRF) and the beneficial and predictive impact of SRF in resolving CME. Accordingly, the presence of cystic spaces alone might be more disruptive to the retinal architecture in the absence of SRF. 3) The assertion of the authors that younger age is associated with a bad 3mo prognosis and might be predictive of late or incomplete response for foveal thickness outcomes is well documented and with practical implications. It seems to be a somewhat paradoxical and counter-intuitive finding due to generally healthier ocular tissues in younger patients which should have caused these patients to achieve better short-term outcomes related to CSFT after treatment. Importantly, inflammatory cytokines may play an important role in the pathogenesis of CRVO in younger patients, where vascular endothelial growth factor (VEGF) inhibition alone may not be sufficient to decrease the inflammatory response. Therefore, addition of a non-specific anti-VEGF substance, *i.e.* intravitreal steroid injection, which inhibits the expression of VEGF and suppresses the expression of the whole panoply of cytokines, chemokines, and growth factors, is mandatory. In 2015, we published a prospective clinical study^[3] on the 3y outcomes of bevacizumab treatment in patients with acute (≤1mo after the occlusion was diagnosed) central/hemicentral retinal vein occlusions (central/hemicentral RVOs). Of these patients, 50% had ischemic central/hemicentral RVOs, 17.5% of the patients experienced SRF and no one had CME. The results of this study showed, for the first time, evidence suggesting that early treatment administered immediately after clinical onset of the venous occlusion provided significant and sustained improvements in visual acuity and foveal thickness with inactive disease (dry retina and stable visual acuity for at least 6mo after the last injection) in most phakic patients with acute central/hemicentral RVOs, making this treatment option a rational and viable therapeutic strategy. In conclusion central/hemicentral RVO has to be considered an ophthalmic emergency. Therefore, therapy with anti-VEGF

agents has to be promptly applied as soon as possible after RVO onset. Every delay of therapy adversely influences the deterioration of visual functions, which are difficult to restore even with subsequent treatment. Regardless of the anti-VEGF agents used^[4] and regardless of the treatment approaches chosen (treat-and-extend/*pro re nata* algorithm)^[5], the efficacy of therapy depends primarily on the precociousness of the therapy after RVO diagnosis.

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Conflicts of Interest: Călugăru D, None; Călugăru M, None.

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Author Reply to the Editor

Dear Editor,

We thank Dr. Călugăru D and Dr. Călugăru M for their comments on our paper published by the *International Journal of Ophthalmology*^[1]. We acknowledge and understand their comments, and would like to shed some light on them.

Response: 1) We admit that our study has a few limitations, which are already acknowledged in our paper, but there might be additional ones we did not foresee. In our study, the duration of central retinal vein occlusion (CRVO) ranged from 1 to 144wk, which was similar to some previous studies^[2-3]. Because the acute phase of non-ischemic CRVO was already over when the patients consulted, anti-vascular endothelial growth factor (VEGF) treatment could have been delayed due to various reasons. We might agree that the conclusion of the study is valid only for patients with cystoid macular edema (CME) at baseline and a duration of CRVO >3mo, but maybe patients would benefit more from the treatment if they receive it in the early phase, which still needs to be confirmed. In our

future studies, we will take into consideration the different durations of CRVO among patients. But for now, our results do not allow reaching further or more refined conclusions. 2) We asserted that the frequency of CME alone decreased from 60% at baseline to 41.7% after 3mo of therapy and that the frequency of CME with SRF decreased from 40% at baseline to 1.7% after 3mo of therapy. About 50% of patients with CME and more than 90% of patients with subretinal retinal fluid (SRF) responded to treatment with a complete resolution at 3mo. Furthermore, 9 of 25 patients with CME and SRF at baseline showed CME alone after 3mo. These results strongly suggest that SRF is easier to treat than CME, rather than CME with SRF. 3) Younger patients should achieve better short-term central subfield foveal thickness (CSFT) outcomes after treatment due to their generally healthier ocular tissues compared with older patients. Although we could not exclude the effects of the small sample size, the impact of age on the response to retinal thickness outcomes after bevacizumab treatment should be considered. As we know, younger patients with CRVO may present a higher frequency of inflammatory conditions compared with older patients. Therefore, VEGF inhibition alone may not be sufficient to decrease the inflammatory response, especially in younger patients with CRVO. Accordingly, addition of an anti-angiogenic and anti-inflammatory agent may be more effective in younger patients, but no anti-inflammatory agent was used in the present study and we agree that additional studies are still necessary to address this issue adequately.

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