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LETTER TO THE EDITOR

Bevacizumab treatment of macular edema in CRVO and BRVO: long-term follow-up (BERVOLT study: bevacizumab for RVO long-term follow-up)

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Dear Editor:

The article by Kornhauser et al [1] summarized their clinical experience with the efficacy and safety of intravitreal bevacizumab (IVB, Avastin; Genentech, Inc., San Francisco, CA, USA) injections in the treatment of patients with branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). We would like to address the long-term results of this series regarding the efficacy of IVB injections in patients with macular edema (ME) following CRVO. The study has several shortcomings that prevent the validation of their results:

1. The study was conducted retrospectively, with the possible existence of bias. Thus, patients who were treated with laser photocoagulation or triamcinolone acetonide prior to the study were not excluded. In some cases, three IVB injections were administered at 1-month intervals, with a follow-up examination 1 month after the third injection. For other patients, the frequency of injections was based on the clinical evaluation of the treating ophthalmologist.
2. Patients were not divided into non-ischemic and ischemic subtype groups. Neither fluorescein angiography nor assessment of the presence of relative afferent pupillary defect were routinely performed.
3. The treatment schemes for injections and re-injections were not clearly specified.
4. There were no data on patients with "no residual macular edema", defined as central macular thickness (CMT)< 300 μm [2], or on anatomical types of ME (cystic changes within neurosensory retinal/subretinal fluid).
5. The comparison with the CRUISE [3] and RAVE [4] trials was not suitable, because the CRUISE trial [3] enrolled patients who almost exclusively experienced non-ischemic occlusions (98.5 %), while the RAVE trial [4] included only patients with ischemic occlusions.
6. The reference data were not updated with the available long-term results of the trials that had dealt with the efficacy of therapy with bevacizumab [5], ranibizumab (Lucentis; Genentech, Inc., San Francisco, CA, USA) [6], and aflibercept (Eylea; Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA) [7, 8].
7. The overall neovascular complication rate of 25 % in the treated patients was extremely high. Our 10-year natural history prospective study [9] of 147 patients with acute CRVO (<1 week of CRVO onset) revealed a 28.2 % cumulative prevalence of neovascular glaucoma.

Additionally, there was a discrepancy between the changes in visual acuity (VA) and CMT. While improving vision was minimal (a gain of approximately five Early Treatment Diabetic Retinopathy Study letters), CMT was significant decreased at the third month, after which it increased to 423 μm by the end of the observation period. Of note, this value is much more than the cutoff (252 μm) for the upper level of normal CMT, i.e., the average macular thickness measurements in healthy eyes (212±20 μm) [10] plus two standard deviations. The persistence of edematous macular changes despite bevacizumab treatment is a sign of active and progressive disease, requiring further treatment with antiangiogenic agents. The deterioration in outcome measures could be explained by the low frequency of injections (pro re nata

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regimen) and the long interval of time from CRVO diagnosis to initiation of treatment (average 2.9 months), during which the patients went without treatment. These factors favored the delayed occurrence of ischemic and irreversible lesions of the macular ganglion cell complex, close to the foveola, with ME being a minor factor.

In 2015, we published a prospective clinical study [5] on the 3-year outcomes of bevacizumab treatment in patients with acute (≤1 month after the occlusion was diagnosed) central/hemi-central retinal vein occlusions (C/HCRVO). Of these patients, 50 % had ischemic C/HCRVOs. The results of this study showed, for the first time, evidence suggesting that early treatment administered immediately after clinical onset of venous occlusion provides significant and sustained improvement in VA and CMT, with inactive disease (dry retina and stable visual acuity for at least 6 months after the last injection) in most phakic patients with acute C/HCRVOs, making this treatment option a rational and viable therapeutic strategy.

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Compliance with ethical standards

Disclosure The authors have full control of the primary data and have agreed to allow Graefe's Archive for Clinical and Experimental Ophthalmology to review their data upon request.

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

References

1. Kornhauser T, Schwartz R, Goldstein M, Neudorfer M, Lowenstein A, Barak A (2015) Bevacizumab treatment of macular edema in CRVO and BRVO: long-term follow-up. (BERVOLT study: Bevacizumab for RVO long-term follow-up). Graefes Arch Clin Exp Ophthalmol. doi:10.1007/s00417-01-3130-z
2. Epstein DLJ, Algvere PV, von Wendt G, Seregard S, Kvanta A (2012) Bevacizumab for macular edema in central retinal vein occlusion: a prospective, randomized, double-masked clinical study. Ophthalmology 119:1184–1189
3. Campochiaro PA, Brown DM, Awh CC, Lee SY, Gray S, Saroj N, Murahashi WY, Rubio RG (2011) Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. Ophthalmology 118:2041–2049
4. Brown DM, Wykoff CC, Wong TP, Mariani AF, Croft DE, Schuetzle KL (2014) Ranibizumab in preproliferative (ischemic) central retinal vein occlusion. The rubeosis and-VEGF (RAVE) trial. Retina 34:1728–1735
5. Călugăru D, Călugăru M (2015) Intravitreal bevacizumab in acute central/hemicentral retinal vein occlusions: three-year results of a prospective clinical study. J Ocul Pharmacol Ther 31:78–86
6. Campochiaro PA, Sophie R, Pearlman J, Brown DM, Boyer DS, Heier JS, Marcus DM, Feiner L, Patel A (2014) Lont-term outcomes in patients with retinal vein occlusion treated with ranibizumab. The RETAIN study. Ophthalmology 121:209–219
7. Heier JS, Clark WL, Boyer DS, Brown DM, Vitti R, Berliner AJ, Kazmi H, Ma Y, Stemper B, Zeitz O, Sandbrink R, Haller JA (2014) Intravitreal aflibercept injection for macular edema due to central retinal vein occlusion. Two-year results from the COPERNICUS study. Ophthalmology 121:1414–1420
8. Ogura Y, Roider J, Korobelnik JF, Holz FG, Simader C, Schmidt-Erfurth U, Vitti R, Berliner AJ, Hiemeyer F, Stemper B, Zeitz O, Sandbrink R (2014) Intravitreal aflibercept for macular edema secondary to central retinal vein occlusion. 18-month results of the phase 3 GALILEO study. Am J Ophthalmol 158:1032–1038
9. Călugăru M (1987) Les resultats d'une enquete sur la survenue du glaucome neovasculaire après occlusion de la veine centrale de la retine. J Fr Ophtalmol 10:479–483
10. Chan A, Duker JS, Ko T, Fujimoto JG, Schuman JS (2006) Normal macular thickness measurements in healthy eyes using status optical coherence tomography. Arch Ophthalmol 124:193–198