• Comment •

Comment on "Correlation between macular ganglion cell-inner plexiform layer thickness and visual acuity after resolution of the macular edema secondary to central retinal vein occlusion"

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Received: 2018-09-21 Accepted: 2019-02-18

DOI:10.18240/ijo.2019.04.29

Citation: Călugăru D, Călugăru M. Comment on "Correlation between macular ganglion cell-inner plexiform layer thickness and visual acuity after resolution of the macular edema secondary to central retinal vein occlusion". *Int J Ophthalmol* 2019;12(4):695-696

Dear Editor,

We would like to address several issues with the study of Kim *et al*[1].

The study was retrospectively conducted with the existence of a selection bias attributable to inclusion of 2 completely different etiologic subgroups of patients with nonischemic central retinal vein occlusion (CRVO), namely, patients older than 50y, who usually have common systemic conditions such as hypertension and diabetes; and patients younger than 50y, in whom other mechanisms, such as the hyperviscosity syndrome or inflammatory condition, should be specifically considered.

There were no descriptions of the criteria used for the diagnosis of nonischemic CRVOs at enrollment and at 3mo, when the fluorescein angiography was performed, especially when intraretinal hemorrhage areas persisted and prevented a clear angiographic evaluation of the retinal capillary nonperfusion zones. Notably, fluorescein angiography provides no information at all or sometimes provides misleading information on the retinal capillary nonperfusion in at least one third of the eyes during the early, acute phase of CRVO[2].

I do not agree with the assertion of the authors that the ischemic CRVO has no correlation with visual acuity (VA) in spite of anti-vascular endothelial growth factor (VEGF) treatment due to irreversible damages which have already occurred caused by severe ischemia in the inner retinal layers. Our prospective clinical study[3] on the 3y results of bevacizumab (Avastin, Genentech, Inc., South San Francisco, CA, USA) treatment in patients with acute (≤1mo after the occlusion was diagnosed) central/hemicentral retinal vein occlusions (RVO) substantiated for the first time, evidence suggesting that early treatment applied immediately after the clinical onset of venous occlusion provided significant and sustained improvements in VA and central macular thickness (CMT) with inactive disease (dry retina and stable VA for at least 6mo after the last injection) in most phakic patients with acute central/hemicentral RVO, making this treatment option a rational and viable therapeutic strategy. Specifically, the best-corrected visual acuity (BCVA) improved with a mean of 17.15 and 26.81 letters in nonischemic and ischemic occlusions, respectively, at the end of the study. Bevacizumab was more effective in patients with ischemic occlusions who required a significantly higher number of injections than the nonischemic forms.

The investigation of the inner retinal layer changes was limited to the analyzing of the retinal ganglion cell complex. Of note, the three layers of this complex [the retinal nerve fiber layer (RNFL), the retinal ganglion cell layer, and the inner plexiform layer] were not measured at the same retinal areas, namely, the thickness of the RNFL was measured in the frame of the optic nerve (peripapillary RNFL thickness), while the thickness of the retinal ganglion cell and inner plexiform layers were measured in the macula. Noting was stated referring to the evaluation of the disorganization of retinal inner layers (DRIL), which was defined as the horizontal extent (per B-scan) in microns for which any boundaries between the retinal ganglion cell complex, inner nuclear layer, and outer plexiform layer could not be identified[4]. The DRIL, as a predictor of VA in eyes with macular edema (ME) secondary to CRVO[5-6], would have characterized better the qualitative status of inner retinal layers than did the quantification of the quantitative changes of the thickness of the retinal ganglion cell complex.

The authors considered the ischemia and repetitive anti-VEGF injections as the main causes of the damages to the inner retinal layers in CRVO. In fact, the 3.70 injections of intravitreal anti-VEGF agents administrated to patients of this series had no deleterious visual effect. On the contrary, these injections had beneficial impact because they caused the ME to be resolved in patients of the ME-eye group.

The following relevant data are missing from the study: the stratification of the patient age (>50y/≤50y); the stratification of the DRIL severity (mild/severe); the mean duration of the symptoms after CRVO onset at presentation; the optical coherence tomography patterns of ME (diffuse/ subretinal fluid/intraretinal cystic changes/mixed type) and the location of the intraretinal cystoid fluid (retinal ganglion cell layer or inner/outer nuclear layers) at baseline in patients of the ME eye group; the CMT and BCVA at enrollment in the two groups of eyes (*e.g.* ME eye and non-ME eye groups); the enlargement of the avascular zone at enrollment and at the end of the study in the two groups of eyes; the treatment (if any) applied to patients in the non-ME eye group during the 13.2mo of follow-up period; the type of anti-VEGF agents used for the treatment of ME in patients of the ME eye group; the prevalence of vitreoretinal interface abnormalities (vitreomacular adhesion/traction, epiretinal membranes, full-thickness macular hole, and lamellar macular hole) at enrollment; the alterations of the photoreceptor cell layer (outer nuclear layer disorganization/thinning, external limiting membrane band disruption, discontinuity of the ellipsoid zone, and the interdigitation zone loss); the qualitative status of the retinal pigment epithelial band-Bruch membrane complex and the grading of the retinal pigment epithelium (RPE) changes (pigment migration within the neurosensory retina, RPE porosity, microrips or blowouts in the RPE, focal RPE atrophy, RPE thickening, presence of reticular pseudodrusen); and the subfoveal choroidal thickness at enrollment and at the end of the study.

The results of this study suggest that inner retinal damages occurring in patients with ME secondary to nonischemic CRVO may lead to permanent visual impairment after treatment. However, the validation, extrapolation, and generalizability of the authors' conclusion can be made only by statistical analyses including all the missing baseline potential predictive factors mentioned by us in addition to the baseline characteristics already evaluated in this study, which serve as potential prognosticators influencing functional and anatomic improvements.

Altogether, regardless of the antiangiogenic agents chosen [*e.g.* bevacizumab/ranibizumab (Lucentis, Genentech, Inc.)/ aflibercept (Eylea, Regeneron, Tarrytown, NY, USA)], the treatment paradigms used (*e.g.* treat-and-extend, *pro re nata*, fixed-interval, or escalated algorithm), the patient age, the baseline BCVA, and the form of CRVO (ischemic/nonischemic occlusion), the efficacy of treatment depends primarily on the promptness of the therapy after CRVO onset[2-3,6].

ACKNOWLEDGEMENTS

All authors were involved in design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review or approval of the manuscript. The authors have no proprietary of commercial interest in any of the material discussed in this article. The authors have full control of the primary data and they agree to allow the International Journal of Ophthalmology to review their data if requested.

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

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