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OUTCOMES IN RETINAL VEIN OCCLUSIONS PRESENTING WITH POOR VISUAL ACUITY TREATED WITH ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY. PROGNOSIS AND PREDICTIVE FACTORS

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ABSTRACT

The authors are commenting on the study entitled**:** "Outcomes in retinal vein occlusions presenting with poor visual acuity treated with anti-vascular endothelial growth factor therapy. Prognosis and predictive factors" published by Light et al. in Ophthalmology Retina. (Doi.prg/1010161.oret.2020.11.010. Published on November 19, 2020), which assessed visual acuity and spectral domain optical coherence tomography outcomes in patients with retinal vein occlusion treated with anti-vascular endothelial growth factor agents demonstrating habitual corrected visual acuity of worse than 20/320 before any ocular therapy, with at least 6 months of follow-up. The authors concluded that a delay from symptom onset to first injection of 30 days or more portended higher incidence of incident sequelae (neovascular events or need for adjunct therapies). However, the validation, extrapolation, and generalizability of the authors'conclusion can be made only by statistical analyses including all the missing baseline factors mentioned by us in addition to the baseline characteristics already evaluated in this study, serving as potential prognosticators influencing anatomical and functional improvements after intravitreal injections of antangiogenic agents.

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INTRODUCTION

We read with interest the study by Light *et al.* (2020) which assessed visual acuity and spectral domain optical coherence tomography (SD-OCT) outcomes in patients with retinal vein occlusion (RVO) treated with anti-vascular endothelial growth factor (VEGF) agents demonstrating habitual corrected visual acuity (HCVA) of worse than 20/320 before any ocular therapy, with at least 6 months of follow-up. The central retinal vein occlusion (CRVO) patients (n = 39) gained a median of 20 letters relative to baseline at both 6 and 12 months and showed a change in central subfield thickness (CST) of -504.1 µm and -552.3 µm, respectively. Branch RVO (BRVO) and hemiretinal vein occlusion (HRVO) (n = 13) gained a median of +45 and +57.5 letters at 6 and 12 months, respectively, and showed reductions of 299.6 µm and 355.2 µm of CST, respectively, on SD OCT. The authors concluded that a delay from symptom onset to first injection of 30 days or more portended higher incidence of incident sequelae (neovascular events or need for adjunct therapies). We would like to address several challenges that have arisen from this study which can be specifically summarized below.

First, the imaging assessment did not include all patients. Thus, interpretable fluorescein angiography (FA) studies were obtained at the beginning of the study following period, before initiation of any therapy on 20 CRVO patients (51.2%) and 10 BRVO and HRVO patients (76.9%). Few patients had undergone longitudinal FA. Twenty five CRVO patients (64.10%) and 5 BRVO patients (38.46%) underwent SD-OCT imaging. On the other hand the inclusion of the HRVO patients in the BRVO group is questionable. Although the HRVOs respond to treatment in a manner more akin to BRVO than CRVO, the CRVO and HRVO are pathogenetically similar. In cases of CRVO, the only existing central retinal vein trunk within the optic nerve is involved, whereas patients with HRVO have 2 central retinal vein trunks as a congenital anomaly and develop an occlusion in only one of them. Taking together, these findings may have confounded the final results.

Second, the FA analysis performed on 20 CRVO patients showed significant nonperfusion in 3 cases (15%), extensive intraretinal hemorrhage (either with preserved perfusion or to an extent that precluded assessment of perfusion status) in 8 cases (40%), and intact perfusion with only mild to moderate hemorrhage in 9 cases (45%). It

follows that the CRVO group contained both phenotypes of occlusions, that is nonischemic and ischemic occlusions. Inclusion in the study and pooled analysis of patients with the 2 forms of CRVO (ischemic and nonischemic occlusions) cannot be made because they have totally different pathogeneses, clinical features and evolutions, prognoses and management. Although an HCVA improvement of 20 letters was achieved at month 12 and the median time from onset to first injection was 25 days, the rather high proportion of the total of incident sequelae in the CRVO cohort (48.7%) at the end of the study showed that the patients were under-treated. Also, the comparison of the final anatomic and functional outcomes of this study with those of the Rave (Brown *et al.*2014) and Cruise (Campochiaro *et al.* 2011) studies is inappropriate. Thus, the Rave study (Brown *et al*.2014) included 20 patients with ischemic CRVO (preproliferative CRVO) treated with ranibizumab (Lucentis, Genentech Inc, South San Francisco, CA, USA) 9 months, monitored then 3 months without treatment, and ranibizumab therapy was reinstated during the following 24 months on a pro re nata basis..Improvement in visual acuity and gain in CST were 21.4 letters and 282 µm, respectively at month 36 and approximately 50% of cases developed neovascular complications. The Cruise study (Campochiaro et al.2011), a 12-month trial, included patients with macular edema secondary to non-iscbemic CRVO (98.5% of patients had perfused retinal status) which were treated at a mean time of 3 months since CRVO diagnosis.

Third, the following relevant data, which should have been included in the statistical analyses, are missing from the study: the proportion of patients with ocular hypertension/glaucoma and systemic comorbidities (arterial systemic hypertension, diabetes, dyslipidemia, cardiovascular diseases, cerebrovascular diseases, obesity, hyperviscosity syndrome, antinflammatory conditions); the proportion of the nonischemic occlusions converted to ischemic forms over the course of 12 months; the SD-OCT patterns of the vitreoretinal interface abnormalities (vitreomacular adhesion, full-thickness macular hole, lamellar macular hole, combined epiretinal membrane and vitreomacular traction); the SD-OCT patterns of macular edeama (diffuse/subretinal fluid/cystic changes/mixed type); the location of the cystoid macular edema on SD-OCT (inner or outer nuclear layers/ganglion cell layer); the existence or otherwise of the disorganization of retinal inner layers and its severity (mild, severe, or severe with damaged ellipsoid zone [EZ]); the damages of the photoreceptor cell layer (thinning/disorganization of the outer nuclear layer, external limiting membrane band defects, EZ disruption, interdigitation zone loss); the qualitative status of the retinal pigment epithelial band – Bruch membrane complex (pigment migration within neurosensory retina, retinal pigmenmt epithelium [RPE] porosity, microrips or blowouts in the RPE, focal RPE atrophy, RPE thickening); the prevalence of the subretinal hyperreflective material and its composition (blood/fibrin/fluid/scar/choroidal neovascularization); the subfoveal choroidal thickness, and the proportion of eyes considered "dry"on SD-OCT at the end of the study.

Fourth, nothing was stated regarding our prospective clinical study (Călugăru *et al*.2015) on the 3-year outcomes of bevacizumab (Avastin; Genentech, Inc.,) treatment in patients with acute (≤ 1 month after the occlusion was diagnosed) central/hemi retinal vein occlusions (central/HRVO). Of these patients 50% had ischemic occlusions with a median baseline visual acuity of 5 letters (Călugăru *et al*.2015). Our study yielded different final results in comparison with those reported in the present study, namely, a mean visual acuity gain of 17.15 and 26.81 letters in the nonischemic and ischemic forms, respectively, and a CFT decreased with a mean of 300.49µm and 351 µm for nonischemic and ischemic occlusions, respectively; 2 mild cases of neovascular glaucoma, which were rapidly reversed after intravitreal bevacizumab injections in combination with topical steroids, cycloplegics, and a fixed combination of timolol and dorzolamide; and 5 cases with macular edema caused by subretinal fluid that resolved after bevacizumab injections, with rapid restoration of macular morphology. This was the first study to report evidence documenting that early treatment, applied 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 6 months after the last injection) in most phakic patients with acute central/HRVOs, making this treatment option a rational and viable therapeutic strategy. Bevacizumab was more effective in patients with ischemic occlusions who required a significantly higher number of injections than the nonischemic forms (a mean number of 9.7 and 8.7 injections, respectively).

Fifth, the acute central/HRVO has to be considered an ophthalmic emergency. Therefore, therapy with anti-VEGF agents has to be promptly applied as soon as possible after CRVO onset. The sooner the treatment is started after CRVO onset, the sooner the patient is likely to have gains in BCVA and foveal thickness. Any delay in initiating therapy will adversely affect the restoration of visual functions, which are difficult to recover even with subsequent treatment. Regardless of the antiangiogenic agents chosen (eg, bevacizumab/ranibizumab/aflibercept [Eylea; Regeneron Pharmaceuticals, Tarrytown, NY, USA]), the treatment paradigms used (eg, treat-and-extend, pro re nata, fixed-interval, or escalated algorithm), the patient age, and the type of occlusion (ischemic/nonischemic form), the efficacy of treatment depends primarily on the promptness of the therapy after CRVO onset, which can be considered as a putative key driver portending the visual and anatomic outcomes (Călugăru *et al.* 2013).

Altogether, the study found that patients with RVO demonstrating poor initial visual acuity showed visual and anatomic benefit with anti-VEGF therapy, most often observed shortly after initiation of treatment. However, the validation, extrapolation, and generalizability of the authors'conclusions can be made only by statistical analyses including all the missing baseline factors mentioned by us in addition to the baseline characteristics already evaluated in this study, serving as potential prognosticators influencing anatomic and functional improvements after intravitreal injections of anti-VEGF agents.

Acknowledgments/disclosure

All authors have completed and submitted the ICMJE form for disclosure of potential conflicts of interest. No financial disclosures. Both authors (D.C and M.C) were involved in the 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 full control over the primary data and they agree to allow the International Journal of Development Research to review their data if requested.

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