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REVIEW ARTICLE OPEN ACCESS

EFFICACY AND SAFETY OF INTRAVITREAL AFLIBERCEPT TREAT-AND-EXTENT FOR MACULAR EDEMA IN CENTRAL RETINAL VEIN OCCLUSION: THE CENTERA STUDY

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ABSTRACT

The authors are commenting on the study entitled**:** "Efficacy and safety of intravitreal aflibercept treat-and-extend for macular edema in central retinal vein occlusion: Centera study" published in Am J Ophthalmol by Korobelnik 2021; 227(July): 106-115, which assessed the efficacy and safety of intravitreal aflibercept administered using a treat-and-extend dosing regimen in 160 treatment-naïve patients with macular edema secondary to central retinal vein occlusion. The authors concluded that intravitreal aflibercept administered in a treat-and-extend treatment paradigm improved functional and anatomic outcomes in patients with macular edema resulting from central retinal vein occlusion during a 76 week follow-up period. However, the validation, extrapolation, and generalizabilty of these findings can be made only by regression analyses including all the missing data referred to above by us in addition to the baseline characteristics already assessed in this study, serving to identify the potential prognosticators influencing the efficacy and safety of intravitreal aflibercept using a treat-and extend approach for macular edema due to central retinal vein occlusion.

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INTRODUCTION

We read with interest the study by Korobelnik *et al.* (2020) which assessed the efficacy and safety of intravitreal aflibercept (IVT-AFL; Eylea; Regeneron Pharmaceuticals Inc., CA, USA) administered using a treat-and-extend dosing regimen in 160 treatment-naïve patients with center-involved macular edema secondary to central retinal vein occlusion (CRVO). In a 76-week follow-up period the clinically meaningful improvements in best-corrected visual acuity (BCVA) and in central retinal thickness (CRT) were 20,3 letters and -496.1 µm, respectively. 65,6% of patients ($p < 0.0001$) gained ≥ 15 letters from baseline to week 76 and 45.0 % of patients ($p = 0.8822$) achieved a mean treatment interval of ≥ 8 weeks during the treat-and-extend phase. The post hoc analysis demonstrated that 63.1% and 67.5% of patients achieved a last and next planned treatment interval of ≥ 8 weeks, respectively. The authors concluded that IVT-AFL administered in a treat-and-extend treatment paradigm improved significantly functional and anatomic outcomes in patients with CRVO-associated macular edema over 76 weeks. The safety profile of IVT-AFL was consistent with that of previous studies. We would like to address several challenges that have arisen from this study which can be specifically summarized below.

First, there was a selection bias attributable to inclusion in the study and pooled analysis of patients with 2 completely different etiological subgroups with definitely different prognoses, namely, patients older than 50 years who usually have common systemic vascular conditions, such as hypertension and diabetes, and patients less than 50 years, in whom other mechanisms, such as the hyperviscosity syndrome or inflammatory condition should be specifically considered. Likewise, 2 forms of CRVO, namely, with (6.9%) and without capillary non-perfusion areas (93.1%) on fluorescein angiography (FA) having totally different pathogeneses, clinical features and evolutions, prognoses, and management were lumped together. Patients received treatment at the discretion of the physicians in the 42 study centers in Australia, Canada, Denmark , France, Germany, Italy, Spain, and the UK and 9 patients showed abnormal gonioscopy without being specified what this abnormality consisted of. Taken together, these findings may have confounded the results.

Second, the authors stated that in the Centera study as well as in the Copernicus (Boyer *et al.* 2012) and Vibrant (Campochiaro *et al.* 2015) studies patients showed improvements in functional and anatomic outcomes indicating that IVT-AFL therapy was effective in patients with both phenotypes of CRVO, that is, nonischemic and ischemic CRVO. Accordingly, we inferred from this assertion that the 11 patients with capillary nonperfusion areas on FA in the Centera study were considered by the authors as ischemic forms of CRVO although the size of the retinal zones of nonperfusion was not specified. What criteria were used by the authors to label a CRVO as presenting ischemic form of the disease ? Of note, the diagnostic criteria for the ischemic type of CRVO are determined based on the angiography result. In cases with angiographically clear evidence of retinal capillary nonperfusion zones, the criteria include ≥ 10 disc

areas of retinal nonperfusion. If marked and exensive intraretinal hemorrhages prevent a clear angiographic evaluation of the retinal capillary nonperfusion areas, we suggested (Călugăru *et al*.2015) that the presence of at least 4 of the following 5 criteria to be taken into account: the BCVA ≤ 20/ 400 Snellen equivalent; the ability to see ≤ V/ 4e isopter based on the Goldmann perimeter; the presence of relative afferent pupillary defects in patients with a normal fellow eye; the extensive ocular fundus changes (striking amount of hemorrhages, venous tortuosity, cotton wool spots [>5], disc and macular edema); and an intraocular pressure reduction in the occluded eye of ≥ 4 mmHg compared with the congener eye. It is worthy to note that the FA provides no information at all or sometimes provides misleading data on the retinal capillary nonperfusion in at least one third of the eyes during the early, acute phase of CRVO (Călugăru *et al.* 2017). 87.5% of the eyes in the Centera study were acute CRVOs treated within 8 weeks of diagnosis.

Third, in the assessment of the final results of this study we considered the currently available assertion that evaluation of outcomes has to be guided by anatomical measure data with visual changes as a secondary guide (Freund et al. 2015). Accordingly, the efficacy of IVT-AFL administered using a treat-and-extend strategy was only partly documented. Specifically, although there were clinically meaningful improvements in BCVA and in CRT (20.3 letters and -496.1 μm, respectively), nothing was stated regarding the optic coherence tomography (OCT) patterns of the macular edema (diffuse/subretinal fluid/cystic changes/mixed type) and the proportion of eyes considered "dry" on OCT at the end of the study.

Fourth, following several relevant data which should have been included in the statistical analyses were missing from the study: the stratification of the patient age (≤ 50 years/> 50 years); the OCT patterns of the vitreoretinal interface abnormalities (epiretinal membrane, vitreomacular adhesion, full-thickness macular hole, lamellar macular hole, and combined epiretinal membrane and vitreomacular traction); the disorganization of the retinal inner layers and its severity (mild, severe, or severe with damaged ellipsoid zone [EZ]) at presentation and at the end of the study; the OCT patterns of macular edema (diffuse/subretinal fluid/cystic changes within neurosensory retina/mixed types) at presentation; the location of the intraretinal cystoid fluid on OCT (ganglion cell layer/inner or outer nuclear layers) at presentation and at the completion of the study; the damages of the photoreceptor cell layer (thinning/disruption of the outer nuclear layer; external limiting membrane band defects, EZ disruption, and interdigitation zone loss) at presentation and at week 76; the qualitative status of the retinal pigment epithelial band – Bruch's membrane complex (pigment migration within the neurosensory retina, sub retinal pigment epithelium [RPE] fluid, RPE porosity, micro-rips or blowouts in the RPE, focal RPE atrophy, and RPE thickening) at presentation and at week 76; the proportion of the nonischemic CRVOs that developed capillary nonperfusion areas on FA and their location during the follow-up period; the subfoveal choroidal thickness at the study enrollment and at the end of the follow-up period; the proportion of the patients with ocular hypertension/glaucoma and systemic comorbidities (arterial systemic hypertension, diabetes, dyslipidemia, cardiovascular diseases, cerebrovascular diseases, obesity, hyperviscosity syndromes, and inflammatory conditions) at presentation; the prevalence of the subretinal hiperreflective material and its composition (fibrosis, blood, fibrin, exudation, lipid, viteliform material or neovascular tissue) at presentation and at week 76. Conceivably, the design and the final outcomes of this study might have been different if all these missing variables had been taken into account.

Altogether, the authors showed that clinically meaningful and significant improvements in functional and anatomic outcomes were achieved with IVT-AFL administered using a treat-and-extend dosing regimen in patients with CRVO-emergent macular edema.We believe that the validation, extrapolation, and generalizability of these findings can be made only by regression analyses including all the missing data referred to above by us in addition to the baseline characteristics already assessed in this study, serving to identify the potential prognosticators influencing the efficacy and safety of IVT-AFL using a treat-and extend paradigm for macular edema resulting from CRVO over 76 weeks of follow-up after the initiation of treatment.

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