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MULTIPLE EFFECTS OF INTRAVITREAL AFLIBERCEPT ON MICROVASCULAR REGRESSION IN EYES WITH DIABETIC MACULAR EDEMA

Dan Călugăru and *Mihai Călugăru

Department of Ophthalmology, University of Medicine Cluj-Napoca/Romania

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ABSTRACT

The authors are commenting on the article entitled "Multiple effects of intravitreal aflibercept on microvascular regression in eyes with diabetic macular edema" published by Sugimoto *et al.* in Ophthalmology Retina; http:/dx.doi.org/10.1016/j.oret.2019.0600. Published online: June 14, 2019. The authors of this study concluded that the intravitreal injections of aflibercept reduced significantly the mean number of microaneurysms from 49.6 to 24.8 and the mean ischemic index from 55.5% to 28.8% at 3 months after initial treatment. However, the validation, extrapolation, and generalizability of these findings are questionable because 60% of the patients were additionally treated with panretinal photocoagulation during the study period, what affected the final outcomes, making impossible distinction between the effects of aflibercept injections and panretinal photocoagulation.

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INTRODUCTION

The prospective study by Sugimoto *et al*. (2019) evaluated the effects of intravitreal aflibercept (IVA; Eylea, Regeneron Pharmaceuticals, Tarrytown, New York, USA) injections on the number of microaneurysms (MAs) and the size of non-perfused areas (NPAs) in eyes with diabetic macular edema (DME). The authors concluded that IVA can improve the best-corrected visual acuity (BCVA), central retinal thickness (CRT), and stage of diabetic retinopathy, as shown by a reduction in the size of NPAs and in the number of MAs which was correlated with the decrease in the CRT. We would like to address several challenges that have arisen from this study.

1. All 25 eyes of 25 DME patients included in the study were treated with 3 consecutive monthly IVA injections and 15 of them (60%) were additionally treated by panretinal photocoagulation (PRP). The effect of IVA on the number of the MAs and the size of the NPAs could not be evaluated because the design of this study lacked a real washout period, which is essential among the 2 periods of treatment in terms of aliased effects. Thus, the impact of the significant carryover effects of the PRP may be confounded with direct treatment effects of IVA injections because these effects could not be estimated separately; carryover effects may bias the interpretation of data analysis.
2. The authors of this study focused mainly on the ultra-widefield fundus fluorescein angiography (UWFFA)-confirmed mid-periphery and peripheral retinal ischemia and less on investigating the central ischemia. Importantly, more than 10 disc areas of nonperfusion confined to the retinal periphery (beyond the posterior pole) cause development of new vessels in a small proportion of cases. Instead, posterior pole nonperfusion of more than 10 disc areas results in development of new vessels in most cases (Călugăru *et al.* 2018). The optical coherence tomography angiography (OCTA) which detects capillary perfusion and capillary density in both the posterior pole (macula) and the mid-periphery, was not used for delineation and quantification of the foveal avascular zone (FAZ), a sensitive indicator of ischemia, whose enlargement would be defined more precisely the macular ischemia (e.g., FAZ

***Corresponding author: Mihai Călugăru,**
Department of Ophthalmology, University of Medicine Cluj-Napoca/Romania

enlargement > 1000 µm in at least one diameter) than did the procedures employed in this series. Moreover, quantitative OCTA metrics (vessel density and flow index) for the 4 en-face zones including the superficial and deep capillary plexuses, the outer retina (photoreceptors), and the choriocapillaries (choroid) were not analysed.

3. We agree with the authors' assertion that the specific anti-VEGF agents (e.g., bevacizumab, [Avastin; Genentech, Inc., San Francisco, California, USA], ranibizumab [Lucentis; Genentech, Inc.,], and aflibercept) represent the first-line therapy for the treatment of DME. However, the VEGF inhibition alone may not be sufficient to suppress the whole panoply of proinflammatory and proangiogenic cytokines, chemokines, and growth factors associated with the multifactorial pathophysiology of DME. They are maximally expressed in the ischemic lesions of the long-standing DME and exacerbate the deterioration primarily caused by VEGF in the initially damaged macular ganglion cell complex. Therefore, the addition of a non-specific anti-VEGF substance (e.g., a corticosteroid implant), is mandatory (Călugăru *et al.* 2018a).
4. The following pertinent data are missing in the study: the duration of the DME before entering the study after diabetes onset; the optical coherence tomography patterns of the DME (sponge-like swelling/cystoid macular edema/serous neuroretinal detachment/mixed type) and the location of the cystoid type (ganglion cell layer/inner/outer nuclear layers); the integrity of the ganglion cell complex; the qualitative status of the photoreceptor cell layer (the disorganization/thinning of the outer nuclear layer, the disruption/absence of the external limiting membrane band, the ellipsoid zone, and the interdigitation zone); the changes of the retinal pigment epithelial band-Bruch membrane complex (pigment migration within the neurosensory retina, retinal pigment epithelium [RPE] porosity, micro-rips or blowouts in the RPE, focal RPE atrophy, RPE thickening); the quantification of the subretinal drusenoid deposits; and the systemic comorbidities associated with DME.
5. The benefit of targeted PRP to areas of nonperfusion in a patient with DME is questionable. We believe that the retinal lesions that develop after PRP increase the vascular endothelial growth factor (VEGF) expression, induce breakdown of the blood-retina barriers, destruction of normal retinal tissue, and hard exudates formation, especially in patients with high serum lipid. Laser may reduce the BCVA gains that are achieved with aflibercept monotherapy and causes visual field defects. The pre-existing DME prior to PRP results in overburdened RPE (creeping atrophy), so that PRP could aggravate DME. We favour long-term antiangiogenic treatment and add PRP only in patients with intraocular neovascularization unless this complication subsides after medical treatment.
6. The authors thoroughly investigated the multiple effects of IVA on the improvements of the microvasculature in eyes with DME but nothing was stated regarding the adverse effects of aflibercept. Specifically, aflibercept treatment may result in a significant subfoveal choroidal thickness loss (Gharbiya *et al.* 2015) by suppressing the choroidal vascular hyperpermeability and vasoconstriction as well as by more pronounced reductions of choriocapillaris endothelium thickness and number of fenestrations. The prolonged inhibition of VEGF using aflibercept may affect the integrity of the choriocapillaris, considering the key role of VEGF-A in the regulation of the survival and permeability of the choriocapillaris. Thus, choroidal vascular impairment may affect the integrity of the RPE and outer retina favoring development of the fovea-involving geographic atrophy, because the choroid is involved in maintaining the perfusion of the outer retinal layers and is the sole source of metabolic exchange (nourishment and oxygen) for the fovea (Călugăru *et al.* 2018b). In addition, through the fragment crystallizable domain, aflibercept can bind to the fragment crystallizable receptor of both choriocapillaris endothelial cells and red blood cells, leading to complement-mediated cell death.

Altogether, the authors of this study concluded that the IVA injections reduced significantly the mean number of microaneurysms from 49.6 to 24.8 and the mean ischemic index from 55.5% to 28.8% at 3 months after initial treatment. However, the validation, extrapolation, and generalizability of these findings are questionable because 60% of the patients were additionally treated with PRP during the study period, what affected the final outcomes, making impossible distinction between the effects of aflibercept injections and PRP.

Dan Călugăru, MD, PhD
Mihai Călugăru, MD, PhD
Department of Ophthalmology, University of Medicine,Cluj-Napoca, Romania

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