



SHORT COMMUNICATION

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GUIDELINES ON DIABETIC EYE CARE. THE INTERNATIONAL COUNCIL OF OPHTHALMOLOGY RECOMMENDATIONS FOR SCREENING, FOLLOW-UP, REFERRAL, AND TREATMENT BASED ON RESOURCE SETTINGS

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ABSTRACT

The authors are commenting the article entitled "Guidelines on diabetic eye care. The International Council of Ophthalmology recommendations for screening, follow-up, referral, and treatment based on resource settings" published by Wong *et al.* in *Ophthalmology*; 2018; 125(10): 1608-1622. The conclusion resulting from this article is that regardless of the intravitreal pharmacotherapy chosen, namely, specific (bevacizumab, ranibizumab or aflibercept) or nonspecific (corticosteroid implant) anti-vascular endothelial growth factor agents, the efficacy of the treatment depends primarily on the promptness of the therapy after diabetic macular edema diagnosis. Both groups of anti-vascular endothelial growth factor substances provide similar rates of vision improvement, but with superior anatomic outcomes and fewer injections in the corticosteroid implant-treated eyes. However, more patients receiving the corticosteroid implant lose vision mainly due to cataract.

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We would like to address several issues with the study of Wong *et al.* (2018).

1) There were no data on the optical coherence tomography patterns of the diabetic macular edema (DME) (sponge-like swelling/cystoid macular edema/ serous neuroretinal detachment/ mixed type) nor on the location of the cystoid type (ganglion cell layer/inner/outer nuclear layers). Of note, the location of the cystoid edema in the outer nuclear layer is more destructive in disorganization of the retina than that in the ganglion cell/inner nuclear layers. Importantly, there is a greater effect of anti-vascular endothelial growth factor (VEGF) agent in patients with cystoid macular edema associated with subretinal fluid (compared with patients without subretinal fluid) as well as a beneficial and protective effect of subretinal fluid in resolving cystoid macular edema by improving the areas of outer retinal ischemia. Accordingly, the presence of cystic spaces alone might be more disruptive to the retinal architecture, favoring the development of the atrophy, in the absence of subretinal fluid (Călugăru *et al.* 2017).

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2. We hypothesized that a whole panoply of proinflammatory and proangiogenic cytokines, chemokines, and growth factors may be associated with the multifactorial pathophysiology of the 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 (Călugăru *et al.* 2016).

3. The appropriate management of diabetic retinopathy (DR) requires a thorough investigation of the photoreceptor cell layer, which includes the assessment of the following alterations: the disorganization/thinning of the outer nuclear layer; the disruption/absence of the external limiting membrane band, the ellipsoid zone, and the interdigitation zone; and the changes of the retinal pigment epithelial band-Bruch membrane complex (pigment migration within the neurosensory retina, retinal pigment epithelium (RPE) porosity, microrips or blowouts in the RPE, focal RPE atrophy, RPE thickening, presence of reticular pseudodrusen).

4. The presumed pharmacologic advantages of aflibercept (Eylea, Regeneron Pharmaceuticals Inc., Tarrytown, NY) over bevacizumab (Avastin, Genentech, Inc., South San Francisco,

CA) or ranibizumab (Lucentis, Genentech, Inc.) (for example, a higher binding affinity to all isoforms of VEGF-A, activity against VEGF-B, placental-derived growth factor, and galectin-1, as well as prolonged time of the intraocular VEGF-A suppression) were not confirmed by several studies. Unlike bevacizumab, which has a protective effect against occlusion of choriocapillaris induced by photodynamic therapy (Mukai *et al.* 2010), and ranibizumab, which does not impair the choroidal thickness (Gharbiya *et al.* 2015), aflibercept treatment may result in a significant subfoveal choroidal thickness loss by suppressing the choroidal vascular hyperpermeability and vasoconstriction as well as by more pronounced reductions of choriocapillaris endothelium thickness and number of fenestrations (Gharbiya *et al.* 2015). In the short-term, the significant subfoveal choroidal thickness thinning by aflibercept does not seem to result in visual deleterious effects. However, in the long-term, 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, the 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. 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.

5. Nothing was stated regarding the diabetic choroidopathy, which consists in intrachoroidal vascular abnormalities and which may directly induce choroidal ischemia, leading to RPE dysfunction. The progressive thickening of the choroid layer caused by increasing the severity of DR (from no DR to proliferative DR) and development of DME (being thickest in eyes with serous neuroretinal detachment type of DME) denotes progression of the diabetic choroidopathy (Kim *et al.* 2013).

6. The specific anti-VEGF drugs (e.g., bevacizumab/ranibizumab/aflibercept) represent the front-line therapy for the treatment of DME but only the VEGF inhibition may not be sufficient to decrease inflammatory response. Therefore, the addition of a non-specific anti-VEGF substance (e.g., corticosteroid implant) is mandatory.

Altogether, regardless of the intravitreal pharmacotherapy chosen, namely, specific or nonspecific anti-VEGF agents, the efficacy of the treatment depends primarily on the promptness of the therapy after DME diagnosis (Călugăru *et al.* 2016). Both groups of anti-VEGF substances provide similar rates of vision improvement, but with superior anatomic outcomes and fewer injections in the corticosteroid implant-treated eyes.

However, more patients receiving the corticosteroid implant lose vision mainly due to cataract (Călugăru *et al.* 2017, 2018, 2018a).

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