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RESEARCH ARTICLE

RANDOMIZED TRIAL OF WIDE-FIELD GUIDED PRP FOR DIABETIC MACULAR OEDEMA TREATED WITH RANIBIZUMAB

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ABSTRACT

The authors are commenting on the article entitled "Randomized trial of wide-field guided PRP for diabetic macular oedema treated with ranibizumab" published by Talks *et al*. in Eye 2019; 33(6):930-937. After thorough analysis of the issues related to the addition of targeted panretinal photocoagulation to areas of nonperfusion in patients with macular diabetic oedema the authors concluded that the specific anti-vascular endothelial growth factor drugs (e.g., bevacizumab/ ranibizumab/aflibercept) represent the front-line therapy for the treatment of diabetic macular oedema but only the vascular endothelial growth factor inhibition may not be sufficient to decrease inflammatory response. Therefore, addition of a non-specific anti-vascular endothelial growth factor substance, (e.g., corticosteroid implant) is mandatory. As for the role of targeted panretinal photocoagulation to areas of nonperfusion, the retinal lesions that develop after panretinal photocoagulation increase vascular endothelial growth factor expression and induce breakdown of blood-retina barrier dysfunction and hard exudates formation. The pre-existing diabetic macular oedema prior to panretinal photocoagulation results in overburdened retinal pigment epithelium, so that panretinal photocoagulation could aggravate diabetic macular oedema.

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INTRODUCTION

The study by Talks *et al*. (2019) evaluated in patients with diabetic macular oedema (DMO) and peripheral ischaemia if the targeted panretinal photocoagulation (PRP) may reduce the number of ranibizumab injections. We would like to address several issues that have arisen from this study, which can be specifically summarized below.

1. The comparison between the two groups of patients (ranibizumab [Lucentis; Genentech, Inc., San Francisco, California, USA] only group and ranibizumab + PRP group) was questionable because there was a significant difference concerning the mean baseline best-corrected visual acuities (BCVA) (73.68 and 67.29 Early Treatment Diabetic Retinopathy Study [ETDRS] letters, respectively) and an obvious difference related to the mean baseline macular thicknesses (378.36 and 405.67 µm, respectively). Likewise, the study included two patients in each study group, that had mild new vessels detected on the baseline ultra-widefield fundus fluorescein angiography (UWFFA) as well as two patients in each group with proliferative diabetic retinopathy (PDR) although both the rubeosis and PDR were specifically set as exclusion criteria. Taken together these findings may have confounded the results.

2. There were no details with regard to the stages of the nonproliferative diabetic retinopathy (mild/moderate/severe), and the DMO defined as retinal thickening or hard exudates at or within 1 disc diameter of the macula center and which is most commonly classified into being clinically significant or not as well as center-involved/non-center-involved. Nothing was stated with respect to the stratification of the DMO eyes by OCT patterns (sponge-like swelling/cystoid macular edema/subfoveal neuroretinal detachment/mixed type) and the location of the cystoid type (ganglion cell layer/inner/outer nuclear layers) if it was present in some cases of the both groups (Călugăru *et al*.2017).

3. We do not agree the authors' assertion that local vascular endothelial growth factor (VEGF) at the macula is the main cause of DMO. Of note, VEGF is only one of the proven contributors associated with the pathogenesis of DMO. The complex pathophysiologic process occurring in DMO is attributed to the hyperglycemia-induced oxidative stress and inflammation as well as to the subsequent upregulation of the various growth factors and cytokines. We documented that a panoply of proinflammatory and proangiogenic cytokines, chemokines, and growth factors may be associated with the multifactorial pathophysiology of DMO, suggesting that the pathogenesis of DMO is not only related to VEGF

dependency. They are maximally expressed in the ischemic lesions of the long-standing DMO and exacerbate the deterioration primarily caused by VEGF in the initially damaged macular ganglion cell complex (Călugăru *et al*.2016). The specific anti-VEGF drugs (e.g., bevacizumab [Avastin; Genentech Inc]/ranibizumab/aflibercept [Eylea, Regeneron Pharmaceuticals Inc., Tarrytown, New York, USA]) represent the front-line therapy for the treatment of DMO but VEGF inhibition alone may not be sufficient to decrease inflammatory response. Therefore, addition of a non-specific anti-VEGF substance, (e.g., corticosteroid implant) which inhibits the upregulation of VEGF and suppresses the expression of the whole inflammatory factors, is mandatory (Călugăru *et al*.2017a). Otherwise, patients will be impeded to achieve maximal visual and anatomic benefits.

4. The benefit of targeted PRP to areas of nonperfusion in a patient with DMO is questionable. We believe that the retinal lesions that develop after PRP increase VEGF expression and induce breakdown of blood-retina barrier dysfunction and hard exudates formation, especially in patients with high serum lipid. Laser may reduce the BCVA gains that are achieved with ranibizumab monotherapy. The pre-existing DMO prior to PRP results in overburdened retinal pigment epithelium (RPE), so that PRP could aggravate DMO. We favour long-term antiangiogenic treatment and add PRP only in patients with intraocular neovascularization unless this complication subsides after medical treatment.

5. The authors of this study focus mainly on the UWFFA-confirmed peripheral retinal ischaemia and less on investigating the central ischaemia. 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. On the contrary, 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 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 enlargement > 1000 μm in at least one diameter) than did the procedures employed in this series. In addition, the role of the FAZ area in predicting BCVA outcomes was not assessed. Moreover, the perfusion indices (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.

6. The following relevant data are missing from the study: the duration of the DMO before entering the study after diabetes onset; the number of patients who underwent macular laser after 6 months and those who developed rubeosis or new vessels that were not controlled by injections.; the existence or not of the disorganization of the retinal inner layers and its severity (mild/sever/severe with damaged ellipsoid zone [EZ]); the damages of the photoreceptor cell layers comprising thinning of the outer nuclear layer, external limiting membrane band defects allowing fluid to enter the retina and causing "cystoid macular degeneration", EZ disruption, interdigitation zone loss, and hyperreflective foci in the neuroretina and subretinal space; the changes of the retinal pigment epithelial band-Bruch membrane complex (pigment migration within the neurosensory retina, RPE porosity, microrips or blowouts in the RPE, focal RPE atrophy, RPE thickening, presence of reticular pseudodrusen, and diffuse ooze within or adjacent to the decompensated RPE); and the existence or otherwise of a diabetic choroidopathy, which consists in intrachoroidal vascular abnormalities and which may directly induce choroidal ischemia, leading to RPE dysfunction (Călugăru *et al.*2018a).

Altogether, the authors of this study concluded that the addition of targeted PRP to areas of nonperfusion in a patient with DMO does not reduce the number of injections required in the first year of ranibizumab therapy. However, the validation, extrapolation, and generalizability of the these findings can be made only by regression analyses including all the missing baseline factors mentioned by us in addition to the baseline characteristics already assessed (Călugăru *et al*.2016a, 2017a).

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