• Comment and Response •

Comment on "Anatomical and functional changes after dexamethasone implant and ranibizumab in diabetic macular edema: a retrospective cohort study"

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Dear Editor,

The study by Mastropasqua *et al*[1] evaluated the efficacy and safety of ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA, USA; RBZ group) and dexamethasone implant (Ozurdex; Allergan Irvine., CA, USA; DEX group) intravitreal treatments in 50 patients with treatment-naïve center involved diabetic macular edema (DME) by means of functional and morphological assessments during a 6-month follow-up. The best-corrected visual acuity (BCVA) improved significantly in both groups with a greater increase in the DEX group compared to the RBZ group and central macular thickness decreased significantly without statistically significant differences between the 2 groups. The retreatment rate at 180d was 0.65 and 0.50 in the RBZ group and DEX group, respectively. The authors concluded that both treatments were very effective for DME treatment with a lower retreatment rate in the DXE group. We would like to address several challenges that have arisen from this study which can be specifically summarized below.

The study had a retrospective design with a relatively short follow-up (6mo). During this period of surveillance 2 out of 25 patients in the DEX group developed intraocular pressure increase requiring hypotonic eye drops. It is to be assumed that in the long term a part of patients in the DEX group would have lost the BCVA mainly due to cataract.

The authors stated that they encompassed in this study only patients with center-involved DME without subretinal fluid component. And yet, the structural spectral domain-optical coherence tomography (SD-OCT) images centered on the fovea clearly displayed in the Figures 2 and 3[1] the existence of the subretinal fluid (serous neuroretinal detachment) in the imagines of 2 patients included in the study.

The following critical data are missing from the study: the duration of the DME before entering the study after diabetes onset; the optical coherence tomography (OCT) patterns of vitreoretinal interface abnormalities (*e.g.*, epiretinal membranes, vitreomacular adhesion/traction, full-thickness macular hole, lamellar macular hole, and combined epiretinal membranes and vitreomacular traction); the existence or not of the disorganization of the retinal inner layers (DRIL) and grading of its severity [mild, severe, or severe with damaged ellipsoid zone (EZ)]; the SD-OCT patterns of the center-involved DME (*e.g.*, sponge-like swelling/cystoid macular edema/serous neuroretinal detachment/mixed type) and the location of the intraretinal cystoid fluid (*e.g.*, inner/outer nuclear layer or ganglion cell layer); the integrity of the foveal photoreceptor layer; the subretinal hyperreflective material and its composition (blood/fibrin/exudation/scar/choroidal neovascularization); and the subfoveal choroidal thickness[2].

The authors of this study did not take into consideration the currently available recommendations of the European School of Advanced Studies in Ophthalmology, that created a classification of the diabetic maculopathy based purely upon SD-OCT[3]. It utilizes the following seven distinct parameters of an OCT structural image going through the center of the fovea, each of them is to be assessed separately: the foveal thickness or the macular volume, the intraretinal cysts, the EZ or external limiting membrane status, the presence of DRIL, the number of hyperreflective foci, the subretinal fluid, and the vitreoretinal changes.

The optical coherence tomography angiography (OCTA) was carefully used to quantify the perfusion indices (vessel density and blood flow index) in the superficial and deep capillary plexuses and the choriocapillaris before and after treatment. However, the authors did not evaluate the macular ischemia,

that is, the macular nonperfusion area which is defined as the area consisting of the foveal avascular zone (FAZ) and the parafoveal nonperfusion area (parafoveal capillary dropouts) examined using OCTA. The OCTA was not used for delineation and quantification of the 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). Likewise, the BCVA was not correlated with the macular microperimetry, the superficial and deep macular nonperfusion areas, and the disruption of the foveal EZ zone band in the 2 groups of treatment.

Nothing was stated regarding the diabetic choroidopathy, which consists in intrachoroidal vascular abnormalities and which may directly induce choroidal ischemia, leading to retinal pigment epithelial dysfunction. The progressive thickening of the choroid layer caused by increasing the severity of diabetic retinopathy (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[4].

Altogether, the authors found that the two different intravitreal treatments were safe and very efficacious allowing a fast improvement of the anatomical and functional outcomes in a 6mo follow-up period. However, the validation, extrapolation, and generalizability of these findings can be made only by regression analyses including all the missing baseline factors referred to above by us in addition to the baseline characteristics already assessed. We believe that the specific anti-vascular endothelial growth factor (VEGF) drugs [*e.g.*, bevacizumab (Avastin; Genentech Inc.), ranibizumab/aflibercept (Eylea; Regeneron Pharmaceuticals, Tarrytown, NY, USA)] represent the front-line therapy for the treatment of DME, but the VEGF inhibition alone may be not sufficient to suppress the whole panoply of the 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, addition of a non-specific anti-VEGF substance, *e.g.*, intravitreal steroid injection, which inhibits the upregulation of VEGF and suppresses the expression of the whole inflammatory factors is mandatory. Otherwise, patients will be impeded to achieve maximal visual and anatomic benefits[2,5].

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All authors were involved in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Conflicts of Interest: Călugăru D, None; **Călugăru M,** None.

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Authors Reply to the Editor:

Dear Editor,

I would like to thank Călugăru *et al* for commenting on our paper entitled "Anatomical and functional changes after dexamethasone implant and ranibizumab in diabetic macular edema: a retrospective cohort study".

In their letter the authors state that it is to be assumed that in the long term a part of patients included in the DEX group would lose the BCVA mainly due to cataract.

We agree with the authors that some of patients could develop cataract in long-term follow up. Indeed it is already known that the incidence of cataract in patients that underwent DEX implant during a 12-month follow up is 37.8%[1]. In our retrospective study with 6-month follow up, 14 out of 25 eyes of the DEX group were pseudophakic, the others had medium lens opacities according to Lens Opacities Classification System, as reported in the inclusion criteria of the study.

In addition, we enrolled treatment naïve patients with no proliferative moderate DR stage and center-involved DME type with subretinal fluid component as documented on the OCTA images provided in the manuscript and as detailed reported in the figure legends. We apologize for a typo (with subretinal fluid component instead of without subretinal fluid component) in the methods section of the manuscript.

Moreover, Călugăru *et al* state that we did not follow the recommendations of the European School of Advanced Studies in Ophthalmology for diabetic maculopathy classification based purely upon SD-OCT because of our paper lacks of some data including the status of outer/inner retinal layers, OCT patterns of DME, FAZ and subfoveal choroidal thickness. We deliberately limited ourselves to discuss on these data

because several publications describing OCT biomarkers are already available in literature and can give a much deeper and wider view on the matter[2-4].

Furthermore, the FAZ circularity was previously not significantly associated with DR progression in both univariate and multivariate analyses[5].

Therefore, we preferred to focus our attention on the efficacy and safety of two types of treatments (RZB and DEX) quantifying in detail perfusion parameters such as superior capillary plexus density, deep capillary plexus density and choriocapillaris density by means of OCTA, as well as macular sensitivity and BCVA.

The authors further stress the importance of corticosteroids as well as anti-VEGF agents in DME therapy. It is known that anti-VEGF treatment directly inhibits the activity of VEGF and also can modulate other proinflammatory cytokines and chemokines levels that play an important role in the inflammatory cascade mechanism leading to EMD pathogenesis as previously described in an our work[6]. Corticosteroids have been shown to inhibit both VEGF and other inflammatory factors' expression, causing a significant strengthening of the blood-retinal barrier[7-8].

Finally, the authors regret the fact that we did not include a correlation between BCVA and macular sensitivity and other anatomical/perfusion parameters in the two groups of treatment. Undoubtedly, it would be very interesting in the future to get a deeper insight in evaluating these missing correlations, the status of the FAZ, the macular ischemia and other perfusion parameters detected with OCTA. Further studies are also needed to investigate on diabetic choroidopathy and its connections with severity and development of DME and possible choroidal changes after intravitreal treatment.

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