

# Comment on: Real-world outcomes of two-year Conbercept therapy for diabetic macular edema

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## Dear Editor,

We read with great interest the study by Cheng *et al*<sup>[1]</sup>, which assessed the two-year outcomes in 30 (36 eyes) diabetic macular edema (DME) patients treated with intravitreal conbercept (Lumitin; Chengdu Kanghong Biotech Co, Ltd, China; IVC) for 3mo. Additional IVC was given at subsequent monthly visits, if needed (3+*pro re nata*). The mean improvement in best-corrected visual acuity (BCVA) was 11 letters and the central retinal thickness (CRT) was significantly reduced by 277.1  $\mu\text{m}$  at 24mo with a mean number of 10.6 injections and without severe eye or systemic adverse events. The authors concluded that IVC is safe and effective for the treatment of DME. We would like to address several challenges that have arisen from this study which can be specifically summarized below.

The study was retrospectively conducted in a relatively small number of patients.

There was a selection bias attributable to inclusion and pooled analysis of 2 types of diabetic retinopathy (DR), that is, nonproliferative ( $n=3$ ) and proliferative ( $n=33$ ) DR, (although the active proliferative DR was an exclusion criterion) as well as patients with ( $n=33$ ) and without ( $n=3$ ) previous laser treatment (panretinal photocoagulation, PRP). Taken together, these findings may have confounded the final results.

There were no details regarding the DME defined as retinal thickening or hard exudates at or within 1 disc diameter of the macula center and which is most commonly classified

into either being clinically significant or not. Moreover, the criteria used to define the clinically significant DME, if it was present in some patients, were not indicated. There were no data on the staging of diabetic maculopathy (early, advanced, severe, and atrophic maculopathy), the spectral domain-optical coherence tomography (SD-OCT) 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).

Patients were excluded if they had intravitreal injection of corticosteroids, such as triamcinolone acetonide (Kenalog; Bayer-Bristol), within 3mo prior to the treatment or intravitreal injection of other anti-vascular endothelial growth factor (VEGF) drugs, such as bevacizumab (Avastin; Genentech, Inc., San Francisco, CA, USA) or ranibizumab (Lucentis; Genentech, Inc.), within 2mo prior to the treatment. Nothing was stated about 91.7% of patients ( $n=33$ ) who had previous PRP, how and when this therapy had been applied, its duration, and if a washout period existed between PRP therapy and Conbercept administration, which is essential among 2 periods of treatment in terms of aliased effects. In the absence of such a period the impact of the significant carryover effects of the PRP on previously presented patients may be confounded with direct treatment effect of Conbercept in the sense that these effects could not be estimated separately; carryover effects may bias the interpretation of data analysis.

In the assessment of the final outcomes of this study we considered the current assertion<sup>[2]</sup> that evaluation of outcomes should be guided by the anatomical measure data with visual changes as a secondary guide. Despite significant visual improvements in the BCVA after treatment (a mean gain of 11 letters from baseline), the structural outcomes of this study showed that 56.7% of patients had CRT>250  $\mu\text{m}$  at month 24. The persistence of high values of the CRT after treatment highlights unresolved macular edema due to insufficient macular deturgescence and indicates that the disease process is still active and progressive requiring further treatment with antiangiogenic agents. 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 (11.4mo duration of DME) and exacerbate the deterioration primarily caused by VEGF in the initially damaged macular ganglion cell complex.

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 VEGF expression, induce breakdown of the blood-retina barriers, produce 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 IVC monotherapy and causes visual field defects. The pre-existing DME prior to PRP results in overburdened retinal pigment epithelium (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.

Nothing was stated regarding the influence which IVC can exert on the diabetic choroidopathy which consists in intrachoroidal vascular abnormalities, and which may directly induce choroidal ischemia, leading to RPE dysfunction. Notably, unlike bevacizumab, which has a protective effect against occlusion of choriocapillaris induced by photodynamic therapy<sup>[3]</sup>, and ranibizumab, which does not impair the choroidal thickness<sup>[4]</sup>, aflibercept (Eylea; Regeneron Pharmaceuticals, Tarrytown, NY, USA) 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<sup>[4]</sup>.

The authors of this study did not consider the currently available recommendations of the European School for Advanced Studies in Ophthalmology international classification<sup>[5]</sup> that classified the diabetic maculopathy based on the SD-OCT microstructural alterations of the outer/inner retina and vitreoretinal interface. From the seven distinct parameters of an SD-OCT structural image going through the center of the fovea, only one was documented in this study, namely, the CRT. The remaining 6 distinct features of this classification, which should have been assessed separately in this study, are as follows:

- 1) Intraretinal cysts with specification of their location if they existed (inner/outer nuclear layers or ganglion cell layers);
- 2) Ellipsoid zone (EZ) or external limiting membrane status;
- 3) Presence of disorganization of the retinal inner layers and grading of its severity (mild, severe, and severe with damaged

EZ); 4) Presence and number of hyperreflective intraretinal foci; 5) Presence of subretinal fluid with serous neuroretinal detachment; 6) Patterns of vitreoretinal interface abnormalities (epiretinal membranes, vitreomacular adhesion/traction, full-thickness macular hole, lamellar macular hole, and combined epiretinal membranes and vitreomacular traction).

Altogether, the authors of this study found that Conbercept significantly improves vision, prevents severe vision loss, and rapidly reduces macular edema. The treatment efficacy was maintained for 24mo. However, the validation, extrapolation, and generalizability of these findings concerning the efficiency of Conbercept treatment and its advantages over other anti-VEGF treatments can only be made by statistical analyses including all the missing baseline potential predictive factors referred to above by us in addition to the baseline characteristics already evaluated in this study, serving to emphasize the key metrics assessing the anatomical and functional benefits of conbercept therapy in DME patients<sup>[6]</sup>.

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

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