• Comment and Response •

Comment on "Microvascular changes after conbercept therapy in central retinal vein occlusion analyzed by optical coherence tomography angiography"

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Dear Editor,

We enjoy reading the retrospectively study by Deng *et al*[1] which investigated microvascular changes in eyes with macular edema resulting from central retinal vein occlusion (CRVO) before and after intravitreal conbercept (Lumintin; Chengdu Kanghong Biotech Co, Ltd., China) injection and evaluated correlations between these changes, best-corrected visual acuity (BCVA), and retinal thickness. The authors concluded that optical coherence tomography angiography (OCTA) enables the non-invasive, layer-specific and quantitative assessment of microvasacular changes, and can be used to obtain quantitative data and more detailed information regarding the vascular network of the superficial capillary plexus (SCP) and deep retinal capillary plexus (DCP), outer retina (photoreceptor), and choriocapillaris (choroid) in eyes with CRVO. We would like to address several issues, which make interpretation of these results challenging.

There was a selection bias attributable to inclusion in the study and pooled analysis of patients with 2 forms of CRVOs (ischemic and nonischemic occlusions) having definitely different pathogenesis, clinical features, prognoses, and management. Likewise, 2 completely different etiologic subgroups of patients have been encompassed and lumped together, namely, patients older than 50y who usually have common systemic conditions such as hypertension, diabetes, and patients younger than 50y, in whom other mechanisms, such as the hyperviscosity syndrome or inflammatory condition should be specifically considered and accounted for. Taken together, these findings may have confounded the results.

The ischemic type of CRVO was defined when the non-perfused area was larger than 10 disc areas on fluorescein angiogram. However, nothing was stated referring to the criteria used for the diagnosis of the ischemic type of CRVO when marked and extensive intraretinal hemorrhages prevented a clear angiographic evaluation of retinal capillary nonperfusion zones. Accordingly, we suggested the presence of at least of 4 of the 5 following criteria: the BCVA score ≤20/400 Snellen equivalent; the ability to see ≤V/4e isopter with the Goldmann perimeter; the presence of the relative afferent pupillary defect in patients having a normal fellow eye; the extensive ocular fundus changes [more striking amount of hemorrhages, venous tortuosity, cotton wool spots (>5), disc and macular edema]; and an intraocular pressure reduction in the occluded eye of ≥4 mm Hg compared with the congener eye[2].

The disorganization of retinal inner layers (DRIL) extent, its severity and correlation with the BCVA were not analysed at presentation and at the end of the study. Accordingly, the DRIL can be divided into 3 groups, namely, the mild DRIL [the boundary between the ganglion cell-inner plexiform layer complex (GCIPL) and inner nuclear layer (INL) cannot be distinguished and is irregular]; the severe DRIL (both the boundaries between the GCIPL and INL and between the INL and outer plexiform layer cannot be delineated and are irregular); and the severe DRIL with damaged ellipsoid zone (EZ).

The latest foveal avascular zone (FAZ) relevant parameters including the FAZ area, the FAZ perimeter (PERIM), the acircularity index (AI), the vessels density within a 300-μm width ring surrounding the FAZ (FD-300) as well as the blood flow area in choriocapillaris were thoroughly quantified on a retina slab in CRVO eyes both before and after conbercept injection. Noting was stated referring to the FAZ diameter whose enlargement would be defined more precisely the macular ischemia (*e.g.*, FAZ enlargement >1000 μm in at least one diameter) than did the criteria employed in this series. In addition, the role of FAZ area in predicting BCVA outcomes in the context of DRIL was not assessed.

The epiretinal membrane was an exclusion criterion for the patients of this study. Noting was stated if the eyes with the other 4 optical coherence tomography patterns of the vitreoretinal interface abnormalities (*e.g.*, vitreomacular adhesiontraction, full-thickness macular hole, and lamellar macular hole) were included or not in this study.

The following relevant data are missing from the study: the age stratification (0<age≤50y) the optical coherence tomography patterns of the macular edema (diffuse, subretinal fluid, cystic changes, and mixed type) and the location of the intraretinal cystoid fluid (inner or outer nuclear layers or ganglion cell layer); the qualitative status of the outer nuclear layer, the external limiting membrane band, the EZ, the interdigitation zone, and the retinal pigment epithelial band-Bruch's membrane complex; the proportion of patients with fibrotic and nonfibrotic scars, the macular atrophy, and the extramacular geographic atrophy; the proportion of patients with subretinal hyperreflective material and its composition (*e.g.*, fibrosis, exudation, blood, fibrin, and choroidal neovascularization): and the subfoveal choroidal thickness[3].

Altogether, the authors of this study revealed 2 significant correlations with regard to the baseline OCTA relevant parameters-detected microvasculature changes in CRVO eyes, namely, the blood flow area in the choriocapillaris negatively correlated with the full foveal and parafoveal retinal thickness and the duration time after onset of CRVO positively correlated with the PAZ parameters. However, the validation, extrapolation, and generalizability of the authors' conclusions can be made only by statistical analyses including all the missing baseline potential predictive factors mentioned by us in addition to the baseline characteristics already evaluated in this study, serving to identify the quantitative OCTA predictive metrics influencing functional and anatomic improvements.

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

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Author Reply to the Editor

Dear Editor,

We really appreciate Dan Călugăru and Mihai Călugăru for their interest in our paper[1] entitled "Microvascular changes after conbercept therapy in central retinal vein occlusion analyzed by optical coherence tomography angiography" and their comments.

In our study there were 16 non-ischemic and 12 ischemic CRVO patients, and the statistical analysis was also performed. A little pity that we did not present those data in this paper due to the reason that no significant differences were found in these OCTA parameters assessed between the non-ischemic and ischemic CRVO eyes. Therefore, we supplement the relevant findings here to avoid confusing the reader (Tables 1-3). Moreover, we thank Dan Călugăru and Mihai Călugăru for their suggestions and supplements in the letter on the criteria used for the diagnosis of the ischemic type of CRVO when marked and extensive intraretinal hemorrhages prevented a clear angiographic evaluation of retinal capillary nonperfusion zones. Since the purpose of our study is to investigate microvascular changes in eyes with CRVO complicated by macular edema before and after intravitreal conbercept injection, the parameters concerning the disorganization of retinal inner layers (DRIL) are dispensable for our study. On the contrary Tang *et al*[2] evaluated the DRIL extent, its severity and correlation with the BCVA in retinal vein occlusion macular edema after intravitreal conbercept injection according to their research purpose.

In addition, our paper has clearly mentioned that the choriocapillaris (for the choroid capillaries) was quantified based on the slab from -10 μm below the Bruch's membrane (BRM) to 30 μm below the BRM, not based on a retina slab as the author stated in the letter. For the FAZ diameter, it was not analyzed due to the disability of OCTA to automatically quantify the diameter. Our study did evaluate the relationship between the FAZ area and BCVA, but probably because of the limitations of our study included the small sample, the short-term follow-up with only one injection, no correlation was found.

In the letter, it is said that "Noting was stated if the eyes with the other 4 optical coherence tomography patterns of the vitreoretinal interface abnormalities (*e.g.*, vitreomacular adhesion/traction, full-thickness macular hole, and lamellar macular hole) were included or not in this study except for the epiretinal membrane". In fact, we have clearly stated that the eyes with other coexisting ocular disorders that could affect the interpretation of OCTA quantitative parameters were also excluded in our study, but we only gave several examples of such coexisting diseases based on the succinct principle of manuscript. In our study, the other 4 optical coherence tomography patterns of the vitreoretinal interface abnormalities were also not included.

At last, as for the missing data of our paper mentioned in the letter, we greatly agree with Pareja-Rios *et al*'s[3] opinions in their reply to Călugăru's similar comment that it is not

Table 1 OCTA parameters evaluated in control, non-ischemic CRVO and ischemic eyes

Variable	Control	Non-ischemic	Ischemic	*P* (control *vs* non-ischemic)	*P* (control *vs* ischemic)	*P* (ischemic *vs* non-ischemic)
Choriocapillaris flow area (mm^2)	2.07±0.14	1.06±0.47	1.26±0.36	0.0002[b]	0.0003[b]	0.3410
FAZ (mm^2)	0.34±0.08	0.32±0.11	0.26±0.1	0.6211	0.0600	0.2574
PERIM (mm)	2.33±0.29	2.38±0.48	2.17±0.52	0.7751	0.3988	0.3803
AI	1.14±0.04	1.21±0.07	1.24±0.12	0.0209[a]	0.0320[a]	0.5302
FD-300 (%)	50.81±2.97	46.72±5.00	45.76±2.40	0.0433[a]	<0.0001[b]	0.6138
SCP-vessel density (%)						
Whole image	47.11±3.32	40.43±5.41	39.49±3.91	0.0057[b]	0.0002[b]	0.6773
Fovea	21.11±3.73	24.66±11.60	26.20±5.64	0.5224	0.1782	0.4716
Parafovea	50.01±3.28	41.57±6.28	40.34±4.62	0.0034[b]	0.0001[b]	0.6449
DCP-vessel density (%)						
Whole image	47.25±3.71	39.88±5.05	38.81±5.81	0.0019[b]	0.0021[b]	0.6832
Fovea	27.32±6.06	28.96±10.78	30.12±7.84	0.1643	0.0811	0.1256
Parafovea	49.60±3.76	41.10±6.37	39.10±6.30	0.0036[b]	0.0008[b]	0.5124

All data are presented as mean±SD, [a]*P*<0.05, [b]*P*<0.01. OCTA: Optical coherence tomography angiography; CRVO: Central retinal vein occlusion; SCP: Superficial capillary plexus; DCP: Deep capillary plexus; FD-300: The vessel density within 300 μm width ring surrounding the FAZ; AI: Acircularity index; FAZ: Foveal avascular zone; PERIM: FAZ perimeter.

Table 2 OCTA parameters evaluated in non-ischemic CRVO eyes before and after treatment

Variable	Pre-injection	Post-injection	*P*
Choriocapillaris flow area (mm^2)	1.06±0.47	1.61±0.33	0.0078[b]
FAZ (mm^2)	0.32±0.11	0.33±0.13	0.0980
PERIM (mm)	2.38±0.48	2.53±0.56	0.2941
AI	1.21±0.07	1.21±0.09	0.9558
FD-300 (%)	46.72±5.00	43.82±4.66	0.0729
SCP-vessel density (%)			
Whole image	40.43±5.41	38.99±5.26	0.1088
Fovea	24.66±11.60	21.49±7.99	0.0790
Parafovea	41.57±6.28	41.16±5.64	0.6882
DCP-vessel density (%)			
Whole image	39.88±5.05	38.79±5.77	0.6735
Fovea	28.96±10.78	25.49±7.84	0.4617
Parafovea	41.10±6.37	40.03±6.05	0.7219

All data are presented as mean±SD, [b]*P*<0.01. OCTA: Optical coherence tomography angiography; CRVO: Central retinal vein occlusion; SCP: Superficial capillary plexus; DCP: Deep capillary plexus; FD-300: The vessel density within 300 μm width ring surrounding the FAZ; AI: Acircularity index; FAZ: Foveal avascular zone; PERIM: FAZ perimeter.

Table 3 OCTA parameters evaluated in ischemic CRVO eyes before and after treatment

Variable	Pre-injection	Post-injection	*P*
Choriocapillaris flow area (mm^2)	1.26±0.36	1.64±0.16	0.0327[a]
FAZ (mm^2)	0.26±0.1	0.29±0.17	0.5444
PERIM (mm)	2.17±0.52	2.28±0.81	0.6755
AI	1.24±0.12	1.21±0.10	0.3392
FD-300 (%)	45.76±2.40	41.96±5.12	0.0554
SCP-vessel density (%)			
Whole image	39.49±3.91	39.49±5.05	>0.9999
Fovea	26.20±5.64	20.49±4.97	0.0870
Parafovea	40.34±4.62	41.18±5.43	0.5130
DCP-vessel density (%)			
Whole image	38.81±5.81	39.44±8.67	0.8127
Fovea	30.12±7.84	28.90±9.08	0.1968
Parafovea	39.10±6.30	40.70±9.56	0.6966

All data are presented as mean±SD, [a]*P*<0.05. OCTA: Optical coherence tomography angiography; CRVO: Central retinal vein occlusion; SCP: Superficial capillary plexus; DCP: Deep capillary plexus; FD-300: The vessel density within 300 μm width ring surrounding the FAZ; AI: Acircularity index; FAZ: Foveal avascular zone; PERIM: FAZ perimeter.

usual for this type of studies to collect as much data as the letter suggest and too much data can increase the complexity, economic cost, and readability of the study.

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