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Study of vessel density by optical coherence tomography angiography in patients with central serous chorioretinopathy after low-fluence photodynamic therapy

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ABSTRACT

Background: To perform a quantitative analysis of retinal and choriocapillaris vessel density (VD) in patients with central serous chorioretinopathy (CSC) after low-fluence verteporfin photodynamic therapy (vPDT), using Optical Coherence Tomography Angiography (OCTA).

Methods: A total of 28 eyes of 27 patients with CSC (21 females, 6 males, mean age 47 ± 11 years) were included in this retrospective study. At baseline and after 6 months after vPDT, we evaluated VD of the superficial capillary plexus (SCP), the deep capillary plexus (DCP) and the choriocapillaris (CC) in different macular areas (whole image, parafovea and fovea). We also analyzed the central foveal thickness (CFT) and subfoveal choroidal thickness (SFCT) with Enhanced Depth Imaging-Optical Coherence Tomography (EDI − OCT).

Results: Eighteen eyes and ten eyes were responders and non responders to low-fluence vPDT, respectively. The responders group showed a significant increase in VD in DCP and CC after treatment ($p < 0.05$). In the non responders group the VD in SCP, DCP and CC did not differ before and after treatment. We also found a significant correlation in responders group between Best-Corrected Visual Acuity (BCVA) and CFT ($r = 0.566$; $p = 0.014$) and between BCVA and the increased VD of CC ($r = -0.559$; $p = 0.016$). In non responders group, the correlation between OCT, OCTA parameters and BCVA was not statistically significant.

Conclusions: OCTA allowed us to enhance our knowledge regarding the pathophysiology of vascular changes in retinal and CC networks after low-fluence vPDT. OCTA may represent a new biomarker to evaluate the efficacy of low-fluence vPDT in the treatment of CSC.

1. Introduction

Central serous chorioretinopathy (CSC) is a chorioretinal disease characterized by serous detachment due to the dilatation and hyperpermeability of choroidal vessels resulting in the accumulation of serous fluid between the neurosensory retina and the retinal pigment epithelium (RPE) [1–3].

Several studies reported the efficacy of verteporfin photodynamic therapy (vPDT) in the CSC treatment because, inducing a temporary choriocapillary occlusion, it reduces the choroidal hyperpermeability and remodels the choroidal vascularization [4,5].

Low-fluence vPDT is a therapeutic protocol that was found to be associated with a lower incidence of adverse effects improving the choroidal perfusion, macular thickness and the visual acuity [6].

In order to better understand the mechanism of action of vPDT on retinal and choroidal vasculature in this chorioretinopathy new diagnostic tools will be needed. Optical coherence tomography angiography (OCTA) is a non-invasive imaging technique that provides detailed informations regarding the retinal and choroidal vascular networks and it is useful in the analysis of vascular perfusion modifications after vPDT in CSC patients [7,8].

The aim of this retrospective study was to perform a quantitative analysis of retinal and CC vessel density (VD) by OCTA at baseline and 6 months after vPDT in responders and non responders CSC patients.

2. Materials and methods

In this retrospective study, a total of twenty-eight eyes of 27 patients

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(21 females, 6 males, mean age 47 ± 11 years) with chronic CSC were enrolled from October 2015 to October 2017 at the Eye Clinic of the University of Naples "Federico II".

All eyes underwent vPDT with a mean circular spot size of 3134.5 ± 1089.5 μm.

At baseline and 6 months after treatment, each patient underwent evaluation of Best-Corrected Visual Acuity (BCVA) according to the Early Treatment of Diabetic Retinopathy Study (ETDRS), slit-lamp biomicroscopy, fundus examination, multimodal imaging, namely multicolor imaging, fluorescein angiography (FA), Spectral-Domain Optical coherence tomography (SD − OCT) (Spectralis, Heidelberg Engineering, Heidelberg, Germany) including enhanced depth imaging OCT (EDI − OCT) module and OCTA (AngioVue, RTVue XR Avanti, Optovue, Inc., Freemont, CA). Indocyanine green angiography (ICGA) was performed to visualize the choroidal hyperpermeability in studied patients.

Patients were divided into two groups: responders and non responders to treatment. The responders group included the patients showing absence of subretinal fluid 6 months after PDT.

OCT parameters measurements were performed by two masked examiners (DM, CC) and a senior expert (GC).

Exclusion criteria were the presence of choroidal neovascularization, previous focal laser treatment or PDT for CSC, clinically significant lens opacities, low-quality of OCT and OCTA images, myopia greater than 6 diopters, uveitis, history of intraocular surgery, absence of vitreoretinal and vascular retinal diseases and congenital eye disorders.

The study was approved by the Institutional Review Board of the University of Naples "Federico II" and the investigation adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from the patients enrolled in the study.

2.1. Low-Fluence vPDT

The participants were subjected to low-fluence PDT with intravenous infusion of verteporfin (Visudyne, Novartis AG, Bülach, Switzerland) for 10 min at a dose of 6 mg/m^2, followed by delivery of diode laser at 689 nm (Visulas 690S; Carl Zeiss Meditec Inc., Dublin, CA, USA). A fluence of 25 J/cm^2, a light dose rate of 300 mW/cm^2, a photosensitization time of 83 s and a spot size with a diameter 1000 μm larger than the greatest linear dimension of the choroidal exudation represented the laser parameters. The exposure to sunlight for 48 h after treatment was not recommended due to a possible skin photosensitivity.

2.2. Spectral-domain optical coherence tomography

SD − OCT was used to evaluate the Central Foveal Thickness (CFT) and the Subfoveal Choroidal Thickness (SFCT). To measure CFT, on the OCT image, we placed a caliper on the inner and outer boundaries, which correspond respectively to the internal limiting membrane and the RPE/Bruch membrane.

The SFCT was measured using the Spectralis OCT device in Enhanced Depth Imaging (EDI) mode. The choroidal thickness was evaluated in the subfoveal region as a manual linear measurement between the outer border of Bruch's membrane and the most posterior identifiable aspect of the choroidal-scleral interface, which is seen as a hyper-reflective layer in the posterior margin of the choroid in EDI mode [9].

2.3. Optical coherence tomography angiography

OCTA images with the Optovue Angiovue System (software ReVue version 2014.2.0.93, Optovue Inc., Fremont, CA, USA) were performed following a standardized protocol based on the split-spectrum amplitude decorrelation algorithm (SSADA), as previously described [10].

Retinal capillary plexus was displayed performing a 6 mm × 6 mm scan over the macular region and the percentage area occupied by the microvasculature in the analyzed region defined the vessel density (VD) [11].

The software automatically calculates the VD in the macular scan considering several retinal vascular networks: superficial capillary plexus (SCP), deep capillary plexus (DCP) and choriocapillaris (CC). Choriocapillary vessel density was defined as the percentage area occupied only by the microvasculature of the choriocapillaris layer. The macular region was divided in whole image, fovea and parafovea according to the ETDRS classification of diabetic retinopathy.

2.4. Statistical analysis

SPSS version 17.0 (SPSS Inc, Chicago, Ill, USA) was used for statistical analysis. The Wilcoxon signed-rank test was used to evaluate the differences in VD of each capillary plexus (SCP, DCP, CC), in CFT and SFCT at baseline and 6 months after treatment in responders and non responders group. Spearman's correlation were assessed between OCT, OCTA parameters and BCVA.

In this study, P value lower than < 0.05 was considered statistically significant.

3. Results

The responders group included 18 eyes of 18 patients (6 female, 12 males, mean age 45 ± 8 years), while the non responders group presented 10 eyes of 9 patients (9 males, mean age 49 ± 12 years). The responders group showed an improvement in BCVA six months after the treatment (-0.11 ± 0.22 logMar vs -0.21 ± 0.11 logMar; p = 0.005) as well as a significant reduction in SFCT (359 ± 114.3 μm vs 285.1 ± 81.7 μm; p = 0.001) and in CFT (345.8 ± 116.3 μm vs 254.4 ± 53.9 μm; p = 0.001) respect to baseline. In non responders group there were no significant differences between baseline and six months after the vPDT in BCVA (-0.1 ± 0.16 logMar vs -0.14 ± 0.13 logMar; p = 0.104), SFCT (376.7 ± 91.6 μm vs 355.4 ± 84.5 μm; p = 0.289) and CFT (318.8 ± 107.2 μm vs 322.3 ± 112.7 μm; p = 0.178).

Analyzing OCTA parameters, in the responders group the VD in SCP did not show significant differences between baseline and after PDT while DCP and CC presented a significant increase in VD in each macular sector (whole image, parafovea and fovea) (Fig. 1). In non responders group, OCTA parameters revealed no significant changes over time (Table 1, Fig. 2).

Regarding the correlations between OCT, OCTA parameters and BCVA in responders group after treatment, a reduced CMT and an increased VD in fovea CC showed a significant correlation with a better BCVA. In non responders group there were no significant correlations between OCT, OCTA parameters and BCVA (Table 2).

4. Discussion

The etiology of CSC remains still unknown although several studies demonstrated the important role played by the choroidal vasculature [12]. The choroid is the vascular layer of the eye, it is generally divided into four layers (classified in order of furthest away from the retina to closest): Haller's layer consisting of larger diameter blood vessels, Sattler's layer consisting of medium diameter blood vessels, choriocapillaris consisting of small diameter vessels and Bruch's membrane, the innermost layer of the choroid [13]. vPDT has been used for a long time to reduce choroidal vascular dilatation and hyperpermeability with half-dose or low-fluence in order to avoid long-term complications [14–16]. In a previous study, we described morphological changes of the choriocapillaris in 28 eyes affected by CSC treated with low fluence vPDT. Six months after therapy, SRF was completely absorbed in 18 eyes (64.3 %) (responders), and incompletely absorbed in 10 eyes (35.7 %) (non-responders). The decrease in CFT and in SFCT was statistically

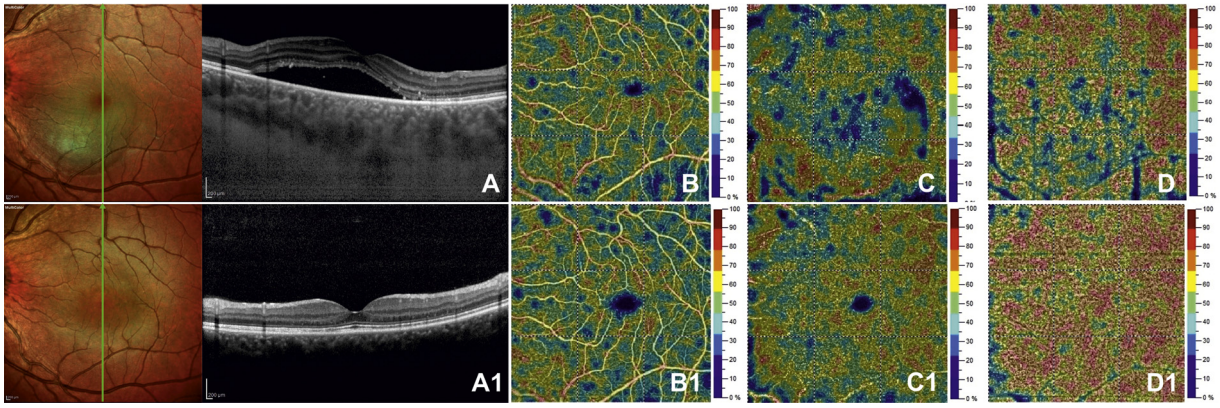

Fig. 1. Left eye of a responder CSC patient to vPDT at baseline and 6 months after treatment. Structural OCT B-scan showed neurosensory retinal detachment, increased CMT and SFCT at baseline (A) and a complete resolution of subretinal fluid after vPDT (A1). OCTA revealed no significant changes in VD in SCP at baseline (B) and after treatment (B1). While a significant increase in VD in DPC (C, C1) and CC (D, D1) was found after vPDT.

significant 6 months after treatment only in responders. Our results showed that low-fluence vPDT induced vascular remodeling of the choriocapillaris improving the blood circulation [17]. In this retrospective study we have used OCTA to assess VD of superficial and deep retinal capillary plexus and of choriocapillaris in order to better understand the mechanism of vascular remodeling 6 months after vPDT in responders and non responders. We observed an increase in VD of the DCP and of the CC only in responders. The increase in VD of the CC corresponded to the characteristic "narrow mesh" pattern seen in our previous study. Non responders didn't show any significant difference in the values of VD in the two retinal capillary plexus or choriocapillaris.

We hypothesized that VD of the superficial capillary plexus didn't change after vPDT in the two groups because vPDT had an effect only on choroidal vessels of Sattler's layer and spared retinal and choriocapillary plexi. Perhaps the increase in VD of deep capillary plexus in responders group occurred after the normalization of CFT due to subretinal fluid reabsorption. We believed that the mechanisms involved in the improved VD of DCP and CC are different. Unlike the choriocapillaries the vessels in the DCP as part of the blood retinal barrier have tighter endothelial junctions and probably more closely associated pericytes.

The increased VD of the choriocapillary was probably a secondary effect of vPDT. We hypothesized that vPDT therapy produces a closure or a diameter reduction of the abnormal leaking choroidal vessels with subsequent relief of the compression on the CC layer and choriocapillary vascular remodeling. vPDT could act on vessels of Sattler's layer inducing hypoxia-inducible factor 1-alpha (HIF-1alpha) and consequent overexpression of vascular endothelial growth factor (VEGF). The increase in VEGF can contribute to increase of VD in choriocapillaris and retinal deep capillary plexus.

It is possible that the occlusion of choriocapillary microvasculature didn't occur because of the reduced fluence of vPDT [18]. Chan et al. observed an increase in VD of the choriocapillaris and of the deep choroidal layer in 22 eyes 1 month after half-dose vPDT and a decrease in the width of the large choroidal vessels [19].

Nassisi et al. noticed in 20 affected eyes an early significant reduction of VD of CC 1 week after vPDT and an increase 1 month after therapy. The authors suggested that these findings were related to the process of recovery of the choriocapillaris caused by VEGF and VEGF-receptor overexpression at the treatment site. In their study CFT was significantly reduced at 1 week and 1month after therapy, while choroidal thickness was significantly reduced only 1 month after vPDT [20]. According to these results, the vascular remodeling and vascular changes could be due to an increase of VEGF in choriocapillary vasculature.

We noted the reduction of CFT, due to the reabsorption of SRF, and of SFCT 6 months after therapy in responders. These structural changes, especially the CFT, correlated with the improvement of BCVA in responders. Furthermore, these findings confirmed that the vascular remodeling was stable after 6 months, as confirmed by MA et al. in their study [4]. In a recent study of Demirel et al., 48 eyes affected by CSC and treated with half-fluence vPDT showed an improvement of BCVA at 1 month, 3 months and 6 months follow-up. The authors also analyzed,

Table 1
Comparison in OCTA parameters between baseline and after vPDT in responders and non responders groups.

	Responders			Non Responders		
	Baseline	Follow up	P value	Baseline	Follow up	P value
Superficial Capillary Plexus (%)						
Whole image	50.79 ± 5.04	50.31 ± 4.21	0.133	50.73 ± 3.44	50.87 ± 3.18	0.758
Parafovea	47.22 ± 3.40	47.76 ± 3.97	0.542	48.25 ± 1.03	48.73 ± 1.41	0.114
Fovea	28.8 ± 4.57	29.03 ± 4.45	0.222	29.51 ± 3.95	29.29 ± 4.24	0.406
Deep Capillary Plexus (%)						
Whole image	48.24 ± 4.30	52.47 ± 3.70	< 0.001	47.45 ± 2.42	48.29 ± 4.14	0.444
Parafovea	49.29 ± 4.40	53.67 ± 4.94	< 0.001	50.72 ± 5.94	51.13 ± 5.92	0.307
Fovea	34.51 ± 4.15	38.72 ± 2.94	< 0.001	35.15 ± 3.55	34.81 ± 3.07	0.383
Choriocapillaris (%)						
Whole image	64.11 ± 3.63	68.13 ± 4.09	< 0.001	65.28 ± 8.08	64.77 ± 8.44	0.240
Parafovea	63.27 ± 5.68	67.65 ± 2.77	< 0.001	63.08 ± 3.86	63.11 ± 3.58	0.497
Fovea	65.18 ± 4.19	68.72 ± 5.46	0.004	64.13 ± 4.82	64.28 ± 4.97	0.959

Data expressed as mean ± SD. The values are expressed as percentage (%) area occupied by the microvasculature of retinal superficial capillary plexus, retinal deep capillary plexus and choriocapillaris.

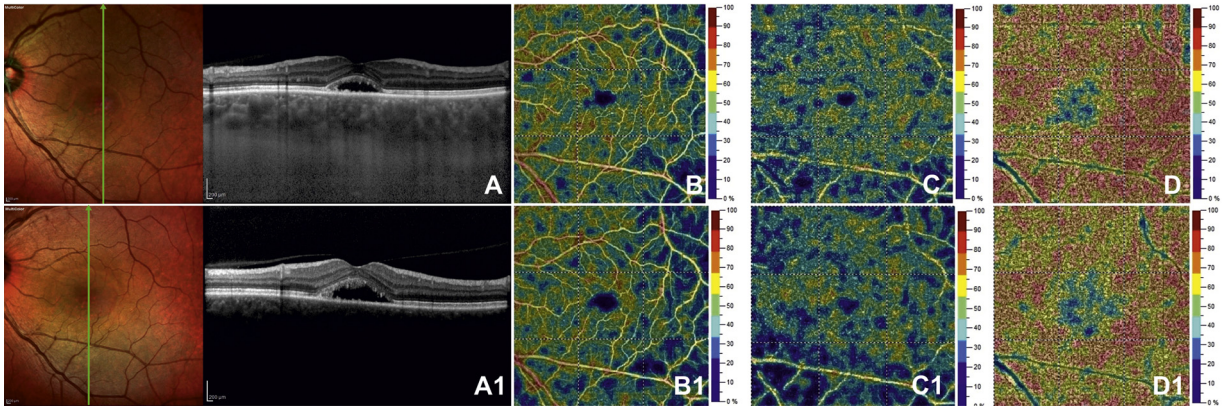

Fig. 2. Left eye of a non responder CSC patient to vPDT at baseline and 6 months after treatment. Structural OCT B-scan showed a persistent subretinal fluid with increased CMT and SFCT that did not modify after treatment (A,A1). OCTA revealed no significant changes in VD in SCP, DCP and CC at baseline (B,C,D) and after treatment (B1,C1,D1).

Table 2
Correlations between OCT, OCTA parameters and BCVA in responders and non responders groups.

Responders	R	P value	Non Responders	R	P value
CFT - BCVA	0.566	0.014	CFT - BCVA	0.74	0.114
SFCT - BCVA	−0.063	0.804	SFCT -BCVA	0.47	0.17
SCP whole - BCVA	−0.334	0.175	SCP whole - BCVA	−0.013	0.972
DCP whole - BCVA	−0.193	0.442	DCP whole - BCVA	−0.388	0.268
CC whole -BCVA	−0.559	0.016	CC whole - BCVA	0.159	0.661

BCVA: Best Corrected Visual Acuity; CFT: Central Foveal Thickness; SFCT: Subfoveal Choroial Thickness; SCP: Superficial Capillary Plexus; DCP: Deep Capillary Plexus; CC: Choriocapillaris.

with OCTA, VD in SCP and DCP and in contrast to our results, they didn't observe any changes 6 months after vPDT, possibly because of the presence of treatment-naïve patients in our study [5]. Recently Yu et al. demonstrated a significant increase of foveal outer nuclear layer (ONL) thickness in eyes with resolved CSC 12 months after half-dose vPDT [21]. This observation could be associated to the increase of VD in DCP, as underlined in our study. In fact the ONL thickening, when the subretinal fluid is reduced and the neuroretina reattaches to the EPR, could be associated to recovery of photoreceptors and therefore to the increase of VD in DCP, one of the main vascular network of photoreceptors [22]. Moreover, we hypothesized that with OCTA examination the early reduced VD in DCP could be attributed to a displacement of this retinal vascular network due to the subretinal fluid, resulting in a less visualization vascular rarefaction.

To the best of our knowledge this is the first study that associates retinal and choriocapillaris vessel density changes with BCVA in CSC after vPDT. The correlation between structural and functional parameters resulted important to better understand the effects of vPDT on this disease. Further longitudinal studies with a wider study group and a longer follow up are needed to better explain this relationship.

Being a retrospective study and the relatively small number of eyes examined in the responder and non-responder groups represent the potential limitations of this study.

In conclusion, OCTA improves our knowledge of the pathophysiology of vascular changes induced by low-fluence vPDT in CSC with the advantage of using a non-invasive and repeatable tool. OCTA could become a useful tool to evaluate the efficacy of low-fluence vPDT in the treatment of CSC.

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Declaration of Competing Interest

None.

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