Short Term Effects of Half-Fluence Photodynamic Therapy on Retinal Vessels and Choroid in Chronic Central Serous Chorioretinopathy

Osman Ahmet Polat[1], Zekeriya Çetinkaya[2], Çağatay Karaca[3]

ABSTRACT

Purpose: To evaluate the short-term effects of half-fluence photodynamic therapy (PDT) on retinal and choroidal vascular parameters obtained by optical coherence tomography angiography.

Materials and Methods: Fifteen patients who underwent half-fluence PDT for chronic central serous chorioretinopathy between 2018-2020 were included in the study retrospectively. Patients underwent optic coherence tomography angiography imaging before and after PDT. Foveal avascular zone (FAZ) area, FAZ perimeter, acircularity index, foveal vascular density 300 microns around FAZ, outer retina flow, choriocapillaris flow and the whole area, foveal, parafoveal and perifoveal vessel densities of superficial and deep capillary networks were compared before and after treatment.

Results: The vessel density of the superficial foveal capillary plexus was significantly decreased after PDT (p=0.044). However whole area, parafoveal and perifoveal vessel densities of superficial capillary plexus were not significantly different. The vessel density of the deep parafoveal capillary plexus was significantly increased after PDT (p=0.027). The whole area, foveal and perifoveal vessel densities of deep capillary plexus were not significantly different before and after PDT (p>0.05). Foveal avascular zone (FAZ) area, FAZ perimeter, acircularity index, outer retina flow and choriocapillaris flow did not change after photodynamic therapy in short term.

Conclusion: This study showed that vessel density of superficial foveal capillary plexus was decreased and vessel density of deep parafoveal capillary plexus was increased in short term after half fluence PDT. However, the foveal avascular zone area, ourter retinal and choroidal flow, choroidal signal voids and vascular densities of other remaining macular vascular areas were not changed.

Keywords: photodynamic therapy, chronic central serous chorioretinopathy, choroid, retinal vessel.

INTRODUCTION

Central serous chorioretinopathy (CSC) is characterized by serous detachment of the neurosensorial retina. It affects predominantly males at working age. Retinal pigment epithelium (RPE) dysfunction and hyperpermeable and thicker underlying choroid were blamed for the presence of subretinal fluid.[1]

Patients with CSC often complain of modestly reduced vision (usually unilateral), associated with scotoma in the central visual field and associated metamorphopsia.[2] Acute CSC is a self-limiting disease with spontaneous absorption of subretinal fluid and vision recovery in most of the patients within 4 months. However, approximately %5 of patients suffer from chronic CSC with persistent subretinal fluid [2]. There is no consensus for the duration threshold for chronic CSC and varies between 3-6 months in previous studies.[2]

Many treatment modalities were reported to be effective for chronic CSC treatment. However, currently available evidence suggests that half-dose (or half-fluence) photodynamic therapy (PDT) should be the treatment of choice.[3,4] PDT is based on local laser activation of verteporfin which is infused intravenously and thought to be effective mainly on choroid.[3,5,6]

1- Asst. Prof., MD, Erciyes University, Faculty of Medicine, Department of Ophthalmology, Kayseri, Turkey

2- MD, Kahramanmaraş Elbistan State Hospital, Kahmaranmaraş, Turkey

3- Asst. Prof., MD, Erciyes University, Faculty of Medicine, Department of Ophthalmology, Kayseri, Turkey

Received: 14.07.2021
Accepted: 17.03.2022

Ret-Vit 2022; 31: 251-256

DOİ:10.37845/ret.vit.2022.31.43

Correspondence Adress:
Osman Ahmet Polat
Erciyes University, Faculty of Medicine, Department of Ophthalmology, Kayseri, Turkey

Phone: +90 555 722 6755
E-mail: osmanahmet@gmail.com

Optic coherence tomography angiography (OCT-A) is a non-invasive imaging tool for vascular structures in the retina and choroid. It makes direct visualization of retinal and choroidal vessels possible with detecting movement of blood cells.[7] Choroidal vascular changes were reported with OCT-A imaging after PDT.[8] As primary pathology in CSC was supposed to be in the choroid, previous studies mainly focused on OCT-A imaging of choroid in patients who underwent PDT. However, verteporfin reaches the retinal vessels and PDT laser beam is also applied to the retinal vessels. To our best knowledge, very short-term effects of half fluence PDT on retinal vessel densities in OCT-A imaging for foveal, parafoveal and perifoveal regions have not been studied before. Therefore, retinal vessels may also be affected by PDT and should be analyzed in this manner.

This study aimed to evaluate the short-term effects of half-fluence PDT on retinal and choroidal vascular parameters obtained by OCT-A.

MATERIALS AND METHODS

Fifteen patients who underwent photodynamic therapy (PDT) for chronic central serous chorioretinopathy (CSC) between 2018-2020 were included in the study retrospectively.

The electronic charts of patients evaluated for ophthalmologic examination including best-corrected visual acuity (BCVA), anterior segment examination with slit-lamp, retinal examination with indirect binocular retinoscopy, fundus fluorescein angiography and OCT. Subretinal fluid was followed up with spectral-domain OCT (Spectralis, Heidelberg Engineering Inc., Heidelberg, Germany). Hyperfluorescent spots in FFA indicating active lesions in the choroid, subretinal serous fluid and increased choroidal thickness in enhanced depth imaging mode OCT (subfoveal choroidal thickness ≥300µm) were used as diagnostic criteria for CSC. The subretinal fluid which persisted for more than six months was accepted for chronic CSC.

Patients with systemic hypertension, refractive errors ≥ ±6 .0 diopters of spherical equivalent, ocular trauma, intraocular surgery, glaucoma, uveitis and previous PDT or PDT for other choroidal lesions in the electronic charts were excluded from the study. Images with a quality score lower than 6/10 and with eye movement artifacts were excluded from the study.

Half fluence photodynamic therapy was performed with a diode laser at 689 nm (Visulas 690S; Carl Zeiss Meditec Inc., Dublin, CA, USA) after infusion of verteporfin (Visudyne, Novartis AG, Bülach, Switzerland) at a dose of 6 mg/m^2 for 10 minutes. A fluence of 25 J/cm2, a light dose rate of 300 mW/cm^2 for 83 seconds was performed for each patient. The spot size was adjusted according to the size of hyperfluorescent hot spots in FFA and the size of subretinal fluid with paying attention to preserve the optic nerve. Patients were advised to wear protective goggles and to protect themselves from sunlight and bright light for five days.

OCT angiography (AngioVue, Optovue Inc., Fremont, California, USA) was performed before and after the photodynamic procedure. OCTA images (6 x 6 mm) were obtained by the Optovue Angiovue System (software RTVue XR, version 2017.1.0.151, Optovue Inc., Fremont, CA, USA). Foveal avascular zone (FAZ) area, FAZ perimeter, acircularity index of the FAZ (AI; the ratio of the circumference of the FAZ and the circumference of an equal area), foveal density 300 (vessel density within 300 µm around FAZ), outer retina and choriocapillaris flows in 1mm radius on the fovea and whole area, foveal, parafoveal and perifoveal vessel densities of superficial and deep capillary networks according to ETDRS(Early Treatment Diabetic Retinopathy Study) chart was recorded from the OCT angiography software.

Enface choriocapillaris images from the OCTA device were used to calculate choriocapillaris signal voids. Images

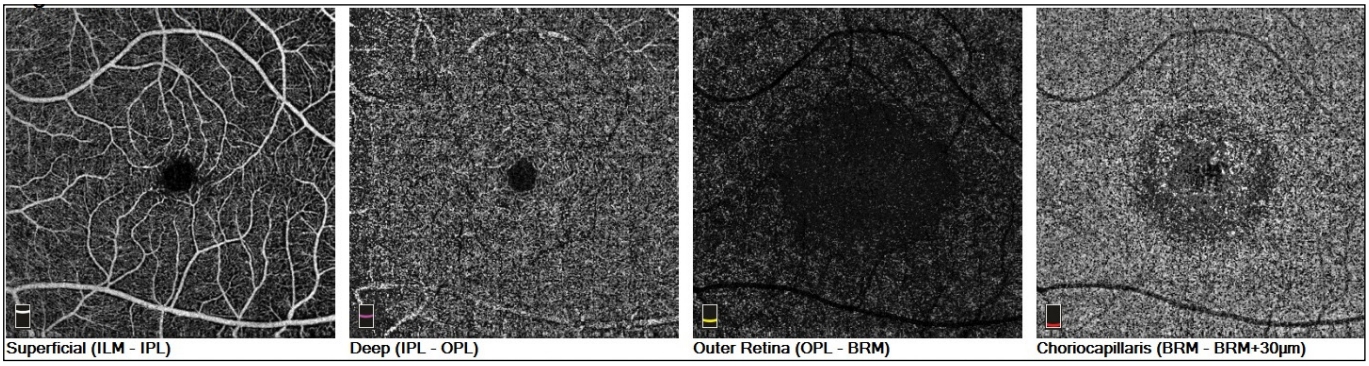

Figure 1: *Sample optical coherence tomography angiography images of a chronic central serous chorioretinopathy patient. Superficial, deep, outer retina and choriocapillaris sections are seen from left to the right, respectively.*

were imported to FIJI software (Plug-in added version of ImageJ, available at public domain: https://imagej.net/Fiji, version:1.53c). After binarization and thresholding in the software, the "calculate particle" function was used to analyze choriocapillaris signal voids which were the percentage of black pixels representing absent or decreased flow signal within CC.

The normal distribution of the data was tested with the Shapiro-Wilk test. The Wilcoxon test and independent t-test were used to compare OCT-A parameters before and after the half fluence photodynamic therapy. The data were presented as median and 15-75 percent. The p-value lower than 0.05 was accepted as statistical significance.

The study was conducted according to the tenets of the Helsinki Declaration and was approved by the ethical committee of Erciyes University's Medical Faculty (Number: 2021/152).

RESULTS

Fifteen patients (10 male and 5 female) who underwent PDT for chronic CSC were included in the study. The mean age was 42 ± 7 years. The first OCT-A images were obtained within 3 days before PDT. The following OCT-A images were performed mean of 6.3 days (min 2 – max 15) after PDT. The median duration of subretinal fluid was 8 months (min 6 – max 15).

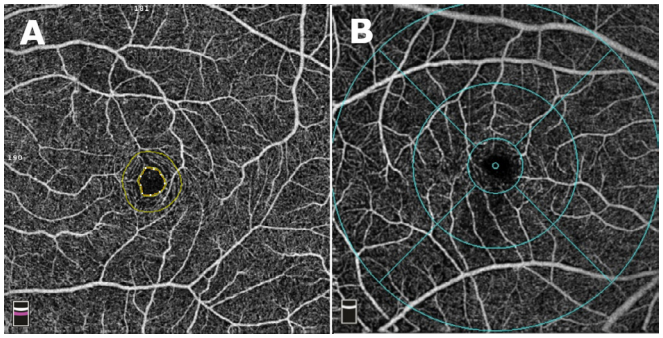

Figure 2: *A) Inner yellow ring: Foveal avascular zone (FAZ). Outer yellow ring: 300 µm around FAZ which is the border for calculation of foveal density 300. B) Foveal, parafoveal and perifoveal rings in the study.*

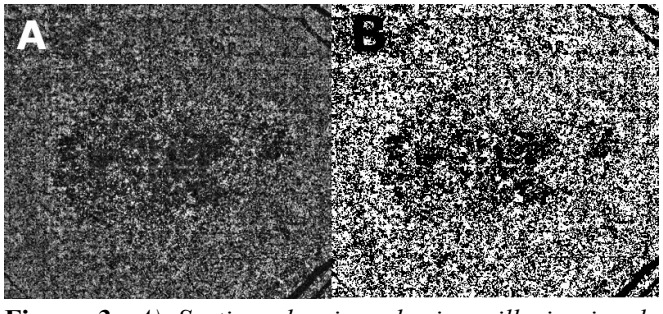

Figure 3: *A) Section showing choriocapillaris signals in optical coherence tomography B) Image afer after binarization and thresholding in the Fiji software.*

Visual acuity, FAZ area, FAZ perimeter, acircularity index, foveal density 300, outer retinal flow and choriocapillaris flow values were not significantly different before and short-term after PDT (Table 1). The vessel density of the superficial foveal capillary plexus was significantly decreased after PDT (p=0.044). However whole area, parafoveal and perifoveal vessel densities of superficial capillary plexus were not significantly different before and after PDT (Table 1). The vessel density of the deep parafoveal capillary plexus was significantly increased after PDT (p=0.027). The whole area, foveal and perifoveal vessel densities of deep capillary plexus were not significantly different before and after PDT (Table 1).

There was no significant correlation between time duration after PDT and superficial foveal vessel density (p=0.49) and deep parafoveal vessel density (p=0.20).

DISCUSSION

Standard dose and fluence PDT was used for choroidal neovascularization before the anti-VEGF era in age-related macular degeneration patients. Histological findings showed that PDT caused ischemia in ICG angiography and vaso-occlusion with thrombosis in human eyes. [9,10] Complications associated with standard fluence PDT were also reported including choroidal neovascular membrane, retina pigment epithelium damage, and vision loss in CSC patients.[9,10] Therefore, half-fluence or half-dose PDT was shown to have fewer complications and recommended for chronic CSC treatment.[11-15] The patients in this study underwent half fluence PDT for chronic CSC treatment.

To our best knowledge, very short-term effects of half fluence PDT on retinal vessel densities in OCT-A imaging for foveal, parafoveal and perifoveal regions have not been studied before. In this study, the CSC patients were evaluated mean of 6.3 days (min 2 – max 15) after the half-fluence PDT. Each foveal, parafoveal, perifoveal and whole regions according to ETDRS chart in superficial and deep capillary plexus were analyzed (Table 1). We found decreased vessel density of superficial foveal capillary plexus (p=0.044) and increased vessel density of deep parafoveal capillary plexus after half-fluence PDT (p=0.027). Other ETDRS areas were not affected in superficial and deep capillary plexus (Table 1). Demirel et al [16] reported that superficial and deep capillary plexus densities were not changed one month after half fluence PDT. However, they did not analyze the vessel densities in foveal, parafoveal and perifoveal regions and presented as the whole macular area and isolated changes in particular

Table 1: *OCT angiography parameters before and after half-fluence photodynamic therapy.*

Parameter	Before *Median (25-75 percentile)*	After *Median (25-75 percentile)*	P-value
Visual Acuity (log MAR)	0.4 (0.3 - 0.4)	0.5 (0.4 - 0.6)	**0.007**
FAZ Area (mm^2)	0.24 (0.18 - 0.33)	0.27 (0.20 - 0.36)	0.27
FAZ Perimeter (mm)	1.92 (1.67 - 2.22)	2.05 (1.75 - 2.3)	0.78
A-circularity Index	1.10 (1.08 - 1.11)	1.09 (1.07 - 1.11)	0.31
Foveal Density 300	52.03 (48.74 - 55.46)	52.40 (50.47 - 54.62)	0.78
Outer Retina Flow	0.37 (0.07 - 0.83)	0.28 (0.06 - 0.69)	0.92
CC Flow	1.71 (1.54 - 1.86)	1.75 (1.49 - 1.92)	0.82
Superficial Whole VD	51.3 (48.8 - 53.4)	50.0 (48.90 - 53.0)	0.73
Superficial Foveal VD	25.7 (19.7 - 29.3)	23.4 (15.1 - 30.4)	**0.044**
Superficial Parafoveal VD	53.2 (50.1 - 56.1)	51.0 (49.5 - 53.3)	0.53
Superficial Perifoveal VD	52.2 (50.3 - 54.5)	51.2 (49.4 - 53.4)	0.71
Deep Whole VD	49.3 (45.7 - 54.1)	51.7 (48.1 - 56.9)	0.11
Deep Foveal VD	36.2 (31.9 - 43.0)	38.1 (30.5 - 43.5)	0.57
Deep Parafoveal VD	52.1 (50.7 - 55.6)	54.7 (53.3 - 59.2)	**0.027**
Deep Perifoveal VD	51.2 (45.3 - 56.4)	51.8 (49.1 - 58.2)	0.26
CC Signal Voids	52.1 (51.3 – 52.9)	50.8 (49.2 – 53.03)	0.46

CC: choriocapillaris.

macular subfields might have overseen.[16] Cennamo et al[17] analyzed retinal vessel densities with OCT-A 6 months after PDT in CSC patients and they found no significant change in superficial capillary plexus. However, the authors found increased foveal, parafoveal and whole are deep capillary plexus densities after half-fluence PDT in the responder group but not in non-responders.[17] They did not report any measurements about the perifoveal region and OCT-A imaging was performed 6 months after the treatment. The results of our study showed in the short term after half fluence PDT. We hypothesized that the increased deep capillary plexus density could be related to the resorbing subretinal fluid which was compressing and displacing deeper capillary plexus. [17]

Chan et al showed that OCT-A high signal intensity in CSC patient and dilated vessels in the choriocapillaris in patients with CSC and the areas in OCT-A was consistent with the leaking areas in fundus fluorescein angiography and indocyanine green angiography.[18] Additionally, CC flow irregularities in OCTA imaging of CSC patients corresponding to leaking areas in ICG were also reported before.[19] OCT-A may also help to diagnose type 1 choroidal neovascularization (CNV) which is seen as RPE elevation in OCT images. OCT-A imaging was shown to reveal CNV corresponding to the hyperpermeable areas in ICGA in 58% of chronic CSC patients.[20] Thus, OCT-A is a valuable diagnostic and follow-up tool in CSC.

Cheng et al. analyzed the gray-color ratios ICGA and showed that 1 month after PDT 82.8% in the half-fluence group and 83.4% in the half-dose group were comparable to changes in ratios of fluorescence before PDT.[13] In another study, authors reported that none of the eyes in the half-fluence group had choroidal hypoperfusion at 1 year after the treatment, contrary to standard dose PDT.[12] These results may indicate that half-dose and half-fluence PDT have less hypoperfusion effect compared to standard PDT.

Decreased CC vessel density[21] and CC flow[22] were reported previously short-term after PDT. Demirel et al[16] showed increased choriocapillaris flow 1 and 6 months after half-fluence PDT. The authors concluded that PDT had a decreasing effect on larger choroidal vessels and spares CC flow.[16] In our study, choriocapillaris flow was not changed in short term after the PDT treatment (p=0.9). This might be explained by that remodeling in big choroidal vessels did not occur in short term and the compression effect of big choroidal vessels on choriocapillaris did not decrease yet.

Chan et al. found that vascular densities of the choriocapillaris and deep choriocapillaris layers were increased after half-dose PDT.[23] However the authors reported that large choroidal vessels were wider in affected eyes of CSC patients which decreased after PDT.[23] In another study, authors stratified the patients according to their responses to PDT and increased deep capillary and

choriocapillaris vessel density was reported 6 months after half-fluence PDT in responder CSC patients. They found a significant correlation between best-corrected visual acuity and choriocapillaris vessel density.[17] The authors hypothesized that PDT may produce a closure or a diameter reduction of the leaking choroidal vessels with decreased compression on the CC layer.

A temporary reduction of the luminal components of the CC and the choroid after half-dose PDT, which returned to baseline one month after PDT was shown before.[24] Liu et al showed that after half-dose PDT vascular alterations with increased flow signal voids in the choriocapillaris persisted at 6 months compared to control eyes and at 3 months compared to unaffected eyes of the patients.[25] In this study, there was no significant change for choroidal signal void ratio after PDT (Table 1). Ma et al[26] utilized swept-source optical coherence tomography en-face imaging binarization and reported that choriocapillaris vascular proportions were decreased after 6 weeks, 6 months and 12 months after half fluence PDT. However, the authors showed that Haller's and Sattler's layers did not change 6 weeks after PDT but decreased after 6 and 12 months.[26] Their results may point to delayed choroidal remodeling, as our study analyzed short-term effects within 3 weeks choriocapillaris flow and signal voids may have remained unchanged (Table 1).

Decreased FAZ area was shown previously 1 and 3 months after half-dose PDT with OCT angiography.[27] In our study half-fluence PDT was performed and in short term and there was no significant difference before and after the treatment for the FAZ area (Table 1). In the same study, vessel density in the 300 microns concentric ring outside the FAZ was decreased after 1 month of PDT treatment.[27] Additionally, the authors found that the vessel density of superficial vessel density was significantly decreased 1 and 3 months after the PDT treatment.[27] Foveal vessel density was not changed in short term for similar 300 microns concentric ring in our study (Table 1). These differences may be explained by the different treatment modalities used for the patients.

Even pointing novel information about half-fluence PDT in the very short term, this study had several limitations. The study sample size was relatively small, and the study had a retrospective nature. The longer OCT-A imaging follow-up of CSC patients was not available and included in the study.

CONCLUSION

This study showed that vessel density of superficial foveal capillary plexus was decreased and vessel density of deep parafoveal capillary plexus was increased in short term after half fluence PDT. However, the foveal avascular zone area, choroidal flow, choroidal signal voids and vascular densities of other remaining macular vascular areas were not changed.

REFERENCES

1. Kaye R, Chandra S, Sheth J, et al. Central serous chorioretinopathy: An update on risk factors, pathophysiology and imaging modalities. Prog Retin Eye Res. 2020;79:100865.
2. Semeraro F, Morescalchi F, Russo A, et al. Central Serous Chorioretinopathy: Pathogenesis and Management. Clin Ophthalmol. 2019;13:2341-52.
3. van Rijssen TJ, van Dijk EHC, Yzer S, et al. Central serous chorioretinopathy: Towards an evidence-based treatment guideline. Prog Retin Eye Res. 2019;73:100770.
4. Nicolo M, Desideri LF, Vagge A, et al. Current Pharmacological Treatment Options for Central Serous Chorioretinopathy: A Review. Pharmaceuticals (Basel). 2020;13:264.
5. Chan WM, Lam DS, Lai TY, et al. Choroidal vascular remodelling in central serous chorioretinopathy after indocyanine green guided photodynamic therapy with verteporfin: a novel treatment at the primary disease level. Br J Ophthalmol. 2003;87:1453-8.
6. Taban M, Boyer DS, Thomas EL, et al. Chronic central serous chorioretinopathy: photodynamic therapy. Am J Ophthalmol. 2004;137:1073-80.
7. Da Pozzo S, Iacono P, Arrigo A, et al. The Role of Imaging in Planning Treatment for Central Serous Chorioretinopathy. Pharmaceuticals (Basel). 2021;14:105.
8. Xu Y, Su Y, Li L, et al. Effect of Photodynamic Therapy on Optical Coherence Tomography Angiography in Eyes with Chronic Central Serous Chorioretinopathy. Ophthalmologica. 2017;237:167-72.
9. Schmidt-Erfurth U, Laqua H, Schlötzer-Schrehard U, et al. Histopathological Changes Following Photodynamic Therapy in Human Eyes. Archives of Ophthalmology. 2002;120:835-44.
10. Schlotzer-Schrehardt U, Viestenz A, Naumann GO, et al. Dose-related structural effects of photodynamic therapy on choroidal and retinal structures of human eyes. Graefes Arch Clin Exp Ophthalmol. 2002;240:748-57.
11. Sartini F, Figus M, Nardi M, et al. Non-resolving, recurrent and chronic central serous chorioretinopathy: available treatment options. Eye (Lond). 2019;33:1035-43.
12. Reibaldi M, Cardascia N, Longo A, et al. Standard-fluence versus low-fluence photodynamic therapy in chronic central serous chorioretinopathy: a nonrandomized clinical trial. Am J Ophthalmol. 2010;149:307-315 e302.
13. Cheng CK, Chang CK, Peng CH. Comparison of Photodynamic Therapy Using Half-Dose of Verteporfin or Half-Fluence of Laser Light for the Treatment of Chronic Central Serous Chorioretinopathy. Retina. 2017;37:325-333.
14. Shin JY, Woo SJ, Yu HG, et al. Comparison of efficacy and safety between half-fluence and full-fluence photodynamic therapy for chronic central serous chorioretinopathy. Retina. 2011;31:119-26.

15. Lim SH, Chang W, Sagong M. Efficacy of half-fluence photodynamic therapy depending on the degree of choroidal hyperpermeability in chronic central serous chorioretinopathy. Eye (Lond). 2013;27:353-62.
16. Demirel S, Ozcan G, Yanik O, et al. Vascular and structural alterations of the choroid evaluated by optical coherence tomography angiography and optical coherence tomography after half-fluence photodynamic therapy in chronic central serous chorioretinopathy. Graefes Arch Clin Exp Ophthalmol. 2019;257:905-12.
17. Cennamo G, Montorio D, Comune C, et al. Study of vessel density by optical coherence tomography angiography in patients with central serous chorioretinopathy after low- fl uence photodynamic therapy. Photodiagnosis Photodyn Ther. 2020;30:101742.
18. Chan SY, Wang Q, Wei WB, et al. Optical Coherence Tomographic Angiography in Central Serous Chorioretinopathy. Retina. 2016;36:2051-8.
19. Teussink MM, Breukink MB, van Grinsven MJ, et al. OCT Angiography Compared to Fluorescein and Indocyanine Green Angiography in Chronic Central Serous Chorioretinopathy. Invest Ophthalmol Vis Sci. 2015;56:5229-37.
20. Quaranta-El Maftouhi M, El Maftouhi A, Eandi CM. Chronic central serous chorioretinopathy imaged by optical coherence tomographic angiography. Am J Ophthalmol. 2015;160:581-587 e581.
21. Nassisi M, Lavia C, Alovisi C, et al. Short-Term Choriocapillaris Changes in Patients with Central Serous Chorioretinopathy after Half-Dose Photodynamic Therapy. Int J Mol Sci. 2017;18:468.
22. Demircan A, Yesilkaya C, Alkin Z. Early choriocapillaris changes after half-fluence photodynamic therapy in chronic central serous chorioretinopathy evaluated by optical coherence tomography angiography: Preliminary results. Photodiagnosis Photodyn Ther. 2018;21:375-8.
23. Chan SY, Pan CT, Wang Q, et al. Optical coherent tomographic angiographic pattern of the deep choroidal layer and choriocapillaris after photodynamic therapy for central serous chorioretinopathy. Graefes Arch Clin Exp Ophthalmol. 2019;257:1365-72.
24. Alovisi C, Piccolino FC, Nassisi M, et al. Choroidal Structure after Half-Dose Photodynamic Therapy in Chronic Central Serous Chorioretinopathy. J Clin Med. 2020;9:2734.
25. Liu J, Chen C, Li L, et al. Assessment of choriocapillary blood flow changes in response to half-dose photodynamic therapy in chronic central serous chorioretinopathy using optical coherence tomography angiography. BMC Ophthalmol. 2020;20:402.
26. Ma DJ, Park UC, Kim ET, et al. Choroidal vascularity changes in idiopathic central serous chorioretinopathy after half-fluence photodynamic therapy. PLoS One. 2018;13:e0202930.
27. Xu F, Zhou L, Lai K, et al. Quantitative Evaluation of Retinal Vessel Density in Central Serous Chorioretinopathy after Half-dose Photodynamic Therapy. Curr Eye Res. 2021:1-10.