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Early retinal and choroidal effect of photodynamic treatment in patients with polypoidal choroidal vasculopathy with or without anti-vascular endothelial growth factor: An optical coherence tomography angiography study

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ABSTRACT

Purpose: To evaluate the early retinal and choroidal effects of the anti-vascular endothelial growth factor (anti-VEGF) therapy combined with photodynamic therapy (PDT) for polypoidal choroidal vasculopathy (PCV).
Methods: Patients diagnosed as having PCV were included in the study. In group 1, intravitreal ranibizumab and PDT was applied to six eyes. In group 2, PDT treatment only was applied to four eyes. Optical coherence tomography (OCT) angiography images and best-corrected visual acuity (BCVA) were taken from all patients before treatment and 3 days after surgery.
Results: The mean age of the patients was 66.00 ± 6.28 years. In group 1, the initial BCVA was 0.70 ± 0.35 logMAR and the final BCVA was 1.1 ± 0.78 logMAR. In group 2, the initial BCVA was 0.47 ± 0.17 logMAR and the final BCVA was 0.50 ± 0.21 logMAR. In group 1, flow rate significantly decreased in the superficial area ($p = 0.028$), the flow rate also decreased in other layers but they were not statistically significant ($p < 0.05$). In group 2, the flow rate decreased but these changes were not statistically significant ($p > 0.05$). Vascular constriction and choroidal ischemia were seen in two patients in group 1.
Conclusion: In the short term, retinal and choroidal blood flow decreased after PDT treatment. However, statistically significant changes were seen only in the superficial area in group 1.

1. Introduction

Polypoidal choroidal vasculopathy (PCV) is a choroidovascular disease characterized by the presence of a branching vascular network (BVN) and choroidal polyps on indocyanine green angiography (ICGA) [1]. ICGA is the most effective method for the diagnosis of PCV [1]. However, ICGA is an invasive method. In contrast, optical coherence tomography angiography (OCTA) is a quick and non-invasive method for diagnosing and following up PCV. Recurrent episodes of exudative retinal detachment, serous or hemorrhagic pigment epithelial detachment (PED), subretinal hemorrhage, and subretinal exudation have been seen on OCT and OCTA imaging [2,3]. Also reddish-orange subretinal nodules seen during the ophthalmoscopic examination may be helpful in the diagnosis of PCV [2]. Eyes with PCV, especially those with a cluster of grape-like polypoidal dilations of the vessels, have higher risks of severe visual loss.

Recent studies determined that anti-vascular endothelial growth factor (VEGF) leads to stabilization of vision, resolution of subretinal hemorrhage, and decreases in macular edema in PCV. However, polypoidal complexes decreased in only 33% [4]. Among the currently available treatment modalities for PCV, verteporfin photodynamic therapy (PDT) seems the most promising, with complete regression of polyps in 73%–99% of patients and stabilized or improved visual acuity (81–100%) [5]. The EVEREST study showed that verteporfin PDT combined with ranibizumab 0.5 mg or alone PDT was superior to ranibizumab (anti-VEGF) monotherapy in achieving complete regression of polyps [6]. Although PDT's effect on the treatment of PCV is noticeable, some adverse effects of this treatment are pronounced. Accordingly, this treatment merits rigorous scrutiny. Therefore, the aim of this study was to determine the early effects of PDT + anti-VEGF and PDT treatment only using OCTA [Optovue].

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2. Methods

2.1. Study design

In this retrospective study, we reviewed the medical records of patients who had PCV and received PDT between January and March 2017. All patients who were diagnosed as having PCV using ICGA, OCT, and OCTA were included in the study and randomly divided into two groups. Group 1; six eyes received PDT after anti-VEGF, group 2; four eyes received PDT only.

Patients with PCV who had no OCT angiography images before treatment were excluded from the study.

Patients with co-existing retinal diseases (e.g., diabetic retinopathy, hypertensive retinopathy, epiretinal membrane) or media opacities that could decrease the visual acuity were not included. Also, those with polyps not located in the foveal 3 × 3 mm foveal OCTA imagining zone excluded from the study.

Written informed consent for the treatment was obtained from all patients, and the study adhered to the tenets of the Declaration of Helsinki.

2.2. Ophthalmic examination

Patients age, sex, OCT angiography, best-corrected visual acuity (BCVA), baseline, before treatment, and 3 days after treatment were collected.

All patients underwent a standardized examination including measurement of BCVA using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at 4 m, slit-lamp biomicroscopy and fundus examination, and measurement of intraocular pressure (IOP) using a Goldmann applanation tonometer. ICGA, OCT imaging (Optovue,Heidelberg, Germany), and OCTA were performed before treatment and within one week after treatment. ICGA was performed using a retinal angiograph (HRA, Heidelberg Engineering, Heidelberg, Germany) with a 30° field of view. OCTA scans were performed using the OCTA system (RTVue- XR Avanti, Optovue Inc., Fremont, CA, USA).

2.3. PDT procedure

A 689-nm laser system (Carl Zeiss, Dublin, CA, USA) was used with an indirect lens (Volk Area Centralis®). All patients underwent light energy (50 J/cm^2) using standard visudyne at a dose of 6 mg/m^2 body surface area, diluted in 30 mL infusion solution in a 10-minute intravenous infusion and time for laser emission (83 s). After PDT, all patients were told to wear protective spectacles and avoid light for 72 h.

2.4. OCT angiography measurement

OCT angiography is a device that allows visualization of the retinal and choroidal vasculature and measurements of blood flow via motion contrast by detecting movement of erythrocytes. The OCTA machine operated at 70,000 A-scans per second to acquire OCTA volumes consisting of 304 × 304 A-scans. OCTA allows visualization four layers of the eye (superficial capillary plexus layer, deep capillary plexus layer, outer retinal layer, and choriocapillaris). Superficial capillary plexus layer images indicate the vasculature from the inner limited membrane to 15 μm below the inner plexiform layer (IPL); deep capillary plexus layer images indicate the vasculature from 15 μm below the IPL to 70 μm below the IPL, and deep capillary layer images represent both median and deep capillary plexus layers (Figs. 1–4). OCTA images (3 × 3 mm) of the central macula were performed to evaluate flow area (Fig. 5).

2.5. Treatment method

Group 1; all injections were performed under sterile conditions after topical anesthesia, 10% povidone-iodine (Betadine; Purdue Pharma, Stamford, CT) scrub was used on the lids and lashes, and 5% povidone-iodine was administered on the conjunctival sac. Intravitreal ranibizumab 0.5 mg/0.5 mL (Lucentis; Novartis, Basel, Switzerland) was injected through the pars plana at 3.5 mm posterior to the limbus with a 30-gauge needle. Three days after the intravitreal injection, standard verteporfin photodynamic therapy (vPDT) and standard protocol (verteporfin 6 mg/m^2, vPDT laser fluence 50 J/cm^2) were applied. Three days after treatment was completed, macular vascular flow was examined using OCTA.

Group 2; Only standard vPDT laser was applied to the PCV areas. Three days after treatment, macular vascular flow was examined using OCTA.

Patients were instructed to return to the hospital if they experienced decreased vision, eye pain, or any new symptoms.

Primary outcome measures of this study included the change in BCVA and OCTA findings.

2.6. Statistical analysis

Visual acuity was converted to the logarithm of the minimum angle of resolution (LogMAR) for statistical analysis. Categorical variables are presented as numbers and percentages, and numeric variables are expressed as mean and standard deviation. The visual acuity and the macular vascular flow values between baseline and the other time points were assessed using the repeated measures test. Categorical variables were compared using the Chi-square test. P values < 0.05 were considered statistically significant.

3. Results

The mean age of the patients was 66.00 ± 6.28 years. The mean age in group 1 (anti-VEGF + PDT) and group 2 (PDT) was 64.50 ± 5.24 years and 68.25 ± 7.84 years, respectively. There were 2 females and 4 males in group 1, and 2 females and 2 males in group 2. There was no significant difference between the two groups as regards sex ($p < 0.05$). In group 1, the initial BCVA was 0.70 ± 0.35 logMAR and the final BCVA was 1.1 ± 0.78 logMAR. In group 2, the initial BCVA was 0.47 ± 0.17 logMAR and the final BCVA was 0.50 ± 0.21 logMAR.

Upon comparison of the foveal flow rate change in the layers in group 1 before and after treatment, we saw a reduction in foveal flow rate in all layers. However, statistically significant changes in the flow area were only seen in the superficial area ($p = 0.028$); flow rate in this area decreased after treatment. When the flow areas were considered in group 2 before and after treatment, although foveal flow rates decreased, no statistically significant changes were observed in any areas ($p < 0.05$).

Serious visual impairment, decreased retinal and choroidal blood flow and increased serous retinal detachment were observed with two patients in group 1 under OCTA (Fig. 6). These two patients' visual acuity decreased to finger counting at one meter from 20/100.

We did not see a closing of the previous polyps and BVN in the early period that was previously seen via ICGA. However, blood flowing areas were generally decreased.

4. Discussion

PDT is an established treatment modality for PCV. The mechanism of action involves a vaso-occlusive effect. When PDT activates the photosensitizer verteporfin at the laser-applied area, it induces vascular thrombosis, reduced perfusion, and PCV regression. A high polyp regression rate of 82%–95% with PDT monotherapy was reported. The EVEREST study reported that verteporfin combined with ranibizumab or PDT alone was superior to ranibizumab monotherapy in achieving complete polyp regression (77.8% and 71.4% vs. 28.6%) in patients

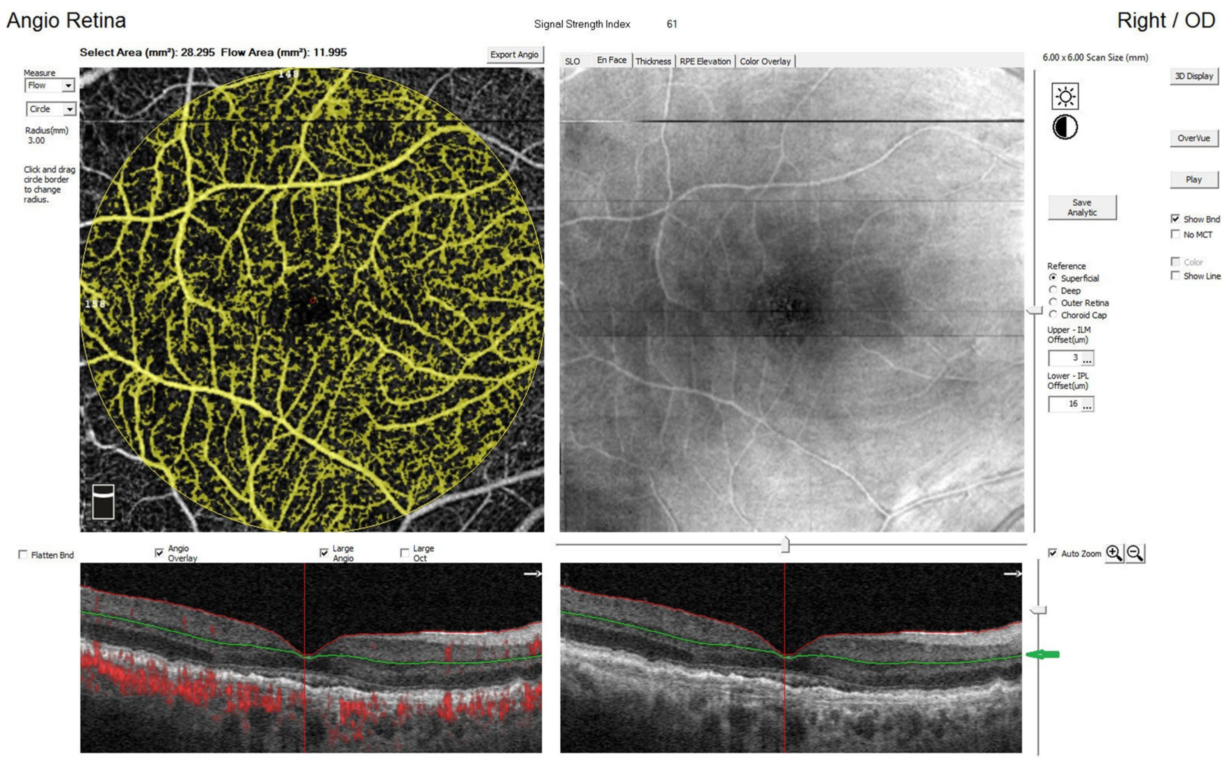

Fig. 1. The flow rate of the superficial zone via OCTA (Green arrow shows the superficial zone of the retina).

with PCV [6]. Gomi et al. showed that vision was improved in 67% of patients with PDT, 17% remained stable, and polyps regressed in 86% of patients in the one-year follow-up period [7]. Ruambiboonsuk et al. reported polyp regression and improved visual acuity following the combined therapy [8].

In the literature there are many reports about the effects PDT and adverse effects. However, the early effects of PDT treatment for PCV have been not assessed very well with OCTA. Intravitreal ranibizumab injection 24–48 h following PDT effectively maintains the level of visual acuity in the eye with PCV, and PDT followed by intravitreal anti-VEGF agents may provide a higher proportion of polyp regression [9]. In our study, we applied PDT after anti-VEGF injection in group 1, and PDT

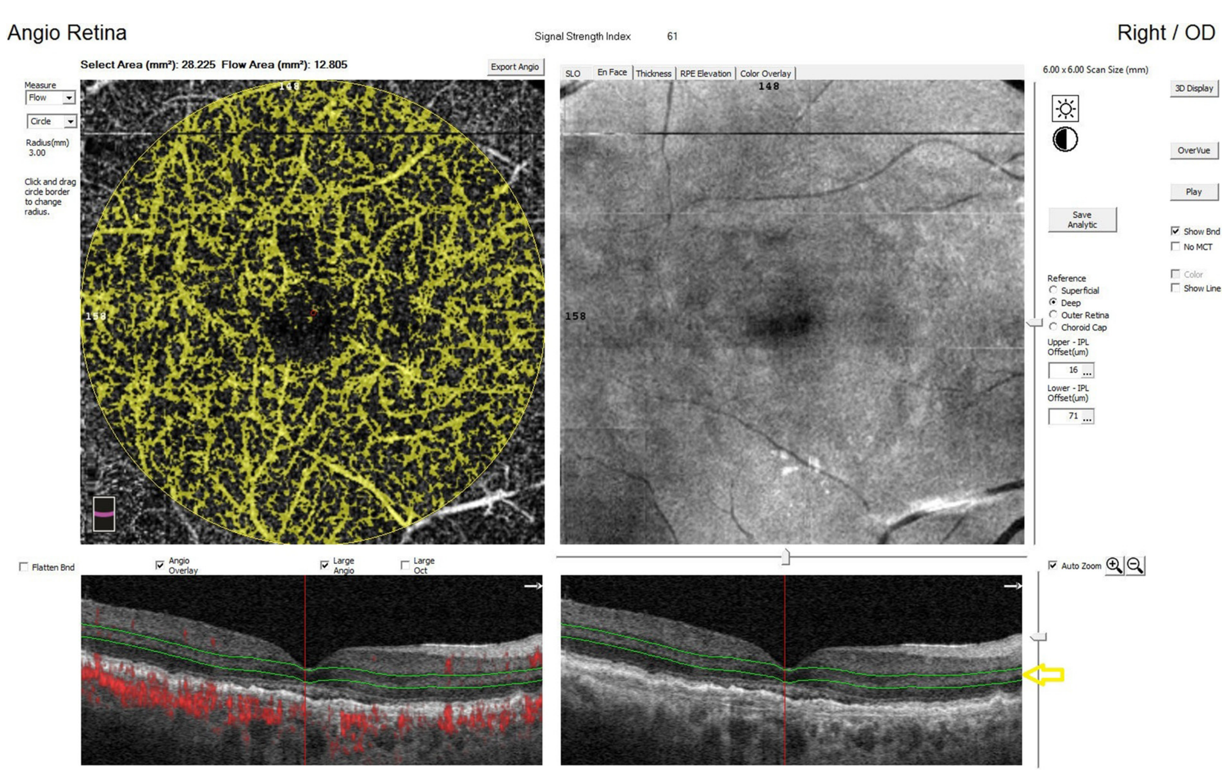

Fig. 2. The flow rate of the deep retinal zone via OCTA (Yellow arrow shows deep retinal zone).

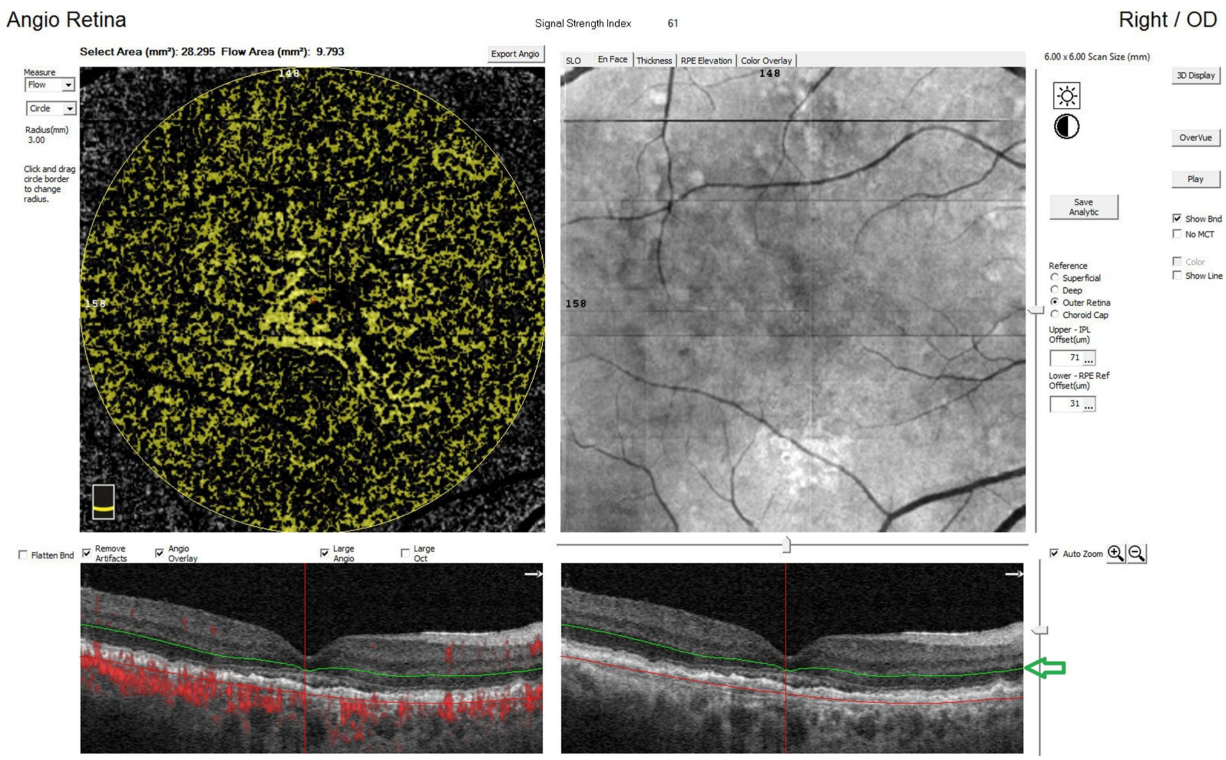

Fig. 3. The flow rate of the outer retinal zone via OCTA (Green arrow shows outer retinal zone).

only in group 2. Choroidal ischemia was seen in two patients in group 1 in the early period. The cause was probably linked with the effect of severe reduction of choroidal perfusion in the combined treatment.

OCTA, which is a non-invasive imaging technology, can visualize chorioretinal microcirculation without an intravenous dye injection, and also it can detect the blood flow of PCV in a short time [10–13]. In the study by Wang et al., 12 patients with PCV were evaluated using OCTA, and it was observed that flow signals were generated in different patterns. These different flow signals of the polypoid lesion and BVN can help us to understand the pathology of PCV [14].

Following the introduction of OCTA, studies are being performed to evaluate its advantages and disadvantages against invasive methods

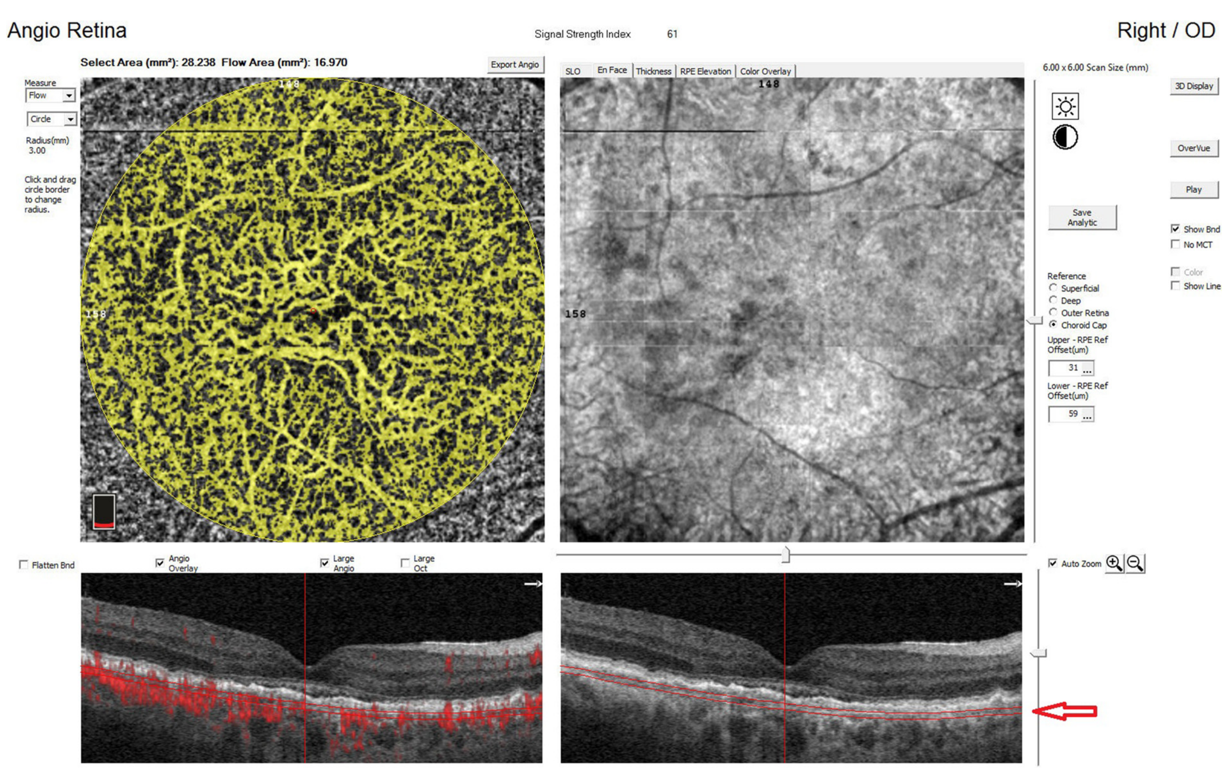

Fig. 4. The flow rate of the choroidal zone via OCTA (Red arrow shows choroidal zone).

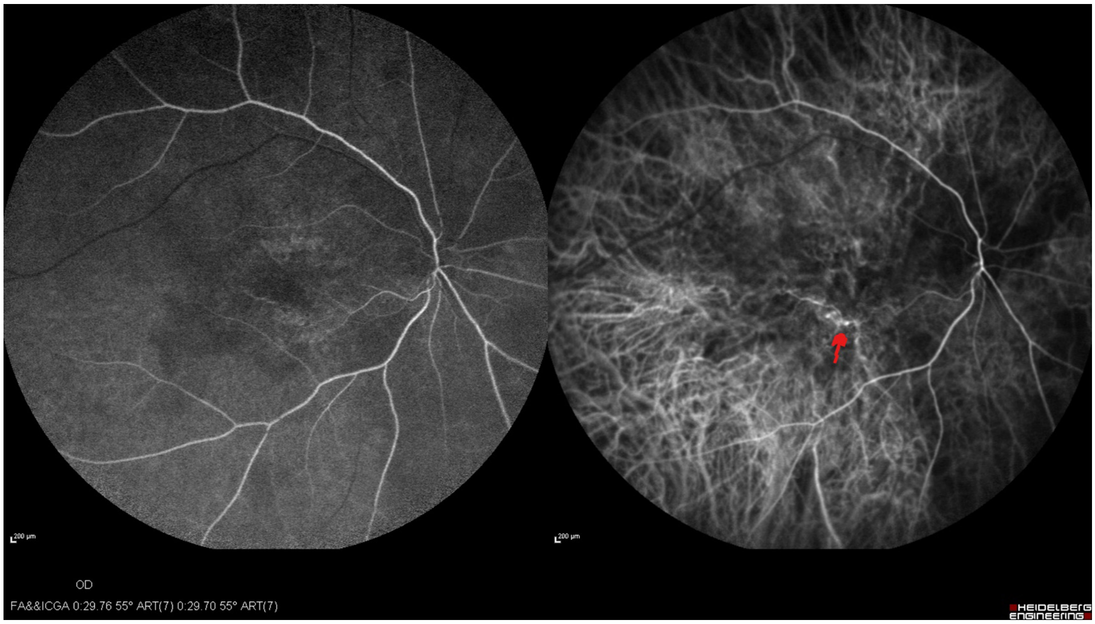

Fig. 5. The red arrow shows polyps and BVN in ICGA image.

(fundus fluorescein angiography and ICG) as regards anatomic and functional imaging. In the study of Inoue et al., 7 patients with PCV were evaluated using OCTA. It was found that OCTA was as successful as ICGA in providing anatomic information about BVN and type 1 NV in PCV. However, OCTA demonstrated only 42.9% of the polyps indicated [15]. Tomiyasu et al. showed that OCTA could detect polyps in 85% of cases, and suggested that the failure in determining polys was related to poor blood flow in the polyp because OCTA actually detected the blood vessel within it [16]. Kim et al. detected only 50% of polyps using OCTA as hyperreflective lessons lesions in the outer layer of the retina [17]. Peiretti et al. reported that OCTA detected 90% of PCV due to chronic central serous chorioretinopathy in their retrospective study [18].

Tomiyasu et al. also followed the pre- and post-treatment (at months 1 and 4) flow area within the polyp and polyp size after treatment with anti-VEGF in one patient using OCTA without dye injection, and reported that OCTA could be beneficial in monitoring the progression and recurrence of polyps throughout the follow-up [16]. In our study, we evaluated early retinal and visual changes after PDT and PDT- anti-VEGF combinations (three days after treatment). We saw that two

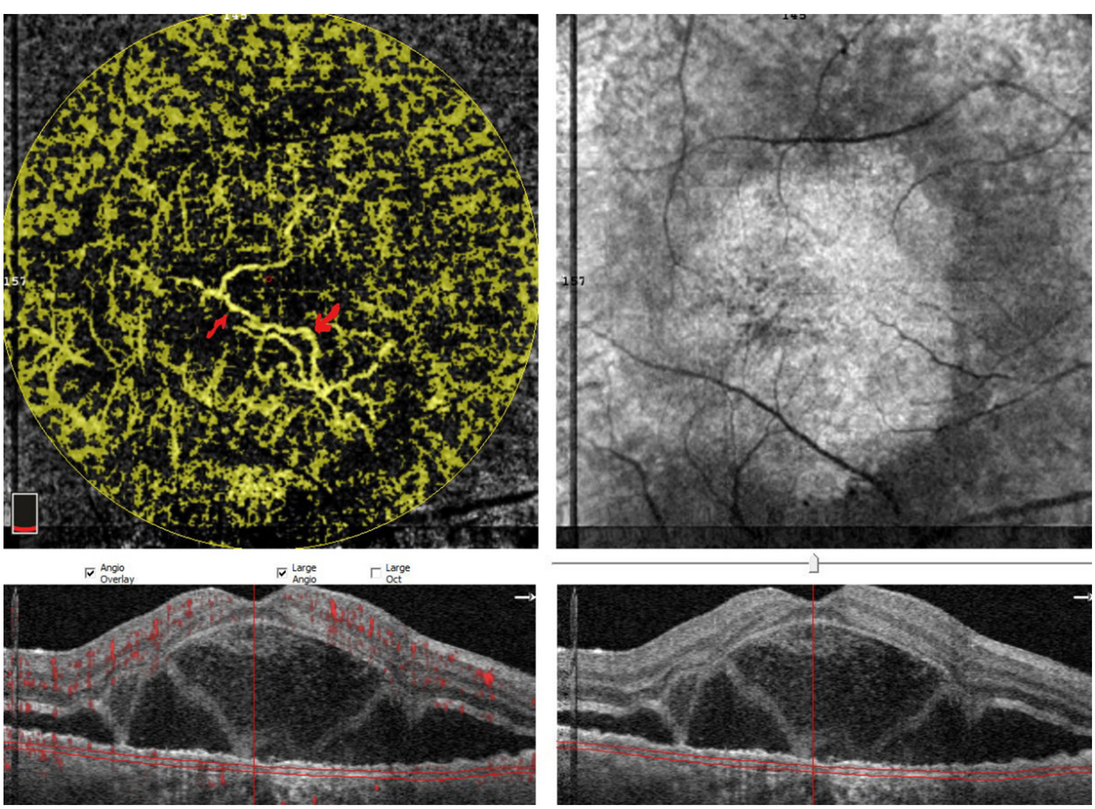

Fig. 6. Decreased choroidal flow rate and serous detachment but branching vascular network and polyp (red arrows show) still seen with OCTA.

patient's vision decreased after treatment in group 1, but the other patients maintained their vision in both group 1 and group 2. It was seen that two patients with severely impaired vision had a decreased flow rate in all 4 layers of the eye. In particular, it was marked in the choroidal line. It was also observed that the image of the polyp became even more prominent in relation with the decrease of flow in other areas despite the flow decrease in the choroidal area. Therefore, OCTA could be used as an effective and noninvasive method to show the progression and recurrence of the polyp in the early period. Although the post-treatment choroidal blood decrease is an expected finding indicating a response to treatment, sometimes serious choroidal blood flow decrease related to photodynamic therapy can result in ischemia, and consequently, visual impairment and serous detachment. According to our study's results, we can say that OCTA is a noninvasive and easy follow-up method to monitor choroidal blood flow after PDT treatment.

Visual loss in PCV occurs depending on recurrence, subretinal hemorrhage, and the greatest linear diameter of the baseline lesion [7,19]. However, subretinal hemorrhage related to the recurrence of polyps outside the PDT lesion was reported as a risk factor for resulting poor vision after PDT treatment [9]. In our study, although sudden visual impairment developed in two patients within 3 days of treatment there was no subretinal hemorrhage in these two patients; however, there was very prominent choroidal ischemia and polyp progression seen under OCTA. Demircan et al. using OCTA reported decreased choroidal perfusion after half-fluence PDT treatment for chronic central serous chorioretinopathy [20]. Our study also showed decreased choroidal perfusion after full-fluence PDT but choroidal ischemia could be seen after full-fluence and intravitreal anti-VEGF combination treatment.

The main limitation of the present study is that it had low participant numbers. However, there are some strengths such as using a new method (OCTA) for the assessment of PDT's effect on choroidal flow for PCV treatment. Also, we assessed PDT's adverse effects and we included a combination treatment group (anti-VEGF + PDT) to assess whether adding anti-VEGF affected choroidal flow due to PDT.

We did not see a closing of the polyps and BVN in the early period. However, blood flowing areas were generally decreased. In the EVEREST study, highly successful results were reported [6]. The effect of photodynamics on polyps and BVN probably starts in the late period with some reactions. To clarify these reactions, further studies are needed. We hope our study draws attention to this issue.

Choroidal ischemia and visual loss related to PDT treatment are possible in the early period. Therefore, further studies are required for patients with visual loss developing in the early period to cast light on the pathology using OCTA, which is a noninvasive method and provides important information on the anatomy and blood flow in the choroidal and other layers.

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Conflict of interest

The authors report no other conflicts of interest in this work.

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