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RETINAL DISORDERS

Two-year results of combined intravitreal ranibizumab and photodynamic therapy for polypoidal choroidal vasculopathy

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Abstract
Background To clarify the efficacy of combined therapy with intravitreal ranibizumab injections and photodynamic therapy (PDT) in patients with symptomatic polypoidal choroidal vasculopathy (PCV).
Methods We retrospectively reviewed 57 treatment-naïve eyes of 57 patients. Thirty-two patients were treated with standard fluence PDT (PDT group), and 25 patients were treated with three consecutive monthly intravitreal injections of ranibizumab and standard fluence PDT (ranibizumab plus PDT group). All patients were followed for at least 24 months.
Results In the ranibizumab plus PDT group, the mean best-corrected visual acuity (BCVA) levels of decimal (logMAR equivalent) significantly improved from 0.30 (0.52) at baseline to 0.55 (0.26) at 24 months ($P<0.001$). In the PDT group, the BCVA levels stabilized from 0.26 (0.58) at baseline to 0.25 (0.60) at 24 months. The mean changes in the BCVA in the ranibizumab plus PDT group and the PDT group were improvement of 2.63 lines and decline of 0.16 lines respectively ($P=0.010$). The mean number of PDTs at 24 months in the ranibizumab plus PDT group and the PDT group were 1.4 and 2.6 respectively. Increased subretinal hemorrhages were seen in eight (18.0 %) eyes, all of which were belonging to the PDT group.
Conclusions Combined intravitreal ranibizumab and PDT was significantly more effective in maintaining and improving VA for PCV patients compared with PDT monotherapy over 24 months.

Keywords Polypoidal choroidal vasculopathy · Ranibizumab · Photodynamic therapy · Vascular endothelial growth factor · Indocyanine green angiography · Age-related macular degeneration · Retinal pigment epithelial detachment · Optical coherence tomography · Retinal pigment epithelium · Bevacizumab

Introduction

Polypoidal choroidal vasculopathy (PCV) is a distinct clinical entity characterized by a branching choroidal vascular network and polypoidal vascular dilations at the border of the network, which was first identified by Yannuzzi et al. [1]. in 1990. Indocyanine green angiography (ICGA) is important for definitively diagnosing PCV, due to it being able to show the abnormal vascular structure clearly [1–4]. It is well-known that PCV is highly prevalent in Asian patients with age-related macular degeneration (AMD), and also develops in Caucasian patients [4–6]. In the natural history of PCV, half of the patients had persistent leakage or repeated bleeding and a poor visual outcome [7]. Therefore, an accurate diagnosis and an appropriate treatment is indispensable for managing patients with PCV.

Choroidal neovascularization (CNV) complexes are comprised of vascular endothelial growth factor (VEGF) [8, 9]. VEGF factors were coexpressed and increased with a positive correlation in the aqueous humor of eyes with active PCV

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[10]. Major clinical trials first reported that ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA, USA) was effective in improving visual acuity (VA) for AMD patients [11, 12]. Treatment using intravitreal ranibizumab has become one of the evidence-based therapy for AMD all over the world [13]. However, anti-VEGF therapy for PCV using bevacizumab (Avastin, Genentech, Inc.) as well as ranibizumab has been reported to be less useful for occluding polypoidal lesions [14–16].

Photodynamic therapy (PDT) with verteporfin (Visudyne®, Novartis Pharma AG, Basel, Switzerland) is effective treatment for PCV patients, and acts by occluding the polypoidal lesions with high efficiency [17–19]. However, 2-year follow-up PDT studies in patients with PCV reported a decline in VA and a high proportion of recurrence of polypoidal lesions [19–21]. In addition, increased subretinal hemorrhages, a well-known complication, may occur after PDT [17–19, 21]. Treatment with combined therapy of anti-VEGF agents and PDT has been reported to be effective for maintaining and improving visual acuity (VA) [22–28]. We also reported the efficacy of combined therapy of ranibizumab and PDT for PCV patients with 6- and 12-month follow-up periods [25, 29]. Recently, the EVEREST study has shown the superior efficacy of intravitreal ranibizumab and PDT or PDT monotherapy compare with ranibizumab monotherapy in achieving complete regression of polyps (77.8 % and 71.4 % vs 28.6 %) in PCV patients with a 6-month follow-up [30].

The purpose of the current study was to clarify the efficacy of combined therapy of intravitreal ranibizumab injections and PDT for patients with symptomatic PCV over 24 months. We also compared the results of combined therapy of ranibizumab and PDT with the previous results of PDT monotherapy for patients with PCV.

Methods

We retrospectively reviewed 57 treatment-naïve eyes of 57 Japanese patients (44 men, 13 women; age range, 54–85 years; mean ± standard deviation, 74.6±7.4 years) with PCV. After the potential risks and benefits were explained in detail, all patients provided written informed consent for the treatment and the retrospective chart review in this study. Thirty-two of the 57 eyes were treated using PDT monotherapy (PDT group) from May 2004 to June 2005, and the remaining 25 eyes were treated using combined therapy of intravitreal ranibizumab injections and PDT from May 2009 to February 2010 (ranibizumab plus PDT group). Ranibizumab became available for medical use in Japan from March 2009. All patients had a baseline VA of 20/40 (0.5 decimal VA) or less, and were followed for at least 24 months at Fukushima Medical University Hospital. The 24-month results for 15 of the 32 eyes in the PDT group, and the 12-month results for 21 of the 25 eyes in the ranibizumab plus PDT group, have been reported previously [19, 29]. The institutional review board/ethics committee at Fukushima Medical University approved the retrospective chart review study of AMD and the retrospective comparative analysis performed in this study.

All patients were treatment-naïve, and a clinical diagnosis of PCV was established based on the ICGA findings of polypoidal lesions. Patients were excluded who had undergone previous treatment for PCV, such as laser photocoagulation, submacular surgery, transpupillary thermal therapy, and intravitreal bevacizumab (IVB); and those with history of vitrectomy, glaucoma, tears in the retinal pigment epithelium (RPE), diabetic maculopathy, retinal vascular occlusion, or idiopathic macular telangiectasia. We used the best-corrected visual acuity (BCVA) measured with a Japanese standard decimal VA chart, and calculated the mean BCVA using the logarithm of the minimum angle of resolution (logMAR) scale. We converted decimal VA into the Early Treatment Diabetic Retinopathy Study (ETDRS) VA letter scores with a mathematical method according to the retreatment guidelines for ranibizumab in Japan [31, 32].

A standardized examination including slit-lamp biomicroscopy with a contact lens, fundus color or red-free photography, fluorescein angiography (FA), ICGA with a fundus camera (TRC-50 FA/IA/IMAGEnet H1024 system, Topcon, Tokyo, Japan), and/or confocal scanning laser ophthalmoscopy (Heidelberg Retina Angiograph 2, Heidelberg Engineering, Heidelberg, Germany) was undergone by all patients. In the PDT group, examinations of optical coherence tomography (OCT) were performed using time-domain OCT (OCT 3000, Carl Zeiss Meditec or OCT-Ophthalmoscope, Nidek-OTI, Gamagori, Japan), or spectral-domain OCT (3D-OCT; Topcon, Tokyo, Japan, or Cirrus OCT; Carl Zeiss, Meditec, Dublin, Calif, USA). In the ranibizumab plus PDT group, spectral-domain OCT (Heidelberg Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) was used for all examinations of OCT. The central retinal thickness (CRT), defined as the distance from the RPE to the inner limiting membrane at the center of the fovea, was measured at baseline and 3, 6, 9, 12, 15, 18, 21, and 24 months after treatment (months 3, 6, 9, 12, 15, 18, 21, and 24 respectively) using internal caliper software in the ranibizumab plus PDT group. FA was performed to determine the lesion type, location, CNV activity, and the greatest linear dimension (GLD). ICGA was performed to determine the presence and location of polypoidal lesions and branching vascular network vessels, and the GLD.

All 57 patients had documented visual loss at baseline. At baseline of the ranibizumab plus PDT group, the initial treatment included intravitreal ranibizumab injection and ICGA-guided PDT 1 or 2 days after the ranibizumab injection, followed by additional intravitreal injections of ranibizumab

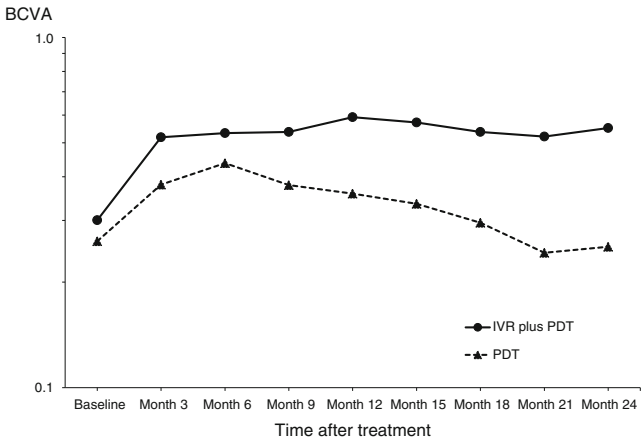

Fig. 1 Graph showing changes in the mean best-corrected visual acuity (BCVA) from baseline to month 24 for patients with polypoidal choroidal vasculopathy in the ranibizumab plus photodynamic therapy (PDT) group and PDT group. In the ranibizumab group, a significant improvement in the mean BCVA is demonstrated at months 3, 6, 9, 12, 15, 18, 21, and 24 compared with baseline ($P<0.0001$, $P<0.0001$, $P<0.0001$, $P<0.0001$, $P<0.0001$, $P<0.001$, $P<0.001$, $P<0.001$ respectively, by the paired *t*-test). In the PDT group, a significant improvement in the mean BCVA is demonstrated at months 3, 6, and 9 compared with baseline ($P<0.0001$, $P<0.0001$, $P=0.014$ respectively, by the paired *t*-test). There is no significant ($P=0.11$, Mann–Whitney *U* test) difference in the mean BCVA between the groups at baseline; nevertheless, there is a significant difference in the mean BCVA at months 12, 15, 18, 21, and 24 ($P=0.014$, $P=0.023$, $P=0.014$, $P=0.0029$ and $P=0.0014$ respectively, Mann–Whitney *U* test). Months 3, 6, 9, 12, 15, 18, 21, and 24 are equivalent to 3, 6, 9, 12, 15, 18, 21, and 24 months after treatment

each month over the following 2 months. Intravitreal ranibizumab was injected 3.5 to 4.0 mm posterior to the corneal limbus into the vitreous cavity using a 30-gauge needle, after topical anesthesia had been applied. In both groups, PDT with the standard dose (6 mg/m^2) of verteporfin was administered according to the protocol of the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) study [33], except for the GLD in cases with ICGA-guided PDT. A 689-nm laser system (Carl Zeiss, Dublin, CA, USA) delivered 50 J/cm^2 of energy with an 83-second exposure time. The GLD based on FA findings was measured in all 57 eyes. In the PDT group, the laser spot size was determined by FA-guided PDT in 25 eyes and ICGA-guided PDT in seven eyes. ICGA-guided PDT was chosen if the lesion was comprised of a large hemorrhage or a large serous pigment epithelial detachment (PED) [19]. The diagnosis of PED of at least 1 disc diameter was made based on FA images and OCT findings of showing an elevation of a highly reflective layer corresponding to the detached RPE. In the ranibizumab plus PDT group, the laser spot size was determined by ICGA-guided PDT in all eyes. The diameter of the laser spot size was calculated by the GLD plus 1 mm in all eyes. In the PDT group, follow-up examinations were performed at least every 3 months. Retreatment was performed if ICGA showed polypoidal lesions or FA showed leakage with evidence of fluid at the macula by OCT. In the PDT group, all retreatments were performed using PDT. In the ranibizumab plus PDT group, after the initial combined therapy of three monthly intravitreal ranibizumab injections and PDT, follow-up examinations including evaluation of the OCT images were performed every month until month 24. Retreatment and follow-up angiography in the ranibizumab plus PDT group were based on the criteria of our previous study [29], i.e., FA and ICGA were performed every 3 months until the polypoidal lesions regressed completely, or performed when new exudative changes or subretinal hemorrhages were seen on fundus examination or OCT after achieving complete regression of the polypoidal lesions. If polypoidal lesions were seen on ICGA, we administered combined therapy of one intravitreal ranibizumab injection and PDT [29]. For patients with residual or new exudative changes in the branching vascular network vessels despite complete regression of the polypoidal lesions detected by ICGA, intravitreal ranibizumab was administered [29]. Additional injections were administered according to the criteria during the second year of the Prospective OCT Imaging of Patients with Neovascular AMD Treated with intraOcular Ranibizumab (PrONTO) study [34], i.e., VA loss of at least 5 letters of the ETDRS score with OCT evidence of fluid at the macula, an increase in the CRT on OCT of at least 100 μm, a new macular hemorrhage, a new area of classic CNV, evidence

Table 1 Baseline patient characteristics

Characteristic	Ranibizumab plus PDT	PDT
Patients, no.	25	32
Women	8	5
Men	17	27
Age (years)		
Mean ± SD	74.0±8.6	75.0±6.5
Eyes, no.	25	32
The mean BCVA (logMAR)		
Mean	0.30	0.26
Median	0.40	0.30
Range	0.01 to 0.5	0.06 to 0.5
Central retinal thickness		
Mean ± SD	385±154	NA
GLD (μm)		
Mean ± SD	4,074±1,459	4,867±1,855
SRD, no (%)	23 (92.0)	26 (81.3)
Edema, no (%)	7 (28.0)	11 (34.3)
PED, no (%)	7 (28.0)	20 (62.5)

BCVA (logMAR) best-corrected decimal visual acuity (logarithm of the minimum angle of resolution equivalent); *PDT* photodynamic therapy; *SD* standard deviation; *GLD* greatest linear dimension; *SRD* serous retinal detachment; *PED* pigment epithelial detachment; *NA* not applicable; because of using time and spectral domain optical coherence tomography

Table 2 Visual and OCT outcomes of the ranibizumab plus PDT group

	Mean BCVA (LogMAR)		Mean changes of BCVA	Mean CRT ± SD (μm)	
		P value[a]			*P* value*
Baseline	0.30 (0.52)	NA	NA	385±154	NA
Month 3	0.52 (0.28)	<0.0001	2.37	167±76	<0.0001
Month 6	0.53 (0.27)	<0.0001	2.49	181±72	<0.0001
Month 9	0.54 (0.27)	<0.0001	2.52	162±46	<0.0001
Month 12	0.59 (0.23)	<0.0001	2.95	162±54	<0.0001
Month 15	0.57 (0.24)	<0.0001	2.79	162±55	<0.0001
Month 18	0.54 (0.27)	<0.001	2.52	167±58	<0.0001
Month 21	0.52 (0.28)	<0.001	2.39	171±54	<0.0001
Month 24	0.55 (0.26)	<0.001	2.63	167±54	<0.0001

OCT optical coherence tomography; *PDT* photodynamic therapy; *BCVA (logMAR)* best-corrected decimal visual acuity (logarithm of the minimum angle of resolution equivalent); *CRT* central retinal thickness; *SD* standard deviation; *Months 3, 6, 9, 12, 15, 18, 21, and 24* = 3, 6, 9, 12, 15, 18, 21, and 24 months after treatment; *NA* not applicable.

[a] Student's *t*-test compared with baseline

of persistent fluid on OCT 1 month after the previous injection, and the appearance of retinal cysts or subretinal fluid or an enlargement of a PED [29].

Statistical analysis was performed using the Student's *t*-test for visual outcomes in each group and CRT in the ranibizumab plus PDT group. Mann–Whitney *U* test or chi-square test was used to compare outcomes between the ranibizumab plus PDT group and the PDT group. A P value of <0.05 was considered statistically significant. We used the logMAR VA scores in both groups for statistical analysis.

Results

All patients were Japanese and were observed for 24 months. The lesions were classified on FA as minimally classic CNV in seven eyes and occult with no classic CNV in 50 eyes, all of which were involving subfovea. Table 1 shows the clinical data from the 25 patients (25 eyes) in the ranibizumab plus PDT group and the 32 patients (32 eyes) in the PDT group. Table 1 shows baseline characteristics between both groups. There were no significant differences in the patient characteristics at baseline between the two groups except for the percentage of patients with PED (P=0.016, Mann–Whitney *U* test). The mean GLD (± standard deviation) measured by FA findings of all lesions was 4,074±1,459 μm in the ranibizumab plus PDT group, and 4,867±1,855 μm in the PDT group, which was not a significant (P=0.10, chi-square test) difference between the two groups. The mean of ICGA-guided GLD in the ranibizumab plus PDT group was 2,883±1,230 μm.

In the ranibizumab plus PDT group, the mean best-corrected visual acuity (BCVA) levels of decimal (logMAR equivalent) significantly improved from 0.30 (0.52) at baseline to 0.55 (0.26) at month 24 (P<0.001) (Fig. 1). Table 2 shows visual outcomes after treatments. The mean changes in BCVA at month 24 were improvements of 2.63 lines. Fourteen of the 25 (56 %) eyes had an increased BCVA of three lines or more; the remaining 11 (44 %) eyes had stable VA (defined as a gain or loss of less than 3 lines of vision) at month 12. At 24 months, 12 (48 %) of 25 eyes had an increase in the BCVA of 3 lines or more, and 13 (52 %) eyes had stable VA (Fig. 2). No patient had a decrease in the BCVA of 3 lines or more during the 24 months. The mean CRT significantly decreased from 385±154 μm at baseline to 167±54 μm at 24 months (P<0.0001). Table 2 shows CRT outcomes after treatments. At baseline, 23 of the 25 eyes had a serous retinal detachment (SRD); seven of the 25 eyes had cystoid macular edema (CME), and seven of the 25 eyes had a PED. The SRD resolved in 23 eyes (100 %) at a mean of 8.7 weeks after baseline. The CME resolved in

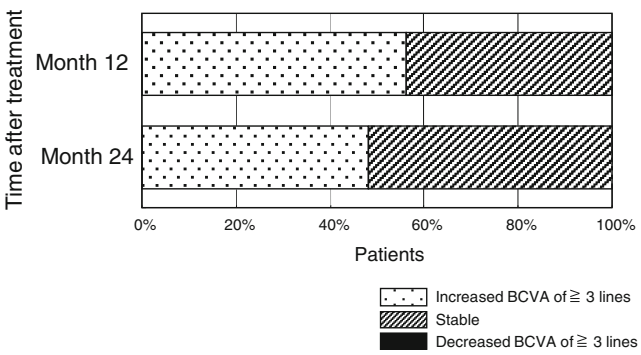

Fig. 2 Graph showing the distribution of the mean best-corrected visual acuity (BCVA) changes from baseline after treatment with combined intravitreal ranibizumab and photodynamic therapy. No eyes had decreased BCVA of 3 lines or more after treatment over 24 months. Months 12 and 24 are equivalent to 12 and 24 months after treatment.

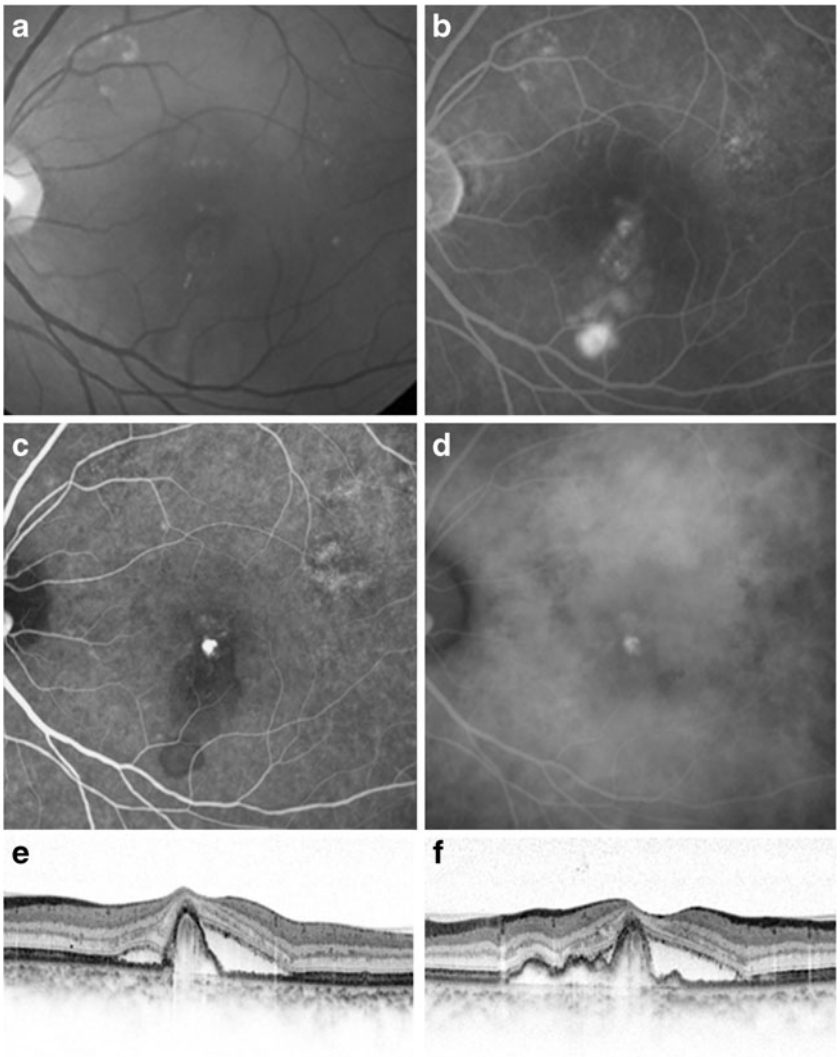

Fig. 3 A 55-year-old man was treated with combined intravitreal ranibizumab with photodynamic therapy (PDT) for polypoidal choroidal vasculopathy. At baseline, the best-corrected visual acuity (BCVA) was 0.5 decimal VA in the left eye. **a** Red-free photograph showing a subretinal hemorrhage, lipid, and a serous retinal detachment (SRD) at the macular area. **b** Fluorescein angiography image showing leakage and occult with no classic choroidal neovascularization. **c** Early-phase indocyanine green angiography (ICGA) image clearly showing polypoidal lesions and branching vascular network vessels. **d** Late-phase ICGA image showing a focal area of intense hyperfluorescence (hot spot). **e**, **f** Baseline horizontal (*right*) and vertical (*left*) optical coherence tomography images showing SRD and anterior protrusion of a highly reflective retinal pigment epithelium line, which corresponds to the polypoidal lesions on ICGA. ICGA-guided PDT was applied (laser spot size, 4,400 μm) 2 days after an intravitreal ranibizumab injection, followed by additional intravitreal injections of ranibizumab each month over the next 2 months

seven eyes (100 %) at a mean of 6.2 weeks after baseline. The PED resolved in five eyes (71.4 %) at a mean of 9.9 weeks after baseline, and decreased in two eyes. Figures 3, 4 and 5 show images obtained from patients treated with intravitreal ranibizumab injections and PDT.

In PDT group, the mean decimal BCVA (logMAR equivalent) levels stabilized from 0.26 (0.58) at baseline to 0.25 (0.60) at 24 month (Fig. 1). Table 3 shows visual outcomes after treatments. The mean changes in BCVA at months 24 were decline of 0.16 lines. Ten (31.3 %) of the 32 eyes had an increased BCVA of three lines or more, 18 (56.3 %) eyes had stable VA, and the remaining four (12.5 %) eyes had a decrease in the BCVA of three lines or more at month 12. At 24 months, nine (28.1 %) of 32 eyes had an increase in the BCVA of three lines or more, 14 (43.8 %) eyes had stable VA, and the remaining nine (28.1 %) eyes had a decrease in the BCVA of three lines or more (Fig. 6). At baseline, 26 of the 32 eyes had a SRD; 11 of the 32 eyes had CME; and 20 of the 32 eyes had a PED. The SRD resolved in 26 (100 %) eyes a mean of 19.6 weeks after baseline. The CME resolved in seven (100 %) eyes a mean of 17.3 weeks after baseline. The PED resolved in 14 (70 %) eyes a mean of 36.1 weeks after baseline and decreased in six eyes. Figures 7, 8 and 9 show images obtained from patients treated with PDT.

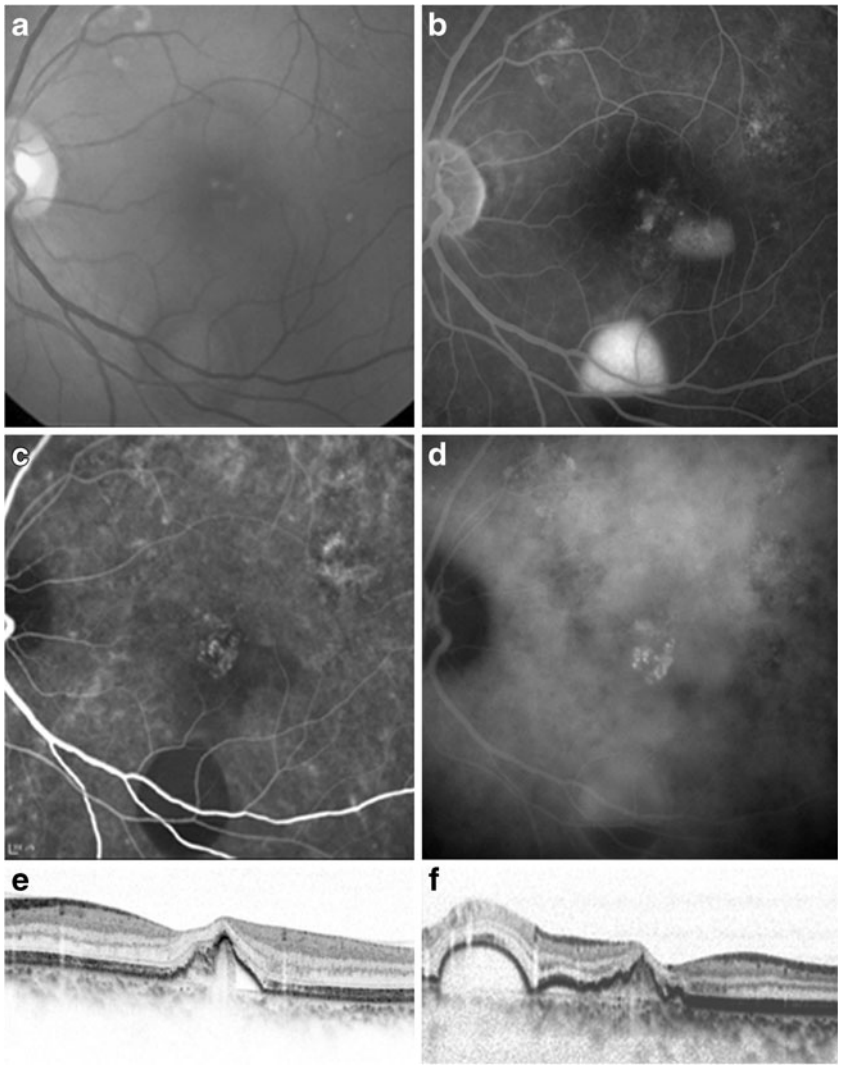

Fig. 4 Twelve months after combined therapy of intravitreal ranibizumab and photodynamic therapy in the same case of Fig. 3. An additional treatment using intravitreal ranibizumab injection was administered during 12 months. The best-corrected visual acuity (BCVA) increased from 0.5 to 1.0 decimal VA. **a** Red-free photograph image showing resolution of a subretinal hemorrhage and lipid at the macular area. **b** Fluorescein angiography image showing no leakage at the macular area. **c**, **d** ICGA shows complete regression of the polypoidal lesions. **e**, **f** Horizontal (*left*) and vertical (*right*) optical coherence tomography images showing resolution of the SRD

While there was no significant (P=0.11, Mann–Whitney U test) difference in the mean BCVA at baseline between the two groups, the mean BCVA values at months 12, 15, 18, 21, and 24 in the ranibizumab plus PDT group were significantly better than that in the PDT group (P=0.014, P=0.023, P=0.014, P=0.0029 and P=0.0014 respectively, Mann–Whitney U test) (Table 4). Although there was no significant (P=0.11, Mann–Whitney U test) difference in the mean changes of BCVA at month 12 between the two groups, the mean changes in BCVA at month 24 in the ranibizumab plus PDT group was significantly better than that in the PDT group (P=0.010, Mann–Whitney U test) (Table 4).

The mean numbers of treatments of PDT and intravitreal ranibizumab injection at months 12 and 24 in the ranibizumab plus PDT group, including the initial treatments, were 1.0 and 3.6 at month 12 and 1.4 and 4.5 at month 24 respectively. In the PDT group, the mean numbers of treatments of PDT at months 12 and 24 were 2.0 and 2.6, which showed

Table 3 Visual outcomes of the PDT group

	Mean BCVA (LogMAR)		Mean changes of BCVA
		P value[a]	
Baseline	0.26 (0.58)	NA	NA
Month 3	0.38 (0.42)	<0.0001	1.62
Month 6	0.44 (0.36)	<0.0001	2.33
Month 9	0.38 (0.42)	0.014	1.61
Month 12	0.36 (0.45)	0.07	1.36
Month 15	0.33 (0.48)	0.18	1.07
Month 18	0.30 (0.53)	0.53	0.53
Month 21	0.24 (0.61)	0.68	−0.33
Month 24	0.25 (0.60)	0.85	−0.16

PDT photodynamic therapy; *BCVA (logMAR)* best-corrected decimal visual acuity (logarithm of the minimum angle of resolution equivalent); *Months 3, 6, 9, 12, 15, 18, 21, and 24* = 3, 6, 9, 12, 15, 18, 21, and 24 months after treatment; *NA* not applicable

[a] Student's t-test compared with baseline

significant differences compared with the ranibizumab plus PDT group ($P<0.0001$, $P<0.001$ respectively, Mann–Whitney U test) (Table 4). After the initial treatment, FA and OCT showed no exudation, and ICGA showed complete regression of polypoidal lesions in all 57 eyes. ICGA showed recurrent polypoidal lesions a mean of 16.3 months after the initial treatment regimen in nine eyes (36 %) of the ranibizumab plus PDT group, and a mean of 13.2 months after the initial treatment in 13 eyes (41 %) of the PDT group (Table 4). Nine eyes with recurrent polypoidal lesions in the ranibizumab plus PDT group received additional treatment of combined therapy of intravitreal ranibizumab and PDT. In the 13 eyes with recurrent polypoidal lesions in the PDT group, retreatment was performed using PDT monotherapy. The mean numbers of treatments of PDT for polypoidal lesions in the ranibizumab plus PDT group and the PDT group were 1.0 and 1.2 at month 12 and 1.4 and 1.6 at month 24 respectively, which showed no significant difference ($P=0.16$, $P=0.77$, respectively, Mann–Whitney U test) (Table 4).

Thirteen (52 %) of the 25 eyes in the ranibizumab plus PDT group and 17 (53 %) of the 32 eyes in the PDT group had complete regression of polypoidal lesions, but recurrent or residual leakage from branching vascular network vessels a mean of 11.1 and 6.2 months after the initial treatment respectively, which showed significant differences in the period ($P=0.0062$, Mann–Whitney U test) (Table 4). Retreatments were performed with intravitreal ranibizumab injection monotherapy for the 13 eyes in the ranibizumab plus PDT group and with PDT monotherapy for the 17 eyes in the PDT group. The mean numbers of retreatments for exudation from branching vascular network vessels in the ranibizumab plus PDT group and the PDT group were 1.1 and 1.0 at month 24, respectively, which showed no significant difference ($P=0.43$, Mann–Whitney U test) (Table 4).

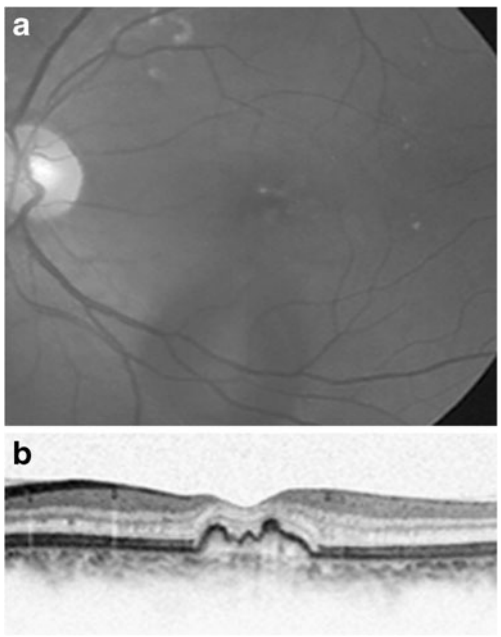

Fig. 5 Twenty-four months after combined therapy of intravitreal ranibizumab and photodynamic therapy in the same case of Figs. 3 and 4. One PDT treatment and four ranibizumab injections are administered over 24 months. The BCVA is 0.9 decimal VA at month 24. **a** Red-free photograph showing no subretinal hemorrhage, lipid, or SRD. **b** A horizontal OCT image showing no exudative changes.

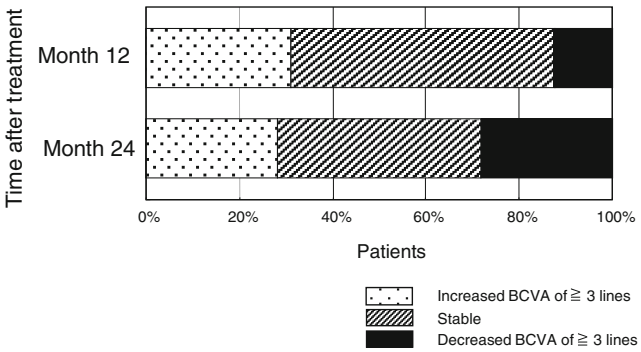

Fig. 6 Graph showing the distribution of the mean best-corrected visual acuity (BCVA) changes from baseline after treatment with photodynamic therapy. Four (12.5 %) eyes at month 12 and nine (28.1 %) eyes at month 24 had a decrease in the BCVA of 3 lines or more. Months 12 and 24 are equivalent to 12 and 24 months after treatment

At month 24, no patients had polypoidal lesions, and two of the 25 eyes had a SRD in the ranibizumab plus PDT group. In the PDT group, two eyes had polypoidal lesions and one eye had a SRD at month 24.

In the PDT group, increased subretinal hemorrhages (>1 disc diameter) were seen in eight (18.0 %) eyes within 6 months (mean, 1.3 month) after the initial PDT that disappeared spontaneously (Table 4). No other complications developed, such as inflammation, increased intraocular pressure over 21 mmHg, severe visual loss, endophthalmitis, progression of cataract, or systemic adverse events in both treatment groups.

Discussion

The current study showed that combined treatment of intravitreal ranibizumab and PDT significantly improved VA at month 24 in patients with PCV compared to PDT monotherapy.

PDT with verteporfin has been shown to be highly effective in resolving the polypoidal lesions and for maintaining or improving the VA in PCV eyes [17–19]. In addition, the Japanese Guidelines for PDT highly recommended PDT in patients with PCV [17]. However, there have been few reports for PDT in PCV patients over 2-year follow-up [19–21, 35]. Kurashige et al. reported that the VA decreased in nine of 41 eyes during a 2-year follow-up [20]. Leal et al. reported a decline in

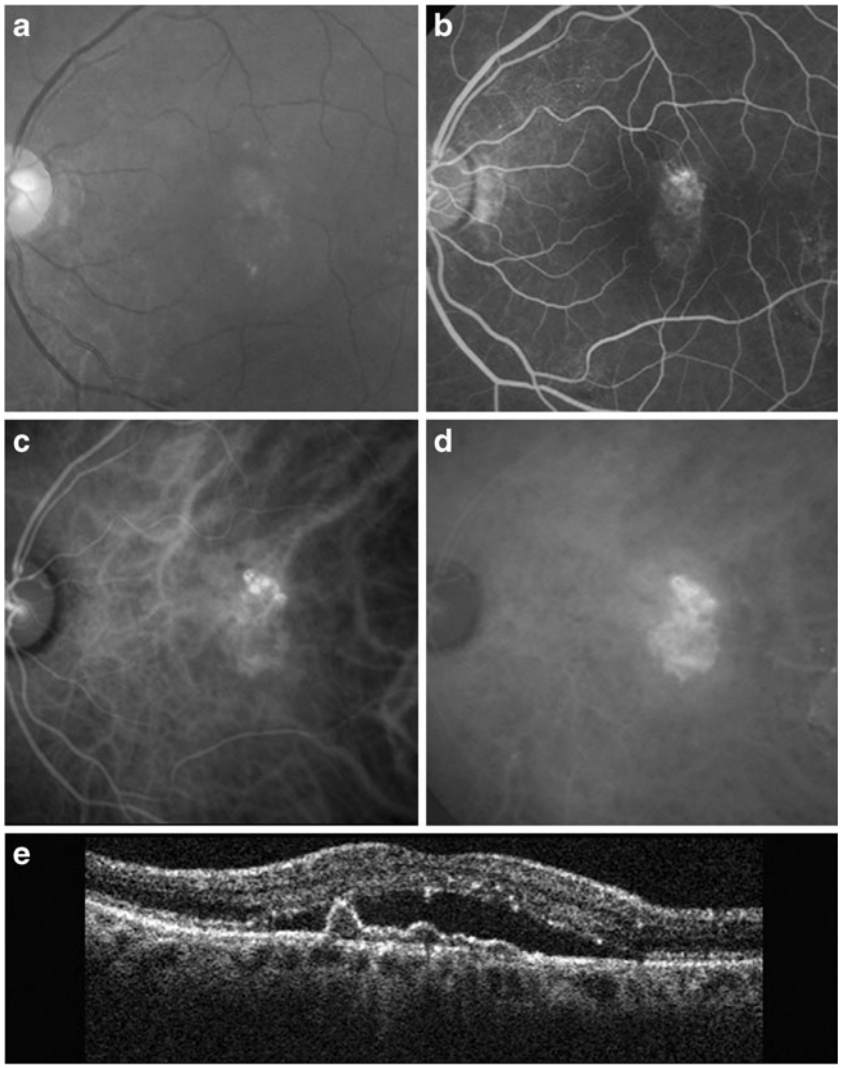

Fig. 7 A 72-year-old man was treated with photodynamic therapy (PDT) for polypoidal choroidal vasculopathy. At baseline, the best-corrected visual acuity (BCVA) was 0.3 decimal VA in the left eye. **a** Red-free photograph showing a serous retinal detachment (SRD) and lipid at the macular area. **b** Fluorescein angiography (FA) image showing leakage and occult with no classic choroidal neovascularization. **c** Early-phase indocyanine green angiography (ICGA) image, clearly showing polypoidal lesions and branching vascular network vessels. **d** Late-phase ICGA image showing a focal area of intense hyperfluorescence. **e** A baseline vertical optical coherence tomography image showing SRD and anterior protrusion of a highly reflective retinal pigment epithelium line, which corresponds to the polypoidal lesions on ICGA. FA-guided PDT was applied (laser spot size, 5,100 μm)

mean logMAR BCVA from 0.91 at baseline to 0.93 at month 36 in a 3-year study of PDT use in PCV [35]. For the PDT group in the current study, the mean decimal BCVA (logMAR equivalent) levels changed from 0.26 (0.58) at baseline to 0.25 (0.60) at month 24. PDT may be less useful for improving VA over 2-year follow-up.

Anti-VEGF therapy using ranibizumab has become the standard therapy for AMD worldwide, after major clinical trials have reported the superior efficacy for patients with AMD [11–13]. However, the efficacy of ranibizumab for patients with PCV has not been unknown based on the major studies. Some studies reported lower efficacy for occluding polypoidal lesions using ranibizumab [15, 16]. In addition, Rouvas et al. [27] and Lai et al. [28] reported the superior efficacy of PDT for occlusion of polypoidal lesions compared to ranibizumab. PDT might be a more appropriate treatment than ranibizumab monotherapy for occluding polypoidal lesions.

Combined therapy of IVB and PDT has been reported to be effective in patients with PCV [22, 23]. Ishikawa et al. [36] reported that combined therapy of IVB and PDT prevented reduction of amplitudes and prolongation of implicit times of the focal macular electroretinograms 1 week after therapy, as seen after PDT alone; PDT may be associated with declines in VA during long-term follow-up. Recently, instead of IVB, the efficacy of combining ranibizumab with PDT has been reported to be effective in patients with PCV [24–29]. We also reported the efficacy of ranibizumab plus PDT for patients with PCV for improving VA at the 12-month follow-up and decreasing retinal and choroidal thickness at the 6-month follow-up [25, 29]. In the current study, we found a significant ($P<0.0001$) improvement in the mean BCVA from baseline at month 24 in the ranibizumab plus PDT group, without adverse events. It is well-known that PDT has induced up-regulation of VEGF [37]. Treatment with both PDT to resolve the polypoidal lesions and anti-VEGF agents to reduce the exudative lesions and up-regulation of VEGF caused by PDT may be a reasonable strategy for maintaining or improving VA and anatomic changes in patients with PCV.

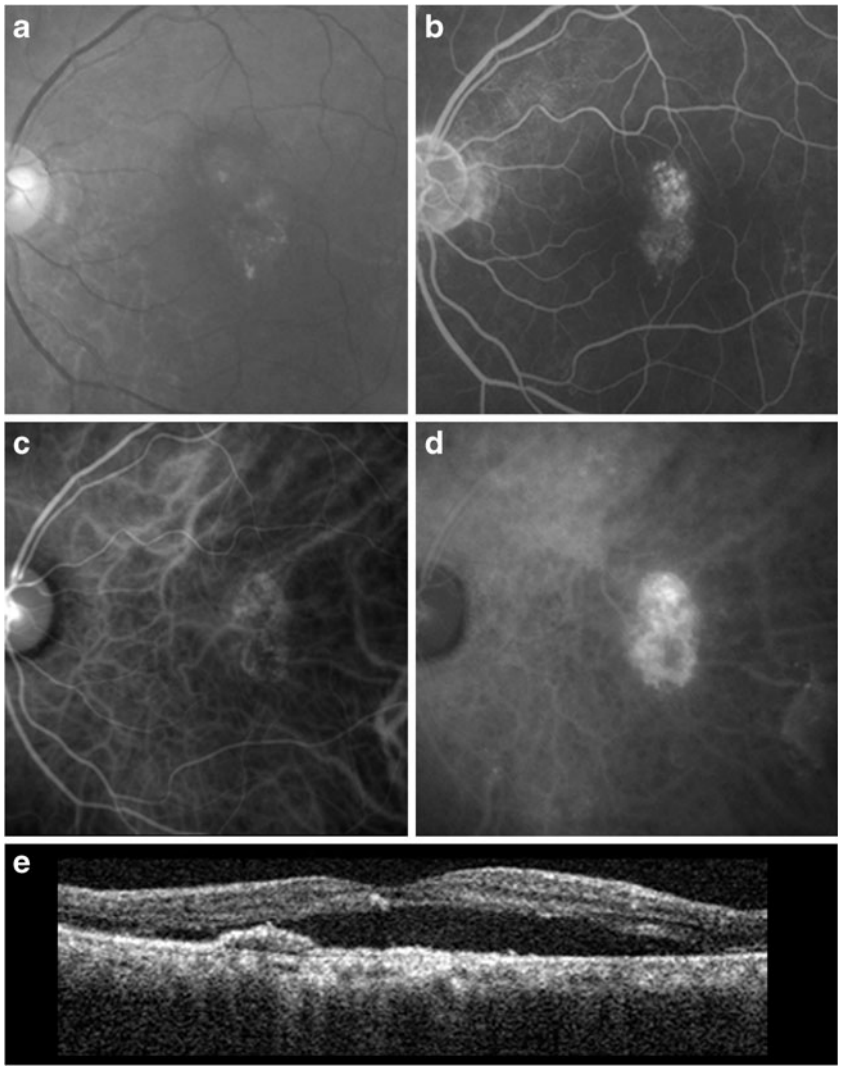

Fig. 8 Twelve months after photodynamic therapy in the same case as Fig. 7. No additional PDT was administered during 12 months. The best-corrected visual acuity (BCVA) decreased from 0.3 to 0.2 decimal VA. **a** Red-free photograph image showing recurrence of a serous retinal detachment (SRD) and lipid at the macular area. **b** Fluorescein angiography image showing leakage at the macular area. **c** Early-phase indocyanine green angiography (ICGA) image, clearly showing complete regression of the polypoidal lesions. **d** Late-phase ICGA image showing a focal area of intense hyperfluorescence. **e** A vertical optical coherence tomography image showing recurrence of the SRD. Retreatment with PDT was applied (laser spot size, 3,650 μm)

The percentage of patients with PED in the PDT group (62.5 %) is much higher than in the ranibizumab plus PDT group (28.0 %). We reported that the visual outcomes after PDT monotherapy were unaffected by a serous PED in eyes with PCV [19]. The poorer visual outcomes in the PDT group may not depend on the high prevalence of PED.

The mean numbers of PDTs at months 12 and 24 in the ranibizumab plus PDT group were 1.1 and 1.4 respectively, which were significantly fewer ($P<0.001$, $P=0.0032$, respectively, Mann–Whitney U test) than that of the PDT group (2.0 and 2.6 respectively). We reported that intravitreal ranibizumab significantly improved VA in patients with PCV with exudative lesions from branching vascular network vessels compared to PDT [38]. Therefore, in the current study intravitreal ranibizumab was administered as retreatment in the ranibizumab plus PDT group, if patients had residual or new exudative changes in the branching vascular network vessels despite complete regression of the polypoidal lesions detected by ICGA after month 3 [29, 38]. So, the difference in the number of PDTs between the ranibizumab plus PDT group and the PDT group is a reasonable result.

In the current study, the numbers of eyes with recurrence polypoidal lesions and the duration of recurrence after the initial treatment were similar between the two treatment groups. The mean numbers of retreatments at month 24 for exudation from branching vascular network vessels in the ranibizumab plus PDT group and the PDT group were 13 eyes (65 %) and 17 eyes (53 %), which showed no significant differences ($P=0.56$, chi-square test). The period of recurrent or residual leakage from branching vascular network vessels in the ranibizumab plus PDT group and the PDT group were a mean of 13.7 and 6.2 months after the initial treatment respectively, which showed significant differences ($P=0.0062$, Mann–Whitney U test). From these results, the significant advantage of using three consecutive monthly intravitreal injections of ranibizumab has been demonstrated as long-time suppression of recurrent leakage from branching vascular network vessels compared with PDT monotherapy.

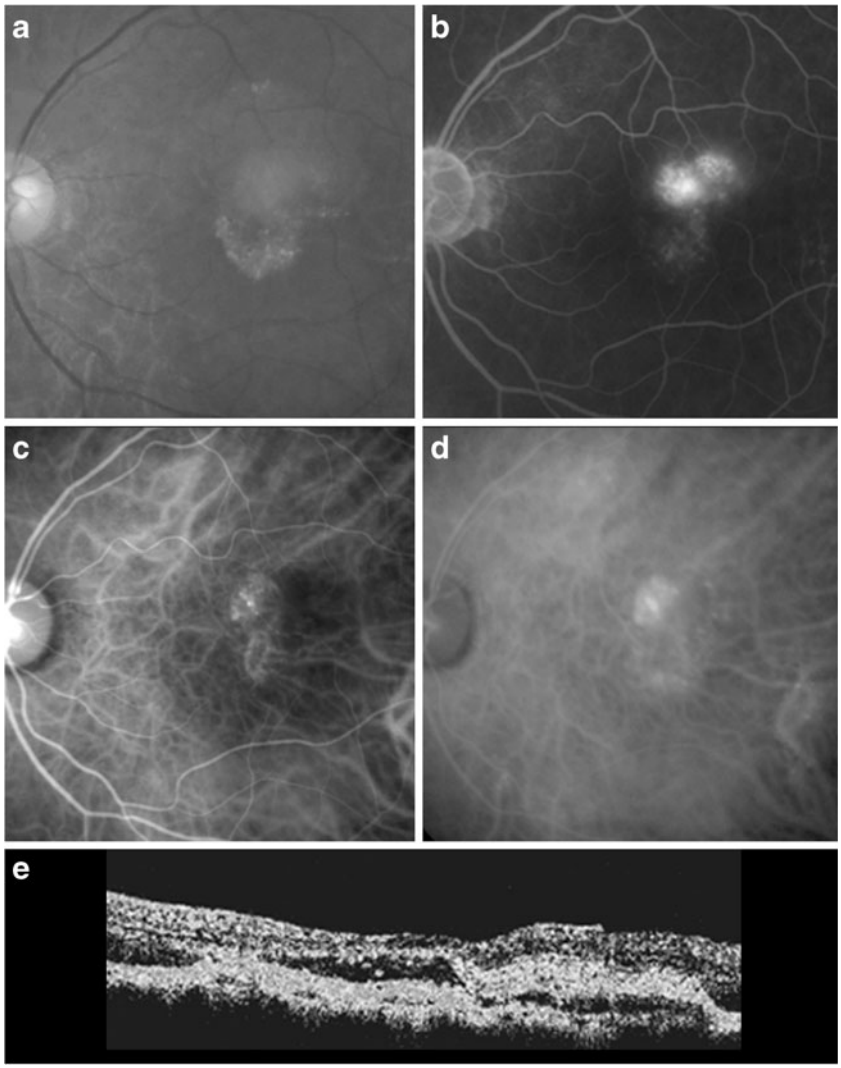

Fig. 9 Twenty-four months after combined therapy of intravitreal ranibizumab and photodynamic therapy in the same case as Figs. 7 and 8. Two PDT treatments were administered over 24 months. The BCVA was 0.15 decimal VA at month 24. **a** Red-free photograph image showing re-recurrence of a serous retinal detachment (SRD) and lipid at the macular area. **b** Fluorescein angiography image showing re-recurrence of leakage at the macular area. **c** Early-phase indocyanine green angiography (ICGA) image showing no polypoidal lesions. **d** Late-phase ICGA image showing persistence of a focal area of intense hyperfluorescence. **e** A vertical optical coherence tomography image showing re-recurrence of the SRD

The mean BCVA values at months 12 and 24 were significantly better in the ranibizumab plus PDT group than in the PDT group (P=0.0088 and P=0.0020 respectively, Mann–Whitney U test), in spite of the fact that there was no significant (P=0.051, Mann–Whitney U test) difference in the mean BCVA at baseline between the two treatment groups. Moreover, the mean changes in BCVA at month 24 was significantly better in the ranibizumab plus PDT group than in the PDT group (P=0.038, Mann–Whitney U test). These data could argue in favour of combined therapy of intravitreal ranibizumab and PDT for patients with polypoidal lesions, and intravitreal ranibizumab monotherapy for patients with residual or new exudative changes in the branching vascular network vessels despite complete regression of the polypoidal lesions detected by ICGA after month 3, which might achieve improvement of VA. Therefore, an accurate diagnosis with high-resolution ICGA obtained by confocal scanning laser ophthalmoscopy, as in the current study, is needed in the evaluation and treatment of PCV. There was the possibility of missing residual subretinal fluid and/or cystic changes and the chance of retreatment because of using time-domain OCT, which might lead to it being less useful for improving visual acuity in the PDT group. We consider that further large prospective randomized studies will be needed to clarify the efficiency of combined therapy of ranibizumab and PDT.

The EVEREST study is the first double-masked randomized controlled trial to evaluate if PDT plus ranibizumab or PDT monotherapy is superior to ranibizumab monotherapy for achieving complete regression of polypoidal lesions (primary outcome) with 6-month follow-up [30]. Recently, this study also has shown the superior efficacy of intravitreal ranibizumab and PDT or PDT monotherapy for achieving complete regression of polyps in PCV patients.

Eight eyes developed unexpected increased subretinal hemorrhages only in the PDT group. While the current study had a small number of cases, we speculated that suppression of VEGF using three consecutive monthly intravitreal injections of ranibizumab could reduce the

Table 4 Comparison of outcomes between the ranibizumab plus PDT group and the PDT group

	Ranibizumab plus PDT	PDT	*P* value[a]
Mean BCVA (LogMAR)			
Baseline	0.30 (0.52)	0.26 (0.58)	0.11
Month 12	0.59 (0.23)	0.36 (0.45)	0.014
Month 24	0.55 (0.26)	0.25 (0.60)	0.0014
Mean changes of BCVA			
Month 12	2.95	1.36	0.11
Month 24	2.63	−0.16	0.010
Complete regression of polypoidal lesions after initial treatment, no (%)	25 (100 %)	32 (100 %)	1.0[b]
Recurrent polypoidal lesions			
No (%)	9 (36 %)	13 (41 %)	1.0[b]
Duration (Mon)	16.3	13.2	0.48
Recurrent leakage from branching vascular network vessels			
No (%)	13 (52 %)	17 (53 %)	1.0[b]
Duration (months)	11.1	6.2	0.0062
Mean no. of treatments at month 24			
PDT	1.4	2.6	<0.001
Injections of ranibizumab	4.5	NA	
PDT for polypoidal lesions	1.4	1.6	0.77
Retreatments for exudation from branching vascular network vessels	1.1 (ranibizumab)	1.0 (PDT)	0.90
Increased subretinal hemorrhages (>1 disc diameter), no (%)	0 (0 %)	8 (18 %)	0.070[b]

PDT photodynamic therapy; *BCVA* best-corrected visual acuity; *Months 12 and 24* = 12 and 24 months after treatment; *GLD* greatest linear dimension; *NA* not applicable

[a] Mann–Whitney *U* test

[b] Chi-square test

activity of CNV, which might lead to a result without the complication of hemorrhages. All eyes were applied ICGA-guided PDT in the ranibizumab plus PDT group; on the other hand, the laser spot size was determined by FA-guided PDT (25 eyes) or ICGA-guided (seven eyes) in the PDT group. Apart from VEGF suppression by ranibizumab being a possible reason for fewer subretinal hemorrhages in the ranibizumab plus PDT group, one possible consideration is the smaller GLD used in ICG-guided PDT. However, the real reason why there were no adverse events in the ranibizumab plus PDT group is unknown.

In conclusion, the current study showed that combined therapy with intravitreal ranibizumab and PDT maintained or improved VA and anatomic changes in patients with PCV without adverse events over 24 months. Visual outcomes in the ranibizumab plus PDT group were significantly better than in the PDT group. It may be more effective for long-term follow-up to change the treatment of intravitreal ranibizumab monotherapy in patients with completely regressed polypoidal lesions after combined therapy but recurrent or residual exudation from branching vascular network vessels. Because this was a small study with a short follow-up, further large and long-term prospective randomized studies are needed to determine the efficacy and safety profiles of combined therapy of ranibizumab and PDT for patients with PCV.

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