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Original Article

Comparison of the effect of reduced-fluence photodynamic therapy with intravitreal bevacizumab and standard-fluence alone for polypoidal choroidal vasculopathy

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Abstract

Background: Photodynamic therapy (PDT) has previously been reported to be effective in treating polypoidal choroidal vasculopathy (PCV), with satisfactory polyp regression. However, the optimum treatment protocol remains controversial. This study compared the effect of reduced-fluence PDT combined with intravitreal bevacizumab (rPDT/IVB) and standard-fluence PDT (sPDT) alone for treating symptomatic PCV in Chinese patients.

Methods: A retrospective review was carried out of the medical records of patients with PCV who were treated with rPDT/IVB (14 eyes of 13 patients) or sPDT (12 eyes of 12 patients) with at least 6 months of follow-up.

Results: The mean best-corrected visual acuity of the rPDT/IVB group improved significantly at the 6-month follow-up ($p = 0.041$). Only one eye (7.1%) in the rPDT/IVB group showed a decrease in visual acuity, compared with four eyes (33.3%) in the sPDT group. A total of 40.0% of eyes in the sPDT group showed increased lipid exudate at follow-up 1 month after treatment, whereas no increase in lipid exudate was observed in the rPDT/IVB group ($p = 0.015$). The mean maximum area of post-treatment hemorrhage in the rPDT/IVB group was smaller than that in the sPDT group (2.57 ± 2.74 mm^2 vs. 12.69 ± 10.28 mm^2, $p = 0.042$).

Conclusion: Combination therapy with rPDT/IVB for patients with PCV showed encouraging results in vision improvement, a lower decrease in visual acuity, significantly less post-treatment lipid exudate and a smaller area of post-treatment hemorrhage at the 6-month follow-up than patients treated with sPDT.

Keywords: combination therapy; intravitreal bevacizumab; photodynamic therapy; polypoidal choroidal vasculopathy; reduced-fluence photodynamic therapy

1. Introduction

Polypoidal choroidal vasculopathy (PCV) has a distinctive choroidal appearance characterized by an abnormal vascular network terminating in polypoidal structures. The disease is more prevalent in Asian populations, with an incidence ranging from 22.3% to 40%, compared with a reported incidence of 4−13.9% in Caucasian patients diagnosed with presumed age-related macular degeneration (AMD).[1−5]

Polypoidal choroidal vasculopathy often follows a remitting−relapsing course associated with subretinal hemorrhage, macular edema and retinal pigment epithelial (RPE) detachment. Although the natural course of PCV is reported to be more favorable than exudative AMD, about 35% to 50% of patients develop a loss of vision due to recurrent bleeding or leakage and RPE atrophy after a longer follow-up period.[1,2,6]

The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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The optimum treatment for PCV remains controversial. Several studies have shown encouraging results with standard-fluence photodynamic therapy (sPDT) with verteporfin (50 J/cm^2 delivered as 600 mW over 83 seconds) in the regression of the polypoidal lesions (85−95%) and vision stabilization or improvement (80.9−95%) at the 1-year follow-up.[3,7,8] However, some studies have shown that sPDT damages the physiological choriocapillary layer beyond the irradiated area and that repeat sPDT results in persistent choriocapillary nonperfusion and can lead to a decrease in vision.[9−11] The vascular endothelial growth factor (VEGF) surge secondary to choriocapillary ischemia may be related to the recanalization of choriocapillaries, which may lead to post-treatment retinal hemorrhage in PCV.[12,13] Furthermore, 19% to 30.8% of patients with PCV experienced retinal hemorrhage or even massive subretinal hemorrhage and vitreous hemorrhage after sPDT.[3,7,14−17] Several studies have shown that the reduced-fluence PDT (rPDT, 25 J/cm^2 delivered as 600 mW over 42 seconds or 300 mW over 83 seconds) resulted in less choriocapillary nonperfusion than sPDT,[18,19] with a similar choroidal neovascularization closure rate.[20] Yamashita et al[21] reported 1-year results of rPDT on patients with PCV and showed improved visual outcome and fewer treatment sessions compared with the results of sPDT from other studies.[22,23]

Intravitreal injection of an anti-VFGF agent is found to reduce exudation in the eyes of patients with PCV, but has a limited effect on the regression of polypoidal lesions.[24,25] The combination therapy of sPDT and intravitreal anti-VEGF injection into the eyes of patients with PCV was found to reduce the incidence of post-treatment subretinal hemorrhage, resulting in a better visual outcome with a similar polyp regression rate to sPDT monotherapy.[13] A recent study of Chinese patients showed that the treatment effect of PDT combined with intravitreal bevacizumab injection was superior to PDT monotherapy within 1 year of follow-up.[26]

Theoretically, the combination of rPDT, which has a reduced extent of physiological choriocapillary closure, and the anti-VEGF, which has both antiangiogenic and antipermeability effects, may result in less post-treatment exudation and hemorrhage, and reduced additional vision loss due to choriocapillary and RPE degeneration. The purpose of this study was to investigate the efficacy and safety of rPDT combined with intravitreal bevacizumab injection (IVB) and sPDT monotherapy in Chinese patients with symptomatic PCV.

2. Methods

This retrospective comparative case series included patients with symptomatic PCV treated with sPDT monotherapy or rPDT and IVB (rPDT/IVB) at Taipei Veterans General Hospital, Taiwan from June 2002 to August 2008. The diagnosis of PCV was based on the presence of characteristic aneurysmal polypoidal lesions with a branching network of choroidal vessels observed in indocyanine angiography (ICGA). The criteria for enrollment were: (1) an absence of evidence suggesting choroidal neovascularization associated with AMD, pathological myopia, idiopathic choroidal neovascularization, presumed ocular histoplasmosis, angioid streak, and other secondary choroidal neovascularization; (2) the absence of other maculopathies, such as diabetic maculopathy; (3) no previous retinal surgery within the last 6 months; (4) no previous PDT treatment within 1 year; and (5) a completed 6-month follow-up after treatment. The Institutional Review Board for Human Research of Taipei Veterans General Hospital approved this study. Informed consent was obtained from each of the participants.

All patients received a comprehensive ocular examination including best-corrected visual acuity (BCVA), intraocular pressure measurement, indirect ophthalmoscopy, slit-lamp biomicroscopy with noncontact lens, color fundus photography before treatment (baseline), and at months 1 and 3 and then at 3-month intervals after treatment. The BCVA was measured with the standard Snellen chart at 6 m. To quantify the visual changes, all Snellen BCVAs were converted to a logarithm of the minimum angle of resolution (logMAR) BCVA. Vision tested with counting fingers was assigned with logMAR 2.0. An increase in BCVA of more than two lines (logMAR BCVA change $\geq$2 lines) was considered an improvement, and a decrease of more than two lines was considered a worsening. The ICGA and/or fluorescein angiography (FA) were evaluated at baseline and at 3-month intervals after treatment. The ICGA was performed with a scanning laser ophthalmoscope (HRA2, Heidelberg Engineering, Heidelberg, Germany) and fundus photography and FA were taken by a digital fundus camera (Canon CF-60UD, Tokyo, Japan) at a 60° view. The presence of hemorrhage and lipid exudate was documented by fundus photography.

Photodynamic therapy with verteporfin (Novartis, Basel, Switzerland) was performed with 6 mg per square meter of body surface area via an intravenous infusion of 30 mL over 10 minutes. Five minutes after complete infusion, the patients received an irradiance of 600 mW/cm^2 with a laser light at 689 nm delivered over 42 seconds (reduced-fluence) or 83 seconds (standard-fluence). The intravitreal bevacizumab injection was performed in an operating room under sterile conditions. For the patients who received rPDT before the injection, the light was dimmed to avoid further photoactivation of verteporfin. Topical anesthesia with 0.5% proparacrine hydrochloride was applied three times before disinfection of the ocular surface and periocular skin with a 5% povidone−iodine solution. Bevacizumab (0.1 mL, 2.5 mg) (Avastin, Roche, Basel, Switzerland) was injected through the inferior pars plana into the vitreous cavity using a 30-gauge needle. Anterior chamber paracentesis was performed before the injection to avoid an intraocular pressure spike. A topical antibiotic was prescribed as prophylaxis against infection. The treatment choice of rPDT/IVB or sPDT was based on the discretion of the retinal specialists (L.I.L., S.J.C., F.L.L., Y.C.S.). Repeat treatments were administered every 3 months to the eyes of patients with either persistent or new hyperfluorescence on ICGA or the presence of leakage on FA suggesting an active lesion. Additional IVB was given during the follow-up period between the 3-month treatment interval of PDT when optical coherent tomography demonstrated cystoid macular edema and/or subretinal fluid.

The primary outcome was to compare the mean BCVA at 6 months with the mean BCVA at baseline of the two groups. Secondary outcomes included the proportion of eyes in the respective group that had improved (≥2 lines), stable (±1 line), or decreased (≤2 lines) vision at 6 months compared with the baseline BCVA, comparison of the mean BCVA of the two groups at the 6-month follow-up, and the PCV regression rate of the two groups at the 6-month follow-up.

The ocular and systemic complications of the treatment were also recorded and analyzed. The changes in lipid exudate of the two groups of patients after treatment were evaluated through fundus photography. Hemorrhagic complication was defined as new hemorrhage or increased hemorrhage after treatment. The area of retinal hemorrhage documented by fundus photography was measured using an industrial computer-aided design software package (GstarICAD 2008 Professional Beijing, China). The measured area was converted to the actual size on the retina in proportion to the magnification of the camera and the software for statistical analysis. The initial size of hemorrhage was defined as the area of new hemorrhage documented after treatment, and the maximum size of hemorrhage was defined as the largest area of hemorrhage documented throughout the follow-up period.

Statistical analysis was performed with SPSS for Windows, Version 15.0 (SPSS Inc., Chicago, IL, USA). The baseline characteristics were analyzed using nonparametric tests for continuous variables and the χ^2 test for categorical variables. The changes in BCVA at 1-month, 3-month and 6-month intervals in each group were analyzed using the Wilcoxon signed rank test. The Mann–Whitney test was used to compare the post-treatment hemorrhage areas between the two groups. All values were presented as mean ± SD for continuous variables and as a percentage for categorical variables. A value of $p < 0.05$ was considered statistically significant.

3. Results

During the study period, 57 patients with symptomatic PCV confirmed by ICGA received PDT. A total of 32 patients was excluded: 12 had concomitant intravitreal triamcinolone injection, seven received rPDT without IVB, five received sPDT and additional IVB during the follow-up period, four received PDT within 1 year or retinal surgery within 6 months before starting the PDT treatment, and four had incomplete medical records and were lost in follow-up. Twenty-five Chinese patients with 26 eligible eyes were therefore included in this study. Fourteen eyes from 13 patients received rPDT/IVB, and 12 eyes from 12 patients received sPDT monotherapy. Table 1 shows the demographic and clinical data. In the rPDT/IVB group, IVB was performed after rPDT on the same day in all patients except one, who received rPDT within seven days after IVB. There was no difference in the mean PDT treatment session between the two groups within the 6-month follow-up period. Five eyes (35.7%) in the rPDT/IVB group and five eyes (41.7%) in the sPDT group required two treatment episodes. All patients in the rPDT/IVB group underwent IVB along with each rPDT session, except for four eyes that received additional IVB within 6 months. No patient in the sPDT group received IVB during the follow-up period. The mean BCVA of the rPDT/IVB group at the 6-month follow-up was significantly better than the baseline mean BCVA ($p = 0.041$, Wilcoxon signed rank test), whereas there was no significant change in the mean BCVA of the sPDT group at the 6-month follow-up (Fig. 1). Although there was no difference

Table 1
Comparison of the clinical data between the two study groups.

	rPDT/IVB (14 eyes of 13 patients)	sPDT (12 eyes of 12 patients)	*p*
Sex			0.495[b]
Male (*n*, %)	10 (76.9)	8 (66.7)	
Female (*n*, %)	3 (23.1)	4 (33.3)	
Age (y, mean ± SD)	72.6 ± 10.4	67.1 ± 9.0	0.327[c]
Baseline BCVA (logMAR, mean ± SD)	0.87 ± 0.60	0.69 ± 0.59	0.361[c]
BCVA at 6–month follow-up (logMAR, mean ± SD)	0.63 ± 0.49	0.65 ± 0.38	0.734[c]
Presence of hemorrhage at baseline (*n*, %)	7 (50.0)	7 (58.3)	0.671[b]
Presence of lipids at baseline (*n*, %)	12 (85.7)	8 (66.7)	0.250[b]
No. of PDT treatment sessions[a] (mean ± SD)	1.4 ± 0.5	1.4 ± 0.5	0.760[c]
Spot size of PDT (μm, mean ± SD)	2749.8 ± 1105.9	3613.3 ± 1296.7	0.085[c]
Follow-up time (mo, mean ± SD)	10.3 ± 3.8	11.0 ± 4.1	0.756[c]

BCVA = best-corrected visual acuity; rPDT/IVB = reduced-fluence photodynamic therapy and intravitreal bevacizumab injection; sPDT = standard-fluence photodynamic therapy.
[a] PDT treatment sessions within the 6-month follow-up.
[b] Pearson chi-square test.
[c] Mann–Whitney test.

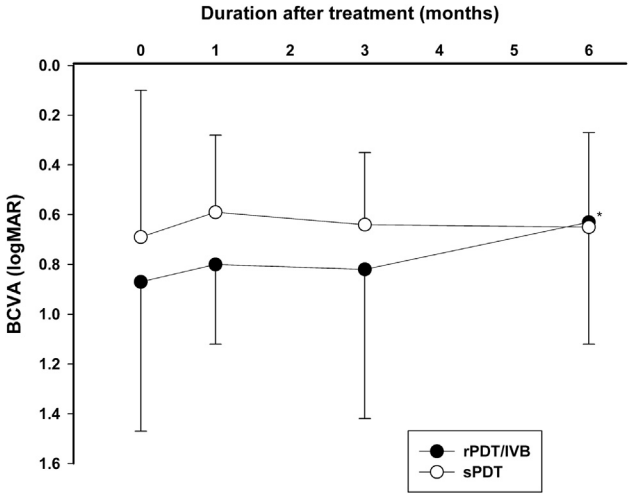

Fig. 1. Changes in the mean logarithm of the minimum angle of resolution (LogMAR) best-corrected visual acuity (BCVA) of the two groups at the 6-month follow-up. In the reduced-fluence photodynamic therapy and intravitreal injection of bevacizumab (rPDT/IVB) group, the mean BCVA at the 6-month follow-up was significantly better than the mean BCVA at baseline (* $p = 0.041$, Wilcoxon signed rank test). sPDT = standard-fluence photodynamic therapy.

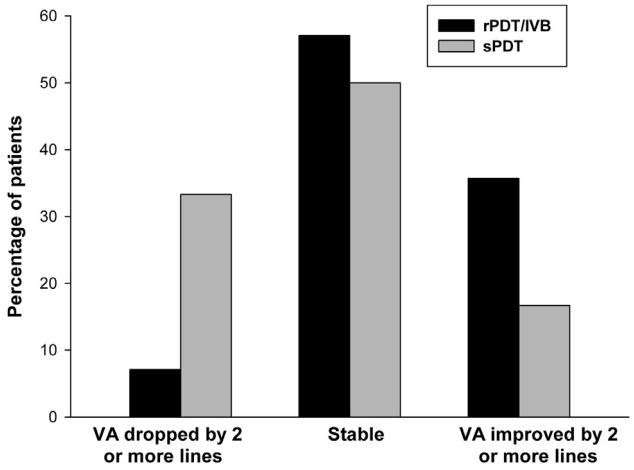

Fig. 2. Changes in the best-corrected visual acuity (BCVA) in patients with polypoidal choroidal vasculopathy treated with reduced-fluence photodynamic therapy combined with intravitreal bevacizumab injection (rPDT/IVB) or standard-fluence photodynamic therapy alone (sPDT) at the 6-month follow-up.

in the mean BCVA at baseline and at the 6-month follow-up between the two groups (Table 1), it is worth noting that only one eye (7.1%) in the rPDT/IVB group suffered a decrease in vision compared with four eyes (33.3%) in the sPDT group (Fig. 2).

Twelve eyes in the rPDT/IVB group had an ICGA examination at the 6-month follow-up. Seven eyes (58.3%) had a regressed polypoidal lesion and five eyes (41.7%) had persistent polyps. In the sPDT group, seven eyes (58.3%) had an ICGA examination at the 6-month follow-up. Three eyes (42.9%) showed polyp regression and four eyes (57.1%) showed a persistence of polyps. A branching vascular network persisted in all eyes at the 6-month follow-up.

Fig. 3 shows the change in lipid exudate after treatment. None of the eyes in the rPDT/IVB group showed increased lipid exudate throughout the follow-up period, whereas 40.0% of eyes in the sPDT group had an increased lipid exudate at the 1-month follow-up ($p = 0.015$, χ^2 test). Five eyes (35.7%) in the rPDT/IVB group experienced post-treatment retinal hemorrhage, and all occurred within 1 month of treatment. In the sPDT group, seven eyes (58.3%) had retinal hemorrhage and six (85.7%) of these developed within 1 month of treatment. All the post-treatment retinal hemorrhages were located adjacent to or within the PCV lesion. The mean maximum size of retinal hemorrhage in the rPDT/IVB group was significantly smaller than that of the sPDT group (Table 2, Figs. 4 and 5). Two eyes in the sPDT group underwent intravitreal injection of tissue plasminogen activator and gas tamponade to displace the submacular hemorrhage. No other ocular complications, such as endophthalmitis and intraocular pressure elevation, or any systemic adverse event was noted during the follow-up period.

4. Discussion

Photodynamic therapy with standard-fluence has been reported to have a satisfactory effect in the treatment of PCV,

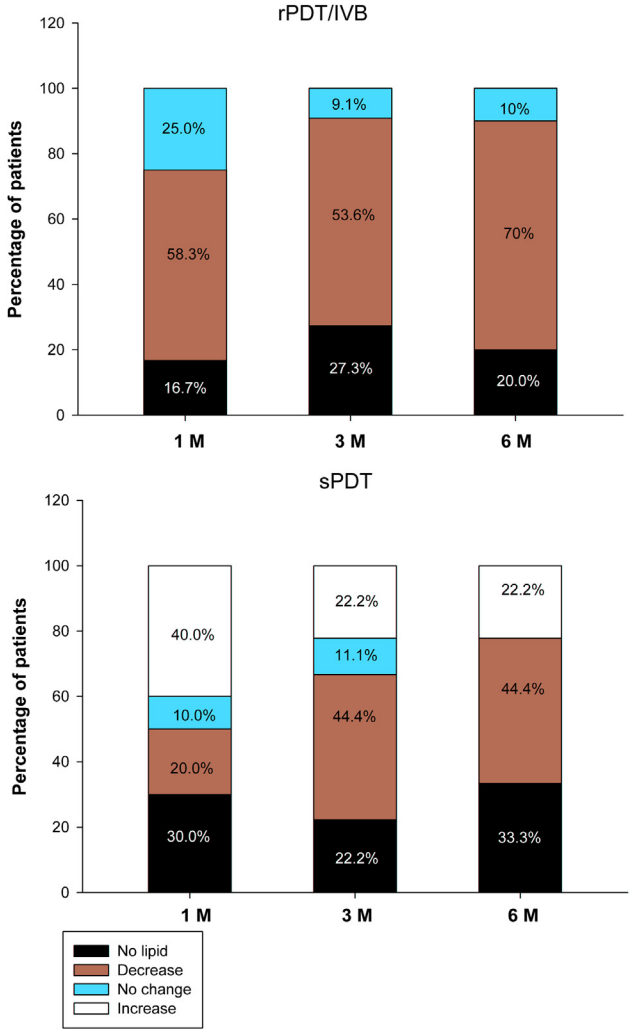

Fig. 3. Changes in lipid exudate at 1 month, 3 months and 6 months post-treatment for the two groups. There was a significant increase in lipid exudate in the standard-fluence photodynamic therapy (sPDT) group compared with the reduced-fluence photodynamic therapy and intravitreal injection of bevacizumab (rPDT/IVB) group at 1 month after treatment ($p = 0.015$, χ^2 test).

Table 2
Retinal hemorrhage after treatment in the two groups.

	rPDT/IVB (14 eyes of 13 patients)	sPDT (12 eyes of 12 patients)	*p*
New hemorrhage (*n*, %)	5 (35.7)	7 (58.3)	0.249[a]
Initial size (mm^2, mean ± SD)	0.87 ± 0.95	8.33 ± 10.26	0.062[b]
Maximum size (mm^2, mean ± SD)	2.57 ± 2.74	12.69 ± 10.28	0.042[b]
Interval between treatment and hemorrhage			0.377[a]
<1 mo (*n*, %)	5 (100.0)	6 (85.7)	
1–3 mo (*n*, %)	0 (0.0)	1 (14.3)	

rPDT/IVB = reduced-fluence photodynamic therapy and intravitreal bevacizumab injection; sPDT = standard-fluence photodynamic therapy.
[a] Pearson chi-square test.
[b] Mann–Whitney test.

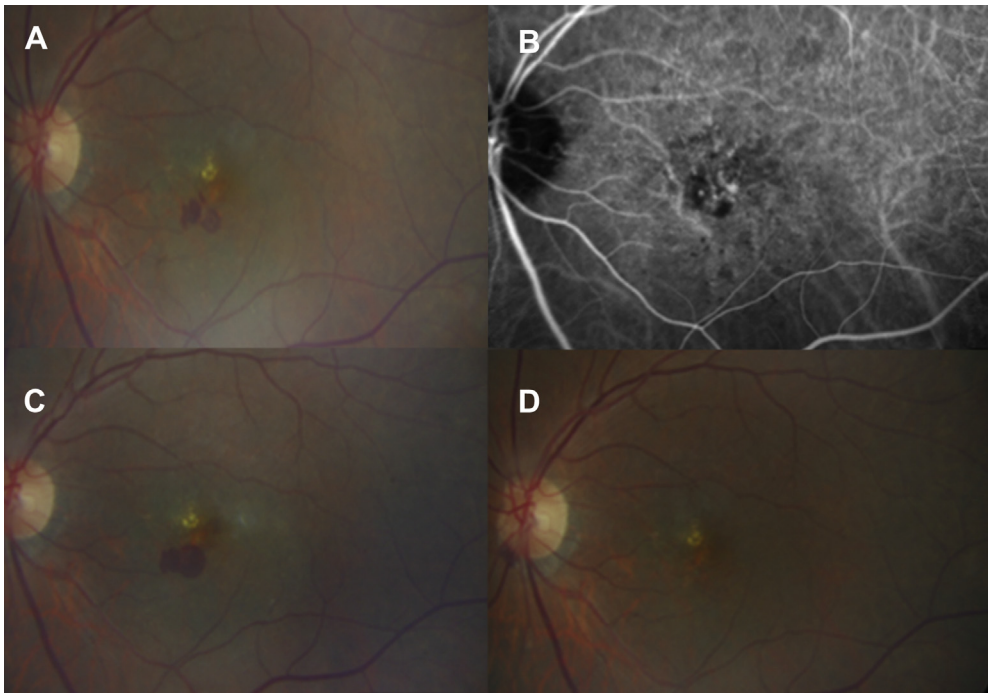

Fig. 4. An 85-year-old man reported blurred vision (20/63) of the left eye for 2 months. (A) Fundoscopic examination showed parafoveal reddish orange nodules with subretinal fluids and subretinal pigment epithelial hemorrhage. (B) Indocyanine green angiography showed a branching vascular network with polypoidal lesions. Reduced-fluence photodynamic therapy with a 1600 μm irradiation spot combined with intravitreal injection of bevacizumab (2.5 mg) was performed. (C) Two weeks after treatment, a new subretinal hemorrhage evolved (0.26 mm^2) and his visual acuity decreased to 20/200. (D) Three months later, the subretinal hemorrhage was absorbed. The visual acuity was 20/63 and subsequently improved to 20/32 at the 6-month follow-up.

with a polyp regression rate exceeding 80%, and vision stabilization or improvement at the 1-year follow-up.[3,7,8] However, some patients have experienced extensive subretinal hemorrhage after PDT, which has compromised their visual acuity.[3,8] In our study, patients in the rPDT/IVB group had an improved BCVA at the 6-month follow-up, less lipid exudate and a smaller area of retinal hemorrhage after treatment than patients in the sPDT group.

There was no significant improvement in the mean BCVA at the 6-month follow-up in the sPDT group, which was comparable with the results of Akaza et al,[22] whereas eyes in the rPDT/IVB group had a significantly better mean BCVA at the 6-month follow-up compared with the mean BCVA at baseline. Moreover, the proportion of eyes having a decrease in vision was also lower in the rPDT/IVB group than in the sPDT group. Similarly, in a study of sPDT combined with ranibizumab for PCV,[13] the mean change in BCVA throughout the study period was significantly better than the contemporary studies of sPDT on PCV.[3,7,8,22,23,27] Sato et al[28] also reported a significant improvement in BCVA at the 6−month follow-up in a series of patients with PCV treated with sPDT and IVB. A study using rPDT and intravitreal ranibizumab also reported significant BCVA improvement at the 1-year follow-up.[29]

The better visual outcome of patients with PCV receiving the combination therapy of PDT and anti-VEGF may be related to the antipermeability effect of anti-VEGF, which can emolliate the vascular hyperpermeability and extravasation after PDT.[30,31] In our study, none of the eyes in the rPDT/IVB group showed increased lipid exudates throughout the follow-up period, which is a prominent sign of vascular leakage,[32] whereas 40% of eyes in the sPDT group had increased lipid exudate in the 1st month after treatment. However, intravitreal bevacizumab injection alone may not play a significant part in preventing a long-term decrease in vision after standard-fluence PDT. A recent study compared the treatment effect of standard-fluence PDT with or without IVB, and showed that the percentage of patients with three or more lines decrease in visual acuity was similar between the two groups (11.1% vs. 12.1%) at the 1-year follow-up.[26] It is postulated that less RPE damage associated with less choroidal ischemia after rPDT may play a part in a smaller decrease in vision after treatment.[18,20,21] Yamashita et al[21] reported that 57% of eyes with PCV that received rPDT had mild to moderate choroidal nonperfusion at 1 week, and 96% recovered to the pretreatment status at the 3-month follow-up. Our study showed that fewer eyes in the rPDT/IVB group experienced more than two lines decrease in visual acuity compared with those in the sPDT group.

Recent studies have shown that extensive subretinal hemorrhage may occur after sPDT.[3,7,14–17] In our study, post-treatment retinal hemorrhage was less severe in the rPDT/IVB group, with smaller initial and maximum areas of hemorrhage than the sPDT group. It was postulated that the occlusion of the choroidal vessels and PCV lesions resulting from PDT, followed by reperfusion (or recanalization), caused this detrimental hemorrhagic complication.[14,16] Several studies have documented significant vascular occlusion[9,33,34]

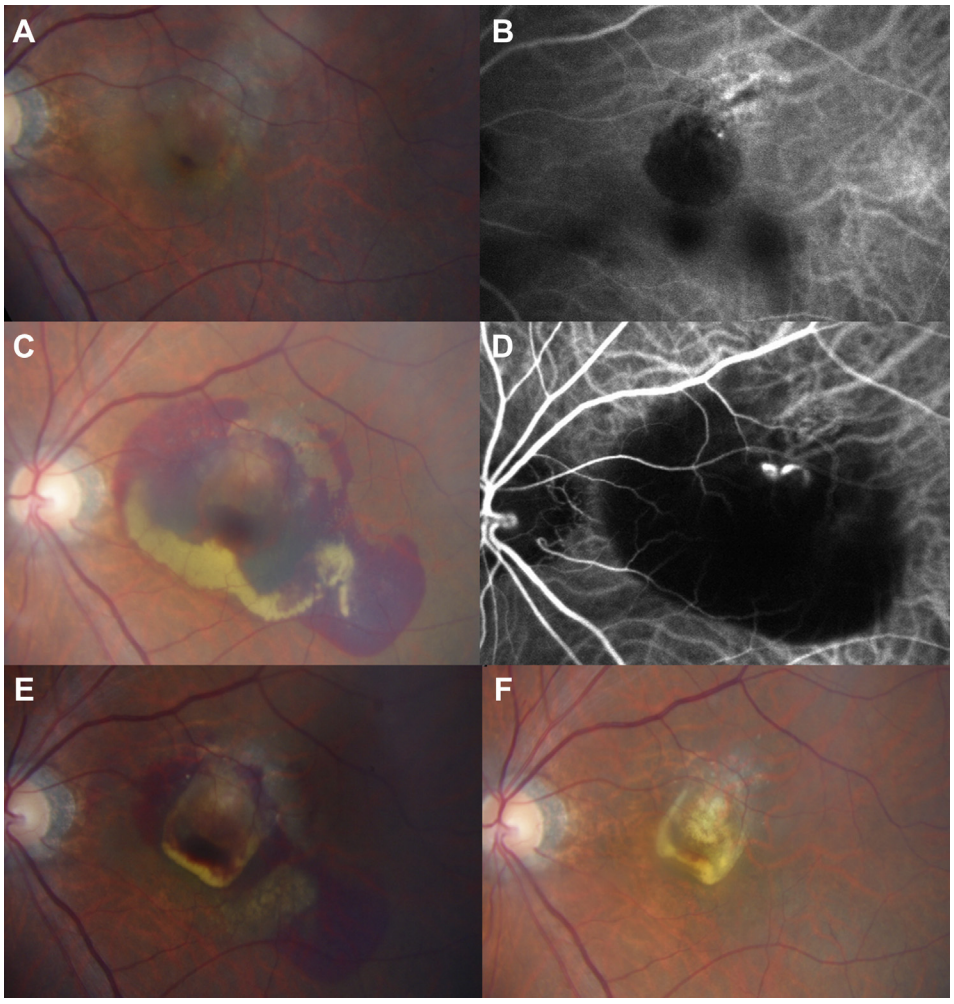

Fig. 5. An 81-year-old man reported blurred vision of the left eye (20/63) for 3 months. (A) Fundoscopic examination showed subretinal hemorrhage, pigment epithelial detachment, subretinal fluid and a reddish-orange nodule. (B) Indocyanine green angiography showed a branching vascular network with polypoidal lesions. Standard-fluence photodynamic therapy (sPDT) was performed with a 4800 μm irradiation spot. (C) Two months after treatment, fundoscopic examination showed increased subretinal hemorrhage with hemorrhagic pigment epithelial detachment. Visual acuity of the left eye was 20/200. (D) Indocyanine green angiography showed two prominent polypoidal lesions. Intravitreal injection of tissue plasminogen activator and gas tamponade was performed to displace the hemorrhage. (E) Two weeks after the operation, the blood at the fovea was displaced. sPDT was performed again with a 4100 μm irradiation spot. (F) Three months after the second PDT, fundoscopic examination showed retinal pigment epithelium atrophy and a glial scar. The visual acuity remained 20/200 in the left eye.

and subsequent up-regulation of VEGF after PDT.[12] With the use of rPDT/IVB, both the choroidal nonperfusion and the VEGF surge can be reduced, which results in less severe post-treatment hemorrhage.[21,26,29,35]

The limitations of our study include a small sample size and short follow-up period, which is in part due to the relative rarity of eligible patients with PCV; the diagnosis was newly established during the study period and a diversity of treatment options was given at that time before a consensus evolved. Exudation after treatment was documented semiquantitatively by changes in lipid exudate on fundus photographs and not quantitatively by optical coherent tomography. Choroidal vascular change after PDT was not documented in this study. Despite these limitations, our study has shown that patients who received rPDT/IVB had improved BCVA at the 6-month follow-up, a smaller decrease in visual acuity, and had less post-treatment hemorrhage and exudate than those who received sPDT monotherapy. Further large prospective randomized studies with long-term follow-up are warranted to establish the optimum treatment for PCV.

Acknowledgments

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