



The 24-month outcomes of intravitreal aflibercept combined with photodynamic therapy for polypoidal choroidal vasculopathy

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Abstract

Purpose This study was prospectively carried out to clarify the effectiveness of visual and anatomical outcomes under combination therapy of intravitreal aflibercept (IVA) and verteporfin photodynamic therapy (vPDT) in over 24 months.

Study design A single-arm prospective exploratory study.

Methods Twenty-six eyes of 26 treatment naïve PCV patients were enrolled in this study. The primary outcome measures were the changes in best corrected visual acuity (BCVA) and the complete polyp regression rate. The secondary outcome measures included central retinal thickness assessed by optical coherence tomography.

Results The patients showed significant improvement in BCVA by 0.14 logMAR units at 12 months and 0.11 logMAR units at 24 months from baseline (both $p < 0.01$). The mean central retinal thickness also significantly decreased at 12 months ($p < 0.001$) and at 24 months ($p = 0.001$). Complete regression of polypoidal lesions was achieved by 15 out of 20 eyes (75%) at 12 months and 11 out of 20 eyes (55%) at 24 months. The mean treatment number was 2.9 courses of IVA and 1.5 courses of vPDT and the mean retreatment free interval after initial therapy was 12.8 months during follow up of 24 months. The complete data from all predetermined examinations were observed in 17 out of 26 enrolled patients (65%) in this study.

Conclusion In this study, combination therapy of IVA and vPDT yielded visual and anatomical improvements in treatment-naïve PCV patients over a 24-month follow-up period.

Keywords Aflibercept · Combination therapy · Polypoidal choroidal vasculopathy · PCV · Photodynamic therapy

Introduction

Polypoidal choroidal vasculopathy (PCV) was first recognized at the 1982 meeting of The Macula Society, and was documented in subsequent reports as a phenotype of exudative age-related macular degeneration (AMD). In the anatomical characteristic, PCV typically displays unique findings of orange-colored protrusions at the posterior fundus [1, 2] and/or distinct polypoidal vascular lesions in indocyanine-green angiography (ICGA) [2–5]. Epidemiologically,

PCV is more prevalent in Asian populations than Caucasian, an example of which is that there over 50% of Japanese exudative AMD patients present PCV [5, 6].

At the present time, anti-VEGF therapy is the first line treatment modality for exudative AMD, whereas photodynamic therapy with verteporfin (Visudyne; Novartis Pharma AG) (vPDT) is only used as a rescue therapy for cases which are refractory to anti-VEGF agents. As for the treatment for PCV, The LAPTOP study, a prospective multicenter randomized trial designed to compare the effectiveness of intravitreal ranibizumab (Lucentis; Novartis Pharma AG) (IVR) and vPDT treatments for PCV, shows that IVR was more effective BCVA than vPDT over 24 months. Moreover, it is reported that intravitreal aflibercept (IVA), the latest anti VEGF agent available, showed higher complete regression rates of polyps with good improvement of BCVA [7].

However, vPDT is known to show better results than anti-VEGF therapy in polyp regression and hence in certain PCV cases it might be preferable to anti VEGF treatment [8].

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It is remarkable that the EVEREST 2 study, the crucial study of the combination therapy of anti VEGF and vPDT, demonstrates preferred effects of combination therapy with IVR and vPDT in visual improvement and the regression of polypoidal lesions over a 12-month follow-up period [9]. In addition, some retrospective reports show that of vPDT + IVR for PCV is effective over a longer time period [10–14]. Therefore, Koh AH et al. recommend the combination therapy of IVR and vPDT as the initial therapy for PCV [8]. As for the effectiveness of combination therapy with IVA and vPDT, our previous reports also show good visual and anatomical outcomes in treatment-naïve PCV patients over 12 months of follow up [15]. This is why combination therapy of anti-VEGF therapy and vPDT has become the common therapy for PCV. We conducted this study to evaluate the 24-month visual and anatomical outcomes of combination therapy of IVA and vPDT for PCV.

Materials and methods

Study design and participants

A single-arm prospective exploratory study of treatment-naïve PCV cases treated by a combination of IVA and vPDT. All cases in this study were Japanese individuals recruited from the Department of Ophthalmology at the Kobe University Hospital in Japan. This study was approved by the Institutional Review Board of Kobe University Graduate School of Medicine, and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects.

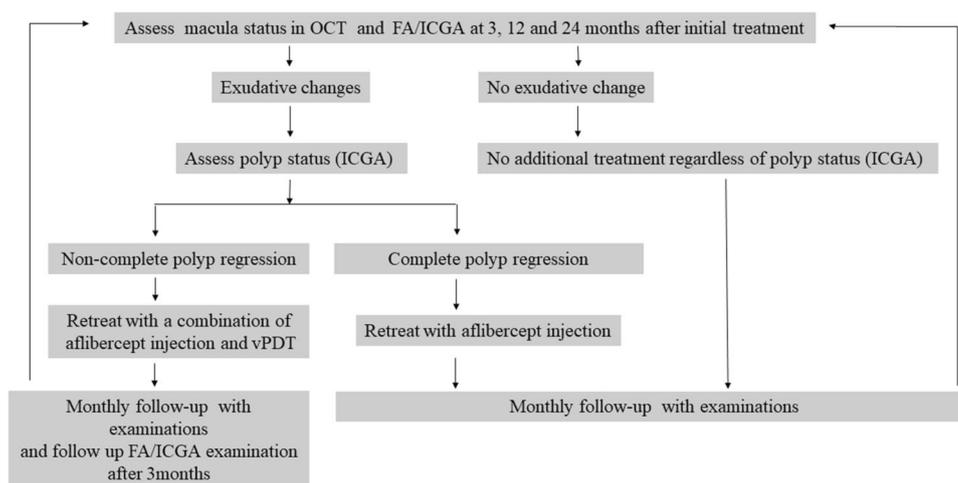
Twenty-six eyes of 26 consecutive treatment-naïve PCV patients aged over 50 years (17 men, 9 women) that showed subfoveal exudative lesions were included in the study (mean age 73.1 years). The patients underwent a single injection of aflibercept followed by vPDT a week later between April 2013 and July 2015 and their progress was followed for 24 months. Prior to starting treatment all patients received detailed ophthalmic examinations, including best-corrected visual acuity (BCVA) measurements, slit lamp biomicroscopy of their fundi, color fundus photography, fluorescein angiography (FA), indocyanine green angiography (ICGA) (HRA2; Heidelberg Engineering) and spectral-domain optical coherence tomography (OCT) (Spectralis; Heidelberg Engineering). The diagnosis of PCV was made in accordance with previous reports [1, 2]. On ICGA the PCV cases in this study showed subretinal reddish-orange protrusions corresponding to the choroidal origin of the polypoidal lesions, typically with the vascular networks in the posterior poles. We enrolled all patients with symptomatic macular naïve PCV, defined by the presence of active macular polyp lesions or branching vascular network on ICGA and

macular exudative changes on OCT or fundus photography. If patients had bilateral PCV, precursor eyes with treatment were enrolled. We excluded patients who had received any previous treatment such as laser photocoagulation, vitrectomy or intravitreal anti-VEGF therapy, and patients who had past histories of retinal vessel occlusion, diabetic retinopathy, uveitis, rhegmatogenous retinal detachment or glaucoma. In addition, we excluded the cases in which it was difficult to diagnose PCV due to large submacular hemorrhages or undefined polypoidal lesions.

Treatment

All patients received a single IVA (2.0 mg of aflibercept in 0.05 ml) and then standard vPDT (a laser light at 689 nm delivered at 50 J/cm² with an intensity of 600 mW/cm² over 83 s) with verteporfin (6 mg/m²) after one week of induction therapy. The laser spot size was determined as 1000 µm added to the area of any polyps and branching vascular networks on the ICG findings. After the initial treatment, the patients were followed-up monthly with examinations including BCVA measurements, slit lamp biomicroscopy and OCT images until 24 months after the initial treatment. We used vertical and horizontal cross sectional OCT images through the fovea to check exudative change macula within 6mm range. Though no additional treatment was applied until the first 3 months after the initial treatment following the original vPDT regimen, additional IVA could be applied according to the physician's discretion in cases with residual or worsening exudative lesion at the macula. Routine FA and ICGA were scheduled at 3, 12 and 24 months of follow-up. The need for additional treatment was evaluated at 3 months based on OCT and FA/ICGA findings. The criteria for ordering additional treatment are shown in Fig. 1. Additional treatment was required if exudative changes such as subretinal or intraretinal fluid was found by OCT. In addition, wherever residual polyp lesions were found by ICGA, a combination therapy of IVA and vPDT was performed and whenever no residual polyp lesion was found by ICGA IVA, monotherapy was performed. After 3 months, additional IVA was performed if required based on OCT findings. Additional FA/ICGA and vPDT were allowed every 3 months at the physician's discretion. If an additional vPDT was performed, FA/ICGA was repeated 3 months later and the necessity for further vPDT was determined by evaluating the state of the polyp lesions. The summary of re-treatment and follow-up criteria is shown in Fig. 1. Patients were followed in accordance with these criteria over a 24-month period.

Fig. 1 Treatment schedule and re-treatment criteria. *OCT* optical coherent tomography, *vPDT* verteporfin photodynamic therapy, *ICGA* indocyanine green angiography, *FA* fluorescein angiography



Outcomes

Main outcomes measures were the changes in BCVA and the rate of complete polyp regression. We evaluated the state of polyps at each session according to the following guidelines. Complete regression of polyps: all polyps detected at baseline regressed and no new polyps were detected on ICGA. Partial regression of polyps: polyps detected at baseline partially regressed and no new polyps were detected on ICGA. Recurrence of polyps: new polyps emerged in the course of follow-up, once polyps that were detected at baseline had regressed.

Secondary outcome measures were anatomical changes from baseline including central retinal thickness (CRT) and the ratio of dry macula as assessed by OCT.

The visual acuity was determined using a Landolt C chart converted to a logarithm of the minimum angle of resolution (logMAR) value for calculation. The CRT indicating the distance between ILM and RPE at the fovea was obtained by OCT by averaging 50 scans in normal and enhanced depth imaging modes, respectively.

Statistics analyses

In this study, intention to treat (ITT) analysis was used as the method of analysis and available case analysis was applied for missing data. The sample size was not estimated before starting this study because of the explanatory nature of the study. However, we used the number of patients in the EVEREST study [16] as a reference. All statistical analyses were performed by MedCalc v.15.4 software (MedCalc Software). The paired t-test or Wilcoxon signed rank test, whichever was appropriate, was performed to compare any two groups. P values less than 0.05 were considered to be statistically significant.

Results

Patient characteristics

Baseline characteristic data for the 26 patients included in the present study are shown in Table 1. Two patients were classified as having a hemorrhagic PED, while 4 patients were classified as having a serous PED. The complete data were observed in 17 patients out of enrolled 26 consecutive treatment-naïve PCV patients because 9 patients with incomplete data missed some of the examinations, including 5 patients who missed monthly follow up and 9 patients who missed ICGA at some regular periods in this study. In particular, 2 patients moved to another hospital,

Table 1 Summary of the patient characteristics at baseline

Clinical characteristics	
Right eye (%)	14 (54%)
Male gender (%)	17 (65%)
Age, mean (\pm SD) (years)	73.1 (7.8)
Baseline LogMAR BCVA (\pm SD)	0.3 (0.3)
Baseline CRT (\pm SD) (μ m)	356 (230)
Baseline maximum PED height (\pm SD) (μ m)	231 (204)
Baseline GLD (\pm SD) (μ m)	3895 (1981)
Maximum polyp size (\pm SD) (μ m)	506 (221)
Multiple polyps (≥ 2)	14 (54%)
Polyp location (sub fovea)	7 (27%)
CVH	9 (35%)
Subretinal hemorrhage ($1 \geq DA$)	6 (23%)
The presence of PED	24 (92%)

SD standard deviation, logMAR logarithm of the minimum angle of resolution, BCVA best corrected visual acuity, CRT central retinal thickness, PED pigment epithelial detachment, GLD greatest linear dimension, CVH choroidal vascular hyperpermeability, DA disc area

one patient died and 6 patients declined ICGA at some point during the 24 months.

Primary outcomes

Visual outcomes

In the time course analysis, the mean BCVA was significantly improved at all time-points measured (0.19, 0.19, 0.17, 0.20 and 0.20 logMAR units at 3, 6, 12, 18 and 24 months, respectively) compared to 0.31 logMAR unit at baseline ($p < 0.001$ at 3 and $p < 0.01$ at 6, 12, 18 and 24 months, respectively) (Table 2a and Fig. 2a). At 24 months after the initial treatment, five eyes (19%) showed an increase in BCVA of ≥ 0.3 logMAR units and one eye (4%) showed a decrease in BCVA of ≥ 0.3 logMAR units.

Regression of polyps

The complete regression of polypoidal lesions on ICGA was observed in 15 eyes (68%) out of 22 at 3 months, 15 eyes (75%) out of 20 eyes at 12 months and 11 eyes (55%) out of 20 at 24 months. Partial regression of polyps was observed by ICGA in 6 (27%) out of 22 eyes at 3 months, 3 (15%) out of 20 eyes at 12 months and 7 (35%) out of 20 eyes at 24 months. Furthermore, the recurrence of polyps occurred in one eye (5%) during 12 months and 4 eyes (20%) during 24 months (Table 3). In the ICGA analyses, 4 eyes were missed at 3 months, 6 eyes were missed at 12 months (all missed eyes with declining ICGA because of no exudative changes on macula at 3 and 12 months) and 6 eyes were missed at 24 months (2 eyes changing hospital, 3 eyes with declining ICGA because of no exudative changes on macula at 24 months and one eye due to the patient's death.).

Anatomical outcomes

Central retinal thickness

The mean CRT was significantly improved compared to baseline at all time-points ($p < 0.001$ at 3 and 12 months, and $p = 0.001$ at 6, 18 and 24 months, respectively) (Table 2b and Fig. 2b).

Dry macula

"Dry macula" (no exudative changes including no intraretinal or subretinal fluid at macula found on OCT) was achieved in 19 eyes (73%) at 3 months, 24 eyes (92%) at 12 months and 18 eyes (75%) at 24 months after treatment. (Table 3)

Treatment numbers

The patients required an average of 1.8 ± 1.0 IVA and 1.3 ± 0.6 vPDT at 12 months and an average of 2.9 ± 1.8 IVA and 1.5 ± 0.8 vPDT at 24 months with mean 3.85 ± 1.05 ICGA evaluations. In this study, a single session of IVA and vPDT were required in 6 eyes which did not show recurrence over 24 months follow up.

In 4 eyes, the recurrence of polyps occurred between 12 months and 24 months after polyp lesions had completely regressed. The mean retreatment free interval after initial therapy was 12.8 months and 6 eyes did not need any retreatment during the follow-up period in the present study.

Adverse events

There was one ocular adverse event of subretinal hemorrhage (> 1 disc diameter). It occurred in an eye with 0.05 logMAR at baseline BCVA, yet the final BCVA in the eye improved by -0.08 logMAR units. There was also one case

Table 2 Time-course changes

	Baseline (n=26)	3 months** (n=26)	6 months* (n=26)	12 months* (n=26)	18 months* (n=25)	24 months* (n=24)
a. In the BCVA after the combination therapy with aflibercept and vPDT						
Mean BCVA (SD)	0.31 (0.29)	0.19 (0.31)	0.19 (0.37)	0.17 (0.33)	0.20 (0.35)	0.20 (0.35)
Median BCVA (IQR)	0.22 (0.05–0.40)	0.13 (0.00–0.40)	0.02 (0.00–0.16)	0.00 (0.00–0.22)	0.05 (0.00–0.24)	0.00 (0.00–0.40)
b. In the CRT after the combination therapy with aflibercept and vPDT						
Mean CRT (SD)	356 (230)	173 (46)	177 (45)	160 (41)	164 (43)	167 (54)
Median CRT (IQR)	326 (223–398)	174 (134–212)	176 (145–195)	155 (134–186)	160 (135–179)	158 (126–199)

BCVA best corrected visual acuity (LogMAR), IQR interquartile range, CRT central retinal thickness, IQR interquartile range

*P value < 0.01 and ** P value < 0.001 calculated by Wilcoxon signed rank test to comparison with baseline. ** P value $= 0.001$ and *** P value < 0.001 calculated by Wilcoxon signed rank test to comparison with baseline

Fig. 2 a Changes in mean LogMAR BCVA in PCV patients undergoing combination therapy with aflibercept and vPDT. The BCVA measured by the Landolt C chart are presented as the logarithm of the minimum angle of resolution (logMAR). The point represents the mean BCVA and the vertical bar represents standard error of the mean BCVA at each time point. Values represent means \pm SE. The P values were calculated by the Wilcoxon rank sum test to compare BCVA between the baseline and each time point. * $p < 0.01$, ** $p < 0.001$. **b** Changes in mean CRT in PCV patients undergoing combination therapy with aflibercept and vPDT. The CRT was defined by OCT as the distance between the internal limiting membrane and the retinal pigment epithelium at the fovea. The point represents the mean CRT and the vertical bar represents standard error of the mean CRT at each time point. Values represent means \pm SE. The P values were calculated by the Wilcoxon rank sum test to compare CRT between the baseline and each time point. ** $p = 0.001$, *** $p < 0.001$

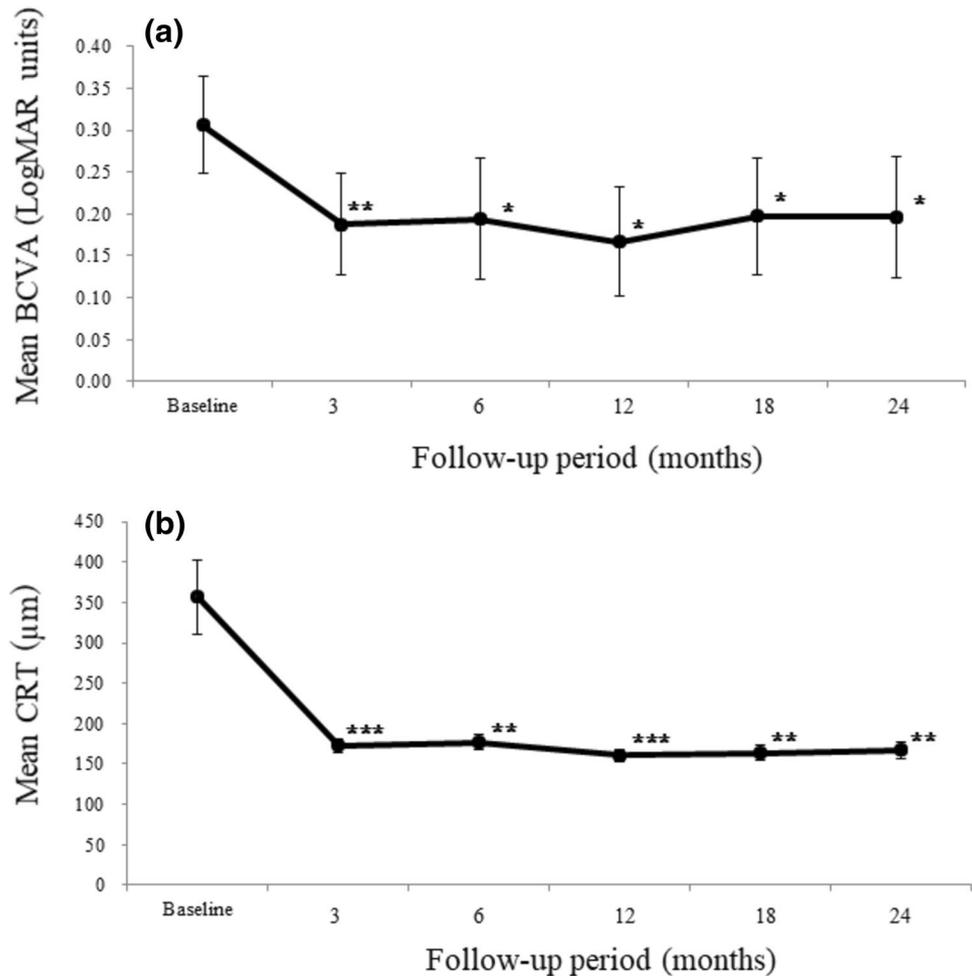


Table 3 Changes in anatomical outcomes of combination therapy with intravitreal aflibercept and verteporfin photodynamic therapy for polypoidal choroidal vasculopathy

	3 months		12 months		24 months	
	Number of eyes (%)	Total number	Number of eyes (%)	Total number	Number of eyes (%)	Total number
Complete regression of polyps	15 (68%)	22	15 (75%)	20	11 (55%)	20
Complete and partial regression of polyps	21 (95%)	22	18 (90%)	20	18 (90%)	20
Recurrence of polyps	0 (0%)	22	1 (5%)	20	4 (20%)	20
Dry macula	19 (73%)	26	24 (92%)	26	18 (75%)	24
Increased subretinal hemorrhages (>1 disc diameter)	0 (0%)	26	0 (0%)	26	1 (4%)	24

Dry macula: no exudative changes including no intraretinal or subretinal fluid found on OCT. Complete regression of polyps: all polyps that detected at baseline regressed and no new polyps were detected on ICGA. Partial regression of polyps: polyps that detected at baseline partially regressed and no new polyps were detected on ICGA. Recurrence of polyps: new polyps occurred in the course of follow-up, once polyps that detected at baseline regressed

of systemic adverse event in which the patient died during the 24 months period.

Representative cases

Figures 3 and 4 show representative cases. Figure 3 shows an eye that needed the minimum number of total

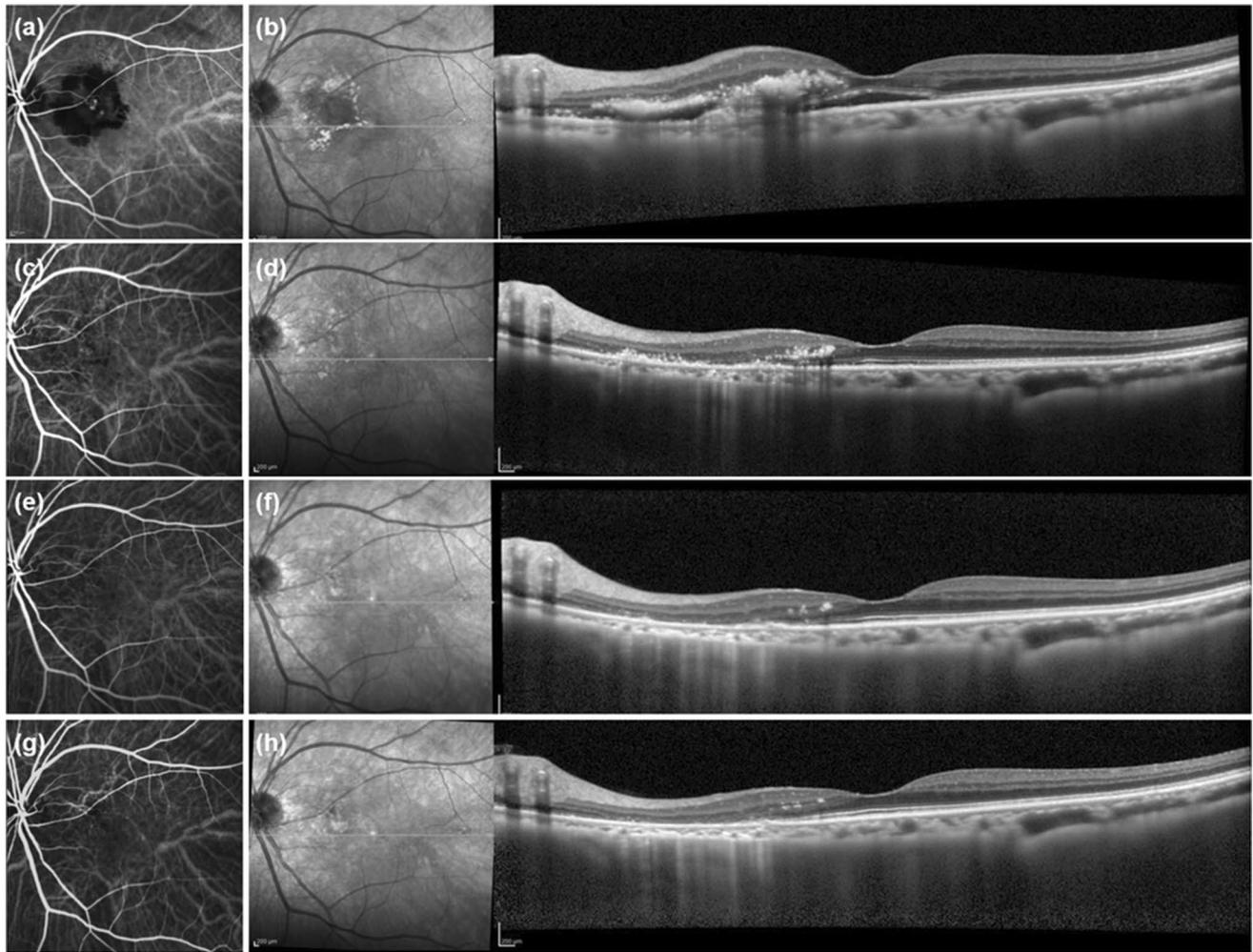


Fig. 3 Images of the clinical course in the left eye of a 74-year-old female with polypoidal choroidal vasculopathy. **a** The polypoidal lesions on indocyanine green angiography (ICGA) is represented as hyper fluorescence lesion beneath subretinal hemorrhage represented as blocked fluorescence area. The best-corrected visual acuity (BCVA) is 0.8 in decimal fraction. **b** Serous detachment (SD), serous pigment epithelial detachment (PED) and hard exudates (HE) at the baseline are shown in the horizontal image of optical coherence tomography (OCT). Morphological improvements are achieved at 3 months after initial treatment. Polypoidal lesions are completely

regressed on ICGA (**c**) and no SD and PED are found on OCT (**d**). The BCVA has improved to 1.0. **e, f** Morphological improvements are maintained at 12 months after initial treatment. The BCVA keeps 1.0 without additional treatment. Morphological improvements are still maintained at 24 months after initial treatment. ICGA shows that complete regression of the polyps is maintained (**g**). OCT shows no SD and PED, and small HE. These findings are similar to those at 12 months (**h**). The BCVA has improved to 1.2 without additional treatment

treatments and Fig. 4 shows an eye that needed the greatest number of vPDT.

Discussion

To the best of our knowledge, this is the first report describing the 24-month outcomes of combination therapy with IVA and vPDT in treatment-naïve PCV patients. Moreover, no study has reported the complete regression rate of polyps by combination therapy with vPDT and anti-VEGF over a 24-month of follow-up period.

The EVEREST 2 study, the latest clinical trial to compare ranibizumab+vPDT with ranibizumab monotherapy for PCV in efficacy and safety over 12-months, showed that vPDT treatment combined with IVR achieved the higher complete polyp regression rate (69.3%) and the better improvement in visual acuity (gained 8.3 letters) compared to IVR monotherapy (34.7% and gained 5.1 letters, respectively) [9]. In addition, recent meta-analyses that combined intravitreal anti-VEGF and vPDT report results of better long-term visual outcomes and lower incidence rates of retinal hemorrhage than vPDT monotherapy [17, 18]. Therefore, an expert panel on PCV treatment

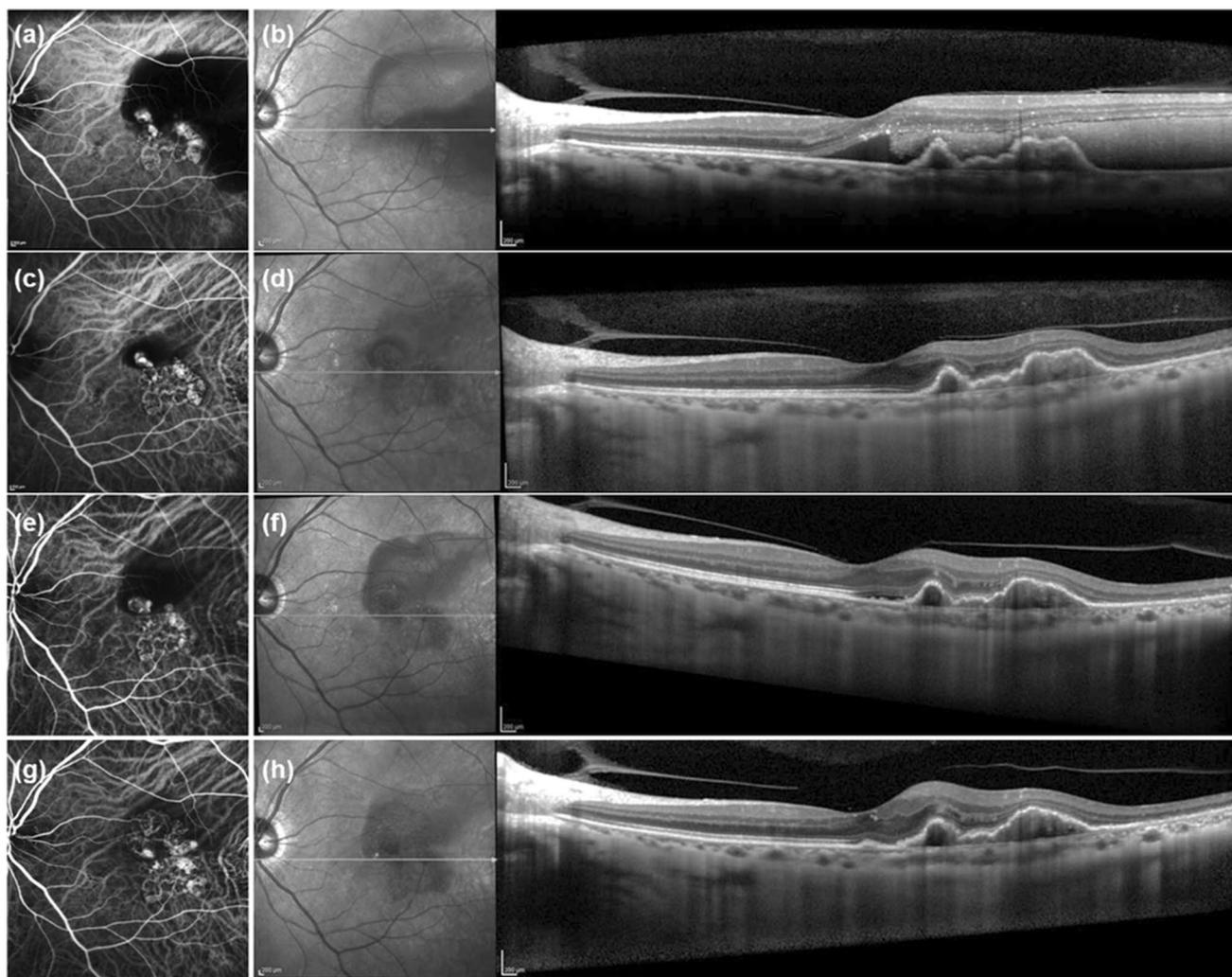


Fig. 4 Images of the clinical course in the left eye of a 61-year-old male with polypoidal choroidal vasculopathy. **a** Indocyanine green angiography (ICGA) shows the bulging polypoidal lesions with a branching vascular network (BVN) at the baseline. The best-corrected visual acuity (BCVA) is 0.9 in decimal fraction. **b** Multiple pigment epithelial detachments (PEDs) beneath serous retinal detachment (SD) with subretinal hemorrhage and at the baseline are shown in the horizontal image of optical coherence tomography (OCT). Morphological changes at 3 months are the following; no change of polyps

with BVN on ICGA (**c**) and no SD and residual PEDs unchanged on OCT (**d**). The BCVA has improved to 1.2. Morphological changes at 12 months are the following; unchanged polyps with BVN on ICGA (**e**) and a recurrence of SD and unchanged PED on OCT (**f**). The BCVA of 1.2 is maintained after 2 courses of IVA and 2 courses of vPDT. Morphological changes at 24 months are the following; deteriorating polyps with BVN on ICGA (**g**) and no SD and unchanged PED on OCT (**h**). The BCVA of 1.2 is kept after 4 courses of IVA and 3 courses of vPDT

concluded that the combination therapy of vPDT and anti-VEGF should be the first-line treatment in subfoveal and juxtafoveal PCV [8].

However, several recent reports propose the merits of IVA monotherapy which achieved preferable outcomes in complete polyp regression (55.4% and 69.8%) and visual acuity at 12 months [12, 19]. The stronger therapeutic effect of IVA over IVR for PCV might be derived from not only a higher affinity for VEGF-A and a longer half-life of aflibercept compared with ranibizumab, but also the ability of aflibercept to blockade VEGF-B and PIGF [20, 21]. Actually, many studies report that IVA showed good visual and anatomical

outcomes in the PCV cases which were refractory to IVR [22, 23].

Hence, it might be possible that the combination therapy of IVA+vPDT could yield good visual and anatomical outcomes on PCV because of the associated synergistic effects.

In our previous report as well as another report, IVA+vPDT achieved complete polyp regression in 78% and 68% of PCV cases at 12 months [15, 24]. Complete regression of polyps was comparable to IVR+vPDT combination therapy in the EVEREST 2 study and might be superior to the results of IVA monotherapy reported in previous studies [9, 12, 19]. Moreover, two recent reports showed

similar visual outcomes with less numbers of treatment in combination therapy than IVA monotherapy [24, 25]. In this study, our results also show that IVA+vPDT significantly improved BCVA at 24 months compared to baseline of PCV patients with 2.9 ± 1.8 IVA and 1.5 ± 0.8 vPDT with mean 3.85 ± 1.05 ICGA at 24 months of follow-up. Therefore, an advantage of combination therapy might be to provide good visual and anatomical outcomes with fewer treatment sessions, though frequent fundus angiography sessions including ICGA would be needed to follow up patients longer term. Moreover, the FUJISAN study, a comparative study of initial or deferred vPDT combined with IVR for PCV, showed that patients with initial vPDT significantly receive less vPDT and IVR than patients with later vPDT [26]. The PLANET study, a comparative study of IVA monotherapy and IVA+ rescue vPDT, shows that IVA with rescue PDT did not appear to provide any additional functional benefits [27]. These might indicate that combination therapy with IVA and vPDT could be a first line treatment for PCV rather than the rescue treatment.

In the ICGA analyses, the rates of complete polyp regression were 68% at 3 months, 75% at 12 months and 55% at 24 months. When interpreting the complete polyp regression at 24 months, the possibility of underestimation should be considered as ICGA were missed in 6 eyes, 4 eyes of which achieved 'Dry macula' at 24 months. However, because the recurrences of polyps occurred in 4 eyes on and after 12 months and 'Dry macula' at 24 months decreased to 75% from 92% at 12 months, the deterioration of these anatomical outcomes at 24 months might indicate that there were some problems concerning long term maintenance of PCV.

To the best of our knowledge, there are no reports that evaluate the 24-month outcomes with IVA monotherapy in treatment-naïve PCV patients, but there are some reports on combination therapy with vPDT+IVR for treatment-naïve PCV patients in longer term period of up to 24 months [10–14]. The improvement of BCVA and treatment numbers at 24 months in this study were comparable to those in previous reports of combination therapy with vPDT+IVR, but data on polyp regression at 24 months was not shown in those reports.

To make a direct comparison between the effect of IVA and IVR combined with vPDT for PCV is difficult since the initial treatment regimen varies among studies [17]. Further studies will be needed to clarify this issue.

As for the adverse events, retinal hemorrhage related to vPDT for exudative AMD is known to be a major concern [28, 29]. However, a recent report demonstrates that the incidences of post-treatment hemorrhages in the combination of IVR and vPDT were less than those in vPDT monotherapy [9, 17]. Since anti VEGF therapy suppresses the VEGF expression induced by vPDT, it might result in a lower retinal hemorrhage rate in the combination therapy [30]. In this

study, subretinal hemorrhage over 1 disc diameter occurred in one eye (5%). One patient death (5%) occurred as systemic adverse event during the follow-up period, though it was not clear whether it correlated with the treatment for PCV. This result is comparable to previous reports of combination therapy [10–14].

In the present study, there are four major limitations regarding its study design; a preliminary study, a single arm, a relatively small number of subjects and some incomplete patients.

In addition, it might be controversial whether the number of ICGA cases in this study is sufficient. A prospective study with a larger sample size will be needed to confirm the results of the present study. We considered that the common use of anti-VEGF therapy for AMD including PCV might decrease the number of treatment-naïve PCV patients referred to our hospital. This might be part of the reason why the number of enrolled patients in this study was less than our expectation. However, our results show that combination therapy of IVA and vPDT can yield good visual and anatomical outcomes with a high rate of complete regression of polypoidal lesions in PCV cases over a 24-month follow-up period. This information might be useful in establishing personalized treatment and maintenance for PCV patients for longer terms.

In conclusion, this study showed that combination therapy of IVA and vPDT improved the visual and anatomical outcomes of treatment-naïve PCV patients and was well tolerated over a 24-month follow up period.

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References

1. Yannuzzi LA, Sorenson J, Spaide RF, Lipson B. Idiopathic polypoidal choroidal vasculopathy (PCV). *Retina*. 1990;10:1–8.
2. Uyama M, Matsubara T, Fukushima I, Matsunaga H, Iwashita K, Nagai Y, et al. Idiopathic polypoidal choroidal vasculopathy in Japanese patients. *Arch Ophthalmol*. 1999;117:1035–42.
3. Yannuzzi LA, Ciardella A, Spaide RF, Rabb M, Freund KB, Orlock DA. The expanding clinical spectrum of idiopathic polypoidal choroidal vasculopathy. *Arch Ophthalmol*. 1997;115:478–85.
4. Spaide RF, Yannuzzi LA, Slakter JS, Sorenson J, Orlock DA. Indocyanine green videoangiography of idiopathic polypoidal choroidal vasculopathy. *Retina*. 1995;15:100–10.
5. Ciardella AP, Donsoff IM, Huang SJ, Costa DL, Yannuzzi LA. Polypoidal choroidal vasculopathy. *Surv Ophthalmol*. 2004;49:25–37.

6. Maruko I, Iida T, Saito M, Nagayama D, Saito K. Clinical characteristics of exudative age-related macular degeneration in Japanese patients. *Am J Ophthalmol.* 2007;144:15–22.
7. Yamamoto A, Okada AA, Kano M, Koizumi H, Saito M, Maruko I, et al. One-year results of intravitreal aflibercept for polypoidal choroidal vasculopathy. *Ophthalmology.* 2015;122:1866–72.
8. Koh AH, Chen LJ, Chen SJ, Chen Y, Giridhar A, Iida T, et al. Polypoidal choroidal vasculopathy: evidence-based guidelines for clinical diagnosis and treatment. *Retina.* 2013;33:686–716.
9. Koh AH, Lai TYY, Takahashi K, Wong TY, Chen LJ, Ruamviboonsuk P, et al. Efficacy and safety of ranibizumab with or without verteporfin photodynamic therapy for polypoidal choroidal vasculopathy: a randomized clinical trial. *JAMA Ophthalmol.* 2017;135:1206–13.
10. Saito M, Iida T, Kano M, Itagaki K. Two-year results of combined intravitreal ranibizumab and photodynamic therapy for polypoidal choroidal vasculopathy. *Graefes Arch Clin Exp Ophthalmol.* 2013;251:2099–110.
11. Yoshida Y, Kohno T, Yamamoto M, Yoneda T, Iwami H, Shiraki K. Two-year results of reduced-fluence photodynamic therapy combined with intravitreal ranibizumab for typical age-related macular degeneration and polypoidal choroidal vasculopathy. *Jpn J Ophthalmol.* 2013;57:283–93.
12. Kim M, Kim K, Kim DG, Yu S-Y, Kwak H-W. Two-year results of photodynamic therapy combined with intravitreal antivascular endothelial growth factor for polypoidal choroidal vasculopathy. *Ophthalmologica.* 2011;226:205–13.
13. Lee YA, Yang CH, Yang CM, Ho TC, Lin CP, Huang JS, et al. Photodynamic therapy with or without intravitreal bevacizumab for polypoidal choroidal vasculopathy: two years of follow-up. *Am J Ophthalmol.* 2012;154:872–80.
14. Hata M, Tsujikawa A, Miyake M, Yamashiro K, Ooto S, Oishi A, et al. Two-year visual outcome of polypoidal choroidal vasculopathy treated with photodynamic therapy combined with intravitreal injections of ranibizumab. *Graefes Arch Clin Exp Ophthalmol.* 2015;253:189–97.
15. Matsumiya W, Honda S, Otsuka K, Miki A, Nagai T, Imai H, et al. One-year outcome of combination therapy with intravitreal aflibercept and verteporfin photodynamic therapy for polypoidal choroidal vasculopathy. *Graefes Arch Clin Exp Ophthalmol.* 2017;255:541–8.
16. Koh A, Lee WK, Chen LJ, Chen SJ, Hashad Y, Kim H, et al. EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy. *Retina.* 2012;32:1453–64.
17. Wang W, He M, Zhang X. Combined intravitreal anti-VEGF and photodynamic therapy versus photodynamic monotherapy for polypoidal choroidal vasculopathy: a systematic review and meta-analysis of comparative studies. *PLoS One.* 2014. <https://doi.org/10.1371/journal.pone.0110667>.
18. Tang K, Si JK, Guo DD, Cui Y, Du YX, Pan XM, et al. Ranibizumab alone or in combination with photodynamic therapy vs photodynamic therapy for polypoidal choroidal vasculopathy: a systematic review and Meta-analysis. *Int J Ophthalmol.* 2015;18:1056–66.
19. Oishi A, Tsujikawa A, Yamashiro K, Ooto S, Tamura H, Nakaniishi H, et al. One-year result of aflibercept treatment on age-related macular degeneration and predictive factors for visual outcome. *Am J Ophthalmol.* 2015;159:853–60.
20. Papadopoulos N, Martin J, Ruan Q, Rafique A, Rosconi MP, Shi E, et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. *Angiogenesis.* 2012;15:171–85.
21. Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. *Br J Ophthalmol.* 2008;92:667–8.
22. Kawashima Y, Oishi A, Tsujikawa A, Yamashiro K, Miyake M, Ueda-Arakawa N, et al. Effects of aflibercept for ranibizumab-resistant neovascular age-related macular degeneration and polypoidal choroidal vasculopathy. *Graefes Arch Clin Exp Ophthalmol.* 2015;253:1471–7.
23. Lee MY, Lee WK, Baek J, Kwon OW, Lee JH. Photodynamic therapy versus combination therapy in polypoidal choroidal vasculopathy: changes of aqueous vascular endothelial growth factor. *Am J Ophthalmol.* 2013;156:343–8.
24. Kikushima W, Sakurada Y, Sugiyama A, Tanabe N, Kume A, Iijima H. Comparison of initial treatment between 3-monthly intravitreal aflibercept monotherapy and combined photodynamic therapy with single intravitreal aflibercept for polypoidal choroidal vasculopathy. *Graefes Arch Clin Exp Ophthalmol.* 2017;255:311–6.
25. Takayama K, Kaneko H, Kataoka K, Hattori K, Ra E, Tsunekawa T, et al. Comparison between 1-year outcomes of aflibercept with and without photodynamic therapy for polypoidal choroidal vasculopathy: retrospective observation study. *PLoS One.* 2017. <https://doi.org/10.1371/journal.pone.0176100>.
26. Gomi F, Oshima Y, Mori R, Kano M, Saito M, Yamashita A, et al. Initial versus delayed photodynamic therapy in combination with ranibizumab for treatment of polypoidal choroidal vasculopathy: the Fujisan Study. *Retina.* 2015;35:1569–76.
27. Lee WK, Iida T, Ogura Y, Chen SJ, Wong TH, Mitchell P, et al. Efficacy and safety of intravitreal aflibercept for polypoidal choroidal vasculopathy in the PLANET study. A randomized clinical trial. *JAMA Ophthalmol.* 2018;136(7):786–93.
28. Chan WM, Lam DS, Lai TY, Liu DT, Li KK, Yao Y, et al. Photodynamic therapy with verteporfin for symptomatic polypoidal choroidal vasculopathy: one-year results of a prospective case series. *Ophthalmology.* 2004;111:1576–84.
29. Oh IK, Huh K, Oh J. Risk factors for retinal hemorrhage after photodynamic therapy in age-related macular degeneration. *Ophthalmologica.* 2009;223:78–84.
30. Lee MY, Lee WK, Baek J, Kwon OW, Lee JH. Photodynamic therapy versus combination therapy in polypoidal choroidal vasculopathy: changes of aqueous vascular endothelial growth factor. *Am J Ophthalmol.* 2013;156:343–8.