# INITIAL VERSUS DELAYED PHOTODYNAMIC THERAPY IN COMBINATION WITH RANIBIZUMAB FOR TREATMENT OF POLYPOIDAL CHOROIDAL VASCULOPATHY

## The Fujisan Study

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**Purpose:** To compare the 1-year results of initial or deferred photodynamic therapy (PDT) combined with intravitreal ranibizumab (IVR) for eyes with polypoidal choroidal vasculopathy.

**Methods:** Prospectively, 72 men with treatment-naive polypoidal choroidal vasculopathy were randomized to initial or later PDT combined with IVR. In both groups, 2 additional monthly IVR followed. From Month 3, PDT and IVR were administered according to the retreatment criteria. Mean changes in the best-corrected visual acuity between baseline and Month 12 and central retinal thickness, the rate of eyes showing regression of polypoidal lesions, and number of additional treatments were compared.

**Results:** The best-corrected visual acuity increased by a mean of 8.1 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters in the initial PDT group and 8.8 ETDRS letters in the later PDT group, and there was a no significant difference ($P = 0.59$). The mean central retinal thickness decreased significantly in both groups but more so with combination therapy within the first 4 months; the difference was not significant at Month 12 ($P = 0.30$). The rate of eyes showing resolution of polypoidal lesions at 12 months was 62.1% in the initial PDT group and 54.8% in the later PDT group and again, there was no significant difference ($P = 0.53$). The mean number of additional IVR was 1.5 in initial PDT and 3.8 in later PDT; that of additional PDTs was 0.14 and 0.45, respectively, and they were significantly different ($P < 0.001$ and $P = 0.013$, respectively).

**Conclusion:** Both initial and deferred PDT combined with IVR to treat polypoidal choroidal vasculopathy show the similar visual and anatomical improvements at 12 months. Initial PDT combination leads to significantly fewer additional treatments.

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Polypoidal choroidal vasculopathy (PCV), a subtype of wet age-related macular degeneration (AMD), is characterized by polypoidal choroidal vascular dilatation with or without abnormally branching choroidal vascular networks on indocyanine green angiography (ICGA).[1–6] Polypoidal choroidal vasculopathy is more prevalent in Asian patients than in white patients; nearly half of Japanese patients with wet AMD have PCV.[6,7]

Photodynamic therapy (PDT) with verteporfin (Visudyne; Valeant Ophthalmics, Bridgewater, NJ) is the first approved treatment for wet AMD, and clinical trials of PDT showed better visual responses at 1 year in Japanese patients compared with white patients.[8,9] The racial difference seems to be attributable to greater visual improvement in PCV than in typical wet AMD with choroidal neovascularization after PDT.[10,11] Photodynamic therapy resolves the

polypoidal lesions in PCV and also results in resolution of exudative fluid.[10–14]

However, recently, the first-choice treatment for wet AMD has shifted to anti-vascular endothelial growth factor (VEGF) drugs, such as ranibizumab (Lucentis, Genentech Inc, South San Francisco, CA), from PDT, and the vision-improving effect has been confirmed regardless of race or disease subtype.[15–17] Therefore, eyes with PCV can be treated initially with anti-VEGF drugs; however, they are limited in their ability to resolve polypoidal lesions, for which PDT works effectively.[6,13,18–21]

Combination therapy of PDT and anti-VEGF drugs provides the complementary effects of both treatments,[22–26] but it remains unknown whether PDT should have been administered at the beginning of treatment or during follow-up of anti-VEGF therapy. The purpose of this study was to compare the 1-year treatment results of initial and deferred PDT combined with ranibizumab for PCV.

## Methods

The Fujisan Study was a prospective, multicenter, randomized trial conducted at six Japanese institutions: Osaka University Hospital, Surugadai Nihon University Hospital, Kyushu University Hospital, Kagawa University Hospital, Fukushima Medical University Hospital, and Nagoya University Hospital. The institutional review board/ethics committee of each institution approved the study protocol. The study design adhered to the tenets of the Declaration of Helsinki and guidelines of the Japanese Ministry of Health, Labor, and Welfare. Patients provided written informed consent for participating in the study. The trial was registered with the University Hospital Medical Information Network (UMIN ID: 000004845).

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This prospective study was registered at the Clinical Trial Registry of the University Hospital Medical Information Network (UMIN-CTR; No. UMIN000004845).

Investigators of the Fujisan Study Group are listed in the Appendix.

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Patients were recruited from January 10, 2011, to October 15, 2012. We included men older than 50 years with treatment-naive PCV who met the following criteria. The diagnosis of PCV was based on the finding of lesions showing polyp-like choroidal vessel dilatation (polypoidal lesions or polyps) with or without a branching vascular network on ICGA obtained using the Heidelberg Retina Angiograph (HRA2) or Spectralis HRA (Heidelberg Engineering, Heidelberg, Germany). Only one eye per patient was included in the study. The best-corrected visual acuity (BCVA) levels ranged from 0.1 (Snellen equivalent 20/200) to 0.7 (Snellen equivalent 20/28) using a Landolt C chart. The greatest lesion size was less than 12 Macular Photocoagulation Study disk areas. Excluded were eyes that had central serous chorioretinopathy, retinal vascular disease, any neovascular maculopathy, glaucoma, or a history of intraocular surgery other than phacoemulsification.

Patients were randomized to verteporfin PDT plus intravitreal ranibizumab (IVR) 0.5 mg combination therapy (initial PDT group) or ranibizumab alone (later PDT group) as the initial treatment. To balance the baseline characteristics, we stratified eyes using 8 strata according to BCVA (over and under 54 letters on ETDRS chart), age (over and under 75 year old), and greatest linear dimension (over and under 2,800 $\mu$m) into 2 groups in a 1:1 ratio. In the initial PDT group, PDT (intravenous injection of verteporfin 6 mg/m$^2$ and laser irradiation at 689-nm wavelengths and 600 mW/cm$^2$ irradiance for 83 seconds) was administered within 1 week after the IVR injection. The PDT targets were whole lesions that included polypoidal lesions and branching vascular networks seen on ICGA. In both groups, IVR was administered once for 3 consecutive months. All patients were followed monthly with an ophthalmic examination that included measurement of the BCVA, optical coherence tomography (HRA-Spectralis), color fundus photography, and detailed fundus observation. The BCVA was measured using Landolt C charts at every visit, and the Early Treatment of Diabetic Retinopathy Study (ETDRS) letter chart also was used at baseline and Months 3, 6, and 12. We converted the decimal visual acuity measured using the Landolt C chart into the logarithm of the minimum angle resolution (logMAR) visual acuity for analysis. The central retinal thickness (CRT) was measured on the optical coherence tomography images.

The retreatment criteria for IVR and PDT were as follows: patients were followed monthly and ranibizumab was injected if there was an equivalent visual acuity decrease exceeding five letters on the ETDRS letter chart converted from Landolt C chart, or retinal

hemorrhage, retinal edema, and subretinal fluid according to the retreatment guidelines for ranibizumab in Japan[27] and PDT was administered in combination with an IVR injection if polypoidal lesions were seen with subretinal fluid on the ICGA images obtained every 3 months, and the BCVA was 0.7 or less (Figure 1). For eyes without any reduction of subretinal and/or intraretinal fluid after three consecutive IVR injections and not meeting treatment criteria of PDT, additional IVR was performed according to the each doctor's discretion.

The primary outcome was a difference in the changes in BCVA at 12 months from baseline between the 2 groups. In our preliminary study, the BCVA improved with 0.02 logMAR unit in the initial PDT group and 0.204 in the later PDT group. The SD was 0.278, and the calculated sample size in the comparative study was 74 subjects (37 in each group). This sample provided 80% power to detect a difference between groups (*t*-test, 2-sided $\alpha$ level of 5%).

The full analysis set (FAS) included all randomized patients who received treatment and underwent a baseline and one or more BCVA assessments after baseline. The per-protocol set (PPS) included all patients in the FAS who completed more than 9 scheduled visits including Month 12 without major protocol violations associated with the designated medication.

## Results

The study began with 37 eyes of 37 patients in the initial PDT group and 35 eyes of 35 patients in the later PDT group. Over the course of 1 year, 8 patients in the initial PDT group and 4 patients in the later PDT group withdrew early from the study. The reasons for withdrawal were no improvement in symptoms (two patients in each group), improved symptoms (one patient in each group), severity of other diseases not associated with this study (two patients in the initial PDT group and one patient in the later PDT group), and a change of residence or hospital (three patients in the initial PDT group). Therefore, 37 eyes in the initial PDT group and 35 eyes in the later PDT group were included in the FAS; 29 eyes in the initial PDT group and 31 eyes in the later PDT group were included in the PPS (Figure 2).

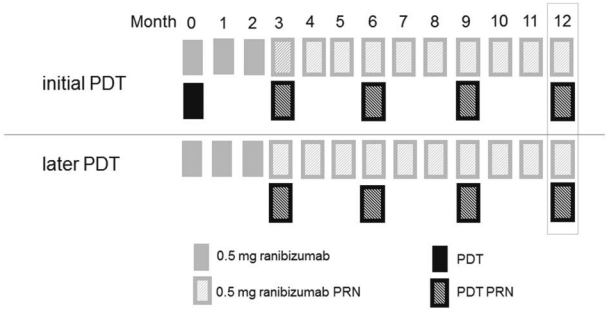


**Fig. 1.** Treatment schedule for initial and later PDT combined with IVR for PCV. PRN, pro re nata.

### *Baseline Characteristics*

The baseline characteristics of the FAS are shown in Table 1. Because of stratification, age, visual acuity, and lesion size were well balanced between groups. The percentages of eyes with bilateral PCVs, multiple polyps, subfoveal polyp(s), subretinal hemorrhage, and pigment epithelial detachment did not differ significantly between the groups. Twelve eyes in each group had mild cataract, and one eye had a history of central serous chorioretinopathy. The patients' characteristics were nearly identical between the FAS and the PPS.

Seventeen patients in the initial PDT group and 20 patients in the later PDT group were treated for hypertension and 4 patients in each group used anticoagulant agents such as warfarin and dabigatran or antiplatelet agents such as aspirin and cilostazol.

### *Changes in BCVA*

The mean ± SD logMAR visual acuities at baseline and Month 12 were 0.52 ± 0.25 and 0.29 ± 0.27 in the initial PDT group and 0.50 ± 0.24 and 0.30 ± 0.27 in the later PDT group, respectively. The mean ± SD ETDRS letter scores at baseline and Month 12 were 53.7 ± 16.9 and 62.3 ± 18.9 in the initial PDT group and 54.5 ± 13.2 and 63.6 ± 11.5 in the later PDT group, respectively. The BCVA levels improved

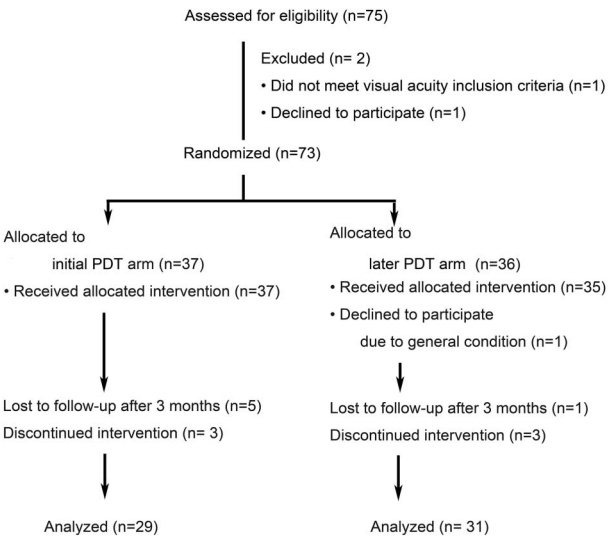


**Fig. 2.** Patient disposition.

Table 1. Baseline Characteristics of the FAS

| | Initial PDT Group | Later PDT Group |
|---|---|---|
| Eyes, n | 37 | 35 |
| Age | | |
| Mean ± SD | 73.6 ± 5.8 | 73.8 ± 7.1 |
| Range | 55–85 | 61–84 |
| Visual acuity, logMAR | | |
| Mean ± SD | 0.50 ± 0.24 | 0.51 ± 0.24 |
| Range | 0.16–1.0 | 0.16–1.0 |
| Visual acuity (ETDRS) (letters) | | |
| Mean ± SD | 54.3 ± 17.9 | 54.9 ± 13.1 |
| Range | 25–78 | 31–74 |
| Greatest linear dimension of lesion, $\mu$m | | |
| Mean ± SD | 3050 ± 812 | 2854 ± 951 |
| Range | 1010–4517 | 1000–5200 |
| Central macular thickness | | |
| Mean ± SD | 360.5 ± 174.4 | 345.6 ± 118.6 |
| Range | 170–1152 | 164–681 |
| Bilatelal PCV | | |
| Eyes, n (%) | 7 (18.9) | 5 (14.3) |
| Subfoveal polyps | | |
| Eyes, n (%) | 16 (43.2) | 19 (54.3) |
| Multiple polyps | | |
| Eyes, n (%) | 21 (56.8) | 24 (68.6) |
| Subretinal hemorrhage | | |
| Eyes, n (%) | 13 (35.1) | 10 (28.6) |
| Pigment epithelial detachment | | |
| Eyes, (%) | 12 (32.4) | 10 (28.6) |

significantly ($P < 0.0001$) in both groups at Month 12 compared with baseline. The mean ± SD differences in the BCVA on logMAR scores and ETDRS letters between baseline and Month 12 were 0.19 logMAR unit (95% confidence interval [CI], 0.13–0.32) and 8.1 ± 1.8 ETDRS letters (95% CI, 4.4–11.7) in the initial PDT group and 0.22 logMAR score (95% CI, 0.11–0.28) and 8.8 ± 1.8 ETDRS letters (95% CI, 5.3–12.5) in the later PDT group, respectively. There was no significant difference between groups ($P = 0.70$ and 0.73). Thirteen (44.8%) eyes in the initial PDT group and 15 (48.4%) eyes in the later PDT group had a BCVA improvement of 15 letters or more. No eyes had a BCVA loss of more than 15 letters.

The mean monthly changes in the logMAR BCVA over 12 months are shown in Figure 3. At Month 1, the logMAR BCVA was significantly ($P < 0.0017$) better than that at baseline in the initial PDT group; in the later PDT group, the improvement did not reach significance ($P = 0.0627$). From Months 2 to 12, the BCVA improved significantly in both groups compared with baseline and did not differ significantly between groups.

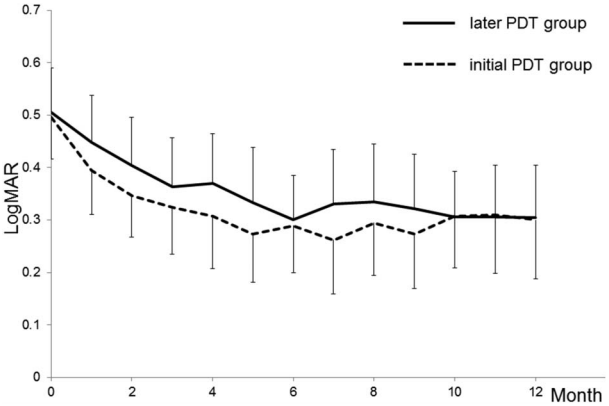


**Fig. 3.** The mean BCVA changes from baseline to 12 months in the initial and later PDT combined with IVR for treating PCV. logMAR, logarithm of the minimum angle of resolution.

To confirm the primary endpoint, we first performed multivariate analysis including baseline BCVA, lesion size, age, bilateral disease, presence of subretinal hemorrhage, pigment epithelial detachment, subfoveal polyps, number of polyps, lens status, and treatment arms to determine the factors affecting the gain in the BCVA. Among them, better baseline BCVA and presence of cataract were negative factors in the improvement in the BCVA over 12 months ($P < 0.001$ and $P = 0.0092$, respectively). After adjusting for the baseline BCVA, there was no significant ($P = 0.68$) difference in the BCVA changes between the 2 groups.

*Changes in Central Retinal Thickness*

At baseline, the mean ± SD CRT was 360.5 ± 174.4 $\mu$m in the initial PDT group and 343.6 ± 108.6 $\mu$m in the later PDT group ($P = 0.63$). The CRT decreased significantly in both groups (Figure 4) at Month 1 and was maintained through Month 12. At Month 2 ($P = 0.0067$), Month 3 ($P = 0.019$), Month 4 ($P = 0.016$), and Month 9 ($P = 0.022$), the CRT decreased more

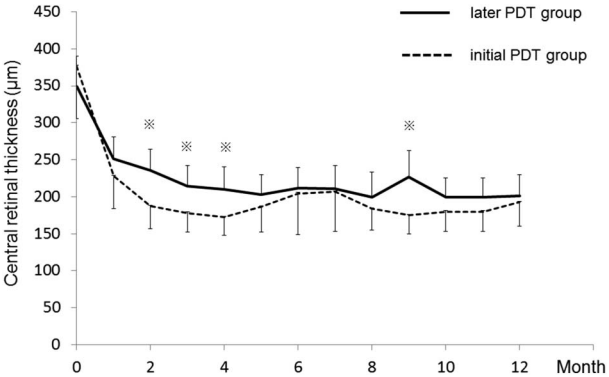


**Fig. 4.** Mean CRT changes from baseline to 12 months in the initial and later PDT combined with IVR for treating PCV.

significantly in the initial PDT group; at other time points, no significant differences were seen between the groups. At Month 12, the mean ± SD were 187.2 ± 87.5 and 206.0 ± 67.3 ($P$ = 0.68). The mean ± SD differences in CRT over 12 months were 184.5 ± 31.1 (95% CI, 131.5–237.5) in the initial PDT group and 145.6 ± 20.6 (95% CI, 93.5–197.7) in the later PDT group, and the difference was not statistically significant ($P$ = 0.30).

At Month 12, 22 (75.8%) eyes in the initial PDT group and 21 (67.7%) eyes in the later PDT group had dry macula, no cystic retinal edema and subretinal fluid on the optical coherence tomography images, which did not differ significantly ($P$ = 0.46) between the groups.

### *Polypoidal Choroidal Vasculopathy Lesions on ICGA*

At baseline, all eyes had polypoidal lesions on the ICGA images. At Month 3, the polyps resolved on the ICGA images in 69.7% of eyes in the initial PDT group and in 30.3% of eyes in the later PDT group, a difference that was significantly ($P$ = 0.0012) higher in the initial PDT group. At Months 6, 9, and 12, the percentages were 72.4%, 64.0%, and 62.1% in the initial PDT group and 56.3%, 50.0%, and 54.8% in the later PDT group, respectively, with no significant ($P$ = 0.19, $P$ = 0.30, and $P$ = 0.53, respectively) differences between the groups.

### *Additional Treatments*

Nineteen eyes in the initial PDT group and 6 eyes in the later PDT group did not have any additional treatments after the initial treatment followed by 2 monthly ranibizumab injections, and this was a significant difference ($P < 0.0001$). The mean ± SD number of additional IVRs from Months 3 to 12 was 1.5 ± 1.8 in the initial PDT group and 3.8 ± 2.3 in the later PDT group, and the eyes in the later PDT group required significantly ($P < 0.0001$) more ranibizumab injections. The mean ± SD number of additional PDT applications was 0.14 ± 0.35 in the initial PDT group and 0.48 ± 0.56 in the later PDT group, and there was also significant differences between the groups ($P$ = 0.0134).

In the later PDT group, 14 eyes had PDT treatment, whereas 17 eyes (54.8%) did not undergo PDT during the study. The first PDT in this group was applied at Month 3 in 7 eyes, at Month 6 in 3 eyes, and at Month 9 in 4 eyes, and the mean interval from the beginning to the first PDT was 5.4 months. Two eyes of this group had PDT twice over 1 year. In the initial PDT group, additional PDT performed at Month 3 in 1 eye, Month 6 in 1 eye, and Month 12 in 2 eyes.

Two eyes in the initial PDT group and three eyes in the later PDT group became refractory to ranibizumab with persistent recurrent fluid even after the three consecutive injections and failed to have protocol-prescribed ranibizumab injections.

### *Treatment-Emergent Adverse Events*

One patient in the later PDT group had a myocardial infarction 11 days after ranibizumab injection and underwent stent surgery. Another eye in the later PDT group developed a new subretinal hemorrhage smaller than 3 disk areas at Month 5, which resolved spontaneously and did not affect the BCVA.

## Discussion

We prospectively evaluated any different efficacies between initial and later PDT combined with anti-VEGF therapy for PCV. Photodynamic therapy resolves polypoidal lesions with subsequent resolution of accompanying fluid, whereas anti-VEGF agents rapidly absorb fluid and improve vision.[6,13,14] Comparing the efficacy of both treatments directly, Oishi et al[28] reported that ranibizumab improved the BCVA more significantly over 12 months than PDT alone. Photodynamic therapy-monotherapy causes subretinal hemorrhage, pigment epithelial tear, atrophy of retinal pigment epithelium, and choriocapillaris in the exposure area in addition to a possible VEGF surge, and those may cause the limited visual improvement after PDT.[10–14] Numerous studies have reported the effectiveness of anti-VEGF therapy for treating PCV on the BCVA[29–33]; however, the main disadvantage of anti-VEGF monotherapy for PCV is less ability to resolve the polypoidal lesions, which leads to early recurrence of fluid.[18–21] Our previous study found that 33% of eyes with PCV had a dry macula 3 months after the first ranibizumab injection, but ICGA showed persistent polypoidal lesions in 65% of eyes.[34] Therefore, the combination of PDT and anti-VEGF is an attractive alternative treatment that compensates for the limitations of both treatments and adds synergistic effectiveness.[22–26]

The EVEREST study was a prospective randomized study with three treatment arms, that is, PDT combined with ranibizumab or alone versus ranibizumab monotherapy.[25] The study reported the superiority of PDT combined with ranibizumab or alone compared with ranibizumab monotherapy in achieving complete regression of polyps. Because it was a 6-month study with a small sample size, the BCVA levels did not differ significantly among the 3 arms, but PDT monotherapy seemed to be less beneficial in improving BCVA.

In clinics, first-line treatment for wet AMD is anti-VEGF monotherapy, and if no baseline ICGA images are obtained, PCV may be suspected only after anti-VEGF therapy proves ineffective.[19–21] Therefore, we should know whether there are any differences in the BCVA between the initial and later PDT combined with anti-VEGF treatment.

The current prospective study showed no superiority in improving vision over 12 months between the initial and later administration of PDT combined with ranibizumab. Our preliminary results had suggested that PDT combination at the beginning was associated with limited BCVA improvement compared with that from ranibizumab monotherapy. However, the results of the current prospective study showed that the BCVA did not vary between two groups. The visual acuity improved significantly in both groups without serious complications, with a mean difference of 0.22 logMAR unit in the initial PDT group and 0.19 logMAR unit in the later PDT group and 8.1 and 8.8 ETDRS letters, respectively. The degree of BCVA improvement over 1 year was remarkably high in this study comparing with that of a previous report[28] of PDT monotherapy (0.05 logMAR score loss) and ranibizumab monotherapy (0.09 logMAR score gain), and such difference is obviously attributable to the use of combination treatment. The mean logMAR BCVA at 1 year was 0.30 in the initial PDT group and 0.29 in the later PDT group, and those were also superior to previous reports, 0.37 and 0.38 logMAR score of ranibizumab monotherapy and 0.73 and 0.62 logMAR of PDT monotherapy.[11,28,29]

The CRT decreased more significantly in the initial PDT group at Months 2, 3, and 4. Earlier resolution of fluid is attributed to PDT; however, such differences disappear later because of the addition of deferred PDT, accumulation of efficacy of ranibizumab after repeated injection and recurrence of the fluid. At Month 12, the CRT in both groups decreased significantly and overall 70% of eyes had no fluid. In other words, at least 30% of eyes with PCV may need further treatments, and this suggests the difficulties of long-term management of PCV.

It should be emphasized that the number of eyes that did not require any additional treatments after the initial treatment phase was significantly more in the initial PDT group, this would be helpful for patients especially from economic reason. The number of additional injections of ranibizumab was significantly higher in the later PDT group, although PDT was not administered in more than half of the eyes in this group. In this study, the criteria for additional PDT did not allow in eyes without subretinal fluid or with better BCVA even if ICGA showed persistent polyps, that is, a sufficient number of ranibizumab injections that maintain a dry macula can eliminate the need for PDT. The mean number of ranibizumab injections over 12 months in the later PDT group was 6.8 (initial 3 injections plus 3.8), and that was higher than in previous reports of ranibizumab monotherapy, 4.2[29] and 4.5,[28] probably due to the difference in the criteria for additional ranibizumab injections; in this study, the presence of any fluid was the criterion for ranibizumab retreatment although previous studies followed the protocol of the PrONTO study.[35] Actually, nearly half of the eyes in later PDT group received additional PDT applications; therefore, more injections should have been performed if PDT was not allowed in this arm. As a result of more ranibizumab injections in the adequate combination with PDT, this study showed better 1-year BCVA compared with that from the previous series of ranibizumab monotherapy.

The major limitations of this study were the small sample size and double-open treatment allocation. To overcome these shortcomings, we included only males to avoid any possible characteristic differences between genders[36] and tried to minimize the differences of baseline patient characteristics between two groups under the stratification and conducted the study in the several institutions according to the common treatment protocols. However, the number of patients lost to follow-up was not insignificant, and also it was differential between the group, and this may be a potential source of bias. Keeping these limitations in mind, this study shows that initial or later PDT administration combined with ranibizumab may not affect the visual and anatomical results at 1 year, although initial combination of PDT decreases the number of subsequent treatments. Oishi et al[37] recently reported the 2-year results of a comparative study of PDT monotherapy and anti-VEGF monotherapy for treating PCV. They found that approximately 20% of patients switched or discontinued treatment because of refractoriness to the initial treatment, which supports the usefulness of combination therapy than each monotherapy alone. Based on the current results, we should not hesitate the use of PDT combined with ranibizumab initially for earlier resolution of exudation and decrease of additional number of treatments, and the achieving the good BCVA.

**Key words:** polypoidal choroidal vasculopathy, photodynamic therapy, ranibizumab, combination.

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## Appendix.

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