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Comparison of the Effect of Ranibizumab and Verteporfin for Polypoidal Choroidal Vasculopathy: 12-Month LAPTOP Study Results

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• PURPOSE: To compare the effect of photodynamic therapy (PDT) and intravitreal ranibizumab in patients with polypoidal choroidal vasculopathy (PCV).
• DESIGN: Randomized clinical trial.
• METHODS: SETTING: Multicenter. STUDY POPULATION: Total of 93 patients with treatment-naïve PCV. INTERVENTION: Patients were randomized to 2 arms. Patients in the PDT arm underwent a single session of PDT with verteporfin, and patients in the ranibizumab arm received 3 monthly ranibizumab injections at baseline. Additional treatment was performed as needed in each arm. MAIN OUTCOME MEASURES: Primary outcome measurement was the proportion of patients gaining or losing more than 0.2 logarithm of minimal angle of resolution (logMAR) units from baseline. Mean change of logMAR and central retinal thickness (CRT) were also evaluated.
• RESULTS: In the PDT arm (n = 47), 17.0% achieved visual acuity gain, 55.3% had no change, and 27.7% experienced visual acuity loss. The results were 30.4%, 60.9%, and 8.7%, respectively, in the ranibizumab arm (n = 46), significantly better than the PDT arm (P = .039). In the PDT arm, mean CRT improved (366.8 ± 113.6 μm to 289.1 ± 202.3 μm, P < .001), but logMAR was unchanged (0.57 ± 0.31 to 0.62 ± 0.40). The ranibizumab arm demonstrated improvement in both CRT (418.9 ± 168.6 μm to 311.2 ± 146.9 μm, P < .001) and logMAR (0.48 ± 0.27 to 0.39 ± 0.26, P = .003). Mean change of logMAR was also greater in the ranibizumab arm (P = .011).
• CONCLUSION: Intravitreal injection of ranibizumab is more effective than PDT for treatment-naïve PCV. (Am J Ophthalmol 2013;156:644–651.

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POLYPOIDAL CHOROIDAL VASCULOPATHY (PCV) IS a subtype of age-related macular degeneration (AMD) characterized by the presence of polypoidal lesions and branching vascular network visualized with indocyanine green angiography (IGA).[1–3] Whereas in white individuals a minority of patients with AMD have PCV, the prevalence of PCV is up to 54% in Asian patients.[3,4] Subclassification of PCV from AMD is important because the optimal treatment for PCV and AMD can differ.[5]

Currently, the first-choice treatment of AMD is administration of anti–vascular endothelial growth factor (VEGF) agents such as ranibizumab, which was shown to have a vision-improving effect in pivotal trials.[6,7] Several reports demonstrated favorable results of anti-VEGF therapy such as bevacizumab[8–10] or ranibizumab[10–16] in patients with PCV. However, other reports have indicated that injections of bevacizumab have limited effect on polyp regression.[17,18] Additional studies have reported that patients who were refractory to anti-VEGF therapy had PCV.[19,20] Thus, the role of anti-VEGF therapy in the treatment of PCV is still under debate.[5]

Photodynamic therapy (PDT), which was widely used before the era of anti-VEGF therapy, is another treatment option for PCV.[3] Many studies have reported the vision-improving effect of PDT for PCV,[21–23] and a retrospective study found that PDT is a better option for PCV than ranibizumab or ranibizumab combined with PDT.[24] However, PDT for PCV is not free of complications, such as subretinal/vitreous hemorrhages, retinal pigment epithelium tear, choroidal ischemia, recurrent bullous retinal detachment, or development of chorioretinal anastomosis.[3] Indeed, studies with more than 2-year follow-up have revealed that the vision-improving effect of PDT declines after the initial year.[25–28]

To compare the efficacy of ranibizumab and PDT for PCV, the EVEREST study was conducted, and its results were recently published.[29] The study included 61 patients with PCV and investigated the efficacy and safety of verteporfin PDT in combination with ranibizumab or PDT alone vs ranibizumab monotherapy. The study concluded that PDT alone or combined with ranibizumab is superior to ranibizumab for polyp regression. However, the sample size did not allow the investigators to conclude which

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treatment is superior with respect to visual acuity (VA). Although regression of polypoidal lesion is a significant aspect of treatment, identifying the treatment that is superior for visual outcome may be more important to patients than polyp regression.

To address this issue, we conducted a clinical trial to compare the vision-improving effect of ranibizumab and PDT in the comparison of ranibizumab (Lucentis) And Photodynamic Therapy On Polypoidal choroidal vasculopathy (LAPTOP study).

METHODS

THE LAPTOP STUDY IS A PHASE IV, PROSPECTIVE, MULTICENTER, randomized trial. Institutional Review Board (IRB)/Ethics Committee approval was obtained at each institution. 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 Japan Medical Association Center for Clinical Trials (JMACCT) on June 22, 2009, ID: JMA-IIA00028.

• **SETTING:** The study was conducted at 5 centers in Hyogo prefecture.

• **PATIENTS:** Patients were recruited from July 1, 2009 to June 30, 2011. We included patients aged older than 50 years with treatment-naïve PCV. PCV was diagnosed based on the presence of polypoidal lesion depicted with IGA. HRA2 (Heidelberg Engineering, Heidelberg, Germany) or TRC-NW7SF (Topcon, Tokyo, Japan) was used to perform IGA. Only 1 eye per patient was included in the study. Exclusion criteria included VA better than 0.6, greatest linear dimension (GLD) greater than 5400 μm, refractive error greater than -6 diopters, or axial length longer than 26.5 mm. The presence of past AMD or central serous chorioretinopathy, retinal vascular disease, glaucoma, angioid streaks, presumed ocular histoplasmosis, history of radiation therapy, or history of ocular surgery other than phacoemulsification were carefully checked and excluded.

• **INTERVENTION:** Patients were randomized in a 1:1 ratio to either verteporfin PDT 6 mg/m^2 or ranibizumab monotherapy 0.5 mg. As the initial treatment, patients in the PDT arm underwent intravenous injection of verteporfin 6 mg/m^2 and laser irradiation at 689 nm wavelength and 600 mW/cm^2 irradiance for 83 s. Irradiance area was set as 1000 μm margin + GLD determined with IGA images, which includes polypoidal lesions and branching vascular networks.[30] Patients in the ranibizumab arm underwent 3 monthly intravitreal injections of ranibizumab 0.5 mg. After the initial treatment, repeat treatment was applied as needed (pro re nata [PRN]; Figure 1). In the PDT arm, we applied retreatment criteria as suggested in the Japanese age-related macular degeneration trial,[31] which included persistent fluorescein leakage. In the ranibizumab arm, we applied retreatment criteria as suggested in the PrONTO study,[32] which included a 0.1-unit decrease of logarithm of minimal angle of resolution (logMAR) in the presence of fluid at the macula detected by optical coherence tomography (OCT), >100-mm increase in CRT, new-onset classic choroidal neovascularization, new macular hemorrhage, persistent macular fluid detected by OCT, and active leakage on fluorescein angiography (FA). The final decision was at the investigators' discretion in each institution.

VA measurement and OCT examination were performed at every visit. FA/IGA was performed every 3 months in the PDT arm and only in cases with prominent changes in the ranibizumab arm. Although the standard interval for monitoring PDT is 3 months,[31,33,34] we assessed the patients every 6 weeks, and retreatment was applied with a minimum treatment interval of 3 months.

• **MAIN OUTCOME MEASURES:** Main outcome measurement for the LAPTOP study was the proportion of patients in each arm gaining or losing logMAR of more than 0.2 at 24 months. Here, we present the preliminary results of our investigation and report the change of VA at 12 months. We measured visual acuity using Landolt C charts and converted the values to logMAR equivalent. We also investigated central retinal thickness (CRT), defined as the vertical distance between the hyper-reflective border of the inner limiting membrane and the outer border of the retinal pigment epithelium (RPE), measured with spectral-domain OCT (Cirrus; Carl Zeiss Meditec, Dublin, California, USA, or Spectralis; Heidelberg Engineering, Heidelberg, Germany). The number of additional treatments and the number of patients who dropped out were also evaluated.

• **STATISTICAL ANALYSIS:** Target sample size was estimated based on the assumption that the proportion of patients who achieve more than 0.2 improvement in logMAR will be approximately 40% in the PDT arm (estimated from previous studies[21–23] and our experience[35,36]) and approximately 15% in the ranibizumab arm.[18] The required sample was calculated as 49 subjects in each arm at 1-sided α-error level of 0.05 and β-error level of 20% (80% power to prove). Accounting for a maximum 20% exclusion or dropout rate, we determined the target sample size as 62 in each arm.

We excluded patients who did not complete the initial 3-month follow-up from final analysis. For the rest of the patients, we applied intention-to-treat analysis policy. Even when patients underwent different treatment or dropped out from periodic treatment, the data were included in the originally assigned arm. The last-observation-carried-forward approach was used for missing data.

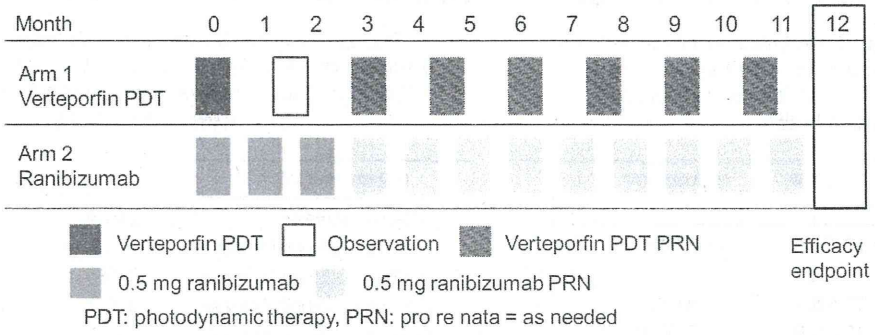

FIGURE 1. Treatment schedule of verteporfin photodynamic therapy and intravitreal ranibizumab for patients with polypoidal choroidal vasculopathy. Patients were randomly assigned to either arm and were treated in an as-needed manner (pro re nata; PRN) and followed up for 12 months.

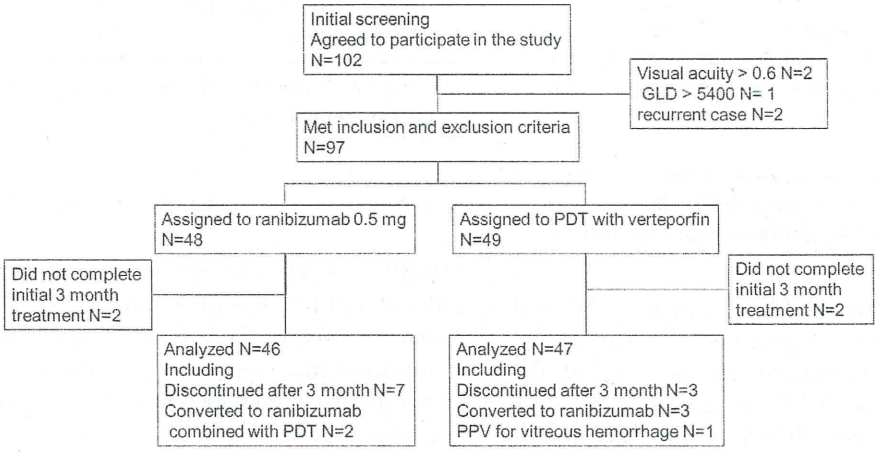

FIGURE 2. Patient disposition in the present study comparing verteporfin photodynamic therapy and intravitreal ranibizumab for polypoidal choroidal vasculopathy. The participants who did not complete initial 3-month treatment were excluded from the analysis. Some patients dropped out from the protocol. However, we employed an intention-to-treat policy, and the data from these participants were included in the final analysis. GLD = greatest linear dimension; PDT = photodynamic therapy; PPV = pars plana vitrectomy.

The χ^2 test was used to compare the percentage of patients with gained, unchanged, or lost VA. Two-way repeated-measures analysis of variance (ANOVA) was used to investigate the difference in mean VA or CRT. Changes in VA or CRT from baseline were assessed using 1-way repeated-measures ANOVA and post hoc Dunnett's test. Statistical analysis was performed using IBM SPSS Statistics ver. 19 (IBM Japan, Tokyo, Japan).

RESULTS

ONE HUNDRED TWO PATIENTS PARTICIPATED IN THE TRIAL, but 5 patients met exclusion criteria and 4 did not complete the initial 3-month treatment. Thus, the study sample consisted of 93 participants (PDT arm 47 patients, ranibizumab arm 46 patients; Figure 2). All patients had subfoveal lesions. Baseline clinical characteristics of each arm are shown in Table 1. Age, sex, visual acuity, GLD, and CRT demonstrated no significant difference between arms.

The mean number of retreatments was 0.8 in the PDT arm and 1.5 in the ranibizumab arm. Three patients in the PDT arm and 7 in the ranibizumab arm did not complete 12-month follow-up. Three patients were converted to ranibizumab treatment and 1 patient received pars plana vitrectomy for vitreous hemorrhage in the PDT arm. Two patients in the ranibizumab arm received ranibizumab combined with PDT. These patients changed the treatment protocol based on their will. Thus, a total of 7 patients in the PDT arm and 9 patients in the ranibizumab arm did not complete the 12-month treatment protocol. Among these dropout/switch treatment patients, 6 patients in the PDT arm showed more than 3 lines of visual loss, whereas 8 patients in the ranibizumab arm showed less than 2 lines of visual acuity change.

TABLE 1. Baseline Clinical Characteristics of Patients With Polypoidal Choroidal Vasculopathy who Were Randomized to Photodynamic Therapy or Intravitreal Injection of Ranibizumab

Characteristics	Photodynamic Therapy (n = 47)	Ranibizumab (n = 46)	P Value
Age (y), mean (SD)	75.0 (8.0)	75.4 (6.9)	.80
Sex, n (%)			.47
Male	32 (68.1)	28 (60.9)	
Female	15 (31.9)	18 (39.1)	
BCVA (logMAR units), mean (SD)	0.57 (0.31)	0.48 (0.27)	.12
BCVA (Snellen equivalent), n (%)			.84
≤0.1 (20/200)	7 (14.9)	5 (10.9)	
>0.1 (20/200) but <0.5 (20/40)	24 (51.1)	24 (52.2)	
≥0.5 (20/40)	16 (34.0)	17 (37.0)	
GLD (μm), mean (SD)	3051.1 (1177.7)	3347.4 (1288.3)	.16
Central retinal thickness (μm), mean (SD)	366.8 (113.6)	418.9 (168.6)	.17

BCVA = best-corrected visual acuity; GLD = greatest linear dimension; logMAR = logarithm of minimal angle of resolution.

The visual outcome at month 12 is shown in Table 2 and Figure 3. The proportion of patients who gained 0.2 logMAR units, demonstrated no change, or lost 0.2 logMAR units was 17.0%, 55.3%, and 27.7% in the PDT arm and 30.4%, 60.9%, and 10.9% in the ranibizumab arm. Results were significantly better in the ranibizumab arm ($P = .039$). When we judged the change of VA by 0.3 logMAR units, the superiority of ranibizumab remained the same ($P = .024$). The ranibizumab arm demonstrated improvement in logMAR at month 3 and maintained this gain compared to baseline except for at month 10. Although the PDT arm also demonstrated improvement in logMAR through month 6, the difference from baseline was not significant. The change of logMAR was superior in the ranibizumab arm ($P = .011$). To confirm that the intention-to-treat analysis did not skew the results, we also analyzed 40 patients in the PDT arm and 37 patients in the ranibizumab arm who completed the 12-month protocol. Two-way repeated-measures ANOVA confirmed that the visual acuity change in the 12 months was still significantly greater in the ranibizumab arm (change of logMAR in PDT arm: 0.55 6 0.30 to 0.55 6 0.38 vs ranibizumab arm: 0.49 6 0.27 to 0.38 6 0.27, $P = .019$).

We also investigated CRT in each arm (Figure 4). CRT decreased from 366.8 μm to 289.1 μm in the PDT arm and from 418.9 μm to 311.2 μm in the ranibizumab arm. Both arms demonstrated significant improvement at the initial visit after treatment and maintained the effect throughout the study period. The change of CRT was not significantly different between the 2 arms ($P = .115$).

TABLE 2. Frequency Distribution of Changes in LogMAR Visual Acuity From Baseline at Month 12 After Verteporfin Photodynamic Therapy or Ranibizumab for Polypoidal Choroidal Vasculopathy

Change in logMAR, n (%)	PDT (n = 47)	Ranibizumab (n = 46)
≥0.6-unit increase	2 (4.3)	1 (2.2)
≥0.5 but <0.6-unit increase	1 (2.1)	0 (0)
≥0.4 but <0.5-unit increase	0 (0)	2 (4.3)
≥0.3 but <0.4-unit increase	2 (4.3)	5 (10.9)
≥0.2 but <0.3-unit increase	3 (6.4)	5 (10.9)
≥0.1 but <0.2-unit increase	7 (14.9)	8 (17.4)
No change	15 (31.9)	20 (43.5)
≥0.1 but <0.2-unit decrease	4 (8.5)	1 (2.2)
≥0.2 but <0.3-unit decrease	0 (0)	1 (2.2)
≥0.3 but <0.4-unit decrease	8 (17.0)	3 (6.5)
≥0.4 but <0.5-unit decrease	1 (2.1)	0 (0)
≥0.5 but <0.6-unit decrease	2 (4.3)	0 (0)
≥0.6-unit decrease	2 (4.3)	0 (0)

logMAR = logarithm of minimal angle of resolution; PDT = photodynamic therapy.

DISCUSSION

THE PRESENT STUDY SHOWED THAT 3 MONTHLY INJECTIONS followed by PRN injections of ranibizumab achieved better visual outcome for PCV patients compared to PDT. The result was rather unexpected. Considering the persistence of polypoidal lesions or branching vascular networks in previous reports,[10,14,18,29,37] we anticipated that long-term results of anti-VEGF therapy would be impaired by recurrent exudation when we started the study. Although PDT sometimes induces severe complications, it can achieve polyp regression in 80%-95% of cases,[22,23,30,38] and we expected the percentage of patients who gained or maintained vision to be superior in this arm.

This result may be an example of the large disparity observed in the treatment of PCV.[39] The gain of logMAR or the equivalent 1 year after PDT ranges from approximately 0.1-0.25 units,[14,16,21–24,39,40] and a recent study involving a relatively large population (n = 85) showed only 0.04 units of improvement.[41] In fact, as shown in Table 2, some patients demonstrated very favorable results and other patients demonstrated miserable results in the PDT arm. Retrospective studies excluding these patients might overestimate the effect of PDT.

Although the disparity also exists in the ranibizumab arm, it appears smaller. Previously reported gains of logMAR 1 year after anti-VEGF therapy for PCV range from 0.12-0.22 units.[9,10,13,15] However, studies involving a relatively small number of patients (n = 7[14] and n = 10[24]) tend to report more extreme results (logMAR gain of 0.31[14] and 0.04,[24] respectively). In this context, we should be careful when evaluating the results of studies with small sample size and/or retrospective design.

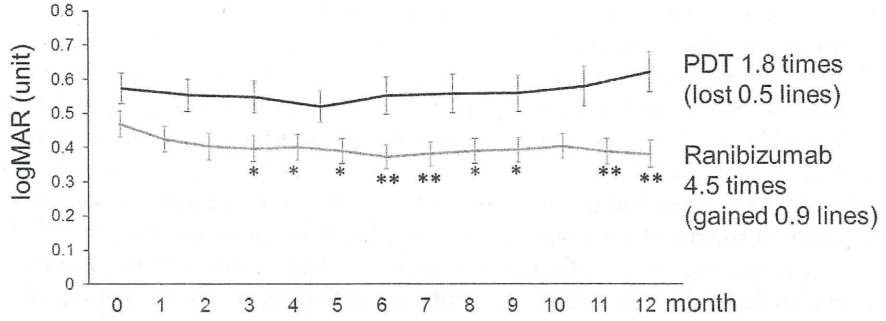

FIGURE 3. Mean changes (± standard error) from baseline in visual acuity over 12 months after verteporfin photodynamic therapy (PDT) or intravitreal ranibizumab for polypoidal choroidal vasculopathy. While the ranibizumab arm demonstrated improvement in visual acuity at 3 months, the change was not significant in the PDT arm. Two-way repeated-measures analysis of variance confirmed that the visual acuity change in the 12 months was significantly greater in the ranibizumab arm. logMAR: logarithm of minimal angle of resolution. Asterisks indicate the significant difference compared to baseline (*$P < .05$, **$P < .01$).

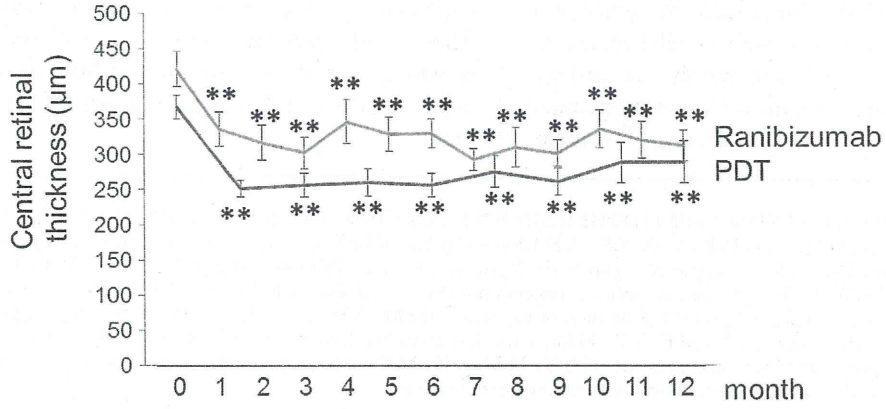

FIGURE 4. Mean changes (± standard error) from baseline in central retinal thickness over 12 months after verteporfin photodynamic therapy (PDT) or intravitreal ranibizumab for polypoidal choroidal vasculopathy. Both treatments resulted in a reduction of central retinal thickness. The effect was confirmed at the initial visit after each treatment. No difference in the change of central retinal thickness was observed between the 2 arms. Asterisks indicate the significant difference compared to baseline (*$P < .05$, **$P < .01$).

Interestingly, we observed no significant difference in changes of CRT between the 2 arms, suggesting that PDT succeeded in achieving regression of exudative changes. There are some concerns that PDT can induce side effects of choroidal vessel occlusion and RPE damage.[42] Although choroidal hypoperfusion shows little evidence of causing detrimental effects on visual function,[43] the possible damage to RPE and photoreceptors may account for the difference between the visual outcome of the PDT and ranibizumab arms. The present results confirm the notion that anatomic regression of polyps or exudative change does not necessarily indicate good visual outcome.[5] In fact, the EVEREST study, the only randomized study comparing ranibizumab and PDT for PCV, concluded that PDT is more effective than ranibizumab in achieving regression of polyps; however, visual acuity was superior in the ranibizumab arm despite the inability to reach statistical significance. Future trials should employ visual acuity as a primary outcome.

The number of retreatments also demonstrated a disparity. The present result (4.5 times/12 months) was similar to those of some previous reports on PCV, for example, 4.0,[14] 4.2,[15] or 4.5[13] retreatments in 12 months. However, the number of retreatments reached 5.5[10] and 9.9[24] in other reports. In addition, studies concerning AMD with an as-needed retreatment strategy tend to report a larger number of retreatments, for example, 5.1,[44] 5.6,[32] 5.7,[45] or 6.9[46] times in 12 months. In fact, Holz and associates suggested that an average of 5.1 injections is required after the 3 initial injections, namely 8.1 treatments for 12 months, to maintain initial gain using theoretical drug and disease modeling.[47] Thus, one could consider the present result to represent undertreatment. The fact that 9 patients in the ranibizumab arm did not

complete 12-month follow-up or converted to another treatment is one possible explanation for the small number of injections. Another explanation is the criteria applied for retreatment. The retreatment criteria allow less than 0.1 unit of logMAR loss, less than 100 μm of CRT increase, or persistent extramacular fluid. In fact, the changes of logMAR and CRT in Figures 3 and 4 show fluctuation that may reflect the possible delay of treatment for recurrence. However, even in the event that the results reflect undertreatment, the conclusion would be the same: intravitreal ranibizumab is superior to PDT monotherapy in achieving visual gain. If we perform more frequent administrations with stricter reinjection criteria, such as any fluid on OCT, the visual outcome would be improved[48] and the superiority to PDT more prominent.

The present study has several limitations, including nonmasked treatment and use of Landolt C chart but not Early Treatment Diabetic Retinopathy Study (ETDRS) chart. In addition, we did not investigate the efficacy of combination therapy of PDT and ranibizumab because we were not able to collect a sufficient number of patients for 3-arm comparison. Since several reports demonstrated a promising effect of the combination therapy,[49] comparison between ranibizumab with or without PDT should be further investigated. Another limitation is the lack of angiographic evaluation. We did not examine periodic angiography in the ranibizumab-treated arm because it does not affect decisions regarding retreatment. We assume that a certain percentage of patients have persistent polyps and almost all patients have branching vascular network, based on previous reports[10,14,15,18,29,37] and our experience. The anatomic/angiographic outcome of ranibizumab therapy may be important when considering long-term results of the treatment. Relatively short follow-up is another limitation. The treatment effect is reported to decline in the second year in patients treated with PDT,[25–28] and similar tendency was reported in ranibizumab-treated patients.[50] To draw more definite conclusions, we need longer follow-up.

Finally, we have presented 1-year results of the randomized LAPTOP trial, which demonstrated the superiority of ranibizumab compared to PDT for the treatment of PCV. These results serve as a guide when considering first-line treatment for PCV. The trial is still ongoing, and the 2-year results will show the long-term effects of each treatment.

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