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Original Article

Impact of Polyp Regression on 2-year Outcomes of Intravitreal Aflibercept Injections: A Treat-and-Extend Regimen for Polypoidal Choroidal Vasculopathy

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We conducted intravitreal aflibercept injections (IVAs) for 37 Japanese patients (28 males, 9 females, mean age 73.4 years) with polypoidal choroidal vasculopathy (PCV), with a treat-and-extend regimen (TER). We evaluated the impact of polyp regression after a loading dose (2-mg IVA 1×/month for 3 months) on the patients' 2-year treatment outcomes. Thirty-seven eyes were treated with IVA by a TER for 2 years. We divided the patients into 2 groups based on their polyp status after the loading dose: polyp regression (PR+) (n = 19) and no polyp regression (PR−) (n = 18). We compared the groups' best-corrected visual acuity (BCVA), central retinal thickness (CRT), recurrence rate, total number of injections, and final treatment interval. Both the BCVA and CRT were significantly improved by the treatment in both groups, with no between-group difference in the amount of change ($p = 0.769$). In the polyp regression (+) group, recurrence was significantly less common ($p = 0.03$), the mean total number of injections was significantly lower ($p = 0.013$), and the mean treatment interval was significantly longer (0.042). Regarding the 2-year outcomes for PCV, the eyes with post-loading-dose polyp regression demonstrated less frequent recurrence and required fewer numbers of injections compared to the eyes without polyp regression.

Key words: polypoidal choroidal vasculopathy, aflibercept, treat-and-extend regimen, polyp regression

Polypoidal choroidal vasculopathy (PCV) is a subtype of exudative age-related macular degeneration (AMD) characterized by multiple, terminal, reddish-orange polypoidal lesions and a branching vascular network that is visible by indocyanine green angiography (ICGA) [1,2]. The prevalence of PCV is higher in Asian patients than Western patients and accounts for nearly half of the presumed AMD cases in Japan [3,4]. Although the visual prognosis for PCV has been reported to be better than that for exudative AMD, the incidence of subretinal hemorrhage in patients with PCV is higher than the incidence in patients with AMD, and PCV has been shown to cause occasional, massive submacular hemorrhages that can eventually result in chorioretinal atrophy and permanent vision loss [5-8].

The primary cause of submacular hemorrhage in PCV is the rupture of polypoidal lesions [3,6]. Polypoidal lesions are the cause of not only submacular hemorrhages but also recurrent fluid accumulation and lipid exudation. Therefore, the regression of polyps, along with the regression of retinal exudation, is con-

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sidered one of the main goals of initial therapy in PCV treatment [3]. However, the relationships between the long-term visual acuity outcome and the number of anti-vascular endothelial growth factor (VEGF) drug injections with the regression of polyps are not yet known. In the EVEREST study, a prospective, multicenter clinical trial that compared the efficacy of different treatment methods for PCV, the regression of polyps was not associated with the change in visual acuity 6 months after the initiation of treatment [5]. It is therefore necessary to investigate the association between polyp regression and long-term PCV treatment progress, which can be evaluated by factors such as changes in visual acuity, the recurrence of retinal exudation, and the number of anti-VEGF drug injections.

Treatment for PCV can consist of photodynamic therapy (PDT), intravitreal injections of anti-VEGF drugs, or a combination of both. Photodynamic therapy is reported to yield a higher likelihood of polyp regression than anti-VEGF drugs such as ranibizumab [5]; however, PDT may also induce subretinal hemorrhages, retinal pigment epithelial tears, and/or choriocapillaris atrophy [9-11]. The risk of serious complications (such as subretinal hemorrhages) is reported to be lower in anti-VEGF therapy than in PDT [5, 12].

As one of the drugs used for anti-VEGF therapy, aflibercept (Eylea®; Bayer HealthCare, Berlin, Germany), a recombinant fusion protein that binds to members of the VEGF family, was recently reported to be effective for improvement of visual acuity and regression of polypoidal lesions in PCV [13-15]. Regarding the treatment regimens using intravitreal injections of aflibercept, fixed regimens, pro re nata regimens (PRN: the as-needed approach), and treat-and-extend regimens (TERs) have been used [16-18]. Among these, a TER is an individualized regimen that aims to decrease the patient's number of clinic visits and number of injections by determining the optimal treatment interval [19]; *i.e.*, the interval between injections is extended gradually after the resolution of the retinal exudation is confirmed. The interval between injections is shortened when retinal exudation recurs.

In one of the typical TER protocols, patients are initially treated with an anti-VEGF drug 1×/month for 3 months as loading dose in order to maintain the drug concentration in the treated eye [20, 21]. In our prior study of 37 patients, our use of a TER of aflibercept for PCV provided significant improvement in visual acuity at 1 year [21]. However, the long-term treatment outcomes including the association between the TER and polyp regression are unknown.

In the present study, we conducted a TER of intravitreal aflibercept injections (IVAs) for 37 patients with PCV and followed-up the patients for 2 years. We also assessed the occurrence of polyp regression after the loading dose to determine the effects of polyp regression on visual acuity, the recurrence of retinal exudation, the number of anti-VEGF drug injections, and the intervals between injections.

Patients and Methods

Patient selection. We retrospectively reviewed the medical records of 37 eyes of 37 consecutive Japanese patients with treatment-naive PCV who had been treated with IVA by a treat-and-extend regimen for at least 2 years at the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences starting between June 2013 and December 2014. The institutional review board of this institution approved this retrospective study, which was conducted according to the tenets of the 1964 Helsinki Declaration. Each patient was informed of the risks and benefits of treatment and gave written informed consent.

PCV was diagnosed based on the presence of abnormal branching vascular networks and characteristic polypoidal vascular lesions seen on ICGA images [1, 5]. Eyes with other retinal diseases, e.g., diabetic retinopathy, retinal vein occlusion, or myopic degeneration, were excluded from this study, as were eyes that had undergone a vitrectomy. During the relevant time period, a total of 45 consecutive patients with treatment-naïve PCV started aflibercept therapy using a TER. However, 8 of these patients were excluded from the study: 5 patients were excluded because they received treatment based on a PRN for the second year after undergoing aflibercept therapy by a TER for 1 year, and the remaining 3 were excluded because they were considered to be non-responders after 1 year and were switched to a different treatment for the second year (2 patients: combination therapy with PDT and aflibercept; 1 patient: intravitreal ranibizumab injection therapy).

Ophthalmologic examinations. All patients underwent a comprehensive ophthalmologic examina-

tion at all visits, which included the measurement of decimal best-corrected visual acuity (BCVA) using a Landolt C acuity chart at 5 meters as well as intraocular pressure measurement, indirect ophthalmoscopy, slit-lamp biomicroscopy with a contact lens, and optical coherence tomography (OCT; swept-source OCT, DRI OCT-1 Atlantis, Topcon, Tokyo or spectral-domain OCT, Spectralis; Heidelberg Engineering, Heidelberg, Germany). Fluorescein angiography (FA) and ICGA were performed at the baseline, 3 months, and 12 months after the first aflibercept injection and were obtained using the Heidelberg Retina Angiograph system (Heidelberg Engineering) with a confocal scanning laser ophthalmoscope. The greatest linear dimension (GLD) of the lesions was measured by both FA and ICGA. The GLD on the fluorescein angiography includes areas of dye leakage, pigment epithelial detachments, and subretinal hemorrhages. The GLD on the indocyanine green angiography includes areas of polypoidal lesions and abnormal branching vascular networks. The regression of polypoidal lesions was evaluated by ICGA at 3 and 12 months after the first injection.

Intravitreal aflibercept therapy by a treat-and-extend regimen. All patients were initially treated with an IVA (2 mg) once per month for 3 months as the loading dose. The monthly injections continued until no retinal exudates (*i.e.*, new subretinal hemorrhage or subretinal and/or intraretinal fluid) were observed on OCT or slit-lamp biomicroscopy. When the retinal exudates were resolved, the interval to the next injection and follow-up period was extended by 2 weeks up to a maximum of 16 weeks, at which point the treatment was maintained at that interval. If the exudation recurred, the interval was shortened by 2 weeks to a minimum interval of 4 weeks. The interval was shortened in increments of 4-6 weeks if the exudation recurred when the interval between injections was ≥ 14 weeks.

Outcome measures. We divided the patients into 2 groups on the basis of their ICGA results after the loading dose: a polyp regression (PR+) group (n = 19) and a no-polyp regression (PR−) group (n = 18). The main outcome measure was the change in BCVA at 2 years from the baseline. The secondary outcomes were the change in the central retinal thickness (CRT), the recurrence rate of PCV, the total number of injections during the 2-year follow-up, and the interval between injections at 2 years.

Statistical analysis. The BCVA was converted to the logarithm of the minimum angle of resolution (logMAR) units for the statistical analysis. Differences in categorical and continuous variables between the two patient groups were tested by Fisher's exact test and the Mann-Whitney *U*-test, respectively. We used a paired *t*-test analysis to examine the differences in the logMAR BCVA and CRT values from the baseline to the 2-year point. All statistical analyses were performed with SPSS ver. 22.0 software (IBM, Armonk, NY, USA). A p-value < 0.05 was considered significant.

Results

Baseline characteristics. A total of 37 eyes of 37 treatment-naive patients with PCV (28 males, 9 females) who underwent aflibercept treatment with a TER were enrolled. All patients were Japanese, and the study group had a mean age of 73.4 years with a range of 55-87 years.

As noted above, there were 19 eyes (51.4%) in the PR+ group and 18 eyes (48.6%) in the PR− group. The mean baseline logMAR BCVA values were 0.37 ± 0.33 in the PR+ group and 0.42 ± 0.41 in the PR− group (Table 1). There was no significant difference in baseline BCVA values between the 2 groups ($p = 0.830$). Further, there were no significant baseline differences between the groups with respect to age, sex, CRT, GLD on FA, GLD on ICGA, number of polyps, or size of the largest polyp (Table 1).

Visual acuity outcomes. In all 37 eyes, the mean logMAR BCVA significantly improved, from 0.39 ± 0.36 at baseline to 0.21 ± 0.30 at year 2 ($p < 0.001$). The mean logMAR BCVA in the PR+ group improved significantly, from 0.37 ± 0.33 (range −0.08 to 1.00) at baseline to 0.17 ± 0.27 (range −0.08 to 0.08) at year 2 ($p = 0.001$). The mean logMAR BCVA in the PR− group also improved significantly, from 0.42 ± 0.41 (range 0.00 to 1.52) at baseline to 0.25 ± 0.33 (range −0.08 to 1.22) at year 2 ($p = 0.001$). There was no significant difference between the 2 groups in the mean change in BCVA from the baseline to year 2 ($p = 0.769$; Table 2). Fig. 1 illustrates the changes in mean BCVA from baseline throughout the follow-up period for each group.

Central retinal thickness. In all 37 eyes, the mean CRT decreased significantly, from 346.1 ± 111.4 μm at baseline to 206.5 ± 68.7 μm at year 2 ($p < 0.001$). The mean CRT in the PR+ group decreased significantly,

Table 1 Baseline clinical characteristics of PCV patients grouped by polyp regression after a loading dose of intravitreal aflibercept injections

	Polyp regression (+) after a loading dose (n = 19)	Polyp regression (−) after a loading dose (n = 18)	*p*
Age, mean ± SD	74.6 ± 6.7	72.1 ± 8.5	0.303
Male sex, n (%)	13 (68.2%)	15 (83.3%)	0.252
Baseline BCVA (LogMAR), mean ± SD	0.37 ± 0.33	0.42 ± 0.41	0.830
CRT (μm), mean ± SD	339.9 ± 118.2	352.7 ± 106.8	0.704
GLD on FA (μm), mean ± SD	3,500 ± 1,432	3,616 ± 1,784	0.832
GLD on ICGA (μm), mean ± SD	2,462 ± 1,073	2,313 ± 766	0.751
Number of polyps, mean ± SD	2.9 ± 2.2	3.3 ± 1.4	0.279

PCV, polypoidal choroidal vasculopathy; BCVA, best-corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution; CRT, central retinal thickness; GLD, greatest linear dimension; FA, fluorescein angiography; ICGA, indocyanine green angiography; SD, standard deviation.

Table 2 Two-year outcomes of the aflibercept therapy with a treat-and-extend regimen for PCV in patients grouped by polyp regression after the loading dose

	Polyp regression (+) after a loading dose (n = 19)	Polyp regression (−) after a loading dose (n = 18)	*p*
BCVA (LogMAR) change from baseline, mean ± SD	−0.20 ± 0.26	−0.17 ± 0.18	0.769
CRT change from baseline (μm), mean ± SD	−143.8 ± 102.0	−135.1 ± 113.4	0.595
Recurrence during 2 years, n (%)	8 (42.1%)	14 (77.8%)	0.030
Total number of injections, mean ± SD	12.4 ± 2.7	15.3 ± 4.2	0.013
Intervals between injections, mean ± SD	12.5 ± 4.2	9.6 ± 4.2	0.042

PCV, polypoidal choroidal vasculopathy; BCVA, best-corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution; CRT, central retinal thickness; SD, standard deviation.

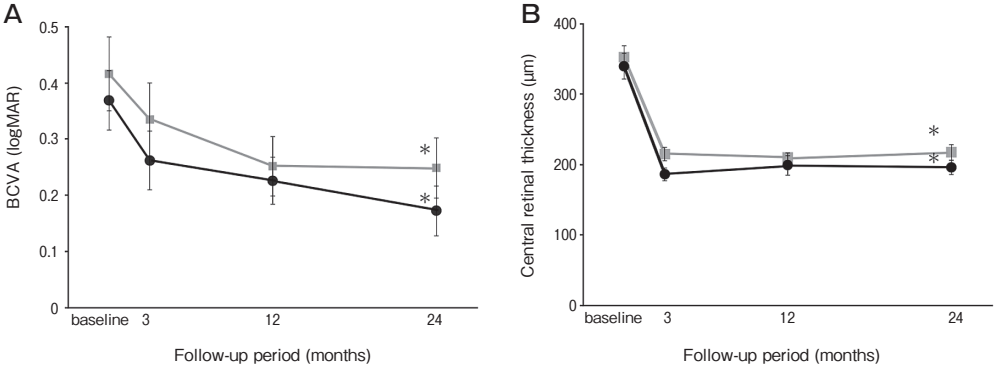

Fig. 1 **A**, Change in mean best-corrected visual acuity (BCVA) for the two groups of patients with PCV; **B**, Change in mean central retinal thickness for both groups. Circles (black line): The PR+ group (n=19). Squares (gray line): The PR− group (n=18). *p=0.001.

from 339.9 ± 118.2 μm (range 153-677 μm) at baseline to 196.1 ± 65.7 μm (range 124-341 μm) at year 2 (p < 0.001). The mean CRT in the PR− group also decreased significantly, from 352.7 ± 106.8 μm (range 208-627 μm) at baseline to 217.6 ± 72.0 μm (range 153-384) at year 2 (p < 0.001). There was no significant difference between the groups in the mean change in CRT from baseline to year 2 (p = 0.595, Table 2). Fig. 2 shows the changes in mean CRT from baseline throughout the follow-up period in each group.

Recurrence rate. Recurrence of PCV within 2 years was observed in 22 eyes (59.5%). PCV recurred in eight eyes (42.1%) in the PR+ group and in 14 eyes (77.8%) in the PR− group, and this difference was sig-

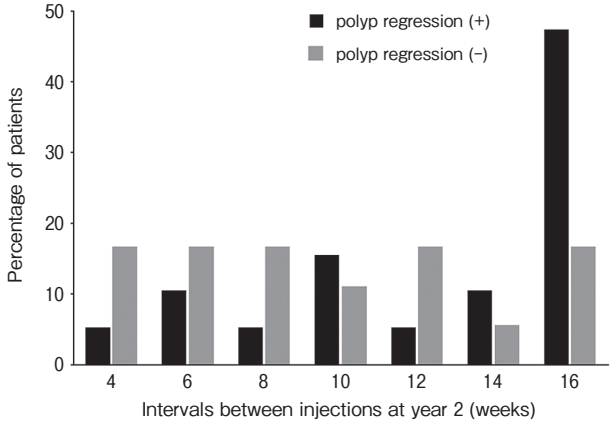

Fig. 2 Distribution of treatment intervals at year 2.

nificant ($p = 0.03$, Table 2).

Total number of injections and the interval between injections. The mean total number of injections in the 2-year treatment period was 13.8 ± 3.7, and the mean interval between injections at year 2 was 11.8 ± 4.4 weeks. The PR+ group showed significantly fewer injections in this period and a significantly longer interval between injections compared to the PR− group. The mean total numbers of injections in the 2-year period in the PR+ group and the PR− group were 12.4 ± 2.7 and 15.3 ± 4.2, respectively ($p = 0.013$, Table 2). The mean intervals between injections at year 2 in the PR+ and PR− groups were 12.5 ± 4.2 weeks and 9.6 ± 4.2 weeks, respectively ($p = 0.042$, Table 2, Fig. 2). The interval between injections was extended to the maximum 16 weeks for nine eyes (47.3%) in the PR+ group and for three eyes (16.7%) in the PR− group (Fig. 2).

Polyp regression course at 1 year and adverse events. In the PR+ group (n = 19) at 1 year, polypoidal lesions continued to be regressed in 15 eyes (83.3%) but recurred in 3 eyes (16.7%); ICGA images were unavailable for one of the patients at 1 year due to an allergy to ICGA. In the PR− group (n = 18) at 1 year, polypoidal lesions had regressed in 4 eyes (22.2%) and had remained in 14 eyes (77.8%). No serious ocular adverse events such as massive subretinal hemorrhage, vitreous hemorrhage, or retinal pigment epithelial tears occurred during the follow-up period. There were no systemic complications. Representative cases are shown in Fig. 3, 4.

Discussion

In this study, although polyp regression after a loading dose did not affect changes in visual acuity, the patients who exhibited polyp regression had a significantly lower PCV recurrence rate, a significantly smaller total number of treatments, and a significantly longer interval between treatments. These results indicate that polyp regression after a loading dose of IVA therapy may serve as a reference for estimating the frequency of long-term PCV recurrence and the number of anti-VEGF drug injections.

These findings also indicate that patients who did not show polyp regression after the loading dose should undergo a TER with a stricter protocol than that used in the present study, in order to prevent the recurrence of PCV. The authors of previous studies described long-term visual acuity decreases in a PRN of anti-VEGF drugs following the recurrence of exudative changes [22, 23]. In the present study, although the PR− group had a significantly higher recurrence rate than the PR+ group, the 2 groups did not differ in visual acuity (Table 2). The lack of difference in visual acuity may have been due to the short observation period of only 2 years. Therefore, over the long term, patients who did not exhibit polyp regression may show lower visual acuity than patients who did show polyp regression. It may thus be advisable to make adjustments to the TER protocol for patients who do not show polyp regression. Going forward, it will be necessary to further clarify the factors that affect treatment progress and to establish more individualized protocols for TERs.

Here we observed that although the TER of aflibercept alone yielded favorable visual acuity, the mean total number of injections in 2 years in the PR− group was 15.3 ± 4.2. Such a high frequency of injections places a great burden on the patient. To resolve this issue, it may be useful to change from aflibercept monotherapy to combination therapy with PDT. Combination therapy with aflibercept and PDT was recently reported to require fewer treatments than aflibercept monotherapy [24, 25]. In addition, PDT is reported to yield a greater polyp regression effect than anti-VEGF drugs [5].

However, the greatest problem with PDT is its risk of inducing subretinal hemorrhages, retinal pigment epithelial tears, and choriocapillaris atrophy [9-11]. Therefore, conducting routine PDT in all cases of PCV may result in severe complications, and PDT should

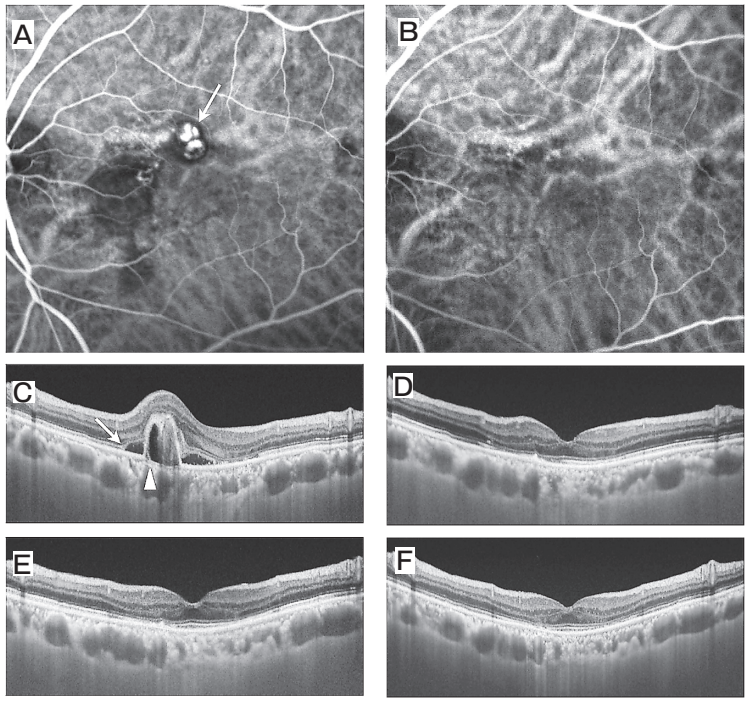

Fig. 3 Images of the clinical course in the left eye of a 73-year-old woman with PCV. **A**, **C**, At baseline, ICGA showed polypoidal lesions (*arrow*). Vertical images through the fovea taken by OCT showed subretinal fluid (*arrow*) and protrusion of the retinal pigment epithelium (RPE) due to a polypoidal lesion (*arrowhead*). The best-corrected decimal visual acuity was 0.3; **B**, **D**, After the loading dose (at 3 months after the initial treatment), ICGA showed complete regression of the polypoidal lesions. OCT showed resolution of the subretinal fluid and RPE protrusion. The visual acuity was 0.4; **E**, At 1 year after the initial treatment, OCT showed no exudative changes. The visual acuity was 0.4; **F**, Two years after the initial treatment, OCT showed no exudative changes. There was no recurrence during the 2 years of follow-up. The injection interval at the final visit was 16 weeks, and the total number of injections during the 2 year treatment period was 11. The visual acuity was 0.4.

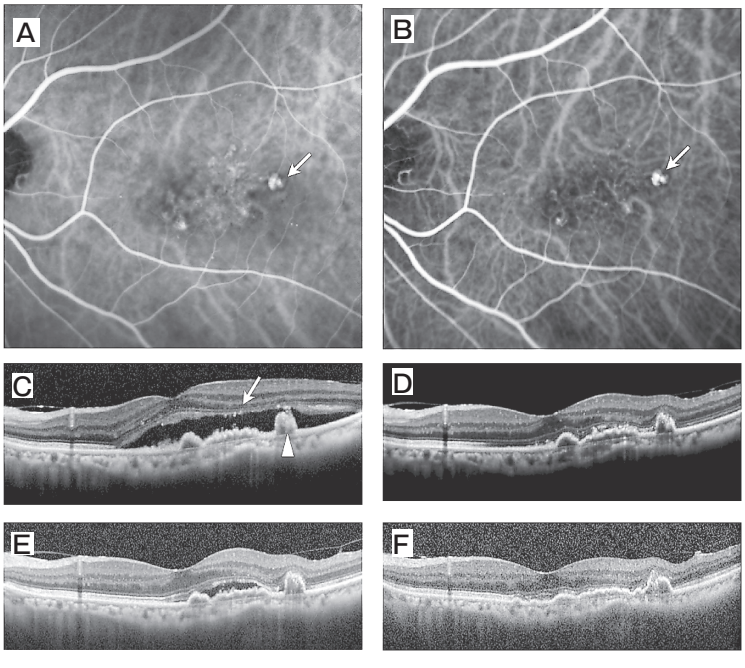

Fig. 4 Images of the clinical course in the left eye of a 78-year-old woman with PCV. **A**, **C**, At baseline, ICGA showed a polypoidal lesion (*arrow*). Horizontal images through the fovea taken by OCT showed subretinal fluid (*arrow*) and protrusion of the RPE due to a polypoidal lesion (*arrowhead*). The best-corrected decimal visual acuity was 0.8; **B**, **D**, After the loading dose (at 3 months after the initial treatment), ICGA showed no regression of the polypoidal lesions. Although OCT showed resolution of the subretinal fluid, the RPE protrusion remained. The visual acuity was 0.9; **E**, At 1 year after the initial treatment, OCT showed recurrence of subretinal fluid (*arrow*). The visual acuity was 0.9; **F**, At 2 years after the initial treatment, although OCT showed no subretinal fluid, the RPE protrusion remained. The injection interval at the final visit was 4 weeks, and the total number of injections during the 2-year treatment period was 22. The visual acuity was 0.9.

thus be restricted to patients who require it. In the present study, polyps remained at 1 year in 77.8% of the 18 patients who did not show polyp regression after the loading dose. In contrast, among the group of 19 patients who showed polyp regression after the loading dose, polyps were still regressed at 1 year in 83.3% of the patients. These results suggest that, for patients who do not demonstrate polyp regression after a loading dose, combination therapy with PDT may lead to an earlier regression of polyps, a lower frequency of PCV

recurrence, and a smaller number of anti-VEGF drug injections.

This study has several limitations including its retrospective study design and small sample size. Other treatment options for PCV such as PDT or a combination of PDT and anti-VEGF therapy were not considered. Further controlled prospective studies with larger sample sizes and longer follow-up periods are needed. In conclusion, we report that polyp regression after a loading dose of IVA therapy using a treat-and-extend regimen for polypoidal choroidal vasculopathy does not affect changes in visual acuity but is associated with PCV recurrence, the total number of anti-VEGF drug injections, and the treatment interval.

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