Recent progress in molecular targeting therapies has improved the overall prognosis of age-related macular degeneration (AMD), a leading cause of blindness worldwide. While most patients receive benefits from treatment with intravitreal anti–vascular endothelial growth factors (anti-VEGFs) such as ranibizumab (IVR)\(^\text{1,2}\) and aflibercept (IVA)\(^\text{3}\), treatment response is not always consistent among patients\(^\text{4-8}\). This can be attributed to differences in the pathogenesis of AMD among individuals.

Generally, AMD is divided into 3 subtypes: typical AMD, polypoidal choroidal vasculopathy (PCV), and retinal angiomatous proliferation (RAP).\(^\text{9}\) PCV, which accounts for almost 50% of AMD patients in Asian countries,\(^\text{10,11}\) is characterized by polypoidal lesions with or without a branching vascular network (BVN) detected by indocyanine green angiography (ICGA).\(^\text{12}\) Most patients with PCV exhibit unilateral disease, similar to those with typical AMD, and do not frequently develop drusen in the unaffected eye, as opposed to RAP, which carries a poorer prognosis compared with PCV and typical AMD.\(^\text{13}\) Because of differences in the clinical course and therapeutic response,\(^\text{14}\) it is important to differentiate between PCV and typical AMD, although patients with both PCV and typical AMD in a single eye have also been reported.\(^\text{15}\) Moreover, reports of the posttreatment prognosis of PCV patients are inconsistent among clinical studies.\(^\text{16-21}\)

For example, a randomized study (the EVEREST study) compared the efficacy of IVR and photodynamic therapy (PDT) for the treatment of PCV and concluded that the latter was more effective in achieving polyp regression.\(^\text{16}\) In contrast, another study (the LAPTOP study) showed that IVR monotherapy was superior to PDT.\(^\text{17}\) These differences probably occurred because of the lack of detailed classifications for the different variants of PCV that exhibit different responses to treatment. Therefore, classifications that accurately represent the prognosis of each variant are desirable.

We previously reported that nonresponders to IVR among patients with different subtypes of AMD exhibit unique fundus findings at baseline.\(^\text{1}\) In the same study, initial fibrovascular pigment epithelial detachment (PED), serous PED, and type 1 choroidal neovascularization were found to be associated with a lack of response to IVR. In the current study, we divided PCV patients into 2 subtypes: single polyp and multiple polyp groups according to indocyanine green angiography and optical coherence tomography (OCT) findings. The outcome measures included changes in best-corrected visual acuity (BCVA) and OCT findings over 2 years after initial IVR.

**RESULTS:** At baseline, the multiple polyps group exhibited a poorer BCVA, larger greatest linear dimension, and higher prevalence of fibrovascular pigment epithelial detachment compared with the single polyp group. Over 2 years, the multiple polyps group showed no improvement in BCVA, although the central retinal thickness (CRT) decreased in both groups. The multiple polyps group exhibited a significantly greater CRT at 1 year and required more injections in the first year compared with the single polyp group; furthermore, it included a higher number of nonresponders judged either by BCVA or fundus findings at 1 year and fundus findings at 2 years.

**CONCLUSIONS:** We propose that the stratification of PCV lesions according to the presence of single or multiple polyps may be valuable to understand the prognosis. (Am J Ophthalmol 2016;166:52–59. © 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).)
into 2 groups on the basis of the presence of a single or multiple polyps and retrospectively analyzed their responsiveness to IVR monotherapy to derive information that will aid in understanding the pathologic course and predicting the prognoses of patients with different variants of PCV treated by IVR monotherapy.

METHODS

This retrospective case series was based on a detailed medical chart review, followed the tenets of the Declaration of Helsinki, and was retrospectively approved by the Ethics Committee of Keio University School of Medicine (No. 2010002) and registered with UMIN-CTR (UMIN000007649).

- **STUDY PARTICIPANTS:** In total, 68 consecutive eyes of 65 patients were diagnosed with PCV. From these, we included 48 eyes of 48 patients with PCV-induced visual loss who received IVR monotherapy at the Medical Retina Division Clinic (AMD Clinic) of the Department of Ophthalmology, Keio University Hospital (Tokyo, Japan) between March 2009 and January 2013. During this period, aflibercept, which was first approved in Japan in November 2012, and another off-label anti-VEGF drug for AMD, bevacizumab, were not used at the hospital. Thus, all PCV patients who needed anti-VEGF therapy were treated with IVR. All patients had attended our clinic for at least 12 months, during which time no medication other than IVR was administered. Patients who had received any other treatment for AMD in the past were excluded; thus, all participants were treatment naïve. All patients who began receiving treatments other than IVR monotherapy after the first year were considered dropouts, and their data before the initiation of another treatment were analyzed. All patients provided informed consent for the use of their data for research purposes.

- **OPHTHALMOLOGIC EXAMINATIONS:** All patients underwent best-corrected visual acuity (BCVA) measurements using refraction tests, slit-lamp examinations, and binocular indirect ophthalmoscopy after pupil dilation with 0.5% tropicamide throughout the study.

- **FLUORESCEIN AND INDOCYANINE GREEN ANGIOGRAPHIES:** Fluorescein angiography and ICGA were performed for AMD diagnosis and PCV definition using a Topcon TRC 50DX retinal camera (Topcon Corporation, Tokyo, Japan). According to the findings of ICGA and optical coherence tomography (OCT), the patients were divided into the single polyp and multiple polyps groups (Figure 1).

- **OPTICAL COHERENCE TOMOGRAPHY:** OCT was performed at every follow-up visit using a Heidelberg Spectralis OCT system (Heidelberg Engineering GmbH, Dossenheim, Germany). The OCT images were used to evaluate central retinal thickness (CRT), central choroidal thickness (CCT), and AMD lesions, including PED. CRT was defined as the distance between the internal limiting membrane and the presumed retinal pigment epithelium (RPE) at the fovea. CCT was defined as the distance from the hyperreflective line corresponding to the Bruch membrane beneath the RPE and the inner surface of the sclera at the foveal center, and was manually measured using the caliper function of the OCT device. Measurements were obtained using the scale bars of the OCT system for reference. A dry macula was defined as the resolution of intra- and subretinal fluid detected by OCT with reference to fundus findings, and in particular to an increase or decrease in hemorrhages. Changes in hemorrhages (eg, retinal or subretinal hemorrhage or hemorrhagic PED) were not always detected by OCT, but could respond to AMD activity. Thus, we also checked fundus photography and excluded those who had increased hemorrhagic findings from the patients with dry macula.

- **INTRAVITREAL RANIBIZUMAB MONOTHERAPY AND FOLLOW-UP:** In the induction phase, ranibizumab (0.5 mg, 0.05 mL) was intravitreally injected via the pars plana under sterile conditions once a month for 3 months. The injections were repeated if follow-up OCT showed evidence of any fluid in the macula, identified as macular edema, subretinal fluid, or PED enlargement. Follow-ups were generally conducted every month after therapy initiation, but in cases where no fluid or hemorrhage was detected for more than 2 months, the interval was extended up to 2 months. Any new intra- or subretinal hemorrhage or unexplained visual loss represented by an increase of >0.2 in logMAR BCVA was treated as appropriate. At each follow-up visit, BCVA was measured and other ophthalmologic examinations, including OCT, were performed.

- **DEFINITION OF NONRESPONDERS TO INTRAVITREAL RANIBIZUMAB:** Nonresponders were defined on the basis of BCVA or fundus findings, as previously reported.

Briefly, patients with an increase of >0.2 in logMAR score at 1 or 2 years after initial IVR therapy were judged as nonresponders on the basis of BCVA. On the basis of fundus findings, nonresponders were judged as patients with aggravated or fresh exudative fundus findings (PED, subretinal fluid, macular edema, or hemorrhage) even after treatment, or those with an increase of >100 μm in CRT between baseline and 1 or 2 years after initial IVR therapy.

- **STATISTICAL ANALYSES:** Data are expressed as means ± standard deviations (SDs). Commercially available software (SPSS, version 21.0; SPSS Japan, Tokyo, Japan) was used for all statistical analyses. The Mann-Whitney U test, χ² test, multiple regression analyses, or Spearman rank
The correlation coefficient was used for comparisons, and a P value of <.05 was considered statistically significant.

**RESULTS**

AMONG THE 48 PCV TREATMENT-NAIVE PATIENTS, 29 EYES of 29 patients (22 men and 7 women) exhibited a single polyp and 19 eyes of 19 patients (12 men and 7 women) exhibited multiple polyps on baseline ICGA before IVR treatment. Among the multiple polyps group, 2, 3, 4, 5, 6, 7, and 12 polyps were found in 4, 4, 3, 1, 3, and 1 patient, respectively. There were 5 dropouts in the second year of treatment, including 1 patient in the single polyp group who was lost to follow-up, 1 patient each in both groups who changed their treatments, and 2 patients in the multiple polyps group who underwent vitrectomy for PCV-associated vitreous hemorrhage.

At baseline, the mean BCVA was significantly poorer in the multiple polyps than in the single polyp group (Table 1, P = .017), while the mean greatest linear dimension (GLD) was larger in the multiple polyps group than in

| TABLE 1. Baseline Characteristics of the Single Polyp and Multiple Polyps Groups |
|---------------------------|---------------------------|---------------------------|
|                          | Single Polyp       | Multiple Polyps | P Value |
| Age (y)                  | 72.1 ± 9.4         | 72.7 ± 7.5      | .72     |
| Best-corrected visual acuity (logMAR) | 0.18 ± 0.26 | 0.37 ± 0.30 | .017* |
| Greatest linear dimension (µm) | 2950.8 ± 3237.3 | 4084.4 ± 1926.4 | .009* |
| Central retinal thickness (µm) | 394.6 ± 156.8 | 384.1 ± 183.6 | .591    |
| Central choroidal thickness (µm) | 218.9 ± 61.7 | 251.3 ± 85.7 | .117    |
| Fibrovascular retinal pigment epithelial detachment, eyes [%] | 5 [29%] | 11 [57.9%] | .004** |
| Follow-up period (mo)    | 22.5 ± 3.2         | 20.7 ± 4.8      | .116    |

For sex, the χ² test was used to evaluate comparisons, and the Mann-Whitney U test was applied for the other comparisons.

*P < .05.
**P < .01.
the single polyp group \( (P = .009) \). Furthermore, the number of eyes with fibrovascular PED \( (f\text{-PED}) \), as detected by fluorescein angiography and OCT, was greater in the multiple polyps group than in the single polyp group \( (P = .004) \). All f-PED lesions corresponded to the presence of a BVN in the multiple polyps group. There was no significant difference in age, sex, baseline CRT, baseline CCT, or follow-up duration between the 2 groups.

The mean BCVA in the single polyp group showed significant improvement at each point compared with that at baseline (Figure 2), while it remained unchanged in the multiple polyps group. Moreover, the mean BCVA was significantly poorer in the multiple polyps group than in the single polyp group at all time points of assessment (Figure 3; 3 months, \( P = .04 \); 1 year, \( P = .003 \); 2 years, \( P = .002 \)), although there was no intergroup difference in mean changes in BCVA at any time point (data not shown).

In total, 21 of 29 eyes (96.6%) in the single polyp group and 14 of 19 eyes (72.2%) in the multiple polyps groups showed maintained or improved BCVA at 1 year after initial IVR therapy \( (P = .019) \), while 21 of 27 eyes (96.4%) and 13 of 16 eyes (81.3%), respectively, showed maintained or improved BCVA at 2 years \( (P = .262) \) (Figure 3).

The mean CRT at 3 months exhibited a decrease relative to that at baseline and remained low throughout 2 years of treatment in both groups (Figure 4). At 1 year, however, the mean CRT was significantly greater in the multiple polyps group \( (297.5 \pm 127.4 \mu m) \) than in the single polyp group \( (226.6 \pm 114.4 \mu m; P = .009) \), with a significantly smaller mean CRT change in the former \( (101.2 \pm 116.1 \mu m) \) than in the latter \( (168.0 \pm 178.6 \mu m; P = .042) \).

Interestingly, the numbers of IVR injections in the first and second years were \( 4.4 \pm 2.1 \) and \( 1.7 \pm 2.0 \), respectively, in the single polyp group and \( 6.0 \pm 2.5 \) and \( 2.3 \pm 2.4 \), respectively, in the multiple polyps group, indicating a significant difference in the first year (Figure 5, \( P = .009) \).

Intra- and subretinal exudative changes had disappeared after the initial 3 injections in 28 eyes (96.6%) in the single polyp group and 15 eyes (78.9%) in the multiple polyps group (Table 2); the eyes in the latter group showed a greater tendency for residual exudative changes after the induction phase \( (P = .051) \). The mean number of injections required before the first complete disappearance of intra- and subretinal exudative changes and the achievement of a dry macula were \( 3.4 \pm 1.4 \) and \( 4.9 \pm 3.3 \) in the single polyp and multiple polyps groups, respectively (Table 2; \( P = .054) \). Among eyes in which a dry macula was achieved, the durations between the last injection before observation of a dry macula and the subsequent

FIGURE 3. Changes in best-corrected visual acuity (BCVA) at 1 and 2 years after initial intravitreal ranibizumab (IVR) therapy in polypoidal choroidal vasculopathy patients in the single polyp and multiple polyps groups. The number of patients with improved or maintained BCVA at 1 year after initial IVR therapy was significantly smaller in the multiple polyps group than in the single polyp group \( (P = .019, \text{Mann-Whitney } U \text{ test}) \).

FIGURE 4. Mean central retinal thickness (CRT) after intravitreal ranibizumab (IVR) therapy in polypoidal choroidal vasculopathy patients in the single polyp and multiple polyps groups. In both groups, the mean CRT was decreased at all time points after initial IVR therapy relative to that at baseline. A significant difference is observed between the 2 groups at 1 year. \( **P < .01 \) by the Mann-Whitney \( U \) test.
injection for recurrence were 11.4 ± 7.1 months and 5.9 ± 6.4 months in the single polyp and multiple polyps groups, respectively, with a significant difference between the groups (Table 2; \( P = .005 \)). Fifteen eyes, including 13 (44.8%) in the single polyp group and 2 (10.5%) in the multiple polyps group (Table 2; \( P = .003 \)), needed no further injections for more than a year after the first remission. The numbers of nonresponders as judged by BCVA were 1 (3.4%) and 6 (31.6%) in the single polyp and multiple polyps groups, respectively, at 1 year (Figure 6); the corresponding numbers were 0 (0%) and 5 (28.3%), respectively, when fundus findings were used for judgment (Figure 6). Thus, the number of nonresponders at 1 year was significantly higher in the multiple polyps group than in the single polyp group according to both criteria (BCVA; \( P = .007 \); fundus findings; \( P = .004 \)). A significant difference was also observed on the basis of fundus findings at 2 years (Figure 6; \( P = .027 \)).

**DISCUSSION**

IN THIS STUDY, WE COMPARED THE RESPONSES OF PCV PATIENTS WITH A SINGLE POLYP OR MULTIPLE POLYPS TO IVR MONOTHERAPY. The multiple polyps group exhibited a poorer BCVA, larger GLD, and higher prevalence of f-PED at baseline compared with the single polyp group. Although the mean BCVA improved with treatment in the single polyp group, it remained poor in the multiple polyps group throughout the 2-year course, with significant differences between the groups. Furthermore, CRT at 1 year after initial IVR therapy was greater in the multiple polyps group than in the single polyp group, although there was an improvement relative to the thickness at baseline in both groups. The multiple polyps group required more injections in the first year, with a shorter period of remission after the initial disappearance of exudative changes. Finally, the number of nonresponders as judged by BCVA and/or fundus findings was higher in the multiple polyps group at 1 and 2 years.

The multiple polyps group exhibited a poor baseline BCVA with a high prevalence of f-PED, which generally manifests after a long clinical course. This suggests that the patients in the multiple polyps group had a longer pathologic history before the initial visit for treatment, although further studies are required to clarify this speculation. With regard to the increased GLD in this group, the widespread polyps around the BVN may have played a role.

The mean CRT decreased after 3 months of initial treatment in both groups, indicating a benefit from anti-VEGF therapy. However, the mean CRT change at 1 year was significantly smaller in the multiple polyps group than in the single polyp group, indicating a difference in treatment responsiveness. Given that pro re nata retreatment was administered, this is consistent with the finding of a higher mean injection rate in the multiple polyps group in the first year. Furthermore, compared with the single polyp group, the multiple polyps group exhibited a higher prevalence of residual fluid after 3 IVR injections and a shorter mean interval before the recurrence of exudative changes after the first remission. These findings suggest that intra- and subretinal exudative changes were rather resistant to IVR and easily recurred in the presence of multiple polyps. Consistent with these findings, the number of eyes with a decreased BCVA was higher in the multiple polyps group at 1 year after initial IVR therapy, most probably because these eyes were exposed to exudative changes during every recurrence, which resulted in an overall longer duration of exposure.

Tsuchikawa and associates reported that widespread PCV with a GLD of more than 1 disc area (DA) was associated with a poorer prognosis compared with PCV involving a smaller area. Although the criteria for stratification were

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![Table 2](image-url)

**TABLE 2.** Achievement of a Dry Macula in the Single Polyp and Multiple Polyps Groups After Intravitreal Ranibizumab Therapy

<table>
<thead>
<tr>
<th>Achieved Dry Macula</th>
<th>Single Polyp</th>
<th>Multiple Polyps</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry macula after 3 initial injections, eyes [%]</td>
<td>28 [96.6%]</td>
<td>15 [78.9%]</td>
<td>.051</td>
</tr>
<tr>
<td>Number of injections to obtain a dry macula</td>
<td>3.4 ± 1.4</td>
<td>4.9 ± 3.3</td>
<td>.054</td>
</tr>
<tr>
<td>Duration to retreatment (mo)</td>
<td>11.4 ± 7.1</td>
<td>5.9 ± 6.4</td>
<td>.003</td>
</tr>
<tr>
<td>No injections for more than 1 year, eyes [%]</td>
<td>13 [44.8%]</td>
<td>2 [10.5%]</td>
<td>.012</td>
</tr>
</tbody>
</table>

The Mann-Whitney U test was applied to evaluate comparisons between the groups.

\( ^a P < .05 \)

\( ^b P < .01 \).
different in our study, the multiple polyps group exhibited a larger GLD at baseline and a worse prognosis with regard to both CRT and BCVA after IVR monotherapy. The previous study showed that widespread PCV was characterized by an increase in GLD after anti-VEGF treatment and was associated with single nucleotide polymorphisms (SNPs), type 2 choroidal neovascularization (CNV), PED covering an area larger than 1 DA, and an increased incidence of massive hemorrhage. Similarly, the multiple polyps group in the present study exhibited a higher prevalence of f-PED, although it remains unclear whether the PED observed in the previous study was of the fibrous type. On the other hand, the multiple polyps group and single polyp group in the present study included 10 (52.6%) and 11 eyes (37.9%) with type 2 CNV and 1 (5.3%) and 3 eyes (10.3%) with massive hemorrhages covering areas larger than 5 DA, respectively, with no significant difference between the groups (data not shown).

Kawamura and associates categorized PCVs according to the presence or absence of feeder and draining vessels to analyze the characteristics in a cross-sectional manner, while Yanagisawa and associates reported that PCV without feeder or draining vessels was associated with an elastin SNP. However, these reports did not mention the prognosis of each group. In addition to our study, these studies and others support the fact that PCV may have further distinct classifications with different phenotypes.

We previously analyzed nonresponders to IVR among patients with all AMD subtypes, typical AMD, PCV with a single or multiple polyps, and RAP and found nonresponder percentages of 14.9% and 17.0% as judged by BCVA and fundus findings at 1 year, respectively. Compared with the proportion of nonresponders among patients with all AMD subtypes in the previous study, the present study demonstrated a larger proportion in the multiple polyps group and a lower proportion in the single polyp group. Furthermore, our previous study reported that f-PED was a risk factor among patients with all AMD subtypes for lack of response to IVR according to BCVA and fundus findings, and this was consistent with the higher prevalence of f-PED in the multiple polyps group in the present study.

**FIGURE 6.** Number of nonresponders to intravitreal ranibizumab (IVR) therapy at 1 and 2 years among polypoidal choroidal vasculopathy patients in the single polyp and multiple polyps groups. The number of nonresponders to IVR therapy at 1 year after initial IVR therapy was significantly greater in the multiple polyps group than in the single polyp group according to both best-corrected visual acuity and fundus findings. A similar difference was also observed on the basis of fundus findings at 2 years. \( **P < 0.01 \) by the \( \chi^2 \) test.
However, the presence or absence of f-PED did not affect nonresponsiveness as judged by BCVA at 1 year by multiple regression analysis after adjusting for age, sex, and the presence of multiple polyps. However, the presence of multiple polyps did have an effect after adjusting for age, sex, and the presence of f-PED (Supplemental Table 1, available at AJO.com). Moreover, GLD, which was larger in the multiple polyps group, did not affect nonresponsiveness as judged by BCVA at 1 year or the number of injections in the first year, as the multiple regression analyses showed after adjusting for age, sex, and polyp multiplicity. However, multiple polyps did have an effect by a similar method with adjustments for age, sex, and GLD (Supplemental Tables 2 and 3, respectively; available at AJO.com). No additive effect was observed to differentiate nonresponders to IVR into details according to levels of risk, even when the other PCV components, such as f-PED and GLD, were combined with polyp multiplicity for analyses (data not shown). Moreover, there was no difference in the duration of a dry macula when eyes were stratified according to the presence or absence of f-PED; nevertheless, among the 11 eyes with f-PED in the multiple polyps group, only 1 (9.1%) remained in remission for more than 1 year, while 4 of 5 eyes (80%) in the single polyp group remained free of exudative changes for over 1 year (data not shown). In contrast, there was a difference when eyes were stratified by polyp multiplicity. These results suggest that polyp multiplicity, but not other PCV components such as f-PED, was responsible for the prognosis.

Interestingly, the number of polyps at baseline was correlated with BCVA at 1 and 2 years, as well as at baseline, respectively (Supplemental Table 4, available at AJO.com), although the number of polyps itself was not correlated with responsiveness to IVR, as long as the patients had multiple polyps. Neither GLD nor f-PED at baseline was correlated with BCVA at 1 or 2 years (data not shown). These facts also support the impact of polyp multiplicity in visual prognosis.

Thus, although the pathologic relationship between f-PED and exudative changes requires further study, the current observations support the importance of classifications by the presence or absence of multiple polyps for predicting the prognosis of PCV.

Mori and associates also reported that only 19% of PCV eyes showed a regression of polyps after 1 year of anti-VEGF therapy,29 while the EVEREST study reported that the regression rate for polyps after 6 months of treatment was 28.6% in the IVR monotherapy group and 77.8% in the verteporfin PDT with IVR group.15 These findings suggest that IVR monotherapy is not very effective for the regression of polyps. This may also partly explain the increased recurrence after IVR monotherapy in the multiple polyps group in the current study, where there was a greater likelihood of remaining nonregressed polyps because of the initially large number of polyps and formation of new polyps.

The difference in responsiveness to IVR between the single and multiple polyps groups could be one reason for the discrepancy in clinical outcome between the EVEREST study16 and the LAPTOP study.17 Thus, it would be interesting to evaluate the effects of adjunctive therapies in PCVs with multiple polyps in a future study.

This study had some limitations. First, we did not record angiograms for most eyes during the treatment course. Second, we did not assess the relationship between residual lesions, including polyps and/or BVN, and the prognosis. Third, we did not investigate SNPs, and fourth, the sample size in this study was small. In addition, this was a retrospective study, and not all patients were examined monthly during the study.

In conclusion, the results of our study suggest that the response to IVR therapy is poorer in PCV patients with multiple polyps than in those with a single polyp. Although further studies are required, we propose that the stratification of PCV lesions by polyp number may be valuable to understand the prognosis of this condition.
REFERENCES


