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Factors predicting 2-year treatment results of ranibizumab therapy for polypoidal choroidal vasculopathy in eyes with good baseline visual acuity

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Abstract

This study aimed to explore predictors of long-term stabilization of polypoidal choroidal vasculopathy (PCV) lesions and vision in response to injection of intravitreal ranibizumab (IVR). The treated eyes had a baseline best corrected visual acuity (BCVA) of at least 0.6 (logarithm of the minimal angle of resolution (logMAR) 0.22).

We treated 45 eyes showing BCVA between 0.6 (logMAR 0.22) and 1.0 (logMAR 0), with IVR for 3 consecutive months. All eyes were confirmed to have subfoveal PCV prior to starting this treatment regimen. Additional IVR was administered at the subsequent monthly visits, if necessitated by evidence of persistent PCV, for up to 23 months after the first ranibizumab injection. The subjects were then carefully followed-up for 24 months, allowing detailed retrospective evaluation of changes in mean BCVA, central retinal thickness (CRT), serous retinal detachment (SRD), hemorrhage, and polypoidal lesion numbers. The relationships between retreatment and each of the baseline characteristics and SRD development during follow-up were analyzed.

The mean logMAR BCVAs were 0.111 ± 0.076, 0.068 ± 0.206 ($P = .0033$) and 0.115 ± 0.265 ($P = .27$) at baseline and at 12 and 24 months, respectively. At 24 months, 87% of eyes had BCVA of 20/40 or better. Not requiring retreatment between 12 and 23 months was found to be significantly associated with the absence of retinal pigment epithelial detachment (RPED) at baseline (odds ratio: 0.262 (95% confidence interval (CI): 0.073–0.946). The rates of retreatment from 12 to 23 months were significantly higher in eyes with SRD at 6 and 12 months than in those without SRD ($P = .004$ and $P < .001$).

In conclusion, during 24 months of antivascular endothelial growth factor (VEGF) therapy using ranibizumab for PCV, BCVA was maintained in those with good visual acuity at baseline. Comprehensive analyses revealed RPED at baseline and SRD development during follow-up to correlate significantly with the need for retreatment between 12 and 23 months. Our observations might facilitate tailoring treatments to individual PCV patients.

Abbreviations: AMD = age-related macular degeneration, BCVA = best corrected visual acuity, BVN = branching vessel network, CI = confidence interval, CNV = choroidal neovascularization, CRT = central retinal thickness, DD = disc diameter, FA = fluorescein angiography, GRD = greatest linear dimension, ICGA = indocyanine green angiography, IVR = intravitreal ranibizumab, log MAR = logarithm of the minimal angle of resolution, OCT = optical coherence tomography, PCV = polypoidal choroidal vasculopathy, PDT = photodynamic therapy, RPE = retinal pigment epithelium, RPED = retinal pigment epithelial detachment, SRD = serous retinal detachment, VEGF = vascular endothelial growth factor.

Keywords: good baseline visual acuity, polypoidal choroidal vasculopathy, ranibizumab

1. Introduction

Ranibizumab (Lucentis; Genentech Inc, San Francisco, CA, Novartis Pharma AG, Basel) is a recombinant humanized monoclonal antibody inhibiting all of the vascular endothelial growth factor (VEGF)-A isoforms. Intravitreal ranibizumab (IVR) is reportedly effective for treating choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).[1–3] Polypoidal choroidal vasculopathy (PCV), a form of CNV related AMD, characteristically shows a branching vessel network (BVN) with polypoidal lesions at vessel termini, a finding which is reportedly demonstrated by indocyanine green angiography (ICGA).[4] Although prior reports have extensively documented the utility of anti-VEGF therapy for PCV, even cases in which vision was maintained or improved by this treatment required repeated administrations and, in some instances, sudden reductions in vision during follow-up were documented.

As we reported previously,[5] serous retinal detachment (SRD) was observed in 42% of PCV cases 12 months after IVR administration, and this finding necessitated an investigation into the effects of persistent and recurrent SRD on visual function and the stability of lesions based on long-term outcomes. Thus, herein, we aimed to explore possible predictors of long-term stabilization of lesions, including ongoing SRD, and vision.

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2. Patients and methods

This was a retrospective study of 50 eyes of 50 consecutive patients. All 50 eyes had PCV treated with IVR and were managed at our institution, Surugadai Nihon University Hospital, during the period from March 2009 to January 2010. After completing the 12-month prospective study,[5] 45 of the 50 eyes were followed-up for a further 24 months after the first IVR injection. ICGA, which demonstrated BVN with polypoidal lesions, confirmed the PCV diagnosis in all 45 eyes. The main eligibility criterion was a best-corrected visual acuity (BCVA) within the 0.6 (equivalent to a logarithm of the minimum angle of resolution (logMAR) of 0.22) to 1.0 (logMAR 0) range, as demonstrated using a decimal BCVA chart. The other eligibility criterion was no prior treatment for the PCV. We included eyes in this study with either a polypoidal lesion or a subvofeal-BVN, as demonstrated by ICGA, as well as evidence of exudation such as SRD or hemorrhagic findings (subretinal, subretinal pigment epithelium (RPE), and/or intraretinal) involving the fovea. We also studied eyes with serous retinal pigment epithelial detachment (RPED) outside the fovea, associated with SRD and/or hemorrhagic findings of the fovea. However, we excluded from this study eyes in which serous RPED was the only foveal abnormality. Any history of cerebrovascular or ischemic heart disease was cause for exclusion from this study. Our study protocol was approved by the Institutional Review Board of Surugadai Nihon University Hospital. All patients enrolled in the present investigation provided written informed consent. Each study participant received a detailed ophthalmological examination, including BCVA determination, slit lamp biomicroscopy of the anterior segment, and dilated funduscopic examination of the posterior pole at each scheduled visit, from the baseline until the final (24-month) follow-up visit. We performed fluorescein angiography, ICGA, and optical coherence tomography (OCT), employing the Spectralis HRA OCT (Heidelberg Engineering, Heidelberg, Germany), at baseline and then repeated these examinations at 3, 6, 9, and 12 months. Detailed fundus examinations and OCT were also performed monthly. All OCT examinations were carried out with vertical and horizontal cross-sections areas centered at the fovea.

All patients were given 3 IVR (0.5 mg per injection), once monthly for 3 months, as the initial treatment for PCV.

In eyes showing hemorrhage at the macula or/and subretinal fluid or/and intraretinal fluid on OCT images, regardless of their BCVA, additional IVR was administered once a month for up to 6 months after the baseline visit to our clinic. IVR was then re-administered at monthly visits from 7 to 23 months, if BCVA deterioration by at least one line in the decimal notation, due hemorrhage at the macula or/and subretinal fluid or/and intraretinal fluid, was detected by OCT at the macula. For patients with BCVA of 0.5 or below at the 12th month or thereafter, combinations of photodynamic therapy (PDT) and IVR were allowed.

The overall number of retreatments, between 3 and 23 months, was calculated. The mean BCVA and central retinal thickness (CRT) at the fovea, determined as part of the baseline evaluation, were then compared with the values measured at 1, 2, 3, 6, 9, 12, and 24 months. SRDs seen on OCT at baseline were compared with SRDs at 3, 6, 9, 12, and 24 months. We also determined whether there was any correlation, at baseline, between the greatest linear dimension (GLD) on ICGA and the mean BCVA of all eyes studied. We measured GLD, on ICGA, employing the longest diameter of the BVN with polypoidal lesions. We also calculated the total number of IVR treatments administered from months 3 to 23.

PCV, a subtype of neovascular AMD, characteristically shows a BVN with polypoidal lesions detectable on ICGA images. Controversy persists as to the origins and locations of both BVN and polypoidal lesions. Our group categorized PCV into 2 subtypes, that is, polypoidal CNV (type 1) and typical PCV (type 2). Polypoidal CNV was described as being located in the sub-RPE space, while typical PCV was located in the choroidal space.[6] Meanwhile, PCV lesions have also been reported to uniformly be located within the sub-RPE space and to show the features of CNV.[7,8] We defined tachyphylaxis as SRD resolution at IVR completion (3 months after the first IVR administration), with subsequent evidence of recurrent and/or persistent serous exudates despite further IVR administrations. Nonresponders were defined as eyes showing either persistent SRD or hemorrhagic findings for the duration of the follow-up conducted for this study.

The paired Wilcoxon signed-rank test was applied for within group, the unpaired Wilcoxon rank sum test for between group, comparisons. The Pearson correlation was employed to quantitatively evaluate the associations between 2 variables. For categorical data, Fisher's exact test was used to evaluate associations. Univariate logistic regression analysis was performed to examine the relationship between each potential predictor and outcome. Multivariate logistic regression was performed to identify predictive factors independently associated with outcome. All values presented herein are means with standard deviations. BCVA was converted to logMAR for all of the statistical analyses. An improvement of 0.3 or more in logMAR BCVA was defined as improved BCVA, while a reduction of at least 0.3 was defined as BCVA deterioration. We used statistical analysis software (SPSS Statistics 18.0, IBM, NY) to perform all of the analyses in this study. A P value of .05 was taken to indicate a statistically significant difference.

3. Results

3.1. Patient background

Baseline characteristics of the 45 eyes are shown in Table 1. Forty-five patients (36 men, 9 women), ranging in age from 46 to 79 years (mean 66.5 ± 7.59 years) were included. As to PCV subtypes, polypoidal CNV and typical PCV accounted for 8 (17.8%) and 37 (82.2%) eyes, respectively. Polyp locations were at the central fovea in 14 eyes (31.1%) and in the extra-foveal area in 31 eyes (68.9%). Polyps were single in 19 (42.2%), multiple in 25 (55.6%), and of the botryoidal type in one eye (2.2%), with no cases having more than one of these polyp types. The mean number of polyps was 2.1 ± 1.4. The maximum BVN diameter was 3388.2 ± 1541.3 μm. SRD was absent in 8 eyes (17.8%) and present in 37 eyes (82.2%). The SRD size was <1 disc diameter (DD) in 13 eyes (28.9%) and 1DD or more in 24 eyes (53.3%). RPED was absent in 26 eyes (57.8%) and present in 19 eyes (42.2%). The RPED size was < 1DD in 6 eyes (13.3%) and 1DD or more in 13 eyes (28.9%). Fibrin was absent in 26 eyes (57.8%) and present in 19 eyes (42.2%). Subretinal hemorrhage was absent in 25 eyes (55.6%) and present in 20 eyes (44.4%). The hemorrhagic lesion was smaller than 1DD in 12 eyes (26.7%) and 1DD or larger in 8 eyes (17.8%).

3.2. Treatment results

The mean logMAR BCVAs were 0.111 ± 0.076, 0.068 ± 0.206 ($P = .0033$) and 0.115 ± 0.265 ($P = .27$) at baseline and at 12 and 24 months, respectively (Fig. 1). At 24 months, 87% of eyes had BCVA of 20/40 or better. At 12 months, BCVA was unchanged in

Table 1

Baseline characteristics of 45 eyes of 45 patients with polypoidal choroidal vasculopathy.

Age, mean ± SD (range)	66.5 ± 7.59 (46–79)
Gender (male/female)	36/9
BCVA, logMAR (mean ± SD)	0.111 ± 0.076
CRT, mean ± SD, μm	273.0 ± 112.8
PCV type (polypoidal CNV/ typical PCV)	8/37
Polyp location (fovea/extra-fovea)	14/31
Polyp type (single/multiple/botryoidal)	19/25/1
Cluster of polyps, eyes (%)	25 (55.6%)
Number of polyps, mean ± SD	2.1 ± 1.4
Maximum BVN diameter, mean ± SD, μm	3388.2 ± 1541.3
SRD, eyes (%)	37 (82.2%)
≧1DD, eyes (%)	24 (53.3%)
RPED, eyes (%)	19 (42.2%)
≧1DD, eyes (%)	13 (28.9%)
Fibrin, no. eyes (%)	19 (42.2%)
Subretinal hemorrhage, eyes (%)	20 (44.4%)
≧1DD, eyes (%)	8 (17.8%)

BVCA = best corrected visual acuity, BVN = branching vessel network, CNV = choroidal neovascularization, CRT = central retinal thickness, DD = disc diameter, log MAR = logarithm of the minimal angle of resolution, PCV = polypoidal choroidal vasculopathy, RPED = retinal pigment epithelial detachment, SD = standard deviation, SRD = serous retinal detachment.

44 eyes (98%) and had deteriorated in one eye (2%). At 24 months, BCVA was improved in one eye (2%), unchanged in 39 eyes (87%) and had deteriorated in 5 eyes (11%). The mean CRT values were 187.5 ± 65.7 μm ($P < .001$) at 12 months and 195.4 ± 106.3 μm ($P < .001$) at 24 months, both of which were significant decreases from the 273.0 ± 112.8 μm measured at baseline. SRD was present in 37 eyes (82.2%) at baseline, and in 9 (20.0%), 20 (44.4%) and 16 (35.6%) eyes at 3, 12, and 24 months, respectively, after starting treatment (Fig. 2).

3.3. Number of treatments

The mean number of IVR treatments was 5.9 ± 2.7 (range, 3–13) at 24 months. Fourteen eyes (31.1%) were not retreated after the initial IVR. Twenty eyes (44.4%) did not require retreatment during the period from 12 to 23 months. The mean number of retreatments was 1.7 ± 1.6 at 12 months and 2.9 ± 2.7 at 24 months. We examined correlations among the numbers of treatments during the periods from 3 to 5 months, from 6 to 11 months and 3 to 11 months and after 12 months. There was a positive correlation between the number of treatments during the period from 6 to 11 months with that after 12 months, and also between the number during the period from 3 to 11 months and that after 12 months ($r = 0.612$ ($P < .0001$) and $r = 0.617$ ($P < .0001$), respectively). Four eyes (9%) had required PDT during this study.

3.4. Factors associated with retreatment

Based on the results of the univariate analysis of baseline characteristics associated with retreatment, there were no significant associations through 24 months. However, not requiring retreatment between 12 and 23 months was significantly associated with the absence of RPED (odds ratio: 0.262 [95% confidence interval (CI): 0.073-0.946]; Table 2).

The associations between SRD at 3, 6, and 12 months and retreatment during the period from 12 to 23 months were examined. The rates of retreatment were significantly higher in groups with SRD at 6 and 12 months than in the other groups ($P = .004$ and $P < .001$; Table 3).

The associations between SRD at 3, 6 and 12 months and the mean number of retreatments during the period from 12 to 23 months were examined and the number was significantly lower in groups with SRD at 6 and 12 months than in the other groups ($P = .004$ and $P < .001$).

3.5. Factors predicting BCVA at 24 months

When SRD rates at 3, 6, and 12 months were examined for associations with changes in logMAR BCVA between baseline and 24 months, the BCVA change in the group with SRD at 6 months (n = 15, +0.15 ± 0.36) was found to be significantly larger than that of the group without SRD (n = 30, −0.07 ± 0.15) ($P = .022$).

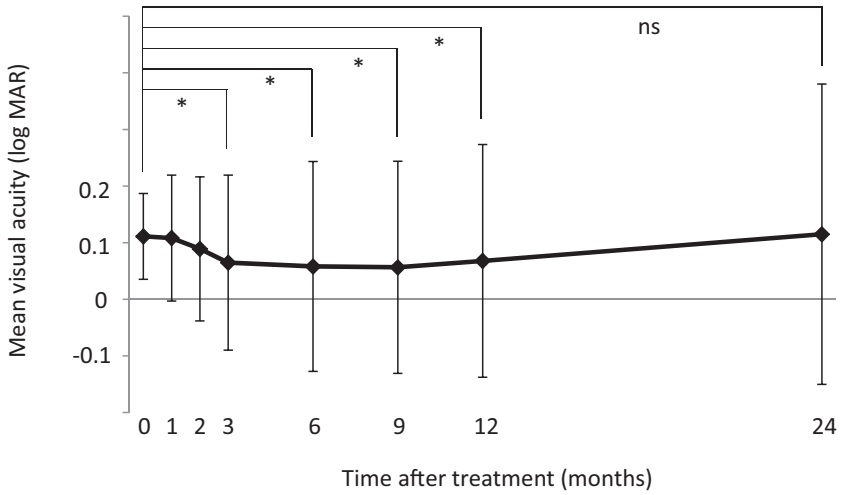

Figure 1. The mean logMAR visual acuity in 45 eyes with PCV treated with IVR injection over a 24-month period. *$P < .05$ versus baseline, Error bars = standard deviation, IVR = intravitreal ranibizumab, logMAR = logarithm of the minimum angle of resolusion, ns = not significant, PCV = polypoidal choroidal vasculopathy.

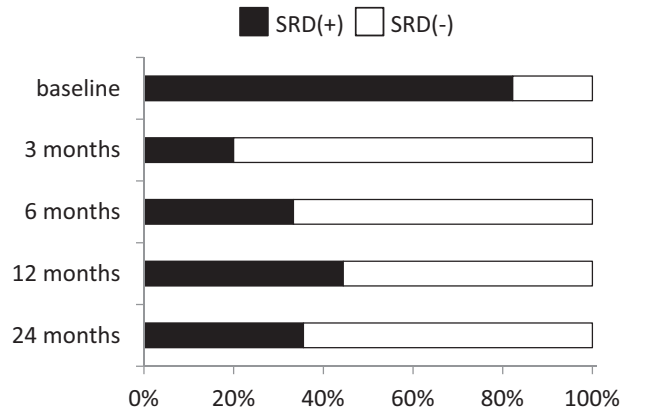

Figure 2. The proportion of PCV with SRD at baseline, 3, 6, 12, and 24 months after starting ranibizumab treatment. Black box shows the proportion of PCV-affected eyes with SRD. White bar shows the proportion of PCV-affected eyes without SRD. PCV = polypoidal choroidal vasculopathy, SRD = serous retinal detachment.

3.6. One factor contributed to tachyphylaxis

Eight eyes (17.8%) met the definition of tachyphylaxis. The presence of RPED was confirmed to be a factor contributing to and associated with tachyphylaxis based on our results of the univariate analysis for associations of baseline parameters with tachyphylaxis (odds ratio: 14.58 [95% CI: 1.61–132.31)].

3.7. One factor contributing to tachyphylaxis was identified in non-responders

Eight eyes (17.8%) showed tachyphylaxis and 2 (4.4%) showed no response. PCV subtype was confirmed to contribute to and be associated with showing either tachyphylaxis or no response to ranibizumab. The odds ratio for eyes showing either tachyphylaxis or no response having polypoidal CNV versus typical PCV was significant, that is, 5.167 (95% CI: 1.004–26.597).

One of the cases is shown in Figure 3.

4. Discussion

Saito et al[9] reported that the natural courses of PCV for patients with good vision are not favorable. Multiple effects of anti-VEGF drugs against AMD in patients with good vision have been reported; BCVA before treatment was improved or maintained 12 months after the start of IVR treatment.[10–12] Regarding PCV in patients with good vision, the past studies have found that BCVA was improved or maintained 12 months after IVR treatment,[9,10] but none of these investigations examined the effects of continued IVR treatment after 12 months. Herein, we confirmed mean BCVA to be significantly improved at 12 months, but not at 24 months, after starting IVR. However, we found that IVR treatment can maintain the BCVA of eyes with PCV but good vision, as 87% of such eyes maintained VA of 20/40 or better at 24 months.

While PCV subtypes (polypoidal CNV / typical PCV), polyp size, polyp clustering, GLD, choroidal vessel hyperpermeability, and RPED are reportedly predictors of the utility of anti-VEGF drugs against PCV,[13–16] no past research has explored morphological changes in macular regions subjected to anti-VEGF drugs as predictors of long-term outcomes. RPED is reportedly associated with vision improvement after IVR treatment for PCV,[14] as well as predicting the development of dry macula.[17] In this study, RPED at baseline was identified as a predictor of the need for IVR retreatment in the second year, in line with the findings of past studies. There are no prior reports, to our knowledge, indicating that baseline SRD predicts the number of anti-VEGF retreatments. We showed the development of SRD during the follow-up period to be a predictor of

Table 2

Univariate analyses of baseline characteristics associated with retreatment between 12 and 23 months.

			Logistic regression analysis			
	Category	n	Odds ratio	Lower limit of 95% CI	Upper limit of 95% CI	*P*-value
Age			0.950	0.876	1.031	.2186
Sex	Male	36	1	–	–	–
	Female	9	1.750	0.401	7.629	.4563
PCV subtype	Typical PCV	37	1	–	–	–
	Polypoidal CNV	8	0.352	0.063	1.975	.2354
LogMAR BCVA			<0.001	<0.001	1.447	.0612
CRT			1.001	0.995	1.006	.8279
Polyp location	Fovea	14	1	–	–	–
	Extra-fovea	31	1.098	0.307	3.921	.8858
Polyp type	Single	19	1	–	–	–
	Multiple	26	0.385	0.114	1.301	.1244
Number of polyps			0.688	0.424	1.117	.1306
BVN			1.000	0.999	1.000	.4168
SRD	<1DD	21	1	–	–	–
	≧1DD	24	0.786	0.241	2.556	.6887
RPED	No	26	1	–	–	–
	Yes	19	0.262	0.073	0.946	.0408
Fibrin	No	26	1	.	–	–
	Yes	19	1.227	0.373	4.034	.7359
Subretinal hemorrhage	No	25	1	–	–	
	Yes	20	1.500	0.458	4.915	.5031

BVCA = best corrected visual acuity, BVN = branching vessel network, CI = confidence interval, CRT = central retinal thickness, DD = disc diameter, PCV = polypoidal choroidal vasculopathy, log MAR = logarithm of the minimal angle of resolution, RPED = retinal pigment epithelial detachment, SRD = serous retinal detachment.

Table 3

Serous retinal detachment characteristics associated with retreatment between 12 and 24 months.

Time	SRD	Retreatment (12–24 months)		*P*-value
		–	+	
Month 3	–	17 (47.2%)	19 (52.8%)	.7095
	+	3 (33.3%)	6 (66.7%)	
Month 6	–	18 (60.0%)	12 (40.0%)	.0040
	+	2 (13.3%)	13 (86.7%)	
Month 12	–	18 (72.0%)	7 (28.0%)	<.0001
	+	2 (10.0%)	18 (90.0%)	

SRD = serous retinal detachment.

retreatment, while the presence of SRD at baseline was not. This raises the possibility of SRD which develops during anti-VEGF drug treatment having an especially marked effect on the stability of PCV lesions. Furthermore, the group free of SRD at 6 months showed better vision improvement than that with SRD, despite receiving fewer retreatments. Nishimura et al,[18] studying eyes with AMD treated with IVR, reported that SRD thickness correlated negatively with the a-wave amplitude on electroretinography. In other words, SRD has an important association with macular functions. Thus, the explanation for eyes without SRD during this study showing greater vision improvement than those with SRD is probably better maintenance of macular functions in the former group.

The predictors of lesion stability identified in this study, that is, baseline RPED and SRD at 6 months, may contribute to the treatment management of PCV in patients with good vision. As anti-VEGF drug treatment is required for a considerable portion of patients even after 12 months, if one or both predictors of lesion stability is present at baseline, patients should be strongly recommended to undergo meticulous monthly examinations or, alternatively, for those unable to make regular clinic visits, to consider a fixed regimen of PDT and anti-VEGF drugs. Also, as

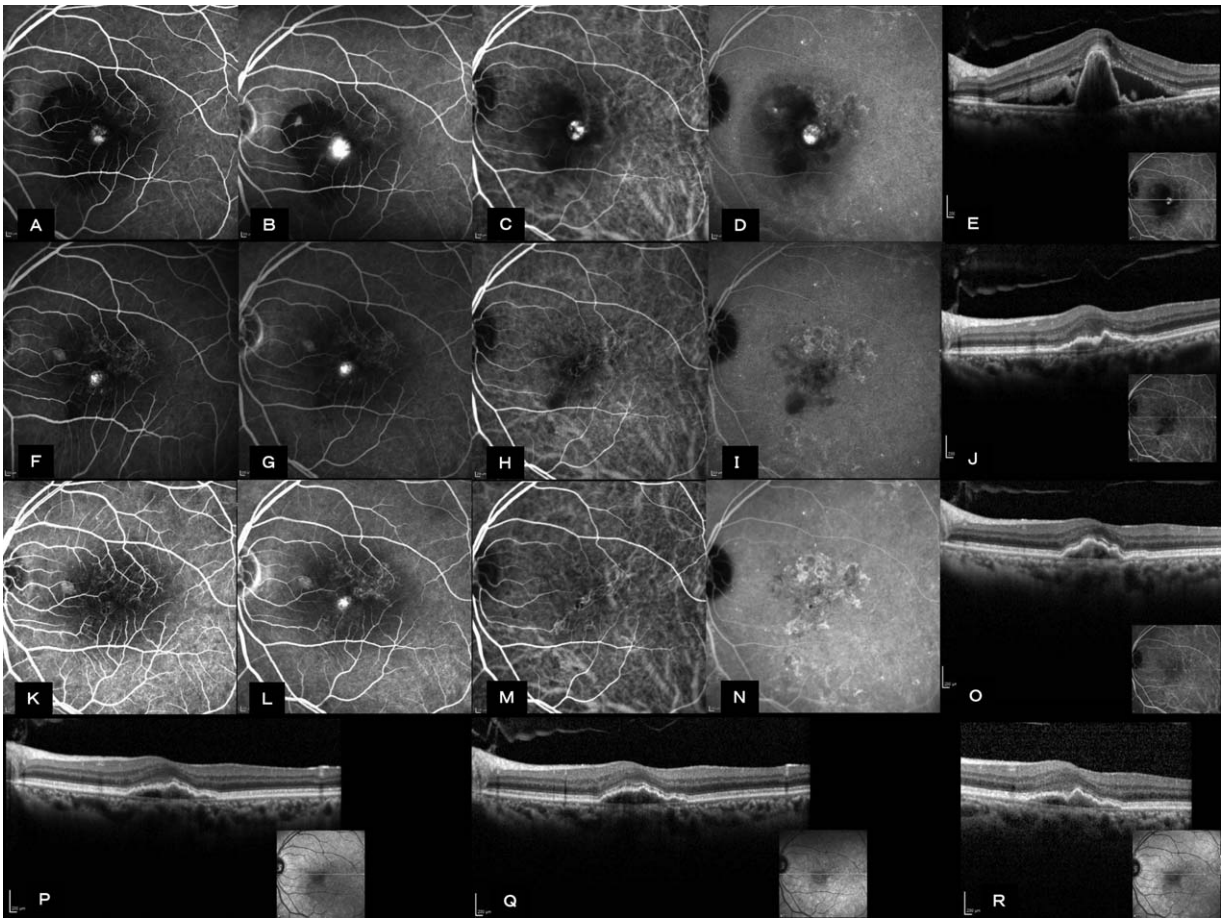

Figure 3. 56-year-old woman. (A–E) VA OS of 0.8, before IVR. (A) FA: early phase. (B) FA: late phase. (C) ICGA: early phase. (D) ICGA: late phase. (E) OCT. FA shows intense leakage corresponding to the polypoidal lesion in the late phase (B). Hyperfluorescence is observed in the early phase (D) of ICGA. This corresponds to the polypoidal lesion. Network vessels are present in the upper temporal area of the polypoidal lesion (E). OCT shows RPED and SRD. Anterior bulging of the highly reflective line indicating the RPE is observed, corresponding to the polypoidal lesion (E). (F–J) Three months later .VA was 0.6 following 3 consecutive monthly IVR injections. (F) FA: early phase. (G) FA: late phase. (H) ICGA: early phase. (I) ICGA: late phase. (J) OCT. FA shows staining following polypoidal lesion disappearance (F, G). ICGA shows no polypoidal lesions (H, I). SRD has disappeared, as shown on OCT (J). (K-O) Twelve months later. Without retreatment after 3 monthly IVR treatments, VA was 0.9. (K) FA: early phase. (L) FA: late phase. (M) ICGA: early phase. (N) ICGA: late phase. (O) OCT. FA shows staining (K, L). ICGA shows network vessels to be more prominent following the disappearance of bleeding, and there are no polypoidal lesions (M, N). A slightly elevated line due to the presence of the polypoidal lesion can still be seen, and SRD has disappeared as shown on OCT (O). (P) Fifteen months later. (Q) Eighteen months later. (R) 24 months later. At each time point, without retreatment after 3 monthly IVR administrations, VA was 1.2. SRD has disappeared as shown on OCT (P-R). FA = Fluorescein angiography, ICGA = indocyanine green angiography, IVR = intravitreal ranibizumab, OCT = optical coherence tomography, RPE = retinal pigment epithelium, RPED = retinal pigment epithelial detachment, SRD = serous retinal detachment.

patients with high visual acuity are likely to receive no treatment in the second year, our findings may provide insights useful for planning additional treatments.

This study has several limitations, most notably the rather small patient number. Due to the retrospective design of this study, not all eyes were treated in accordance with predetermined retreatment criteria. However, 87% of eyes had 20/40 or better vision at 24 months, such that we are confident that treatment remained appropriate even after 12 months. In the future, it is hoped that prospective studies with larger sample sizes will be conducted to confirm our present results.

In conclusion, during 24 months of anti-VEGF therapy using ranibizumab, PCV patients who had good visual acuity at the start of the study maintained BCVA. Comprehensive analyses revealed that RPED at baseline and the development of SRD during follow-up correlated significantly with retreatment between 12 and 23 months. This observation might be applicable to selecting the most appropriate treatments for individual PCV patients.

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Author contributions

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Validation: Mitsuko Yuzawa.
Writing – original draft: Ryusaburo Mori.
Writing – review & editing: Ryusaburo Mori.

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