PROSPECTIVE EVALUATION OF SUBRETINAL VESSEL LOCATION IN POLYPOIDAL CHOROIDAL VASCULOPATHY (PCV) AND RESPONSE OF HEMORRHAGIC AND EXUDATIVE PCV TO HIGH-DOSE ANTIANGIOGENIC THERAPY (AN AMERICAN OPHTHALMOLOGICAL SOCIETY THESIS)

By Gregg T. Kokame, MD, MMM

ABSTRACT

Purpose: The purpose of this study was to determine the following: (1) Is polypoidal choroidal vasculopathy (PCV) a subretinal neovascular process, rather than a choroidal vascular anomaly? and (2) Is a higher dose of ranibizumab (2.0 mg/0.05 mL) more effective in treating PCV than the current dose (0.5 mg/0.05 mL) approved for treatment of age-related macular degeneration?

Methods: Retrospective evaluation of PCV in 104 eyes of 86 patients was accomplished with use of indocyanine green angiography plus optical coherence tomography to localize the branching vascular network and the polyps. Nineteen eyes of 19 patients with active leaking and exudation underwent a prospective open-label trial of monthly high-dose intravitreal ranibizumab (2.0 mg/0.05 mL). The primary outcome was prevention of major vision loss (≤15 ETDRS letters). Secondary outcomes included adverse events, improved vision, and changes in subretinal hemorrhage, subretinal fluid, macular edema, and polypoidal complexes at 6 months.

Results: The PCV vessels were localized beneath the retinal pigment epithelium (RPE) and above Bruch's membrane in 103 (99%) of 104 eyes. In the high-dose ranibizumab trial at 6 months, none of the patients lost ≥15 letters in visual acuity, and 5 (26%) of 19 gained ≥15 letters. Decreases were noted in subretinal fluid in 14 (82%) of 17 eyes, subretinal hemorrhage in 12 (100%) of 12, RPE detachment in 14 (88%) of 16, macular edema in 11 (92%) of 12, and polyps in 15 (79%) of 19 eyes.

Conclusions: PCV vessels are a subtype of subretinal neovascularization located above Bruch's membrane and below RPE. High-dose ranibizumab (2.0 mg/0.05 mL) decreased exudation and hemorrhage and resulted in significant polyp regression, although branching vascular networks persisted.

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INTRODUCTION

Polypoidal choroidal vasculopathy (PCV) is an increasingly recognized cause of exudative and hemorrhagic complications in the macula. Patients with PCV present with subretinal hemorrhage, retinal pigment epithelial detachment (RPED), and subretinal fluid associated with a subretinal network of abnormal branching vessels with characteristic terminal aneurysmal dilations or "polyplike" structures.[1,2] Many of these findings are indistinguishable from subretinal neovascularization associated with age-related macular degeneration (AMD). The diagnosis of PCV is often suspected based on funduscopic findings and optical coherence tomography (OCT). On occasion there are easily visible characteristic reddish-orange, subretinal, polypoidal lesions. However, the only definitive diagnostic test for PCV is indocyanine green (ICG) angiography.[3,4] ICG angiography shows hyperfluorescent polypoidal lesions, or a branching vascular network, or polypoidal lesions at the terminal ends of a branching vascular network, the most characteristic configuration.

First described by Lawrence Yannuzzi at the Macula Society meeting in February 1982 in Miami, Florida,[1] PCV was reported to be a peculiar bleeding disorder with polypoidal, subretinal, vascular lesions and recurrent serous and hemorrhagic detachments of the neurosensory retina and the retinal pigment epithelium (RPE). In the initial report, PCV was found predominantly in white women (10 of 11 patients). According to other early reports, PCV was thought to be rare and to predominantly affect black women.[5] More recently, reports from Asia have shown a remarkably high incidence of PCV in Asian populations. In Japan, studies indicate that up to 54.7% of patients with neovascular AMD have PCV.[6] In addition to the remarkably high Asian incidence of PCV, the disorder is now also being recognized more often in white patients.[7-9]

The presentation of clinical findings in PCV among various ethnic populations is remarkably different. In Asian populations PCV is much more common in males, but in white and black patients it is much more common in females. The earlier reports of PCV were predominantly in white women in the report by Yannuzzi[1] and in black females in the report by Kleiner.[5] Male predominance is evident in series reported from Asia.[10] In addition, polypoidal lesions and complexes are more commonly peripapillary in white and black patients[1,5] but more commonly in the macula in Asian patients.[10] This difference may affect the visual prognosis of leaking and bleeding complications associated with PCV, with a worse prognosis in Asian patients.

The large reddish-orange polypoidal vascular lesions of PCV were initially theorized to be a vascular anomaly of the choroid. Histopathologic evidence is limited, and most of the specimens have come from surgically excised specimens, which does not allow orientation to the usual surrounding structures. In an excised surgical specimen, Okubo and associates[11] noted that the PCV lesion appeared to be a large dilated portion of a normal choroidal venule, although vascular abnormalities extended to the degenerated RPE–Bruch's membrane–choriocapillaris layer. However, histopathologic evaluation of other surgically excised specimens has demonstrated large dilated vascular channels lying usually beneath the RPE and within or above Bruch's membrane.[12-15] In a black female patient with large visible polypoidal vessels who developed hemorrhagic retinal detachment and secondary painful glaucoma, a pathologic evaluation of the enucleated globe was performed. Histopathology showed large, thin-walled cavernous vascular channels

From the Division of Ophthalmology, Department of Surgery, University of Hawaii John A. Burns School of Medicine, Honolulu; Hawaii Macula and Retina Institute, Honolulu, an affiliation of Retina Consultants of Hawaii, Honolulu; and The Retina Center at Pali Momi, an affiliation of Hawaii Pacific Health, Aiea, Hawaii.

within Bruch's membrane.[16] The RPE overlying the abnormal blood vessels was relatively intact, and there was a marked exudative response with fibrin around the vessels. Rosa and colleagues[16] felt that the dilated vascular channels may be an extension of the posterior ciliary arteries. Thus histopathology has shown conflicting findings that fail to determine whether PCV is a choroidal vascular abnormality or a type of subretinal neovascularization.

The purpose of this study was to test two primary hypotheses: (1) PCV is a subretinal neovascular process located above Bruch's membrane, rather than a choroidal vascular anomaly. (2) A higher dose of ranibizumab (2.0 mg) is more effective in eyes with exudative and hemorrhagic complications of PCV than the 0.5-mg dose currently approved for treatment of AMD.

Regarding the first hypothesis, current technology allows the use of high-resolution OCT to localize the vascular lesions of PCV that have been identified with ICG angiography. Since PCV is only reliably imaged by ICG angiography, the ability to utilize OCT to precisely localize structures visualized on ICG angiography can provide important new insights into our understanding of PCV.[3] This technique of OCT evaluation of ICG structures using point-to-point localization was previously evaluated in a series of 18 patients who were predominantly white (16 of 18), with one Asian and one Hispanic patient.[3]

The first purpose of the current study is to evaluate the hypothesis that PCV is a variant of type 1 subretinal neovascularization. Confocal scanning ICG angiography with simultaneous eye-tracked spectral domain OCT was performed in a large consecutive series of eyes diagnosed with PCV, identifying the location of the polypoidal vascular structures visualized on ICG angiography with point-to-point localization. High-resolution OCT can localize the vascular structure to the area above the RPE, the area between the RPE and Bruch's membrane, and the area below Bruch's membrane and within the choroid. If the vascular structures are localized to the area above Bruch's membrane, and not within the choroid, this would support the hypothesis that PCV is a variant of subretinal neovascularization.[4] In the classification system of Gass,[17] type 1 subretinal neovascularization grows underneath and around the RPE, whereas type 2 subretinal neovascularization grows through a break in the RPE and into the subretinal space. PCV has been theorized to be a variant of type 1 subretinal neovascularization below the RPE.[3] However, occasional reports have shown the subretinal vascular lesions of PCV to be actually in the subretinal space and in some cases to have broken through the RPE.[3,18]

Recently, injection of antiangiogenic drugs blocking vascular endothelial growth factor (VEGF) has become the predominant treatment for leaking and bleeding complications in the macula. However, since the funduscopic findings in wet AMD and PCV are often indistinguishable, many eyes with PCV are being treated without being diagnosed as PCV, as ICG angiography is often not performed routinely in clinical practice.[5] This would not be of clinical importance if the two conditions had a similar response to anti-VEGF therapy. However, eyes with PCV have recently been shown to have resistance to antiangiogenic therapy,[19,20] which is the standard of care for exudative AMD. In addition, PCV has been shown to develop in eyes already receiving antiangiogenic drug injections.[20] These findings highlight the importance of making the diagnosis of PCV by ICG angiography.[4]

Treatment of PCV remains controversial. Photodynamic therapy (PDT), the mainstay of treatment in Asia for many years, has been shown to result in anatomic closure of the vascular complex and resolution of serous and hemorrhagic complications. Recently, use of antiangiogenic therapy has resulted in improvement in the exudative and hemorrhagic findings of PCV, but with a low likelihood of regression of the vascular complex anatomically. In the PEARL study,[21,22] involving 1 year of monthly ranibizumab injections similar in design to the MARINA trial or ANCHOR trial for exudative macular degeneration, there was good resolution of leakage and bleeding and a 23% chance of significant visual improvement (visual acuity $\geq$15 letters) in eyes with PCV; this result was not as robust as the 33% seen in the MARINA trial for occult choroidal neovascularization[23] and the 40% seen in the ANCHOR trial for predominantly classic choroidal neovascularization.[24] However, there was significant improvement in vision, which makes antiangiogenic treatment a useful option, although regression of the PCV complex was seen in only 38% of PCV vessels at 1 year.[21] The multicenter, randomized EVEREST study[25] compared the 6-month results of three different treatment groups for PCV: (1) PDT alone; (2) antiangiogenic therapy alone (monthly intravitreal ranibizumab); and (3) combination PDT and intravitreal ranibizumab. Although there was no statistically significant difference in visual results between the three groups, the treatments involving PDT were superior to ranibizumab alone in achieving regression of the polypoidal vascular complex.

Evaluation of the second hypothesis of this current study—use of a higher dose of ranibizumab in eyes with active complications of PCV—is important because of the reported resistance to antiangiogenic drugs in eyes with PCV. This resistance could be due to the possible location of PCV vessels deep to the RPE, shown in some histologic studies, and also to histologic data showing these PCV vessels to be more mature. These factors could account for the lack of anatomic closure of PCV vessels on antiangiogenic therapy, which may be related to an inadequate dose of ranibizumab or other antiangiogenic drugs for PCV. Because of the potential need to cross the RPE to reach the PCV vessels, a higher dose of the drug may be necessary. Another possibility is that the PCV vessels are not as dependent on VEGF, so there would be less response to antiangiogenic therapy alone.

Thus, the purpose of this study was twofold. First, we wanted to assess and localize the position of the subretinal vascular complex in a large consecutive series of eyes diagnosed with PCV by using ICG angiography, and to evaluate the location of these vessels on simultaneous OCT imaging with point-to-point localization of the OCT to the ICG. The location on OCT imaging of the hyperfluorescent vessels on the ICG angiogram can then be evaluated for support of the hypothesis that the PCV complex is above Bruch's membrane and below the RPE, and thus not within the choroid.

Second, we wanted to evaluate the effect of an investigational high dose of ranibizumab (2.0 mg per 0.05 mL) in the treatment of exudative and hemorrhagic complications of PCV to test the hypothesis that a higher ranibizumab dose would be more effective than the usual ranibizumab dose (0.5 mg per 0.05 mL) in the management of hemorrhagic and exudative complications of PCV.

This study evaluated whether a higher dose of ranibizumab may have a more significant effect on the polypoidal complex, which may be located deeper than nonpolypoidal subretinal neovascularization associated with neovascular AMD. This greater effect on the PCV vessels could result in greater decrease in leakage, bleeding, and the PCV complex visualized by the ICG angiogram with

possible visual improvement on treatment. This is the only clinical trial for PCV in the world with access to this investigational high dose of ranibizumab (2.0 mg per 0.05 mL), which is not available commercially.

PATIENTS AND METHODS

Eyes diagnosed with PCV on ICG angiography using the Heidelberg Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany) were retrospectively evaluated using imaging from patients with exudative and hemorrhagic complications of the macula at Retina Consultants of Hawaii. ICG angiography is important in the evaluation and treatment of exudative and hemorrhagic complications in Hawaii, due to the high incidence of PCV in Hawaii. Informed consent for imaging and use of imaging in studies was obtained, but a specific consent form for this retrospective study was deemed not necessary, and this retrospective study was deemed exempt from institutional review board (IRB) approval by the Western Institutional Review Board. This study conformed to the guidelines of the Health Insurance Portability and Accountability Act (HIPAA) and to the guidelines of the Declaration of Helsinki.

The Spectralis HRA+OCT utilizes a dual-laser beam confocal scanning system to simultaneously capture OCT and ICG with point-to-point localization. Analysis allowed ICG angiographic visualization of polypoidal vascular lesions to be correlated with the OCT anatomic findings of these vascular lesions. The polypoidal vascular lesions identified on ICG angiography could be localized anatomically to different positions of depth: (1) above the RPE, (2) below the RPE and above Bruch's membrane, and (3) below Bruch's membrane and within the choroid. Consecutive evaluation of all eyes diagnosed with PCV on ICG angiography was performed by the Hawaii Macula and Retina Institute, and the images were assessed by a single evaluating physician (G.T.K.).

Patients with PCV and active leakage or bleeding were then offered treatment in a prospective clinical trial utilizing an investigational high dose of ranibizumab (2.0 mg per 0.05 mL). An investigational new drug (IND) number had been previously obtained for ranibizumab for PCV in the PEARL trial (ranibizumab, 0.5 mg for PCV).[19,20] This prospective protocol was performed according to a treatment protocol and diagnostic evaluation schedule that was previously approved by the Western IRB (study number 20101755, clinical trials registration number: NCT01248117). IRB approval was obtained for prospective monthly intervention with high-dose ranibizumab (2.0 mg per 0.05 mL) in patients with PCV with active exudation or hemorrhage. Patients signed an informed consent for this prospective therapeutic trial. This study adhered to the guidelines of the Declaration of Helsinki.

The PEARL2 trial (Investigator-Sponsored Trial for Polypoidal Choroidal Vasculopathy with IntravitrEAl Ranibizumab (Lucentis) 2.0 mg) is a prospective, open-label trial of continuous monthly intravitreally administered ranibizumab (2.0 mg) in patients with active hemorrhage, exudation, or recent decrease in vision (defined as a loss of 5 ETDRS letters or 1 Snellen line of vision in the past 6 months) associated with PCV. Major exclusion criteria are (1) a history of previous vitrectomy; (2) previous cataract surgery within 2 months; (3) any other active ocular diseases; (4) any prior PDT in the study eye; (5) treatment with intravitreal steroid, pegaptanib (Macugen), bevacizumab (Avastin), or ranibizumab (Lucentis) within 30 days prior to enrollment; (6) known allergy to any component of the study drug; (7) history of major cardiovascular disease such as myocardial infarction and stroke; (8) poorly controlled hypertension; and (9) major surgery within 28 days prior to enrollment or planned in the next 12 months. Patients diagnosed as having exudative and hemorrhagic complications of PCV at Retina Consultants of Hawaii and the Hawaii Macula and Retina Institute were offered treatment within the PEARL2 trial, and screening was performed to determine eligibility of patients based on the enrollment criteria of the PEARL2 study.

The clinical diagnosis of PCV was suspected based on the funduscopic identification of subretinal reddish-orange spheroidal vascular lesions, subretinal leakage or bleeding, and RPED that was suggestive of PCV. The definitive diagnosis was confirmed by finding the typical features of PCV imaged by ICG angiography, including hyperfluorescent polypoidal lesions with or without a branching vascular network. After detailed explanation and discussion of the potential benefits and risks of this treatment, written informed consent was obtained from all patients. In patients with bilateral PCV, only one eye was chosen as the "study eye." All patients received open-label monthly intravitreal injections of 2.0 mg ranibizumab per 0.05 mL (Genentech Inc, South San Francisco, California) administered once every 30 days (±7 days) for 6 months with an extension study available up to 24 months with a 1.0-mg dose of ranibizumab.

At baseline all patients had a complete ophthalmic examination with ETDRS vision refraction at 4 meters, fluorescein angiography, ICG, and OCT. Intravitreal ranibizumab injections of 2.0 mg/0.05 mL were given monthly from the baseline visit for 6 months with a total of six injections. Ophthalmic examination, visual acuity, and OCT were performed monthly. Fundus photographs, fluorescein angiography, and ICG angiography were done at baseline, at day 14, and at 1, 3, and 6 months.

Primary outcome measures were stabilization of vision (loss $\leq$15 ETDRS letters) and incidence and severity of ocular and systemic adverse events. Secondary outcome measures were changes in visual acuity, subretinal fluid, subretinal/sub-RPE hemorrhage, subretinal exudates, RPED, central foveal thickness, and extent of the polyps and PCV complexes on ICG angiography. A greater than 10% change in central foveal thickness was defined as a significant change for OCT.

RESULTS

Polypoidal choroidal vasculopathy was diagnosed utilizing ICG angiography with the scanning laser ophthalmoscope and point-to-point correlation of the vascular lesions on OCT in 104 eyes of 86 patients (Table 1). Of the 86 patients with PCV, 76% were Asian and 24% were white; 56% were male and 44% female. The median age was 75 years (range - 45 - 93). Location of the PCV vessels was macular in 85%, peripapillary in 9%, and combined macular and peripapillary in 6% of patients.

TABLE 1. CLINICAL CHARACTERISTICS OF POLYPOIDAL CHOROIDAL VASCULOPATHY PATIENTS AT DIAGNOSIS

NO.	GENDER	AGE	ETHNICITY (ASIAN=1, WHITE / OTHER=0)	LATERALITY	POLYP(S) LOCATION	PREVIOUS TREATMENT	BASELINE BCVA	CFT (µm)
1	F	82	1	UNI	Mac	s/p Anti-VEGF s/p PDT w/ Anti-VEGF	20/200	252
2	F	80	1	UNI	Mac	s/p Anti-VEGF	20/25	250
3	M	79	1	UNI	Mac	None	20/70	222
4	F	75	0	UNI	Peri	None	20/80	236
5	F	80	1	UNI	Mac	s/p Anti-VEGF s/p PDT w/ Anti-VEGF	20/60	301
6	M	80	1	BIL	Mac	s/p PDT only (OD) s/p PDT w/ Anti-VEGF (OD) s/p Anti-VEGF (OD) s/p LASER (OD) s/p Anti-VEGF (OS)	20/30 20/200	269 185
7	F	69	1	BIL	Mac	s/p PDT only (OD) s/p Anti-VEGF (OD)	20/25 3’/200	343 296
8	M	69	1	UNI	Mac	s/p Anti-VEGF	20/50	230
9	M	56	1	UNI	Mac	None	20/80	288
10	M	78	1	UNI	Mac	None	20/400	249
11	M	80	0	UNI	Mac	s/p Anti-VEGF	20/40	353
12	F	84	1	UNI	Mac	s/p Anti-VEGF	20/80	186
13	F	87	1	BIL	Mac	s/p PDT w/ Anti-VEGF (OD)	20/40 20/200	215 160
14	F	86	1	BIL	Mac	None	20/200 20/70	390 306
15	F	78	1	BIL	Mac	s/p Anti-VEGF s/p PDT w/ Anti-VEGF	20/100 20/50	182 243
16	F	86	1	UNI	Mac	None	20/200	558

TABLE 1 (Continued)

NO.	GENDER	AGE	ETHNICITY (ASIAN=1, WHITE / OTHER=0)	LATERALITY	POLYP(S) LOCATION	PREVIOUS TREATMENT	BASELINE BCVA	CFT (μm)
17	F	59	1	BIL	Peri Mac	s/p LASER (OD)	20/30 20/40	307 166
18	F	61	1	UNI	Mac	None	20/80	323
19	M	52	0	UNI	Mac	None	20/60	453
20	M	63	0	UNI	Mac	None	3’/200	427
21	M	86	0	UNI	Peri	None	20/40	184
22	M	76	1	UNI	Peri	None	20/20	341
23	M	75	1	UNI	Mac	None	20/32	295
24	M	68	1	BIL	Mac Mac	None	20/63 20/20	301 245
25	F	74	1	UNI	Mac	s/p Anti-VEGF s/p PDT w/ Anti-VEGF	20/50	389
26	M	82	1	BIL??	Mac	None	20/200	303
27	F	62	1	UNI	Mac	None	20/100	379
28	M	82	0	UNI	Mac	None	20/30	334
29	M	69	0	UNI	Mac	None	20/25	391
30	M	86	1	UNI	Mac	s/p Anti-VEGF	20/50	272
31	M	81	1	BIL	Peri Peri	s/p Anti-VEGF (OU)	20/20 20/150	257 428
32	M	84	0	UNI	Mac	s/p PDT s/p PDT w/ Anti-VEGF s/p Anti-VEGF	20/40	244
33	F	67	0	UNI	Mac	None	20/40	300
34	F	75	0	BIL	Mac	None	20/50 20/800	349 593

TABLE 1 (Continued)

NO.	GENDER	AGE	ETHNICITY (ASIAN=1, WHITE / OTHER=0)	LATERALITY	POLYP(S) LOCATION	PREVIOUS TREATMENT	BASELINE BCVA	CFT (μm)
35	F	77	1	BIL	Mac(periph) Mac	s/p LASER (OS) s/p TTT (OS) s/p PDT (OS)	20/30 4'/200	278 612
36	M	81	1	BIL	Mac Mac	s/p Anti-VEGF (OS)	20/40 20/40	320 211
37	M	67	0	UNI	Mac	s/p LASER s/p PDT w/ Anti-VEGF	CF@3	254
38	M	74	0	UNI	Mac	None	20/150	345
39	M	67	0	UNI	Mac	None	20/25	359
40	M	87	1	UNI	Mac	s/p Anti-VEGF	20/40	273
41	M	56	1	UNI	Mac	None	20/30	189
42	M	45	0	UNI	Mac	None	20/30	312
43	M	79	1	UNI	Mac	s/p LASER s/p Anti-VEGF s/p PDT w/ Anti-VEGF	20/200	255
44	F	63	0	UNI	Mac	s/p LASER s/p Anti-VEGF	20/70	235
45	M	82	0	UNI	Mac	s/p Anti-VEGF	20/32	208
46	M	84	1	UNI	Mac	s/p Anti-VEGF	20/40	210
47	F	82	1	UNI	Mac	s/p Anti-VEGF	20/25	235
48	F	85	1	UNI	Mac	s/p LASER s/p Anti-VEGF	20/640	175
49	M	86	1	UNI	Mac	None	4'/200	585
50	M	81	1	UNI	Mac	s/p Anti-VEGF	20/250	365
51	M	81	1	UNI	Mac	None	20/200	406
52	F	76	1	BIL	Mac Mac	None	20/80 3'/200	285 384

TABLE 1 (Continued)

NO.	GENDER	AGE	ETHNICITY (ASIAN=1, WHITE / OTHER=0)	LATERALITY	POLYP(S) LOCATION	PREVIOUS TREATMENT	BASELINE BCVA	CFT (µm)
53	F	75	0	BIL	Mac Mac	s/p Anti-VEGF (OD)	20/50 20/25	307 263
54	M	60	1	UNI	Mac	None	20/25	452
55	M	52	0	UNI	Mac	None	20/30	310
56	F	82	1	UNI	Mac	None	20/80	380
57	F	57	1	UNI	Mac, Peri	None	20/40	259
58	F	68	1	UNI	Mac	s/p PDT s/p PDT w/ Anti-VEGF	20/25	297
59	M	88	1	BIL	Peri Mac	s/p PDT s/p PDT w/ Anti-VEGF (OS)	20/40 20/500	230 101
60	M	84	1	UNI	Mac	s/p PDT w/ Anti-VEGF	3'/200	189
61	F	82	1	UNI	Mac	None	20/40	212
62	M	79	0	UNI	Mac	None	20/20	310
63	F	93	1	UNI	Peri	None	20/50	332
64	F	72	1	UNI	Peri	None	20/30	234
65	M	66	1	BIL	Mac (periph) Mac	None	20/40 20/80	266 174
66	F	85	1	BIL	Mac Mac	None	20/320 20/250	361 459
67	F	93	1	UNI	Mac	None	20/40	329
68	M	57	1	UNI	Mac	s/p ANTI-VEGF	20/50	210
69	M	80	1	UNI	Mac	s/p LASER	20/100	309
70	F	89	1	BIL	Mac Peri	s/p LASER (OD) s/p Anti-VEGF (OS)	20/25 20/40	305 231

TABLE 1 (Continued)

NO.	GENDER	AGE	ETHNICITY (ASIAN=1, WHITE / OTHER=0)	LATERALITY	POLYP(S) LOCATION	PREVIOUS TREATMENT	BASELINE BCVA	CFT (µm)
71	M	63	1	UNI	Mac	s/p Anti-VEGF	20/40	294
72	M	71	1	UNI	Mac	None	20/70	258
73	M	85	1	UNI	Mac(periph)	None	20/50	435
74	F	77	0	UNI	Peri	s/p Anti-VEGF s/p PDT w/ Anti-VEGF	20/400	268
75	M	79	1	UNI	Peri	None	20/40	248
76	M	83	1	UNI	Mac	s/p Anti-VEGF	20/100	288
77	F	82	1	UNI	Mac	None	20/70	228
78	M	86	1	UNI	Mac	None	20/200	287
79	M	69	1	UNI	Mac	s/p Anti-VEGF	20/30	276
80	F	69	1	UNI	Mac	s/p LASER	20/60	215
81	F	76	1	UNI	Mac	None	20/400	294
82	M	75	1	UNI	Mac	None	20/200	344
83	F	75	0	UNI	Mac, Peri	None	20/60	263
84	F	73	1	UNI	Mac	s/p LASER s/p Anti-VEGF	20/400	284
85	M	88	1	UNI	Mac	None	20/30	358
86	F	79	1	UNI	Mac	s/p LASER s/p Anti-VEGF s/p PDT w/ Anti-VEGF	20/70	179

BCVA, best-corrected visual acuity; BIL, bilateral; CF, counting fingers; CFT, central foveal thickness; Mac, macula; OCT, optical coherence tomography; PDT, photodynamic therapy; Peri, peripapillary; Uni, unilateral; VEGF, vascular endothelial growth factor.

The ICG angiogram identified the polyps as hyperfluorescent round or oval lesions, often with a dark halo (Figure 1). There was often a branching vascular network associated with the polyps (Figure 1, top; Figure 2, middle; Figure 3). However, some polyps may be visualized without a significant branching vascular network (Figure 2, bottom; Figure 4). The PCV vessels were located beneath the RPE and above Bruch's membrane in 103 of 104 eyes (99%) (Figures 2 and 3).

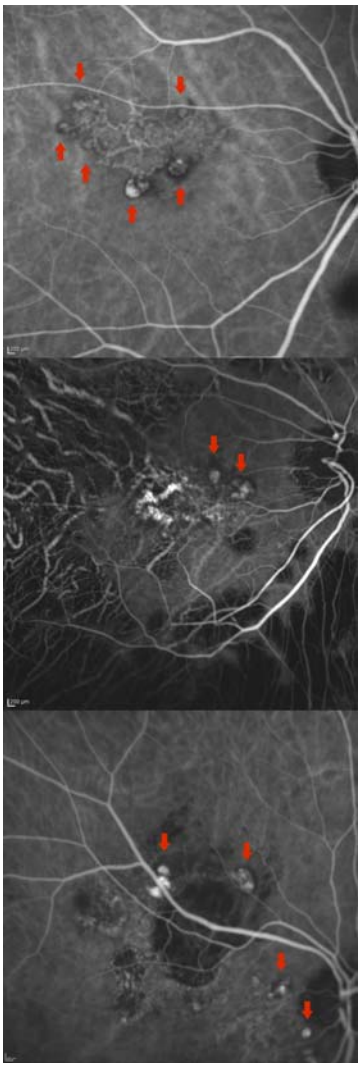

FIGURE 1

ICG angiogram showing hyperfluorescent polyps with surrounding dark halo. Top, Classic presentation of PCV with superior branching vascular network and 2 large central white hyperfluorescent polyps with dark hypofluorescent halo (red arrows) and multiple other polypoidal extensions with dark halos (red arrows). Middle, Two nasal hyperfluorescent polyps with dark halo (red arrows). Bottom, Separate areas of polyps superiorly above a previous laser scar and in the nasal macula. Note the hyperfluorescent polyps with dark halo (red arrows).

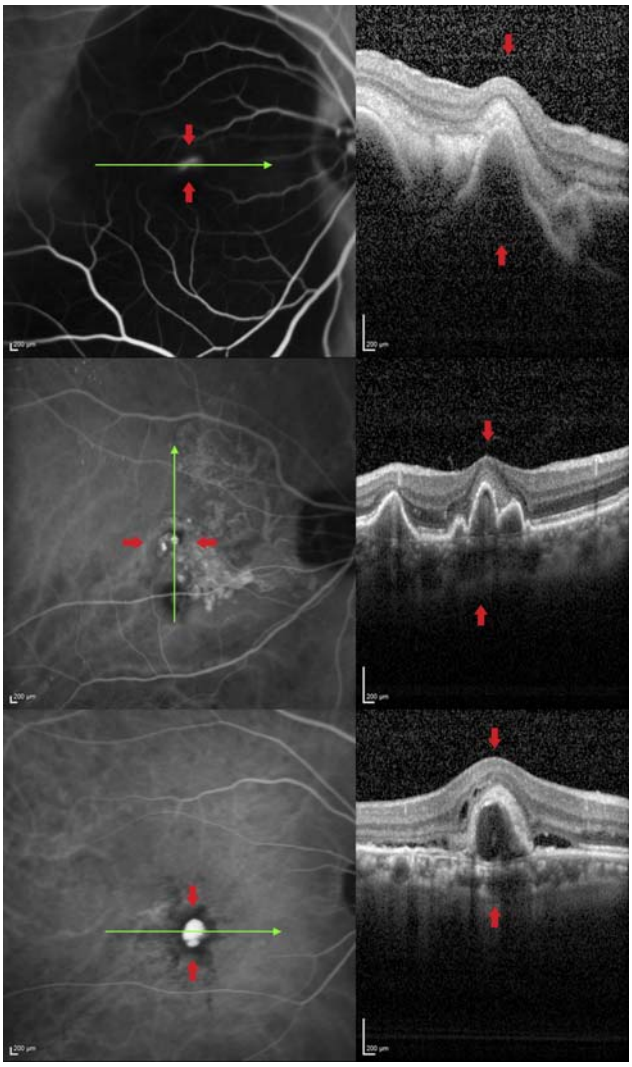

FIGURE 2

Correlated ICG angiogram and eye-tracked OCT of polyps with sharply elevated walls. Top, Dark hypofluorescent RPED with bright hyperfluorescent polyp (red arrows) on the ICG, in which horizontal OCT is performed through the green arrow. The horizontal OCT through the hyperfluorescent polyp corresponds to the inverted U-shaped elevation with steep walls (red arrows) on the OCT. Middle, ICG angiogram showing multiple polyps centrally with a nasal branching vascular network and a small inferior RPED. Note the polyp on the ICG (red arrows) and corresponding sharply elevated inverted U-shaped lesion on the vertical line OCT (red arrows). Bottom, ICG angiogram showing a brightly hyperfluorescent polyp (red arrows) with corresponding horizontal OCT showing sharply elevated inverted U-shaped lesion (red arrows) with cystic macular changes and subretinal fluid just nasal to the polyp.

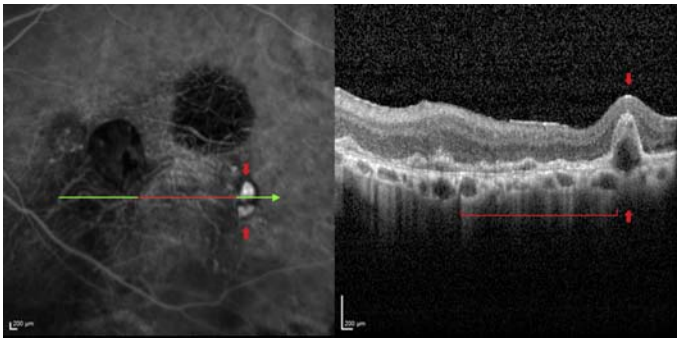

FIGURE 3

Correlated ICG angiogram and eye-tracked OCT of a PCV complex with an inferior branching vascular network (red line) extending to a temporal polyp (red arrowheads) in the left eye (case 35). Note the shallow elevation of the RPE above Bruch's membrane in the area of the branching vascular network ("double line sign," red line) and the inverted U-shaped elevation of the RPE with steep walls in the region of the polyp located above Bruch's membrane and below the RPE (red arrowheads) on OCT. There is also a localized epiretinal membrane on the surface of the retina.

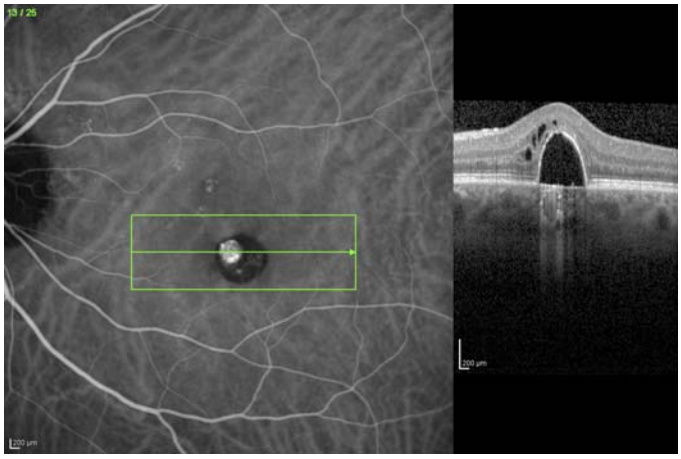

FIGURE 4

Correlated ICG angiogram and eye-tracked OCT of a polyp within a vascularized RPED. ICG angiogram shows a hyperfluorescent white lesion in the nasal aspect of the dark, hypofluorescent RPED. On the horizontal OCT the RPED is a rounded echolucent elevation of the RPE (case 55). Corresponding to the nasal polyp, there is an oval vascular lesion in the choroid below Bruch's membrane. There is cystic change in the retina overlying the RPED and shallow subretinal fluid.

The polyps are seen as oval elevated lesions above Bruch's membrane and under the RPE with steep walls in an inverted U-shape (Figures 2 and 3). There were no cases of polyps visible under the retina and above the RPE, as has been reported in the literature previously.[3,18] In one case, the polypoidal lesion did correlate with a vascular lesion in the choroid, which was oval and demarcated within the inner choroid and beneath Bruch's membrane (Figure 4). The branching vascular network of the polypoidal complex on ICG angiogram was visible as a shallow elevation of the RPE and above Bruch's membrane, which previously has been called the "double line sign" (Figure 3).[26] When there was associated RPED, part of the polypoidal complex localized to the area adjacent to the RPE or within the RPE. Because of the nature of the scanning laser ophthalmoscope, which scans in the plane of the RPE, the RPED appears dark on the ICG angiogram, and the polypoidal complex is often not completely visualized within the RPED. However, once the RPED regresses or resolves after treatment, and follow-up ICG angiography is performed, the polypoidal complex can be better visualized in the area of the resolved RPED (Figures 5 and 6). With associated RPED, the polyps on OCT would often adhere to the undersurface of the RPE hanging down from the RPE ("icicle polyp"), as noted in Figure 6. As the RPED regresses with therapy, the polyp can be visible on OCT in its more characteristic sharply elevated inverted U-shaped configuration (Figure 6).

After evaluating previous treatments, discussion of the PEARL2 study, and reviewing entry criteria, 19 of the 86 patients with PCV met the entry criteria, patient consents were obtained, and patients were screened into the PEARL2 trial. Nineteen eyes of 19 patients (17 Asian and 2 white) entered into the PEARL2 trial, received 6 consecutive monthly high-dose ranibizumab (2.0 mg per 0.05 mL) injections, and were available for the 6-month evaluation. Ranibizumab, 2.0 mg per 0.05 mL, is an investigational dose of ranibizumab that is not commercially available. The commercial dose of ranibizumab known as Lucentis (Genentech) is 0.5 mg per 0.05 mL. This is the only study of PCV in which this investigational dose was made available to evaluate the effect of this high-dose therapy on exudative and hemorrhagic complications of PCV, as well as the PCV complex itself.

There were 6 females and 13 males with a mean age of 77.4 years (range, 57 to 87). None of the patients had significant systemic or ocular adverse events during treatment. The demographic data are summarized in Table 2, and the change in clinical manifestations between baseline and 6 months are summarized in Table 3. Eight eyes were treatment naïve, and 11 eyes had prior anti-VEGF treatment. No eyes had prior PDT. Two eyes had prior focal laser photocoagulation. Six patients had bilateral disease. Typical vascular networks and polypoidal lesions were noted on ICG angiography in all 19 eyes. Macular polyps were found in 17 eyes (89.5%), and peripapillary polyps were found in 2 eyes (10.5%).

Median visual acuity was 20/50 (range, 20/640 to 20/32) at baseline, and this improved to 20/40 (range, 20/400 to 20/20) at 6 months (P=.7656). Mean EDTRS vision was 57.7 letters at baseline and improved significantly to 66.1 letters at 6 months (P=.0117) (Table 4). None of the patients lost ≥15 letters in ETDRS vision at 6 months. Ten eyes (52.6%) improved ≥5 letters, 7 eyes (36.8%) remained unchanged (<5 letters) from baseline, and 2 eyes (10.5%) decreased ≥5 letters at 6 months. Five patients (26.3%) gained ≥15 letters at 12 months. Seven patients (36.8%) gained ≥10 letters, and none of the patients lost ≥10 letters. Statistical analysis for visual acuity, ETDRS vision, and central foveal thickness was performed using the Wilcoxon sign-ranked test utilizing SPSS Program Package 17.0 (SPSS Inc, Chicago, Illinois).

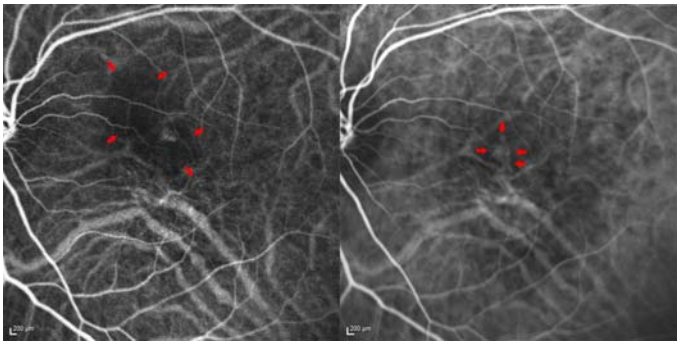

FIGURE 5

Resolution of RPED after treatment with high-dose ranibizumab (2.0 mg/0.05 mL) Left, Pretreatment ICG angiogram of PCV associated with RPED. The RPED appears dark on the ICG angiogram obscuring the normal choroidal vessels (between red arrows) with imaging by the scanning laser ophthalmoscope. Note the polyps and a small part of the branching vascular network are visible as white hyperfluorescent lesions within the RPED (case 56). Right, Post-treatment ICG angiogram of PCV with resolved RPED after treatment in the PEARL2 trial. After resolution of the RPED on antiangiogenic therapy, visibility of the normal choroidal vessels and the branching vascular network (red arrows) is increased. Although the branching vascular network is better visualized, the previously noted polyps have regressed with resolution of the RPED after treatment.

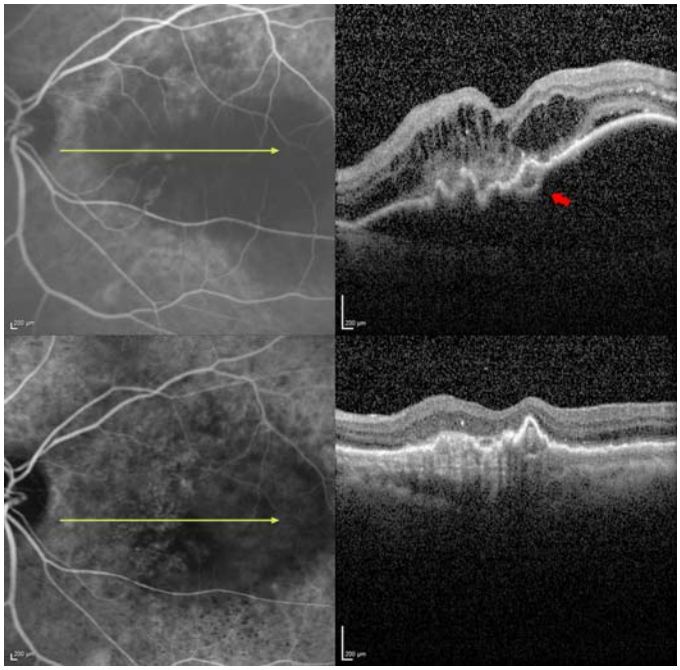

FIGURE 6

Correlated ICG angiogram and eye-tracked OCT of PCV with vascularized RPED. Top, Pretreatment ICG angiogram showing a large dark area associated with RPED and some hyperfluorescent polyps visible in the nasal part of the RPED. The correlated OCT shows elevation of the RPE with overlying intraretinal cystic changes and serous detachment. Note the echogenic lesion on the underside of the RPE corresponding to the polyp attached to the RPE ("icicle polyp") (red arrows). Bottom, Post-treatment ICG angiogram showing decrease in the RPED and decrease in the corresponding hypofluorescent dark spot after treatment in the PEARL2 trial. Note the increased visibility of the entire branching vascular network and the more typical appearance of sharp elevation of the RPE in the region of the polyp. There has been marked resolution of the macular edema.

The initial presenting clinical manifestations included subretinal fluid in 17 of 19 eyes (89.5%), subretinal/sub-RPE hemorrhage in 12 of 19 eyes (63.2%), and RPED in 16 of 19 eyes (84.2%). At 6 months, subretinal hemorrhage resolved in 9 of 12 eyes (75.0%) with initial subretinal hemorrhage and decreased in the remaining 3 eyes (25.0%). Subretinal fluid completely resolved in 14 of 17 eyes (82.4%), resolved but recurred in 1 of 17 eyes (5.9%), and remained stable in 2 of 17 eyes (11.8%). With the use of Heidelberg Spectralis, the ability to track and monitor the changes in patients with RPED is much facilitated. At 6 months, RPEDs resolved in 2 of 16 eyes (12.5%), decreased in 10 of 16 eyes (62.5%), and remained unchanged in 4 of 16 eyes (25.0%).

Significant macular edema at baseline due to PCV was present in 12 of 19 eyes with central foveal thickness >275 µm. In these 12 eyes, macular edema improved at 6 months by -123 µm. The leakage on fluorescein angiography was resolved in 18 of 19 eyes (94.5%) and increased in 1 of 19 eyes (5.3%) due to recurrence of subretinal fluid (patient 1). The polypoidal complexes on ICG angiography decreased in 15 of 19 eyes (78.9%) and remained stable in 4 of 19 eyes (21.1%). The branching vascular network persisted in all eyes but decreased in 3 of 19 eyes (16%). Earlier regression of the polyps was noted, as demonstrated in Figure 7, when there was dramatic resolution of the polyps 2 weeks after the injection of the first dose of high-dose ranibizumab (2.0 mg/0.05 mL). It was determined with the Heidelberg scanning laser ophthalmoscope for ICG angiography and the correlated OCTs, that RPEDs that were large enough could prevent visualization of the branching vascular network and polyps, as the area of the RPED appears dark (Figures 5 and 6). However, once the RPED resolves, then the PCV complex can often be better visualized in the area previously involved by the RPED. This was noted in 12 of 19 cases, in which the RPEDs were visualized as a well-delineated hypofluorescent dark area, which did not allow complete visualization of the polyps or branching vascular network in the RPED on initial evaluation. However, as the RPED resolved, the branching vascular network and occasionally the polyps could be visualized in the area of the previous RPED (Figures 5 and 6).

TABLE 2. CLINICAL CHARACTERISTICS OF PATIENTS IN PEARL2 STUDY (HIGH-DOSE RANIBIZUMAB FOR PCV)

NO.	GENDER	AGE	ETHNICITY (ASIAN=1, WHITE=0)	LATERALITY	STUDY EYE	POLYP(S) LOCATION	PREVIOUS TREATMENT	VISUAL ACUITY		
								Baseline	3 mo	6 mo
1	M	83	1	Unilateral	OD	Mac	R × 13	20/100	20/32	20/40
2	M	63	1	Unilateral	OS	Mac	R × 15, R_1 × 6	20/32	20/32	20/32
3	M	81	1	Unilateral	OD	Mac	B × 3	20/250	20/320	20/320
4	M	75	1	Unilateral	OS	Mac	None	20/32	20/12.5	20/20
5	M	86	1	Unilateral	OS	Mac	R × 23, R_1 × 2	20/50	20/40	20/40
6	F	76	1	Bilateral	OD	Mac	None	20/63	20/50	20/40
7	M	81	1	Bilateral	OS	Mac	R × 3, B × 7, R_1 × 1	20/40	20/40	20/50
8	F	75	0	Unilateral	OD	Mac	B × 5	20/32	20/25	20/20
9	M	87	1	Unilateral	OD	Mac	R × 13	20/40	20/40	20/40
10	M	68	1	Unilateral	OS	Mac	None	20/32	20/40	20/32
11	M	82	0	Unilateral	OS	Mac	B × 18, B/D × 3	20/32	20/20	20/32
12	M	82	1	Bilateral	OS	Mac	None	20/80	20/63	20/40
13	F	59	1	Bilateral	OS	Peri	None	20/32	20/20	20/20
14	F	82	1	Unilateral	OS	Mac	None	20/80	20/40	20/32
15	F	85	1	Unilateral	OD	Mac	ML × 2, B × 5, R × 13, R+D × 2, B+D × 1	20/640	20/500	20/400
16	M	78	1	Bilateral	OD	Mac	None	20/200	20/100	20/63
17	M	57	1	Unilateral	OS	Mac	B × 1	20/250	20/32	20/25
18	M	85	1	Unilateral	OD	Peri	ML × 2	20/40	20/25	20/32
19	F	85	1	Bilateral	OS	Mac	None	20/320	20/320	20/320

B, bevacizumab; D, dexamethasone; Mac, macula; ML, macular laser photocoagulation; Peri, peripapillary; R, ranibizumab; R_1, ranibizumab 1.0 mg.

TABLE 3. CLINICAL CHARACTERISTICS OF BASELINE, MONTH 3, AND MONTH 6 FINDINGS IN PEARL2 STUDY (HIGH-DOSE RANIBIZUMAB FOR PCV)

CASE NO.	INITIAL FUNDUS APPEARANCE				FUNDUS CHANGES AT 3M				FUNDUS CHANGES AT 6M				CFT		LEAKAGE ON FA		POLYP/BVN @ M6	
	SRF	HEM	RPED	EXU	SRF	HEM	RPED	EXU	SRF	HEM	RPED	EXU	BASELINE	6M	3M	6M	POLYP	BVN
1	+	+	+	-	R	↓	↓	-	+r	↓	↓	-	288	219	=	=	=	=
2	+	+	+	+	=	=	=	=	=	R	=	=	284	276	=	=	=	=
3	+	+	+	+	↓	-	↓	=	R	-	↓	=	365	122	↓	R	R	=
4	+	+	+	-	R	R	↓	-	R	R	↓	-	295	252	↓	↓	R	=
5	+	-	+	+	↓	-	↓	=	R	-	=	=	272	198	↓	R	R	=
6	+	+	-	+	R	R	-	=	R	R	-	=	285	189	=	↓	↓	=
7	+	-	+	+	↓	-	=	=	↓	-	=	=	320	222	=	=	=	=
8	+	-	-	-	R	-	-	-	+,R	-	-	-	307	233	↓	↓	R	↓
9	+	-	+	-	R	-	↓	-	R	-	↓	-	273	240	↓	R	=	=
10	+	-	+	-	R	-	=	-	R	-	↓	-	250	219	=	=	=	=
11	+	-	-	-	R	-	-	-	R	-	-	-	249	205	=	=	=	=
12	+	+	+	+	R	R	↓	=	R	R	↓	=	303	168	↓	↓	R	=
13	+	+	+	-	R	R	R	-	R	R	↓	-	307	190	R	=	R	↓
14	+	+	+	-	R	R	↓	-	R	R	↓	-	380	161	↓	↓	R	↓
15	-	-	+	+	-	-	↓	=	-	-	↓	=	175	NA	↓	↓	↓	=
16	+	+	+	+	↓	R	↓	=	R	R	↓	=	249	256	↓	R	↓	=
17	-	+	+	+	-	↓	↓	=	-	=	R, ↓	=	210	211	↓	R	R	=
18	+	+	+	+	R	R	↓	=	R	R	↓	=	485	229	↓	R	R	=
19	+	+	+	+	=	=	↓	=	R	↓	↓	↓	449	261	↓	R	R	=

BVN, branching vascular network; CFT, central foveal thickness (μm); Exu, subretinal exudates; FA, fluorescein angiography; Hem, subretinal/sub-RPE hemorrhage; ICG, indocyanine green angiography; NA, not assessed; R, resolved; +r, recurred; +,R recurred and resolved; RPED, retinal pigmented epithelial detachment;. SRF, subretinal fluid. Symbols: -, absent; +, present; ↑, increased; ↓, decreased; =, stable.

TABLE 4. VISUAL ACUITY FROM BASELINE TO 6 MONTHS AFTER TREATMENT WITH HIGH-DOSE RANIBIZUMAB (2.0 mg/0.05 mL) FOR POLYPOIDAL CHOROIDAL VASCULOPATHY

	ETDRS LETTERS	
	BASELINE	**6 MONTHS**
Mean	57.7	66.1
Standard deviation	20.1	20.3
P value*		.012

*Wilcoxon sign-ranked test was used to compare the ETDRS visual acuity between baseline and 6 months.

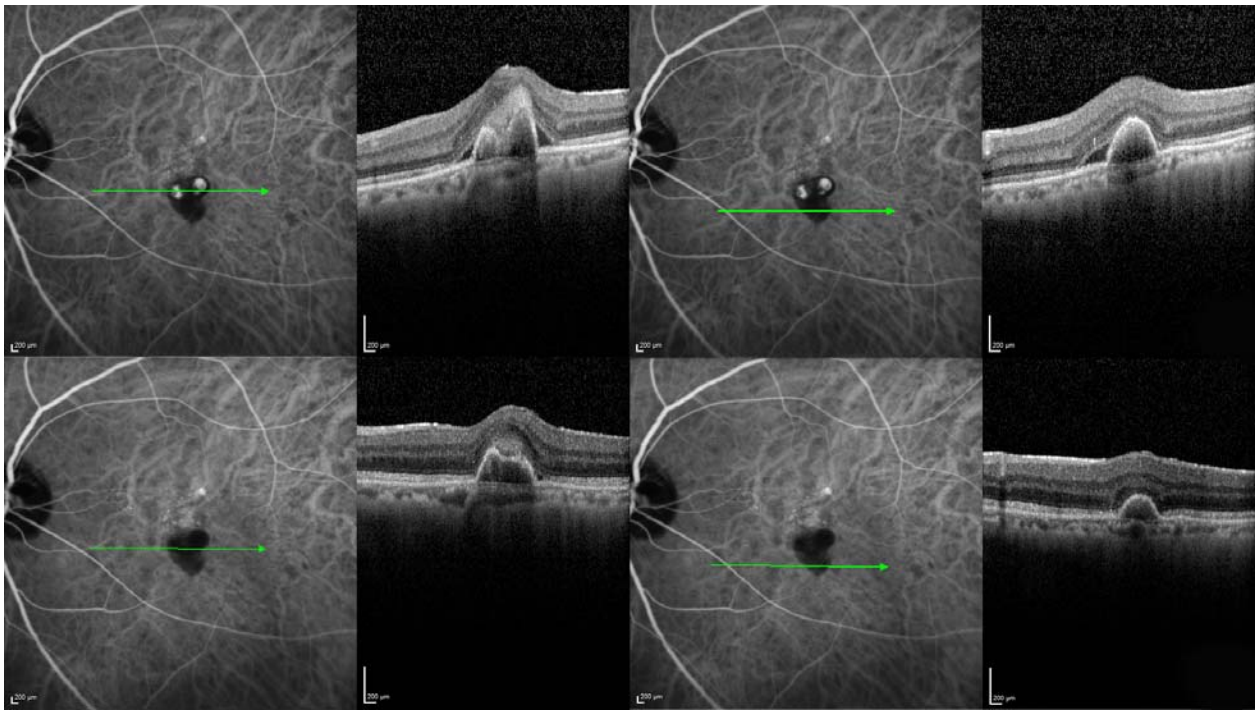

FIGURE 7

Correlated ICG angiogram and eye-tracked OCT showing rapid and complete regression of polyps on ICG angiogram from baseline to 14 days after the first high-dose ranibizumab injection (2.0 mg/0.05 mL). Top left, ICG angiogram showing two polyps with a small RPED inferior to the polyps. OCT shows two sharply elevated inverted U-shaped lesions consistent with the polyps. Top right, Eye-tracked OCT with a horizontal cut through the RPED shows the rounded elevation of the RPED with subretinal fluid nasal to the RPED. Bottom left, Following treatment the ICG angiogram shows nonperfusion of the polyps and the OCT shows decreased height of the polyps and resolved subretinal fluid. Bottom right, Following treatment the ICG-correlated OCT shows decrease in the height of the RPED and resolution of subretinal fluid.

DISCUSSION

Polypoidal choroidal vasculopathy is an increasingly recognized cause of loss of vision related to leaking and bleeding in the macula. The diagnosis can only reliably be made with visualization on ICG angiography of the branching vascular network, the polypoidal lesions or, classically, the polypoidal lesions at the terminal ends of a branching vascular network. Although this was first thought to be a choroidal vascular abnormality, this study confirms that in the great majority of cases, the polypoidal vessels identified on ICG angiography are localized to the region between Bruch's membrane and the RPE. In 103 of the 104 eyes (99%), the polypoidal vascular complex was noted to be above Bruch's membrane and not in the choroid. Even with enhanced-depth imaging OCT utilized in this series, there was only one choroidal vascular abnormality that corresponded to the visible polyp on the ICG angiogram (Figure

4). This could potentially be a choroidal polyp but could also just be a dilated choroidal vessel, as has been noted histopathologically in one PCV case.[16] None of the polypoidal lesions were visible in the subretinal space, as has been previously reported.[3,18]

This study supports the hypothesis that PCV is a type of subretinal neovascularization, rather than a preexisting choroidal vascular abnormality. In the classification system of Gass for subretinal neovascularization,[17] this would be a variant of type 1 subretinal neovascularization, which occurs below the RPE. Freund and colleagues[3] have suggested that PCV is a variant of type 1 subretinal neovascularization, based on a study of 18 eyes with PCV utilizing ICG angiography with simultaneous localization of findings on the OCT. This study of 104 eyes strongly supports that in the great majority of cases, PCV appears to be a variant of type 1 subretinal neovascularization, which lies beneath the RPE and above Bruch's membrane.

Further support that PCV is a type 1 subretinal neovascularization was recently provided by a case that was published from the high-dose ranibizumab PEARL2 trial.[27] This patient initially presented with leakage and serous detachment associated with large orange subretinal polyps and a large PCV complex in the right eye. Since the polyps were extrafoveal, laser treatment was effective at resolving the polyps and exudation with recovery of good and stable vision with 13 years of follow-up. The initial ICG angiogram did not show any evidence of leakage, bleeding, or PCV on ICG angiography in the fellow left eye. Thirteen years later, the patient presented with acute vision loss and hazy vision in the left eye. A serous detachment was associated with a new peripapillary PCV complex on ICG angiogram, which was not present previously. This left eye was treated in the PEARL2 trial with monthly injections of ranibizumab, 2.0 mg/0.05 mL, and showed remarkable resolution of the serous detachment and regression of the polyps and the branching vascular network. Visual acuity recovered to 20/20 vision from 20/40 on initial presentation in the left eye. The documented new development of PCV vessels, and the marked response to antiangiogenic therapy with monthly ranibizumab, 2.0 mg, further support that PCV is a type 1 subretinal neovascularization, rather than a choroidal vascular anomaly.

Since the predominant vascular abnormality is above Bruch's membrane and under the RPE, PCV may not be the best term, since the lesion was not visualized within the choroid, except in possibly one case in this series.[3,26] The findings in this current study showing that the great majority of lesions lie above Bruch's membrane support the theory that PCV is more of a polypoidal neovasculopathy, as described by Freund and associates,[3] rather than a polypoidal vascular lesion in the choroid. Other supportive findings from this study are that the PCV vessels are responsive to antiangiogenic medications, including this investigational high dose of ranibizumab. There was significant decreased leakage and bleeding. In addition, the polyps regressed in size on OCT (Figure 7), and the polyps regressed in 79% of the cases treated with high-dose antiangiogenic therapy with ranibizumab, 2.0 mg per 0.05 mL. This percentage is much higher than in any previously published series for PCV treated with conventional doses of ranibizumab or bevacizumab.

The diagnosis of PCV based on this study may be most accurate when there is careful use of both ICG angiography and corresponding OCT findings in the areas of the vascular abnormality as visualized by ICG angiography. The branching vascular network will appear as a shallow, more diffuse elevation of the RPE, or "double line" sign, as described by Sato and colleagues (Figure 3).[26] The polyps will appear as a sharp elevation of the RPE with an inverted "U" configuration with relatively steep slopes of the elevated RPE (Figures 2 and 3). Point-to-point confirmation of these findings helps to confirm the diagnosis of PCV by visualizing the corresponding elevation of the RPE to the hyperfluorescent lesions noted on ICG angiography. With treatment, the polypoidal lesions can become less visible on ICG angiography, and correspondingly the polypoidal lesions will collapse or become smaller on OCT (Figures 6 and 7). Even when there are not any visible polyps on ICG angiography and on OCT, the branching vascular network in itself can be responsible for significant exudation and subretinal fluid (Figure 8). Since PCV can vary just with natural history, the PCV complex can change over time with resolution of polyps, but usually with persistence of the branching vascular network. The polyps can resolve or change especially after PDT, and less commonly with antiangiogenic therapy alone, so the appearance of PCV on diagnostic testing can change over time, especially with therapy.

Although there has been speculation that PCV is most often associated with chronic choroidal neovascularization,[3] this was not the predominant finding in the majority of these cases. Most cases occurred in the macular region and were relatively localized. In some cases, PCV developed with sudden symptoms, as in the previously discussed case of new PCV in a fellow eye.[27] These findings also support that PCV is a variant of subretinal neovascularization, which can develop suddenly and with new symptoms, and is not associated frequently with chronic subretinal neovascularization or with a preexisting choroidal vascular abnormality.

This series of patients with PCV was predominantly Asian (65 of 86 patients [76%]). As ethnicity has a marked effect on both prevalence and clinical presentation of PCV, this series may be more indicative of the PCV that is seen in Asian populations. The large percentage of eyes with macular PCV, as opposed to peripapillary PCV, is characteristic of PCV in Asian populations.[10] The high percentage of male patients is also characteristic of Asian PCV series.[10] While PCV series with white and black patients have shown a predominance of peripapillary PCV, Asian PCV series have shown a predominance of macular PCV. While white and black PCV series have shown a female predominance,[1,2,5] Asian PCV series have shown a significant male predominance. The etiology of this marked difference in clinical presentation of PCV in different ethnicities is unknown but remains a consistent clinical observation.

Eyes with PCV do not respond as significantly as eyes with exudative AMD without PCV to antiangiogenic drugs, which is the current standard of care for exudative and hemorrhagic complications of subretinal neovascularization in the macula, usually associated with exudative macular degeneration. Although there is usually a significant response with decreased leakage and bleeding, the visual results have not been as robust as that seen in the exudative AMD studies. One-year visual results in prospective studies were 40% vision improvement of ≥15 letters in the ANCHOR trial with predominantly classic subretinal neovascularization,[23] and 33% vision improvement of ≥15 letters in the MARINA trial with occult choroidal subretinal neovascularization.[24]

In the PEARL trial of prospective monthly ranibizumab therapy for PCV at one year, there was 23% vision improvement of ≥15 letters, associated with a significant decrease in leaking and bleeding.[21] Although these results are significant, they are not as robust as what is seen in the macular degeneration trials.

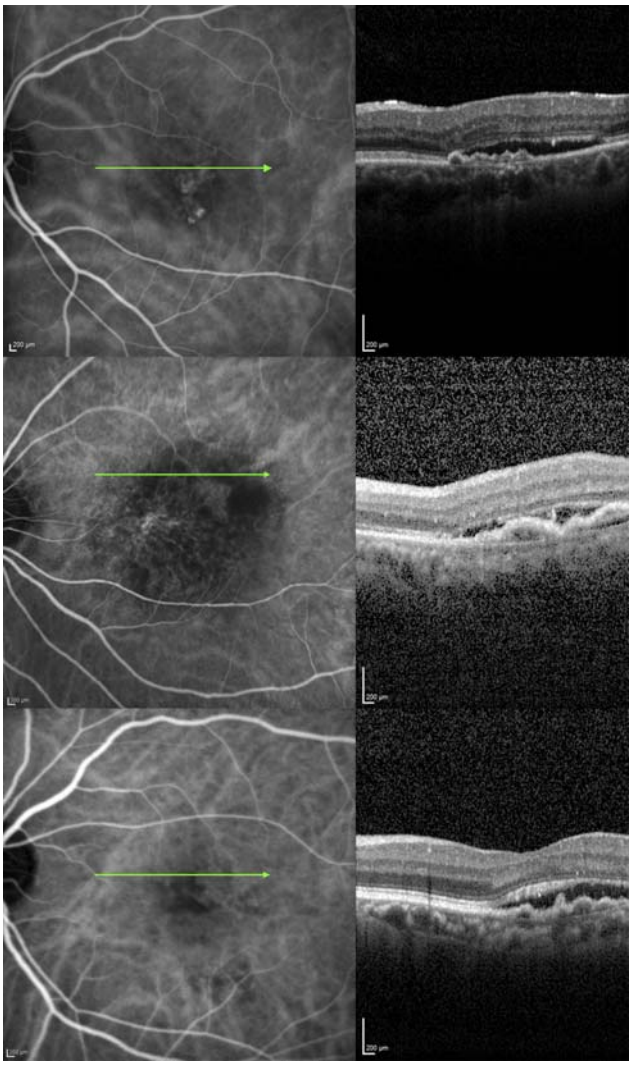

FIGURE 8

Correlated ICG angiogram and eye-tracked OCT showing serous detachment overlying the branching vascular network. Top, ICG angiogram shows the branching vascular network with horizontal OCT localized through the region of the branching vascular network. Note the subretinal fluid overlying the branching vascular network with the "double line sign" (shallow elevation of the RPE above Bruch's membrane). Middle, ICG angiogram showing branching vascular network with shallow elevation of RPE above Bruch's membrane. On the OCT note the subretinal fluid above the branching vascular network. Bottom, ICG angiogram showing a residual branching vascular network without visible polyps. Note that there is significant subretinal fluid over the branching vascular network with shallow elevation of the RPE.

Anatomic changes in the vascular complex of PCV in response to therapy have been disappointing utilizing antiangiogenic therapy alone. Regression of the PCV complexes is uncommon in previous reports utilizing ranibizumab or bevacizumab for PCV. In the PEARL trial at 1 year, there was a 38% regression rate in the polyps, but the branching vascular network persisted in all cases.[21] In the EVEREST trial at 6 months, the ranibizumab group had a 28.6% chance of polyp closure,[25] whereas the PEARL trial at 6 months had a 33% polyp closure rate.[22] This low rate of anatomical PCV closure contrasts with the results of PDT. Photodynamic therapy has been the preferred treatment for PCV in Asia and is the leading recommendation based on an analysis of all recently published studies utilizing a PCV expert panel and literature review.[28] One of the main studies in support of this conclusion is the EVEREST multicenter randomized trial,[25] which was shown to have a significantly higher rate of closure of the vascular complex than ranibizumab therapy alone for PCV. In the combination PDT and ranibizumab study group, there was a 77.8% chance of polyp closure, and in the PDT alone study group there was a 71.4% chance of polyp closure. This significantly higher polyp closure rate at 6 months did not correlate with visual results, which were not statistically significantly different between the ranibizumab alone, PDT and ranibizumab, or PDT alone groups. Although not statistically significant, the visual results at 6 months did trend higher in the ranibizumab alone group with 33.3% ≥15 letters, compared to 21% ≥15 letters for combination PDT and ranibizumab, and 19% ≥15 letters for PDT alone. This indicates that visual results do not necessarily follow the anatomic response of the PCV complex to treatment. The natural history of PCV is variable with a 50% chance of progressive vision loss and a 50% chance of stable vision.[29] This supports that the presence of PCV vessels alone without active leakage or bleeding can be associated with good visual results and that anatomic regression may not be essential to better vision recovery.

Antiangiogenic therapy is an important therapeutic option for exudative and hemorrhagic complications of PCV. There is good evidence of the efficacy of antiangiogenic therapy for exudative and hemorrhagic complications of PCV.[30-35] However, the treatment results are not as robust as seen with bevacizumab and ranibizumab for typical choroidal neovascularization in exudative AMD. In addition, antiangiogenic resistance has been noted in eyes harboring PCV and masquerading as typical exudative AMD,[18,19] and

decreased response to bevacizumab and ranibizumab can develop over time in eyes receiving ongoing intravitreal injections for PCV. Although exudation and hemorrhage associated with PCV improve on treatment, the anatomic regression of polyps and the PCV complex is significantly less with antiangiogenic therapy compared with PDT or PDT with antiangiogenic therapy.[21,22,25] However, the importance of anatomic regression of the PCV complex for vision is still uncertain.

Bevacizumab has been shown in retrospective studies to decrease the leakage and bleeding from PCV complexes.[31-33] However, in the initial study by Gomi and colleagues,[31] the PCV complex persisted in 10 of 11 eyes with intermittent treatment. Although there currently is not any randomized trial or level 1 evidence or any prospective trials on the effectiveness of bevacizumab for PCV, current studies and clinical experience have shown decreased exudation and macular edema with intravitreal bevacizumab. In eyes previously treated with PDT, bevacizumab improved or stabilized vision in 80% of eyes at 24 months with a re-treatment as needed based on OCT findings of persistent or recurrent subretinal fluid and associated vision loss.[34] However, PCV complexes persisted in all 45 eyes, and branching vascular networks actually increased in size in 44% of eyes while receiving therapy. Subretinal fluid and leakage often can develop just associated with the branching vascular networks and not associated with any visible polyps (Figure 8). The effectiveness of bevacizumab decreased during the second year of therapy, indicating a tachyphylaxis effect or increased resistance to bevacizumab, possibly as the subretinal vessels mature.[34]

Ranibizumab has been shown to be effective at decreasing the hemorrhagic and exudative complications of PCV in prospective and retrospective studies. In both the prospective EVEREST trial and the prospective PEARL trial, vision was stabilized and leaking and bleeding complications significantly improved. In the EVEREST trial there was a 33% chance of 3-line improvement,[25] and in the PEARL trial of continuous monthly therapy for PCV, there was a 17% chance of 3-line improvement at 6 months[22] and a 23% chance of 3-line improvement at 1 year.[21] The optimal treatment protocol and regimen with ranibizumab for PCV has still not been determined, but treat and extend and as-needed treatments are commonly used clinically. In addition, anti-VEGF resistance to ranibizumab has been noted in some PCV eyes, which subsequently only responded to combination PDT and intravitreal antiangiogenic injections.[20] As with bevacizumab, there is persistent branching vascular network in all eyes and polyp regression in only 28.6% of eyes in the EVEREST trial at 6 months[25] and in 33% of eyes in the PEARL trial at 1 year.[21] Cho and colleagues[35] retrospectively compared the 6-month results of 52 eyes with PCV treated with ranibizumab and 58 eyes treated with bevacizumab. There was no difference in number of injections, improvement in vision, or decrease in the mean central foveal thickness between bevacizumab and ranibizumab in the treatment of PCV. However, there were a greater number of patients who showed a ≥10% reduction in the central foveal thickness in the ranibizumab group than in the bevacizumab group. As noted previously in other studies, polypoidal complexes decreased in only 20.7% in the bevacizumab group and 25.0% in the ranibizumab group.[36]

Since the PCV vessels are a type 1 subretinal neovascular process lying deep to the RPE, but overlying Bruch's membrane, this anatomic location may possibly require a higher dose of medication to penetrate deeper to the PCV vessels or to overcome relative resistance of these more mature vessels to ranibizumab or other drugs. Because of this, high-dose ranibizumab, 2.0 mg per 0.05 mL, was utilized in the PEARL2 trial, and all eyes in the trial completed at least 6 months of therapy with monthly injections of this high ranibizumab dose. The preliminary PEARL2 results were initially reported at the Macula Society in Jerusalem in 2012, and the complete 6-month results were reported at the Retina Society in Beverly Hills in September 2013. The higher dose did not result in better vision results or more significant resolution of edema or subretinal fluid than the standard 0.5-mg dose of ranibizumab. However, there was a trend noted for higher polyp closure rate (79%) and quicker resolution of polyps on the higher 2.0-mg dose of ranibizumab, than the usual 0.5-mg dose of ranibizumab (28.6% polyp closure rate in PEARL trial at 6 months).[22]

Photodynamic therapy has been the mainstay of treatment for PCV in Asia. Although visual results were similar to ranibizumab therapy, the regression of the PCV was found to be much more in the PDT arms of the EVEREST trial, than in the trial with monthly ranibizumab only.[25] In addition, based on level 1 evidence, a recent advisory group recommended PDT as the first-line treatment for PCV. PDT is often combined with antiangiogenic therapy to allow vascular closure of the PCV complex and to minimize the up-regulation of VEGF after PDT.[28]

Recently, a prospective, multicenter, randomized trial of ranibizumab vs full-fluence PDT (LAPTOP trial)[30] showed for the first time that 0.5 mg of ranibizumab had superior visual results to PDT for treatment-naïve PCV. Treatment was performed in the PDT group with an initial full-fluence PDT (600 mW/cm^2) using a spot size based on the ICG angiogram delineating the polypoidal complex with an additional 1000-µm margin beyond the greatest linear dimension. Patients were then assessed every 6 weeks with a minimum interval between PDT treatments of every 3 months, and re-treatment was based on the Japanese AMD trial, which included persistent fluorescein leakage. The ranibizumab group received 3 monthly initial injections, followed by re-treatment criteria based on the PrONTO study. This re-treatment criteria included >100-µm increase in central foveal thickness, new hemorrhage, persistent fluid on OCT, decrease in vision of 0.1 log unit in the presence of fluid at the macula, active leakage on the fluorescein angiogram, and new-onset classic choroidal neovascularization. There were 47 patients in the PDT arm and 46 patients in the ranibizumab arm. This study did not look closely at the ICG characteristics of the ranibizumab group, as long as the patients were clinically doing well without significant changes. The number of treatments with ranibizumab averaged 4.5 times over 12 months. The number of PDT treatments averaged 1.8 times over 12 months. Central foveal thickness improved in both groups. However, the visual results in the ranibizumab group were 30.4% gaining 0.2 log units, 60.9% remaining stable (change ≤ 0.2 log units), and 10.9% worsening ≥ 0.2 log units. In contrast, the visual results of the PDT group were 17.0% gaining 0.2 log units, 55.3% remaining stable (change ≤ 0.2 log units), and 27.7% worsening ≥ 0.2 log units. The ranibizumab treatment arm achieved significantly better visual results than the PDT treatment arm at 1 year. This is the first comparative study showing a visual benefit of ranibizumab therapy over PDT. However, these results are not confirmed by the EVEREST trial,[25] which did not show a difference visually between the ranibizumab group and the PDT groups.

Although comparison of treatment results between trials is difficult owing to different baseline characteristics, sample size, and treatment protocols, it is useful to compare the visual results of the prospective clinical trials using ranibizumab for 12 months. The EVEREST trial was limited to 6-month results, so the only prospective ranibizumab trials with 12-month data include the PEARL study[21] and the LAPTOP trial.[30] The entrance visual acuity requirements were similar in the PEARL and LAPTOP trials, as the PEARL trial excluded patients with best-corrected visual acuity better than 20/32, and the LAPTOP study excluded patients with visual acuity better than 0.6 or about 20/32. For the LAPTOP study, patients had a 30.4% chance of improvement of ≥10 letters or 0.2 log units with an average of 4.5 treatments over 12 months,[30] as compared to the PEARL study with monthly or 12 treatments over 12 months, in which patients had a 53.8% chance (7 of 13 eyes) of improvement of ≥10 letters or 0.2 log units.[21] The LAPTOP study patients also had a 10.9% chance of worsening of ≥10 letters, compared to a 0% chance in the PEARL study. In the LAPTOP study, the discussion noted that although re-treatment was allowed with a 1-line loss of vision, less than 100 μm of central retinal thickness increase, and persistent extramacular fluid, the results do indicate that there may have been a delay in re-treatment indicating possible undertreatment in the ranibizumab group. The LAPTOP ranibizumab group had an average of 4.5 injections over 12 months, including the first three mandatory injections, which would equate to only 1.5 injections on average being given during the final 9 months of the study during re-treatment evaluations. The PEARL trial had 12 monthly injections with possibly superior visual results to the LAPTOP study, so the optimal therapy for vision is still undetermined, but may fall in between the LAPTOP study protocol and the monthly mandatory treatment protocol regimen. However, even with this possible undertreatment in the LAPTOP study, there was a statistically significant result favoring better visual acuity in the ranibizumab group over the PDT group. The ICG angiogram was not followed in the ranibizumab group, so anatomic results of polyp closure were not obtained in this study. However, as long as exudation and hemorrhage are controlled, this study emphasizes that visual acuity results can still be significant, even when the polyp closure rate is unknown.

Histopathologic studies of PCV have shown evidence of more mature subretinal vessels, which are often hyalinized, and surrounded by significant fibrin. The more mature vessels may cause them to be less responsive to antiangiogenic medications. In addition, since the abnormal blood vessels lie deep to a relatively intact layer of RPE, this could affect the ability of drugs to penetrate down to the level of the polypoidal vascular complex. Because of the decreased anatomic closure rate of PCV with antiangiogenic drugs, compared to therapies including PDT, and because of the less robust visual recovery response of PCV eyes to antiangiogenic therapy, such as ranibizumab, compared to exudative macular degeneration, a higher dose of ranibizumab (2.0 mg per 0.05 mL) was investigated to see if there was an improved visual recovery rate, as well as an improved anatomic regression of the PCV complex. Prospective trials with the conventional dose of ranibizumab (0.5 mg per 0.05 mL) at 1 year were previously published for the PEARL trial.[21]

The strength of this therapeutic trial of high-dose ranibizumab (2.0 mg per 0.05 mL) is the prospective design, the use of ETDRS charts, and the use of the most sensitive method of diagnosing PCV with ICG angiography utilizing the scanning laser ophthalmoscope. There are many weaknesses to this trial, including the lack of a randomized control group, the use of data from only a single center, and the relatively small number of cases compared to much larger numbers that can be obtained in a multicenter prospective study or a larger and longer retrospective study. Although only one reviewer of ICG angiograms was utilized, training from the EVEREST trial ICG reading center in Singapore was obtained prior to initiating this study. In addition, this study was designed to evaluate the effect of monthly therapy, similar to the initial MARINA and ANCHOR studies for exudative AMD, so it is not possible to evaluate the effectiveness of a less frequent or intermittent treatment schedule based on this study.

While the lower conventional dose of ranibizumab (0.5 mg per 0.05 mL) has a robust effect in exudative AMD, the PCV results have not been as robust. Theoretically, the use of a higher dose of ranibizumab has the potential to penetrate to a deeper level in the subretinal space through a predominantly intact RPE, where the PCV vessels are located, as confirmed in this study. In addition, this higher dose may help to overcome a relative anti-VEGF resistance, which has been previously reported in PCV.[17,18] This is the only study with access to this investigational high dose of ranibizumab (2.0 mg per 0.05 mL) for the treatment of PCV. Although visual results were not significantly different than the previously performed PEARL study at 6 months with the standard dose of ranibizumab (0.5 mg per 0.05 mL), the anatomic results show a significant trend toward greater polyp closure, which supports a more significant effect of the higher dose of ranibizumab. At 6 months 79% of the cases showed polyp closure in the PEARL2 study, whereas at 6 months with the commercial dose of ranibizumab only 28.6% of the PEARL study cases showed polyp closure. Early polyp closure was also seen more frequently in the PEARL2 trial (Figure 7) than in the PEARL study. Although it is difficult to compare different clinical trials, the prospective EVEREST study group with PCV showed the polyp closure rate at 6 months to be 28.6%,[25] whereas the PEARL2 study, with a higher dose of ranibizumab, showed a polyp closure rate at 6 months of 79%. In the 6 month trial from Korea comparing bevacizumab and ranibizumab,[35] polypoidal complexes decreased in only 20.7% in the bevacizumab group and 25.0% in the ranibizumab group. Although it is not possible to statistically compare these studies, there is a trend toward a higher polyp closure rate (79% in PEARL2) with the higher dose of ranibizumab, which supports further research into higher doses of current drugs, or new agents that penetrate deeper and through the RPE to the level of the PCV vessels.

Any classification system for PCV should provide guidance with the therapeutic options currently available for PCV. The main factors affecting treatment choice for PCV include the symptom level of the patient, the visual acuity, and the clinical findings noted on diagnostic studies, such as the associated degree of exudation, hemorrhage, or RPED. For the majority of cases, the main treatment decision currently is whether to begin with antiangiogenic therapy or with PDT. However, the first level of the classification would be whether the patient is symptomatic or asymptomatic. If the patient is asymptomatic and without vision loss, and because the natural history is variable with good visual acuity possible with observation,[28] then observation could be considered, as long as central fixation is not threatened by hemorrhage or exudation. If the patient is symptomatic, then treatment should be considered. The level of visual

acuity is the next factor determining the decision on therapy. If visual acuity is 20/50 or better, or relatively good, then antiangiogenic therapy with an intravitreal injection becomes more likely, due to the significant ability to decrease leaking and hemorrhage. Photodynamic therapy can uncommonly cause sudden vision loss in 2% of cases.[36] The etiology of the sudden and dramatic vision loss can be related to acute subretinal hemorrhage,[36] choroidal ischemia,[37,38] and profuse subretinal fibrinous exudation.[38,39] Because of this risk, PDT would more likely be avoided in eyes with relatively good visual acuity. Utilizing antiangiogenic therapy thus minimizes the rare but significant potential complications of PDT, which can result in sudden vision loss, and would be more devastating in eyes with good visual acuity. If visual acuity is 20/60 or worse, then PDT with or without antiangiogenic therapy or steroids becomes more likely, as there is significant support for this treatment both anatomically and visually in previous studies. This treatment also minimizes the need for frequent re-treatments, as PDT treatments are usually performed every 3 months. However, when there is persistent leakage or subretinal fluid, despite resolution of polyps after PDT, then continued antiangiogenic therapy may be necessary,[34] in between the potential PDT every 3 months. The branching vascular network in itself, even without polyps, can be a significant cause of exudation and leakage (Figure 8).

In summary, PCV appears to be a polypoidal neovasculopathy with the vascular components of the PCV complex located between Bruch's membrane and the RPE, rather than in the choroid, in the great majority of cases. Since PCV is most likely a subtype of subretinal neovascularization, it does respond to antiangiogenic therapy. However, due to the location of the blood vessels beneath the RPE, and to the relative resistance to antiangiogenic therapy reported and observed in PCV eyes, the treatment response is not as robust for PCV as what is seen in AMD. Utilizing a higher investigational dose of 2.0 mg ranibizumab for monthly injection for PCV showed no difference in visual results, reduction in macular edema, or reduction in subretinal hemorrhage than the standard dose of 0.5 mg ranibizumab. The anatomic ICG results did show a trend toward greater polyp closure with the 2.0-mg dose than what was previously seen with the 0.5-mg ranibizumab dose. However, it is still undetermined if polyp closure or decrease in the branching vascular network significantly affects the visual outcome in PCV eyes in the long term. However, the significantly greater polyp closure rate does support potential future research into higher doses of existing medications, or the development of new medications that penetrate deeper below the RPE, for more effective and long-term results in PCV complications.

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