Continuous anti-VEGF treatment with ranibizumab for polypoidal choroidal vasculopathy: 6-month results

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ABSTRACT

Aim To evaluate the short-term efficacy and safety of monthly intravitreal injections of ranibizumab in patients with polypoidal choroidal vasculopathy (PCV) and active exudation or haemorrhage.

Methods A prospective, open-label trial of monthly intravitreal ranibizumab (0.5 mg) injections for PCV in 12 eyes of 12 patients was performed. The primary outcome measures were stabilisation of vision (loss <15 ETDRS letters). Secondary outcome measures included incidence of ocular and systemic adverse events, and changes in subretinal haemorrhage, central foveal thickness (CFT) and polypoidal complexes on indocyanine green angiography at 6 months.

Results Baseline findings included eight eyes with subretinal fluid, six eyes with subretinal haemorrhage and five eyes with macular oedema (CFT >275 μm). No patient lost ≥15 letters in visual acuity at 6 months. Subretinal fluid decreased in 5/8 eyes (63%). Subretinal haemorrhage resolved in 6/6 eyes (100%). Macular oedema improved in 4/5 eyes (80%). Polypoidal complexes decreased in 4/12 (33%) eyes. There were no ocular or systemic adverse events.

Conclusions Continuous monthly intravitreal ranibizumab is safe and well tolerated in eyes with PCV. Preliminary results show stabilisation of vision, resolution of subretinal haemorrhage and a decrease in macular oedema. Polypoidal lesions decreased in 4/12 (33%) eyes, but branching choroidal vessels persisted.

INTRODUCTION

Polypoidal choroidal vasculopathy (PCV) is characterised by a branching choroidal vascular network with polypoidal-shaped choroidal vascular lesions that result in subretinal leakage, subretinal haemorrhage, macular oedema and retinal pigment epithelial detachment (RPED).[1–6] Uyama *et al* prospectively followed the natural history of 14 eyes of 12 consecutive patients with PCV for at least 2 years.[7] Half of the patients had repeated bleeding and leakage, resulting in macular scarring and progressive visual loss. Sho *et al* also reported that the severe vision loss (0.2 or worse) was noted in 34.5% (38 of 110 eyes) of PCV cases, and was caused by degeneration and atrophy of the retinal pigment epithelium (RPE), persistent serous retinal detachment, subretinal fibrovascular proliferation and massive submacular haemorrhage.[4]

Currently, PCV with vision-threatening complications such as recurrent bleeding or persistent exudation does not have a widely accepted and effective method of treatment. Photodynamic therapy (PDT) with verteporfin has been utilised to stabilise vision.[8–11] However, extensive subretinal haemorrhage may occur after PDT in PCV eyes.[8 12 13] Furthermore, subretinal haemorrhage and subretinal fluid recur after PDT due to new or recurrent PCV.[9–11]

Recently, vascular endothelial growth factor (VEGF) concentrations in the aqueous were found to be markedly increased in eyes with PCV when compared with normal controls.[14] Histopathological specimens also showed strong expression of VEGF in the vascular endothelial cells and the RPE cells of PCV specimens.[15] These data support the potential role for the use of anti-VEGF treatment in PCV. Bevacizumab (a humanised full-length anti-VEGF antibody) has been evaluated retrospectively in 11 eyes with PCV by Gomi *et al* with six eyes receiving one injection, three eyes receiving two injections and one eye receiving three injections.[16] Exudation improved at 3 months, but bevacizumab was ineffective in diminishing choroidal vascular changes. The authors recommended further study of anti-VEGF therapy in PCV with ranibizumab, because of its smaller molecular weight and possible increased penetration deep to the retinal pigment epithelium to the choroidal vascular abnormalities of PCV.[16 17]

Ranibizumab is a humanised anti-VEGF antibody fragment that inhibits all forms of biologically active VEGF-A.[18] Intravitreal injection of ranibizumab was approved by the Food and Drug Administration (FDA) in the USA for treating exudative age-related macular degeneration (AMD) on 30 June 2006. The MARINA and ANCHOR trials were two randomised, double-blinded, pivotal phase III clinical trials.[19 20] For predominantly classic choroidal neovascular membranes in exudative AMD monthly ranibizumab injections were superior to PDT with verteporfin monotherapy showing better visual outcomes, and low rates of serious ocular adverse events.[19] However, the efficacy of ranibizumab for exudative and haemorrhagic complications in PCV is not yet known. The purpose of this current study is to prospectively evaluate the efficacy and safety of monthly intravitreal injections of ranibizumab in eyes with PCV, which show active exudation or bleeding.

PATIENTS AND METHODS

The PEARL trial (Investigator-Sponsored Trial for Polypoidal Choroidal Vasculopathy with Intravitreal Ranibizumab (Lucentis)) is an ongoing, prospective, open-label, trial of continuous monthly intravitreal ranibizumab (0.5 mg) in patients with active haemorrhage, exudation or recent decrease in vision (defined as a loss of five ETDRS letters or one Snellen line of vision in the past 6 months) associated with PCV. Major exclusion criteria are: (1) previous vitrectomy; (2)

previous cataract surgery within 2 months; (3) other active ocular diseases; (4) treatment with intravitreal steroid, pegaptanib (Macugen), bevacizumab (Avastin), or PDT with verteporfin within past 30 days; (5) known allergy to ranibizumab; (6) history of major systemic vascular events such as myocardial infarction and stroke; (7) poorly controlled hypertension; (8) major surgery within 28 days prior to enrolment or planned over next 12 months. This study was approved by the institutional review board of Hawaii Pacific Health.

The clinical diagnosis of PCV was based on funduscopic identification of subretinal reddish-orange spheroidal lesions, serous retinal detachment or macular oedema due to subretinal exudation, subretinal haemorrhage or RPED. The definitive diagnosis of PCV was confirmed by indocyanine green (ICG) angiography with typical features of PCV including branching vascular networks and polypoidal vascular lesions. After detailed explanation of the potential risks and benefits of treatment, written informed consent was obtained from all patients. In patient with bilateral PCV, only one eye was entered into the study. All patients received multiple, open-label, monthly, intravitreal injections of 0.5 mg of ranibizumab (Lucentis, Genentech, South San Francisco, California) administered once every 30 days (±7 days) with continuous treatment being planned for 12 consecutive months.

At baseline all patients had a complete ophthalmic examination with ETDRS vision refraction at 4 m, fluorescein angiography (FA), ICG angiography using Heidelberg video angiography (Heidelberg HRA 2 Angiography, Heidelberg Engineering, Germany) and optical coherence tomography (OCT). Intravitreal ranibizumab injections were given monthly beginning at the baseline visit and five subsequent visits, with the 6-month results being evaluated after six injections. Ophthalmic examination, visual acuity and OCT were performed monthly. ETDRS vision, FA and ICG angiography were done at 1, 3 and 6 months.

The primary outcome measures are stabilisation of vision (loss <15 ETDRS letters) and incidence and severity of ocular and systemic adverse events. The secondary outcome measures are changes in visual acuity, subretinal fluid, subretinal/sub-RPE haemorrhage, subretinal exudates, RPED, central foveal thickness (CFT), leakage on FA and polypoidal complexes as imaged on ICG angiography. The changes in fluorescein leakage and polypoidal complexes were determined by comparing FA and ICG frames at similar times after dye injection at baseline and 6 months. The data were interpreted and agreed upon by two observers (GTK, LY).

RESULTS

Twelve eyes of 12 consecutive patients (11 Asian and one Caucasian) entered into the PEARL trial received six monthly ranibizumab injections, and were available for the 6-month data evaluation. There were two females and 10 males with a mean age of 75 years (range: 63–94). None of the patients had significant systemic or ocular adverse events during treatment. The demographic data are summarised in table 1, and the change in clinical manifestations between baseline and 6 months is summarised in table 2. Ten of the eyes were treatment-naïve, while two eyes (cases 2 and 3) had prior PDT. Four patients had bilateral disease. Typical vascular networks and polypoidal lesions were noted on ICG angiography in all 12 eyes. Macular polyps were found in all but one eye (92%), and peripapillary polyps were found in two eyes (17%). Macular polyps were noted in all 11 Asian patients, but only peripapillary polyps were noted in the one Caucasian patient.

The median visual acuity was 20/80 (range: HM-20/40) at baseline and 20/80 (range: CF-20/20) at 6 months. The mean EDTRS vision was 43.8 letters at baseline and 51.0 letters at 6 months. None of the patients lost ≥15 letters in ETDRS vision at 6 months. At 6 months, seven eyes (58%) improved ≥5 letters, four eyes (33%) remain unchanged (<5 letters) form baseline, and one eye (8%) decreased ≥5 letters. Two patients (17%) gained ≥15 letters at 6 months (see example in figure 1).

The initial presenting clinical manifestations included subretinal fluid in 8/12 eyes (67%), subretinal/sub-RPE haemorrhage in 6/12 eyes (50%), RPED in 6/12 eyes (50%), and subretinal exudates in 9/12 (75%) eyes. At 6 months, subretinal haemorrhage resolved in all six eyes with initial subretinal haemorrhage. Subretinal fluid completely resolved in 3/8 eyes (38%), decreased in 2/8 eyes (25%), remained stable in 2/8 eyes (25%) and increased in 1/8 eyes (13%). RPED decreased in 3/6 eyes (50%), completely resolved in 1/6 eyes (17%) and was stable in 2/6 eyes (33%).

Significant macular oedema at baseline due to PCV was present in 5/12 eyes with CFT >275 μm. In these five eyes, macular oedema improved significantly in 4/5 eyes (80%) (figure 2). In one case, the oedema did not respond, with CFT being higher at 6 months than at baseline. The leakage on FA was decreased in 9/11 (82%) eyes and remained stable in 2/11 eyes (18%). FA was not available in one patient (case 8) due to fluorescein allergy. The polypoidal complexes on ICG angiography decreased in 4/12 eyes (33%), but choroidal vascular complexes persisted in all 12 eyes (see example in figure 3).

Table 1 Demographic data and clinical presentation of patients

No	Age, gender	Laterality	Study eye	Polyp(s) location	Previous treatment	Visual acuity		
						Baseline	3 months	6 months
1	68, M	Unilateral	OS	Mac		20/80	20/100	20/125
2	94, M	Unilateral	OD	Mac	PDT×1	20/100	20/63	20/63
3	70, M	Unilateral	OD	Mac	PDT×5	20/250	20/200	20/160
4	78, M	Unilateral	OD	Mac		20/80	20/80	20/80
5	72, M	Bilateral	OS	Mac		20/80	20/100	20/80
6	70, M	Unilateral	OD	Mac		HM	HM	CF
7	66, M	Bilateral	OS	Mac, Peri		20/80	20/63	20/80
8	74, F	Unilateral	OS	Peri		20/63	20/63	20/40
9	88, M	Unilateral	OS	Mac		20/63	20/25	20/32
10	78, M	Bilateral	OS	Mac		CF@2F	20/320	20/400
11	63, M	Bilateral	OD	Mac		20/40	20/16	20/20
12	80, F	Unilateral	OS	Mac		20/160	20/200	20/125

CF, counting finger; HM, hand motion; M, male; OD, right eye; OS, left eye; Mac, macula; PDT, photodynamic therapy; Peri, peripapillary.

Table 2 Comparing the change in clinical manifestations between baseline and 6 months

	Initial fundus appearance				Fundus changes at 6 months				CFT		Leakage on FA at 6 months	Polyp(s) on ICG at 6 months
No	SRF	Hem	PED	Exu	SRF	Hem	PED	Exu	Baseline	6 months		
1	–	–	+	+			±↓	↓	177	172	↓	=
2	–	+	–	+		R		↓	193	153	↓	=
3	–	+	–	–		R			159	135	=	=
4	±	+	+	–	=	R	=		198	268	↓	=
5	±	–	–	+	=			↓	236	281	↓	↓
6	+	–	–	+	↑			=	711	895	=	=
7	+	–	+	+	↓		=	↑	534	263	↓	=
8	+	+	–	+	R	R		↑	598	213	NA	↓
9	+	–	+	+	↓		↓	=	239	230	↓	=
10	–	+	+	+		R	↓	R	220	185	↓	↓
11	+	+	–	–	R	R			494	206	↓	↓
12	+	–	+	+	R		R	↓	429	177	↓	↑

–, absent; +, present; ±, minimal; ↑, increased; ↓, decreased; =, stable; CFT, central foveal thickness (μm); Exu, subretinal exudates; FA, fluorescein angiography; Hem, subretinal/subretinal pigment epithelium haemorrhage; ICG, indocyanine green angiography; NA, not assessed; PED, pigmented epithelium detachment; R, resolved; SRF, subretinal fluid.

DISCUSSION

Polypoidal choroidal vasculopathy is increasingly recognised as a major cause of serosanguinous macuolopathy and vision loss throughout the world, but the incidence is especially high in Asian countries and Asian people living throughout the world.[17] Although the natural history of PCV was previously reported to be more favourable than AMD, one-third to one-half of PCV patients develop severe and progressive visual loss.[1–4 7] The most important causes of severe visual loss are repeated subretinal haemorrhage and persistent leakage from PCV lesions,[4 7] which are the hallmark clinical characteristics of PCV.[1–4] The repeated injuries eventually result in atrophy of the RPE and fibrovascular scars. Resolving subretinal haemorrhage and decreasing leakage from PCV lesions may be an important and reasonable approach to stabilising visual acuity and preventing subretinal scarring. However, the pathogenesis of PCV and the mechanism leading to recurrent haemorrhage and leakage are poorly understood. The reports of increased VEGF in the aqueous humour, and VEGF expression in the vascular endothelial cells and RPE cells in PCV eyes[14 15] suggests that VEGF may play a role in PCV lesions.

Utilising monthly intravitreal ranibizumab as the anti-VEGF therapy in this PEARL study, and based on the short-term findings in these 12 eyes, ranibizumab is effective in limiting bleeding and leaking in PCV eyes and should be further studied. In contrast to these results, a previous study by Gomi *et al* utilising one to three intermittent injections of bevacizumab in a retrospective study showed an initial decrease in subretinal fluid in 4/5 eyes, but recurrent subretinal fluid in three of the four eyes which initially responded.[16] As Gomi and colleagues suggested in their paper,[16] these results suggest a more promising effect of ranibizumab in maintaining vision in actively leaking or bleeding eyes with PCV, potentially due to its smaller molecular mass and better potential penetration through the retina and RPE to the level of the choroidal vascular abnormalities, as well as the continuous monthly injections.

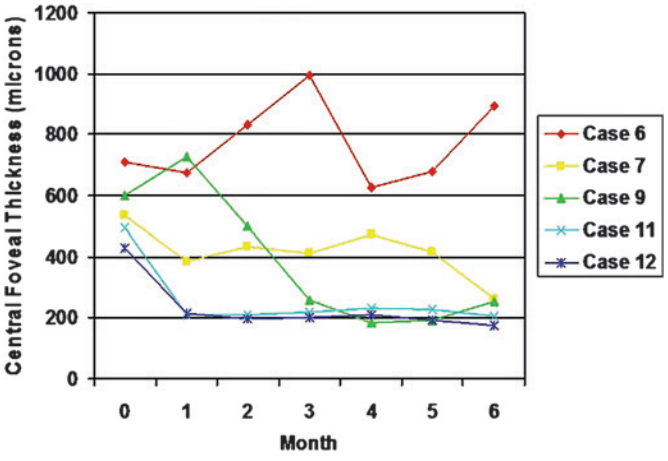

Figure 1 Graph showing the central foveal thickness of five eyes with polypoidal choroidal vasculopathy and significant macular oedema (central foveal thickness ≥275 μm) throughout the 6 months of ranibizumab therapy.

Macular oedema based on CFT improved in four of five eyes (80%) in this study with a baseline CFT greater than 275 μm (figure 2). One eye (case 6) showed no response to ranibizumab therapy with progressive increase in CFT over 6 months (figure 2). A similar decrease in macular oedema was noted after three monthly bevacizumab injections in a study by Lai *et al*.[21] The improvement in oedema demonstrated with ranibizumab in the PEARL study and bevacizumab in the Lai study[21] suggest that short-term continuous anti-VEGF therapy does have significant effects at reducing macular oedema in most, but not all PCV eyes.

These vision results for PCV after treatment with ranibizumab can be compared with treatment results with ranibizumab for choroidal neovascularisation (CNV) in exudative AMD.[19 20] In the ANCHOR trial for predominantly classic CNV, 40.3% of patients treated with monthly ranibizumab gained ≥15 letters at 12 months.[19] In the MARINA trial for occult CNV, 33.8% of patients gained ≥15 letters at 12 months.[20] In both studies, visual acuity improvement mostly occurred in the first 3 months with stabilisation of vision thereafter.[17 18] If PCV responds to ranibizumab similarly to AMD, most of the vision improvement in our 12 eyes would have occurred by this 6-month evaluation. While 17% of the PCV eyes in our smaller study gained ≥15 letters after 6 months, this is lower than that seen in the larger multicentred ranibizumab trials in exudative AMD.

The choroidal vascular branching network and polypoidal complexes have been resistant and poorly responsive to anti-VEGF therapy with bevacizumab.[16 22] In the Gomi *et al* study, choroidal vascular abnormalities remained on ICG angiography in 10 of 11 eyes after one to three intermittent injections of bevacizumab.[16 17] In the Lai *et al* study[21] involving three monthly bevacizumab injections, intravitreal bevacizumab was

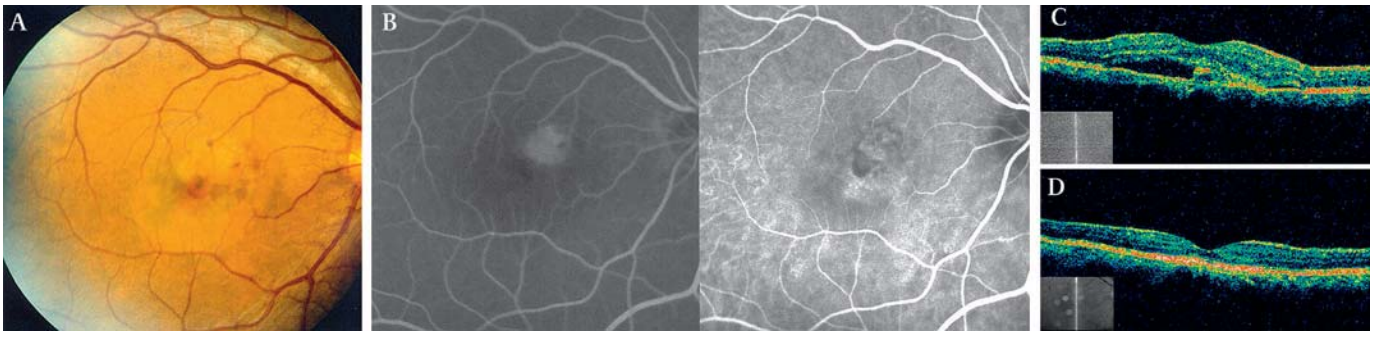

Figure 2 Case 11 presented at baseline with an Early Treatment of Diabetic Retinopathy Study visual acuity of 20/40. (A) Baseline fundus photograph showing macular oedema, subretinal haemorrhage and retinal pigment epithelium thickening. (B) Baseline late-phase fluorescein angiography/indocyanine green. Fluorescein angiography shows occult leakage, and indocyanine green confirms vascular complex and polypoidal lesions. (C) Optical coherence tomography at baseline confirming macular oedema and subretinal fluid. (D) Optical coherence tomography at month 6 showing resolution of subretinal fluid and return of normal foveal depression. The Early Treatment of Diabetic Retinopathy Study visual acuity improved to 20/20.

felt to have limited effectiveness in causing regression of the polypoidal lesions. In this PEARL trial utilising six monthly injections of ranibizumab, polypoidal complexes remained the same in seven of 12 eyes (58%) at 6 months. In four of 12 eyes (33%), there was a decrease in the polypoidal complex (figure 3). In one eye, there was progressive enlargement of the PCV complex, similar to a case in the Gomi *et al* study with bevacizumab.[16] All 12 eyes in this study had persistence of the branching choroidal vascular network at 6 months. Although there was some visible decrease in the PCV complex in 1/3 of eyes in the PEARL trial, the branching vascular complex persists in most eyes on anti-VEGF therapy. As previously proposed for bevacizumab,[16 17 22] even though ranibizumab is a smaller molecule with a theoretically better ability to penetrate through the retina and retinal pigment epithelium (RPE) to the choroidal vascular abnormalities of PCV,[18 22] the location of the PCV vessels beneath the RPE may prevent adequate penetration of the intravitreal anti-VEGF drugs to reliably induce PCV regression. In one eye with resolution of polyps in the Gomi series,[16] there was atrophic RPE, for which the authors speculated a possible increased penetration of bevacizumab into the sub-RPE space resulting in polyp regression. In addition, instead of being a variant of choroidal neovascularisation (CNV),[7 23] PCV may instead be an inner choroidal vascular abnormality,[5 24 25] which could also explain a different response of PCV to ranibizumab. Future clinical and basic science studies are necessary to better understand the pathogenesis of PCV and guide future therapy.

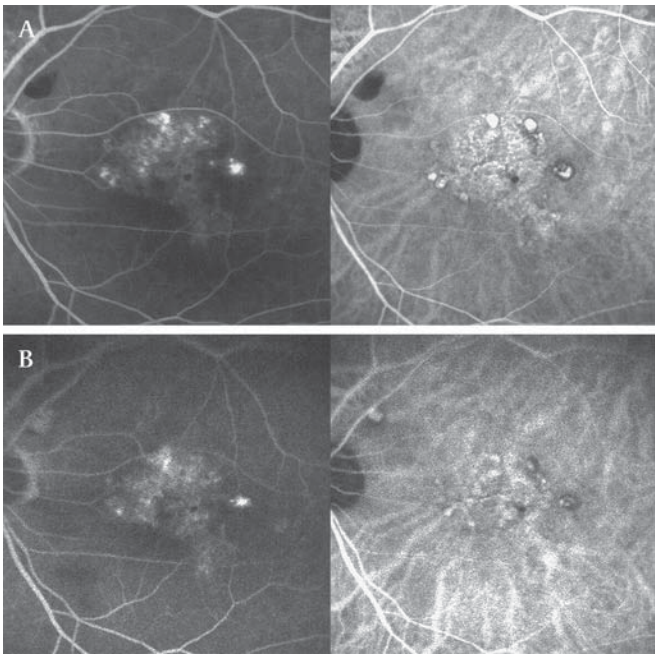

Figure 3 Case 5. (A) Baseline late-phase fluorescein angiography/indocyanine. Note the large vascular complex and the markedly hyperfluorescent superotemporal polypoidal lesions. (B) Month 6 late-phase fluorescein angiography/indocyanine. Note the marked decrease in the superotemporal polypoidal lesions but persistence of the branching vascular complex.

PDT in recent studies showed good results in reduction in leakage and regression of polyps in PCV eyes.[8–11] However, severe visual loss due to extensive subretinal haemorrhages is not uncommon after PDT.[8 12 13] In addition, PDT itself can result in a temporary increase in VEGF.[15] Future studies involving combination therapy are ongoing and may provide better potential therapy for PCV. In the Lai *et al* study,[22] adding PDT to bevacizumab monotherapy appeared to show more promise than bevacizumab therapy alone.

This PEARL trial provides the first prospective data on anti-VEGF therapy for bleeding and exudative complications of PCV. Ranibizumab does appear to have a significant effect on decreasing bleeding and exudation in PCV. However, regression of the PCV complex on ICG angiography was noted in only four of 12 eyes (33%). The PEARL trial supports a further study of ranibizumab in the treatment of PCV. Combination therapies, such as PDT and anti-VEGF therapy, are also important to consider in the treatment of PCV, which is being increasingly recognised as a major cause of serosanguinous maculopathy and vision loss around the world.

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