

One-year real-world outcomes of ranibizumab 0.5 mg treatment in Taiwanese patients with polypoidal choroidal vasculopathy: a subgroup analysis of the REAL study

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Abstract

• **AIM:** To assess the effectiveness and safety of ranibizumab 0.5 mg in Taiwanese patients with polypoidal choroidal vasculopathy (PCV) by performing a retrospective exploratory subgroup analysis of the REAL study.

• **METHODS:** REAL was a 12-month, observational, prospective, non-interventional phase IV post-marketing surveillance study conducted at 9 centers in Taiwan. The study collected data as part of the routine patient visits from the medical records of patients with neovascular age-related macular degeneration treated with ranibizumab 0.5 mg according to local standard medical practice and local label and/or reimbursement guidelines. The presence of PCV at baseline was determined using indocyanine green angiography.

• **RESULTS:** At baseline, PCV was diagnosed in 64 of the 303 enrolled patients (21.1%). Of these, 41 patients (64.1%) had received prior treatment; 15 (23.4%) patients had received ranibizumab. The intent-to-treat population included 58 patients; 47 (80%) who received ranibizumab and 11 (20%) who received ranibizumab plus photodynamic therapy (PDT; 9 patients received once, 2 patients received twice). Bevacizumab was used as a concomitant medication in a similar percentage of patients who received ranibizumab (43%, $n=20$) or ranibizumab plus PDT (45%, $n=5$). In patients who received ranibizumab, visual acuity (VA) at baseline was 50.1 ± 12.9 Early Treatment Diabetic Retinopathy Study letters, and the gain at month 12 was 1.1 ± 17.8 letters. In patients who received ranibizumab plus PDT, VA at baseline was 51.4 ± 15.9 letters, and there was a marked gain in VA at month 12 (14.0 ± 9.2 letters, $P=0.0009$). In the intent-to-treat population, the reduction in central retinal subfield thickness from baseline at month 12 was 69.6 ± 122.6 μm (baseline: 310.8 ± 109.8 μm , $P=0.0004$). The safety results were consistent with the well-characterized safety profile of ranibizumab.

• **CONCLUSION:** In real-world settings, ranibizumab 0.5 mg treatment for 12mo results in maintenance of VA and reduction in central retinal subfield thickness in Taiwanese patients with PCV. Improvements in VA are observed in patients who received ranibizumab plus PDT. There are no new safety findings.

• **KEYWORDS:** observational study; polypoidal choroidal vasculopathy; ranibizumab; Taiwan; visual acuity

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INTRODUCTION

Polypoidal choroidal vasculopathy (PCV), a subtype of neovascular age-related macular degeneration (nAMD), is an exudative maculopathy characterized by polypoidal subretinal vascular lesions associated with hemorrhagic detachments of the retinal pigment epithelium^[1-3]. The frequency of PCV diagnosis in patients with nAMD has increased with the advent of indocyanine green angiography (ICGA), which is considered the gold standard for PCV diagnosis^[4-5].

The prevalence of PCV is reportedly higher among Asians compared with Caucasians, and ranges from 23% to 55% among Asians initially diagnosed with nAMD^[6-8]. In Taiwan, PCV has been reported in nearly 50% of patients with an initial diagnosis of nAMD, and the consequences of PCV appear to be worse among Taiwanese patients than in other ethnic groups^[9-11]. However, only limited studies have assessed the treatment patterns and outcomes for PCV in the Taiwanese population^[9,11]. Anti vascular endothelial growth factors (anti-VEGFs) are the standard of care for nAMD, while the optimal treatment for PCV is still under consideration, as verteporfin photodynamic therapy (vPDT), anti-VEGFs, or a combination of the two therapies are all under investigation^[4-5].

REAL, a 12-month, prospective, observational multicenter study conducted in Taiwan, was the first study to assess the real-world outcomes of ranibizumab 0.5 mg treatment in Taiwanese patients with nAMD. The primary results from the study in nAMD patients are reported elsewhere^[12]. Here, we present the results from a retrospective exploratory analysis in the subgroup of Taiwanese patients with PCV.

SUBJECTS AND METHODS

REAL was an open-label, prospective, observational, non-interventional phase IV post-marketing surveillance study conducted from July 22, 2010, to April 02, 2013, at 9 centers in Taiwan. The study collected data as part of the routine patient visits from the medical records of patients treated with ranibizumab 0.5 mg according to local standard medical practice and local label and/or reimbursement guidelines in Taiwan. The observational period for each patient was 12mo after initiation of treatment with ranibizumab 0.5 mg. After enrolment, data were collected from the patients' medical records on day 1 and at months 3, 6 [best-corrected visual acuity (BCVA) assessment only], and 12. Patients could voluntarily withdraw from the study for any reason at any time. The investigators could also discontinue study treatment for a given patient or withdraw the patient from study if they considered continuation to be detrimental to the patient's well-being for any reason. The study adhered to the tenets of the Declaration of Helsinki, the International Conference on Harmonization and Good Clinical Practice guidelines. The protocol and amendments were approved by the independent

ethics committee or institutional review board for each participating center. Patients provided written informed consent.

The study included male or female Taiwanese patients with newly diagnosed or previously treated primary or recurrent subfoveal choroidal neovascularization (CNV) secondary to nAMD and a BCVA score between 73 and 20 letters (inclusive; approximately 20/40 to 20/400 Snellen equivalent) in the study eye.

Efficacy endpoints included the following parameters: mean change in BCVA and central retinal subfield thickness (CSFT) from baseline to months 3, 6 (only BCVA), and 12; proportion of patients with an increase (gain of ≥ 5 letters), no change (change of ≤ 4 letters), or decrease (loss of ≥ 5 letters) in BCVA at months 3, 6, and 12; and presence of subretinal fluid (SRF), CNV, hemorrhage, hemorrhagic retinal pigment epithelial detachment (HRPED), pigment epithelial detachment (PED), lipids, SRF (apparent), and scar at baseline, month 3 and month 12. The BCVA measurements were performed in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS) testing charts for visual acuity (VA) at a testing distance of 4 meters. CSFT and SRF were assessed using optical coherence tomography (OCT). The occurrence of CNV, its type and location at baseline, and regression of CNV lesions were assessed using fluorescein angiography (FA). Other parameters were assessed using color fundus photography. Safety endpoints included monitoring and recording of all adverse events (AEs) and serious AEs, and monitoring of intraocular pressure (IOP). The efficacy and safety results were summarized descriptively.

Patients who received at least one dose of ranibizumab during the observational period and had baseline and at least one post-baseline assessment of the effectiveness variable (BCVA) were included in the intent-to-treat (ITT) population. Patients who received at least one dose of ranibizumab and had at least one post-baseline safety assessment for the observational period were included in the safety population. The presence of PCV at baseline was diagnosed using ICGA.

RESULTS

Overall, 303 Taiwanese patients with nAMD were enrolled, of whom 228 (75.2%) completed the study, and 75 (24.8%) withdrew from the study. The mean age of the patients was 72.4y, and a higher proportion (65.6%) was male. At baseline, PCV was diagnosed in 64 (21.1%) patients of whom 48 (75.0%) completed the study. The reasons for discontinuation were withdrawal of consent ($n=15$) and lost to follow-up ($n=1$). The mean \pm standard deviation (SD) age of the patients was 68.7 \pm 9.7y and a higher proportion (64.1%) were male (Table 1). ICGA was not performed in 83 (27.4%) patients.

Prior treatment was defined as medication for AMD in the 3mo prior to first injection. Patients could have received more than one type of prior treatment for AMD during this period.

Table 1 Patient baseline demographics and disease characteristics (safety population)

Parameters	Patients with PCV (n=64)	n (%)
Age at first injection (y), mean±SD	68.7±9.7	
Gender		
Male	41 (64.1)	
Female	23 (35.9)	
BMI (kg/m ²), mean±SD	24.6±3.2	
Prior treatment		
No	23 (35.9)	
Yes	41 (64.1)	
Ranibizumab	15 (23.4)	
Bevacizumab	22 (34.4)	
Verteporfin/photodynamic therapy	11 (17.2)	
Tocopherol nicotinate	1 (1.6)	

AMD: Age-related macular degeneration; BMI: Body mass index; ICGA: Indocyanine green angiography; PCV: Polypoidal choroidal vasculopathy; SD: Standard deviation.

Efficacy The ITT population included 58 patients with PCV. In these patients, the BCVA at baseline was 50.4±13.4 letters. The change in BCVA from baseline at month 3 was +2.7±12.4 letters (*P*=0.114), at month 6 was +2.4±17.1 letters (*P*=0.336), and at month 12 was +3.8±17.1 letters (*P*=0.131).

Of the 58 patients, 47 (80%) received only ranibizumab 0.5 mg and 11 (20%) received ranibizumab 0.5 mg plus PDT during the study. In the 47 patients who received only ranibizumab 0.5 mg, the BCVA at baseline was 50.1±12.9 letters and the change in BCVA from baseline at month 12 was +1.1±17.8 letters (*P*=0.714; Figure 1). Similar mean changes in BCVA from baseline were observed at months 3 and 6 (Figure 1). In the patients who received ranibizumab 0.5 mg plus PDT, the mean baseline BCVA was 51.4±15.9 letters and the change in BCVA from baseline at month 12 was +14.0±9.2 letters (*P*=0.0009; Figure 1). Improvements in mean BCVA were also observed at months 3 and 6 (Figure 1).

At month 12, the proportion of patients with a gain in BCVA of ≥5 letters [*n*=27 (57.5%)] was higher than those with a loss of ≥5 letters [*n*=12 (25.5%)]; 8 (17.0%) patients had no change in BCVA (Figure 2).

The CSFT at baseline was 310.8±109.8 μm, and the change from baseline at month 3 was -77.3±95.5 μm (*P*<0.0001) and at month 12 was -69.6±122.6 μm (*P*=0.0004). The proportion of patients with SRF in the study eye decreased from baseline (77.6%) to month 12 (19.0%, *P*<0.0001; Table 2). Similarly, at month 12, there was a decrease from baseline in the presence of hemorrhage (12.1% vs 69.0%, *P*<0.0001), HRPED (3.5% vs 25.9%, *P*=0.003), PED (22.4% vs 55.2%, *P*=0.02), SRF apparent (13.8% vs 72.4%, *P*<0.0001), and lipids (29.3% vs 56.9%, *P*=0.013) but an increase in the presence of scar (39.7% vs 19.0%, *P*=0.0005; Table 2).

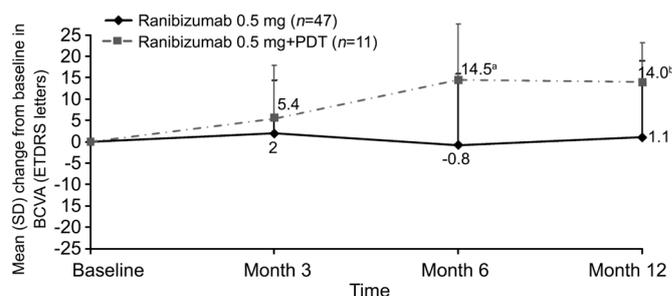


Figure 1 Mean change from baseline in BCVA in patients with PCV by treatment received (ITT population) ^a*P*=0.007 vs baseline; ^b*P*=0.0009 vs baseline.

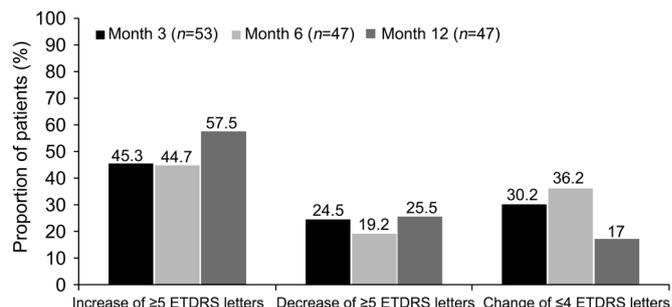


Figure 2 Proportion of patients with categorical changes in BCVA at months 3, 6 and 12 (ITT population).

At baseline, CNV was present in 51 (87.9%) patients; most had occult CNV, and most CNVs were located in the subfoveal region (Table 3). At month 12, complete regression of lesions was observed in 4 (6.9%) patients (Table 3).

Treatment Exposure The number of ranibizumab 0.5 mg injections was 3.2±1.5; the exposure was similar in those who received additional PDT and those who did not (3.5±1.8 and 3.1±1.4 injections, respectively). The number of bevacizumab injections received as concomitant medication during the study was similar between the ranibizumab (1.1±1.8 injections, range 0-7) and ranibizumab plus PDT groups (0.5±0.5 injections, range 0-1). A similar percentage of patients in the ranibizumab and ranibizumab plus PDT groups received bevacizumab as concomitant medication during the study [43% (*n*=20/47) and 45% (*n*=5/11), respectively]. Of the 5 patients who received bevacizumab in the ranibizumab plus PDT group, all received only 1 injection, and mostly on the same day that they received PDT. Of the 20 patients in the ranibizumab group who received bevacizumab, the number of injections ranged from 1 to 7 (mean±SD: 2.7±1.9). The difference in the number of bevacizumab injections shows that patients treated with ranibizumab plus PDT need fewer additional treatments than those treated with ranibizumab alone. Of the 11 patients who received PDT, two received PDT twice and the remaining nine received PDT once during the study.

Safety At least one AE was reported in 22 (34.4%) patients, and serious AEs were reported in 6 (9.4%) patients (Table 4). None of the serious AEs were considered by the investigator to

Table 2 Categorical changes from baseline at months 3 and 12 in optical coherence tomography and color fundus photography parameters in the study eye (ITT population) *n* (%)

Parameters	Patients with PCV (<i>n</i> =58)		
	Baseline	Month 3	Month 12
Optical coherence tomography			
SRF			
Absent	13 (22.4)	30 (51.7)	35 (60.3)
Present	45 (77.6)	23 (39.7)	11 (19.0)
NA/ND	0	5 (8.6)	12 (20.7)
Color fundus photography			
Hemorrhage			
Absent	18 (31.0)	24 (41.4)	32 (55.2)
Present	40 (69.0)	13 (22.4)	7 (12.1)
NA/ND	0	21 (36.2)	19 (32.8)
HRPED			
Absent	42 (72.4)	30 (51.7)	37 (63.8)
Present	15 (25.9)	6 (10.3)	2 (3.5)
NA/ND	1 (1.7)	22 (37.9)	19 (32.8)
PED Lipid			
Absent	25 (43.1)	24 (41.4)	26 (44.8)
Present	32 (55.2)	12 (20.7)	13 (22.4)
NA/ND	1 (1.7)	22 (37.9)	19 (32.8)
Lipids			
Absent	25 (43.1)	16 (27.6)	22 (37.9)
Present	33 (56.9)	20 (34.5)	17 (29.3)
NA/ND	0	22 (37.9)	19 (32.8)
SRF (apparent)			
Absent	16 (27.6)	20 (34.5)	31 (53.5)
Present	42 (72.4)	17 (29.3)	8 (13.8)
NA/ND	0	21 (36.2)	19 (32.8)
Scar			
Absent	46 (79.3)	23 (39.7)	16 (27.6)
Present	11 (19.0)	11 (19.0)	23 (39.7)
NA/ND	1 (1.7)	24 (41.4)	19 (32.8)

BCVA: Best-corrected visual acuity; HRPED: Hemorrhagic retinal pigment epithelial detachment; ITT: Intent-to-treat; NA/ND: Not assessed/not determined; PCV: Polypoidal choroidal vasculopathy; PED: Pigment epithelial detachment; SRF: Subretinal fluid. The ITT population included patients who received at least one dose of ranibizumab 0.5 mg during the observational period and had a baseline and at least one post-baseline BCVA assessment.

be related to ranibizumab. The most frequently reported ocular and non-ocular AEs (reported in $\geq 2\%$ of patients) are shown in Table 4. All other ocular and non-ocular AEs were reported in one (1.6%) patient each. There were no reports of retinal hemorrhage.

Chest pain and myositis were the treatment-related AEs reported, and both occurred in the same patient [$n=1$ (1.6%)]. There were no deaths or discontinuations due to AEs. The IOP at baseline was 13.5 ± 2.4 mm Hg. There was no significant

Table 3 Categorical changes from baseline at months 3 and 12 in fluorescein angiography parameters in the study eye (ITT population) *n* (%)

Category	Patients with PCV (<i>n</i> =58)	
	Baseline	
CNV		
Present		51 (87.9)
NA/ND		7 (12.1)
CNV type		
100% classic		0
Predominantly classic		5 (8.6)
Minimally classic		8 (13.8)
Occult		33 (56.9)
NA/ND		12 (20.7)
CNV location		
Subfoveal		27 (46.6)
Juxtafoveal		13 (22.4)
Extrafoveal		4 (6.9)
More than one location		2 (3.5)
NA/ND		12 (20.7)
Lesion regression from baseline		
Complete regression	Month 3	Month 12
>50% regression	0	4 (6.9)
<50% regression	13 (22.4)	6 (10.3)
Progression	10 (17.2)	9 (15.5)
No change	0	3 (5.2)
NA/ND	1 (1.7)	3 (5.2)
	34 (58.6)	33 (56.9)

BCVA: Best-corrected visual acuity; CNV: Choroidal neovascularization; ITT: Intent-to-treat; NA/ND: Not assessed/not determined; PCV: Polypoidal choroidal vasculopathy.

mean change in IOP from baseline at months 3 (0.0 ± 2.7 mm Hg, $P=0.97$) and 12 (0.6 ± 2.5 mm Hg, $P=0.20$).

DISCUSSION

REAL was the first study assessing the effectiveness of ranibizumab 0.5 mg in a real-life setting in Taiwanese patients with nAMD, and the study demonstrated that ranibizumab 0.5 mg maintained VA and delayed disease progression for up to 12mo. Consistent with these findings, the exploratory analysis of the REAL study showed that ranibizumab 0.5 mg resulted in numerical increase in VA, reductions in the mean CSFT and a delay in disease progression at month 12 in patients with PCV. In the REAL study, of the 219 patients in whom ICGA was performed, PCV was diagnosed in 64 (29%) patients. Higher proportions have been reported in other real-life setting studies, but those studies had small sample sizes^[9-10]. Also, the diagnosis of PCV still remains a challenge, in spite of the use of ICGA for diagnosis, because of the possibility of PCV being misdiagnosed for conditions such as stage 1 retinal angiomatous proliferation or micro-aneurysms with similar presentation on ICGA^[13], or under diagnosed if the polyps are masked by PED or hemorrhage at baseline.

Table 4 Incidence of adverse events during the study (safety population)

Preferred term	Patients with PCV (n=64)	n (%)
Total No. of AEs	22	(34.4)
Serious AEs	6	(9.4)
Angina pectoris	1	(1.6)
Urinary tract infection	1	(1.6)
Cholelithiasis	1	(1.6)
Post laminectomy syndrome	1	(1.6)
Dizziness	1	(1.6)
Hypertensive heart disease	1	(1.6)
Prostate cancer	1	(1.6)
AEs with a $\geq 2\%$ incidence		
Ocular AEs		
Cataract	2	(3.1)
Vitreous haemorrhage	2	(3.1)
Non-ocular AEs		
Cough	3	(4.7)
Upper respiratory tract infection	3	(4.7)
Atrial fibrillation	2	(3.1)
Chest pain	2	(3.1)
Rhinitis allergic	2	(3.1)

AE: Adverse event; PCV: Polypoidal choroidal vasculopathy. The safety population included patients who received at least one dose of ranibizumab 0.5 mg during the observational period and had at least one post-baseline safety assessment. The serious AEs of hypertensive heart disease and prostate cancer occurred in one and the same patient. Medical Dictionary for Regulatory Activities (MedDRA) version 15.0.

In our analysis, the mean age of patients diagnosed with PCV was lower (68.7y) than those of the overall population with nAMD (72.4y), and most patients (64.1%) were male. This finding is consistent with previous studies in Asians, including Taiwanese patients, which show that PCV is generally diagnosed at an earlier age ranging between 60 to 70y than nAMD ($\geq 70y$), with predominance (71%) in males^[5,10-11,14]. Most patients (64.1%) in this study had received prior treatment for AMD in the 3mo before the first ranibizumab 0.5 mg injection. In these mostly treatment-exposed patients, ranibizumab 0.5 mg treatment for 12mo maintained VA and decreased CSFT. These results are of relevance, as treatment-exposed patients generally do not show as much treatment gains as treatment-naïve patients^[15-16]. Consistent with this observation, an interim analysis of LUMINOUS, a 5-year prospective observational global study showed that VA and CSFT gains at 1-year were better in treatment-naïve than treatment-exposed PCV patients^[17]. Similarly, visual and anatomic improvements with ranibizumab 0.5 mg treatment were observed in treatment-naïve Japanese patients with PCV in the LAPTOP study^[18-20].

In the REAL study, there were marked improvements in VA at month 12 in the subgroup of patients with PCV who received ranibizumab 0.5 mg plus PDT, suggesting additional benefits with combined ranibizumab plus PDT treatment. These findings are consistent with previous reports^[21-23]. Similar findings were observed at month 12 in the phase IV 24-month EVEREST II study (8.3 vs 5.1 ETDRS letters, $P=0.013$ ^[24], NCT01846273^[25]). Complete regression of polyps was also higher with combination therapy versus ranibizumab monotherapy in EVEREST^[22] and EVEREST II^[24] studies; similar findings have been reported in other studies in Asian patients^[21,23]. These findings were also confirmed by a Meta-analysis that showed polyp regression and maintained or improved VA with the combination therapy compared with the respective monotherapies in patients with PCV^[26]. The mean number of ranibizumab injections in this study was similar between those who received ranibizumab monotherapy (3.1) or combination therapy with PDT (3.5), which was lower than those reported in other observational studies in Asian patients (range, 4.0-4.5) where VA improvements were observed over 12mo^[23,27-28]. However, as the number of injections administered in the REAL study was driven by reimbursement decisions, the study did not answer if ranibizumab 0.5 mg plus vPDT would have been associated with a reduction in ranibizumab injection, compared with ranibizumab monotherapy, as observed at month 6 in EVEREST^[22] and at month 12 in the EVEREST II study^[24], considering the time frame this study observed. Further studies are required on the optimal treatment options as well as the optimal treatment intervals for PCV^[5,29]. Results from randomized clinical studies, in which patients are regularly monitored and access to anti-VEGF agents is not a limiting factor, show that VA gains are higher than those in real-world studies. In the phase IV DRAGON study that assessed ranibizumab monotherapy in Chinese patients with nAMD for up to 2y, in the subset of patients with PCV, notable VA gains of 12.7/9.4 (baseline, 54.1/54.6) ETDRS letters at the end of 1y and 12.3/9.7 ETDRS letters at the end of 2y were observed in monthly/PRN group, respectively; the mean number of injections was 11.2/8.4 and 4.9/6.0 at 1 and 2y respectively^[30]. Similarly, in the phase IIIb/IV PLANET study, aflibercept monotherapy for 1-year resulted in BCVA gains of 10.7 ETDRS letters with a mean 8.1 injections^[31]. The strength of this exploratory analysis of the REAL study is that it was the first to provide real-life data in Taiwanese patients with PCV, thereby addressing to some extent the gap of limited information in such populations. It also provides further evidence regarding the need for accurate diagnosis and appropriate treatment of PCV. The analysis was limited by the short duration and observational nature of the study, lack of a control group, exploratory nature of the analysis,

and the limited sample size. In addition, because the study was observational, ICGA was investigator-graded and there was no protocol-specified criterion; the machines used for assessments were not standardized and were those available at the participating sites as part of routine clinical practice; and the exact timing and fluence of PDT was not collected per protocol.

To conclude, in this first real-life study of ranibizumab 0.5 mg in Taiwanese patients, ranibizumab 0.5 mg treatment for 12mo maintained VA and decreased CSFT in patients with PCV, consistent with the findings observed in the overall population with nAMD. Improvement in VA was observed in patients with PCV who received PDT in addition to ranibizumab 0.5 mg. There were no new safety findings. These real-world findings confirm the benefits of ranibizumab across all patients with nAMD, including those with PCV, and add to the evidence on treatment of PCV in Taiwanese patients.

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