Photodiagnosis and Photodynamic Therapy 27 (2019) 227–233

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Prognostic factors for combined ranibizumab and prompt verteporfin photodynamic therapy for polypoidal choroidal vasculopathy

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ARTICLE INFO

Keywords:
Polypoidal choroidal vasculopathy
Photodynamic therapy
Ranibizumab
Verteporfin
Recurrent hemorrhage
Polyp regression

ABSTRACT

Purpose: To investigate the prognostic factors for the combined therapy of ranibizumab and prompt verteporfin photodynamic therapy (vPDT) for eyes with polypoidal choroidal vasculopathy (PCV).

Methods: Sixty-two PCV eyes of 62 patients that received the initial treatment of intravitreal ranibizumab followed by vPDT within 1 week plus a 2nd intravitreal ranibizumab 1 month later in one single medical center were retrospectively enrolled. Best-corrected visual acuity (BCVA) and parameters obtained from optical coherence tomography at baseline, 3 months, 6 months and 1 year were measured and compared. Factors associated with polyp regression, recurrent hemorrhage and visual improvement were analyzed.

Results: After the loading treatment, complete and partial polyp regression was achieved in 53.6% and 39.3% of cases, respectively at Month 3. The mean logarithm of the minimum angle of resolution of BCVA improved from 0.64 ± 0.38 to 0.55 ± 0.46 ($P = 0.008$) at Month 12. Recurrent hemorrhage ($P = 0.001$) and previous anti-vascular endothelial growth factor (VEGF) treatment ($P = 0.017$) were associated with poorer visual improvement at Month 12. Incomplete polyp regression ($P = 0.038$) and previous anti-VEGF treatment ($P = 0.005$) were associated with a higher risk of recurrent hemorrhage.

Conclusions: Recurrent hemorrhage was associated with poor visual improvement after combined ranibizumab and vPDT for PCV. Complete polyp eradication was associated with a lower risk of recurrent hemorrhage. Patients who had previously received anti-VEGF were associated with recurrent hemorrhage and poor visual improvement; more frequent follow-ups and more aggressive subsequent treatments may be needed for these cases.

1. Introduction

Polypoidal choroidal vasculopathy (PCV) is characterized by polypoidal choroidal vascular dilatation which is presented as focal hyperfluorescence in the early phase of indocyanine green angiography (ICGA), associated with or without branching vascular network (BVN) [1–3]. Visual loss can occur due to subretinal hemorrhage, serous retinal pigment epithelial detachment (RPED), and neurosensory detachment [4]. Ranibizumab, one of the anti-vascular endothelial growth factor (anti-VEGF) agent, has been shown to be effective in improving best-corrected visual acuity (BCVA) and resolving subretinal fluid (SRF) in patients with PCV [5–7]. However, patients receiving anti-VEGF treatment alone experienced lower polyp regression, persistent leakage, and early recurrence, thus requiring more injections [2,3,8]. Verteporfin photodynamic therapy (vPDT) is capable of resolving polypoidal lesions; however, it is associated with high rates of secondary hemorrhage (2–33%), retinal pigment epithelium (RPE) tears (0–66%), and transient surges of vascular endothelial growth factor (VEGF) levels [4,9–19]. Anti-VEGF treatment before or together with vPDT has been found to reduce the extents of VEGF surges and the possibilities of secondary hemorrhage or RPE tear [20,21].

In previous clinical trials or real-world experiences of PCV management, combination therapy of anti-VEGF and vPDT achieves higher rate of complete polyp regression and maximizes the improvement of visual acuity [2,3,22–32]. In most of these studies, however, three initial monthly injections of anti-VEGF were administered based on the treatment guideline for neovascular age-related macular degeneration (nAMD). Nevertheless, Lee et al. reported that, in PCV patients who received the combination therapy of vPDT with one intravitreal injection of ranibizumab (IVR), the VEGF concentration in aqueous humor

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https://doi.org/10.1016/j.pdpdt.2019.06.004
Received 9 April 2019; Received in revised form 21 May 2019; Accepted 7 June 2019
Available online 10 June 2019

remained low three months after therapy [20]. Due to the economic burden for patients in real-world settings, we used only two loading IVR for initial combination therapy. Furthermore, only few studies reported the prognostic factors after combination therapy [27,32–36]. In this study, we aimed to evaluate the prognostic factors for two loading doses of IVR and prompt vPDT as the initial treatment for PCV in a real-world setting.

2. Materials and methods

2.1. Study population

This is a retrospective cohort study which adhered to the tenets of the Declaration of Helsinki. Institutional Review Board approval was obtained from National Taiwan University Hospital (NTUH). Patients who were diagnosed as PCV and received the combination therapy of two loading doses of IVR with prompt vPDT for PCV at NTUH from July 2012 to June 2016 were retrospectively recruited. Inclusion criteria included: (1) one or more polyps with early subretinal focal hyperfluorescence detected by ICGA and active leakage shown on fluorescein angiography; and (2) any of the following features including subretinal hemorrhage, sub-RPE hemorrhage, intraretinal cyst (IRC), SRF and serous RPED documented by fundus photography taken with Canon CR-DGi (Canon Inc., Tokyo, Japan) or optical coherence tomography (OCT) by Cirrus OCT (Carl Zeiss Meditec, Inc, Dublin, CA) or RTVue Premier (Optovue, Inc, Fremont, CA). Exclusion criteria included: (1) eyes with suspected central serous chorioretinopathy; (2) concurrent retinal vascular diseases such as diabetic retinopathy or retinal venous occlusion; and (3) intravitreal or posterior subtenon injection of triamcinolone acetonide, previous intravitreal injection of anti-VEGF, any retinal laser, or any intraocular surgery within three months before treatment. For the patients with both eyes matching the inclusion criteria, only the eye which received treatment first was recruited.

2.2. Treatment protocol

All eyes received IVR at 0.5 mg per eye, followed by the standard vPDT treatment (verteporfin 6 mg/m^2, full laser irradiance 600 mW/cm^2, treatment time 83 s) within one week. The PDT was applied to the whole lesions demonstrated by ICGA, including the polypoidal lesions and branching vascular networks. Second IVR was performed one month after the initial loading treatment. After the loading treatment, repeated vPDT treatment was performed only in the presence of persistent or new polypoidal lesion on ICGA along with SRF or new subretinal hemorrhage, with an interval of at least three months since the previous PDT. On the other hand, additional IVR would be administered if there was persistent disease activity (subretinal hemorrhage, sub-RPE hemorrhage, IRC, SRF or serous RPED) on OCT with an interval of at least 28 days since the previous IVR.

2.3. Outcome measurements

BCVA and OCT parameters including central retinal thickness (CRT), SRF, serous RPED, and IRC were recorded at baseline, Month 3, Month 6, and Month 12. Polyp regression was detected by ICGA performed at Month 3 and categorized as complete regression (disappearance of the hyper-fluorescence in all polyps), partial regression (decreased polyp number and/or the size of the hyper-fluorescent area), or no regression (persistent polyps without decrease in number or size). Possible vPDT-related hemorrhage was defined as new subretinal or sub-RPE hemorrhage occurring within 3 months after vPDT [18]. Recurrent hemorrhage, which was defined as new subretinal or sub-RPE hemorrhage occurring three months after vPDT, was also recorded during the follow-up period. Hemorrhagic events were documented by color fundus photography.

Table 1
Baseline characteristics.

Baseline Characteristics	Mean ± SD or n (%)
Age (year)	68.7 ± 9.5
Sex, female	22 (35.5%)
LogMAR of BCVA(Snellen)	0.64 ± 0.38 (20/87)
Central retinal thickness (μm)	303 ± 91
Greatest linear dimension (μm)	3066 ± 1340
Subfoveal / juxtafoveal polyps	38 (61.3%)
Multiple polyps	42 (67.7%)
Subretinal hemorrhage	38 (61.3%)
Subretinal fluid	49 (79.0%)
Serous RPED	29 (46.6%)
Intraretinal cysts	24 (38.7%)
Previous anti-VEGF	25 (40.3%)

BCVA, best-corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution; RPED, retinal pigment epithelium detachment; VEGF, vascular endothelial growth factor.

2.4. Statistical analysis

Paired *t*-tests were used for the comparison of logarithm of the minimum angle of resolution (logMAR) of BCVA and CRT at baseline and after treatment. Fisher's exact tests were used for comparing categorical data, and Kruskal-Wallis tests were used for comparing numerical data. Multiple linear regression models were used to analyze the prognostic factors for visual improvement at Month 12 with adjustment for baseline BCVA. A *P* value of less than 0.05 was considered statistically significant. SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

3. Results

Sixty-two eyes from 62 patients were recruited in this study. The mean age was 68.7 ± 9.5 years, and 35.5% of the patients were female. Multiple polyps were detected in 42 eyes (67.7%). Among all eyes, 25 eyes had previously received anti-VEGF treatment, whereas 37 eyes were treatment-naïve. The baseline characteristics are shown in Table 1.

3.1. Treatment outcomes

On average, the numbers of IVR administered was 3.4 ± 1.5 (range: 2–7), and the numbers of vPDT performed was 1.4 ± 0.6 (range: 1–3) within one year. Only one case had new subretinal hemorrhage with suspected polyp rupture within two months of the initial vPDT (Fig. 1). No other cases had RPE tear during the follow-up periods. After treatment, the mean logMAR of BCVA improved significantly from 0.64 ± 0.38 (20/87) at baseline to 0.50 ± 0.40 (20/63) at Month 3 ($P < 0.001$), 0.55 ± 0.42 (20/70) at Month 6 ($P = 0.008$), and 0.55 ± 0.46 (20/70) at Month 12 ($P = 0.008$) (Fig. 2). At Month 12, 30 of the 62 eyes (48.4%) showed improved vision (change in logMAR of BCVA of -0.1 or less), 22 eyes (35.5%) maintained stable in vision ($-0.1 <$ change in logMAR of BCVA < 0.1), while ten eyes (16.1%) experienced visual deterioration (change in logMAR of BCVA of 0.1 or more).

The mean CRT decreased from 303 ± 91 μm at baseline to 244 ± 74 μm at Month 3 ($P < 0.001$), 250 ± 78 μm at Month 6 ($P < 0.001$), and 254 ± 83 μm at Month 12 ($P = 0.002$) (Fig. 2). The changes in OCT characteristics after treatment are shown in Fig. 3.

3.2. Polyp regression

Of the 62 eyes, 28 (45.2%) received ICGA at Month 3. Among those eyes, complete polyp regression was noted in 15 eyes (53.6%), partial regression was noted in 11 eyes (39.3%), and two eyes (7.1%) had no

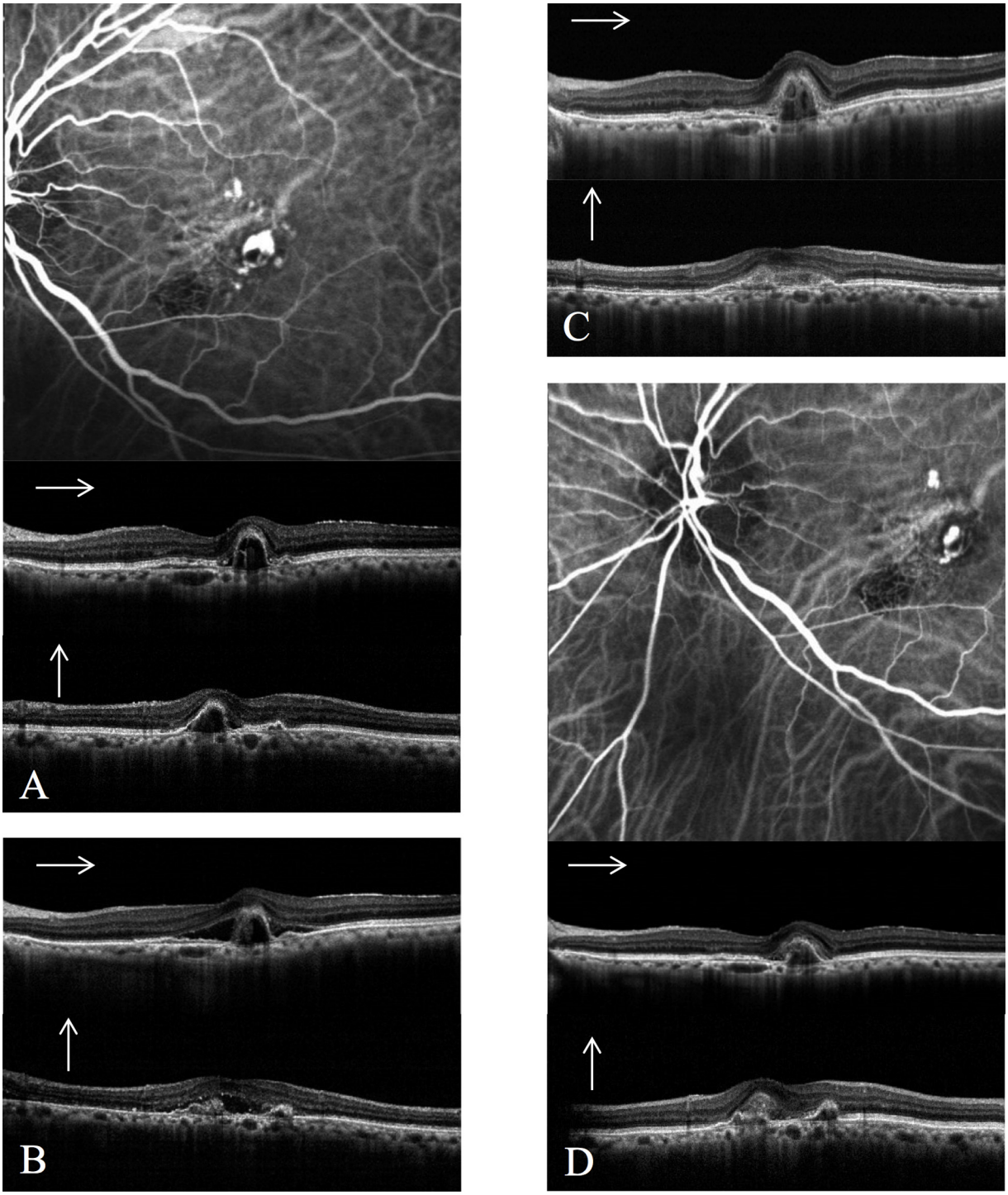

Fig. 1. An 82-year-old female patient who had mild subfoveal hemorrhage at her left eye after receiving the combination therapy. (A) Optical coherence tomography (OCT) revealed a U-shaped retinal pigment epithelial detachment which represented the presence of polyp at temporal and inferior juxtafoveal areas, and indocyanine green angiography (ICGA) revealed several clustered or confluent polyps at fovea and branched vascular network, as well as several small polyps at perifoveal area. The best-corrected visual acuity (BCVA) was 20/63. (B) Three weeks after photodynamic therapy (PDT), increased subretinal fluid, collapse of the polyp at inferior juxtafoveal area with suspected rupture and hemorrhage within the polyps were noted. The BCVA was still 20/63. (C) Seven weeks after PDT, the subretinal fluid resolved, while the hemorrhage within and outside the polyps slightly increased. The BCVA remained at 20/63. (D) Three months after PDT, the subretinal hemorrhage mostly resolved, while the ICGA revealed that the polyps at fovea decreased in numbers and sizes, and most small polyps at perifoveal area regressed. The BCVA remained at 20/63.

regression. Baseline characteristics were compared between eyes with complete, partial, or no polyp regression (Table 2); only the percentages of eyes with multiple polyps were significantly different among the groups ($P = 0.004$). Among the 21 eyes with multiple polyps, ten of them (47.6%) had complete polyp regression and eleven had partial regression (52.4%). Among the remaining seven eyes with single polyp, five (71.4%) showed complete polyp regression after the initial treatment and two (28.6%) had no regression.

For those with complete polyp regression, visual improvement was noted with a borderline significance at Month 3 ($P = 0.054$), and such

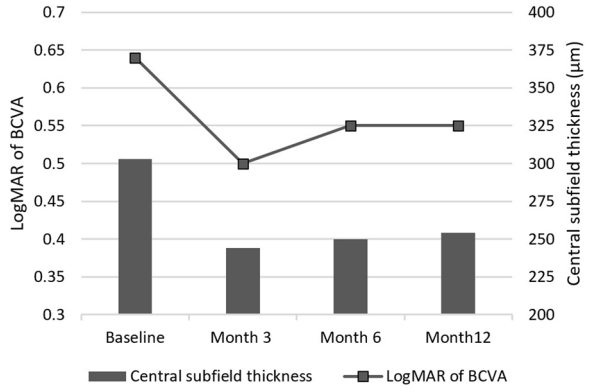

Fig. 2. Changes in the mean logarithm of the minimum angle of resolution of best-corrected visual acuity and central retinal thickness after combined ranibizumab and verteporfin photodynamic therapy.

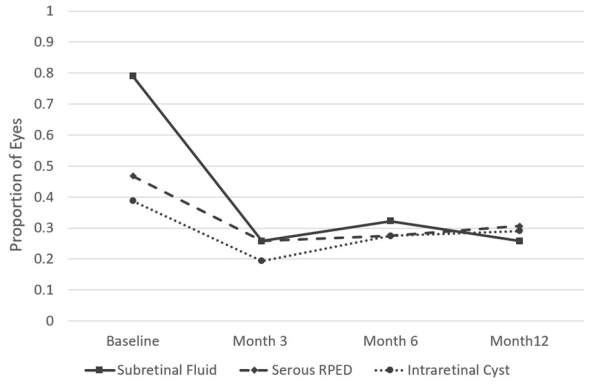

Fig. 3. Changes in the proportions of eyes with subretinal fluid, serous retinal pigment epithelial detachment, and intraretinal cyst after combined ranibizumab and verteporfin photodynamic therapy.

improvement maintained at Month 12 ($P = 0.10$). For those with partial polyp regression, visual improvement was noted at Month 3 ($P = 0.15$) but deteriorated again at Month 12 ($P = 0.85$). For the two eyes with no polyp regression, there was no visual improvement at Month 3 and 12 (Fig. 4A).

3.3. Recurrent hemorrhage

Recurrent subretinal or sub-RPE hemorrhage happened in 11 of the 62 eyes (17.8%) at a mean of 6.1 ± 2.0 months (range, 3.3–10.0 months) within one-year follow-up. Table 3 showed the characteristics in eyes with or without recurrent hemorrhage. Eyes with recurrent hemorrhage had a thinner baseline CRT (246 ± 73 μm) than those without recurrent hemorrhage (317 ± 90 μm) ($P = 0.025$). Nine of the 11 (81.8%) eyes who had recurrent hemorrhage had previously received anti-VEGF treatment, which was significantly higher than the proportion of anti-VEGF treated eyes among those with no recurrent hemorrhage (16/51 = 31.4%) ($P = 0.005$). For the 28 eyes receiving ICGA at Month 3, eight of them had recurrent hemorrhage. Those with complete polyp regression had the lowest rate of recurrent hemorrhage (2/15 = 13.3%); those with partial polyp regression had a higher rate of recurrent hemorrhage (4/11 = 36.3%); those without polyp progression had the highest recurrent hemorrhage (2/2 = 100%) ($P = 0.038$).

For those without recurrent hemorrhage, significant visual improvement was noted at Month 3 ($P < 0.001$) and such improvement persisted at Month 12 ($P < 0.001$). For those with recurrent hemorrhage, visual improvement was noted at Month 3 ($P = 0.10$) but deteriorated to a poorer vision than baseline at Month 12 ($P = 0.10$) (Fig. 4B).

3.4. Prognostic factors for visual improvement at month 12

The correlations between baseline and follow-up characteristics and change in logMAR of BCVA at Month 12 were analyzed using multiple linear regression models (Table 4). Eyes that had received previous anti-VEGF treatments had poorer visual improvement than treatment-naïve eyes ($P = 0.017$). Those with recurrent hemorrhage also had poorer visual improvement at Month 12 ($P = 0.001$). Compared to eyes with complete polyp regression, those with partial or no progression tended to have poorer visual improvement, although the differences were statistically insignificant ($P = 0.20$ and 0.58, respectively). Other baseline factors, such as lesion size, number of polyps, and OCT characteristics, showed no significant correlation with visual improvement at Month 12.

4. Discussion

The current study demonstrated that eyes with incomplete or no polyp regression experienced more recurrent hemorrhage, which along with previous anti-VEGF treatment were two prognostic factors for poor visual improvement after combined ranibizumab and vPDT for PCV. Only few existing studies have investigated the prognostic factors for PCV treatment with combination therapy [27,32–36]. For eyes treated with vPDT and intravitreal injection of bevacizumab, those with smaller and more distant polyps had better visual prognosis [34].

Table 2
Predicting factors for polyp regression at Month 3 by Kruskal-Wallis tests or Fisher's exact tests.

	Mean ± SD or n (%)			*P* value
	Complete regression (n = 15)	Partial regression (n = 11)	No regression (n = 2)	
Age (year)	71.7 ± 10.7	70.9 ± 9.0	64.5 ± 3.5	0.340
Sex, female	8 (53.3%)	8 (72.7%)	1 (50%)	0.610
LogMAR of BCVA at baseline (Snellen)	0.67 ± 0.44 (20/94)	0.71 ± 0.37(20/103)	0.46 ± 0.34(20/58)	0.610
Central retinal thickness at baseline (μm)	308 ± 100	288 ± 83	175 ± 16	0.064
Greatest linear dimension (μm)	3453 ± 1372	3563 ± 1930	1700 ± 990	0.150
Subfoveal / juxtafoveal polyps	8 (53.3%)	8 (72.7%)	0 (0%)	0.200
Multiple polyps	10 (66.7%)	11 (100%)	0 (0%)	0.004
Subretinal hemorrhage at baseline	10 (66.7%)	8 (72.7%)	1 (50%)	1.000
Subretinal fluid at baseline	13 (86.7%)	9 (81.8%)	0 (0%)	0.057
Serous RPED at baseline	7 (46.7%)	6 (54.6%)	0 (0%)	0.600
Intraretinal cyst at baseline	4 (26.7%)	3 (27.3%)	0 (0%)	1.000
Previous anti-VEGF	5 (33.3%)	5 (45.5%)	1 (50%)	0.850

BCVA, best-corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution; RPED, retinal pigment epithelium detachment; VEGF, vascular endothelial growth factor.

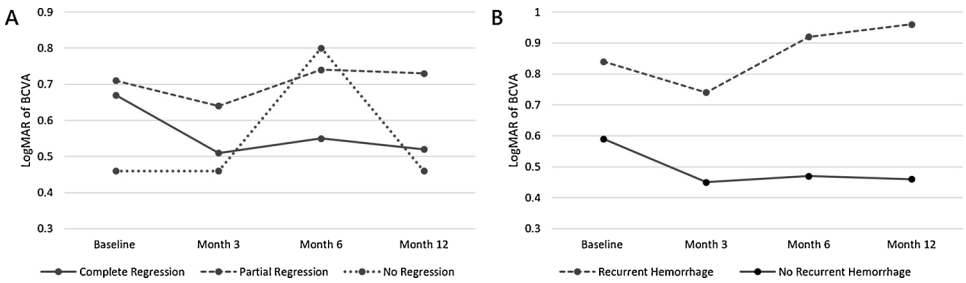

Fig. 4. (A) Changes in the mean logarithm of the minimum angle of resolution of best-corrected visual acuity for eyes with different statuses of polyp regression at Month 3. (B) Changes in the mean logarithm of the minimum angle of resolution of best-corrected visual acuity in eyes with or without recurrent hemorrhage within 1 year.

Table 3
Predicting factors for recurrent hemorrhage by Kruskal-Wallis tests or Fisher's exact tests.

	Mean ± SD or n (%)		*P* value
	Recurrent hemorrhage (n = 11)	No recurrent hemorrhage (n = 51)	
Age (year)	69.9 ± 9.7	68.4 ± 9.5	0.83
Sex, female	7 (63.6%)	33 (64.7%)	1
LogMAR of BCVA at baseline	0.84 ± 0.44 (20/138)	0.59 ± 0.36 (20/78)	0.13
Central retinal thickness at baseline (μm)	246 ± 73	317 ± 90	0.025
Greatest linear dimension (μm)	3536 ± 2333	2962 ± 1015	0.69
Subfoveal / juxtafoveal polyps	8 (72.7%)	29 (58.0%)	0.50
Multiple polyps	7 (63.6%)	34 (69.4%)	0.73
Subretinal hemorrhage at baseline	7 (63.6%)	31 (60.8%)	1
Subretinal fluid at baseline	8 (72.7%)	39 (83.0%)	0.42
Serous RPED at baseline	7 (63.6%)	20 (42.6%)	0.32
Intraretinal cyst at baseline	4 (36.4%)	18 (38.3%)	1
Previous anti-VEGF	9 (81.8%)	16 (31.4%)	0.005
Polyp Regression at Month 3 (complete regression:partial regression:no regression)	2: 4:2	13:7:0	0.038

BCVA, best-corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution; RPED, retinal pigment epithelium detachment; VEGF, vascular endothelial growth factor.

Table 4
Prognostic factors for change of logarithm of the minimum angle of resolution of best-corrected visual acuity at Month 12 by multiple linear regression analysis with adjustment for baseline BCVA.

	Coefficient	*P* value
Age (year)	−0.001	0.78
Sex (F:0, M:1)	0.097	0.18
LogMAR of BCVA at baseline	−0.021	0.83
Central retinal thickness at baseline (μm)	$5.77*10^{-4}$	0.16
Greatest linear dimension (μm)	$4.32*10^{-6}$	0.88
Extrafoveal vs. subfoveal / juxtafoveal polyps	0.097	0.19
Single polyp vs. multiple polyps	−0.004	0.96
Subretinal hemorrhage at baseline	−0.014	0.85
Subretinal cyst at baseline	0.021	0.82
Serous RPED at baseline	0.083	0.25
Intraretinal cyst at baseline	−0.072	0.35
Treatment naïve vs. previous anti-VEGF	0.171	0.017
Polyp regression at Month 3		
Complete regression	0 (reference)	
Partial regression	0.168	0.20
No regression	0.137	0.58
Recurrent hemorrhage	0.286	0.001

BCVA, best-corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution, RPED, retinal pigment epithelium detachment; VEGF, vascular endothelial growth factor.

Greatest linear dimension at baseline also predicted visual improvement in patients treated with vPDT and intravitreal injection of aflibercept [36]. As for those treated with vPDT and ranibizumab, poor baseline visual acuity [27], abnormal choroidal vasculature in foveal avascular zone [27], male gender [35] and larger greatest linear dimension [35] all predicted poor visual outcome. Subretinal hemorrhage due to recurrent polyps outside the PDT lesion was associated with visual acuity loss after treatment [32] Recently, with the aid of enhanced depth imaging OCT, Baek et al. [33] reported the pachychoroid feature and high vascularity had greater response to combination therapy. In contrast, we found that neither the size and location of polyps nor the baseline OCT characteristics were associated with visual improvement in the present study. The only two factors that were significantly correlated with poor visual improvement were recurrent hemorrhage and previous anti-VEGF treatment. Recurrent hemorrhage will further damage RPEs and photoreceptors and inevitably lead to poor visual outcome [34]. Consistent with our study, Cho et al. reported that eyes with massive submacular hemorrhage during follow-up had poor visual outcome. They also found that the cluster type of polyp had a higher risk of massive submacular hemorrhage, while the eyes treated with PDT followed by anti-VEGF injections had a lower rate of hemorrhage [37]. In the present study, 17.8% of eyes experienced recurrent hemorrhage after the loading treatment; eyes with complete polyp regression had a lower rate of recurrent hemorrhage (13.3%) than those with partial or polyp regression (36.4% and 100%, respectively). Eyes with complete polyp regression had significant visual improvement during the one-year follow-up, while those with partial polyp regression did not. Our observation emphasized the clinical importance of achieving polyp regression, which may be associated with a lower risk of recurrent hemorrhage and the resulting visual loss.

Nowadays, the combination therapy has been proposed as the first-line therapy based on previous clinical trial and real-world experience [21,29,31,32,38,39]. Work synergistically, PDT had the pro-thrombotic effect on the polyps, and the anti-VEGF targeted the leaking vessels. Moreover, anti-VEGF offset the rising VEGF after the application of PDT [19,20]. Despite of similar effect on polyp regression, it achieved better visual outcome, better anatomical improvement, and less vPDT-related hemorrhage than vPDT monotherapy [2,22,38]. The combination therapy also achieved superior visual acuity improvement, higher complete polyp regression rate, and required fewer injections than anti-VEGF monotherapy, which is important for real-world practicing [3,21]. However, a standard regimen is yet to be determined. The loading dosage of three monthly injections of anti-VEGF was based on the guideline of nAMD treatment and was used in most of the existing studies [21]. However, Lee et al. showed that the aqueous VEGF level remained undetectable in most patients three months after the initial IVR and vPDT [20]. They suggested that the three consecutive monthly anti-VEGF injections may not be a necessary loading treatment. In a real-world setting, economic burden may stop patients from completing treatment. In Taiwan, only vPDT but not anti-VEGF was reimbursed for PCV before December 2016. Therefore, we administered only two instead of three consecutively monthly IVR as the initial therapy accompanied with vPDT in this study. The mean improvement in logMAR of BCVA was 0.14 at Month 3 and 0.09 at Month 12, which was

comparable to the other real-world outcomes that also used combined anti-VEGF and vPDT for PCV in the literature [23,24,27,29,31,32,39]. The polyp regression rate was also similar to previous studies [27,29,31,32], with 53.6% of complete polyp regression and 39.3% of partial regression. The mean numbers of IVR was 3.4, which was less than those in EVEREST II study (5.2) and the real-world studies adopting combination therapy with three initial consecutive monthly IVR (3.4˜5.1) [3,23,26,29,31], and much less than the numbers in the studies using anti-VEGF monotherapy (4˜8.6) [2,3,21,23,38,40]. The mean number of vPDT within one year was 1.4, which is also similar to the results in the EVEREST II study (1.5) [21] and real-world studies (1.1˜1.7) [3,23,26,29,31]. This means that 2 doses of ranibizumab in combination with vPDT are good enough as the initial therapy for PCV. Such results are important because the fewer injection numbers in the present study are easier to achieve in a real-world setting due to the limitation of reimbursement and economic burden. Since comparable outcomes and benefits could be accomplished with fewer injections, two consecutive monthly IVR could be considered as the loading treatment in the combination therapy for real-world practicing.

Verteporfin PDT may induce hemorrhagic complications because of the change in choroidal blood flow even in combination with anti-VEGF, although such hemorrhage usually resolves without treatment and had minor negative effect on visual outcome [13]. In the EVEREST II trial, more patients in the combined therapy group had retinal hemorrhage than those receiving IVR monotherapy; however, they still preserved better visual acuity overall [21]. In the present study, only one eye showed possible vPDT-related polyp rupture and hemorrhage. The extent was limited and it did not impair visual acuity. Taken together, the combination therapy is relatively safe and the hemorrhagic complication does not constitute a major concern.

Most previously published real-world studies about PCV recruited only treatment-naïve eyes. Tomita et al. [24] reported a group of 66 PCV patients treated with combination therapy, of whom 10 had been treated previously with intravitreal injections of anti-VEGF, and 27 had been treated previously with PDT. They found that the PDT-treated eyes had the worst visual improvement after combination therapy, while there was no difference between treatment-naïve eyes and anti-VEGF treated eyes [24]. We also recruited and included patients who had received prior anti-VEGF treatments in the present study because this was more relevant to the real-world settings. We found that those who had received anti-VEGF treatments previously had a higher rate of recurrent hemorrhage and poorer visual improvement. The reason might be that patients with persistent polyp and disease activity after prior anti-VEGF treatment have had longer disease durations and have suffered more severe damage to the photoreceptors and RPEs. On the other hand, the rate of polyp regression after the initial combination treatment was not inferior in these patients according to the present study. Therefore, combined treatment of ranibizumab and vPDT remains an optimal therapy for these patients having received anti-VEGF treatments previously, but they may need more frequent follow-ups and more aggressive treatment subsequently.

This study has some limitations because of its retrospective nature. First, ICGA was only performed in 45.2% eyes at Month 3. It is possible that patients with good responses to the treatment were less likely to receive repeated ICGA. Indeed we found that patients who received ICGA at Month 3 had a higher rate of recurrent hemorrhage than those who did not (28.6% vs 8.8%, $P = 0.052$), although the visual acuity was not significantly different between these two groups. Second, the evaluation of poly regression may be confounded by size and number of polyps. Compared to multiple or larger polyps, single polyp had more chance to be classified as complete regression. Third, the follow-up intervals after Month 3 varied, ranging from one month to three months. Longer follow-up interval may cause delayed treatment and result in poor visual prognosis for those with recurrent disease activity. However, this better reflect the real-world practice where it is difficult to follow every patient monthly. Long-term follow-up is necessary in the future investigation.

In conclusion, we found that recurrent hemorrhage was the key associating factor for poor visual improvement after combined ranibizumab and prompt vPDT for PCV, and incomplete polyp eradication was a predicting factor for recurrent hemorrhage. Patients who had previously received anti-VEGF were also associated with poor visual outcomes; more frequent follow-ups and more aggressive subsequent treatments may be needed for these cases.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

The work was completed in the Department of Ophthalmology, National Taiwan University Hospital, Taipei, Taiwan. No authors have any conflict of interest or source of funding to disclose. English editing was provided by the Department of Medical Research at National Taiwan University Hospital.

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