

REVIEW

Polypoidal choroidal vasculopathy treatment options: A meta-analysis

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Abstract

Background: Combined treatment with intravitreal anti-vascular endothelial growth factor (anti-VEGF) and verteporfin photodynamic therapy (PDT) is widely used for patients with polypoidal choroidal vasculopathy (PCV), although clinical evidence regarding the therapeutic efficacy and safety of such treatment remains lacking.

Design/Methods: We performed a meta-analysis of previously reported studies comparing combination treatment, PDT monotherapy, and anti-VEGF monotherapy. Primary outcome measures included changes in best-corrected visual acuity (BCVA) and central retinal thickness (CRT). The proportion of patients with polyp regression was regarded as the secondary outcome measure.

Results: Twenty studies (three RCTs and 19 retrospective studies) involving 1,178 patients with PCV were selected. Significant differences in the proportion of patients with polyps were observed between the PDT and anti-VEGF monotherapy groups at 3 and ≥ 6 months ($P < .00001$; and $P = .0001$, respectively). Significantly greater reductions in CRT were observed in the anti-VEGF than in the PDT group at the 3-month follow-up ($P = .04$). Significantly greater improvements in BCVA were observed in the combined therapy group than in the PDT monotherapy group at 3, 6, 12, and 24 months ($P = .03$; $P = .005$; $P = .02$; and $P < .00001$, respectively). Combined treatment also resulted in significantly greater improvements in BCVA than monotherapy with anti-VEGF at 6 and 24 months ($P = .001$; $P < .00001$, respectively), and significantly greater polyp regression than that observed following anti-VEGF treatment at 3 and ≥ 6 months ($P < .00001$; $P < .0001$, respectively).

Conclusions: Combined therapy involving anti-VEGF agents and PDT may be more effective in improving long-term outcomes for patients with PCV than monotherapy.

KEYWORDS

combination therapy, intravitreal anti-VEGF, meta-analysis, photodynamic therapy, polypoidal choroidal vasculopathy

Qian and Li contributed equally to the work of this manuscript.

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1 | INTRODUCTION

Polypoidal choroidal vasculopathy (PCV), first identified and reported by Yannuzzi et al¹ is a clinically distinct choroidal abnormality with a high prevalence in Asian populations.² PCV is characterised by an abnormal branching vascular network (BVN) and polypoid dilations observed via indocyanine green angiography (ICGA), which is the gold standard for diagnosing PCV.³ The main therapeutic strategies for PCV vary according to the clinical pathological manifestations of the disease and include intravitreal anti-vascular endothelial growth factor (VEGF) agents, verteporfin photodynamic therapy (PDT), and combined therapy with anti-VEGF and PDT.

Currently, PDT is widely regarded as effective in the treatment of PCV due to the regression of polyp-like dilations in spite of the relative lack of visual improvement within 2 years.⁴ Wong et al⁵ also reported that the visual outcome in eyes with PCV was stable until 2 years, while the outcome at 3 years worsened, particularly in eyes that experienced recurrence.

Anti-VEGF agents such as bevacizumab, ranibizumab, and aflibercept are recombinant humanised monoclonal antibodies that have been reported to improve visual functioning by restoring normal retinal thickness and reducing elevated levels of VEGF.⁶ However, research has suggested that anti-VEGF therapy is less effective in ensuring the regression of polyps and that the risk of subretinal haemorrhage increases following PDT monotherapy.^{7,8}

Considering the advantages and disadvantages of PDT monotherapy and anti-VEGF monotherapy,^{7,9} combined treatment with anti-VEGF agents and PDT may result in both regression of polyps and anti-angiogenesis. However, there is currently no consensus regarding the appropriate treatment for PCV.

Several meta-analyses¹⁰⁻¹² to date have compared various treatments for PCV, although these studies have not been comprehensive. For example, Tang et al¹¹ analysed only those studies involving ranibizumab, while Wang et al¹² failed to compare anti-VEGF monotherapy to PDT monotherapy. To evaluate the best therapeutic strategy for PCV, we performed a comprehensive meta-analysis to compare the efficacy of PDT monotherapy, monotherapy with intravitreal anti-VEGF agents, and combined treatment with PDT and anti-VEGF agents. Therapeutic effect estimates were determined based on the means and standard deviations (SD) of changes in best-corrected visual acuity (BCVA), relative to baseline, using the logarithm of the minimum angle of resolution (logMAR); reductions in central retinal thickness (CRT) at follow-up points; and the proportion of patients exhibiting polyp regression following treatment. We also evaluated the occurrence of ocular adverse events, including subretinal haemorrhage, which are essential in determining the most appropriate course of treatment for PCV.

2 | MATERIALS AND METHODS

Reporting of the study conforms to PRISMA statement and the broader EQUATOR guidelines.¹³

2.1 | Literature search

Five databases (PubMed, EMBASE, Web of Science, Medline and Cochrane Library) were last searched for relevant studies on December 31, 2016. The following terms were used and adapted for the searches in each database: (“polypoidal choroidal vasculopathy” OR PCV) AND (“vascular endothelial growth factors” OR “anti-VEGF” OR “angiogenesis inhibitors” OR ranibizumab OR lucentis OR “Rhu-Fab V2” OR bevacizumab OR avastin OR aflibercept OR VEGF-Trap) AND (“photodynamic therapy” OR PDT). There was no restriction on language or study design. When titles and/or abstracts fit the index words, the full article was retrieved.

2.2 | Inclusion and exclusion criteria

The following inclusion criteria were used for the present meta-analysis: (i) comparative study design; (ii) comparison of anti-VEGF+PDT vs PDT treatment, or anti-VEGF vs PDT treatment, for PCV; (iii) population consisting of treatment-naïve patients with PCV of any sex and race; and (iv) report of at least one of the following outcomes: best-corrected visual acuity (BCVA), central retinal thickness (CRT), proportion of patients who achieved complete regression of polyps, and incidence of subretinal haemorrhage. Reports with incomplete text, full text without raw data, review articles, case reports, meeting abstracts, and duplicate publications were excluded, along with those including patients who had received previous treatment for PCV. Patients whose initial therapeutic strategy had changed were also excluded. For cases in which articles reported results associated with the same trial, the most recent report was included, although additional data could be obtained from previous reports.

2.3 | Data extraction and quality assessment

Data regarding the following study characteristics were extracted from all included studies: (i) basic information: name of first author, the year of publication, location of the study, and trial design; (ii) patient information: age, gender, duration of follow-up; (iii) treatment details: intervention groups (including sample number); and (iv) outcomes: means and standard deviations (SDs) of BCVA and CRT after treatment at a specific follow-up period, the number of patients who achieved complete regression of polyps, and the number of patients with subretinal haemorrhage.

Data not reported in articles was obtained from *ClinicalTrials.gov* when necessary, if available.

We also evaluated the methodological quality of included RCTs, which were analysed for bias using the Cochrane Risk of Bias Tool,¹⁴ while the methodological quality of retrospective studies was assessed using the modified Newcastle-Ottawa scale,¹⁵ which consists of three factors: patient selection, comparability of the study groups, and outcome assessment. A score of 0-9 stars is allocated to each study, except RCTs. RCTs and retrospective studies achieving seven or more stars are considered to be of high quality.

2.4 | Evaluation indicators

Indicators of treatment efficacy included mean changes in BCVA and CRT, as well as the extent of polyp regression from baseline at different follow-up points. Safety indicators included the incidence of subretinal haemorrhage following treatment.

2.5 | Statistical analysis

Statistical analysis was performed using Review Manager 5.3.5 software (Cochrane Collaboration). In the present meta-analysis, continuous data (eg, BCVA) were expressed as means and standard deviations, and weighted mean differences (WMD) were calculated. Dichotomous data (eg, number of events) were evaluated via odds ratios (OR). Continuous outcomes were reported as mean differences with a 95% confidence interval (CI), while dichotomous outcomes were reported as risk ratios with 95% CI. A P value $<.05$ was considered statistically significant. A Chi-square test (P value) and the I^2 statistic were used to quantify the statistical heterogeneity among studies. If no heterogeneity among studies was observed ($P > .1$ or $I^2 < 50\%$), the fixed-effects model was used for the analysis; otherwise, the random-effects model was used. Forest plots were used to display the summary weighted estimates, while funnel plots were used to assess publication bias.

3 | RESULTS

3.1 | Search results

A total of 235 studies were initially identified using the index words, of which 92 were excluded as duplicate studies, 25 were excluded as reviews, 13 were excluded because of incomplete text, and 79 were excluded based on the titles and abstracts. The remaining 26 studies were retrieved for full-text review. Among them, two articles were excluded as case reports, and two articles were

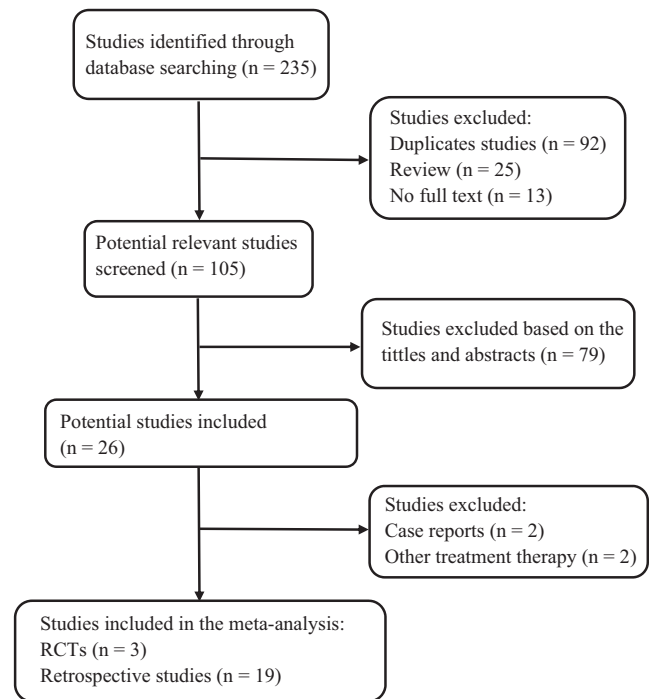


FIGURE 1 Flow diagram of literature screening

excluded because they included additional treatment strategies for PCV. A final total of 22 studies¹⁶⁻³⁷ were included in the present meta-analysis. The study selection process is shown in Figure 1.

3.2 | Characteristics of the eligible studies

The present meta-analysis included 22 studies with a total of 1,178 patients with PCV. The basic characteristics of these studies are shown in Table 1. The mean age of patients across all studies ranged from 53 to 75.8 years, while study duration ranged from 1 to 36 months. Among the included studies were three RCTs¹⁶⁻¹⁸ and 19 retrospective comparative studies.¹⁹⁻³⁷ Specific interventions and *pro re nata* (PRN) retreatment regimen used within each trial are listed in Table 1. All retrospective studies had received scores of at least seven stars and were considered to be of high quality.

3.3 | Comparison of intravitreal anti-VEGF monotherapy and PDT monotherapy

As BCVA is an essential functional outcome measure, we considered changes in BCVA to be most important for evaluating treatment efficacy. The pooled results revealed no significant difference in BCVA change between the PDT group and anti-VEGF group at 3, 6, 12, and 24 months in either RCTs or retrospective studies.

TABLE 1 Characteristics of the 22 trials

Trials (Author, y)	Location	Design	Treatment Group (patients)	Age (y)		Gender		GLD (μm)		Interventions	PRN retreatment regimen	Follow-up (mo)
				Mean	SD	M/F	Mean	SD				
Koh ¹⁵ , 2012	Singapore	RCT	IVR (n = 21)	69.3	8.27	15/6	<5400		PDT + IVR 0.5 mg	1 + PRN PDT, 3 + PRN IVR	1, 3, 6	
			PDT (n = 21)	62.2	9.77	15/6	<5400		PDT 6 mg/m ² + sham	1 + PRN PDT		
			IVR + PDT (n = 19)	63.8	8.30	11/8	<5400		IVR 0.5 mg	3 + PRN IVR		
Oishi ¹⁶ , 2013	Japan	RCT	IVR (n = 46)	75.4	6.9	28/18	3347.4 \pm 1288.3		IVR 0.5 mg	3 + PRN IVR	3, 6, 12	
			PDT (n = 47)	75.8	8.0	32/15	3051.1 \pm 1177.7		PDT 6 mg/m ²	1 + PRN PDT	24	
Lee ¹⁷ , 2013	Korea	RCT	PDT (n = 8)	66.33	7.85	5/3	NR		PDT 6 mg/m ²	NR	1, 3	
			IVR + PDT (n = 12)	63.68	8.78	11/1			IVR 0.5 mg + PDT 6 mg/m ²			
Lai ¹⁸ , 2008	Hong Kong	Retro	IVB (n = 8)	64.9	7.6	6/2	NR		IVB 1.25 mg	3 + PRN IVB	12	
			IVB + PDT (n = 7)	64.0	7.1	5/2			IVB 1.25 mg + PDT 6 mg/m ²	3 + PRN IVB, 1 + PRN PDT		
Lee ¹⁹ , 2008	Korea	Retro	IVB (n = 8)	63	7	3/1	NR		IVB 1.25 mg	1 + PRN IVB	6	
			IVB + PDT (n = 4)	53	7	8/0			IVB 1.25 mg + PDT	1 PDT, 1 + PRN IVB		
Lim ²⁰ , 2012	Korea	Retro	IVB (n = 5)	68.6	7.2	5/0	NR		IVB 1.25 mg	3 + PRN IVB	12	
			IVB + PDT (n = 5)	57.4	7.2	3/2			IVB 1.25 mg + PDT	3 + PRN IVB, 1 + PRN PDT		
Gomi ²¹ , 2010	Japan	Retro	PDT (n = 85)	70.9	6.8	68/17	2521 \pm 996		PDT	1 + PRN PDT	3, 6, 12	
			IVB + PDT (n = 61)	70.9	7.1	44/16	2626 \pm 1138		IVB 1.25 mg + PDT	1 + PRN IVB, 1 + PRN PDT		
Mitamura ²² , 2010	Japan	Retro	IVB (n = 22)	73.0	8.9	17/5	3651 \pm 1833		IVB 1.25 mg	NR	3	
			PDT (n = 49)	69.6	7.8	42/7	3718 \pm 1665		PDT			
Kim ²³ , 2011	Korea	Retro	PDT (n = 19)	65.9	8.4	13/6	3626.3 \pm 1334.6		PDT 6 mg/m ²	1 + PRN PDT	1, 3, 6, 9	
			IVB + PDT (n = 20)	64.8	8.3	15/5	3287.5 \pm 1335.9		IVB 1.25 mg + PDT 6 mg/m ²	1 + PRN IVB, 1 + PRN PDT	12	
Lai ²⁴ , 2011	Hong Kong	Retro	IVR (n = 7)	64.6	7.9	4/3	3610 \pm 2240		IVR 0.5 mg	3 + PRN IVR	3, 12	
			PDT (n = 12)	65.6	11.0	10/2	2580 \pm 707		PDT 6 mg/m ²	1 + PRN PDT		
Maruko ²⁵ , 2011	Japan	Retro	IVR + PDT (n = 16)	71.3	11.8	8/8	3490 \pm 1170		IVR 0.5 mg + PDT 6 mg/m ²	3 + PRN IVR, 1 + PRN PDT	1, 3, 6	
			PDT (n = 16)	71.8	10.4	12/4	3013 \pm 1059		PDT 6 mg/m ²	1 PDT (no PRN)		
Rouvas ²⁶ , 2011	Greece	Retro	IVR + PDT (n = 11)	71.0	9.8	6/5	2095 \pm 1122		IVR 0.5 mg + PDT 6 mg/m ²	3 IVR, 1 PDT (no PRN)	1, 3, 6	
			IVR (n = 16)	66.5		4/6	NR		IVR 0.5 mg	3 + PRN IVR	3, 6, 12	
Saito ²⁷ , 2011	Japan	Retro	PDT (n = 11)	62.9		5/6			PDT 6 mg/m ²	1 + PRN PDT		
			PDT + IVR (n = 9)	64.67		4/5			IVR 0.5 mg + PDT 6 mg/m ²	3 + PRN IVR, 1 + PRN PDT	3, 6	
Saito ²⁷ , 2011	Japan	Retro	IVR (n = 25)	75.1	6.4	21/4	5010 \pm 2055		IVR 0.5 mg	3 + PRN IVR	3, 6	
			PDT (n = 34)	74.8	6.3	26/8	4549 \pm 1692		PDT	1 + PRN PDT		

(Continues)

TABLE 1 (Continued)

Trials (Author, y)	Location	Design	Treatment Group (patients)	Age (y)		Gender		GLD (μm)		Interventions	PRN retreatment regimen	Follow-up (mo)
				Mean	SD	M/F	Mean	SD				
Song ²⁸ , 2011	Korea	Retro	IVR (n = 15)	60.6	± 10.7	6/9	NR	NR	NR	IVR 0.5 mg	1 + PRN IVR	12
			PDT + IVR (n = 9)	56.9	± 12.1	0/9				IVR 0.5 mg + PDT	1 + PRN IVR, 1 + PRN PDT	
Lee ²⁹ , 2012	Taiwan	Retro	PDT (n = 33)	65.6	± 9.5	18/15	2832	± 1092		PDT	1 + PRN IVR	3, 6, 9, 12
			PDT + IVB (n = 36)	67.8	± 9.8	21/15	2619	± 843		IVB 1.25 mg + PDT	1 + PRN IVR, 1 + PRN PDT	15, 18, 24
Inoue ³⁰ , 2013	Japan	Retro	IVR (n = 33)	73.2	± 7.5	19/14	4171	± 2631		IVR 0.5 mg	1 + PRN IVR	3, 6, 12
			PDT (n = 44)	71.0	± 7.8	30/14	3640	± 2120		PDT 50 J/cm ²	1 + PRN PDT	18, 24
Kang ³¹ , 2013	Korea	Retro	IVR (n = 23)	68.05	± 8.12	NR	2790.05	± 871.50		IVR 0.5 mg	3 + PRN IVR	3, 6, 12
			PDT (n = 19)	66.21	± 9.00		2810.87	± 974.10		PDT 6 mg/m ²	1 + PRN PDT	24
			IVB + PDT (n = 44)	70.00	± 7.75		2815	± 910.12		IVB 0.5 mg + PDT 6 mg/m ²	3 + PRN IVB, 1 + PRN PDT	
Saito ³² , 2013	Japan	Retro	PDT (n = 32)	75.0	± 6.5	27/59	4867	± 1855		PDT 6 mg/m ²	1 + PRN PDT	3, 6, 12
			IVR + PDT (n = 25)	74.0	± 8.6	17/8	4074	± 1459		IVR 0.5 mg + PDT 6 mg/m ²	3 + PRN IVR, 1 + PRN PDT	24
Sakurada ³³ , 2013	Japan	Retro	PDT (n = 34)	70.1	± 7.1	25/9	2364	± 716		PDT 6 mg/m ²	1 + PRN PDT	3, 6, 12
			IVR + PDT (n = 24)	73.2	± 7.4	16/8	2039	± 847		IVR 0.5 mg + PDT 6 mg/m ²	1 + PRN IVR, 1 + PRN PDT	24
Gomi ³⁴ , 2015	Japan	Retro	IVR (n = 35)	73.8	± 7.1	NR	NR	NR		IVR 0.5 mg	3 + PRN IVR, PRN PDT	3
			PDT + IVR (n = 37)	73.6	± 5.8					IVR 0.5 mg + PDT	3 + PRN IVR, 1 + PRN PDT	
Kikushima ³⁵ , 2016	Japan	Retro	IAI (n = 33)	72.7	± 8.5	25/8	2041	± 1273		IAI 2.0 mg	3 + PRN IAI	3, 6, 9, 12
			PDT + IAI (n = 33)	73.4	± 8.3	22/11	1692	± 747		IAI 2.0 mg + PDT 6 mg/m ²	1 + PRN IAI, 1 + PRN PDT	
Sakai ³⁶ , 2016	Japan	Retro	IVR (n = 20)	75.3	± 8.1	13/7	2937	± 1040		IVR 0.5 mg	3 + PRN IVR	6, 12, 18
			PDT + IVR (n = 25)	72.6	± 6.2	21/4	2800	± 823		IVR 0.5 mg + PDT 6 mg/m ²	3 + PRN IVR, 1 + PRN PDT	24, 30, 36

IVR, intravitreal ranibizumab; IVB, intravitreal bevacizumab; IAI, intravitreal aflibercept injection; PDT, photodynamic therapy; PRN, pro re nata.

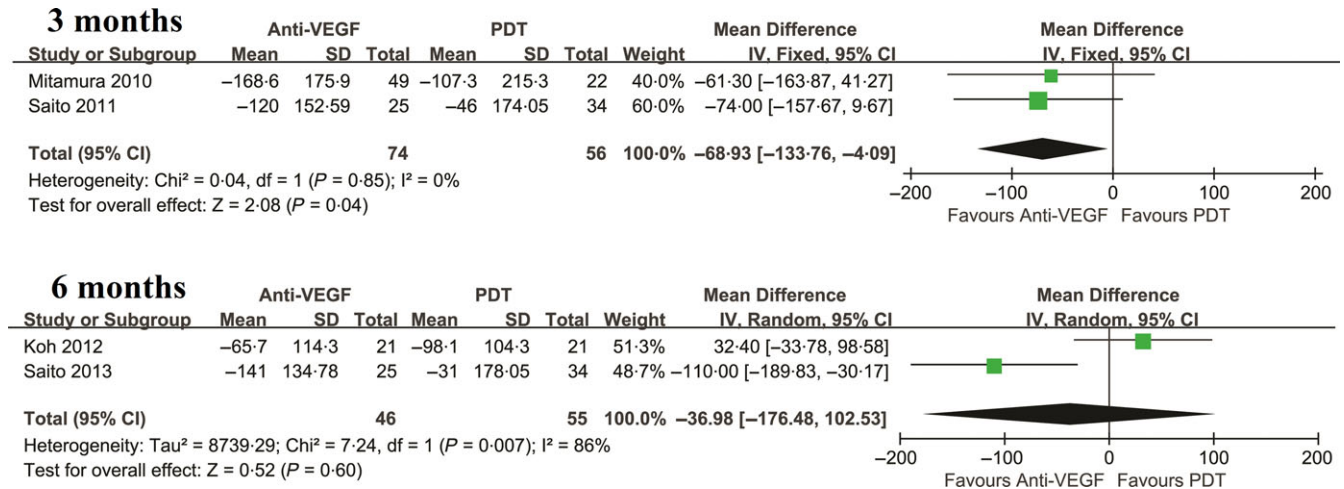


FIGURE 2 Mean change in CRT for the comparison of PDT and anti-VEGF at 3,6 mo. SD, standard deviation; IV, inverse variance; CI, confidence interval. PDT: photodynamic therapy; PCV: polypoidal choroidal vasculopathy; anti-VEGF: anti vascular endothelial growth factor

TABLE 2 Comparison of PDT monotherapy and anti-VEGF monotherapy for PCV

Outcome of interest	Studies (n)	WMD/OR (95% CI)	P	Study heterogeneity		
				χ^2	P	I^2 (%)
Comparison of mean change in BCVA from baseline at follow-up points (logMAR)						
3 mo	7	0.01 (-0.07, 0.08)	.86	13.66	.03	56
6 mo	5	0.01 (-0.06, 0.09)	.75	8.42	.08	52
12 mo	5	-0.01 (-0.13, 0.12)	.93	15.57	.004	74
24 mo	3	0.03 (-0.16, 0.22)	.77	10.49	.005	81
Comparison of mean change in CRT from baseline at follow-up points						
3 mo	2	-68.93 (-133.76, -4.09)	.04	0.04	.85	0
6 mo	2	-36.98 (-176.48, 102.53)	.60	7.24	.007	86
Comparison of the proportions of patients with polyp regression						
3 mo	3	15.23 (5.77, 40.20)	<.00001	3.11	.21	36
≥ 6 mo	2	6.32 (2.44, 16.38)	.0001	0.00	.98	0

PDT, photodynamic therapy; NA, not available; logMAR, logarithm of the minimal angle of resolution; CRT, central retinal thickness; PCV, polypoidal choroidal vasculopathy; anti-VEGF; anti-vascular endothelial growth factor; WMD, weighted mean difference; OR, odds ratio; CI, confidence interval; χ^2 , chi-square statistic; P, P-value; I^2 , I-square heterogeneity statistic; Bold italic values indicate statistically significant results.

Central retinal thickness (CRT) was also evaluated to assess changes in retinal health following treatment (Figure 2). The pooled results revealed that anti-VEGF agents significantly reduced CRT compared with PDT at 3 months ($P = .04$) with no heterogeneity ($P = .85$, $I^2 = 0\%$), although no significant difference was observed at 6 months. Furthermore, our results indicated that there were significant differences in polyp regression between the two groups at 3 and 6 or more months ($P < .00001$; and $P = .0001$, respectively).

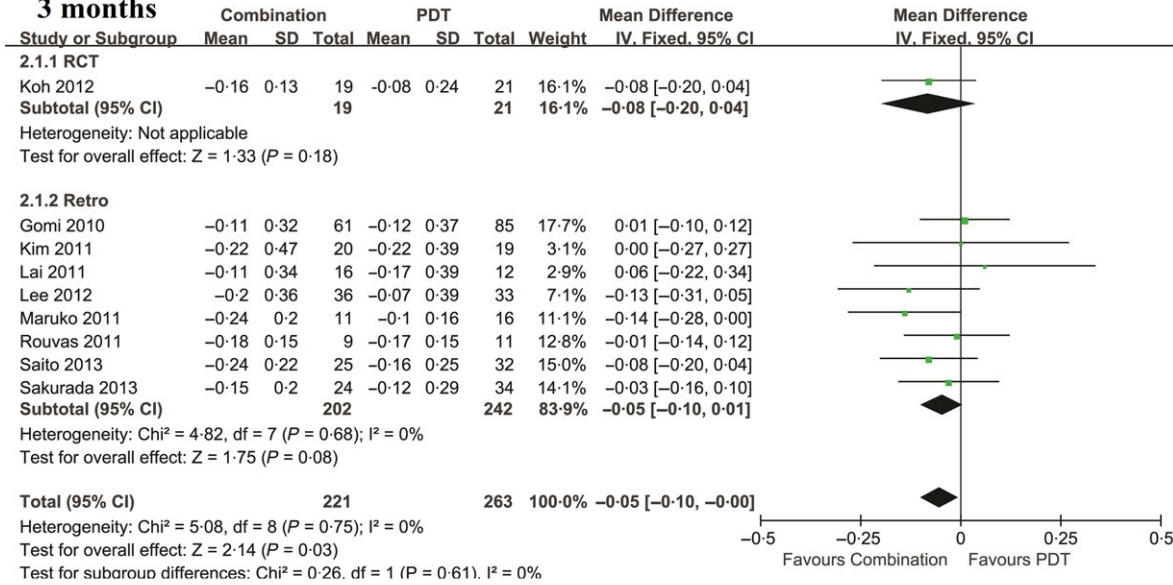
All results for the comparison of PDT monotherapy and anti-VEGF monotherapy for the treatment of PCV are shown in Table 2.

3.4 | Comparison of combined treatment and PDT monotherapy

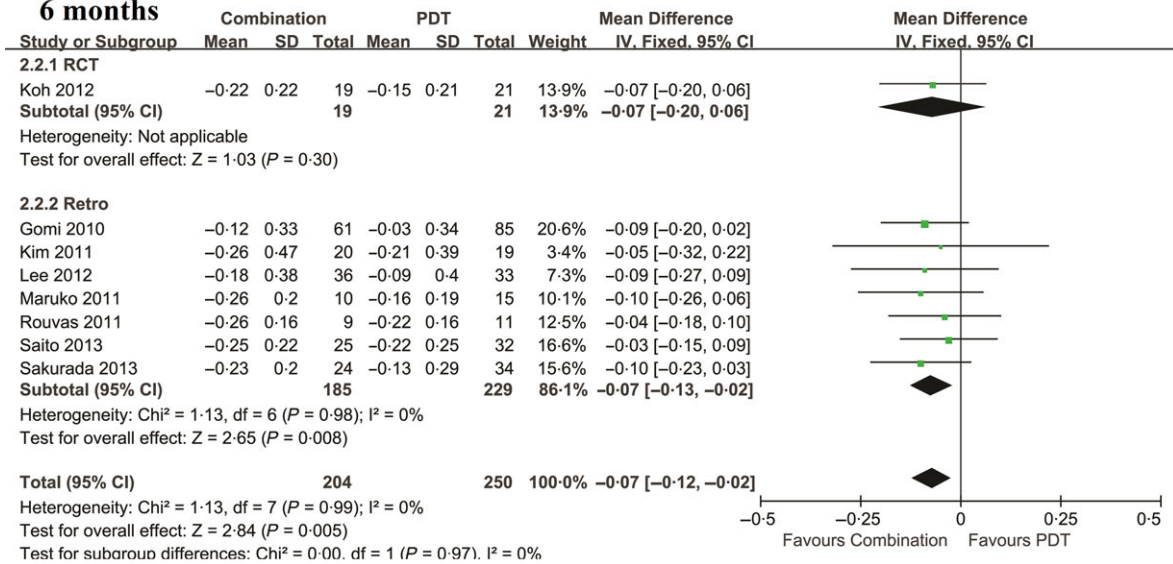
Combined treatment resulted in significantly greater improvements in BCVA than PDT monotherapy at 3, 6, 12, and 24-months after treatment in patients with PCV

FIGURE 3 Mean change in BCVA for the comparison of combined therapy and PDT monotherapy at 3, 6, 12, and 24 mo. SD, standard deviation; IV, inverse variance; CI, confidence interval; BCVA; best corrected visual acuity; PDT: photodynamic therapy; PCV: polypoidal choroidal vasculopathy; anti-VEGF: anti vascular endothelial growth factor

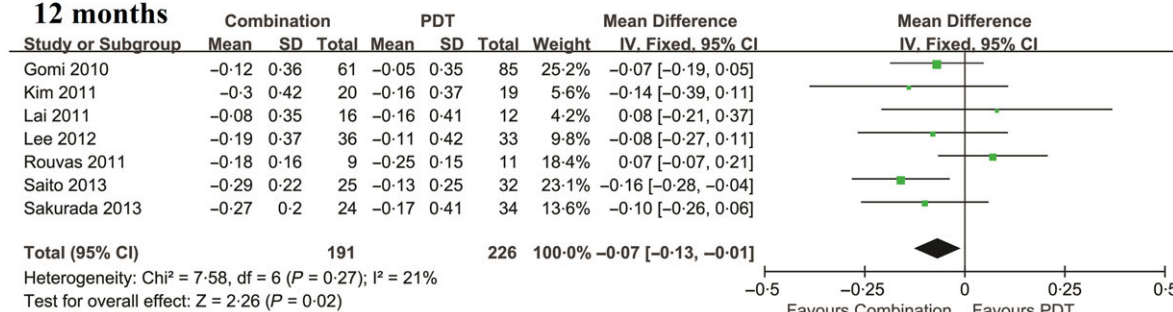
3 months



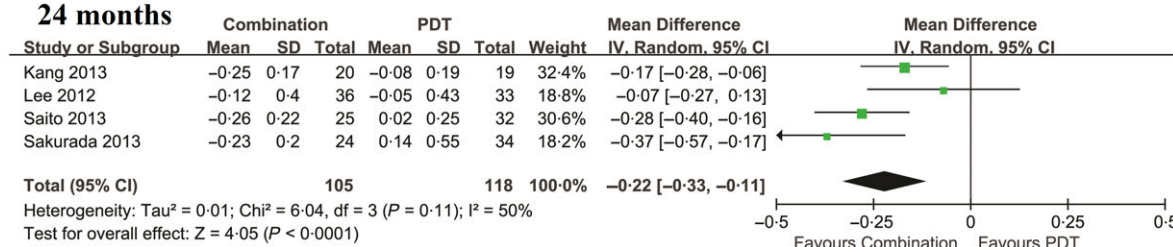
6 months



12 months



24 months



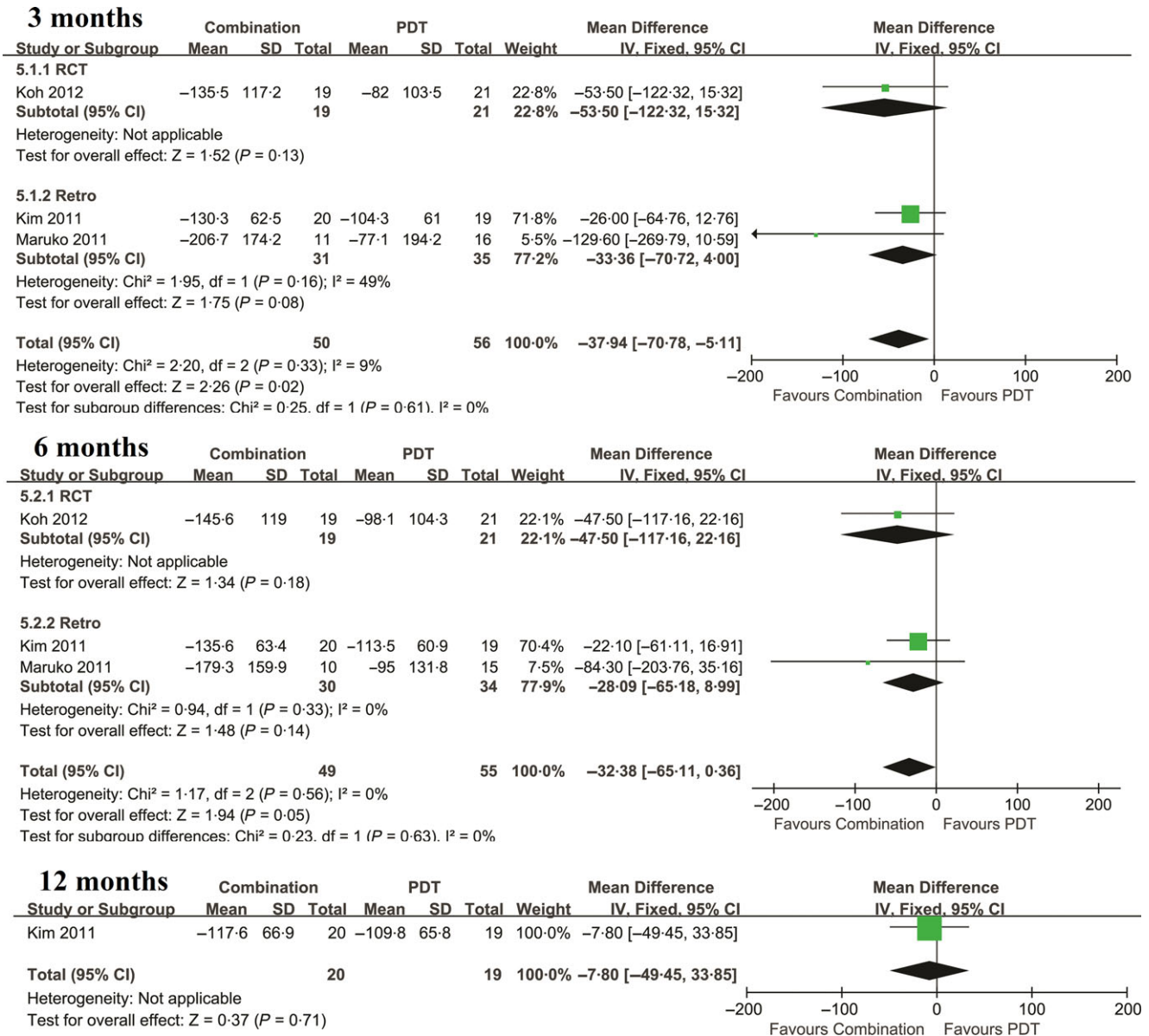


FIGURE 4 Mean change in CRT for the comparison of combined therapy and PDT at 3, 6, and 12 mo. SD, standard deviation; IV, inverse variance; CI, confidence interval. CRT: central retinal thickness; PDT: photodynamic therapy

($P = .03$; $P = .005$; $P = .02$; and $P < .0001$, respectively) (Figure 3). In contrast, no significant difference in the proportion of patients exhibiting improvements in VA (at least three lines) was observed at any time point when pooled ORs were calculated.

No significant heterogeneity was observed among studies with continuous data. Therefore, a random-effects model was used to analyse changes in CRT occurring from baseline to 3 months and 6 months after each treatment. Combined treatment resulted in significantly greater reductions in CRT at 3-months than PDT alone ($P = .02$), although no significant differences were observed at 6 months (Figure 4). No significant differences in polyp regression were observed between the two groups at either the 3- or ≥ 6 -month follow-up ($P = .32$; and $P = .75$, respectively).

All results for the comparison of combined treatment and PDT monotherapy for PCV are shown in Table 3.

3.5 | Comparison of combined treatment and intravitreal anti-VEGF monotherapy

The mean change in BCVA from baseline for each study was analysed at 3, 6, 12, and 24 months. Combined treatment resulted in significantly greater improvements in BCVA when compared with anti-VEGF treatment at 6 and 24 months ($P = .001$; $P < .00001$, respectively), with no heterogeneity ($P = .60$, $I^2 = 0\%$; $P = .43$, $I^2 = 0\%$, respectively). However, the pooled results revealed that there was no significant difference

TABLE 3 Comparison of combined treatment and PDT monotherapy for PCV

Outcome of interest	Studies (n)	WMD/OR (95% CI)	P	Study heterogeneity		
				χ^2	P	I ² (%)
Comparison of mean change in BCVA from baseline at follow-up points (logMAR)						
3 mo	9	-0.05 (-0.10, 0.00)	.03	5.08	.75	0
6 mo	8	-0.07 (-0.12, -0.02)	.005	1.13	.99	0
12 mo	7	-0.07 (-0.13, -0.01)	.02	7.58	.27	21
24 mo	4	-0.22 (-0.33, -0.11)	<.0001	6.04	.11	50
Comparison of mean change in CRT from baseline at follow-up points						
3 mo	3	-37.94 (-70.78, -5.11)	.02	2.20	.33	9
6 mo	3	-28.09 (-65.18, 0.36)	.05	1.17	.56	0
12 mo	1	-7.80 (-49.45, 33.85)	-	-	-	-
Comparison of the proportions of patients with polyp regression						
3 mo	4	1.36 (0.74, 2.52)	.32	1.37	.71	0
≥6 mo	4	1.16 (0.47, 2.87)	.75	1.31	.73	0

PDT, photodynamic therapy; NA, not available; logMAR, logarithm of the minimal angle of resolution; CRT, central retinal thickness; PCV, polypoidal choroidal vasculopathy; WMD, weighted mean difference; anti-VEGF: anti-vascular endothelial growth factor; combined treatment: treatment with PDT and anti-VEGF agents; OR, odds ratio; CI, confidence interval; χ^2 , chi-square statistic; P, P-value; I², I-square heterogeneity statistic; Bold italic values indicate statistically significant results.

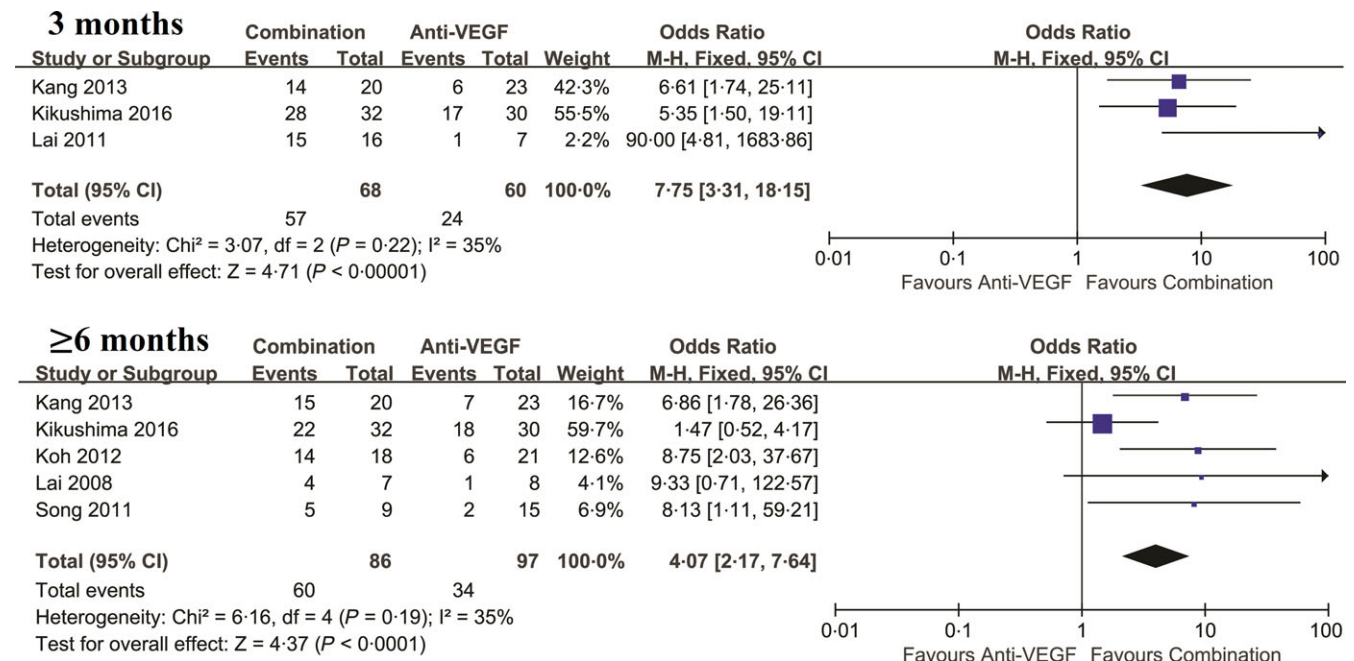


FIGURE 5 Proportion of patients with polyp regression following combination therapy and Anti-VEGF monotherapy at 3, and ≥6 mo. CI, confidence interval; PDT: photodynamic therapy; anti-VEGF: anti vascular endothelial growth factor

in BCVA change between combined treatment and anti-VEGF treatment at 3 and 12 months. Furthermore, no significant differences in CRT reduction were observed between combined treatment and anti-VEGF treatment at 6 and 12 months.

Data regarding the regression of polyps at 3 and ≥6 months were available for three and five studies,

respectively (Figure 5). The pooled results revealed that there were significant statistical differences between the two groups at 3 and ≥6 months (P < .00001; P < .0001, respectively).

All results for the comparison of combined treatment and anti-VEGF monotherapy for PCV are shown in Table 4.

TABLE 4 Comparison of combined treatment and intravitreal Anti-VEGF monotherapy for PCV

Outcome of interest	Studies (n)	WMD/OR (95% CI)	P	Study heterogeneity		
				χ^2	P	I ² (%)
Comparison of mean change in BCVA from baseline at follow-up points (logMAR)						
3 mo	4	-0.06 (-0.17, 0.06)	.34	7.60	.06	61
6 mo	5	-0.12 (-0.19, -0.05)	.001	2.77	.60	0
12 mo	7	-0.06 (-0.17, 0.06)	.34	12.72	.05	53
24 mo	2	-0.29 (-0.39, -0.19)	<.00001	0.63	.43	0
Comparison of mean change in CRT from baseline at follow-up points						
6 mo	2	-28.50 (-123.29, 66.28)	.56	4.34	.04	77
12 mo	3	5.84 (-79.86, 91.55)	.89	4.72	.09	58
Comparison of the proportions of patients with polyp regression						
3 mo	3	7.75 (3.31, 18.15)	<.00001	3.07	.22	35
≥6 mo	5	4.07 (2.17, 7.64)	<.0001	6.16	.19	35

PDT, photodynamic therapy; NA, not available; logMAR, logarithm of the minimal angle of resolution; CRT, central retinal thickness; PCV, polypoidal choroidal vasculopathy; WMD, weighted mean difference; anti-VEGF: anti-vascular endothelial growth factor; combined treatment: treatment with PDT and anti-VEGF agents; OR, odds ratio; CI, confidence interval; χ^2 , chi-square statistic; P, P-value; I², I-square heterogeneity statistic; Bold italic values indicate statistically significant results.

3.6 | Adverse events

As it has been widely reported that PDT may result in subretinal haemorrhage, we also evaluated whether intravitreal anti-VEGF agents reduced the incidence of haemorrhage in the included studies. When compared to PDT monotherapy, combined treatment was associated with a significantly lower incidence of subretinal haemorrhage (1 optic disc diameter) during the follow-up period, with no heterogeneity ($P = .17$, $I^2 = 38\%$). The pooled results are shown in Figure 6 ($P = .02$). However, no significant differences in the incidence of subretinal haemorrhage were observed between combined treatment and anti-VEGF monotherapy ($P = .85$; Figure 7).

4 | DISCUSSION

Whether PCV is a subtype of neovascular age-related macular degeneration (nAMD) remains controversial³⁸ As some

researchers have suggested that the two conditions are associated with different demographic features, clinical characteristics, and natural history, etc.^{39,40} However, both PCV and nAMD are regarded as abnormal vasculopathies arising from the choroidal vasculature, potentially resulting in recurrent serous exudation and haemorrhages.³⁸ Furthermore, increased levels of VEGF are observed in the affected eyes or patients with PCV and nAMD. Currently, anti-VEGF therapy is the standard treatment for nAMD. Thus, anti-VEGF may also represent a valuable treatment option for PCV. Intravitreal anti-VEGF injection results in rapid resolution of retinal oedema and subretinal fluid, restoring macular morphology and visual function⁴¹ In addition, PDT has proven more effective for the treatment of PCV than thermal laser photocoagulation, as it is associated with minimal retinal damage.

The scientific debate regarding the comparative effectiveness of these treatment strategies for PCV has remained unsettled for many years. Hence, this meta-analysis aimed

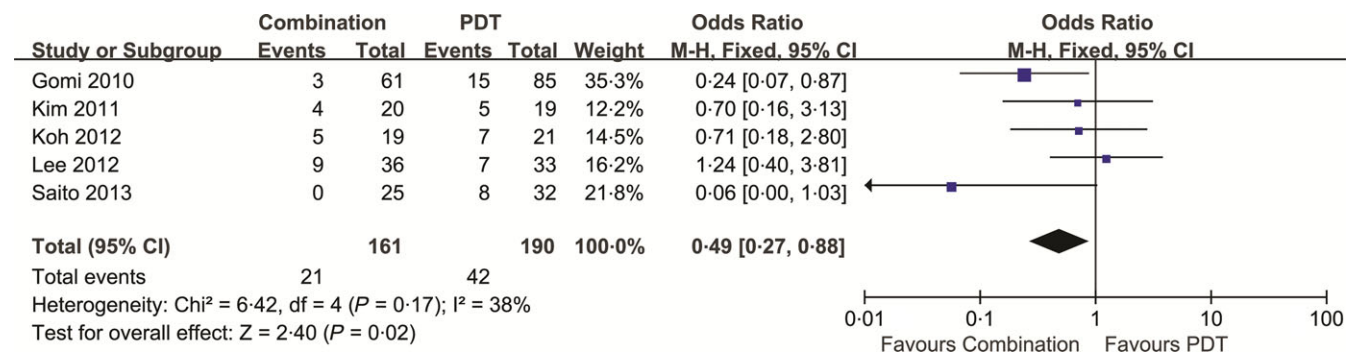


FIGURE 6 Proportion of patients with subretinal haemorrhage following combination and PDT therapy. CI, confidence interval. PDT: photodynamic therapy

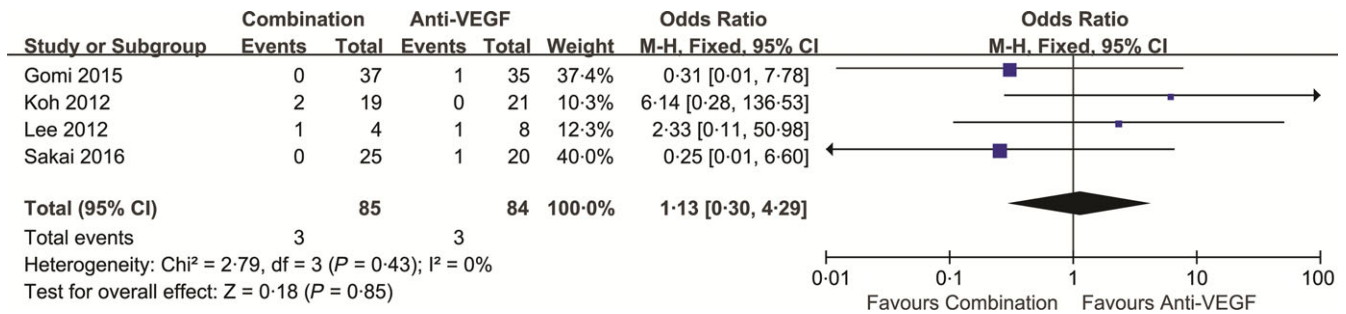


FIGURE 7 Proportion of patients with subretinal haemorrhage following combination and anti-VEGF monotherapy. CI, confidence interval. PDT: photodynamic therapy

to comprehensively compare the three strategies in terms of BCVA, CRT, proportion of patients experiencing polyp regression, etc. BCVA, an exceedingly important outcome, can be regarded as a primary measure of treatment efficacy, although CRT and polyp regression are important for evaluating treatment efficacy, as these reflect anatomical outcomes.

Our findings revealed that anti-VEGF treatment was more effective in reducing CRT than PDT at 3 months but not at 6 months, while PDT was more effective than anti-VEGF in achieving regression of polyps at 3 months and 6 or more months. However, these two monotherapy procedures appear to be equivalent in terms of BCVA change from baseline at all follow-up time points.

Although PDT monotherapy aims to produce polyp regression, no significant reductions in CRT were observed. In contrast, anti-VEGF monotherapy significantly reduced CRT at 3 months, although it was significantly less effective in regressing and suppressing the recurrence of polyps than PDT. Generally, these findings suggest that neither PDT monotherapy nor anti-VEGF monotherapy is the best option for the treatment of PCV, although each possesses distinct advantages over the other.

Considering the shortcomings of the two monotherapies, combination therapy may allow for more comprehensive treatment with regard to RCT reduction, polyp regression, and BCVA improvement than PDT monotherapy or anti-VEGF monotherapy. Specifically, the direct effect of PDT on polypoidal lesions, as confirmed via ICGA, and the subsequent resolution of exudative fluid can likely lead to a favourable visual outcome.⁴² Some studies have reported that PDT was superior to anti-VEGF therapy in terms of polyp regression.^{25,27,32} As for intravitreal anti-VEGF injections, the rapid resolution of exudative fluid and retinal oedema can play an important role in ensuring favourable BCVA outcomes.¹⁰

In this meta-analysis, combined therapy utilising PDT and anti-VEGF was superior to PDT in improving BCVA at all follow-up points, suggesting that anti-VEGF may

overcome the deficiencies of PDT monotherapy with regard to this aspect. Furthermore, BCVA improvements seemed to decrease with time in the PDT monotherapy group, suggesting that additional PDT may be necessary to sustain these improvements. Sato et al⁴³ also suggested that several additional PDT sessions would be necessary to treat patients with PCV recurrences over longer follow-up periods.

We further observed that combined treatment resulted in significantly greater improvements in BCVA when compared to anti-VEGF monotherapy at the 6- and 24-month follow-up points, suggesting that combination therapy is more effective than anti-VEGF monotherapy in improving BCVA.

At 3 months, combined therapy was associated with significantly greater decreases in CRT than PDT, indicating that anti-VEGF treatment also plays a role in reducing exudative lesions. However, no significant differences in CRT reduction were observed between the groups at 6 months, suggesting that the efficacy of anti-VEGF in reducing CRT is only maintained over a short period of time. Furthermore, no significant difference in CRT reduction was observed between combined treatment and intravitreal anti-VEGF treatment, suggesting that PDT has little influence on CRT. Taken together, our findings indicate that PDT plays a greater role in polyp regression than anti-VEGF, consistent with the results of two previous meta-analyses.^{11,12}

Many studies have reported that PDT may lead to an increased risk of intraretinal or subretinal haemorrhage, thereby resulting in ischaemic damage to normal choroidal tissue.^{16,17,22-25} Among them, subretinal haemorrhage, the most common and most reported adverse event, may also limit visual improvement following PDT.⁴⁴ However, our findings indicate that these disadvantages can be reduced via combined therapy with PDT and anti-VEGF, in accordance with the conclusions of Cheung et al⁴⁵ As the risk of subretinal haemorrhage decreases with anti-VEGF, combined treatment may be both safer and more effective than PDT monotherapy.

Recently, the administration of intravitreal corticosteroids has been utilised as an auxiliary treatment strategy in many clinical trials. Intraocular inflammatory cytokines are likely to be elevated in PCV eyes, especially in the presence of subretinal haemorrhage or macular oedema.⁴⁶ Ho et al⁴⁷ reported that the majority of patients responded well to corticosteroid treatment, with significant responses observed as early as 1 week after initiation of triple therapy including photodynamic therapy, intravitreal aflibercept, and intravitreal dexamethasone. Liang et al⁴⁸ also evaluated the efficacy and adverse effects of treatment with low-dose intravitreal triamcinolone acetonide (IVTA).

PCV results in alterations of the choroidal structure, which can be detected by enhanced depth imaging optical coherence tomography (EDI-OCT).⁴⁹ Thus, such alterations may be useful in evaluating the efficacy of particular treatment strategies. Daizumoto et al⁵⁰ reported that intravitreal aflibercept was effective in the treatment of PCV via significant correlations of the pachychoroid index, a kind of index reflecting choroidal structures.

Recently, several studies reported favourable visual and anatomical outcomes following aflibercept monotherapy with fixed or treat-and-extend (TAE) retreatment regimens in patients with PCV. Hosokawa et al⁵¹ reported that intravitreal aflibercept injections delivered as part of a TAE regimen are effective in improving BCVA and CRT in eyes with PCV. In another retrospective interventional case series of 58 eyes, TAE intravitreal aflibercept was associated with improvements in BCVA and regression of polypoidal lesions.⁵² In one study involving Japanese patients with treatment-naïve PCV, treatment with intravitreal aflibercept every 2 months following three initial monthly doses resulted in significant increases in BCVA and a high rate of polyp resolution at 12 months.⁵³ Lee et al⁵⁴ reported that fixed-dose treatment with aflibercept was associated with favourable outcomes in patients with PCV patients at the 12-month follow-up. The results of these studies⁵¹⁻⁵⁴ have led many physicians to prefer the use of this modality, rather than PDT. As only one study involving aflibercept was included in the present meta-analysis, we were unable to sufficiently compare outcomes between aflibercept monotherapy and combination therapy. Thus, future studies should aim to perform this comparison.

Our study possesses several strengths in comparison with previous systematic reviews of PCV treatment. First, our meta-analysis included the most recent work, analysing studies published as late as December 31, 2016. Second, we performed a comprehensive comparison of PDT monotherapy, anti-VEGF monotherapy, and combined treatment using strict inclusion and exclusion criteria. Third, we included studies of all anti-VEGF agents

(ranibizumab, bevacizumab, and aflibercept) approved by the Food and Drug Administration (FDA), rather than those evaluating a single anti-VEGF.

However, this work may have some limitations. First, inadequate random sequence generation and blinding may have resulted in selection bias, and patients with PCV whose condition worsened may have switched treatment. Nonetheless, selection bias was less likely to occur, as the major study characteristics of the eyes in the three groups were comparable at baseline. Second, some studies did not report all detailed outcome indicators, which caused some comparison only included two or three studies. For example, when comparing the mean change in CRT from baseline between combined treatment and PDT monotherapy at 6 months, the pooled results were insufficient for determining a statistically significant difference ($P = .05$). Therefore, more data may have resulted in a statistically significant difference. Third, publication bias cannot be fully excluded because we could not gain access to unopen results and unpublished studies. Nevertheless, the findings of the present meta-analysis suggest that combined treatment with PDT and intravitreal anti-VEGF injection therapy results in better long-term improvements in VA, reductions in CRT, and more substantial regression of polyps. These findings indicate that combined therapy may be more effective than monotherapy in the treatment of PCV. Despite these encouraging findings, the inherent limitations of the included studies should be considered. Hence, more detailed data at different follow-up time points and further large-volume RCTs are required to improve the accuracy and robustness of our findings for clinical application.

CONFLICTS OF INTEREST

All authors declare that they have no conflicts of interest.

AUTHORS' CONTRIBUTIONS

All authors conceived of and designed the experimental protocol. Qian TW & Li XX collected the data. Qian TW & Zhao MY analysed the data. Qian TW and Li XX wrote the first draft of the manuscript. Qian TW & Xu X reviewed and revised the manuscript and produced the final version. All authors read and approved the final manuscript.

Qian TW & Li XX contributed equally to this work and should be considered co-first authors.

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