• Meta-Analysis •

Combined therapy versus anti-vascular endothelial growth factor monotherapy for polypoidal choroidal vasculopathy: a Meta-analysis

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Abstract

• AIM: To evaluate the efficacy and safety of anti-vascular endothelial growth factor (VEGF) combined with photodynamic therapy (PDT) versus anti-VEGF monotherapy for polypoidal choroidal vasculopathy (PCV).

• METHODS: We conducted a Meta-analysis of 9 studies to compare the efficacy and safety between combined therapy and anti-VEGF monotherapy for PCV. The programs of RevMan 5.3 and Stata 12.0 were used to analyze data.

• RESULTS: The best corrected visual acuity (BCVA) in combined therapy group were significantly better than those of anti-VEGF monotherapy group at 6, 24 and 36mo, with pooled weighted means differences (WMDs) of 0.12 (0.06, 0.18), 0.25 (0.12, 0.38) and 0.28 (0.13, 0.43), respectively. The central retinal thickness (CRT) reductions in combined therapy group were higher than that in anti-VEGF monotherapy group at 1, 3, 6 and 9mo, with pooled WMDs of 63.90 (20.41, 107.38), 33.47 (4.69, 62.24), 30.57 (0.12, 60.01) and 28.00 (2.51, 53.49), respectively. The regression rate of polyps in combined therapy group was much higher than that in anti-VEGF monotherapy group [RD: 0.47 (0.26, 0.68); *P*<0.0001]. The adverse event retinal hemorrhage did not differ significantly between the two groups.

• CONCLUSION: Our findings clearly document that anti-VEGF combined with PDT is a more effective therapy for PCV compared with anti-VEGF monotherapy. Furthermore, combined therapy does not increase the incidence of retinal hemorrhage.

• KEYWORDS: vascular endothelial growth factor; photodynamic therapy; polypoidal choroidal vasculopathy

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INTRODUCTION

Polypoidal choroidal vasculopathy (PCV) is one of the common sight-threatening eye diseases characterized by polypoidal and aneurysmal dilatations at the terminals of the branching network in the inner choroid[1-3]. It results in severe visual loss in some patients secondary to recurrent serosanguinous detachment of retinal pigment epithelium or occasional massive submacular hemorrhage[4]. Although several treatment modalities for PCV are available currently, more reliable evidences are still needed for ophthalmologists to make the best choice.

Anti-vascular endothelial growth factor (VEGF) therapy is a treatment modality that is being investigated in PCV. The increased expression of VEGF in the eyes with PCV provides a biologic rationale for the treatment with anti-VEGF agents[5-6]. Relevant studies demonstrated a rapid resolution of exudative fluid from polypoidal lesions and subsequent rapid visual recovery after anti-VEGF therapy[7-9]. Due to its rapid effects, simple operation and low risk, anti-VEGF monotherapy is easy to achieve the patient's satisfaction, so it's wildly used by many clinicians in the treatment of PCV. However, despite the visual improvement, anti-VEGF monotherapy showed a limited effect on polyp regression[10].

Photodynamic therapy (PDT) has been widely used in the treatment of PCV, as various studies have shown that it can result in regression of polyps and visual improvements[11-13]. However, evidence suggests that PDT is only an efficient treatment in a short term[2,12-14]. Moreover, the visual threatening hemorrhagic complications after PDT have been reported in up to 30% of eyes, and repeated PDT induced choroidal ischemia, which can lead to the increase of VEGF expression[5-6,12-16].

Therefore, combining anti-VEGF with its anti-angiogenic and anti-permeability effects and PDT with its angio-occlusive effects may lead to synergistic effects in PCV treatment. To

date, several studies comparing combined therapy (anti-VEGF combined with PDT) with anti-VEGF monotherapy have been conducted[15,17-24]. However, they only included a small sample size and no definitive conclusions have been reached yet. Therefore, we performed a Meta-analysis of the available published literature to compare the outcomes of combined therapy and anti-VEGF monotherapy.

MATERIALS AND METHODS

This Meta-analysis was reported in accordance with Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[25]. All stages of literature search, study selection, data extraction, and quality assessment were performed independently by two reviewers (Han LH and Yuan LF). And all disagreements were resolved by discussion until a consensus was reached.

Literature Search A systematic search of the Cochrane Library, PubMed and Embase *via* Ovid database system was performed to identify relevant studies. The following terms, adapted for Ovid database, were used for the searches "polypoidal choroidal vasculopathy" OR "PCV" AND "endothelial growth factor" OR "VEGF" OR "angiogenesis inhibitor" OR "Lucentis" OR "Ranibizumab" OR "Bevacizumab" OR "Avastin" OR "Pegaptanib" OR "Macugen" OR "Conbercept" OR "Aflibercept" OR "Eylea" AND "photodynamic therapy" OR "PDT". The "Include Related Terms" function in Ovid database was also used to broaden the search, and the websites of professional associations and Google Scholar were also searched for additional information. The computer search was supplemented with manual searches of the reference lists of all relevant studies, review articles and conference abstracts. The final search was carried out in May 2016 and was updated on January 6, 2017, without restrictions regarding publication year, language, or methodological filter.

Inclusion and Exclusion Criteria All available randomized controlled trials (RCTs) and non-randomized comparative studies (NRSs) that compared combined therapy (anti-VEGF combined with PDT) with anti-VEGF monotherapy, and that had at least one of the quantitative outcomes mentioned in the next section of this paper, were included. Reviews, case reports, comments, editorials, letters, and registered protocols were excluded.

Data Extraction The following information was extracted from each study: first author; year of publication; study design; inclusion and exclusion criteria; location of the trial; follow up; number of patients in each group; baseline patient characteristics; and outcomes of interest. The numbers of withdrawal and patients reporting adverse events were also recorded.

Outcome Measures The following outcomes were used to compare combined therapy with anti-VEGF monotherapy: 1) visual outcomes: mean best corrected visual acuity (BCVA) change at months 1, 3, 6, 9, 12, 24 and 36; 2) anatomical outcomes: mean change in central retinal thickness (CRT) at months 1, 3, 6, 9, 12 and 24; regression rate of polyps at month 3; 3) adverse events: incidence of retinal hemorrhage.

Quality Assessment The methodological quality of studies was assessed using a previously reported quality assessment system for both randomized and non-randomized studies[26]. The system includes 27 items distributed to five subscales: reporting (10 items), external validity (3 items), internal validity-bias (7 items), internal validity-confounding (selection bias) (6 items), and power (1 item). And the total score for each study was presented as a percentage of the maximum achievable score. The scores not lower than 50% are considered to be of high quality.

Statistical Analysis Data from this Meta-analysis are presented in accordance with PRISMA guidelines. All Meta-analyses and sensitivity analyses were performed using RevMan (version 5.3), and publication bias analyses were performed using Stata (version 12.0; StataCorp, College Station, TX, USA). Weighted mean difference (WMD) and risk difference (RD) were used to compare continuous and dichotomous variables, respectively. And the outcomes were reported with 95% confidence interval (CI).

The heterogeneity among the studies was accessed using a chi-square test with the significance set at $P<0.10$. The percentage of heterogeneity was evaluated using the I^2 statistic, ranging from 0 to 100%. If there was a statistical heterogeneity between studies ($P<0.10$, $I^2>50\%$), a random-effect model was used to combine data. Otherwise, a fixed-effect model was used ($P>0.10$, $I^2<50\%$).

Subgroup analysis was performed according to type of study design (RCT or NRS). Sensitivity analysis was performed by iteratively excluding each study and recalculating the combined estimate based on the remaining studies, and only outcomes that were reported in no less than four studies were included in sensitivity analysis[2]. The potential publication bias was evaluated with Begg's and Egger's tests using Stata software.

The data are presented as mean±standard deviation (SD) or mean±95% CI. The unavailable SD values were estimated according to Cochrane Handbook 5.3.5 (chapter 16.1.2). A $P<0.05$ was considered to be statistically significant, except where otherwise specified.

RESULTS

Characteristics of Included Studies Nine studies including two RCTs[17-18] and seven NRSs[15,19-24] were included in the final analysis (Figure 1). The characteristics of the included studies are shown in Table 1. A total of 317 cases (153 cases of

Table 1 Characteristics of studies included in this Meta-analysis

Studies (first author, year)	Design	Center	Location	Follow-up (mo)	No. of eyes combined/anti-VEGF	Mean age (a) combined/anti-VEGF	Sex (M/F) combined /anti-VEGF
Koh A, 2012	RCT	7	Hong Kong, Singapore, Korea, Taiwan, Thailand	6	19/21	63.8±8.30/69.3±8.3	(11/8)/(15/6)
Lim JY, 2012	RCT	1	Korea	12	5 / 5	57.8±7.9/68.6±7.2	(3/2)/(5/0)
Sakurai M, 2014	NRS	1	Japan	12	17 / 30	74.8±5.8/73.9±8.1	(13/4)/(20/10)
Lai TY, 2011	NRS	1	Hong Kong	12	16 / 7	71.3±9.8/64.6±7.9	(8/8)/(4/3)
Kang HM, 2014	NRS	1	Korea	24	20 / 23	70.0±7.6/68.1±8.1	(NA)/(NA)
Song MH, 2011	NRS	1	Korea	12	9 / 15	56.9±12.1/60.6±10.7	(0/9)/(6/9)
Rouvas AA, 2011	NRS	2	Greece	12	9 / 10	64.67±NA/66.5±NA	(4/5)/(4/6)
Kikushima W, 2016	NRS	1	Japan	12	33 / 33	73.4±8.3/72.7±8.5	(22/11)/(25/8)
Sakai T, 2016	NRS	1	Japan	36	25 / 20	72.6±6.2/75.3±8.1	(21/4)/(13/7)

RCT: Randomized controlled trial; NRS: Non-randomized comparative study; PDT: Photodynamic therapy; RF-PDT: Reduced-fluence photodynamic therapy; M/F: Male/female; NA: Not available. Combined group: Eyes treated with intravitreal anti-VEGF agents combined with PDT or RF-PDT; Anti-VEGF group: Eyes treated with intravitreal anti-VEGF agents only. The data are shown as mean±standard deviation (SD) or mean.

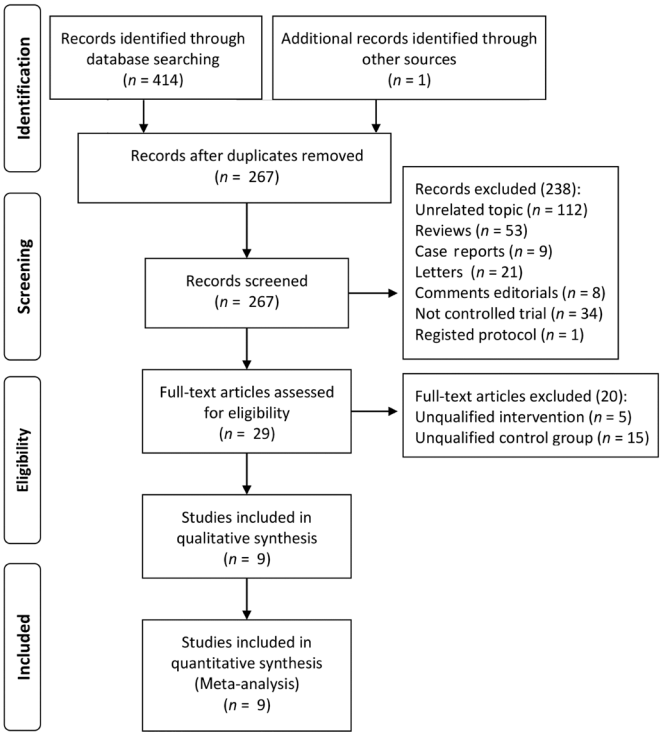

Figure 1 Flow diagram of included studies for this Meta-analysis.

combined therapy and 164 cases of anti-VEGF monotherapy) were enrolled. PCV was confirmed by indocyan-nine green angiograph (ICGA). ICGA and OCT were used in the same way in all included studies. Characteristics of lesions and treatment exposures included in the Meta-analysis are shown in Table 2. The quality assessment is summarized in Table 3. All of the studies scored over 50% and were considered to be of high quality.

Visual Outcomes BCVA was one of the most important criterion for evaluating efficacy. The pooled WMDs (with 95% CIs) of logMAR BCVA improvements from the baseline and the comparisons between the two groups (combined therapy group *vs* anti-VEGF monotherapy group) by Meta-analysis are presented in Table 4 and Figure 2.

In combined therapy group, the mean BCVA improved continuously from month 3 to 36 compared with baseline BCVA. The pooled WMDs at 3, 6, 9, 12, 24 and 36mo were 0.19 (0.12, 0.26), 0.23 (0.17, 0.29), 0.24 (0.16, 0.33), 0.24 (0.17, 0.30), 0.22 (0.09, 0.34) and 0.21 (0.06, 0.36), respectively. In anti-VEGF monotherapy group, the mean BCVA only improved at month 3, 6, 9 and 12 after initial treatment, with pooled WMDs of 0.11 (0.03, 0.19), 0.10 (0.02, 0.19), 0.13 (0.03, 0.23) and 0.10 (0.02, 0.18), respectively. Furthermore, it deteriorated at month 24 and month 36. There was no evidence of heterogeneity across the above trials.

Comparisons between the two groups showed that the treatment effects in combined therapy group were significantly better than those of anti-VEGF monotherapy group at month 6, 24 and 36, with pooled WMDs of 0.12 (0.06, 0.18), 0.25 (0.12, 0.38) and 0.28 (0.13, 0.43), respectively. No significant difference was found at other months. There were significant heterogeneities at month 1, 3 and 12, so the random-effect models were used to combine data.

After being normalized to the baseline before treatment, logMAR BCVA increased by 8.0%-39.4% in combined treatment group in 36mo, but, in anti-VEGF monotherapy group, it only showed 7.3%-20.9% increase from month 1 to 12, and even a 6.4% decrease at month 24 and a 11.2% decrease at month 36 (Figure 2B).

Anatomical Outcomes The pooled WMDs of CRT reductions from the baseline and the comparisons between the two

Table 2 Characteristics of lesions and treatment exposures included in this Meta-analysis

Studies (first author, year)	Lesion GLD (mm)		Interventions		No. of treatments	
	Combined	Anti-VEGF	Combined	Anti-VEGF	Combined	Anti-VEGF
Koh A, 2012	NA	NA	PDT+IVR 0.5 mg (1-24h after PDT)	IVR 0.5 mg+ sham PDT	1.4±0.5 PDT, 5.0±2.6 IVR	7.4±2.4 IVR
Lim JY, 2012	NA	NA	IVB 1.25 mg+PDT within 7d before or after IVB)	IVB 1.25 mg	3.6±0.89 IVB, 1 PDT	3.0±0 IVB
Sakurai M, 2014	2576±1002	1474±909	IVR 0.5 mg+RF-PDT (1-24h after IVR)	IVR 0.5 mg	3.4 IVR, 1 RF-PDT	4.3 IVR
Lai TY, 2011	3490±1170	3610±2240	PDT+IVR 0.5 mg (30min after PDT)	IVR 0.5 mg	1.2 PDT, 3.4 IVR	0.6 PDT, 4.0 IVR
Kang HM, 2014	2815±910	2790±872	PDT+IVB 0.5 mg (the same day as the PDT)	IVR 0.5 mg or IVB 1.25 mg	1.33±0.17 PDT, 11.00±1.46 IVB	10.12±1.46 IVR/ IVB
Song MH, 2011	NA	NA	PDT+IVR 0.5 mg (within 3d after PDT)	IVR 0.5 mg	1 PDT, 4.33±2.78 IVR	4.47±2.10 IVR
Rouvas AA, 2011	NA	NA	IVR 0.5 mg+PDT (7±2d after IVR)	IVR 0.5 mg	1.67 PDT, 5.0 IVR	6.9 IVR
Kikushima W, 2016	1692±747	2041±1273	IVA 2 mg+PDT (15min after the start of the injection)	IVA 2 mg	3.42±0.94 IVA, 1 PDT	4.6±1.6 IVA
Sakai T, 2016	2800±823	2937±1040	IVR 0.5 mg+PDT (1 or 2d after IVR)	IVR 0.5 mg	5.08±2.45 IVR, 1.32 PDT	7.65±2.74 IVR, 0.3 PDT

GLD: Greatest linear dimension; PDT: Photodynamic therapy (6 mg/m^2, 50 J/cm^2, 600 mW/cm^2, 83s); RF-PDT: Reduced-fluence photodynamic therapy (6 mg/m^2, 50 J/cm^2, 42s); IVR: Intravitreal ranibizumab; IVB: Intravitreal bevacizumab; IVA: Intravitreal aflibercept; NA: Not available. Combined group: Eyes treated with intravitreal anti-VEGF agents combined with PDT or RF-PDT; Anti-VEGF group: Eyes treated with intravitreal anti-VEGF agents only. The data are shown as mean±standard deviation (SD) or mean.

Table 3 Quality assessment for studies included in this Meta-analysis

Studies (first author, year)	Quality score components					Scores	
	I	II	III	IV	V	Total	Percentage
Koh A, 2012	11	3	6	3	0	23	71.88%
Lim JY, 2012	11	1	5	4	0	21	65.63%
Sakurai M, 2014	10	1	5	2	1	19	59.38%
Lai TY, 2011	10	1	5	2	0	18	56.25%
Kang HM, 2014	9	1	5	2	1	18	56.25%
Song MH, 2011	10	1	5	2	0	18	56.25%
Rouvas AA, 2011	9	1	5	2	0	17	53.13%
Kikushima W, 2016	9	1	5	2	1	18	56.25%
Sakai T, 2016	10	1	5	2	1	19	59.38%

I: Reporting; II: External validity; III: Internal validity-bias; IV: Internal validity-confounding (selection bias); V: Power.

groups by Meta-analysis are presented in Table 5 and Figure 2C. In both groups, the CRT reductions from the baseline are statistically significant during the 36 months' follow-up. But the CRT reductions in the combined therapy group were higher than that in the anti-VEGF monotherapy group in early stages, and the differences were statistically significant at month 1, 3, 6 and 9, with pooled WMDs of 63.90 (20.41, 107.38), 33.47 (4.69, 62.24), 30.57 (0.12, 60.01) and 28.00 (2.51, 53.49), respectively.

After being normalized to the baseline before treatment, CRT reduced by 40.1%-42.3% in combined treatment group at month 1, 3, 6 and 9, but it only showed 23.5.2%-29.9% reduction in anti-VEGF monotherapy group at those time points. The differences of CRT reduction between the two groups at month 12 and 24 were not significant (Figure 2B).

Four studies reported the data for regression rate of polyps at month 3. Analysis of these data showed that the regression rate in combined therapy group was much higher than that in anti-VEGF monotherapy group [RD: 0.47 (0.26, 0.68); P<0.0001] (Table 5; Figure 3).

Adverse Events Retinal hemorrhage was the most common complication associated PCV treatment. Six studies including 218 patients reported the frequency of retinal hemorrhage, and the pooled data showed no significant difference between the two groups [RD: 0.01 (-0.05, 0.07); P=0.80] (Table 5; Figure 4).

Subgroup Analysis, Sensitivity Analysis and Publication Bias There was no statistically significant difference in all available subgroup analyses except the comparison at month 3 and 6. The results of sensitivity analyses showed that 76.3% (29/38) of the Meta-analysis results were stable, and 23.7% (9/38) of the results were not stable and the patterns of difference were changed when a certain study was excluded (Table 6).

We only tried to evaluate the publication bias of the comparisons between the two groups when the number of studies is no less than four. Begg's tests (P>0.05) and Egger's tests (P>0.05) showed no evidence of publication bias.

Table 4 Comparisons of logMAR BCVA by Meta-analysis

Outcomes of interest	No. of studies	WMD (95% CI)	Heterogeneity			*Z*	*P*
			Chi^2	*P*	I^2		
Mean logMAR improvement in combined therapy group (follow-up *vs* baseline)							
Month 1	4	0.07 (-0.04, 0.18)	3.26	0.35	8%	1.32	0.19
Month 3	7	0.19 (0.12, 0.26)	6.92	0.33	13%	5.62	<0.00001
Month 6	7	0.23 (0.17, 0.29)	4.66	0.59	0	7.05	<0.00001
Month 9	4	0.24 (0.16, 0.33)	3.39	0.34	11%	5.55	<0.00001
Month 12	8	0.24 (0.17, 0.30)	5.49	0.60	0	6.79	<0.00001
Month 24	2	0.22 (0.09, 0.34)	0.13	0.72	0	3.32	0.0009
Month 36	1	0.21 (0.06, 0.36)	NA	NA	NA	2.82	0.005
Mean logMAR improvement in anti-VEGF monotherapy group (follow-up *vs* baseline)							
Month 1	4	0.05 (-0.04, 0.14)	2.22	0.53	0	1.12	0.26
Month 3	7	0.11 (0.03, 0.19)	2.32	0.77	0	2.79	0.005
Month 6	7	0.10 (0.02, 0.19)	3.16	0.79	0	2.51	0.01
Month 9	4	0.13 (0.03, 0.23)	2.03	0.57	0	2.52	0.01
Month 12	8	0.10 (0.02, 0.18)	8.86	0.26	21%	2.34	0.02
Month 24	2	-0.04 (-0.21 0.12)	0.05	0.82	0	0.52	0.60
Month 36	1	-0.07 (-0.29, 0.15)	NA	NA	NA	0.63	0.53
Comparisons of logMAR improvement between the two groups (combined therapy group *vs* anti-VEGF monotherapy group)							
Month 1	4	0.01 (-0.07, 0.10)	8.35	0.04	64%	0.25	0.80
Month 3	7	0.08 (-0.00, 0.17)	23.55	0.0006	75%	1.86	0.06
Month 6	7	0.12 (0.06, 0.18)	7.58	0.27	21%	3.89	<0.0001
Month 9	4	0.09 (-0.01, 0.19)	0.23	0.97	0	1.78	0.07
Month 12	8	0.10 (-0.01, 0.22)	20.16	0.005	65%	1.76	0.08
Month 24	2	0.25 (0.12, 0.38)	0.35	0.55	0	3.81	0.0001
Month 36	1	0.28 (0.13, 0.43)	NA	NA	NA	3.57	0.0004

BCVA: Best corrected visual acuity; WMD: Weighted mean difference; CI: Confidence interval; Combined therapy: Intravitreal anti-VEGF agents plus PDT; PDT: Photodynamic therapy.

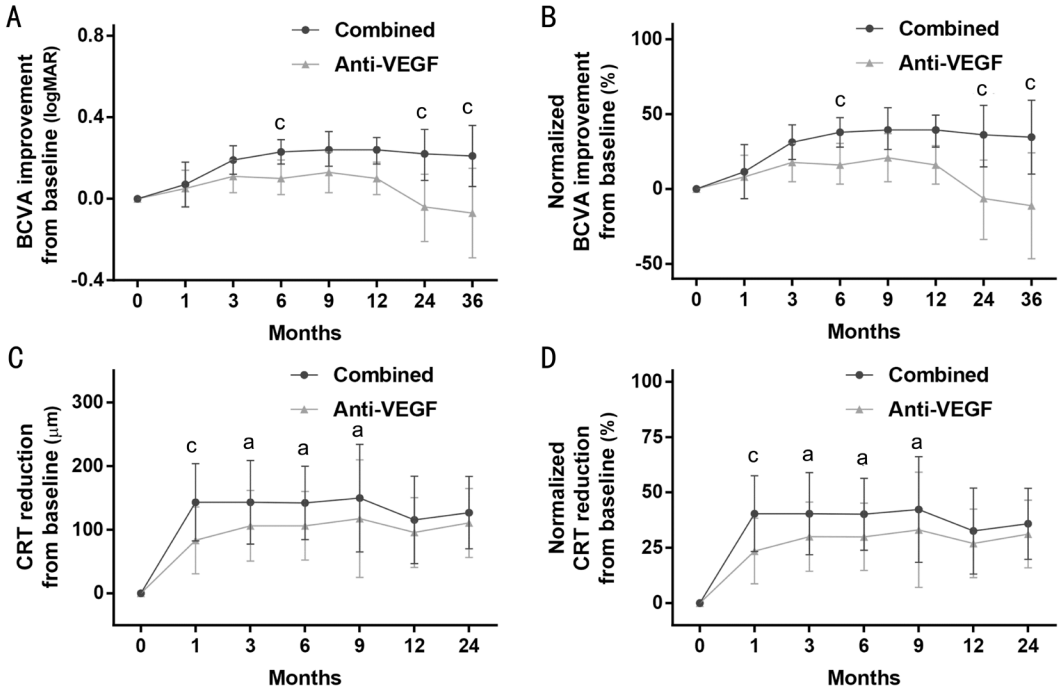

Figure 2 LogMAR BCVA improvement and CRT reduction from baseline A: LogMAR BCVA improvement from baseline; B: Normalized logMAR BCVA improvement from baseline; C: CRT reduction from baseline; D: Normalized CRT reduction from baseline. Outcomes are presented as WMD with 95% CI. Comparisons between the two groups (combined therapy group *vs* anti-VEGF monotherapy group) by Meta-analysis: $^aP<0.05$, $^cP<0.001$.

Table 5 Comparisons of anatomical outcomes and dverse event by Meta-analysis

Outcomes of interest	No. of studies	WMD or RD (95% CI)	Heterogeneity			*Z*	*P*
			Chi^2	*P*	I^2		
Anatomical outcomes							
CRT reduction							
Mean CRT reduction in combined therapy group (follow-up *vs* baseline)							
Month 1	4	143.07 (82.44, 203.70)	10.15	0.02	70%	4.63	0.00001
Month 3	6	143.13 (77.38, 208.87)	51.88	<0.00001	90%	4.27	0.0001
Month 6	6	142.18 (84.52, 199.83)	42.14	<0.00001	88%	4.83	<0.00001
Month 9	4	149.72 (65.13, 234.31)	39.11	<0.0001	92%	3.47	0.0005
Month 12	6	115.46 (46.71, 184.22)	48.49	<0.00001	90%	3.29	0.001
Month 24	1	126.96 (70.08, 183.84)	NA	NA	NA	4.37	<0.0001
Mean CRT reduction in anti-VEGF monotherapy group (follow-up *vs* baseline)							
Month 1	4	83.43 (30.87, 135.99)	12.12	0.007	75%	3.11	0.002
Month 3	6	106.33 (50.94, 161.71)	23.83	0.0002	79%	3.76	0.0002
Month 6	6	106.19 (52.37, 160.00)	23.94	0.0002	79%	3.87	0.0001
Month 9	4	117.41 (25.08, 209.73)	25.62	0.0001	88%	2.49	0.01
Month 12	6	95.71 (40.89, 150.53)	29.99	0.0001	83%	3.42	0.0006
Month 24	1	110.68 (56.39, 164.97)	NA	NA	NA	4.00	<0.0001
Comparisons of CRT reduction between the two groups (combined therapy group *vs* anti-VEGF monotherapy group)							
Month 1	4	63.90 (20.41, 107.38)	7.23	0.06	58%	2.88	<0.004
Month 3	6	33.47 (4.69, 62.24)	7.66	0.18	35%	2.28	0.02
Month 6	6	30.57 (0.12, 60.01)	5.57	0.35	10%	1.97	<0.05
Month 9	4	28.00 (2.51, 53.49)	4.24	0.24	29%	2.15	0.03
Month 12	6	11.90 (-23.39, 47.19)	5.63	0.34	11%	0.66	0.51
Month 24	1	16.28 (-44.35, 76.91)	NA	NA	NA	0.53	0.60
Regression of polyps (combined therapy group *vs* anti-VEGF monotherapy group)							
Month 3	4	0.47 (0.26, 0.68)	7.77	0.05	61%	4.40	<0.0001
Incidence of adverse event (combined therapy group *vs* anti-VEGF monotherapy group)							
Retinal hemorrhage	6	0.01 (-0.05, 0.07)	2.42	0.79	0	0.25	0.80

CRT: Central retinal thickness; WMD: Weighted mean difference; RD: Risk difference; CI: Confidence interval; Combined: Intravitreal anti-VEGF inhibitors plus PDT; PDT: Photodynamic therapy.

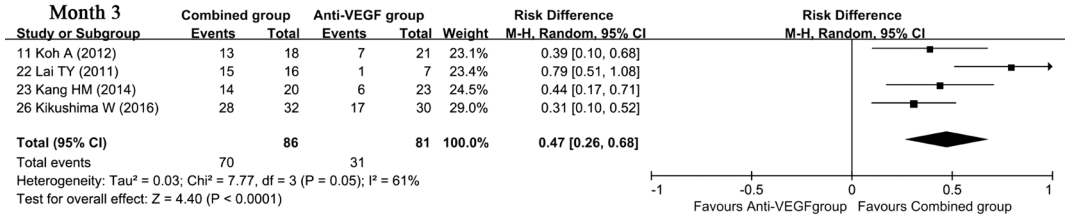

Figure 3 Forest plot displaying the pooled estimate of regression rate of polys Combined therapy group *vs* anti-VEGF monotherapy group.

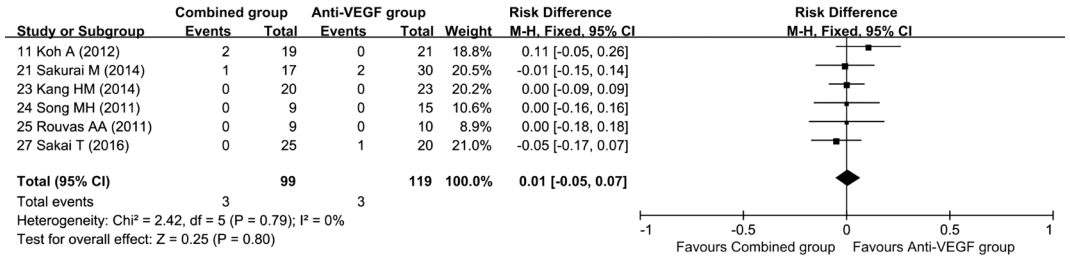

Figure 4 Forest plot displaying the pooled estimate of retinal hemorrhage Combined therapy group *vs* anti-VEGF monotherapy group.

DISCUSSION

This Meta-analysis of two RCTs and five non-randomized comparative studies including 317 cases, showed that combined therapy (anti-VEGF combined with PDT) was superior to anti-VEGF monotherapy in terms of visual and anatomical outcomes. No significant difference was found in

Table 6 Results of sensitivity analyses

Outcomes of interest	A certain exclued study	Original significance	Significance after a certain study was exclued
Mean logMAR improvement in anti-VEGF monotherapy group (follow up *vs* baseline)			
Month 6	[26]	S	NS
Month 9	[26]	S	NS
Month 12	[22], [26]	S	NS
Comparisons of logMAR improvement between the two groups (combined therapy group *vs* anti-VEGF monotherapy group)			
Month 3	[11], [22]	NS	S
Month 12	[22]	NS	S
Mean CRT reduction in anti-VEGF monotherapy group (follow up *vs* baseline)			
Month 9	[24]	S	NS
Comparisons of CRT reduction between the two groups (combined therapy group *vs* anti-VEGF monotherapy group)			
Month 3	[11], [21], [24]	S	NS
Month 6	[11], [21], [24], [25]	S	NS
Month 9	[21], [24], [25]	S	NS

Combined: Intravitreal anti-VEGF inhibitors plus PDT; PDT: Photodynamic therapy; S: With significance; NS: No significance.

retinal hemorrhagic complication between the two groups. Thus, the combined treatment seems to be a rational approach for PCV.

Treatment strategies for PCV include thermal laser photocoagulation, verteporfin PDT, anti-VEGF therapies, and combination of these[27]. Although several treatment modalities for PCV are available currently and several relevant studies with small samples were conducted, more reliable evidences are still needed for ophthalmologists to make the best choice.

Recently, several Meta-analyses, comparing these treatment modalities for PCV, were publish and some consensuses were reached. Two Meta-analyses, comparing combined therapy with PDT monotherapy, confirmed that combined therapy resulted in better visual acuity[2,28]. But, three Meta-analyses, comparing anti-VEGF with PDT, got conflicting conclusions[28-30]. Tang *et al*[28] and Yong *et al*'s[29] results showed that anti-VEGF and PDT appeared to be comparable in terms of visual acuity improvement. On the contrary, Liu *et al*'s[30] Meta-analysis suggested that anti-VEGF (intravitreal ranibizumab) had better effect on the improvement of visual acuity in PCV. Furthermore, none of the Meta-analyses compared the efficacy between combined therapy and anti-VEGF monotherapy. Therefore, we performed this Meta-analysis of the available literature to compare the outcomes of combined therapy with anti-VEGF monotherapy.

BCVA is one of the most important criterions for evaluating the efficacy on PCV. Our results showed that the mean BCVA in combined therapy group improved continuously from month 3 to 36 compared with the baseline BCVA. However, the mean BCVA in anti-VEGF monotherapy group just improved from month 3 to 12 after initial treatment and deteriorated from month 24 to 36. These results indicated that the treatment effects of combined therapy lasted longer than those of anti-VEGF monotherapy.

Comparisons between the two groups showed that the treatment effects in combined therapy group at month 6, 24 and 36 were significantly better than those of anti-VEGF monotherapy group, and no significant difference was found at other months. This suggested that combined therapy may be much better than anti-VEGF monotherapy in early and long-term treatment for PCV.

The normalized analyses of the two groups showed that logMAR BCVA increased by 8.0%-39.4% in combined treatment group during the 36 months' follow-up. However, in anti-VEGF monotherapy group only 7.3%-20.9% increase from month 1 to 12, and even a 6.4% decrease at month 24 and a 11.2% decrease at month 36 were observed. These results showed that the BCVA improved more in combined therapy group.

Taken together, the above results showed that the BCVA improvement in combined therapy group not only lasted longer but also was much better than that in anti-VEGF monotherapy group.

CRT is defined as the distance between the internal limiting membrane and the inner surface of the retinal pigment epithelium at the fovea, and it can be non-invasively, accurately, rapidly and conveniently measured by OCT, so CRT has been widely used in evaluating the anatomical changes of PCV. Our results showed that the CRT reduced from the baseline in both groups during 24 months' follow-up, but combined treatment had better effects during the first 9 months' follow-up.

Regression rate of polyps is another important indicator in evaluating the anatomical changes of PCV. Our results showed that the regression rate of polyps in combined treatment group was much higher than that in anti-VEGF monotherapy group at month 3. This suggested that combined treatment had better effect in regression of polyps at early stage. Various trials

have also shown that anti-VEGF treatments are effective in improving visual acuity, reducing leakage and resolving fluids, but ineffective in polyp regression[13-15,17,22,31], which is consistent with our results.

Retinal hemorrhage is one of the major sight-threatening problems related to PCV treatment[15,17,20-21,32-38]. In this Meta-analysis, our data showed no significant difference between combined therapy and anti-VEGF monotherapy. Several studies have reported that PDT usually cause more complications of retinal hemorrhage[35,39]. But a recent Meta-analysis demonstrated that combined therapy appeared to result in lower rate of retinal hemorrhage compared with PDT, which is due to the fact that anti-VEGF agents could block the increased VEGF expression induced by PDT[2]. This may explain why combined therapy did not bring more changes of retinal hemorrhage than anti-VEGF monotherapy in our study.

Heterogeneity is often a concern in Meta-analysis. Substantial heterogeneity was observed in some analyses, especially in the comparison of BCVA improvement between the two groups, and the comparison of CRT follow-up with the baseline, which is not surprising and can be partially explained by the following facts: most of the included studies are non-randomized; various matching criterions were different; measurements of outcomes were non-standardized; patients were from different population including Asians and Europeans. Using random-effect models in pooling the data might reduce the effect of heterogeneity.

To assess the impact of a certain single study on the estimates, we performed a sensitivity analysis by iteratively excluding each study to assess stability of the Meta-analysis results. Our results showed that most of the Meta-analyses were stable. We also tried to evaluate potential publication bias with Begg's and Egger's tests in comparisons between the two groups when number of studies is no less than 4, which showed no evidence of publication bias. This showed that our results have certain reliability.

A number of strengths can be found in this Meta-analysis. Firstly, to our knowledge, this is the first Meta-analysis comparing combined therapy with anti-VEGF monotherapy in treatment of PCV. Secondly, the Meta-analysis was a direct comparison between combined therapy and anti-VEGF monotherapy, rather than an indirect comparison. Thirdly, the Meta-analysis had strict inclusion and exclusion criteria. Fourthly, we strictly followed the guideline of PRISMA statement and Cochrane Handbook for Systematic Reviews of Interventions, including literature search, data extraction, and statistical analysis, thereby making our results more scientific and reliable. Thus, our study might provide the most up-to-date information in this area.

This Meta-analysis has some limitations that should be taken into account. Firstly, most of the included studies were NRSs, which might result in selection bias. Nonetheless, the major baseline characteristics of the two groups were comparable, therefore, selection bias was less likely to occur. Secondly, included studies used ranibizumab, bevacizumab or aflibercept as anti-VEGF agent, so there might be a difference between the three agents in treating PCV. However, recent studies have demonstrated that ranibizumab and bevacizumab have similar efficacy in treating age-related macular degeneration and PCV[40-43], and that ranibizumab and aflibercept have similar efficacy in BCVA improvement in PCV[44]. Thirdly, "grey literature" was not included in this study, which might result in publication bias. Fourthly, substantial heterogeneity was observed in some analyses. Using random-effects models in pooling data might reduce, but will not abolish, the effect of heterogeneity. Fifthly, sensitivity analysis showed that a minority of the Meta-analyses were not stable, which might reduce the reliability of the results. Sixthly, the longest follow-up duration of included studies was only 36mo. Also, there were only two studies which had 24-month follow-up and there was only one study which had 36-month follow-up, which could result in bias in functional and anatomical outcomes. So more data of longer duration are needed to determine the efficacy and safety of combined treatment over long term. Finally, only 9 studies with small sample size were included in this Meta-analysis, and more large-sample-sized studies are needed to evaluate the efficacy of the treatments in PCV.

In conclusion, to our knowledge, this is the first Meta-analysis comparing combined therapy with anti-VEGF monotherapy for PCV. Our findings clearly document that anti-VEGF combined with PDT is a more effective therapy for PCV compared with anti-VEGF monotherapy. Furthermore, combined therapy does not increase the incidence of retinal hemorrhage.

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REFERENCES

1 Ciardella AP, Donsoff IM, Huang SJ, Costa DL, Yannuzzi LA. Polypoidal choroidal vasculopathy. *Surv Ophthalmol* 2004;49(1):25-37.

2 Wang W, He M, Zhang X. Combined intravitreal anti-VEGF and photodynamic therapy versus photodynamic monotherapy for polypoidal choroidal vasculopathy: a systematic review and meta-analysis of comparative studies. *PLoS One* 2014;9(10):e110667.

3 Spaide RF, Yannuzzi LA, Slakter JS, Sorenson J, Orlach DA. Indocyanine green videoangiography of idiopathic polypoidal choroidal vasculopathy. *Retina* 1995;15(2):100-110.

4 Uyama M, Wada M, Nagai Y, Matsubara T, Matsunaga H, Fukushima I, Takahashi K, Matsumura M. Polypoidal choroidal vasculopathy: natural history. *Am J Ophthalmol* 2002;133(5):639-648.

5 Tong JP, Chan WM, Liu DT, Lai TY, Choy KW, Pang CP, Lam DS. Aqueous humor levels of vascular endothelial growth factor and pigment epithelium-derived factor in polypoidal choroidal vasculopathy and choroidal neovascularization. *Am J Ophthalmol* 2006;141(3):456-462.

6 Matsuoka M, Ogata N, Otsuji T, Nishimura T, Takahashi K, Matsumura M. Expression of pigment epithelium derived factor and vascular endothelial growth factor in choroidal neovascular membranes and polypoidal choroidal vasculopathy. *Br J Ophthalmol* 2004;88(6):809-815.

7 Song JH, Byeon SH, Lee SC, Koh HJ, Kwon OW. Short-term safety and efficacy of a single intravitreal bevacizumab injection for the management of polypoidal choroidal vasculopathy. *Ophthalmologica* 2009;223(2):85-92.

8 Gomi F, Sawa M, Sakaguchi H, Tsujikawa M, Oshima Y, Kamei M, Tano Y. Efficacy of intravitreal bevacizumab for polypoidal choroidal vasculopathy. *Br J Ophthalmol* 2008;92(1):70-73.

9 Hikichi T, Higuchi M, Matsushita T, Kosaka S, Matsushita R, Takami K, Ohtsuka H, Ariga H. One-year results of three monthly ranibizumab injections and as-needed reinjections for polypoidal choroidal vasculopathy in Japanese patients. *Am J Ophthalmol* 2012;154(1):117-124.e1.

10 Tsujikawa A, Ooto S, Yamashiro K, Tamura H, Otani A, Yoshimura N. Treatment of polypoidal choroidal vasculopathy by intravitreal injection of bevacizumab. *Jpn J Ophthalmol* 2010;54(4):310-319.

11 Nowak-Sliwinska P, van den Bergh H, Sickenberg M, Koh AH. Photodynamic therapy for polypoidal choroidal vasculopathy. *Prog Retin Eye Res* 2013;37:182-199.

12 Spaide RF, Donsoff I, Lam DL, Yannuzzi LA, Jampol LM, Slakter J, Sorenson J, Freund KB. Treatment of polypoidal choroidal vasculopathy with photodynamic therapy. *Retina* 2002;22(5):529-535.

13 Oishi A, Kojima H, Mandai M, Honda S, Matsuoka T, Oh H, Kita M, Nagai T, Fujihara M, Bessho N, Uenishi M, Kurimoto Y, Negi A. Comparison of the effect of ranibizumab and verteporfin for polypoidal choroidal vasculopathy: 12-month LAPTOP study results. *Am J Ophthalmol* 2013;156(4):644-651.

14 Inoue M, Arakawa A, Yamane S, Kadonosono K. Long-term outcome of intravitreal ranibizumab treatment, compared with photodynamic therapy, in patients with polypoidal choroidal vasculopathy. *Eye (Lond)* 2013;27(9):1013-1020.

15 Rouvas AA, Papakostas TD, Ntouraki A, Douvali M, Vergados I, Ladas ID. Photodynamic therapy, ranibizumab, and ranibizumab with photodynamic therapy for the treatment of polypoidal choroidal vasculopathy. *Retina* 2011;31(3):464-474.

16 Schmidt-Erfurth U, Schlötzer-Schrehard U, Cursiefen C, Michels S, Beckendorf A, Naumann GO. Influence of photodynamic therapy on expression of vascular endothelial growth factor (VEGF), VEGF receptor 3, and pigment epithelium-derived factor. *Invest Ophthalmol Vis Sci* 2003;44(10):4473-4480.

17 Koh A, Lee WK, Chen LJ, Chen SJ, Hashad Y, Kim H, Lai TY, Pilz S, Ruamviboonsuk P, Tokaji E, Weisberger A, Lim TH. EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy. *Retina* 2012;32(8):1453-1464.

18 Lim JY, Lee SY, Kim JG, Lee JY, Chung H, Yoon YH. Intravitreal bevacizumab alone versus in combination with photodynamic therapy for the treatment of neovascular maculopathy in patients aged 50 years or older: 1-year results of a prospective clinical study. *Acta Ophthalmol* 2012;90(1):61-67.

19 Sakurai M, Baba T, Kitahashi M, Yokouchi H, Kubota-Taniai M, Bikbova G, Oshitari T, Yamamoto S. One-year results of intravitreal ranibizumab combined with reduced-fluence photodynamic therapy for polypoidal choroidal vasculopathy. *Clin Ophthalmol* 2014;8:235-241.

20 Lai TY, Lee GK, Luk FO, Lam DS. Intravitreal ranibizumab with or without photodynamic therapy for the treatment of symptomatic polypoidal choroidal vasculopathy. *Retina* 2011;31(8):1581-1588.

21 Kang HM, Koh HJ. Two-year outcome after combination therapy for polypoidal choroidal vasculopathy: comparison with photodynamic monotherapy and anti-vascular endothelial growth factor monotherapy. *Ophthalmologica* 2014;231(2):86-93.

22 Song MH, Ryu HW, Roh YJ. One-year results of intravitreal ranibizumab with or without photodynamic therapy for polypoidal choroidal vasculopathy. *Ophthalmologica* 2011;226(3):119-126.

23 Kikushima W, Sakurada Y, Sugiyama A, Tanabe N, Kume A, Iijima H. Comparison of initial treatment between 3-monthly intravitreal aflibercept monotherapy and combined photodynamic therapy with single intravitreal aflibercept for polypoidal choroidal vasculopathy. *Graefes Arch Clin Exp Ophthalmol* Epub 2016 Aug 17.

24 Sakai T, Okano K, Kohno H, Tsuneoka H. Three-year visual outcomes of intravitreal ranibizumab with or without photodynamic therapy for polypoidal choroidal vasculopathy. *Acta Ophthalmol* 2016;94(8):e765-e771.

25 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6(7):e1000097.

26 Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;52(6):377-384.

27 Imamura Y, Engelbert M, Iida T, Freund KB, Yannuzzi LA. Polypoidal choroidal vasculopathy: a review. *Surv Ophthalmol* 2010;55(6):501-515.

28 Tang K, Si JK, Guo DD, Cui Y, Du YX, Pan XM, Bi HS. Ranibizumab alone or in combination with photodynamic therapy vs photodynamic therapy for polypoidal choroidal vasculopathy: a systematic review and Meta-analysis. *Int J Ophthalmol* 2015;8(5):1056-1066.

29 Yong M, Zhou M, Deng G. Photodynamic therapy versus anti-vascular endothelial growth factor agents for polypoidal choroidal vasculopathy: a meta-analysis. *BMC Ophthalmol* 2015;15:82.

30 Liu L, Ma J, Duan P, Liu Y, Yin ZQ. Practicability confirmation by meta-analysis of intravitreal ranibizumab compared to photodynamic therapy to treat polypoidal choroidal vasculopathy. *Mol Vis* 2015;21:1130-1141.

31 Lai TY, Chan WM, Liu DT, Luk FO, Lam DS. Intravitreal bevacizumab (Avastin) with or without photodynamic therapy for the treatment of polypoidal choroidal vasculopathy. *Br J Ophthalmol* 2008;92(5):661-666.

32 Lee MY, Lee WK, Baek J, Kwon OW, Lee JH. Photodynamic therapy versus combination therapy in polypoidal choroidal vasculopathy:

changes of aqueous vascular endothelial growth factor. *Am J Ophthalmol* 2013;156(2):343-348.

33 Saito M, Iida T, Kano M, Itagaki K. Two-year results of combined intravitreal ranibizumab and photodynamic therapy for polypoidal choroidal vasculopathy. *Graefes Arch Clin Exp Ophthalmol* 2013;251(9): 2099-2110.

34 Sakurada Y, Iijima H. Two-year results of photodynamic therapy with or without intravitreal ranibizumab for polypoidal choroidal vasculopathy. *J Ocul Pharmacol Ther* 2013;29(9):832-836.

35 Lee YA, Yang CH, Yang CM, Ho TC, Lin CP, Huang JS, Chen MS. Photodynamic therapy with or without intravitreal bevacizumab for polypoidal choroidal vasculopathy: two years of follow-up. *Am J Ophthalmol* 2012;154(5):872-880.e2.

36 Kim SJ, Yu HG. Efficacy of combined photodynamic therapy and intravitreal bevacizumab injection versus photodynamic therapy alone in polypoidal choroidal vasculopathy. *Retina* 2011;31(9):1827-1834.

37 Maruko I, Iida T, Sugano Y, Saito M, Sekiryu T. Subfoveal retinal and choroidal thickness after verteporfin photodynamic therapy for polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2011;151(4):594-603.e1.

38 Gomi F, Sawa M, Wakabayashi T, Sasamoto Y, Suzuki M, Tsujikawa M. Efficacy of intravitreal bevacizumab combined with photodynamic therapy for polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2010; 150(1):48-54.e1.

39 Hirami Y, Tsujikawa A, Otani A, Yodoi Y, Aikawa H, Mandai M, Yoshimura N. Hemorrhagic complications after photodynamic therapy for polypoidal choroidal vasculopathy. *Retina* 2007;27(3):335-341.

40 Krebs I, Schmetterer L, Boltz A, Told R, Vécsei-Marlovits V, Egger S, Schönherr U, Haas A, Ansari-Shahrezaei S, Binder S; MANTA Research Group. A randomised double-masked trial comparing the visual outcome after treatment with ranibizumab or bevacizumab in patients with neovascular age-related macular degeneration. *Br J Ophthalmol* 2013;97(3):266-271.

41 Kodjikian L, Souied EH, Mimoun G, Mauget-Faÿsse M, Behar-Cohen F, Decullier E, Huot L, Aulagner G; GEFAL Study Group. Ranibizumab versus bevacizumab for neovascular age-related macular degeneration: results from the GEFAL Noninferiority Randomized Trial. *Ophthalmology* 2013;120(11):2300-2309.

42 Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Culliford LA, Reeves BC; IVAN study investigators. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. *Lancet* 2013;382(9900):1258-1267.

43 Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE, Toth C, Redford M, Ferris FL 3rd. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 2012;119(7):1388-1398.

44 Cho HJ, Kim KM, Kim HS, Han JI, Kim CG, Lee TG, Kim JW. Intravitreal aflibercept and ranibizumab injections for polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2016;165:1-6.