• Clinical Research •

Combined photodynamic therapy and ranibizumab for polypoidal choroidal vasculopathy: a 2-year result and systematic review

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Abstract

● AIM: To report a cohort of patients with polypoidal choroidal vasculopathy (PCV) treated with photodynamic therapy (PDT) followed by intravitreal ranibizumab injection 24-48h later, and to compare the results between eyes with PCV treated by PDT followed by intravitreal anti-vascular endothelial growth factor (VEGF) injection and intravitreal anti-VEGF injection followed by PDT by Meta-analysis.

● METHODS: Retrospective study and systematic literature review. Medical records of patients with PCV who were initially treated using PDT followed by intravitreal ranibizumab injection 24-48h after PDT and had completed at least 2y follow-up were reviewed and analyzed. Clinical data, including age, sex, best-corrected visual acuity (BCVA), fundus photograph, fluorescein angiography, indocyanine green angiography and optical coherence tomography were investigated. A systematic literature review was also conducted, and a visual outcome of studies over 1y was compared using Meta-analysis.

● RESULTS: A total of 52 patients were included in the study. Mean BCVA at baseline and follow-up at 1 or 2y were 0.71±0.61, 0.51±0.36 and 0.68±0.51 logMAR, respectively. The cumulative hazard rate for recurrence at 1 and 2y follow-up was 15.4% and 30.3% respectively. The percentage of eyes with polyps regression at 3, 12 and 24mo follow-up was 88.5%, 84.6% and 67.3% respectively. A Meta-analysis based on 22 independent studies showed the overall vision improvements at 1, 2 and 3y follow-up were 0.13±0.04 (*P*<0.001), 0.12±0.03 (*P*<0.001), 0.16±0.06 (*P*<0.001), respectively. The proportion of polyps regression at 1y follow-up was 64.6% (95%CI: 51.5%, 77.7%, *P*<0.001) in 434 eyes treated by intravitreal anti-VEGF agents before PDT and 76.0% (95%CI: 64.8%, 87.3%, *P*=0.001) in 199 eyes treated by intravitreal anti-VEGF agents after PDT.

● CONCLUSION: Intravitreal ranibizumab injection 24-48h following PDT effectively stabilizes visual acuity in the eye with PCV. PDT followed by intravitreal anti-VEGF agents may contribute to a relatively higher proportion of polyps' regression as compared to that of intravitreal anti-VEGF before PDT.

● **KEYWORDS:** polypoidal choroidal vasculopathy; photodynamic therapy; intravitreal ranibizumab injection; Meta-analysis

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INTRODUCTION

Polypoidal choroidal vasculopathy (PCV) is characterized by the presence of terminal dilatations of the abnormal branching vascular network (BVN) and terminal polypoidal structures from the inner choroid[1]. Photodynamic therapy (PDT) combined with intravitreal anti-vascular endothelial growth factor (VEGF) agents has been widely used for PCV treatment and has shown favorable visual outcome[1-33]. However, the optimal time of intravitreal anti-VEGF agents before or after PDT is still controversial. Sprouting of new blood vessels was observed 24h post PDT at the edge of the PDT zone and the level of VEGF was found to be significantly up-regulated 6h after PDT[13]. The combination treatment of anti-VEGF agent 24h after PDT would therefore result in a considerable inhibition of re-growth of the vasculature post PDT[13,34]. Administration of a ranibizumab injection 2d before PDT achieved significantly better visual outcomes compared with the injection 7d before PDT[22]. While most of the studies utilized intravitreal anti-VEGF agents injection several days before PDT for patients with PCV[3,5-6,8,13,17,19-20,22-24,31], there are a few studies treated paitents with PCV by combined PDT and intravitreal anti-VEGF agents injection in the same day[7,11,15,18] or intravitreal anti-VEGF agents injection after PDT[4,12]. We

here reported a cohort of Chinese patients with PCV treated with intravitreal ranibizumab injection 24-48h after PDT. The visual outcome and proportion of polyps regression at follow-up, along with the results from literature, were included for further systemic reviews and Meta-analysis to compare the difference on visual acuity (VA) outcome and polyps regression between intravitreal anti-VEGF agents injection before and after PDT.

SUBJECTS AND METHODS

Enrollment of Study Subjects Records of 183 patients with PCV from November 2000 to January 2014 were retrospectively reviewed. The records of 52 patients who were initially treated using PDT followed by intravitreal ranibizumab injection and followed up for at least 24mo were included. This study was approved by the Ethics Committee of Beijing Tongren Hospital and adhered to the tenets of the Declaration of Helsinki. The diagnosis of PCV was established by the presence of single or multiple focal areas of hyperfluorescence arising from the choroidal circulation within the first 6min after injection of indocyanine green with or without an associated BVN[1]. Inclusion criteria: 1) patients with PCV; 2) patients were initially treated using PDT followed by intravitreal ranibizumab injection. Exclusion criteria: 1) patients failed to finish at least 24mo follow-up; 2) patients without VA records during follow-up; 3) patients without examinations of polyps either by optical coherence tomography (OCT) or fluorescence angiography (FA) or indocyanine green angiography (ICGA) during follow-up.

Examinations at Baseline All patients underwent comprehensive ophthalmological examinations, including best-corrected visual acuity (BCVA) testing using a decimal VA chart, slit-lamp biomicroscopy, dilate fundus examination with indirect ophthalmoscopy, color fundus photograph with a digital fundus camera, FA, ICGA (Spectralis OCT+HRA; Heidelberg Engineering, Heidelberg, Germany) and OCT. OCT images were obtained either by time-domain OCT (Stratus; Carl-Zeiss Meditec, Dublin, California, USA) or spectral-domain OCT (Spectralis OCT+HRA; Heidelberg Engineering, Heidelberg, Germany). BCVA, the greatest linear diameter (GLD) of the lesion (defined as the diameter of the lesion including the entire and polypoidal lesions at the early phase of ICGA), type of PCV[35], baseline OCT characteristics, central foveal thickness (CFT, defined as the distance between the internal limiting membrane and the inner surface of the retinal pigment epithelium), sex, age, and present history were recorded as the baseline data.

The Initial Combined Therapy Patients were initially treated with ICGA-guided PDT and an intravitreal ranibizumab injection 24-48h after PDT. For PDT, all patients received a 6 mg/m^2 infusion of verteporfin (Visudyne; Novartis AG, Bŭlach, Switzerland) over a period of 10min, followed by the use of a diode laser at 689 nm to the choroidal neovascularization (CNV) 15min after infusion started. A total light energy of 50 J/cm^2 and light dose rate of 600 mW/cm^2 for 83s were used to cover the entire polyps and BVN lesion when the lesion was not involved fovea, and only polyps when the BVN was involved the fovea. The PDT lesion included an additional 500 μm covering the border on each side, small and multiple PDT spots were used to cover the lesion. An intravitreal ranibizumab 0.5 mg injection was performed 24-48h after PDT. For intravitreal injections, topical anesthesia was applied, and 10% povidone-iodine was used to scrub eyelids and lashes, 5% povidone was applied for more than 90s, and a sterile lib speculum was put between the eyelids. Ranibizumab (0.5 mg/0.05 mL, Lucentis; Novartis AG, Bŭlach, Switzerland) injected into the vitreous cavity through the inferior sclera using a 30-gauge needle, 3.5 mm posterior to the corneal limbus. Sterile cotton was pressed over the injection site for more than 60s to prevent leakage.

Follow-up and Re-treatment Protocol Follow-up visits were scheduled at 1mo after the initial treatment and then 2, 3, 4, 5, 6, 9, 12, 18 and 24mo afterward. The examination included BCVA, dilated fundus examination, color fundus photography and OCT. An improvement of ≥0.3 logarithm of the minimal angle of resolution (logMAR) VA was defined as visual gain and a decrease of ≥0.3 in logMAR VA was defined as VA loss[4]. ICGA and FA were also performed at 3mo follow-up or at timepoint where there was suspicion of recurrence detected by either fundus photography (new subretinal hemorrhage or new orange subretinal nodular lesions) or OCT (recurrence of subretinal or intraretinal fluid). PCV recurrence was defined as the reappearance of active PCV lesions on ICGA with subfoveal leakage on FA or new subretinal hemorrhage on the fundus photograph after at least 6mo free of treatment[4]. The polyps detected by ICGA were classified as polyps within PDT lesion, polyps outside PDT lesion, polyps with complete regression on ICGA and polyps that could not be classified due to optic media haze. Polyps with complete regression was defined as there was no hyperfluorescence lesion on early ICGA[4]. Polyps that could not be classified due to optic media haze were not considered as polyps with complete regression.

All patients were followed up for at least 24mo. Subjects were reassessed monthly if recurrence occurred or polyps were persistent. If there was incomplete regression or recurrence of polyps following initial treatment on ICGA, patients were retreated with PDT monotherapy (without significant subretinal fluid) or a combination of PDT and ranibizumab (with significant subretinal fluid). PDT spots in retreatment were small and multispots to cover the polyps. If there was complete regression of polyps detected by ICGA but leakage on FA with clinical or OCT signs of activity, patients were treated with intravitreal ranibizumab injections[4].

Statistical Analysis Statistical analysis was performed using R version 3.20 (http://www. R-project.org). Patient characteristics were retrieved from their medical charts and recorded in Epidata EntryClientversion2.0.3.15 (http://epidata.dk). BCVA results were converted to logMAR value for statistical analysis. Mean and standard deviation (SD) were calculated for continuous variables with normal distribution. Median with quartiles was calculated for continuous variables with a non-normal distribution. The *t*-test or Mann-Whitney *U* test was carried out for continuous variables. The Chi-square test or Fisher's exact test was carried out for discrete data. To explore the changes in BCVA at each time point, repeated-measurement ANOVA with Huynh-Feldt correction was performed using the time point as the within group factor. The Wilcoxon signed-rank test was carried out to compare visual acuity at follow-up to that at baseline. To explore the potential prognostic factors for VA worse in the cohort, several factors, including present history, multiple polyps, distance from largest polyp to fovea, subfoveal hemorrhage, type of pigment epithelial detachment (PED), GLD of the lesion, BCVA at baseline, CFT at baseline, recurrence, subretinal hemorrhage during follow-up, and diminishment of polyp before 6mo, were compared between eyes with VA loss and eyes without VA loss at the most recent follow-up by univariate analysis (Table 1). Variables with *P* value ≤0.4 in the univariate analysis were further enrolled in a binary backward stepwise logistic regression model. These included the history of symptoms, present history, GLD at baseline, CFT at baseline, subretinal hemorrhage during follow-up, recurrence, recurrence outside the PDT lesion. One variable was included or excluded from the model each time by comparing the Akaike information criterion (AIC) value, and the model that had the lowest AIC was chosen. To explore the recurrence of PCV after combined treatment, a survival analysis was performed using the Kaplan-Meier curve.

Systematic Literature Review and Meta-analysis A review of all English and Chinese articles using PubMed, Embase and CNKI up to and including September 2015 was carried out, using the following search strings: polypoidal choroidal vasculopathy AND (verteporfin OR photodynamic) AND (bevacizumab OR ranibizumab OR anti-VEGF OR anti-VEGF OR pegaptanib sodium). The inclusion criterion was all articles reporting VA in logMAR or VA that would be converted to logMAR with at least 1y of follow-up. The retrieved articles were filtered manually to exclude duplicates, reviews and articles of insufficient relevance, case reports with ≤3 patients[4]. Data were extracted separately by Zhao M and Zhou HY.

For the Meta-analysis, the key outcome was the mean change of VA in logMAR scores between baseline and follow-up. The proportion of polyps regression at 3, 12mo follow-up were also investigated. In studies where multiple publications were produced from the same cohorts, only the reports with the longest follow-up were included. In studies where the outcome of PDT was reported separately from PDT combined with intravitreal anti-VEGF therapy, the outcomes of the group with combined therapy were treated as independent results and included in our Meta-analysis. Meta-analysis was performed using R version 3.20 (http://www. R-project.org) and the Metafor Package. Pearson's correlation coefficient was estimated from studies with a reported SD of VA. The median of Pearson's correlation coefficient was used in calculating the SD of the mean VA change in studies without a reported SD of VA. The *Q* statistic and I^2 was calculated to test the heterogeneity. If the heterogeneity was significant (*P* of Chi-square <0.1 or I^2>75%), a random effect Meta-analysis with the weighed mean difference (WMD) estimator was used. Otherwise, a fixed-effect Meta-analysis was performed. The data were further classified and subgroup analyzed by whether intravitreal anti-VEGF agents was finished before PDT.

RESULTS

Basic Characteristics of the Patients In total, 52 eyes of 52 patients who had completed at least a 2y follow-up after the initial combination therapy were analyzed. The mean age of patients was 65.4±7.4y at diagnosis. There were 31 male and 21 female patients. Detailed characteristics of patients are listed in Table 1. There were 5 patients with bilateral involvement; among them, one patient's right eye and four patients' left eyes were enrolled in the study. Baseline FA showed occult CNV in all eyes. Despite the first combined therapy, during a mean follow-up of 35.6±8.6mo (ranging from 24 to 101mo), mean total numbers of PDT were 1.6±0.9 (ranging from 1 to 4), and the mean total number of intravitreal ranibizumab injections was 4.6±2.6 (ranging from 1 to 13). During the first year of follow-up (52 eyes), a mean of PDT sessions [1.3±0.2 (ranging from 1 to 4)] and a mean of intravitreal ranibizumab injections [3.4±1.8 (ranging from 1 to 8)] were performed. During the second year of follow-up (52 eyes), a mean of 0.3±0.2 (ranging from 0 to 1) PDT sessions and 1.9±2.0 (ranging from 0 to 7) intravitreal ranibizumab injections were performed. During the third year of follow-up (18 eyes), a mean of 0.2±0.2 (ranging from 0 to 2) PDT sessions and 1.6±1.3 (ranging from 0 to 4) intravitreal ranibizumab injections were performed.

Visual Outcomes After Combined Therapy The mean BCVA was 0.71±0.61, 0.51±0.36 and 0.68±0.51 logMAR at baseline, 1 and 2y follow-up, respectively. Changes to mean BCVA from baseline during the 2y follow-up are shown in Figure 1. Compared with baseline BCVA (0.71±0.61), the mean BCVA peaked at 12mo (0.51±0.36, *P*=0.03) and decreased at 21mo (0.56±0.41, *P*=0.09) by the Wilcoxon signed-rank test. The variation pattern of BCVA was significant and was analyzed by repeated-measurement ANOVA with the Huynh-Feldt correction (*P*<0.001). At 1y follow-up, 21 of 52 patients

Table 1 The baseline and follow-up characteristics of 52 eyes (52 patients) with PCV treated with PDT followed by infravitreal ranibizumab injection

Characteristics	Total	Eyes without VA loss (*n*=43)	Eyes with VA loss (*n*=9)	*P*
Age of diagnosis (a)	65.4±7.4	63.3±7.6	62.5±7.9	0.78[a]
Male	31 (59.6)	22	9	0.01[b]
History of symptom median [1st,3rd IQR] (m)	3 [2,12]	3 [1.5,10]	3 [2,18]	0.25[c]
Eyesight (right)	29 (55.8%)	22	7	0.27[d]
BCVA at baseline	0.71±0.61	0.78±0.58	0.35±0.20	0.03[a]
Greatest linear dimension (μm)	3498.4±1954.2	3614.4±2064.3	2650.0±1247.5	0.35[c]
Central foveal thickness (μm)	272.0±194.6	261.7±195.7	363.7±159.7	0.10[c]
Multiple polyp lesions	21 (40.4%)	16	5	0.52[d]
Distance from the largest polyp to fovea (μm)	957.7±500.6	982.2±536.3	841.1±251.9	0.79[c]
Presence of subretinal hemorrhage >1 disc diameter	22 (42.3%)	16	6	0.21[d]
Location of the largest lesion				0.48[b]
Subfoveal	2 (3.8%)	1	1	
Juxtafoveal	44 (84.6%)	36	8	
Extrafoveal	6 (11.5%)	6	0	
Type of PED				0.26[d]
Hemorrhagic	29 (55.8%)	26	3	
Serous	23 (44.2%)	17	6	
Complete 1a follow-up	52 (100%)	43	9	
Complete 2a follow-up	52 (100%)	43	9	
Complete 3a follow-up	18 (34.6%)	12	6	
Recurrence	29 (55.8%)	22	7	0.27[b]
At polyps outside the PDT lesion	18 (34.6%)	12	6	0.06[b]
At polyps within PDT lesion	11 (21.1%)	10	1	0.71[b]
Subretinal hemorrhage during follow-up	23 (44.2%)	16	7	0.08[b]
Diminish of polyp before 6mo	29 (55.8%)	25	4	0.78[b]
VA gain at 1a	21 (40.4%)	-	-	-
VA loss at 1a	1 (1.9%)	-	-	-
VA gain at 2a	15 (28.8%)	-	-	-
VA loss at 2a	9 (17.3%)	-	-	
No. of intravitreal ranibizumab injections median [1st,3rd IQR]	4 [3,5]	4 [3,5]	5 [4,7]	0.13
No. of PDT median [1st,3rd IQR]	1 [1,2]	1 [1,2]	1 [1,2]	0.17

[a]*t*-test; [b]Fisher exact test; [c]Wilcoxon Mann-Whitney rank test; [d]Chi-square test.

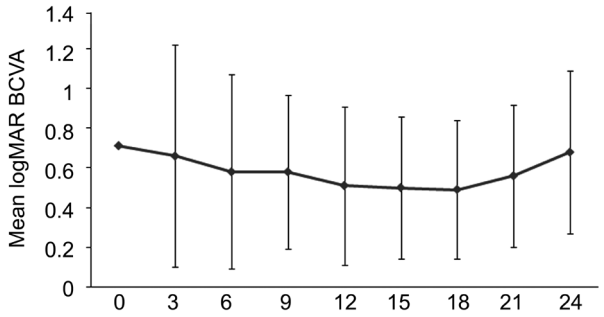

Figure 1 Mean VA changes during follow-up of eyes with PCV treated by PDT followed by intravitreal ranibizumab injection 24-48h later.

showed VA gain, and 1 patient showed VA loss. At 2y follow-up, 15 patients showed VA gain and 9 patients showed VA loss. Potential risk factors were compared between eyes with VA loss and eyes without VA loss (Table 1). VA loss was evaluated by the difference between VA at the latest follow-up and VA at baseline. In the binary backward stepwise logistic analysis model, taking these two variables as independent variables (AIC=37.2), better BCVA at baseline (RR=0.09, 95%CI: 0.01-0.94, *P*=0.03), recurrent polyp outside the PDT lesion (RR=0.19, 95%CI: 0.04-0.9, *P*=0.008) and subretinal hemorrhage (RR=0.17, 95%CI: 0.03-0.92, *P*=0.02) were risk factors for VA loss. There was an interaction between subretinal hemorrhage during follow-up and recurrent polyps outside the PDT lesion (*P*=0.03). The eyes with recurrence due to polyps outside the PDT lesion had a higher percentage of subretinal hemorrhage (14/18) during follow-up compared with eyes with recurrence due to polyps within the PDT lesion (2/11, *P*=0.001). When the interaction of these two variables was taken into consideration in binary logistic regression,

better BCVA at baseline (RR=0.09, 95%CI: 0.01-0.94, *P*=0.02), and subretinal hemorrhage due to recurrent polyps outside the PDT lesion (RR=0.11, 95%CI: 0.02-0.56, *P*<0.001) were risk factors of VA loss (AIC=33.96). The subretinal hemorrhage due to recurrent polyps within the PDT lesion was not a risk factor included in the final model. In eyes with recurrent polyps accompanied with subretinal hemorrhage during follow-up, the mean number of intravitreal ranibizumab injections was greater in eyes with recurrent polyps within the PDT lesion (7.4±3.6) compared with that in eyes with recurrent polyps outside the PDT lesion (4.5±0.7, *P*=0.003). There was no significant difference in the mean number of PDT sessions between eyes with recurrent polyps within the PDT lesion (2.8±1.3) compared with that in eyes with recurrent polyps outside the PDT lesion (1.8±0.8, *P*=0.32). From the last treatment to the occurrence of subretinal hemorrhage, the mean number of follow-ups was greater in eyes with subretinal hemorrhage due to recurrent polyps within PDT lesion (4±2.3) was greater than eyes with subretinal hemorrhage due to recurrent polyps outside PDT lesion (2±1.8, *P*=0.038).

Compared with baseline BCVA (0.71±0.61), the mean BCVA peaked at 12mo (0.51±0.36, *P*=0.03) and decreased at 21mo (0.56±0.41, *P*=0.09) by the Wilcoxon signed-rank test. The variation pattern of BCVA was significant and was analyzed by repeated-measurement ANOVA with the Huynh-Feldt correction (*P*<0.001).

Complete Regression and Recurrence of Polyps Complete regression of polyps was found in 46 eyes (88.5%), 44 eyes (84.6%), and 35 eyes (67.3%), at 3, 12 and 24mo follow-up, respectively. Twenty-nine out of 52 (55.8%) eyes had recurrence during follow-up. The median survival time for recurrence was 34.2mo, estimated by survival analysis (Figure 2). The cumulative hazard rate for recurrence was 15.4%, 30.3% at 1 and 2y follow-up. The mean number of intravitreal ranibizumab injections was greater in eyes with recurrent PCV (5.6±2.8) compared with that in eyes without recurrent PCV (3.3±1.7, *P*=0.003). The mean number of PDT sessions was greater in eyes with recurrent PCV (1.2±0.4) compared with that in eyes without recurrent PCV (1.9±1.0, *P*=0.03). The GLD of the lesion at baseline (*P*=0.37), the type of PED (*P*=0.14), the distance from the largest polyp to fovea at baseline (*P*=0.21), and the response to combined therapy at 3mo (*P*=0.64) or 6mo (*P*=0.62) did not influence the recurrence interval. Among the seven eyes with recurrence within 12mo of follow-up, 5 eyes had polyps within PDT lesion and 2 eyes had polyps outside the PDT lesion. Among the 17 eyes with recurrence between 12mo and 24mo of follow-up, 10 eyes had polyps within the PDT lesion and 7 eyes had polyps outside the PDT lesion.

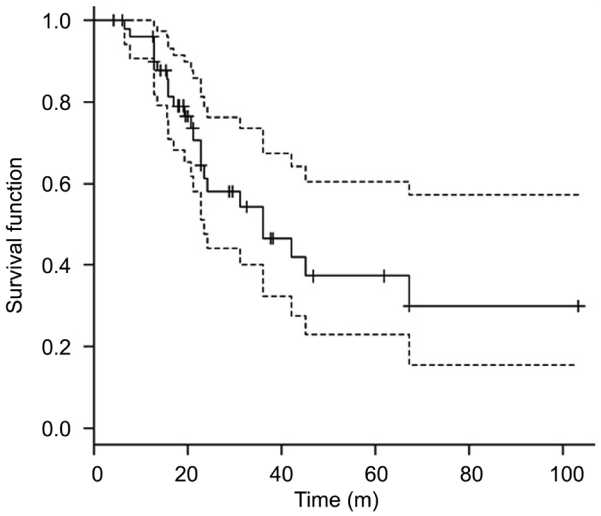

Figure 2 Kaplan-Meier estimate with 95% confidence bounds of recurrence of PCV during follow-up.

Systematic Literature Review and Meta-analysis A total of 163 articles were initially identified from an initial literature search. Nineteen articles were selected after checking for inclusion and exclusion criteria. The results are summarized in Table 2. The 22 studies included in our systematic review showed 0-15% of eyes with VA loss of 0.3 logMAR at the end of 1y follow-up[3-12,14-15,17-19,22-26]. There were 8 studies with a 2y follow-up visual outcome, in which 10%-59% of eyes had a VA loss of 0.3 logMAR or more at the end of 2y follow-up[7-11,23,25].

The pooled data for visual outcome are summarized in Figure 3. The final Meta-analysis was based on 22 independent results (including this retrospective study) and included 917, 317 and 74 eyes with 1, 2 and 3y follow-up, respectively. The overall vision improved by 0.13±0.04 logMAR (*P*<0.001, result of heterogeneity test: *Q*=31.23, I^2=43.5%, *P* of Chi-square=0.3), 0.12±0.03 logMAR (*P*<0.001, result of heterogeneity test: *Q*=4.94, I^2=41.7%, *P* of Chi-square=0.76), 0.16±0.06 logMAR (*P*<0.001, result of heterogeneity test: *Q*=4.30, I^2=54.8%, *P* of Chi-square=0.03) at 1, 2 and 3y follow-up, respectively. The visual outcome was not significantly different between eyes treated by intravitreal anti-VEGF agent before and after PDT at 1y (*P*=0.56) or 2y follow-up (*P*=0.73).

The overall vision improved by 0.13±0.04 (*P*<0.001), 0.12±0.03 (*P*<0.001), 0.16±0.06 (*P*<0.001) at 1, 2 and 3y follow-up, respectively.

There were 13 studies reported proportion of polyps regression at 3mo after the initial combined therapy, the proportion of polyps regression at 3mo after initial combined therapy was 76.3% (95%CI: 70.6%-87.5%, *P*<0.001, result of heterogeneity test: *Q*=10.2, I^2=79.6%, *P* of Chi-square<0.001) in 351 eyes treated by intravitreal anti-VEGF agents before PDT and 78.0% (95%CI: 62.6%-93.4%, *P*<0.001, result of heterogeneity test: *Q*=13.74, I^2=37.39%, *P* of Chi-square=0.58) in 86 eyes treated by intravitreal anti-VEGF agents after PDT. There

Table 2 Characteristics of studies included in this Meta-analysis

First author	Study design	Year	No. of eyes	Treatment	Time interval (d)[d]	BCVA (SD)				Proportion of polyps regression (%)	
						0	12mo	24mo	36mo	3mo	12mo
Gomi F[3]	PR[f]	2015	37	PDT R[a]	7	0.5 (0.25)	0.29 (0.27)	NA	NA	69.7	62.1
Wong IY[26]	RN	2015	19	PDT R	7	0.64 (0.37)	0.41 (0.25)	NA	NA	NA	42.1
Hata M[7]	RN	2014	95	PDT R	-3- -4[a]	0.62 (0.40)	0.53 (0.44)	0.62 (0.45)	NA	NA	63.2
Lee JH[14]	RN	2015	33	PDT B[b]	3	0.49 (0.27)	0.30 (0.29)	NA	NA	72.7	69.7
Lee JH[14]	RN	2015	30	PDTh[c] B	3	0.56 (0.38)	0.41 (0.43)	NA	NA	43.3	3.3
Ho M[4]	RN[e]	2014	74	PDT R	-0.5	0.82 (0.54)	0.73 (0.54)	NA	NA	NA	81
Saito M[9,31]	RN	2014	25	PDT R	1-2	0.30 (0.52)	0.59 (0.23)	0.55 (0.26)	NA	100	100
Sakurai M[5]	RN	2014	17	PDT R	1	0.55 (0.05)	0.38 (0.23)	NA	NA	82.3	NA
Sato T[22]	RN	2013	59	PDT R	7	0.41 (0.39)	0.36 (0.35)	NA	NA	78	NA
Sato T[22]	RN	2013	40	PDT R	2	0.46 (0.35)	0.27 (0.26)	NA	NA	85	NA
Jeon S[8]	RN	2013	40	PDT B	3-4	0.67 (0.36)	0.47 (0.32)	0.48 (0.38)	0.55 (0.46)	NA	NA
Kang HM[10]	RN	2013	34	PDT R/B	-7	0.59 (0.35)	0.32 (0.35)	0.36 (0.35)	NA	94.1	88.3
Yoshida Y[23]	RN	2013	14	PDTh R	3	0.58 (0.38)	0.37 (0.38)	0.35 (0.29)	NA	71.4	78.6
Sakurada Y[25]	RN	2013	24	PDT R	7	0.51 (0.22)	0.24 (0.28)	0.28 (0.32)	NA	NA	NA
Lee YA[14]	RN	2012	36	PDT B	7	0.73 (0.36)	0.54 (0.38)	0.61 (0.43)	NA	NA	NA
Tomita K[24]	RN	2012	66	PDT R	3-4	0.47 (0.37)	0.29 (0.29)	NA	NA	NA	79.1
Park DH[17]	RN	2012	65	PDT R	7	0.93 (0.43)	0.78 (0.52)	NA	NA	NA	74.5
Ricci F[18]	RN	2012	17	PDT R	-2	0.45 (0.29)	0.29 (0.28)	NA	NA	NA	94.1
Sagong M[19]	RN	2012	16	PDT B	7	0.76 (0.45)	0.46 (0.34)	NA	NA	87.5	81.2
Kim M[11]	RN	2011	22	PDT R/B	-7	0.43 (0.33)	0.28 (0.24)	0.39 (0.28)	NA	NA	NA
Lai TY[12]	RN	2011	16	PDT R	0	0.70 (0.35)	0.62 (0.35)	NA	NA	93.8	NA
Moon SW[15]	RN	2011	22	PDT R/B	-7	0.45	0.28	NA	NA	NA	53.8
Gomi F[6]	PR	2010	61	PDT B	1	0.48 (0.38)	0.37 (0.41)	NA	NA	78.7	43.8
Current study	RN	2015	52	PDT R	-1- -2	0.71 (0.61)	0.51 (0.36)	0.51 (0.68)	NA	80.8	71.1

[a]R: Ranibizumab; [b]B: Bevacezumab; [c]PDTh: Reduced-fluence PDT; [d]Time interval for time interval between PDT and intravitreal anti-VEGF injection- is for PDT followed by intravitreal anti-VEGF injection; [e]RN: Retrospective, non-randomized; [f]PR: Prospective randomized. NA: Data that is unable to find.

were 16 studies reported the regression of polyps at the end of follow-up. Among them, 4 studies reported the proportion of polyps regression at 24mo after initial combined therapy and 12 studies reported that at 12mo after initial combined therapy. The proportion of polyps regression at 1y follow-up was 64.6% (95%CI: 51.5%-77.7%, P<0.001, result of heterogeneity test: Q=12.76, I^2=87.2%, P of Chi-square<0.001) in 434 eyes treated by intravitreal anti-VEGF agents before PDT and 76.0% (95%CI: 64.8%-87.3%, P=0.001, result of heterogeneity test: Q=9.07, I^2=56.1%, P of Chi-square=0.11) in 199 eyes treated by intravitreal anti-VEGF agents after PDT.

DISCUSSION

In this study, we retrospectively investigated the 2y visual outcome and polyps regression rate of eyes with PCV, treated initially using PDT followed by intravitreal ranibizumab injection 24-48h after PDT and explored the potential risk factors for the VA loss. Significant improvement of mean BCVA was maintained 12 to 21mo after the first combined therapy. The proportion of polyps regression were decreased during follow-up.

The VA outcomes of patients with PCV after combined treatment varied greatly among studies with a different follow-up period. Numerous previous studies reported favorable 1y visual outcomes of combined therapy of PCV[3-6,12-13,15,17-19,22,24,26,30]. However, studies with 2 or more years of follow-up showed less favorable results[7-8,11,14,23,25,28,31]. Similar to the VA loss after long term follow-up[7-8,23,31] study reported that the rate of VA loss at 2y follow-up (17.3%) was greater than that at 1y (1.9%). The studies included in our systematic review showed that the rate of VA loss was 0-15% at 1y and 10%-59% at 2y[2-26,31], which was coincided with our findings. The mean BCVA in Meta-analysis showed that a mean VA gain was observed

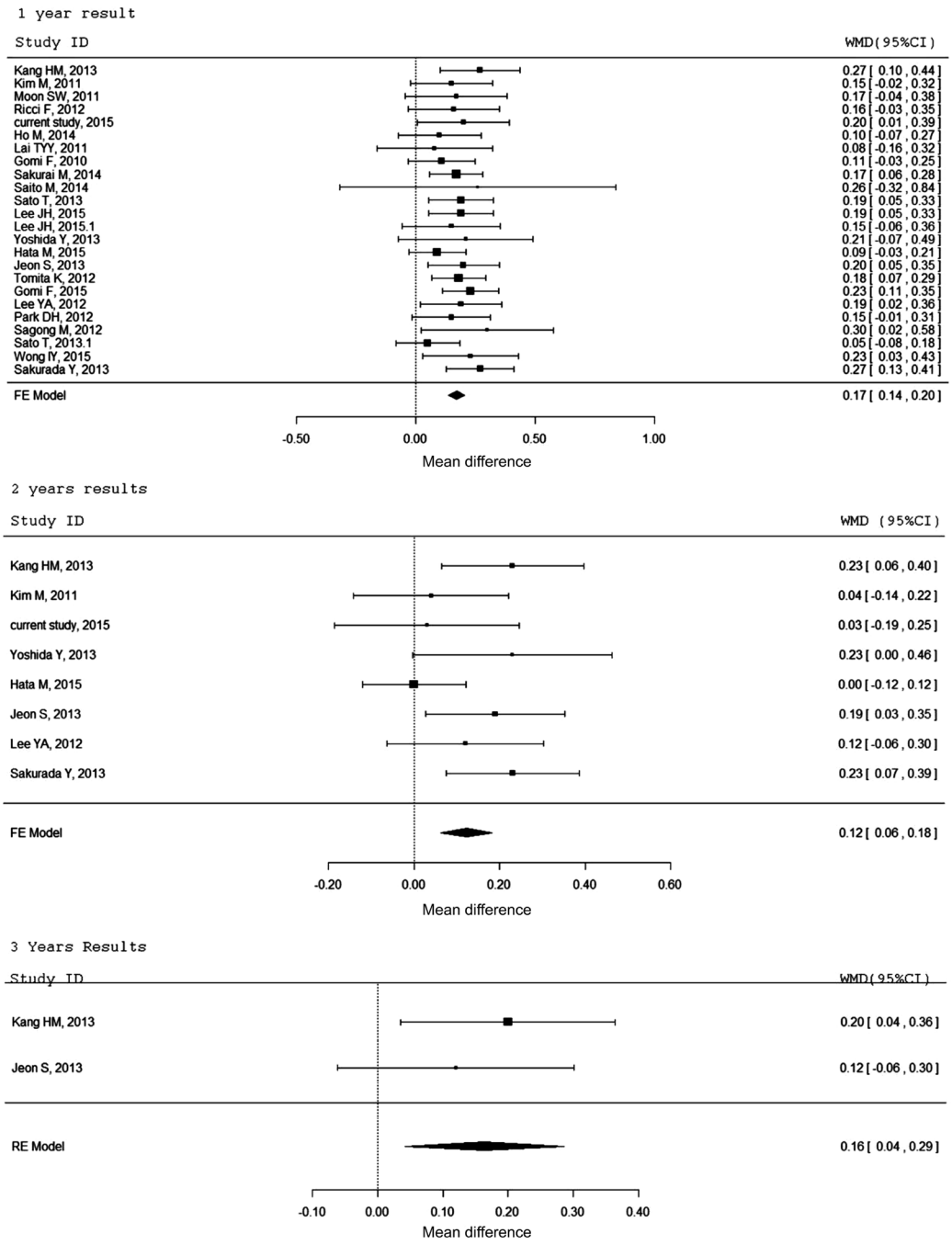

Figure 3 Forest plot for Meta-analysis with studies included in the Meta-analysis.

at 1, 2 and 3y follow-up, while in the current retrospective cohort of patients with PCVs, VA improvement at 1y follow-up was not maintained at 2y follow-up. VA was stable at 2y follow-up compared to VA at baseline. We tried to investigate the risk factors related to the VA results in our cohort. Several risk factors for VA loss have been reported, such as recurrence[3,5,7-9,32,35-38], subretinal hemorrhage[2-3,5,8,36], and GLD of the lesion at baseline[4-5,31]. In our study, with a binary backward stepwise logistic analysis, better BCVA at baseline and the occurrence of subretinal hemorrhage due to recurrent polyps outside the PDT lesion during follow-up were related to VA loss at 2y follow-up. Few studies have demonstrated the effect of the site of recurrent polyps on VA loss. In the current study, we showed that only subretinal hemorrhage due to the recurrence of polyps outside the PDT lesion was a risk factor for poor VA outcome. Subretinal hemorrhage right after combined treatment or due to recurrent polyps within the PDT lesion was not a risk factor for VA loss. Intravitreal ranibizumab injection has been effective in the absorption of subretinal fluid[33,37]. Fewer incidences of subretinal hemorrhage have been reported after combined therapy than after PDT monotherapy[33-35]. The mean number of intravitreal ranibizumab injections and follow-up in eyes with recurrent polyps within the PDT lesion was greater than eyes with recurrent polyps outside the PDT lesion in the current study. Intravitreal ranibizumab injection and intense follow-up after treatment may contribute to preventing severe VA loss in eyes with subretinal hemorrhage right after PDT or due to recurrent

polyps within the PDT lesion in our study. Further study with more cases with recurrent polyps within or outside the PDT lesion may help to explain the relationship between the position of recurrent polyps, subretinal hemorrhage and VA loss. The recurrence was not related to VA loss at the end of follow-up in our study, similar to previous study[33,36]. There were more intravitreal ranibizumab injections and PDT sessions in eyes with recurrence compared with eyes without recurrence. Early detection of recurrence and repeated combined therapy of PDT and intravitreal ranibizumab injections may contribute to less number of eyes with VA loss in eyes with recurrence.

The difference of efficacy of combined intravitreal anti-VEGF agents before or after PDT was explored by Meta-analysis. There was no significant heterogeneity among studies include in our Meta-analysis with either 1 or 2y follow-up regarding to visual acuity. The heterogeneity of polyps regression was of significance among studies in which patients were treated by PDT after intravitreal anti-VEGF agents, while was not among studies in which patients were treated by PDT before intravitreal anti-VEGF agents. Since all studies include in our Meta-analysis used the same diagnosis criteria for PCV[1], the universal character of presence of polyps makes the clinical variation contribute little to the heterogeneity[38]. We found there were different among those studies in regarding to time-interval between PDT and intravitreal anti-VEGF agents, anti-VEGF agents, PDT protocol, retreatment protocols. The limitations of the number of studies hold us back from further conducting sub-group analysis. The heterogeneity was possibly caused by the methodological differences among studies. Our Meta-analysis showed although there was no significant difference on mean BCVA outcome between combining intravitreal anti-VEGF agents before or after PDT, the proportion of polyps regression at 1y follow-up was greater in eyes treated by intravitreal anti-VEGF agents following PDT compared to eyes treated by intravitreal anti-VEGF agents before PDT. As mentioned above, there were several factors might influence the result, such as reduced fluence PDT, different anti-VEGF agents, lacking of randomized controlled study, limit results of longer follow-up. A well designed prospective randomized study might be required to explore the optimal time for intravitreal anti-VEGF agents before or after PDT in treating eyes with PCV.

There were limitations to our study. We only reported a cohort of patients with PCV treated by PDT followed by intravitreal ranibizumab injection 24-48h later, without a control group of patients with PCV treated by intravitreal ranibizumab before PDT, we could not show the optimal time for intravitreal ranibizumab injection in combined therapy in the current retrospective study. The retrospective study design is prone to bias. For example, in the long follow-up period at a tertiary center, a significant number of patients failed to continue their treatment and follow-up. The patients with recurrence and aggressive disease tended to be more compliant during follow-up. There was no strict and specified interval for ICGA or FA, and the judgment of recurrence and decision of repeated combined treatments might be delayed for one or two months. There might have been an inter-device difference in the OCT results, as some were time-domain OCT and others spectral-domain OCT. Taking into account that CFT measured by time-domain OCT is thinner[39] and a great proportion of patients in our study had CFT measured by time-domain OCT, we omitted the result of CFT changes during follow-up. Because most of the patients underwent time-domain OCT at baseline, we considered the CFT at baseline as a potential risk factor for visual outcome in the statistical analysis. Further prospective study with a fixed spectral-domain OCT device may help to demonstrate the nature of changes to CFT after combined treatment. Because we had only 9 eyes with VA loss, other risk factors failed to relate to poor visual outcome in our study, including larger lesion size, proximity to fovea, type of PED, and scar or atrophy of the macula. Further studies should look into the potential risk factors in detail. It is well-known repeat PDT treatments may damage the retinal pigment epithelial[35-38], the 2 cases with visual loss who had experienced subretinal hemorrhage due to recurrent polyps within the original PDT lesion in our cohort did not show significant RPE damages on their follow-up OCTs. The protocol of PDT treatment using small and multispots to cover the recurrent polyps and the macular sparing treatment may help to reduce the damages of PDT to retinal pigment epithelial at fovea. Further studies with longer follow-up and more recurrent cases may help to address the relationship between retinal pigment epithelial damages and visual acuity loss. For the pooled analysis, we failed to include studies without logMAR scores of mean BCVA at baseline or most recent follow-up. Pooling data from such heterogeneous studies may limit the application of the results of this Meta-analysis. The variations in study design, follow-up period, anti-VEGF agents and population should be taken into account when interpreting the results.

In conclusion, we showed that PDT followed by intravitreal ranibizumab injection 24-48h after PDT was effective at achieving stabilization of VA and polyps regression in eyes with PCV for a 2y follow-up. Combining of intravitreal anti-VEGF agents following PDT was as effective as combining intravitreal anti-VEGF agents before PDT in VA outcomes, but show a greater proportion of polyps regression.

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