Photodiagnosis and Photodynamic Therapy 20 (2017) 215–220

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

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

Photodynamic therapy in combination with ranibizumab versus ranibizumab monotherapy for polypoidal choroidal vasculopathy: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Photodynamic therapy
Ranibizumab
Polypoidal choroidal vasculopathy
Meta-analysis
Systematic review

ABSTRACT

Purpose: To perform a systematic review and meta-analysis to compare the outcome and serious adverse effects of intravitreal ranibizumab (IVR) monotherapy *vs*. combined treatment of IVR and photodynamic therapy (PDT) on polypoidal choroidal vasculopathy (PCV).

Methods: A computerized online search was performed using PubMed, EMBASE, Cochrane Library, Web of Science and China National Knowledge Infrastructure (CNKI) database. The quality of included studies was evaluated according to the Newcastle-Ottawa Scale. Stata 11.0 software was used to do the Meta-analysis.

Results: After a detailed systematic review, 4 articles (5 study samples) were included for this meta-analysis. PCV eyes treated with PDT combined with IVR achieved better best-corrected visual acuity (BCVA) than IVR monotherapy group throughout a follow-up of 12(th) month (weight mean difference [WMD] in BCVA, 0.132; 95% CI, 0.029–0.234, $p = 0.012$). Further meta-analysis including studies with 24-month follow up period showed that BCVA at 24(th) month was also better in the combined treatment group than the monotherapy group (WMD in BCVA = 0.234; 95% CI, 0.071–0.398, $p = 0.005$). There were no significant differences both in serious ocular adverse effects and non-ocular adverse effects ($p > 0.05$) between two groups.

Conclusions: Treatment of PCV by PDT combine with IVR is valuable in improving visual acuity and maintaining long term effectiveness. Given the inherent limitations of the included research, future studies are needed to further validate and update the findings in this area.

1. Introduction

As a disease involving the choroidal circulation, polypoidal choroidal vasculopathy (PCV) is present in both men and woman particularly within individuals of African-American and Asian descent. First described by *Yannuzzi* in 1980, it is characterized by recurrent sub-retinal and sub-retinal pigment epithelium bleeding in middle aged black women [1]. The understanding of PCV has evolved rapidly during the recent two decades. The characteristic lesion of PCV is an inner choroidal vascular network of vessels ending in an aneurysmal bulge or outward projection, clinically as a reddish orange, spheroid and polyp-like structure in fundus. To date, the treatment methods for PCV include photodynamic therapy (PDT), anti-vascular endothelial growth factor (VEGF) agent such as intravitreal ranibizumab (IVR) and combination both PDT and IVR [2,3]. There were four meta-analyses to explore the best therapeutic schedule for PCV, but lacking of the efficacy evaluation for IVR alone and in combination with PDT [4–7]. This present meta-analysis aimed to compare the efficacy of IVR alone and in combination with PDT. The outcome contributes to further understanding the clinical treatment of PCV.

2. Methods

2.1. Search strategy

Five databases including PubMed, EMBASE, Cochrane Library, Web of Science and China National Knowledge Infrastructure (CNKI) were last searched on March 1, 2017. For maximum sensitivity, the search

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http://dx.doi.org/10.1016/j.pdpdt.2017.09.008
Received 5 May 2017; Received in revised form 13 September 2017; Accepted 17 September 2017
Available online 19 September 2017
1572-1000/

strategy for free text and thesaurus terms including “polypoidal choroidal vasculopathy”, “PCV”, “ ranibizumab”, “lucentis”, “photodynamic therapy”, “PDT”, “photodynamic treatment” and “photochemotherapy”. Manual searching of bibliographies was performed and relevant researches were also included. Only Chinese and English researches were included in this meta-analysis.

2.2. Inclusion and exclusion criteria

Published comparative studies, regardless of design or sample size, were included if they satisfied criteria at list (1) treatment-naive patients with PCV; (2) anti-VEGF versus combination treatment of PDT and IVR; (3) used standard-fluence IVR (0.5 mg/0.05 mL) and standard-fluence verteporfin (6 mg/m^2) PDT (50 J/cm^2); (4) reported sufficient outcomes as following: best-corrected visual acuity (BCVA), and serious ocular or systemic adverse events; (5) sufficient data to perform pooled analysis with other studies. Exclusion criteria were: (1) subjects received previous intervention for PCV; (2) review, letter, and conference abstracts were also excluded. Two authors (LL and JYW) independently scanned the full texts of retrieved articles, and determined whether they met inclusion criteria or not. Disagreements were resolved by discussion and consensus of all the authors.

2.3. Data extraction and quality assessment

The following data of included studies were extracted: (1) basic data: first author, publication year, location, study design, various intervention groups, number, age and gender of subjects, and duration of follow-up; (2) outcomes: The mean change of BCVA from baseline; mean change of CMT from baseline, number of treatments, and serious ocular or systemic adverse events.

The quality of included studies was evaluated and assessed using the Newcastle-Ottawa Scale (NOS) [8]. In addition, this meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [9].

2.4. Statistical analysis

Weighted mean difference (WMD) was presented for measurement data. Statistical heterogeneity across the including studies was evaluated by the chi-square test, and inconsistency was calculated by I^2. If significant statistical heterogeneity did not exist among the including studies, the fixed-effect method was used to pool the data. Otherwise, a random-effects method (Der Simonian-Laird method) was used. The publication bias was evaluated by Egger‘s line regression tests and Begg's funnel plot. All statistical analyses were performed with Stata 11.0 software (http://www.stata.com; Stata Corporation, College Station, TX). P value of < 0.05 was considered statistically significant.

3. Results

3.1. General characteristics of the included studies

After searching PubMed, EMBASE, Cochrane Library, Web of Science and CNKI databases, 145 studies were initially found. 81 studies were excluded for duplicated publication or duplicated used data. After reading the full-text of the articles, 59 publications were excluded. One randomized controlled trial [10] was excluded as it was the only study with a follow-up duration of 6 months and could not be pooled for *meta*-analysis with other eligible studies of different follow up period. Finally, four articles (5 study samples) [11–14] with 60 eyes with IVR, and 70 eyes with combination therapy were included in this

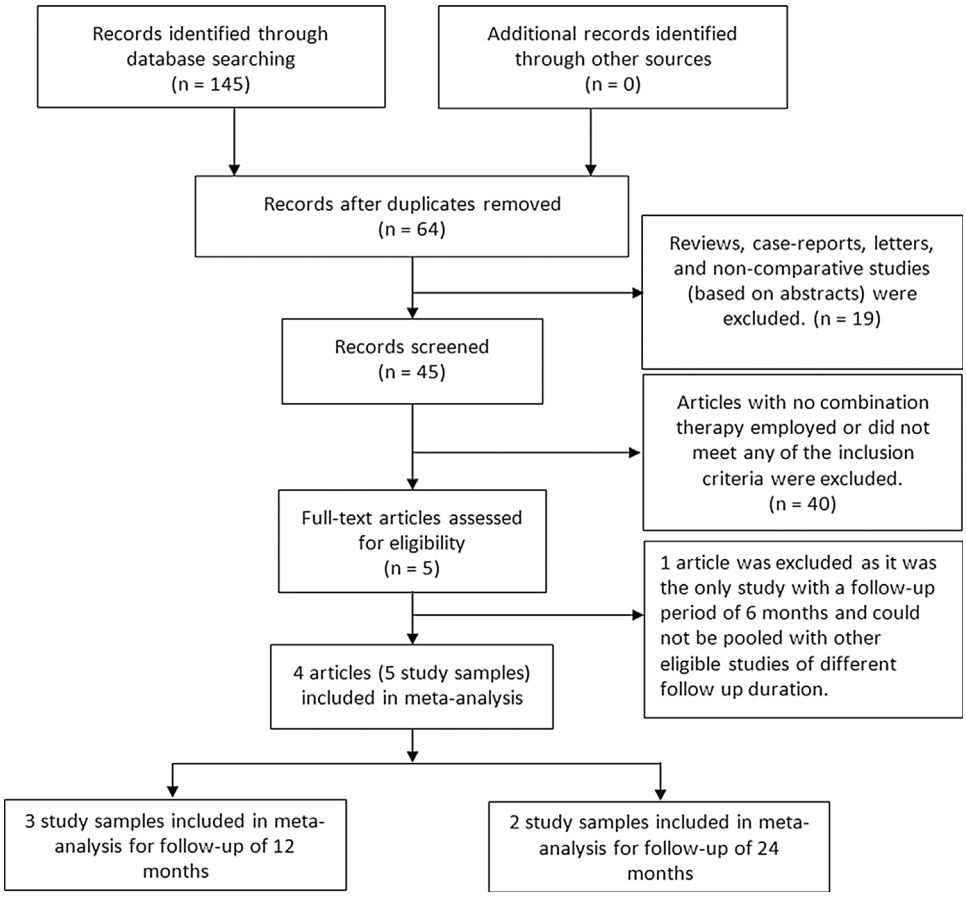

Fig. 1. Selecting flowchart for trials on the effects of ranibizumab monotherapy *vs.* combination therapy to treat polypoidal choroidal vasculopathy (PCV).

Table 1
Characteristics of included studies.

Study	Publication year	Location	Trial methods	Follow-up (months)	NO. of eyes		Age(year)	
					IVR group	Combination group	IVR group	Combination group
Rouvas et al. [11]	2011	Greece	Retrospect	12	10	9	66.5	64.67
Lai et al. [12]	2011	Hong Kong	Retrospect	12	7	16	64.6 ± 7.9	71.3 ± 9.8
Kang et al. [13]	2013	Korea	Retrospect	24	23	20	68.05 ± 8.12	70.00 ± 7.75
Sakai et al. [14]	2016	Japan	Retrospect	36 (including 12 and 24 months)	20	25	75.3 ± 8.1	72.6 ± 6.2

Study	Sex(male/female)		Type of OCT	Intervention		Number of Treatments (mean ± SD)(range)		Patients characteristics	NOS score
	IVR group	Combination group		IVR group	Combination group	IVR group	Combination group[a]		
Rouvas et al. [11]	4/6	4/5	SD	IVR (0.5 mg,3 + PRN)	PDT(50 J/cm^2, PRN) + IVR (0.5 mg, 3 + PRN)	6.9(3–11)IVR	1.67(1–2)PDT; 5(3–6)IVR	(1) Treatment-naive patients with PCV; (2) VA ≤ 20/30; (3) Identification of polyps and interconnecting vessels on the ICGA; (4) Presence of subretinal hemorrhages or exudation.	5
Lai et al. [12]	4/3	8/8	N/A	IVR (0.5 mg,3 + PRN)	PDT(50 J/cm^2, PRN) + IVR (0.5 mg, 3 + PRN)	4.0(3–6)IVR	1.2(1–2)PDT; 3.4(3–6)IVR	(1) Age ≥18 years; (2) PCV as defined by the presence of branching network of choroidal vessels with terminating aneurysmal polypoidal lesions in ICGA1, 2; (3) LogMAR BCVA from 0.1 to 1.6 or better (Snellen equivalent).	8
Kang et al. [13]	N/A	N/A.	TD	IVR (0.5 mg,3 + PRN)	PDT(50 J/cm^2, PRN) + IVR (0.5 mg, 3 + PRN)	10.12 ± 1.46 IVR	1.67 ± 0.65 PDT; 11.00 ± 2.61 IVR	(1) Treatment-naive patients with symptomatic PCV; (2) Presence of BVN and polypoidal lesions on ICGA; (3) without other fundus disease.	5
Sakai et al. [14]	13/7	21/4	SD	IVR (0.5 mg,3 + PRN)	PDT(50 J/cm^2, PRN) + IVR (0.5 mg, 3 + PRN)	7.65 ± 2.74 IVR	1.32 ± 0.56 PDT; 5.08 ± 2.45 IVR	Treatment-naive patients with symptomatic PCV.	6

PCV: polypoidal choroidal vasculopathy; OCT: optical coherence tomography; VA: visual acuity; BCVA: best corrected visual acuity; N/A: not applicable; ICGA: indocyanine green angiography; BVN: branching vascular network; SD: spectral domain; TD: time domain; GLD: greatest linear dimension; LogMAR: logarithm of minimal angle of resolution; IVR: intravitreal ranibizumab; PDT: photodynamic therapy; NOS: Newcastle-Ottawa Scale; PRN: Pro re nata; 3 + PRN: 3 monthly injections followed by pro re nata treatment.

[a] All combination group's patients treated with PDT received a 6 mg/m^2 infusion of verteporfin followed by laser then underwent IVR injection on same day. Additional combination therapy was given in case of recurrent or residual PCV during follow-up examination.

meta-analysis (Fig. 1). The main characteristics of the included four publications are shown in Table 1. One of these four included articles consisted of 2 study samples and provided two visual acuity outcomes for 12 and 24-month follow-up endpoints, respectively. Hence, we 'included' this article [14] for both the analysis of 12- and 24-month follow up period.

3.2. Visual outcomes

Visual acuity (VA) was the most important outcome for evaluating treatment efficacy. The pooled results revealed that at the 12 month follow up, change in logarithm of minimal angle of resolution (LogMAR) VA was significantly better in the combination group than in the IVR group (WMD, 0.132; 95% CI, 0.029-0.234, p = 0.012, Fig. 2). Similarly, at the 24 month follow up, change in LogMAR was significantly better in the combination group than in the IVR group (WMD, 0.234; 95% CI, 0.071-0.398, p = 0.005, Fig. 3). There was no substantial statistical heterogeneity across studies. The outcomes of combination treatment (IVR + PDT) compared to IVR monotherapy appear to significantly improve VA.

3.3. Adverse events

There were insufficient data about adverse effects (AEs) across including studies, so the AEs were not pooled in this meta-analysis. However, the details of serious AEs in every study were shown in Table 2. There was no significant difference on any AEs frequency between IVR and combination group according to c^2- test (Table 2).

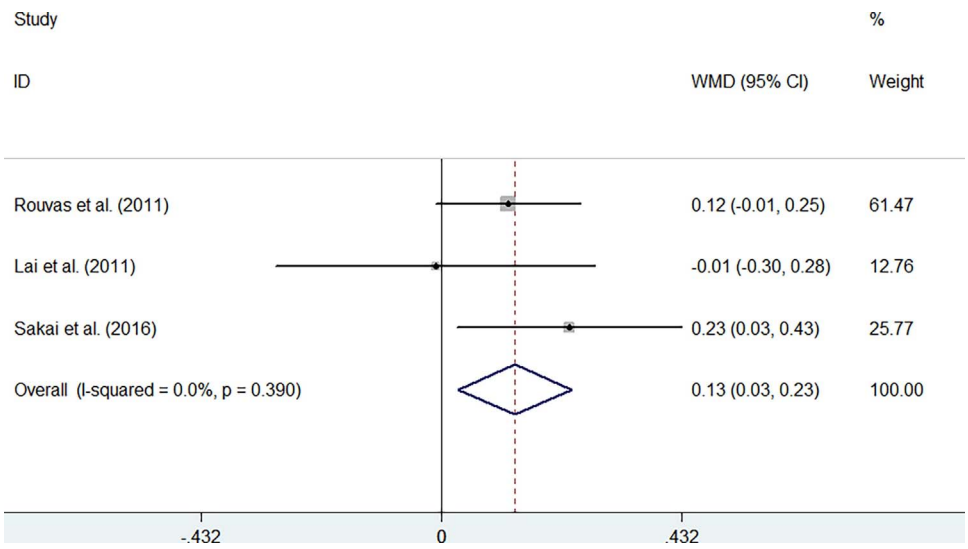

Fig. 2. Three studies evaluated the visual acuity in a 12-month follow-up after the treatments.

There was insufficient data about central retinal thickness (CRT); therefore, changing of CRT was not pooled in this meta-analysis.

3.4. Publication bias

Publication bias was assessed according to Egger's and Begg's tests based on mean changes in LogMAR VA at 12 months. There was no significant publication bias among the included studies (Egger's test, $p = 0.554$; Begg's test, $p = 0.602$), and Begg's funnel plot was shown in Fig. 4.

4. Discussion

To the best of our knowledge, it is the first meta-analysis to evaluate the clinical efficacy and safety of IVR monotherapy *vs.* combination of IVR and PDT in treatment of PCV.

With the aged tendency of population, PCV is more prevalent in the World especial in Asian populations [15,16]. To date, the actual mechanism of PCV is not fully understood. As it is characterized by subretinal and intraretinal haemorrhage, orange retinal lesions, macular choroidal neovascularization, the major treatment modality for PCV was vascular endothelial growth factor (VEGF). A meta-analysis by *Wang* et al. aiming to evaluate the efficacy and safety of PDT combined with intravitreal anti-VEGF agents compared to those of PDT monotherapy in the treatment of PCV showed combined treatment appeared to result in better VA and lower retinal haemorrhage [4]. Comparing with PDT monotherapy, IVR treatment has non-inferiority both in stabilizing and in improving BCVA. The combination treatment of PDT and IVR can exert a synergistic effect on improving BCVA by Tang et al.[5]. Another study showed that the outcomes of IVR treatment compared to PDT appeared to significantly improve BCVA, decrease the CRT, and reduce the invalidation rate [6]. However, the other meta-analysis by *Yong* et al. suggested that PDT was greater reduction of CRT at six months, and it was superior to IVR treatment in achieving complete polyp regression [7]. In addition, the latest meta-analysis showed that combining of intravitreal anti-VEGF agents following PDT was as effective as combining intravitreal anti-VEGF agents before PDT in visual acuity outcomes [17]. So the optimum treatment for PCV remains controversial and there is no evidence-based study to compare the efficacy of IVR monotherapy *vs.* combination treatment of PDT and IVR. This systemic review and meta-analysis revealed that compared with IVR monotherapy, treatment of PCV with combined therapy (PDT + IVR) was associated with better visual. Combination therapy might also help on the maintenance of vision improvement. Previous study by *Hatz K* et al. [18] showed that eyes with PCV underwent combination therapy had prolonged stabilization of VA and regression

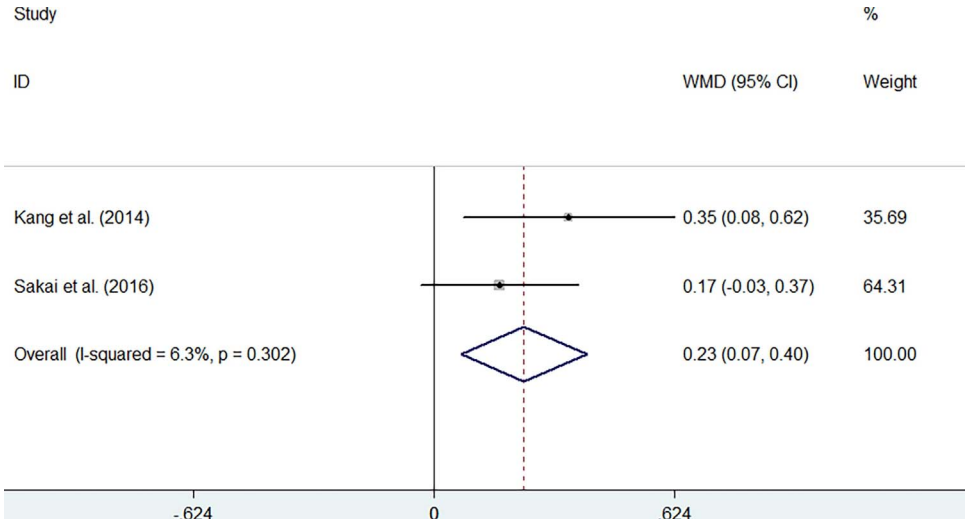

Fig. 3. Two studies evaluated the visual acuity in a 24-month follow-up after the treatments.

Table 2
Main serious ocular adverse events and systemic adverse events (%).

	IVR monotherapy group (n = 60)	Combination therapy group (n = 70)	χ^2	p
Serious ocular AEs			2.48	0.12
Submacular haemorrhage	1 (1.67)	0		
Retinal pigment epithelium tear	1 (1.67)	0		
Subretinal fibrosis	5 (8.33)	3 (4.28)		
Total	7 (11.67)	3 (16.85)		
Non-ocular AEs			0.04	0.84
Hypertension	3 (5)	3 (4.28)		
Total	3 (5)	3 (4.28)		

AEs: adverse effects.

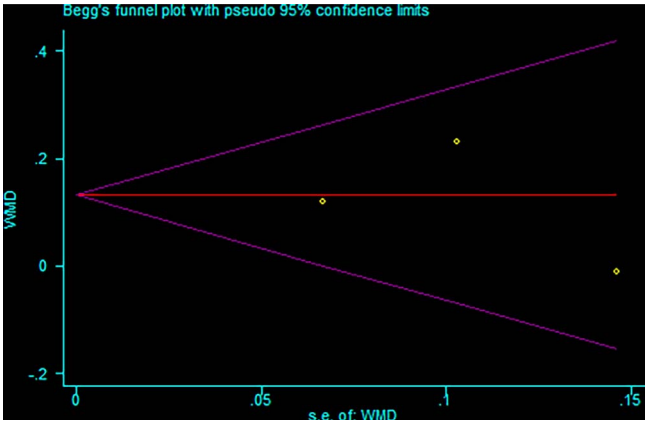

Fig. 4. The Begg's funnel plots did not reveal any evidence of obvious asymmetry in this meta-analysis at 12-month evaluation.

of polyps. However, a multicenter, randomized, active controlled, double-masked, exploratory study [10] showed that the mean change in BCVA from baseline to 6-month was 9.2 ± 12.4 (mean ± standard deviation) letters in the IVR group, and 10.9 ± 10.9 letters in the combination group. The proportion of patients gaining ≥15 letters were 33.3% (of 21 patients) in the IVR group and 21% (of 19 patients) in the combination group, respectively. Although patients in both two groups had a gain in visual acuity during the 6-month follow-up period, that study did not demonstrate significant differences in BCVA changes. It is worthy to note that this particular study was not included in our current meta-analysis as it was the only study with a follow-up duration of 6 months and could not be pooled for meta-analysis with other included studies of either 12- or 24-month follow up period.

Except visual improvements, no significant difference in serious AEs was observed between IVR monotherapy and combination therapy in current systematic review.

There was no significant heterogeneity among studies include in our meta-analysis with either 12 or 24 months follow-up regarding to BCVA. However, there were several limitations in this meta-analysis. First, only four studies were included in this meta-analysis; Secondly, only Chinese and English researches were included in this meta-analysis; Thirdly, according to insufficient data, it can hardly evaluate the efficacy of two treatment on the regression of polyps and CRT in this meta-analysis.

5. Conclusion

Generally speaking, the outcomes of this meta-analysis confirmed that the first-line therapy for PCV might be IVR combine with PDT, which could efficiently improve BCVA. Future large-scale, multicenter, prospective, long-term RCTs are still needed to confirm the outcomes of IVR combine with PDT in the treatment of PCV.

Competing interests

The authors declare that they have no competing interests.

Funding

This paper was supported by the National Natural Science Foundation of China (No. 81300783). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors' contributions

All authors conceived of and designed the experimental protocol. LL, YCT and JYW collected the data. LL and SY were involved in the analysis. LL, JYW and CYC wrote the first draft of the manuscript. All authors read and approved the final manuscript.

Acknowledgment

Thanks for Mrs. Heither Hope in SUNBO foreign language school for language editing.

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