·Informatics Research·

Meta-analysis of best corrected visual acuity after treatment for myopic choroidal neovascularization

Lin Zhou [1,2], Yi-Qiao Xing [1], Tuo Li [2], Yin Li [1,2], Xiu-Sheng Song [2], Jia-Zhang Li [2]

[1]Department of Ophthalmology, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei Province, China
[2]Department of Ophthalmology, the Central Hospital of Enshi Autonomous Prefecture, Enshi Clinical College of Wuhan University, Enshi 445000, Hubei Province, China
Correspondence to: Tuo Li. No.158 Wuyang Road Enshi, Enshi 445000, Hubei Province, China. oph_zl@163.com
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Abstract

• AIM: To compare the best corrected visual acuity (BCVA) between Verteporfin with photodynamic therapy (PDT) and intravitreal anti-vascular endothelial growth factor (anti-VEGF) in patients with myopic choroidal neovascularization (CNV).

• METHODS: Published literature from Medline, Premedline, Embase and the Cochrane Library from inception until November 2013 were retrieved. All studies evaluating the BCVA between Verteporfin with PDT and intravitreal anti-VEGF for myopic CNV were included. The results were pooled using mean difference (MD), a corresponding 95% confidence interval (CI).

• RESULTS: Finally, five studies enrolled 349 eyes were included in the meta-analysis. We inferred that the BCVA of myopic CNV after the treatment of anti-VEGF was significantly better compared with Verteporfin with PDT (MD=0.25, 95%CI:0.17-0.33, Z=5.97, P<0.00001).

• CONCLUSION: This meta-analysis suggests that intravitreal anti-VEGF could have a better BCVA after treatment than Verteporfin with PDT for myopic CNV.

• **KEYWORDS:** myopic choroidal neovascularization; Verteporfin with photodynamic therapy; anti-vascular endothelial growth factor; meta-analysis

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INTRODUCTION

Myopia is a known cause of severe visual loss in young and middle-aged patients and a major cause of low vision worldwide, with a prevalence of around 50%-70% in certain urban areas [1-4]. High myopia, also known as pathologic myopia (<-6.0 dioptres) is characterized by an excessive extension of the eyeball and degenerative changes of the retina, choroid, and sclera. Posterior staphyloma, chorioretinal atrophy, and lacquer cracks in the Bruch membrane were commonly detected in patients with high myopia [5]. Choroidal neovascularization (CNV) is the most frequent vision-threatening macular complication clinically observed in pathologic myopia[1]. CNV is a pathologic ocular occurrence in which aberrant blood vessels expand from the choroid to the retinal pigment epithelium, reaching the retina, that could bleed and leak serous fluid due to their altered permeability eventually[6]. Myopic CNV is an important cause of blindness and visual handicap [7-10].

We have taken many years to develop an ideal treatment that would arrest the progress of myopic CNV, and store a degree of lost visual acuity. The traditional management options for myopic CNV include thermal laser photocoagulation, direct thermal laser. However, these treatments may cause retinal pigment epithelium (RPE) damage and sometimes iatrogenic CNV [11]. In 2000 Verteporfin with photodynamic therapy (PDT) was approved by the U.S. Food and Drug Administration for the treatment of subfoveal CNV [12]. Studies had demonstrated beneficial visual outcomes in the majority of patients [11]. Recently, clinical investigations have studied a new class of drugs for CNV, that is anti-VEGF such as ranibizumab, bevacizumab, which have been used worldwide for the treatment of CNV[13-15]. Recent studies have also demonstrated the efficacy of intravitreal anti-VEGF for the treatment of myopic CNV patients [16-20], and this therapy was widely accepted.

However, the assessment of anti-vascular endothelial growth factor (anti-VEGF) in comparison to Verteporfin with PDT for myopic CNV has not been sufficiently made in large sizes. The study conducted a meta-analysis based on controlled clinical trials to investigate the best corrected visual acuity (BCVA) after treatment between Verteporfin with PDT and anti-VEGF of myopic CNV, in order to get a convincing and precise conclusion.

METHODS

Search Strategy We searched Medline, Premedline, Embase and the Cochrane Library from inception until November 2013. The search strategy was based on combinations of medical subject headings and keywords, we did not restrict to specific languages or years of publication and the minimum number of patients to be included for meta-analysis was not defined. The key words are enumerated as follows: PDT and anti-VEGF [or "ranibizumab and bevacizumab"]. Conducted literature comparing the BCVA of myopic CNV after the treatment between anti-VEGF and PDT were searched both in the register for clinical trials. All terms were further expanded to include all the secondary headings. Two authors, including a professional librarian, retrieved the data independently by using guidelines published by the Cochrane Collaboration. For conflicting evaluations, a consensus was reached by following a discussion.

Inclusion Criteria Potentially relevant reports were evaluated by checking their titles and abstracts and then procured the most relevant publications for a closer examination. The following criteria were used to include studies for the meta-analysis:1) Controlled trials are included, there is no limitation to sample size and language. 2) The trials which investigated the treatment between anti-VEGF and Verteporfin with PDT for myopic CNV. 3) The final objective of these studies is BCVA. 4) With sufficient available data to estimate an MD with 95% CI. 5) Trials conform with ethical standards which means all of the patients participated in the trial voluntarily.

Exclusion Criteria The following criteria were used to exclude studies for the meta-analysis: 1) The finally objective of these studies did conclude BCVA. 2) Insufficient or unclearly described data was of no use. 3) Duplicate data were excluded.

Statistical Analysis Data from studies which compared the BCVA of myopic CNV after the treatment between anti-VEGF and PDT. The object of BCVA in each study was extracted as mean±standard deviation (SD). MD and 95% CIs were calculated for all eligible studies in the meta-analysis. A Chi-square-based Q statistic test was performed to assess heterogeneity [21]. Theoretically, if the database from each article was homogeneous (P<0.05 was considered to be statistically significant) and I^2 tests (I^2>50%: significant heterogeneity; I^2<25%: insignificant heterogeneity), a fixed-effects model was utilized for the difference of variables; otherwise, a randomized-effect model was preferred, which provided more conservative estimates of treatment effects than the fixed-effects model[22]. We used the fixed effects model (Mantel-Haeszel method) in the meta-analysis of rare events as it has been shown to be the more appropriate and less biased approach compared to the random effects model [23]. Forest plots were constructed for visual display of relative risk of an individual study [24]. All statistical analysis were performed spontaneously using the Review Manager 5.0.21.0 software, available through the Cochrane Collaboration.

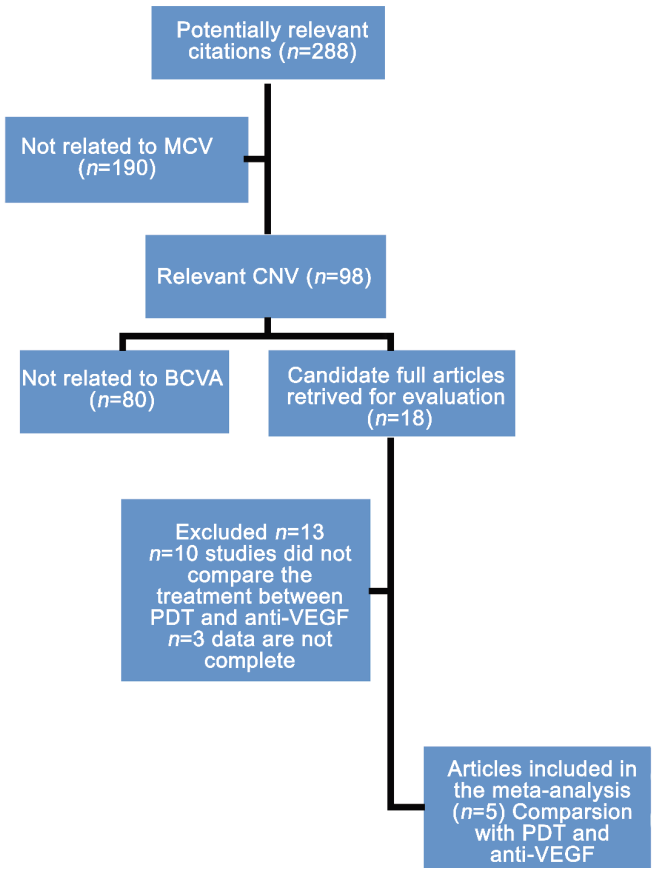

Figure 1 Flow chart of literature search and study selection MCV: Myopic choroidal neovascularization; CNV: Choroidal neovascularization; BCVA: Best corrected visual acuity; PDT: Photodynamic therapy; anti-VEGF: Anti-vascular endothelial growth factor.

RESULTS

Literature Search and Meta-analysis Databas Initially, we identified 288 potential citations, according to the key words PDT (or "photodynamic therapy") or anti-VEGF [or "ranibizumab and bevacizumab"] or myopic CNV, in which 18 articles are potentially appropriate for the meta-analysis. Evaluation of these eighteen studies found that ten studies did not compare the treatment between PDT and anti-VEGF; yet three studies were excluded as data are not complete. As a result, a total of five studies met the inclusion criteria and were identified as eligible articles (Figure 1)[27-31]. Among the five studies, we conduct a meta-analysis of Verteporfin with PDT and anti-VEGF for the therapy of myopic CNV.

Characteristics of Trails The table shows characteristics of five trials respectively. The analysis assigned 349 patients who were diagnosed with myopic CNV by indocyanine green angiography (IGGA) or fundus fluorescein angiography

Table 1 Characteristics of the studies included in the meta-analysis of five articles

First author (a)	Country	Trial type	Sample size (eye)			Basic BCVA (mean±SD) (logMAR)		Time of follow-up (mo)	BCVA after treatment (mean±SD) (logMAR)	
			Total	PDT	Anti-VEGF	PDT	Anti-VEGF		PDT	Anti-VEGF
Yoon JU[25],2010	Korea	Retrospective	104	51	63	0.54±0.37	0.57±0.46	24	0.60±0.48	0.33±0.34
Hayashi K[29],2009	Japan	open-label, consecutive	87	43	44	0.68±0.29	0.61±0.41	12	0.60±0.48	0.33±0.34
El Matri L[27], 2011	Tunisia	Retrospective	80	40	40	0.88±0.45	0.90±0.85	12	0.90±0.54	0.60±0.85
Parodi MB[28],2010	Italy	Retrospective	37	18	19	0.45±0.27	0.52±0.24	12	0.67±0.27	0.40±0.24
Ikuno Y[26], 2009	Japan	open-label, interventional	31	20	11	0.74±0.20	0.68±0.29	12	0.90±0.36	0.49±0.29

BCVA: the best corrected visual acuity; mo: month.

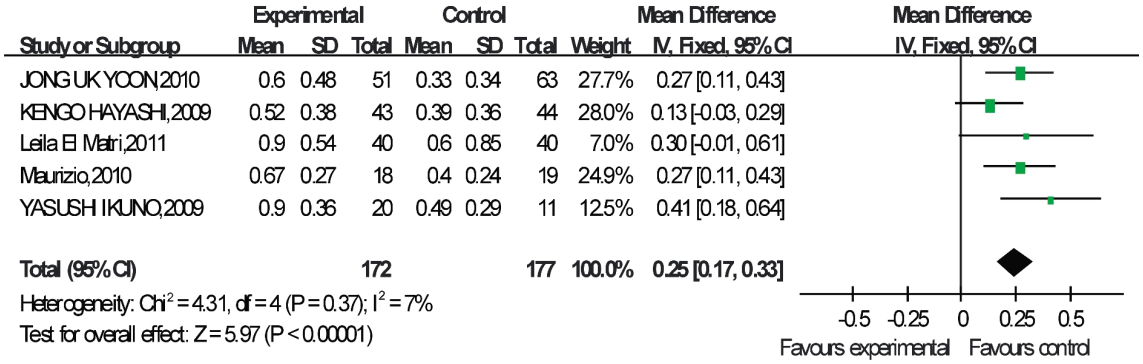

Figure 2 Results of meta-analysis of PDT and anti-VEGF CI: Confidence interval; MD: Mean difference; Experimental: Photodynamic therapy; Control: intravitreal Anti-vascular endothelial growth factor.

(FFA), received the treatment of anti-VEGF (ranibizumab or bevacizumab) or photodynamic therapy with Verteporfin. The treatment method reached the same standard. PDT group, all the patients received a 6-mg/m^2 infusion of Verteporfin over 10min followed by laser delivery at 689 nm for 83s, 15min after the start of the infusion. The anti-VEGF group, bevacizumab 1.25 mg or ranibizumab 0.05 mg, were injected into the vitreous cavity. After injections, all patients were instructed to apply antibiotic eyedrops for 1wk. Retreatment was depended on the physician's decision.

Quality Assessment of Studies According to Cochrane Handbook for systematic reviews of intervention, we make a quality assessment of five studies. The study which is randomized, perform an adequate allocation, conceal the sequence and set blindly, have a baseline comparability, illustrate the reasons for the loss to follow-up, use intention to treatment is of lowest possibility for the bias, that can be ranked as grade A. On the contrary, if the study cannot match any standards listed above, we rank it as grade C. If part of standards are matched, the study can be ranked as grade B. All of the articles involved in this meta-analysis could be ranked as grade B.

Meta-analysis

Comparison of Verteporfin with photodynamic therapy and intravitreal anti -vascular endothelial growth factor The comparison is a review of five articles, which is a meta-analysis of BCVA for 349 patients suffered from myopic CNV after treatment of Verteporfin with PDT or anti-VEGF[25-29]. Heterogeneity between the results of different studies was conducted (P=0.37, I^2=7%) and fixed-effects models were used. The results of meta analysis showed that the BCVA of patients with CNV after the treatment of anti-VEGF was significantly better compared with PDT (MD=0.25, 95% CI:0.17-0.33, Z=5.97, P<0.00001), which is showed in Figure 2. We performed a sensitivity analysis excluding each study in turn from the pooled analysis. The exclusion of anyone did not significantly modify the results.

DISCUSSION

High myopia, generally defined as a refractive error of -6.0 diopter or greater, is very common in Europe, Asia, and some ethnic groups in United States [30-33]. CNV is a common pathological endpoint of myopia, which could lead to edema, haemorrhages, and fibrosis, causing visual impairment and blindness [34]. A recent prospective study revealed that more than 90% of patients with myopic CNV have vision worse than 20/200 5 to 10y after disease onset [35], indicating the importance of developing effective treatment options for CNV.

Inflammation and angiogenes are important pathogenesis in the process of CNV[34]. A two-component model for CNV has been proposed to describe CNV: 1) the vascular component of CNV is composed of vascular endothelial cells, pericytes and precursors of endothelial cells; 2) the extravascular component is comprised of inflammatory cells (macrophages,

lymphocytes, granulocytes, and foreign body giant cells), glial cells, RPE cells and fibroblasts [36]. Hence inflammation and angiogenesis are the targets of therapeutic approaches for choroidal neovascularization, such as intra-vitreous injection of triamcinolone acetonide (TA), intra-vitreous injection of anti-VEGF.

However, there is no doubt that treatment modalities are not limited to intra-vitreous injection of TA, intra-vitreous injection of anti-VEGF. Thermal laser photocoagulation and Verteporfin with PDT are also effective. In our study, we have made meta-analysis to compare the BCVA of myopia CNV after the treatment between anti-VEGF and Verteporfin with PDT.

The benefits of Verteporfin with PDT have been reported by Several clinical trials in the United States and some European countries [37-39]. Guidelines for Verteporfin with PDT were based on the results of these trials in predominantly Caucasian populations. In PDT, Verteporfin is injected into the vein and activated by laser light at 689 nm to produce reactive radicals resulting in occlusion of the vessels at the laser application site. Verteporfin with PDT, promotes the absorption of subretinal fluid (SRF) by choroidal vascular remodeling and reduction of choroidal hyperpermeability, which has been shown to be safe and effective for idiopathic CNV[40]. However, PDT might result in irreversible damages. Firstly, massive subretinal hemorrhaging may occur after treatment, leading to vitreous hemorrhage. Secondly, PDT can cause damage resulting in complications such as retinal pigment epithelium (RPE) tearing, retinal atrophy, and scarring. Lastly, recurrent or newly developed lesions are not infrequent, affecting visual acuity over time[41-43].

VEGF is an important angiogenesis factor, produced by the RPE and retinal photoreceptors, which could initiate and support the growth of abnormal CNV [44]. Pegaptanib sodium, was the first anti-VEGF drug approved by the US Food and Drug Administration for the treatment of exudative AMD, and was found to be more effective in reducing visual loss compared with controls. Recently, various reports have shown that intravitreal injection of another anti-VEGF drug, ranibizumab and bevacizumab which was initially developed for the treatment of metastatic colon cancer, was also effective in the treatment of CNV. Several studies have also demonstrated the efficacy of intravitreal anti-VEGF for the treatment of myopic CNV patients [45-47], and such treatment has become widely accepted.

To the best of our knowledge, this is the first meta-analysis assessing the BCVA of patients suffered from myopic CNV after the treatment between anti-VEGF and Verteporfin with PDT. Due to the relatively small sample sizes of previous studies, reliable assessment of the efficiency of the treatment of PDT, anti-VEGF might be hindered. We performed the current systematic meta-analysis of five relevant studies involving 349 patients, by systemically reviewing all available published studies described the BCVA after different treatment of myopic CNV. Evidence from five controlled trials investigating 349 patients revealed that the BCVA of patients with CNV after the treatment of anti-VEGF was significantly better compared with Verteporfin with PDT [25-29]. As the incomplete data of central retinal thickness and central macular thickness after treatment of these five studies, we can do nothing to conduct reviews for these items above.

Obviously, meta-analysis has advantages compared to individual studies, however, some potential limitations in our study should be considered. Firstly, this meta-analysis was limited by the small sample size, especially in subgroup analysis aforementioned, which needs further investigations. Secondly, these patients have different terms of life style, age and environment. Additionally, the basic methods among the studies could not be absolutely united, which might have affected the results. Thirdly, the time of follow-up among these study is not united, the analysis we conducted ignored this item, which might have affected the results. At last, not all studies we collected are double-masked randomized. retrospective nature of literatures might exclude the patients with excellent or bad courses that could cause bias in the results .Which indicated that though the meta-analysis can send us a sign to the clinical application and clinical treatment, clinicians and patients should continue to carefully weight up the benefits and harms between the two available treatment options.

Taken together, the present meta-analysis we had conducted provide a piece of evidence that anti-VEGF have advantages over Verteporfin with PDT for the BCVA of patients with myopic CNV, which might promote the potential for clinical application and clinical treatment response prediction. However, More randomized contholled trials are expected urgently to further ascertain the conclusion.

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