

# Combined therapy and antivascular endothelial growth factor monotherapies for polypoidal choroidal vasculopathy

## A protocol for the systematic review and network meta-analysis of efficacy and safety

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### Abstract

**Background:** Different antivascular endothelial growth factor (VEGF) monotherapy regimens and photodynamic therapy (PDT) combined with anti-VEGF therapy are available for patients with polypoidal choroidal vasculopathy (PCV). However, the comparative efficacy and safety of different anti-VEGF monotherapy regimens and combined therapy with PDT and anti-VEGF remains unknown. The aim of our study is to evaluate the efficacy and safety of anti-VEGF monotherapies and combined therapy in patients with PCV.

**Methods:** We will systematically search PubMed, Embase, and the Cochrane library for eligible studies. The Cochrane Collaboration's tool for assessing the risk of bias in a randomized trial and the ROBINS-I tool will be used to assess the risk of bias in the included studies. The primary outcome is the mean change in best corrected visual acuity from baseline. The secondary outcomes are the mean change in central retinal thickness from baseline and the number of serious adverse events.

**Results:** The result will generate a comprehensive suggestion for the treatment of PCV.

**Conclusion:** The results of the network meta-analysis will be submitted in a peer-reviewed journal for publication.

**Ethics and dissemination:** The study does not involve human subjects and requires no ethical approval or patient consent. The results of the network meta-analysis will be submitted in a peer-reviewed journal for publication and generate a comprehensive suggestion for the treatment of PCV.

**Abbreviations:** AMD = age-related macular degeneration, BCVA = best corrected visual acuity, PCV = polypoidal choroidal vasculopathy, PDT = photodynamic therapy, VEGF = vascular endothelial growth factor.

**Keywords:** antivascular endothelial growth factor monotherapy, combined therapy, network meta-analysis, photodynamic therapy, polypoidal choroidal vasculopathy

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YZ and XL contributed equally to this work.

*Ethics approval and consent to participate:* Ethics approval and consent are not necessary because this study is a network meta-analysis based on the published studies.

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## 1. Introduction

Polypoidal choroidal vasculopathy (PCV), which was first described and reported by Yannuzzi et al in the 1980s,<sup>[1]</sup> has been generally acknowledged in recent years as a clinical subtype of age-related macular degeneration (AMD).<sup>[2]</sup> In general, PCV is more prevalent in particular racial groups, especially in Asian individuals, and the prevalence of PCV accounts for 22.3% to 61.6% of patients diagnosed with exudative AMD.<sup>[3–5]</sup> The pooled prevalence of PCV in white individuals with exudative AMD is 8.7%.<sup>[6]</sup> Although the pathogenesis and genetic risk factors for PCV remain unclear, a missense variant in FGD6 confers an increased risk of PCV.<sup>[7]</sup> PCV is clinically characterized by an abnormal vascular network of subretinal pigment epithelium of choroidal origin with aneurysmal dilatations, retinal pigment epithelial detachment, lipid exudation and recurrent, large subretinal hemorrhages<sup>[8,9]</sup> and can cause serious and even permanent vision loss in people younger than those with classic exudative AMD.<sup>[6]</sup> The gold standard for diagnosing PCV is polypoid dilations and abnormal branching of the vascular network presented in indocyanine green angiography.<sup>[10]</sup> Currently, the main therapies for PCV include photodynamic therapy (PDT),

anti-VEGF agents, and combined therapy using anti-VEGF and PDT.

PDT has been demonstrated to be an effective and selective strategy to regress polypoidal retinal lesions and to improve visual acuity.<sup>[11]</sup> In addition, fewer PDT treatments per year were needed for PCV patients to obtain visual acuity than were for cases of wet AMD.<sup>[12]</sup> The polyps and exudative lesions can regress with PDT therapy. However, the incomplete occluded branching vascular network could be a residual lesion, resulting in leakage and inducing choroidal neovascularization. The complications after PDT, such as hemorrhage-affected vision and choroidal ischemia, increased VEGF expression.<sup>[13]</sup>

The high expression of VEGF agents in the aqueous humor and vascular endothelium of PCV patients establishes the biological foundation of anti-VEGF therapy,<sup>[14]</sup> which includes ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA), bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA), and recently, aflibercept (Eylea, Regeneron, Tarrytown, NY, and Bayer HealthCare, Berlin, Germany). Anti-VEGF therapy performs well for improving visual function, reducing retinal thickness, and reducing levels of VEGF. However, the deficiency of anti-VEGF monotherapy is the regression of polyps, which was confirmed by the EVEREST study.<sup>[15]</sup> The reason for different responsiveness could be different balances of VEGF agents and angiogenic epithelium-derived growth factor levels.<sup>[16]</sup> Therefore, to maximize visual acuity outcome and polypoidal lesion regression, combined therapy with PDT and anti-VEGF is widely used in clinical practice to produce the synergistic effects of angio-occlusion and antiangiogenesis.<sup>[17]</sup>

However, the most effective treatment for PCV has not yet been confirmed because of the shortage of head-to-head randomized controlled trials and the limitations of traditional meta-analyses. Hence, we plan to perform a systematic review and network meta-analysis to evaluate the efficacy and safety of each therapy alone and PDT in combination with anti-VEGF.

## 2. Method

This study will conform to the PRISMA-NMA<sup>[18]</sup> checklist and will be performed based on the established protocol (PROSPERO: CRD42018104619). Ethical approval is not necessary because this study is based on aggregate data and does not involve humans.

### 2.1. Eligibility criteria

The PICOS strategy (patients, intervention, comparisons, outcome, study design type) determines the eligibility criteria for this study.

**2.1.1. Patients and comparison of interventions.** Studies that contain patients with PCV treated by different anti-VEGF monotherapies and combined therapy with PDT and anti-VEGF will be included. Studies that provide insufficient data on the mean change in best corrected visual acuity (BCVA) from baseline will be excluded. There are no limitations on age, gender, and ethnic distribution.

**2.1.2. Outcomes.** The primary outcome is the mean change in BCVA from baseline. The secondary outcomes are the mean change in central retinal thickness from baseline and the number of serious adverse events.

**2.1.3. Study design.** The present study will evaluate published randomized and nonrandomized controlled trials comparing different anti-VEGF monotherapies and combined therapy using PDT and anti-VEGF for the treatment of PCV patients.

### 2.2. Information sources and search strategy

The PubMed, Embase, and the Cochrane library will be systematically searched for eligible trials through July 15, 2018. We will identify additional studies in the reference catalog of relevant studies.

Search strategy of PubMed was as follows:

#1 (((((ranibizumab) OR bevacizumab) OR aflibercept)) OR photodynamic therapy) OR verteporfin for polypoidal  
#2 (PCV) OR polypoidal choroidal vasculopathy  
#3 #1 AND #2

### 2.3. Selection process and data management

Two reviewers will independently select and screen the title and abstract of each retrieved study according to the eligibility criteria and extract the relevant information and data from the included studies using Microsoft Excel 2016. The selection process summary will be based on the PRISMA flow diagram. The data will include the study features, patients' characteristics, data needed for quality assessment, and outcome indicators. The patient's characteristics will contain the types of interventions received, drug dosages, therapeutic regimens, mean age, sample size, and outcome indicators.

### 2.4. Risk of bias of individual studies

Two investigators will independently evaluate the risk of bias of each selected RCT and nonrandomized studies using the Cochrane Collaboration's tool and ROBINS-I tool, respectively.<sup>[19,20]</sup> Disagreements will be discussed and resolved with a third reviewer.

### 2.5. Data synthesis and statistical analysis

**2.5.1. Measures of treatment effects.** Different measures will be used to evaluate the same outcomes. Continuous outcomes will be analyzed by calculating the weighted mean difference (WMD), and dichotomous outcomes will be pooled with an odds ratio (OR). The result of the network meta-analysis will be presented with WMD or OR and relative 95% CIs for each possible treatment. Heterogeneity will be assessed with the  $Q$ -statistic and  $I^2$  index. If  $P < .1$  or  $I^2 > 50\%$ , it presents moderate heterogeneity at least, and the random-effects model should be used.<sup>[21,22]</sup>

### 2.6. Data analysis

First, traditional pairwise meta-analyses of all outcomes and comparisons at each time point will be performed using the random-effects model. Each head-to-head comparison will involve 2 RCTs at least.<sup>[23]</sup> In the absence of head-to-head evidence, an indirect treatment comparison meta-analysis will be used to retrieve indirect, available evidence. Then, a network meta-analysis with a Bayesian random-effects model will be performed in a frequentist framework assuming equal heterogeneity parameters in all comparisons and considering the correlation caused by the multiarm studies.<sup>[24]</sup> Except for pooled

WMDs or ORs with 95% CIs, all relative ranking probabilities of different anti-VEGF monotherapies, PDT monotherapy, and combined therapy will be presented as surface under the cumulative ranking curve (SUCRA) values. The probability of the most effective treatment (first, second, third, and so on) will be calculated. The SUCRA analysis is used to summarize and report the probability values, which is a simple average rank transformation to provide a hierarchical treatment to reflect the location and variance of therapeutic effects. The larger the SUCRA value, the better the rank of intervention, with a maximum SUCRA of 1.0.<sup>[25,26]</sup>

The consistency between direct and indirect evidence in the network will be assessed by the node splitting method.<sup>[27]</sup> There is no significant difference between direct and indirect evidence when 95% CIs of inconsistency factors are zero or  $P > .05$ .<sup>[27]</sup>

A funnel plot of sample and effect size will be drawn to determine whether there is a publication bias in the network meta-analysis. The contour-enhanced funnel plot will be used to help interpret the funnel scatter plot.<sup>[28,29]</sup> We also intend to generate the network geometry, a graphical presentation of evidence network, which is an essential item in network meta-analysis.<sup>[18]</sup>

We will employ Stata version 14. (Stata Corp, College Station, TX) and R v3.5.0 (gemtc package and rjags package) to perform the statistical analysis.

### 3. Discussion

Currently, the optimal therapy for PCV is still uncertain. Both anti-VEGF therapy, PDT, and combined therapy are all available for patients with PCV. To our knowledge, this study will be the first network meta-analysis in the field to comprehensively compare different therapies for PCV. We hope our work can obtain a ranking of multiple therapies and provide recommendations for ophthalmologists.

#### Author contributions

**Conceptualization:** Meixia Zhang, Yun Zhang, Xun Li

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**Writing – original draft:** Yun Zhang, You Tang, Tiancong Chang, Misha Chen

**Writing – review & editing:** Meixia Zhang, Xun Li, Zhaolun Cai

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