INPLASY PROTOCOL

To cite: Shi et al. Efficacy of traditional Chinese medicine combined with ranibizumab in patients with neovascular age-related macular degeneration: a meta-analysis. Inplasy protocol 2022100077. doi: 10.37766/inplasy2022.10.0077

Received: 19 October 2022

Published: 19 October 2022

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Support: **NSFC.**

Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None declared.

Efficacy of traditional Chinese medicine combined with ranibizumab in patients with neovascular age-related macular degeneration: a meta-analysis

Shi, SS[1]; Yang, L[2]; Yang, GH[3]; Qi, BY[4]; Chao, GJ[5].

Review question / Objective: **To evaluate the efficacy of traditional Chinese medicine (TCM) combined with ranibizumab in patents with neovascular age-related macular degeneration (nAMD).**
Eligibility criteria: **Studies will be considered eligible for inclusion if they met the following criteria: (a) the patients had nAMD; (b) intervention measures: experimental group was TCM combined with ranibizumab, control was only ranibizumab or ranibizumab plus placebo; (c) drug dose, method and observation time: ranibizumab (Novartis Pharma Schweiz AG) 0.05 ml by intravitreal injection, once a month for three months, observation time was three months; (d) the follow observation indicators were reported: best corrected visual acuity (BCVA), central macular thickness (CMT); (e) literature quality: articles were scored by the Jadad score and score ≥ 3; and (f) study was RCT design. The exclusion criteria will be as follows: (a) the articles lacked sufficient original data of patients' information, which is important to estimate results; (b) no desired observation indicators were reported; and (c) the ingredients of the Chinese medicine were not clearly described. (d) Editorials, letters, duplicate publications, reviews, conference abstracts, basic research, and case reports were also excluded.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 October 2022 and was last updated on 19 October 2022 (registration number INPLASY2022100077).

INTRODUCTION

Review question / Objective: **To evaluate the efficacy of traditional Chinese medicine (TCM) combined with ranibizumab in patents with neovascular age-related macular degeneration (nAMD).**

Condition being studied: **Age-related macular degeneration (AMD) is a common degenerative disease of macular tissue and**

is the leading cause of blindness in the elderly population. In 2020, there were approximately 196 million persons suffering from AMD worldwide, which is 9% of all cases of blindness and is expected to be approximately 288 million AMD patients by 2040 . In developed countries, people over 70 years old have a high risk of developing AMD, and approximately one-third of people over 80 years old have AMD. AMD can be divided into dry AMD and wet AMD (also called neovascular AMD, nAMD), in which nAMD forms subretinal choroidal neovascularization (CNV), resulting in exudation, hemorrhage and retinal edema that leads to irreversible visual impairment. With the aging of the fundus tissues and organs, choriocapillary atrophy occurs, and oxygen is insufficient for the retina. Hypoxia stimulates the overexpression of vascular endothelial growth factor (VEGF), which promotes the occurrence and development of nAMD. Currently, anti-VEGF agents remain the most valid approach to inhibit the progression of nAMD based on clinical and basic research. There was an obvious fall in blindness in a large number of patients with AMD during the past three decades, which was attributed to the use of anti-VEGF agents. Ranibizumab, a recombinant humanized monoclonal antibody fragment, can bind to VEGF-A to inhibit its biological activity. Ranibizumab has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for nAMD treatment. Although anti-VEGF therapy was proven to stabilize and even improve visual function in nAMD, nearly half of patients suffer from poor prognosis. Furthermore, patients need to repeatedly accept anti-VEGF treatment over a long period of time, and the cost is huge, even though some people have no response to anti-VEGF agents. Previous studies pointed out that traditional Chinese medicine (TCM) combined with ranibizumab could further improve the treatment effect for CNV and reduce the recurrence of nAMD at low cost by different targets and pathways. Therefore, our study scientifically will assess the clinical effect of TCM combined with ranibizumab by collecting RCTs.

METHODS

Search strategy: A literature search will be performed in electronic public databases, including PubMed (Medline), Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), China Biology Medicine (CBM), WanFang, and Chongqing VIP, from inception to September 2022. The search terms are "macular degeneration", "AMD", "exudative age-related macular degeneration", "neovascular age-related macular degeneration", "Ranibizumab", "Lucentis", "anti-VEGF", "traditional Chinese medicine", "Chinese medicine", "Chinese herbal", "Chinese patent medicine", and "Randomized". The English and Chinese articles are all considered. Additionally, the references of important reviews are also screened to avoid omission. Two researchers will independently perform the literature search to resolve disagreements by consensus. The third researcher will make a decision when there are disagreements.

Participant or population: The patients had nAMD.

Intervention: The experimental group was TCM combined with ranibizumab.

Comparator: The control was only ranibizumab or ranibizumab plus placebo.

Study designs to be included: Randomized controlled trial will be included in this study.

Eligibility criteria: Studies will be considered eligible for inclusion if they met the following criteria: (a) the patients had nAMD; (b) intervention measures: experimental group was TCM combined with ranibizumab, control was only ranibizumab or ranibizumab plus placebo; (c) drug dose, method and observation time: ranibizumab (Novartis Pharma Schweiz AG) 0.05 ml by intravitreal injection, once a month for three months, observation time was three months; (d) the follow observation indicators were reported: best corrected visual acuity

(BCVA), central macular thickness (CMT); (e) literature quality: articles were scored by the Jadad score and score ≥ 3; and (f) study was RCT design. The exclusion criteria will be as follows: (a) the articles lacked sufficient original data of patients' information, which is important to estimate results; (b) no desired observation indicators were reported; and (c) the ingredients of the Chinese medicine were not clearly described. (d) Editorials, letters, duplicate publications, reviews, conference abstracts, basic research, and case reports were also excluded.

Information sources: A literature search will be performed in electronic public databases, including PubMed (Medline), Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), China Biology Medicine (CBM), WanFang, and Chongqing VIP, and Clinical Trial Registry.

Main outcome(s): The main outcome is : best corrected visual acuity (BCVA).

Additional outcome(s): The additional outcome is : central macular thickness (CMT).

Data management: The data management will be from inception to September2022.

Quality assessment / Risk of bias analysis: Our study will use two methods to assess the quality of the literature. First, the Cochrane literature quality evaluation criteria: ① whether the literature design reflects random assignment; ② whether the literature conceals the trial allocation scheme; ③ whether the literature is blinded among the three parties: the children meibomian cyst, the physician who administered the intervention, and the statistician who evaluated the results; ④ whether the outcome data to be collated are comprehensive and without missing; ⑤ whether the literature has selective reporting bias for positive results; and ⑥ other bias. The risk of bias is also mapped for the included literature with the help of Review Manager 5.3 software. Second, a modified JADAD score is used to re-evaluate the quality of the included literature.

Strategy of data synthesis: The observation indicators for analysis are BCVA and CMT, which are both continuous variables. The mean difference (MD) and corresponding 95% confidence interval (CI) will be calculated for analysis. Potential heterogeneity will be measured by Cochran's Q test ($p < 0.1$, indicating the existence of significant statistical heterogeneity). Moreover, the quantitative I2 statistic will be utilized for evaluation of heterogeneity. I2≥50% indicates the existence of significant heterogeneity. This will allowe the use of a fixed-effects model; otherwise, a random-effects model is used. Sensitivity analysis will be performed to identify the potential influence of each study set on the pooled MD. Begg's and Egger's tests will be used to evaluate potential publication bias. RevMan 5.3 and STATA V.14.0 will be employed for data analyses. All tests are 2-tailed, and a P value <0.05 is regarded as statistically significant.

Subgroup analysis: If P ≤ 0.1 and I2 ≥ 50% indicate heterogeneity in the literature, further, subgroup analysis will be performed according to different type of BCVA examination.

Sensitivity analysis: Sensitivity analysis will be performed to identify the potential influence of each study set on the pooled MD.

Country(ies) involved: China.

Keywords: Traditional Chinese medicine; ranibizumab; neovascular age-related macular degeneration; meta-analysis.

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