Comparison of Efficacy and Safety between Conbercept and Ranibizumab in Neovascular Age-Related Macular Degeneration: A Meta-Analysis of Randomized Controlled Trials

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Keywords

Conbercept · Ranibizumab · Age-related macular degeneration · Vascular endothelial growth factor · Meta-analysis

Abstract

Background: Conbercept, as a novel vascular endothelial growth factor (VEGF) inhibitor, was approved for the treatment of neovascular age-related macular degeneration (nAMD) in China. **Objective:** This study aimed to compare the efficacy and safety between conbercept and ranibizumab in patients with nAMD. **Methods:** Several databases (PubMed, Web of Science, China National Knowledge Infrastructure, and WANFANG) were searched for the results of studies describing conbercept and ranibizumab for the treatment of nAMD. Sixteen randomized controlled trials including 1,224 eyes met our search criteria and were assessed. **Results:** Conbercept and ranibizumab had comparable effects on improving visual acuity at 3 months (standardized mean difference [SMD]: -0.19; 95% confidence interval [CI]: -0.46 to 0.08; $p = 0.17$) and 6–12 months (SMD: -0.01; 95% CI: -0.20 to 0.18; $p = 0.90$). At 3 months and 6–12 months, the differences in the change of central macular thickness in conbercept and ranibizumab groups were 1.06 μm (95% CI: -3.52 to 5.64; $p = 0.65$) and -0.12 μm (95% CI: -9.26 to 9.02; $p = 0.98$).

In the short term, there was no significant difference between the 2 groups with respect to ocular adverse events (odds ratio [OR]: 0.86; 95% CI: 0.46–1.61; $p = 0.63$). No significant differences were observed in the recovery rate of choroidal neovascularization leakage between conbercept and ranibizumab at both 3 months (OR: 1.49; 95% CI: 0.83–2.68; $p = 0.18$) and 6–12 months (OR: 0.66; 95% CI: 0.18–2.43; $p = 0.53$). There were significant differences between conbercept and ranibizumab in terms of decreasing intraocular pressure (weighted mean difference [WMD]: -1.74; 95% CI: -2.28 to -1.20; $p < 0.00001$), the plasma VEGF level (WMD: -21.49; 95% CI: -26.28 to -16.70; $p < 0.00001$), and the C-reactive protein level (WMD: -1.16; 95% CI: -1.45 to -0.87; $p < 0.00001$) in the short term. **Conclusion:** Conbercept was similar to ranibizumab in terms of efficacy and safety for the treatment of nAMD in China. Further studies with longer term observation are needed to support this conclusion.

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Introduction

Age-related macular degeneration (AMD) is the leading cause of visual deterioration and blindness in elderly patients in the industrialized countries [1]. Neovascular

(exudative or wet) AMD (nAMD), characterized with choroidal neovascularization (CNV), is responsible for 80% of the cases with severe vision loss or blindness due to AMD [2]. Vascular endothelial growth factor (VEGF) plays important roles in CNV by increasing vascular permeability, inflammatory response, and endothelial cell proliferation [3]. Anti-VEGF agents, including ranibizumab (Lucentis®; Genentech Inc., South San Francisco, CA, USA), aflibercept (Eylea®; Regeneron Inc., Tarrytown, NY, USA), and bevacizumab (Avastin®; Genentech Inc.), have revolutionized the treatment of nAMD. Ranibizumab and aflibercept were approved by the US Food and Drug Administration (FDA) (2006, 2011) and by the European Medicines Agency (2007, 2012) [4, 5]. Conbercept (or KH902, Lumitin; Chengdu Kang Hong Biotech Co., Ltd., Sichuan, China), which is a novel anti-VEGF agent and similar in structure to aflibercept [6], has been approved for the treatment of nAMD by the China State FDA and was recently admitted directly to the phase III clinical trials in the USA [7]. However, the application of conbercept has not been popular for patients with nAMD in the world [8].

Cost-effectiveness analysis concluded that conbercept was a cost-effective alternative compared to ranibizumab for the treatment of nAMD in China [9]. The methodology of the meta-analysis appears robust, which may reveal results that are not apparent in the individual RCT. Therefore, meta-analyses comparing the effectiveness and safety of both drugs could be useful from a clinical and public health-care perspective; however, such analyses are rare. We systemically searched and analyzed randomized controlled trials (RCTs) to compare the efficacy and safety between conbercept and ranibizumab in patients with nAMD.

Methods

This meta-analysis was confirmed to the recommendations of the Cochrane Handbook and reported according to the PRISMA reporting guidelines for meta-analysis and systematic review. The PRISMA checklist is provided in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000519815).

Literature Search

We searched the PubMed, Web of science, WANFANG, and China National Knowledge Infrastructure for an end date of April 12, 2020. The following MESH terms were used in title/abstract: “Macular Degeneration or Age-Related Macular Degeneration or AMD or ARMD or nAMD” and “ranibizumab or Lucentis” and “conbercept or KH902 or Lumitin.” No language restrictions were used in the search.

Inclusion and Exclusion Criteria

All studies were included if they met the following criteria: (1) RCTs, (2) studies comparing conbercept monotherapy and ranibizumab monotherapy for nAMD patients, and (3) studies that reported at least one quantitative outcome of efficacy and safety. Studies that met the following criteria were excluded: (1) review articles, meeting abstracts and preclinical studies; (2) patients with glaucoma, cataracts, or retinopathy caused by diabetes or hypertension; (3) studies with duplicated population; and (4) follow-up time <3 months.

Study Selection

Figure 1 shows a flow chart of the selection process used to identify relevant studies. Two investigators independently extracted and summarized the studies using predetermined inclusion and exclusion criteria. Any disagreement was resolved by discussion. The main outcomes were mean visual acuity (VA) change, mean central macular thickness (CMT) change, and ocular adverse events (OAEs). The other outcomes were CNV recovery rate, mean intraocular pressure (IOP) change, mean plasma VEGF change, and mean plasma C-reactive protein (CRP) change.

Data Collection and Risk of Bias Assessment

The levels of evidence of included studies were rated by 2 authors according to the checklist developed by the Cochrane Collaboration [10]. The items consisted of 7 factors: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The authors independently assessed the quality of the studies, and any disagreement was resolved by discussion.

Data Synthesis and Analysis

All analyses were performed using Review Manager 5.3 and Stata SE 15.0. The standardized mean difference (SMD) was used to analyze the outcome of mean VA change because of different units of measurement in the included studies. In addition, the weighted mean difference (WMD) and odds ratios (ORs) were used to analyze the remaining continuous and dichotomous variables, respectively. All results were reported with 95% confidence intervals (CIs). If continuous data were presented as means and range values, the standard deviation was calculated using the technique described by Hozo et al. [11]. Heterogeneity between studies was assessed by the χ^2 and I^2 statistic. The random-effects model was used if the p value was <0.1; otherwise, the fixed-effects model was reported [12]. Begg's test and funnel plot analyses were used to screen for potential publication bias of comparative treatment effects which was reported in >10 studies. Sensitivity analysis was performed to evaluate the influence of especial studies on the overall estimate of the outcomes with more than ten studies.

Results

Included Studies

After searching the literature, 15, 41, 44, and 25 studies published in PubMed, Web of Science, China National Knowledge Infrastructure, and WANFANG, respectively,

Fig. 1. Flow diagram of studies identified, included, and excluded. CNKI, China National Knowledge Infrastructure.

were identified (Fig. 1). Of these studies, 48 articles were screened for the full-text review, and 32 articles were excluded as follows: 5 were studies with no related outcomes, 17 were studies with no comparison groups, 8 were not RCTs, and 2 were <3 months follow-ups. Finally, 16 studies [13–28] with 1,224 eyes were included in this meta-analysis. Agreement between the 2 authors was 100% for study selection and 94% for quality assessment of trials after examination of references listed for studies. Study outcomes are shown in Table 1.

Characteristics of Included Studies

The characteristics of included studies are shown in online supplementary Table 2. All the included studies were RCTs and conducted in China. There were 614 eyes in the conbercept group and 613 eyes in the ranibizumab group. The follow-up time ranged from 3 to 12 months;

13 studies had a short-term (3 months) follow-up, and 5 studies had a long-term (6–12 months) follow-up after the first injection. The most common treatment regimen was 3 monthly injections of conbercept or ranibizumab followed by as-needed, except 3 studies without reporting this information.

Quality assessment of RCTs (online suppl. Fig. 1) showed that all the included studies had an adequate random sequence generation; however, all the studies did not report the method of allocation concealment. Therefore, the risk of selection bias related to allocation concealment was uncertain. All the studies failed to report blinding method, so the risks of performance bias and detection bias were uncertain. All RCTs have adequately assessed each outcome without a loss of follow-up. No registration information or protocols available in all the included studies, it is unclear whether all the predesigned outcomes

Table 1. Results of meta-analysis comparison of conbercept and ranibizumab groups

Outcomes of interest	Studies, <i>n</i>	Conb eyes, <i>n</i>	Rani eyes, <i>n</i>	WMD/SMD/OR (95% CI)	<i>p</i> value	Study heterogeneity			
						χ^2	df	<i>I</i> ² , %	<i>p</i> value
Main outcomes									
Mean VA change (3 months)	13	460	461	−0.19 (−0.46, 0.08)	0.17	50.31	12	76	<0.00001
Mean VA change (6–12 months)	5	217	216	−0.01 (−0.20, 0.18)	0.90	0.23	4	0	0.99
Mean CMT change (3 months)	12	425	426	1.06 (−3.52, 5.64)	0.65	16.91	11	35	0.11
Mean CMT change (6–12 months)	5	217	216	−0.12 (−9.26, 9.02)	0.98	0.28	4	0	0.99
OAEs (3 months)	8	302	302	0.86 (0.46, 1.61)	0.63	2.07	4	0	0.72
Other outcomes									
CNV recovery rate (3 months)	4	120	120	1.49 (0.83, 2.68)	0.18	2.87	3	0	0.41
CNV recovery rate (6–12 months)	2	102	101	0.66 (0.18, 2.43)	0.53	0.08	1	0	0.77
Mean IOP change (3 months)	3	95	95	−1.74 (−2.28, −1.20)	<0.00001	2.81	2	29	0.24
Mean plasma VEGF change (3 months)	3	95	95	−21.49 (−26.28, −16.70)	<0.00001	4.00	2	50	0.14
Mean plasma CRP change (3 months)	3	95	95	−1.16 (−1.45, −0.87)	<0.00001	1.12	2	0	0.57

Conb, conbercept; Rani, ranibizumab; WMD, weighted mean difference; SMD, standardized mean difference; OR, odds ratio; 95% CI, 95% credible interval; VA, visual acuity; CMT, central macular thickness; CNV, choroidal neovascularization; IOP, intraocular pressure; VEGF, vascular endothelial growth factor; CRP, C-reactive protein; OAEs, ocular adverse events.

have been reported. Of all RCTs, there were no other biases caused by conflict of interest and unbalance baseline parameter.

Main Outcomes

Mean Change in VA

The measured VA values were converted to logarithm of the minimum angle of resolution units. Thirteen studies [13–17, 19–23, 25, 27, 28] that assessed 921 eyes compared the mean change in VA between conbercept and ranibizumab in the short term (3 months post-first treatment). Pooling the data showed that conbercept and ranibizumab had comparable effects on improving VA (SMD: −0.19; 95% CI: −0.46 to 0.08; $p = 0.17$). High heterogeneity ($\chi^2 = 50.31$, $df = 12$, $p < 0.00001$; $I^2 = 76\%$) was observed among studies (Fig. 2a).

At later follow-up time points (6–12 months), 5 studies [18, 21, 23, 24, 26] including 433 eyes had the data allowing estimation of the VA change. The pooled data showed no significant difference between the 2 groups (SMD: −0.01; 95% CI: −0.20 to 0.18; $p = 0.90$), with no significant heterogeneity among studies ($\chi^2 = 0.23$, $df = 4$, $p = 0.99$; $I^2 = 0\%$) (Fig. 2b).

Mean Change in CMT

Pooling the data from 12 studies [13–17, 19–21, 23, 25, 27, 28] that assessed the CMT change in 851 eyes showed that the change in CMT in conbercept-treated eyes was similar to ranibizumab-treated eyes (WMD: 1.06; 95%

CI: −3.52 to 5.64; $p = 0.65$) at the 3-month follow-up. No significant heterogeneity was observed among studies ($\chi^2 = 16.91$, $df = 11$, $p = 0.11$; $I^2 = 35\%$) (Fig. 3a).

At later follow-ups (6–12 months after the first treatment), 5 studies [18, 21, 23, 24, 26] including 433 eyes assessed CMT thinning, which showed that there was no significant difference between conbercept and ranibizumab (WMD: −0.12; 95% CI: −9.26 to 9.02; $p = 0.98$). There was no significant heterogeneity among studies ($\chi^2 = 0.28$, $df = 4$, $p = 0.99$; $I^2 = 0\%$) (Fig. 3b).

Ocular Adverse Events

Eight studies [14, 15, 20, 22–26] including 604 eyes compared the incidence of any OAEs between conbercept and ranibizumab during the 3-month follow-up. No systemic adverse events and serious OAEs were reported, and most common OAEs included transient elevation of IOP and conjunctival hemorrhage. Of the 8 studies, 3 studies [14, 25, 26] reported no OAEs. The pooled data demonstrated no statistically significant difference in the incidence of OAEs between the conbercept and ranibizumab groups (OR: 0.86; 95% CI: 0.46–1.61; $p = 0.63$), with no significant heterogeneity among studies ($\chi^2 = 2.07$, $df = 4$, $p = 0.72$; $I^2 = 0\%$) (Fig. 4a).

Other Outcomes

The Rate of CNV Recovery

The CNV recovery rate is defined as the proportion of eyes with complete or partial closure of CNV leakage after

Fig. 2. Differences in VA (logMAR) changes between conbercept and ranibizumab treatment at 3 (**a**) and 6–12 months (**b**). VA, visual acuity; logMAR, logarithm of minimum angle of resolution; SMD, standardized mean difference; CI, confidence interval.

treatment. The data of CNV recovery rate were available for 240 eyes across 4 studies [13, 15, 20, 27] at the 3-month visit. A pooled analysis showed no significant difference in the rate of CNV recovery between 2 groups (OR: 1.49; 95% CI: 0.83–2.68; $p = 0.18$). There was no significant heterogeneity among studies ($\chi^2 = 2.87$, $df = 3$, $p = 0.41$; $I^2 = 0\%$) (Fig. 4b).

At the 6–12 months visit, only 2 studies [18, 26] including 203 eyes compared the recovery rate of CNV between conbercept and ranibizumab. There was no significant difference in the rate of CNV recovery between the conbercept and ranibizumab groups (OR: 0.66; 95% CI: 0.18–2.43; $p = 0.53$), with no significant between-study heterogeneity ($\chi^2 = 0.08$, $df = 1$, $p = 0.77$; $I^2 = 0\%$) (Fig. 4c).

Mean Change in IOP

The IOP level was measured with the noncontact tonometer before and after the treatment, and the IOP value was recorded as millimeters of mercury. Three studies [13, 22, 25] assessed the IOP change in 190 eyes at 3 months post-start-of-treatment. A significant difference was observed between the conbercept and ranibizumab groups (mean difference [MD]: -1.74; 95% CI: -2.28 to -1.20; $p < 0.00001$), with no significant heterogeneity among studies ($\chi^2 = 2.81$, $df = 2$, $p = 0.24$; $I^2 = 29\%$) (Fig. 5a).

Mean Change in Plasma VEGF Level

Three studies [13, 22, 25] (190 eyes) reported the mean change in the plasma VEGF level during the 3-month

Fig. 3. Differences in CMT changes between the conbercept and ranibizumab injection at 3 (a) and 6–12 months (b). CMT, central macular thickness; MD, mean difference; CI, confidence interval.

follow-up period. The pooled analysis showed a significant difference between conbercept and ranibizumab (MD: -21.49; 95% CI: -26.28 to -16.70; $p < 0.00001$). There was no significant heterogeneity among studies ($\chi^2 = 4.00$, $df = 2$, $p = 0.14$; $I^2 = 50\%$) (Fig. 5b).

Mean Change in Plasma CRP Level

The mean change in the plasma CRP level was reported in 3 studies [13, 22, 25] (190 eyes) at the early follow-up time point (3 months). The pooled data revealed a significant difference between conbercept and ranibizumab treatment groups (MD: -1.16; 95% CI: -1.45 to -0.87; $p < 0.00001$). No significant heterogeneity was observed among studies ($\chi^2 = 1.12$, $df = 2$, $p = 0.57$; $I^2 = 0\%$) (Fig. 5c).

Publication Bias

Figure 6 shows Beggs's funnel plot of the studies included in this meta-analysis that reported the mean

change in VA and the CMT at the 3-month visit. There was evidence of publication bias by Begg's test ($p = 0.012$) in VA change at 3 months, with asymmetry in the funnel plot as shown in Figure 6a. However, no obvious publication bias was detected by Begg's test ($p = 0.732$) for the comparison effects on the CMT.

Sensitivity Analysis

In the sensitivity analysis, the heterogeneity was decreased with removing Liang et al. [25] and Liu et al. [13] for VA improvement ($\chi^2 = 4.38$, $df = 10$, $p = 0.93$; $I^2 = 0\%$) but not for CMT thinning at 3 months after the first treatment. After removing the studies, there was no change in the significance of VA improvement (SMD: 0.02; 95% CI: -0.12 to 0.16; $p = 0.74$) and CMT thinning at 3 months (WMD: 4.67; 95% CI: -0.38 to 9.73; $p = 0.07$). Therefore, the results in respect of VA and the CMT were robust.

Fig. 4. Differences in the incidence of OAEs and the rate of CNV recovery between conbercept and ranibizumab. Differences in the incidence of OAEs during the first 3 months (**a**); differences in the rate of CNV recovery at 3 months (**b**) and 6–12 months (**c**). OAEs, ocular adverse events; CNV, choroidal neovascularization; CI, confidence interval; OR, odds ratio.

Discussion and Conclusion

Our meta-analysis of 16 RCTs including 1,224 eyes compared the safety and efficacy (VA, CMT, CNV leakage, IOP, plasma VEGF level, and CRP level) between conbercept and ranibizumab for the patients with nAMD in the short term (3 months) or long term (6–12 months), respectively. This meta-analysis showed that conbercept and ranibizumab have similar effects on VA improving and CMT thinning at different follow-up time points (3 months or 6–12 months). This result was

different from a meta-analysis by Wang et al. [29], which reported that BCVA was significantly better in the conbercept-treated eyes than in the ranibizumab-treated eyes, regardless of the duration of the follow-up. However, Wang et al.'s study [29] which included only 3 RCTs and 2 retrospective studies was less clinically valid than our meta-analysis which included 16 RCTs. Besides, Zhang et al.'s study [30] that assessed CMT in 395 eyes from 6 RCTs demonstrated that conbercept was more effective in terms of decreasing CMT than ranibizumab according to different follow-up times (varied

Fig. 5. Differences in the mean changes of IOP (**a**), plasma VEGF (**b**), and CRP (**c**) level between conbercept and ranibizumab at 3 months. IOP, intraocular pressure; VEGF, vascular endothelial growth factor; CRP, C-reactive protein; MD, mean difference; CI, confidence interval.

from 1 to 12 months), which was also inconsistent with our results based on 12 RCTs. More high-quality studies tended to minimize the risk of bias; therefore, this meta-analysis might be more rigorous in evaluating the effect of conbercept and ranibizumab on VA and CMT improvement. More importantly, a meta-analysis of long-term outcomes is conducive to get more valuable conclusions as nAMD is a chronic disease. Therefore, our meta-analysis of 6–12 months outcomes might be relatively meaningful in comparing the changes in VA and the CMT of 2 anti-VEGF drugs.

We also found no significant differences in the rate of CNV recovery between 2 groups at both 3 months and 6–12 months visit. Similarly, Wang et al. [29] reported no differences in complete and partial closure of CNV

between conbercept and ranibizumab groups, which is consistent with our results. The rate of CNV recovery at 6–12 months further reflected the ability of 2 drugs to control the disease/CNV in the long term. Therefore, these results indicate that conbercept and ranibizumab have similar treatment effects for nAMD patients.

Intravitreal conbercept has been reported to be a well-tolerated treatment for AMD, with no systemic adverse events or serious adverse events [31]. The adverse events in intravitreal injections of anti-VEGF drugs tended to be short-term events. The most common OAEs are associated with intravitreal injections, such as increased IOP and conjunctival hemorrhage [31]. In this meta-analysis, only 604 eyes compared the incidence of OAEs, which demonstrated no significant difference between

Fig. 6. Beggs's funnel plot of the mean VA change (a) and CMT change at 3 months (b). SMD, standardized mean difference; WMD, weighted mean difference; s.e., standard error; VA, visual acuity; CMT, central macular thickness.

conbercept-treated eyes and ranibizumab-treated eyes at the 3-month visit.

The upregulation of VEGF plays a crucial role in the process of choroidal neovascularization. Intravitreal injections of VEGF inhibitors have been thought to be the main way to prevent further neovascularization. However, multiple intravitreal injections of anti-VEGF agents, which could increase the potential risks, are inevitable to maintain a therapeutic level of VEGF inhibition. Therefore, several studies have investigated the systemic VEGF level after intravitreal injection of ranibizumab or conbercept in nAMD patients to eliminate these limitations [32–35]. In these studies, the reduction in serum VEGF concentration did not occur after intravitreal injection of ranibizumab in nAMD patients [32–34]; however, a significant reduction in serum VEGF concentration was detected and lasted for 1 month after a single injection of conbercept [35]. In our meta-analysis, 3 RCTs assessed the plasma VEGF level after monthly injections of anti-VEGF drugs. This meta-analysis showed a great difference in the systemic VEGF level between conbercept and ranibizumab groups during the 3-month follow-up period. However, the 3-month follow-up is too short to draw a meaningful conclusion because nAMD patients might need a long-term treatment in the clinical practice. Therefore, a long-term observation is necessary to study the effect of anti-VEGF drugs on the plasma VEGF level.

The structural and pharmacokinetic difference between conbercept and ranibizumab may lead to a possible difference in the systemic VEGF level. Ranibizumab is a

recombinant monoclonal immunoglobulin G1 isotype antibody antigen-binding fragment, which can neutralize all isoforms of VEGF-A [36]. Conbercept is a fusion protein that combines domain 2 of VEGFR-1 and domain 3 and 4 of VEGFR-2 with the Fc fragment of human immunoglobulin G [37]. Domain 4 of VEGFR-2 is essential for receptor dimerization and enhances the rate of VEGF association to the receptor, which helped to explain the high serum-free VEGF affinity of conbercept indirectly [8]. Pharmacokinetics studies have shown that conbercept has a higher binding affinity to VEGF-A165 than ranibizumab and binds to all isoforms of VEGF-A, VEGF-B, VEGF-C, and PlGF with high affinity [8]. The interaction between FcRn and Fc was thought to extend the half-lives of molecules with an Fc fragment in circulation [38], which may better explain the longer continuous effects of conbercept on the serum VEGF level. In addition, conbercept has a 38-fold greater half inhibitory concentration value than that of ranibizumab [39], which implicated the prolonged suppression of systemic VEGF levels.

AMD is a complex, degenerative, and progressive disease involving the multiple genetic and environmental factors. The recent studies have appointed a great role of inflammation in the pathogenesis of AMD [40, 41]. CRP, as a systemic inflammatory marker, may be associated with higher risk of AMD [42, 43]. Therefore, the inflammatory biomarker CRP may provide a method of evaluating the effectiveness of the anti-VEGF agents for nAMD individuals. In the present meta-analysis, conbercept-treated patients showed a different benefits in the plasma

CRP level compared to ranibizumab-treated patients during 3 months after initial injections. However, longer term follow-up is also needed to evaluate the effectiveness of anti-VEGF drugs in the reduction of the circulating CRP level because nAMD patients need to receive long-term treatment.

The VEGF-VEGFR system involves in several pathological conditions related not only to angiogenesis but also to inflammation, which may partially explain the possible difference in reduction of systemic inflammation [44]. There are 2 forms of VEGFR1: one form of soluble VEGFR1/Fms-like tyrosine kinase-1 and the other form of full-length VEGFR1 with tyrosine kinase. The sVEGFR1/Fms-like tyrosine kinase-1, which carries only the ligand-binding region, functions as a decoy receptor by trapping its ligands VEGF-A, PlGF, and VEGF-B, inducing a proangiogenic response. The full-length VEGFR1 is expressed in monocyte/macrophage cells, transducing an inflammatory signal for the migration and cytokine/chemokine production of these cells [45, 46]. The inhibition of VEGF was reported to suppress the expression of inflammatory cytokines, such as IL-1, IL-6, and TNF α [47]. Therefore, VEGF inhibition might play an important role in decreasing the plasma CRP level via the VEGFR1-monocyte/macrophage axis.

Pathologic states such as hypoxia or ischemia may break the balance between proangiogenic and antiangiogenic factors, which is conducive to the formation of new blood vessels. In nAMD, ischemia is a risk factor for the development of CNV [48, 49]. Previous studies have shown that lowering IOP alleviates the retinal ischemic process via improving blood perfusion in retinal blood vessels [50, 51]. Therefore, we speculated the reduction of IOP might be beneficial for preventing nAMD progression. Interestingly, the present study demonstrated a statistically significant difference between the 2 groups, which might be explained by a possible difference in the 2 anti-VEGF drugs in the plasma VEGF level. VEGF downregulation will inhibit the development of new vessels over the iris and the iridocorneal angle and then facilitates the aqueous humor outflow, which will lead to IOP reduction for patients with nAMD [52].

This meta-analysis has some limitations that need to be taken into account. First, a 3-month follow-up is not a sufficient time to confirm the advantages of conbercept with regard to the reduction of IOP, plasma VEGF level, and CRP level because nAMD is a chronic disease. Further studies with long-term follow-up periods are needed to draw meaningful conclusions. Second, longer term

(such as 2- or 3-year) outcomes are required to draw more valuable conclusions, although most of the results are similar in terms of VA, CMT, and CNV recovery rates. Third, these studies were only conducted in China, so the efficacy and safety of conbercept need to be assessed in other countries.

In conclusion, this meta-analysis indicates both conbercept and ranibizumab are effective choices in terms of functional and morphological parameters for nAMD at 3 months and 6–12 months post-start-of-treatment. Besides, both drugs are safe treatment strategies for nAMD at the 3-month visit.

Statement of Ethics

An ethics statement was not required for this study type as no human or animal subjects were used.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

X.W. and W.L. designed the study. X.W. and C.Y. developed the search strategy for the identification of articles and identified the articles. X.W., C.Y., and J.Y. acquired and analyzed the data. X.W., Y.X., and Y.L. drafted the manuscript. W.L. helped to revise the manuscript with all the other authors. All the authors approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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