Systematic Review and Meta-Analysis

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Ranibizumab and conbercept for treating wet age-related macular degeneration in China

A systematic review and meta-analysis

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Abstract

Background: This study aimed to evaluate the therapeutic effects of ranibizumab and conbercept on wet age-related macular degeneration.

Methods: Randomized controlled trials comparing ranibizumab and conbercept in the treatment of wet age-related macular degeneration were searched in the PubMed, Medline, EMbase, Cochrane Library, China National Knowledge Infrastructure, Wanfang databases, and Weipu Journal. Two reviewers independently extracted the data and assessed the methodological quality. Data analysis was performed using Rev Man 5.3 software for statistical analysis.

Results: A total of 16 randomized controlled trials, including 1018 patients, were included, and the results showed that the effect of ranibizumab on uncorrected visual acuity was not significantly different from that of conbercept (Mean difference [MD] = -.03, 95% Confidence interval [CI] [-.10-.05], $P = .47$), and there was no significant difference between the two drugs in the effect on best-corrected visual acuity (MD = .00, 95% CI [-.02-.03], $P = .73$). The effect of conbercept on intraocular pressure was better than that of ranibizumab (MD = 1.61, 95% CI [1.05-2.17], $P < .001$). The effect of ranibizumab on central macular thickness was not significantly different from that of conbercept (MD = 1.31, 95% CI [-3.81-6.43], $P = .62$). Conbercept had a better inhibitory effect on choroidal neovascularization than ranibizumab (MD = .49, 95% CI [.32-.76], $P = .001$).

Conclusion: The effects of ranibizumab on uncorrected visual acuity, best corrected visual acuity, and central macular thickness were not significantly different from those of conbercept. Conbercept is associated with a lower risk of increased intraocular pressure and regression of choroidal neovascularization compared with ranibizumab.

Abbreviations: BCVA = best corrected visual acuity, CI = confidence interval, CNV = choroidal neovascularization, IOP = intraocular pressure, MD = mean difference, RCT = randomized controlled trial, UCVA = uncorrected visual acuity, VEGF = vascular endothelial growth factor, wAMD = wet age-related macular degeneration.

Keywords: conbercept, meta-analysis, ranibizumab, wet age-related macular degeneration

1. Introduction

Age-related macular degeneration involves aging-related changes in the macular tissue structure and is the primary cause of irreversible visual impairment and blindness in the elderly above 60 years of age. It is classified into dry age-related macular degeneration and wet age-related macular degeneration (wAMD); the incidence of wAMD is lower than that of dry age-related macular degeneration; however, the visual impairment associated with wAMD is more severe.[1] Currently, the clinical treatment of wAMD involves intravitreal injection of anti-vascular endothelial growth factor (VEGF) drugs (ranibizumab and conbercept). These have become the most commonly

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This study is a systematic review; hence, ethics committee approval was not required.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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used drugs to treat wAMD because of their curative effect and few adverse effects.[2,3] Researchers have studied the efficacy of ranibizumab and conbercept from different perspectives[4,5]; however, it is not clear which drug is more effective for treating wAMD. Both ranibizumab and conbercept are anti-VEGF drugs, and can bind to multiple VEGF targets. They can also regulate the permeability of the blood-retinal barrier, improve retinal edema, inhibit regression of choroidal neovascularization (CNV), improve best-corrected visual acuity (BCVA), and have no effect on intraocular pressure (IOP). However, both are short-acting drugs, and repeated injections are required.

The aim of this study was to analyze the data of randomized controlled trials (RCTs) comparing ranibizumab and conbercept in the treatment of wAMD, to explore the advantages and disadvantages of these drugs in the treatment of wAMD, and to provide the latest evidence for the clinical treatment of wAMD.

2. Materials and methods

2.1. Including and excluding criteria

2.1.1. We included articles on studies that met the following inclusion criteria. (1) type of study: RCT; (2) type of participants: patients diagnosed with wAMD; (3) one group received intravitreal injection of ranibizumab, and the other group received intravitreal injection of conbercept. The two groups had no differences in the baseline parameters except the injected drugs; (4) outcomes included uncorrected visual acuity (UCVA), BCVA, CMT, and CNV.

2.1.2. We excluded the following types of articles. (1) studies that were not RCTs; (2) the target population was inconsistent with the diagnostic criteria of wAMD; (3) duplicate publications; (4) reviews, letters, comments, and animal research; (5) low-quality clinical trials; and (6) studies that did not derive corresponding indicators.

2.2. Search strategy

Seven databases (PubMed, Medline, EMbase, Cochrane Library, China National Knowledge Infrastructure, Wanfang database, and Weipu Journal) were searched for the relevant studies published between January 2016 and June 2019. The following search terms were used in combination: Ranibizumab, Conbercept, wet age-related macular degeneration, exudative macular degeneration, treatment, and random. There were no restrictions on language or study design. We also searched the bibliographies of the retrieved articles for potentially relevant articles.

2.3. Data abstraction and quality assessment

Two reviewers independently retrieved the eligible studies according to the search strategy and selection criteria. Disagreements between the two authors were resolved by discussion or consultation with a third reviewer. The extracted data included the first author(s), sample size, age, details of interventions, outcomes, follow-up periods, and adverse events. The quality of studies was assessed by referring to the Cochrane Handbook 5.2, which contains guidelines about the evaluation of randomization, allocation concealment, blinding, incomplete outcome data, withdrawals and dropouts, and other biases. Based on the six criteria, the quality of the included documents was divided into three levels: A, B, and C. The above criteria were fully met, and had a least possibility of various biases, it was categorized as grade A; if some studies met the above criteria, and had a moderate possibility of various biases, it was categorized as grade B; studies that did not meet the above criteria, and had a high possibility of various biases were categorized as grade C.

2.4. Statistical analysis

Statistical analysis was performed using Review Manager software (version 5.3) from the Cochrane Collaboration. In this meta-analysis, the mean difference (MD) and odds ratio were used to analyze continuous and dichotomous outcomes with a 95% confidence interval (CI). Statistical significance was set at $P < .05$. A chi-square test with P-value and I^2 statistic was used to quantify the statistical heterogeneity between the studies. If no heterogeneity between the studies was observed ($P > .1$, $I^2 < 50\%$), the fixed effects model was used for the analysis; else, the random-effects model was used. Forest plots displayed summary weighted estimates, and funnel plots were used to assess publication bias.

3. Results

3.1. Search results

A total of 139 potential articles were identified with an electronic-based search; we excluded 30 articles after screening their titles and abstracts and retrieved the full texts of the 109 remaining articles. Finally, 16 studies[6–21] met the inclusion criteria and were included in this meta-analysis (Fig. 1).

3.2. Characteristics of eligible studies

All included studies were RCTs, and the characteristics of these studies are summarized in Table 1. Studies were published from 2016 to 2019, and all were conducted in China. The sample size of the 16 studies ranged from 40 to 102, and the course of treatment varied from 1 to 12 months; all studies reported the outcomes at follow-up.

3.3. Methodological quality of included studies

All studies described an appropriate randomization procedure and complete outcome data, but none of them mentioned allocation concealment and blinding. Two out of 10 studies described patient withdrawals and dropouts[12,16] (Table 2).

3.4. Treatment outcomes

3.4.1. UCVA. Eight studies[6,12–16,19,21] reported the outcomes of UCVA at the end of the treatment period. The outcome of the heterogeneity test showed statistical significance ($P < .001$), $I^2 = 97\%$; hence, the random-effects model was used for the analysis. The results showed that the difference was not statistically significant (MD = -.03, 95% CI (-.10-.05), $P = .47$), suggesting that there was no significant difference between ranibizumab and conbercept in improving the UCVA (Fig. 2).

3.4.2. BCVA. Six studies[7,9–11,18,20] reported the outcomes for BCVA at the end of treatment. The outcome of the heterogeneity test showed no statistically significant difference ($P = .38$), $I^2 = 6\%$; hence, the fixed-effects model was used for the analysis, and

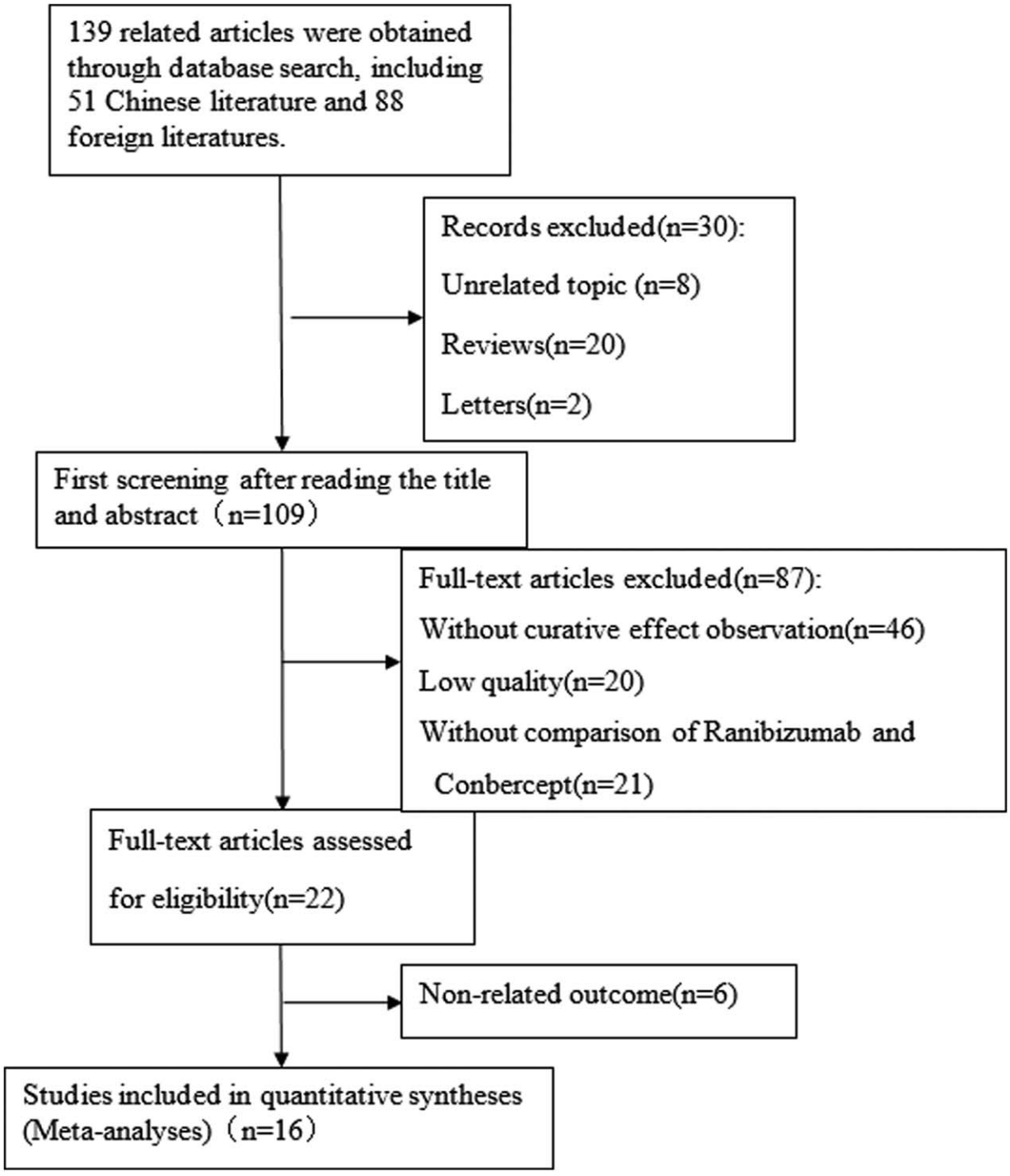

Figure 1. Flow diagram of included studies for this meta-analysis.

the results showed that the difference was not statistically significant (MD = .00, 95% CI [-.02-.03], $P = .73$), indicating that there was no significant difference between ranibizumab and conbercept in improving the BCVA (Fig. 3).

3.4.3. CMT. Thirteen studies[7–14,17–21] reported the CMT measurements at the end of treatment. The outcome of the heterogeneity test showed no statistically significant difference ($P = .59$), $I^2 = 0\%$; hence, the fixed-effects model was used for the analysis. The results showed that the difference was not statistically significant (MD = 1.31, 95% CI (-3.81-6.43), $P = .62$], indicating that there was no significant difference between ranibizumab and conbercept in improving the CMT (Fig. 4).

3.4.4. CNV. Seven studies[7,12–15,17,21] reported the CNV outcomes at the end of treatment. The outcome of the heterogeneity test showed no statistically significant difference ($P = .38$), $I^2 = 7\%$; hence, the fixed-effects model was used for the analysis. The

Table 1

Characteristics of the eligible studies.

Studies (first author, year)	Location	Patients No.	Group (R/C)	Course of treatment (mo)	Follow-up (mo)
Deng[6],2018	China	48	24/24	12	3–6
Zhang[7],2017	China	40	20/20	3	1–3
Liang[8],2019	China	60	30/30	3	3
Lv[9],2016	China	84	42/42	3	3
Liu[10],2018	China	68	34/34	3	3
Lei[11],2018	China	60	30/30	3	3–6
Hu[12],2018	China	48	24/24	3	3
Yang[13],2018	China	48	24/24	3	1–3
Fan[14],2018	China	78	39/39	3	1–3
Shi[15],2019	China	60	30/30	3	1–3
Zhang[16],2016	China	60	30/30	3	1–3
Shu[17],2018	China	80	40/40	3	1–3
Cai[18],2016	China	58	30/28	3	1–3
Ma[19],2019	China	82	41/41	3	1–3
Xue[20],2019	China	102	51/51	1	1
Niu[21],2016	China	40	20/20	3	1–3

C = Conbercept, R = Ranibizumab.

Table 2

Quality of the included studies.

Studies (first author, year)	Randomization	Allocation concealment	Blinding	Incomplete outcome data	Withdrawals and dropouts
Deng[6],2018	Yes	NMT	NO	Yes	NMT
Zhang[7],2017	Yes	NMT	NO	Yes	NMT
Liang[8],2019	Yes	NMT	NO	Yes	NMT
Lv[9],2016	Yes	NMT	NO	Yes	NMT
Liu[10],2018	Yes	NMT	NO	Yes	NMT
Lei[11],2018	Yes	NMT	NO	Yes	NMT
Hu[12],2018	Yes	NMT	NO	Yes	MT
Yang[13],2018	Yes	NMT	NO	Yes	NMT
Fan[14],2018	Yes	NMT	NO	Yes	NMT
Shi[15],2019	Yes	NMT	NO	Yes	NMT
Zhang[16],2016	Yes	NMT	NO	Yes	MT
Shu[17],2018	Yes	NMT	NO	Yes	NMT
Cai[18],2016	Yes	NMT	NO	Yes	NMT
Ma[19],2019	Yes	NMT	NO	Yes	NMT
Xue[20],2019	Yes	NMT	NO	Yes	NMT
Niu[21],2016	Yes	NMT	NO	Yes	NMT

MT = mentioned, NMT = not mentioned.

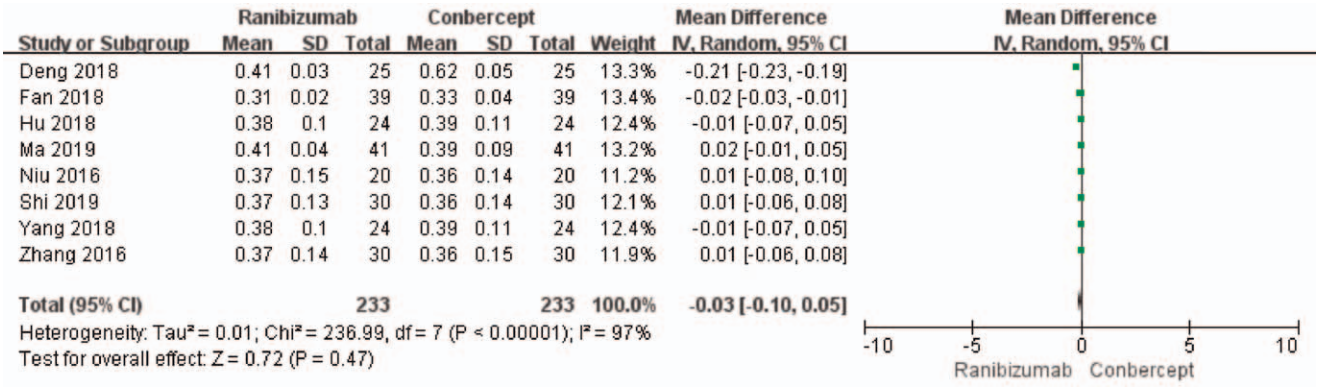

Figure 2. Forest plot showing the effect of Ranibizumab and Conbercept used for the treatment of wAMD on UCVA.

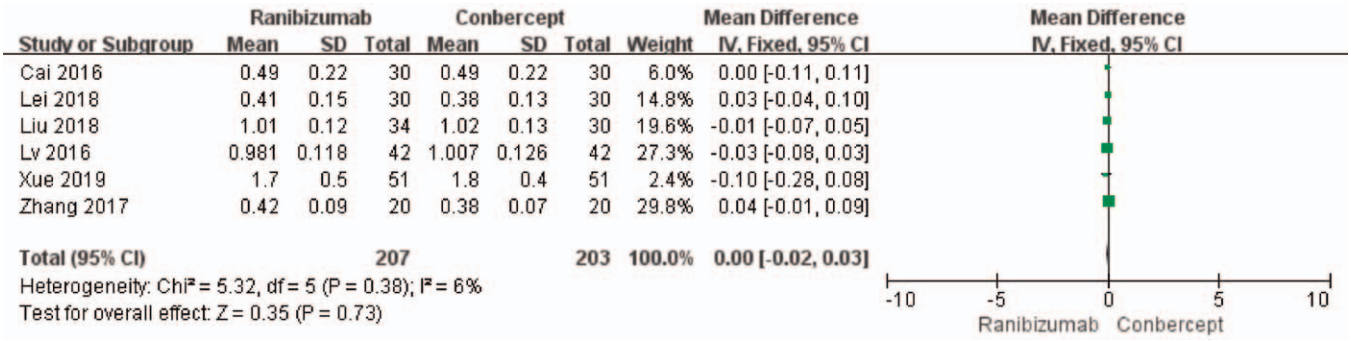

Figure 3. Forest plot showing the effect of Ranibizumab and Conbercept used for the treatment of wAMD on BCVA.

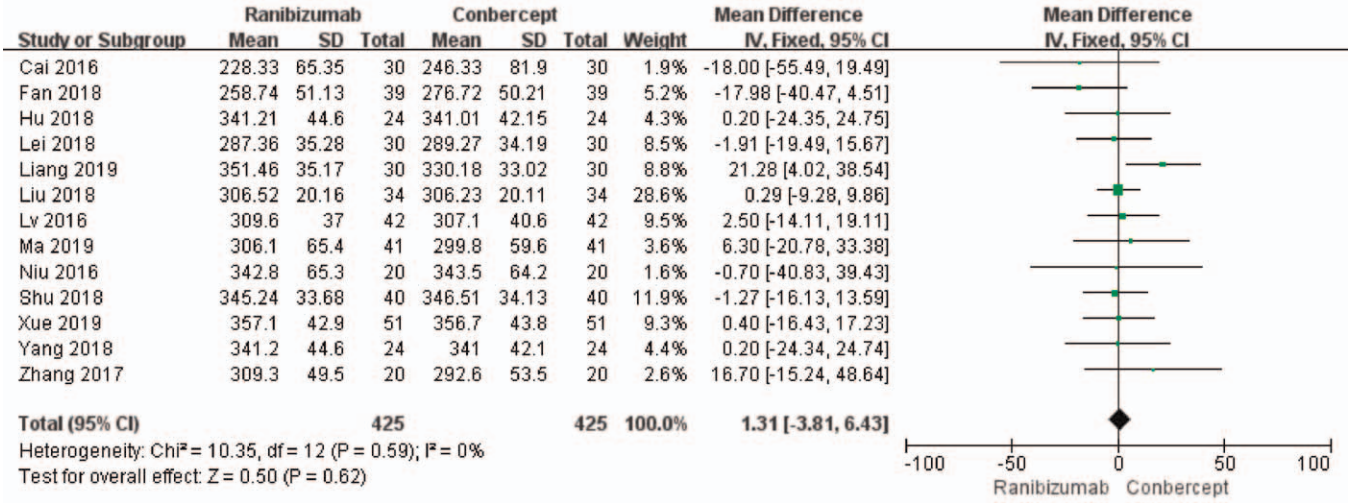

Figure 4. Forest plot showing the effect of Ranibizumab and Conbercept used for the treatment of wAMD on CMT.

results showed that the difference was statistically significant (MD = .49, 95% CI (.32-.76], $P = .001$), indicating that conbercept has a better inhibitory effect on CNV than ranibizumab. (Fig. 5).

3.4.5. IOP. Two studies[6,8] reported the effect on IOP at the end of treatment. The outcome of the heterogeneity test showed no statistically significant difference ($P = .79$), $I^2 = 0\%$; hence, the fixed-effects model was used for the analysis. The results showed that the difference was statistically significant (MD = 1.61, 95% CI [1.05-2.17], $P < .001$), indicating that conbercept can better decrease the IOP than ranibizumab. (Fig. 6).

4. Discussion

This systematic analysis included 16 studies that evaluated and compared the efficacy of ranibizumab and conbercept in the treatment of wAMD. All included trials had clear diagnostic criteria, inclusion criteria, and exclusion criteria. Visual electrophysiology and ocular hemodynamics were also reported. The results showed that there was no significant difference between ranibizumab and conbercept in improving the UCVA and BCVA, and there was no significant difference in the improvement of retinal edema between the drugs. Although IOP is not an indicator of treatment efficacy, it might increase following the injection of anti-VEGF drugs and cause secondary glaucoma or transient damage to the optic nerve. Therefore, this study focused on the impact of the two drugs on IOP and found that conbercept was more effective in reducing IOP than ranibizumab.

Conbercept was more effective in inhibiting CNV that occurs with wAMD, than ranibizumab. Although the inhibitory effect of conbercept on CNV was stronger than that of ranibizumab, there was no difference in the improvement of UCVA, BCVA, and macular thickness compared to that with ranibizumab. This suggests that the factors affecting vision might not only come from CNV; however, the low incidence of CNV will also reduce the risk of bleeding. Nevertheless, the correlation of CNV with macular edema needs further research. In addition, the limited literature included in this study might also have an impact on the results.

wAMD is a common cause of loss of BCVA in the elderly, and VEGF has been shown to play an important role in the formation of wAMD-associated CNV.[22] Currently, the main treatment for wAMD is an intravitreal injection of anti-VEGF drugs, and a study involving a total of 2227 patients with wAMD in several countries has shown that ranibizumab is an effective treatment for wAMD. However, if the treatment was not continued after 120 days, the BCVA did not improve further and was not

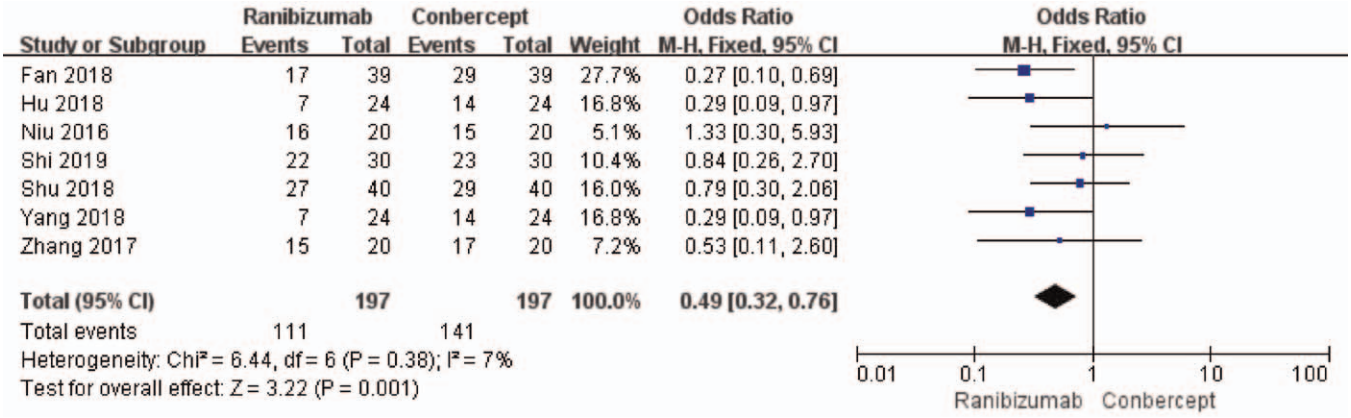

Figure 5. Forest plot showing the effect of Ranibizumab and Conbercept used for the treatment of wAMD on CNV.

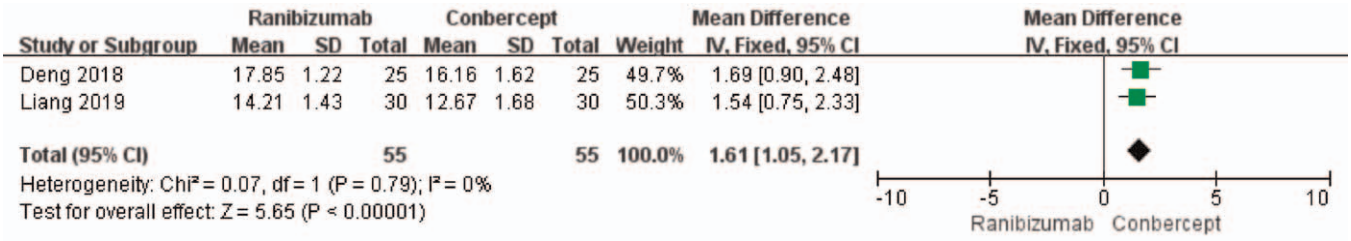

Figure 6. Forest plot showing the effect of Ranibizumab and Conbercept used for the treatment of wAMD on IOP.

maintained thereafter.[23] In another study, the clinical observation of 109 patients with wAMD showed that continuous treatment with ranibizumab stabilized or improved 93.2% of the visual acuity in the seventh year after treatment.[24] Intravitreal injection of ranibizumab and conbercept did significantly improve visual acuity in patients with wAMD.[25] Conbercept is a novel VEGF inhibitor used for the treatment of wAMD. In recent years, many studies have reported that conbercept has good efficacy, no obvious adverse reactions, and good safety in the treatment of wAMD. Conbercept injection for three consecutive months can maintain the BCVA at a high level.[26] Conbercept might be more effective than ranibizumab in decreasing the plasma levels of VEGF.[27]

Wang included eight randomized controlled studies and four retrospective studies with a total of 853 patients. They found that conbercept was superior to ranibizumab in terms of visual improvement after treatment.[28] However, our study found that the two drugs did not show a significant difference in visual improvement. The reason for this discrepancy might be the differences between the included studies and the number of patients analyzed.

However, this meta-analysis was limited by the following factors (1) It included only 16 studies that assessed a total of 1016 patients. (2) The included studies were not of very high quality and all were conducted in China. (3) None of the studies mentioned allocation concealment or blinding. (4) Adverse reactions were not reported in all studies; hence, it was not clear whether there are adverse reactions associated with the use of ranibizumab and conbercept in the treatment of wAMD.

The significance of this analysis is that it shows conbercept is superior to ranibizumab in inhibiting the occurrence of CNV and reducing complications associated with wAMD. Future studies, with large sample sizes, multicentric, and adequately blinded randomized controlled trials are necessary.

5. Conclusions

The effects of ranibizumab and conbercept on UCVA, BCVA, and CMT were not significantly different from each other. Compared with ranibizumab, conbercept effectively reduced IOP and promoted CNV regression. Due to the limitations of this meta-analysis, more data and more RCTs are required, which can provide further guidance for the clinical setting.

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