

A systematic review and meta-analysis to compare the efficacy of conbercept with ranibizumab in patients with macular edema secondary to retinal vein occlusion

Weishai Liu, MD^a, Yanjie Li, PhD^{a,*}, Rongxia Cao, MD^a, Zichao Bai, MD^a, Weiqin Liu, MD^b

Abstract

Background: The objective of this review and meta-analysis is to investigate the efficacy of conbercept and ranibizumab, combined with or without laser photocoagulation, in patients with macular edema secondary to retinal vein occlusion (RVO-ME).

Methods: Several databases have been used to identify relevant publications. After screening, a meta-analysis was conducted to compare conbercept and ranibizumab with the support of RevMan 5.3 (Cochrane Library Software, Oxford, UK).

Results: In this study, 9 randomized controlled trials and 6 retrospective trials were included with a total of 1180 patients. No significant difference was found in best corrected visual acuity (BCVA) or central macular thickness (CMT) in the baseline parameters [BCVA (weighted mean difference (WMD): -0.01 ; 95% confidence interval (CI): -0.03 to 0.01 ; $P = .17$), CMT (WMD: 20.14 ; 95% CI: -26.70 to 66.97 ; $P = .40$). No significant differences were found in the improvements of BCVA and adverse events (AEs) between the 2 groups after injection of loading dosage [the 1st month BCVA (WMD: -0.01 ; 95% CI: -0.04 to 0.02 ; $P = .54$), the 3rd month BCVA (WMD: -0.02 ; 95% CI: -0.05 to 0.01 ; $P = .23$), the 6th month BCVA (WMD: -0.02 ; 95% CI: -0.05 to 0.01 ; $P = .27$), AEs (odds ratio: 0.84 ; 95% CI: 0.38 to 1.84 ; $P = .66$)]. However, there were significant differences between conbercept and ranibizumab treatment in terms of CMT [1st month CMT (WMD: -11.70 ; 95% CI: -19.71 to -3.68 ; $P < .01$), 3rd month CMT (WMD: -10.08 ; 95% CI: -15.62 to -4.53 ; $P < .01$), 6th month CMT (WMD: -15.83 ; 95% CI: -22.88 to -8.78 ; $P < .01$)] and the number of injections (WMD, -0.36 ; 95% CI: -0.68 to -0.04 ; $P = .03$).

Conclusion: The current pooled evidence suggested that both therapies of intravitreal conbercept and intravitreal ranibizumab with or without laser photocoagulation are effective in vision function in RVO-ME patients, and confirmed that conbercept has advantages over ranibizumab in terms of CMT and the number of injections for treating RVO-ME. In addition, conbercept has the statistically same visual gains and safety as ranibizumab in RVO-ME patients. Longer-term follow-up surveys on the safety and effectiveness of these 2 treatment regimens are required.

Abbreviations: AEs = adverse events, BCVA = best corrected visual acuity, CI = confidence interval, CMT = central macular thickness, RVO-ME = retinal vein occlusion macular edema, WMD = weighted mean difference.

Keywords: conbercept, ranibizumab, retinal vein occlusion

Editor: Undurti N. Das.

WL and YL contributed equally to this work.

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

The authors report no funding and conflicts of interest.

^a Department of Ophthalmology, The First hospital of Shanxi Medical University, Taiyuan City, ^b Wenzhou Medical University, China.

* Correspondence: Yanjie Li, Department of Ophthalmology, The First Hospital of Shanxi Medical University, No. 85 Jiefang South Road, Yinze District, Taiyuan City 030001, Shanxi Province, China (e-mail: liyanjie-0311@126.com).

Copyright © 2020 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Liu W, Li Y, Cao R, Bai Z, Liu W. A systematic review and meta-analysis to compare the efficacy of conbercept with ranibizumab in patients with macular edema secondary to retinal vein occlusion. *Medicine* 2020;99:21(e20222).

Received: 21 April 2019 / Received in final form: 3 April 2020 / Accepted: 8 April 2020

<http://dx.doi.org/10.1097/MD.0000000000002022>

1. Introduction

Retinal vein occlusion (RVO) is the second most common vascular disease of the retina, with the first being diabetic retinopathy, in which various complications such as macular edema, may occur with a consequent visual impairment or visual loss.^[1] RVO also can lead to many serious complications, including retinal hemorrhage, macular edema, and neovascular glaucoma. Among these complications, macular edema secondary to RVO is the main cause of visual impairment and visual loss.^[1] RVO based on localization of venous occlusion is mainly divided into 3 types, including branch retinal vein occlusion (BRVO) that accounts for 80% of the RVO, hemi-retinal vein occlusion (HRVO) as well as central retinal vein occlusion (CRVO).^[2] According to the diagnostic criteria of American CRVO group,^[3] CRVO can be subdivided into 2 types on the basis of fluorescein fundus angiography (FFA):

- (1) perfused CRVO, characterized by retinal circulation stasis, blood capillary leakage, and capillary without perfusion area < 10 PD, still has blood perfusion. This type generally has a better prognosis;

(2) nonperfused CRVO is marked by retinal capillary without perfusion area > 10 PD.

Clinical studies have shown^[11] that 34% of perfused CRVO patients can develop into nonperfused CRVO patients. A multicenter epidemiological study^[4] showed that the global prevalence of CRVO is as high as 0.8%. The incidence of CRVO in China is 0.1%. Therefore, more than 1.3 million people in China suffer from visual impairment or loss caused by CRVO every year.^[5] BRVO and CRVO are of the most clinically relevant and frequently occurring types. Both could lead to macular edema, a complication that is caused by the accumulation of fluid in the outer plexiform layer of the retina, as a result of the destruction of the blood-retinal barrier and high permeability of the vasculature. The incidence of macular edema secondary to perfused CRVO is 30%, while the nonperfused CRVO is 75%.^[1,2] Currently, there is no standard intervention for the treatment of CRVO-ME, and the most commonly used methods are laser photocoagulation and drug therapy. The mechanism of laser photocoagulation for macular edema is that lasers can be absorbed by the melanin of retinal pigment epithelium, further damaging some photoreceptors in the hypoxic area and reducing the retinal oxygen consumption.^[6] And lasers directly destroy abnormal neovascularization, reducing the leakage of neovascularization. At the same time, the photocoagulation spots produce adhesion, so that the edema of the retina is closer to the choroidal capillaries to obtain a richer blood supply, promoting the absorption of edema and the retinal recovery of the structure and function. Grid-pattern and scatter photocoagulation are 2 types of laser photocoagulation. Owing to the damages to the retina, and limited visual acuity improvements from a long-term perspective, either grid-pattern or scatter laser coagulation has been employed in combination with anti-angiogenic therapy for RVO-ME patients non-responsive to anti-angiogenic agent monotherapy.^[7] Under normal physiological conditions, the tight junctions between retinal capillaries, together with the drainage function of the retinal pigment epithelium (RPE), jointly prevent the accumulation of fluid under the neurosensory layer or the RPE layer. Vascular endothelial growth factor (VEGF) has been proven to play a key part in the abnormal pathophysiologic process.^[8] Various factors, including hypoxia and ischemia as well as other stimuli, could up-regulate VEGF expression, which was found to be increased in the fluids of RVO patients' eyes.^[9] In addition, a higher intravitreal VEGF level was noted to correlate with a severer clinical manifestation.^[10] Therefore, several anti-angiogenic drugs, such as conbercept, bevacizumab and ranibizumab, have been widely applied in the therapy of macular edema.^[11,12] They have been reported to provide a fast and obvious decrease of the central macular thickness (CMT) and a marked improvement in best corrected visual acuity (BCVA) in the therapeutic process of macular edema. Ranibizumab (or Lucentis; Novartis, Basel, Switzerland), which is widely adopted in wet age-related macular degeneration patients, also applied in diabetic macular edema patients, is a high-affinity recombinant antigen-binding fragment. The 48 kDa drug binds to all kinds of receptors of VEGF-A.^[11,13] Conbercept (also known for Lumitin, or KH903, Kang Hong Biotech Co, Ltd, Sichuan, China) is a recombinant anti-angiogenic fusion protein, structurally similar to aflibercept (Eylea, Regeneron Pharmaceuticals, Eastview, NY), another fusion protein binding to all isoforms of placental growth factor (PlGF), VEGF-A, and VEGF-B. The 143 kDa drug engineered in Chinese hamster ovary cells (CHO) was a protein with a human cDNA sequence.^[14,15] Moreover, it has been

confirmed that conbercept has a more powerful binding affinity for VEGF than that of ranibizumab, owing to the special Fab fragment with the attached fourth extracellular domain of VEGFR-2.^[16,17] It also has been reported that some patients with diabetic macular edema who are ineffective to bevacizumab or ranibizumab (regardless of the number of injections) are still responsive to the treatment with conbercept.^[16] Several meta-analyses have assessed the effectiveness of intravitreal ranibizumab (IVR) and intravitreal conbercept (IVC) for treating RVO-ME patients.^[18–21] However, they focus either on therapy methods, such as intravitreal anti-VEGF agents, laser photocoagulation, and intravitreal dexamethasone, or on the different dosages of ranibizumab for treating this condition. – treatment regimens (conbercept 0.5 mg, ranibizumab 0.5 mg) are often adopted during the course of administering anti-VEGF agents. It is still unknown whether the conbercept and ranibizumab groups have the same outcomes in a large sample size. Therefore, we performed this meta-analysis based on 9 randomized controlled trials (RCTs) and 6 retrospective trials (Given that conbercept is currently only used in China to treat RVO-ME, all studies came from China) to compare the effectiveness of ranibizumab 0.5 mg and conbercept 0.5 mg, with or without laser photocoagulation.

2. Methods

2.1. Literature search

Relevant studies in human subjects were spotted by searching WanFang data, the China National Knowledge Infrastructure (CNKI), OVID, Springer, WOS, PubMed, EMBASE, Cochrane Library, and clinicaltrials.gov up to March 20, 2019. The search was performed, with the following Medical Subject Heading terms: “retinal vein occlusion or macular edema,” and “ranibizumab or Lucentis,” and “conbercept or KH903 or Lumitin,” with a filter restricting the results to only clinical trials. Language restrictions were limited within English and Chinese in the retrieval.

2.2. Inclusion and exclusion criteria

When papers met the following inclusion standards, the publications were selected:

1. study design – RCTs or retrospective trials;
2. intervention – IVR vs IVC treatment, or IVR plus laser photocoagulation vs IVC plus laser photocoagulation treatment;
3. population – RVO-ME patients;
4. duration – at least 3 months' follow-up;
5. outcome variables – assessing at least 1 of the outcomes mentioned below.

Papers were excluded if

1. they were animal experimental studies, meeting abstracts, case reports, review articles, letters, or editorials; or
2. they were duplicated in those databases.

2.3. Outcome measures

The variables we have adopted were:

1. the BCVA presented in LogMAR, indicating functional improvement;
2. the CMT, measured with the aid of optical coherence tomography ;

3. the number of AEs; and
4. the number of injections during the follow-up periods.

2.4. Data extraction

The methodological quality of the papers was separately evaluated by 2 reviewers, who also collected and sorted the data in an optimal procedure. All disagreements about data extraction have been solved by discussion until the 2 reviewers reached a consensus. The following basic data were extracted from each study and filled out in a pre-set form comprising first author, publication year, study design, type of diagnosis, treatment regimen, period of follow-up, dosage, sample size, inclusion and exclusion criteria, and other records.

2.5. Quality assessment

In accordance with the Cochrane Handbook for Systematic Reviews of Interventions, the risk-of-bias tool was used to assess papers quality. Papers with factors that are not in line with the principles would have been marked with a high risk of bias. Six basic facets affecting the quality of RCTs were evaluated: completeness of outcome reporting, management of incomplete outcome data, personnel and outcome assessors, patient blinding, allocation concealment, as well as sequence generation.

2.6. Statistical analysis

This systematic review was conducted according to the Preferred Reporting Protocols for Systematic Reviews and Meta-Analyses (PRISMA) statement.^[22] The odds ratios (ORs) and weighted mean differences (WMDs) were adopted to compare dichotomous and continuous variables respectively. Chi-squared test was used to assess the statistical heterogeneity between studies, and I^2 statistic was adopted to evaluate the quantity of heterogeneity. A condition, $I^2 > 50\%$ and $P < .05$ at the same time, was regarded as heterogeneity. If there was interstudy heterogeneity shown by evidence, a random-effects model was applied or else we adopted the fixed-effects model. All results were recorded with 95% confidence intervals (CI). We performed the subgroup analyses to separately estimate the effects of the adoption of laser photocoagulation at baseline and the last follow-up. We created standard funnel plots to visualize their symmetry and further to test the potential publication bias.

All analyses were based on published studies. Thus, no ethical approval and informed consent were required.

3. Results

3.1. Selection of qualified studies

This study selection procedure is presented in Figure 1. A total of 167 possibly related papers were noted by our extensive literature retrieval, 89 of which were dropped out after reviewing titles and abstracts, and 61 were excluded due to duplication or low quality. Of the remaining 17, 2 were excluded for being unable to extract outcomes of interest. Thus, 9 RCTs and 6 retrospective trials were included in the final meta-analysis.^[23–37]

3.2. Study characteristics

The basic characteristics of the 15 trials, including randomized controlled trials and retrospective trials are presented in Table 1.

Nine RCTs and 6 retrospective trials, were enrolled in this study. All the trials were conducted in China. Among these trials, 4 trials were carried out to compare conbercept plus laser photocoagulation versus ranibizumab plus laser photocoagulation in patients with RVO. And 10 compared conbercept with ranibizumab, without the combination of laser photocoagulation. The sample size ranged from 30 to 384.

3.3. BCVA

Among all studies, only 1 study reported BCVA in ETDRS letters, and we transformed ETDRS into LogMAR. The BCVAs of the follow-up in the first ($n=844$), third ($n=1032$) and sixth ($n=541$) month were presented. The pooled results revealed that no significant differences were found in BCVA before treatment ($n=1078$) (WMD: -0.01 ; 95% CI: -0.03 to 0.01 ; $P=.17$) and after treatment (the 1st month BCVA (WMD: -0.01 ; 95% CI: -0.04 to 0.02 ; $P=.54$), the 3rd month BCVA (WMD: -0.02 ; 95% CI: -0.05 to 0.01 ; $P=.23$), the 6th month BCVA (WMD: -0.02 ; 95% CI: -0.05 to 0.01 ; $P=.27$) between the conbercept and ranibizumab group. A similar outcome was observed between the IVC cohort and the IVR cohort, when we have the studies subgrouped according to whether adopting laser photocoagulation or not (Fig. 2). No substantial statistical heterogeneity was observed across all studies.

3.4. CMT

CMT is viewed as one of the most relevant prognostic factors for ME levels. Hence it was also evaluated in the current study. All the CMTs were recorded with the aid of optical coherence tomography pictures from the first time to the last time of the follow-up period in both the IVC cohort and the IVR cohort. The CMTs were collected in the first ($n=946$), third ($n=1134$), and sixth ($n=643$) month during the follow-up. There was no statistically significant difference in CMT at baseline ($n=1180$) when comparing the conbercept group with ranibizumab group (WMD: 20.14 ; 95% CI: -26.70 to 66.97 ; $P=.40$). However, CMT significantly differed between the conbercept group and ranibizumab group after treatment whether or not with the combination of laser photocoagulation (1st month CMT (WMD: -11.70 ; 95% CI: -19.71 to -3.68 ; $P<.01$), 3rd month CMT (WMD: -10.08 ; 95% CI: -15.62 to -4.53 ; $P<.01$), 6th month CMT (WMD: -15.83 ; 95% CI: -22.88 to -8.78 ; $P<.01$)). RVO-ME patients applied with monthly injections of conbercept had a more obvious reduction of CMT from the initial thickness in comparison with RVO-ME patients applied with ranibizumab. Subgroup analyses were also conducted to compare the IVC group to the IVR group. All these analyses exhibited statistically significant differences showing the advantage of the IVC group over the IVR group (Fig. 3)

3.5. Number of intravitreal injections

Given that 1+PRN regimen and 3+PRN regimen were performed, we also compared the number of injections. Seven trials ($n=704$) reported intravitreal injection numbers. There was a significant heterogeneity ($I^2=81\%$) in this analysis, so a random-effects model was used. Pooled results indicated that (WMD, -0.36 ; 95% CI: -0.68 to -0.04 ; $P=.03$) there was a significant difference. In other words, conbercept groups experienced fewer injections, compared to ranibizumab groups (Fig. 4).

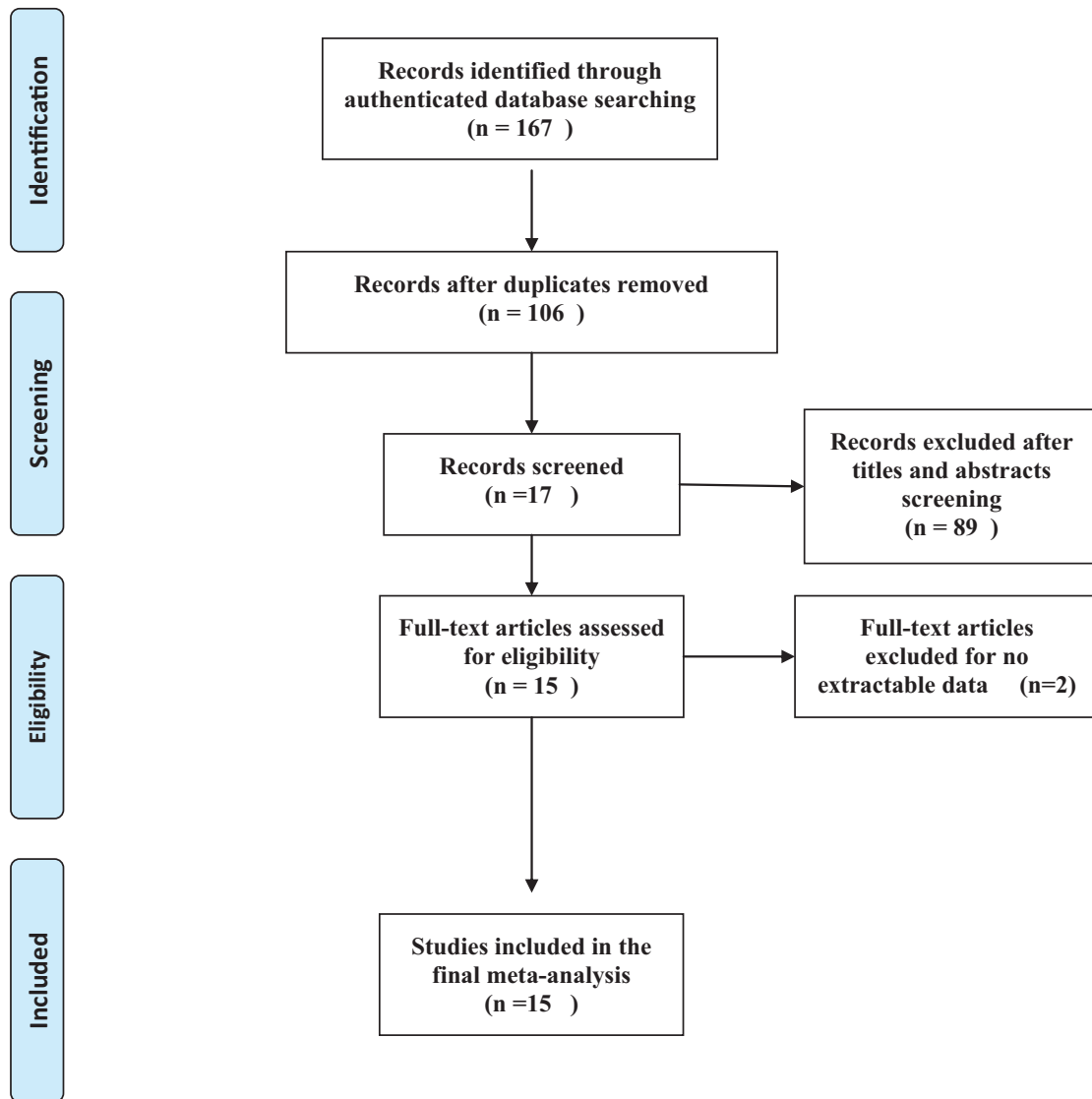


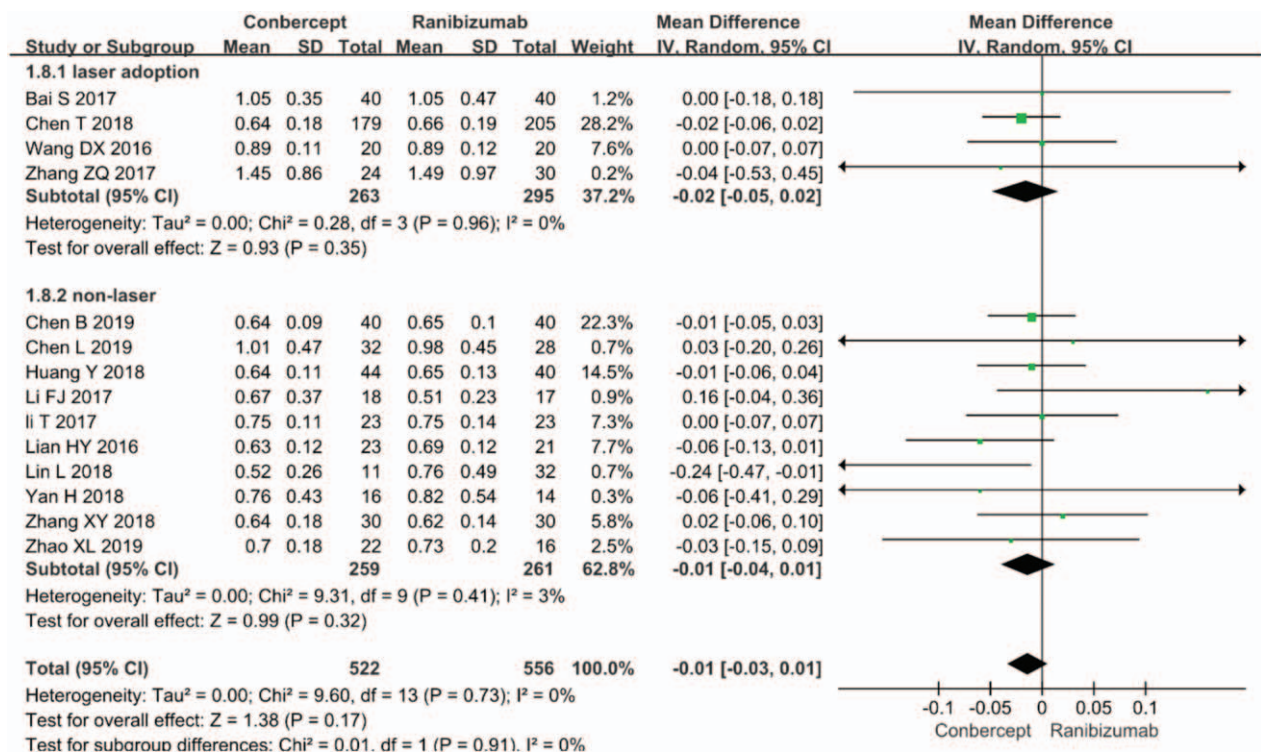
Figure 1. Flow diagram of study selection and identification.

Table 1

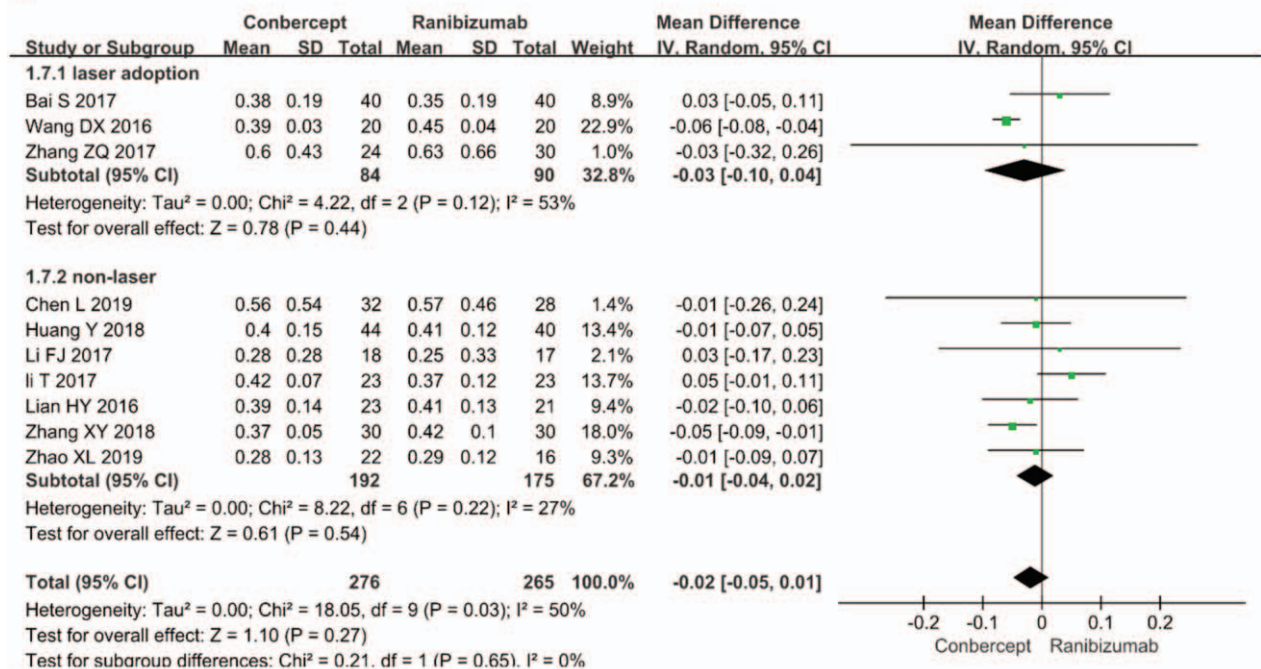
Characteristics of included studies.

Name and published yr	Collection period	Number of eyes IVC	IVR	RVO type	Protocol	Design	Follow-up period (mo)	
Bai S ^[24]	2017	2015.1–2016.1	40	40	BRVO	1 + PRN + L	RCT	6
Chen B ^[23]	2019	2014.3–2018.5	40	40	BRVO	1 + PRN	RCT	3
Chen L ^[27]	2019	2015.9–2017.2	32	28	CRVO + BRVO	1 + PRN	Retro	6
Chen T ^[25]	2018	2015.9–2016.12	179	205	CRVO + BRVO	1 + PRN + L	RCT	3
Chen X ^[26]	2018	2015.6–2017.1	50	52	CRVO	3	RCT	6
Huang Y ^[28]	2018	2013.2–2016.12	44	40	CRVO	3	Retro	6
Li FJ ^[36]	2017	2015.4–2016.4	18	17	BRVO	1 + PRN	RCT	6
Li T ^[29]	2017	2015.10–2017.3	23	23	CRVO	3 + PRN	Retro	6
Lian HY ^[30]	2016	2014.5–2015.8	23	21	CRVO	3 + PRN	Retro	6
Lin L ^[37]	2018	2017.6–2018.1	11	32	BRVO	1 + PRN	RCT	3
Wang DX ^[34]	2016	2014.3–2015.3	20	20	CRVO	3 + PRN + L	RCT	6
Yan H ^[31]	2018	2014.1–2017.1	16	14	BRVO	1	Retro	3
Zhang XY ^[32]	2018	2016.5–2017.5	30	30	CRVO + BRVO	1 + PRN	RCT	6
Zhang ZQ ^[35]	2017	2014.1–2016.6	24	30	BRVO	1 + PRN + L	RCT	6
Zhao XL ^[33]	2019	2016.1–2017.1	22	16	BRVO	1 + PRN	Retro	6

IVC = intravitreal conbercept; IVR = intravitreal ranibizumab; CRVO = central retinal vein occlusion; BRVO = branch retinal vein occlusion; PRN = pro re nata; L = laser photocoagulation; RCT = random controlled trial; Retro = retrospective trial



A



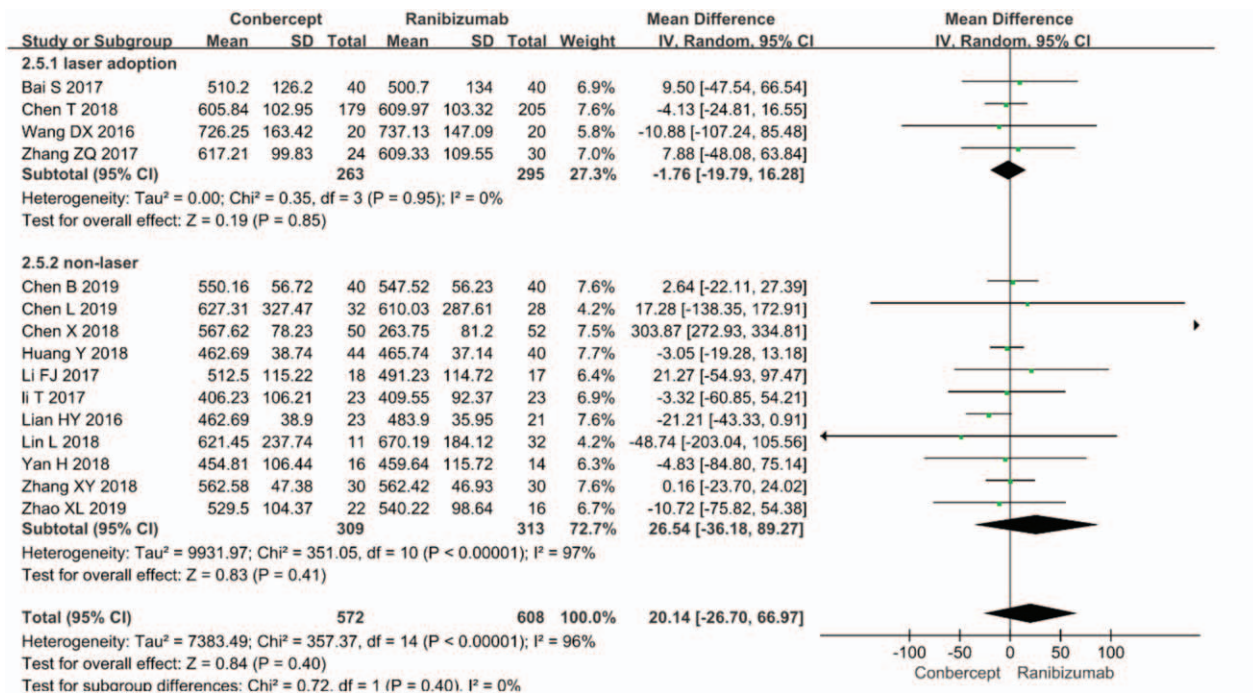
B

Figure 2. Forest plots of sub-analyses of best corrected visual acuity in retinal vein occlusion macular edema patients before (A) and after 6 mo (B) of treatment with conbercept or ranibizumab.

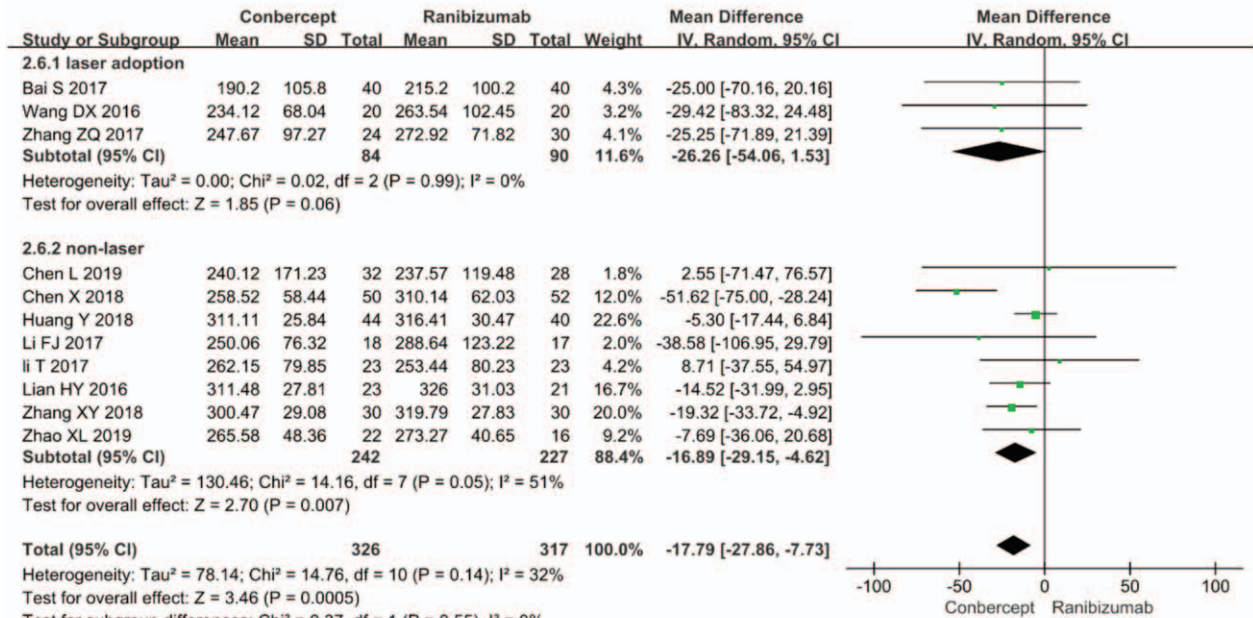
3.6. AEs

AEs are worthy of paying attention, so we also analyzed the data to compare the number of AEs between the IVC cohort and the IVR cohort. Eight studies (n=848) reported AEs, including floaters in front of the eye, pain at the injection site, increased

corneal edema, intraocular pressure, subconjunctival hemorrhage, anterior chamber inflammation, etc. The rest studies either did not report AEs or no adverse event occurred. No serious adverse event (vitreous hemorrhage, retinal proliferation, retinal tears, transient cerebral ischemia, cerebral hemorrhage) was reported in all the studies. Fixed-effects model analysis was



A



B

Figure 3. Forest plots of sub-analyses of central macular thickness in retinal vein occlusion macular edema patients before (A) and after 6 mo (B) of treatment with conbercept or ranibizumab.

adopted, owing to the heterogeneity test results ($P = .85, I^2 = 0\%$). No statistical difference was found (Fig. 5) in the AEs between these 2 regimens (IVC 0.5 mg and IVR 0.5 mg) (OR: 0.74; 95% CI: 0.44 to 1.24; $P = .25$).

3.7. Publication bias and sensitivity analysis

In this study, the BCVAs of meta-analysis and the results of CMT were analyzed sensitively by the method of eliminating documents one by one. The results showed that the findings of meta-analysis

before and after exclusion were consistent, indicating that the combined results were stable and reliable. Relatively symmetrical funnel plots showing the distribution indicated there was little potential publication bias, in spite of a trial of small sample size enrolled in this analysis (Fig. 6).

4. Discussion

Cone cells are relatively concentrated in the macula, which is responsible for the most sensitive part of central vision. Long-

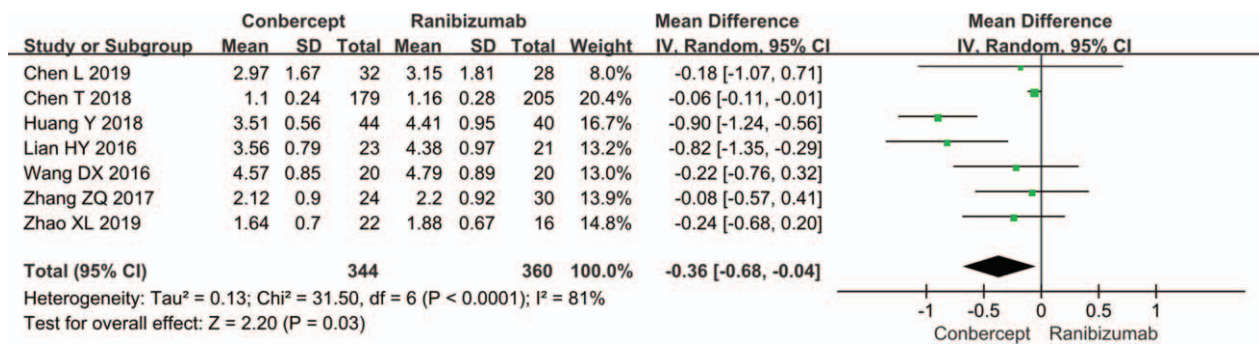


Figure 4. Comparison between conbercept and ranibizumab for the number of injections in patients with retinal vein occlusion macular edema.

term macular edema leads to a large number of apoptosis of cone cells and irreversible damages to visual function.^[38] Occlusive retinal veins result in ischemia and hypoxia at the same time, both of which are the stimuli of the release of VEGF.^[39] Then the destruction of tight junctions between capillaries by the increased level of VEGF increases vascular permeability, promoting fluid exudation and accumulation between the Henle fibers in the outer plexiform layer.^[40] Ranibizumab, a powerful-affinity recombinant segment, has the ability to block all corresponding receptors of VEGF-A, and has been confirmed to be a good choice in the therapy of some neovascular diseases of retina including RVO.^[41] Two large-size studies, BRAVO and HORIZON, respectively, have tested the effectiveness and potential AEs of ranibizumab for the treatment of BRVO-induced ME.^[42,43] Conbercept is now only available in China. It is a novel anti-angiogenic drug with a similar structure to aflibercept, sharing the same Fc segment of human immunoglobulin G(IgG) fused with VEGFR-1 and VEGFR-2. What makes these 2 agents different is that conbercept includes an additional VEGFR-2 binding domain, which possibly increases the association rate of VEGF and extends its periods of half-life in the human vitreous. Conbercept, in the treatment process, also has presented to be well tolerated and displayed its powerful effectiveness in other ME diseases.^[41]

In the present meta-analysis, we have reviewed the literature on treatment of RVO-ME regarding the effectiveness and side effects, which compared ranibizumab and conbercept. The

analyzed results of these trials exhibited that conbercept and ranibizumab were feasible to treat RVO-ME. Furthermore, conbercept and ranibizumab were comparably effective, and both IVR and IVC led to marked visual improvements, demonstrated by the LogMAR, and noticeable reductions of CMT. The regimens to treat ME secondary to RVO mainly consist of 3+pro re nata (PRN) and 1+PRN protocol. Intravitreal injection of either ranibizumab or bevacizumab, through PRN strategies, as the MARVEL study exhibited, has shown to be effective in BCVA improvement and CMT reduction.^[44] Miwa confirmed that 3+PRN and 1+PRN strategies experienced similar visual outcomes at the last time of the follow-up,^[45] which were similar to ours. However, conbercept group experienced fewer injections compared to ranibizumab group. A certain amount of VEGF is necessary to maintain a relatively stable balance of the choroidal and retinal microenvironment. Studies revealed that treatment with anti-VEGF agents could trigger the apoptosis of multiple types of cells in the retina, such as retinal ganglion cells (RGCs), and those within the inner nuclear layer such as amacrine cells as well as bipolar cells.^[46,47] Another study indicated that repeated intravitreal injections may lead to unexpected retinal degeneration and atrophy in the macula, bringing about ultimate visual function impairment.^[48] Therefore, the treatment with PRN strategies reduced the number of injections unnecessary and unfavorable side effects. In addition, a systemic review^[49] also indicated that prolonged high-level exposure to anti-VEGF

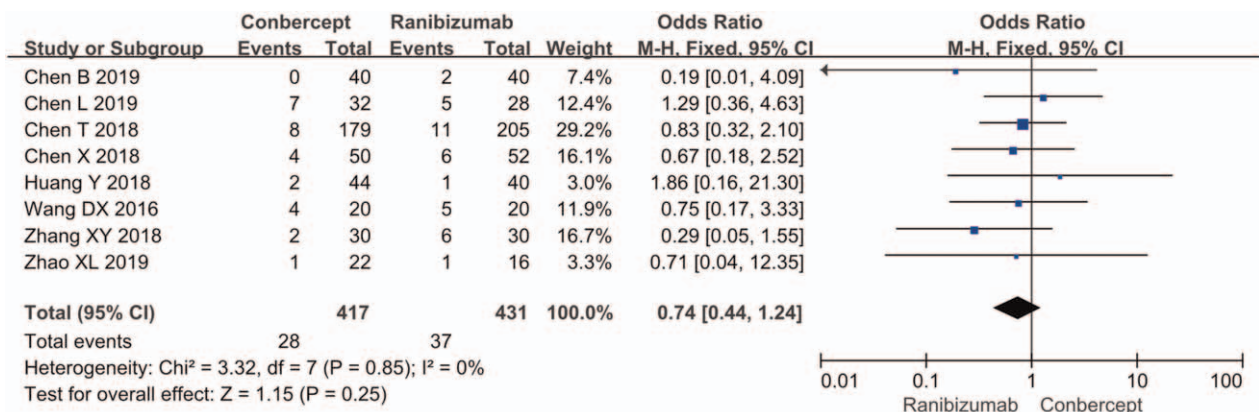


Figure 5. Comparison between conbercept and ranibizumab for the adverse events in patients with retinal vein occlusion macular edema.

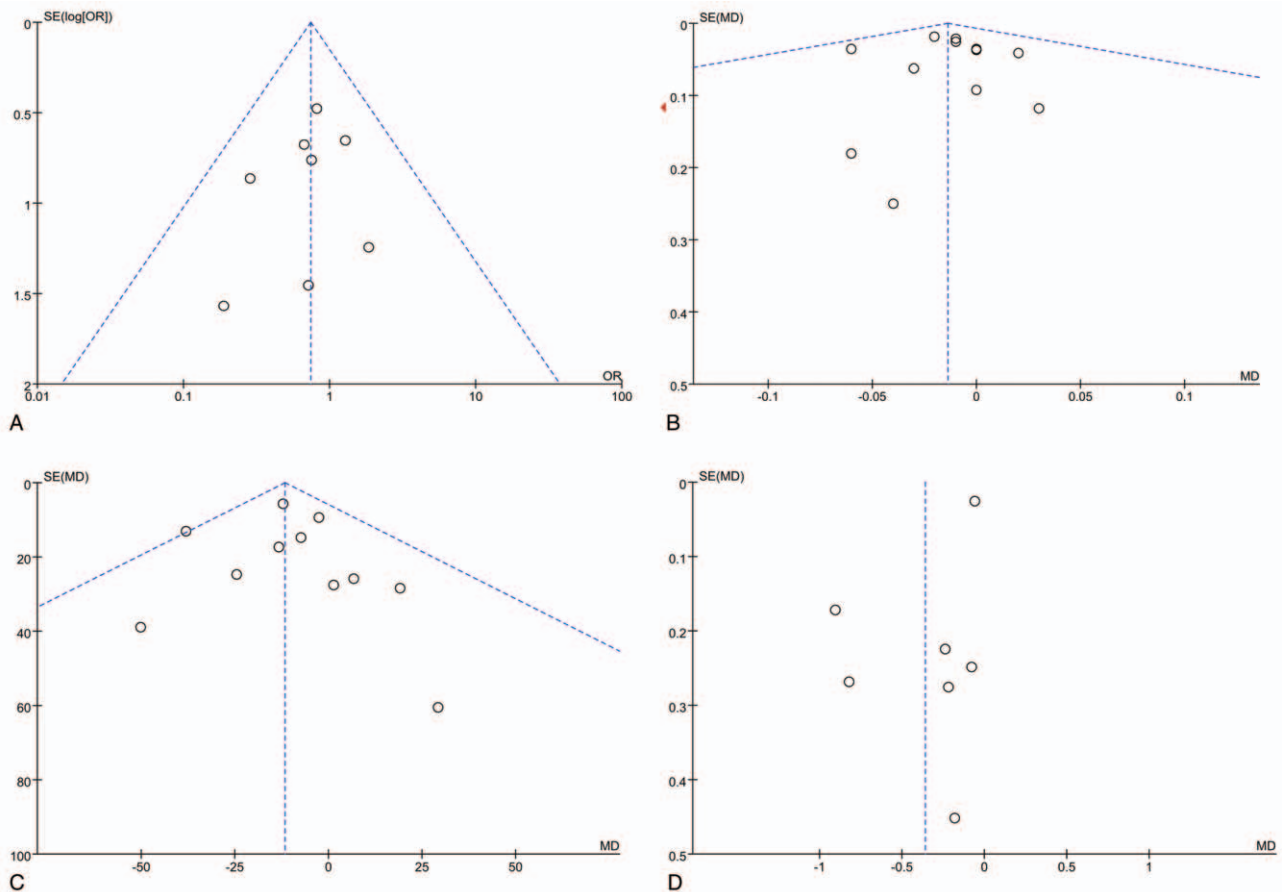


Figure 6. Funnel plots of publication bias: adverse events (A), initial best corrected visual acuity (B), central macular thickness after 1-mo treatment (C), and number of injections (D).

harbored the potential for cerebrovascular accidents and increased risks for death. A latest meta-analysis^[20] showed that 0.5 mg of IVR regimen and 0.3 mg of that had the similar results with regard to BCVA and effectiveness as well as AEs, and that the number of IVC 0.5 mg (larger dose) monthly injection was obviously correlated with the reduction of CMT. Some researchers^[50] are concerned about the serious AEs of arterial thromboembolism with anti-VEGF treatment, but the current meta-analysis suggested that there was no such an adverse event that happened during the follow-up periods within the 2 groups. Our data revealed that intravitreal injection of conbercept or ranibizumab is safe for patients to treat RVO-ME. In an attempt to achieve reliable outcomes, we conducted subgroup analyses according to whether or not adopting laser photocoagulation, the results of which indicated that all subgroups did not substantially change the merged results. The majority of comparisons in the current meta-analysis showed no heterogeneity.

This analysis has numbers of advantages. Firstly, a relatively large sample size has been acquired. Secondly, this current meta-analysis meets rigorous inclusion and exclusion standards. In addition, reviewers have rigorously obeyed the statement of PRISMA and the rules of Cochrane Handbook for Systematic Reviews of Interventions through the whole document retrieval, literature filtration, quality assessment as well as data analysis, which makes the conclusion drawn by us more valid and reliable. Although this current study contains a complete record

of the presently available trials on the effectiveness of IVC and IVR for treating RVO-induced macular edema, we also have to underline some limitations. The first disadvantage of this systematic review and meta-analysis is the enrolled trials with relatively short follow-up periods. Longer follow-up surveys after the first injection would have provided more accurate clinical findings with certainty in treatment recommendations. Another possible shortcoming presented in this study is that the enrolled studies consisted of 2 types of treating regimens, which may bring about heterogeneity, and compromise the final outcomes. However, subgroup analyses in this study have shown that the IVC with or without laser photocoagulation and IVR with or without laser photocoagulation subgroups presented statistically similar outcomes and did not change the pooled outcomes. Moreover, only a few trials revealed the effective rate, and they had different standards to define effective rate, which made it hard to analyze sufficient data for meaningful outcomes. Fourth, we have failed to subgroup-analyze the outcomes according to RVO type, because some trials did not declare the RVO type or combined CRVO and BRVO in 1 study. Another limitation of this study is that the analysis of the number of injections was on the basis of data collected from trials with diverse treating regimens and follow-up periods. At last, we were unable to access the data from unpublished results and unextractable papers, so publication bias cannot be completely excluded.

5. Conclusions

The current pooled evidence suggested that both therapies of intravitreal conbercept and intravitreal ranibizumab with or without laser photocoagulation are effective in improving visual function in RVO-ME patients, and indicated that conbercept shows advantages over ranibizumab in terms of CMT and number of injections for the treatment of RVO-ME. In addition, conbercept has the statistically same visual gains and safety as ranibizumab in RVO-ME patients. More long-term follow-up surveys on the efficacy and side effects of these 2 treatment strategies are required.

Author contributions

Conceptualization: Weishai Liu, Yanjie Li.

Data curation: Rongxia Cao, Zichao Bai.

Formal analysis: Weishai Liu, Weiqin Liu

Software: Rongxia Cao, Zichao Bai.

Supervision: Yanjie Li.

Validation: Yanjie Li.

Writing – original draft: Weishai Liu, Weiqin Liu

Writing – review & editing: Weishai Liu, Yanjie Li

References

- McIntosh RL, Rogers SL, Lim L, et al. Natural history of central retinal vein occlusion: an evidence-based systematic review. *Ophthalmology* 2010;117:1113–23.
- Klein R, Moss SE, Meuer SM, et al. The 15-year cumulative incidence of retinal vein occlusion: the Beaver Dam Eye Study. *Arch Ophthalmol* 2008;126:513–8.
- Group TC. Natural history and clinical management of central retinal vein occlusion. *Arch Ophthalmol* 1997;115:486–91.
- Rogers S, McIntosh RL, Ning C, et al. The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. *Ophthalmology* 2010;117:313–9.
- Liang X, Wei W, Liu , et al. Retinal vein occlusions and mortality: the Beijing Eye Study. *Am J Ophthalmol* 2007;144:972–3.
- Hayreh SS, Zimmerman MB, Podhajsky P. Hematologic abnormalities associated with various types of retinal vein occlusion. *Graefes Arch Clin Exp Ophthalmol* 2002;240:180–96.
- Thorell MR, Goldhardt R. Update in the management of macular edema following retinal vein occlusions. *Curr Ophthalmol Rep* 2016;4:38–47.
- Campochiaro PA, Hafiz G, Shah SM, et al. Ranibizumab for macular edema due to retinal vein occlusions: implication of VEGF as a critical stimulator. *Mol Ther* 2008;16:791–9.
- Noma H, Funatsu H, Harino S, et al. Vitreous inflammatory factors in macular edema with central retinal vein occlusion. *Jpn J Ophthalmol* 2011;55:248–55.
- Boyd SR, Chakravarthy ZI, Allen U, et al. Correlation of increased vascular endothelial growth factor with neovascularization and permeability in ischemic central vein occlusion. *Arch Ophthalmol* 2002;120:1644–50.
- Ferrara N, Damico L, Shams N, et al. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. *Retina (Philadelphia)* 2006;26:859–70.
- Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med* 2015;372:1193–203.
- Jampol LM, Bressler NM, Glassman AR. Revolution to a new standard treatment of diabetic macular edema. *JAMA* 2014;311:2269–70.
- Li X, Xu G, Wang Y, et al. Safety and efficacy of conbercept in neovascular age-related macular degeneration: results from a 12-month randomized phase 2 study: AURORA study. *Ophthalmology* 2014;121:1740–7.
- Zhang M, Zhang J, Yan M, et al. Recombinant anti-vascular endothelial growth factor fusion protein efficiently suppresses choroidal neovascularization in monkeys. *Mol Vis* 2008;14:37–49.
- Qiao G, Dong WJ, Dai Y, et al. Diabetic macular edema in proliferative stage treated with anti-vascular endothelial growth factor agent and triamcinolone acetonide by laser-based strategies. *Int J Ophthalmol* 2017;10:1113–9.
- Zhang M, Zhang J, Yan M, et al. A phase 1 study of KH902, a vascular endothelial growth factor receptor decoy, for exudative age-related macular degeneration. *Ophthalmology* 2011;118:672–8.
- Glanville J, Patterson J, McCool R, et al. Efficacy and safety of widely used treatments for macular oedema secondary to retinal vein occlusion: a systematic review. *BMC Ophthalmol* 2014;14:7.
- Pielen A, Feltgen N, Isserstedt C, et al. Efficacy and safety of intravitreal therapy in macular edema due to branch and central retinal vein occlusion: a systematic review. *PLoS One* 2013;8:e78538.
- Song WT, Xia XB. Ranibizumab for macular edema secondary to retinal vein occlusion: a meta-analysis of dose effects and comparison with no anti-VEGF treatment. *BMC Ophthalmol* 2015;15:31.
- Mitry D, Bunce C, Charteris D. Anti-vascular endothelial growth factor for macular oedema secondary to branch retinal vein occlusion. *Cochrane Database Syst Rev* 2013;31:CD009510.
- Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006–12.
- Chen B. Comparison of the therapeutic effect and safety of anti-VEGF drugs on macular edema secondary to non-ischemic retinal vein occlusion. *Int Eye Sci* 2019;19:426–9.
- Bai S. Efficacy of intravitreal ranibizumab or conbercept combined with laser photocoagulation for macular edema secondary to branch retinal vein occlusion. *Int Eye Sci* 2017;17:648–51.
- Chen T, Yang L. Efficacy of retinal photocoagulation combined with ranibizumab or conbercept in patients with macular edema secondary to retinal vein occlusion. *Int Eye Sci* 2018;18:1594–8.
- Chen X, Jiang YH, Wang FL, et al. Efficacy and safety of conbercept ophthalmic injection and ranibizumab injections in the treatment of CRVO macular edema. *Drug Eval Res* 2018;41:279–82.
- Chen L. Comparison of effects and safety of intravitreal injection of ranibizumab and conbercept for cystoids macular edema secondary to retinal vein occlusion. *Chin J Ophthalmol Otorhinolaryngol* 2019;19:26–30.
- Huang Y, Ye MY, Wu X. Observation on the short-term efficacy of different regimens for macular edema in central retinal vein occlusion. *Pract J Clin Med* 2018;15:118–20.
- Li T, Wang J, Han Y, et al. Comparison of efficacy of conbercept and ranibizumab in the treatment of macular edema secondary to central retinal vein occlusion. *Clin Res* 2017;4:150.
- Lian HY, Ding Q, Chen ZS. Short-term efficacy of conbercept versus ranibizumab for macular edema in central retinal vein occlusion. *Chin J Ocul Fundus Dis* 2016;32:367–71.
- Yan H, Li GL. Efficacy of conbercept versus ranibizumab for macular edema secondary to branch retinal vein occlusion. *J Clin Ophthalmol* 2018;26:5–9.
- Zhang XY, Wu ZX, Yang RB. Comparison of efficacy of Intravitreal injection of conbercept and ranibizumab in the treatment of macular edema secondary to retinal vein occlusion in middle-aged and elderly patients. *Chin J Ger* 2018;38:1414–6.
- Zhao XL, Zhang D, Liao K, et al. Comparative study of conbercept and ranibizumab in the treatment of macular edema secondary to non-ischemic branch retinal vein occlusion. *Chin J Ophthalmol Otorhinolaryngol* 2019;19:39–42.
- Wang DX. Comparative Studies of Conbercept with Ranibizumab for the Treatment of Macular Edema Due to Central Retinal Vein Occlusion. NanChang: NanChang University; 2016.
- Zhang ZQ. The Efficacy of Retinal Photocoagulation Combining with Lucentis or Conbercept on Ischemic-Type Macular Edema Due to Branch Retinal Vein Occlusion. ZunYi: ZunYi Medical College; 2017.
- Li FJ, Guo JL, Ma AH, et al. Comparison of conbercept with ranibizumab for the treatment of macular edema secondary to branch retinal vein occlusion. *Curr Eye Res* 2017;42:1174–8.
- Lin L. Efficacy of Intravitreal Ranibizumab and Conbercept for the Treatment of Macular Edema Secondary to Branch Retinal Vein Occlusion. ShenYang: China Medical University; 2018.
- Garweg JG, Wenzel A. Diabetic maculopathy and retinopathy. Functional and sociomedical significance. *Ophthalmologie* 2010;107:628–35.

- [39] Helmy YM, Atta Allah HR. Optical coherence tomography classification of diabetic cystoid macular edema. *Clin Ophthalmol (Auckland)* 2013;7:1731–7.
- [40] Uji A, Murakami T, Nishijima K, et al. Association between hyper-reflective foci in the outer retina, status of photoreceptor layer, and visual acuity in diabetic macular edema. *Am J Ophthalmol* 2012;153:710–7.
- [41] Huang Z, Ding Q, Yan M, et al. Short-term efficacy of conbercept and ranibizumab for polypoidal choroidal vasculopathy. *Retina (Philadelphia)* 2018;39:889–95.
- [42] Heier JS, Campochiaro PA, Yau L, et al. Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial. *Ophthalmology* 2012;119:802–9.
- [43] Campochiaro PA, Heier JS, Feiner L, et al. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology* 2010;117:1102–12.
- [44] Narayanan R, Panchal B, Das T, et al. A randomised, double-masked, controlled study of the efficacy and safety of intravitreal bevacizumab versus ranibizumab in the treatment of macular oedema due to branch retinal vein occlusion: MARVEL Report No. 1. *Br J Ophthalmol* 2015;99:954–9.
- [45] Miwa Y, Muraoka Y, Osaka R, et al. Ranibizumab for macular edema after branch retinal vein occlusion: one initial injection versus three monthly injections. *Retina (Philadelphia)* 2017;37:702–9.
- [46] Doguizi S, Ozdek SJR. Pigment epithelial tears associated with anti-VEGF therapy: incidence, long-term visual outcome, and relationship with pigment epithelial detachment in age-related macular degeneration. *Retina* 2014;34:1156–62.
- [47] Mantelli F, Lambiasi A, Colafrancesco V, et al. NGF and VEGF effects on retinal ganglion cell fate: new evidence from an animal model of diabetes. *Eur J Ophthalmol* 2014;24:247–53.
- [48] D'Amore PA. Vascular endothelial cell growth factor- α : not just for endothelial cells anymore. *Am J Pathol* 2007;171:14–8.
- [49] Avery RL, Gordon GM. Systemic safety of prolonged monthly anti-vascular endothelial growth factor therapy for diabetic macular edema: a systematic review and meta-analysis. *JAMA Ophthalmol* 2016;134:21–9.
- [50] Tan MH, McAllister IL, Gillies ME, et al. Randomized controlled trial of intravitreal ranibizumab versus standard grid laser for macular edema following branch retinal vein occlusion. *Am J Ophthalmol* 2014;157:237–47.