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ORIGINAL PAPER

Efficacy and safety of intravitreal conbercept and triamcinolone acetonide for wet age-related macular degeneration in China: a meta-analysis

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Abstract

Background Several studies have investigated the efficacy and safety of Conbercept versus Triamcinolone acetonide for the treatment of wet age-related macular degeneration (wAMD), but the results are controversial. Therefore, this meta-analysis aims to evaluate the efficacy and safety of Conbercept versus Triamcinolone acetonide for the treatment of wAMD.

Methods A total of seven databases were searched for literature on the treatment of wAMD with Conbercept, with the search period from database inception to May 2024. Patients in the experimental group received Conbercept treatment, while patients in the control group received Triamcinolone acetonide treatment. The observed indicators included central macular thickness, incidence of adverse reactions, clinical efficacy, and best-corrected visual acuity. Relative risk (RR) and mean difference (MD) were used as effect measures.

Results A total of 12 studies with 864 patients were included in the meta-analysis. The results showed that the experimental group had a significantly better central macular thickness (MD = −42.68, 95% CI = −55.04 ~ −30.32, $P < 0.001$), clinical response rate (RR = 1.25, 95% CI = 1.12 ~ 1.39, $P < 0.001$), and best-corrected visual acuity (MD = 0.16, 95% CI = 0.12 ~ 0.20, $P < 0.001$) compared to the control group. In terms of adverse events, the overall incidence of adverse events was lower in the experimental group (RR = 0.26, 95% CI = 0.14 ~ 0.51, $P < 0.001$) compared to the control group. Specifically, the incidence of intraocular pressure elevation (RR = 0.33, 95% CI = 0.12 ~ 0.94, $P = 0.04$) and intraocular inflammation (RR = 0.17, 95% CI = 0.03 ~ 0.97, $P = 0.05$) was lower in the experimental group compared to the control group, but there was no significant difference in the incidence of subconjunctival hemorrhage (RR = 0.7, 95% CI = 0.14 ~ 3.5, $P = 0.66$) and corneal edema (RR = 0.2, 95% CI = 0.04 ~ 1.12, $P = 0.07$).

Conclusion Conbercept demonstrated superior efficacy in treating wAMD compared to triamcinolone acetonide, with a lower incidence of adverse reactions. However, the current meta-analysis included a limited number of studies, with only two studies evaluating best-corrected visual acuity (BCVA). Further high-quality randomized controlled trials (RCTs) are warranted to validate these findings.

Keywords Wet age-related macular degeneration · Conbercept · Triamcinolone acetonide · Meta-analysis

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10792-024-03346-9.

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Abbreviations

wAMD	Wet age-related macular degeneration
RR	Relative risk
MD	Mean difference
RCTs	Randomized controlled trials
I^2	Percentage of variation
VEGF	Vascular endothelial growth factor
PDT	Photodynamic therapy
NMPA	National Medical Products Administration
RoB	Risk of bias
CI	Confidence intervals
FFA	Fundus fluorescein angiography

Introduction

Due to the global aging population, the prevalence of age-related macular degeneration (AMD) is increasing worldwide and has become a leading cause of irreversible blindness in older adults [1]. Studies have shown that there are racial disparities in AMD prevalence, with Europeans and Asians having higher rates than other races [2, 3]. In the United States, AMD affects over 8 million people, with 1.75 million in the late stage [4]. The prevalence of AMD in China is also high, and it is estimated that the number of AMD patients in China will increase to 55.19 million by 2050 [5]. Dry age-related macular degeneration (dAMD) and wet age-related macular degeneration (wAMD) are the two primary forms of age-related macular degeneration (AMD) [6, 7]. Among patients with AMD, although the proportion of those with dAMD is higher, patients with wAMD are more likely to experience severe vision loss. Approximately 90% of AMD patients with severe vision loss suffer from wAMD [8].Currently, there is no effective treatment for dry AMD, while wAMD can be treated with anti Vascular endothelial growth factor (VEGF) drugs or photodynamic therapy (PDT) [9, 10].

Due to the limitations of intravitreal photodynamic therapy (PDT), such as high treatment cost and high recurrence rate, anti-VEGF drugs have become the first-line treatment for wAMD. Conbercept, a new-generation anti-VEGF drug, can bind to multiple VEGF subtypes, including VEGF-A and VEGF-B, competitively inhibit the binding of VEGF to its receptors, and block the activation of the VEGF family of receptors, thereby inhibiting neovascularization and reducing vascular permeability [11]. This can reduce subretinal hemorrhage and exudation, alleviate retinal edema, improve macular pathology, and ultimately improve patient vision [12]. Conbercept was approved by the National Medical Products Administration (NMPA) of China for the clinical treatment of wAMD in 2013 [13]. Compared to other anti-VEGF agents, Conbercept incorporates multiple structural domains of the VEGF receptor, particularly the fourth extracellular domain of VEGFR-2. The addition of this structure significantly enhances Conbercept's ability to bind to VEGF, with an affinity for VEGF that is 100 times greater than that of the monomer form [14]. Other anti-VEGF drugs, such as Ranibizumab and Bevacizumab, primarily rely on the binding to a single target. Conbercept inhibits the formation of new blood vessels by binding to VEGF and preventing it from binding to its receptors. In contrast, drugs like Aflibercept, while also inhibiting VEGF, have different targets and binding mechanisms, which may lead to varying therapeutic effects and side effects [15]. Triamcinolone acetonide is a long-acting corticosteroid that can inhibit the formation of new blood vessels and is effective in reducing inflammation in patients with exudative AMD [16]. It was one of the first and most widely used corticosteroids for intravitreal injection and remains a primary alternative when patients do not respond well to anti-VEGF drugs [17, 18].

Current research on the use of Conbercept versus Triamcinolone acetonide for the treatment of wAMD has yielded conflicting results. Therefore, this meta-analysis aims to evaluate the efficacy and safety of Conbercept compared to Triamcinolone acetonide for the treatment of wAMD and provide evidence-based medicine for clinical treatment. To provide a comprehensive understanding of the study's scope, we clarify the hierarchy of outcomes. The primary outcomes, which are central to our investigation, include central macular thickness and the incidence of adverse events. These measures are critical for evaluating the immediate impact and safety profile of the treatments under comparison. Additionally, we have identified secondary outcomes that provide a deeper insight into the treatments' long-term efficacy and visual improvement. These include clinical efficacy, assessed through fundus fluorescein angiography, and best-corrected visual acuity, which are pivotal for understanding the broader implications of our treatment approaches on patients' quality of life.

Methods

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19].

Inclusion and exclusion criteria

Inclusion criteria

(1) Participants: Patients diagnosed with wAMD based on ophthalmic examination; Age 60 years or older; Excluded patients with glaucoma, cataract, retinal detachment, cognitive impairment, or prior ocular treatment. (2) Interventions: Conbercept, without restriction on type, dose, duration, or route of administration. (3) Comparison: Triamcinolone acetonide. (4) Outcomes: The primary outcomes were central macular thickness and the incidence of adverse events; the secondary outcomes were clinical efficacy and best-corrected visual acuity. (5) Study design: Randomized controlled trials (RCTs).

Exclusion criteria

(1) Non-RCTs, including review articles, case reports, conference abstracts, and other non-controlled studies; (2) Studies that combined Conbercept or Triamcinolone acetonide with other medications in either the treatment or control arm; (3) Exclude diabetic retinopathy, retinal vein occlusion patients and patients with combined retinal pathology; (4) Studies with incomplete or uninterpretable data; (5) Duplicate publications; (6) Studies with low methodological quality.

Search strategy

A comprehensive literature search was conducted across the Cochrane Library, PubMed, Embase, Chinese Biology Medicine disc, China National Knowledge Infrastructure, Wanfang Data, and the China Science and Technology Journal Database (VIP). To ensure a comprehensive and accurate search, we utilized Medical Subject Headings (MeSH) with free words to retrieve the literature. The search strategy was refined to include the following MeSH terms and their associated subheadings: "Macular Degeneration" [MeSH], "Age-Related Macular Degeneration", "Conbercept", "anti-vascular endothelial growth factor", and "triamcinolone acetonide" [MeSH]. The search strategy employed the following Boolean terms: (("Macular Degeneration"[Mesh]) OR "Age-Related Macular Degeneration") AND ("Conbercept" OR ("Conbercept" AND "anti-vascular endothelial growth factor") AND (("Triamcinolone Acetonide"[Mesh]) OR ("triamcinolone acetonide" AND "anti-vascular endothelial growth factor"). The search encompassed all publications from the inception of each database up to May 2024. Each database was searched independently by two researchers (F. Y. and R. H.), followed by cross-verification to ensure the accuracy and completeness of the retrieved literature. No language restrictions were applied.

Study selection and data extraction

Data were independently extracted by two researchers and then cross-checked (F. Y. and R. H.). Any discrepancies were resolved through discussion. The following data were extracted: first author, year of publication, country, study design, sample size, patient age, treatment interventions for the experimental and control groups, treatment duration, follow-up duration, and outcome indicators.

Assessment of risk of bias in included studies

Two independent reviewers (F. Y. and R. H.) assessed the risk of bias (RoB) using the Cochrane Collaboration's RoB tool in seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Each item was rated as "low risk", "high risk", or "unclear risk".

Data synthesis and analysis

Review Manager 5.4 software was used for data analysis. Relative risk (RR) and 95% confidence intervals (CI) were selected to evaluate dichotomous variables, and mean difference (MD) and 95%CI for continuous variables. We assessed heterogeneity using the percentage of variation (I^2) test [20]. This statistic represents the percentage of variation across studies due to heterogeneity rather than chance. Heterogeneity was considered low if $P > 0.05$ and $I^2 < 50\%$, and thus a

fixed-effects model was used; otherwise, a random-effects model was employed. The funnel plot was created for assessing publication bias. Besides, the sensitivity analyses were performed using Stata 17.0 software.

Clinical efficacy was assessed based on fundus fluorescein angiography (FFA) images and categorized into three groups: marked response (complete disappearance or reduction of macular leakage and obscuring fluorescence by > 50%), response (reduction of macular leakage and obscuring fluorescence by 10–50%), and no response (reduction of macular leakage and obscuring fluorescence by < 10% or no significant change). Clinical efficacy was calculated using the following formula: (marked response + response) / total number of cases × 100%.

Results

Results of literature retrieval

The PRISMA flowchart for this meta-analysis is shown in Fig. 1. According to the search strategy, 220 studies were initially retrieved. After applying the exclusion criteria, 12 studies [21–32] were finally retained for inclusion in this meta-analysis.

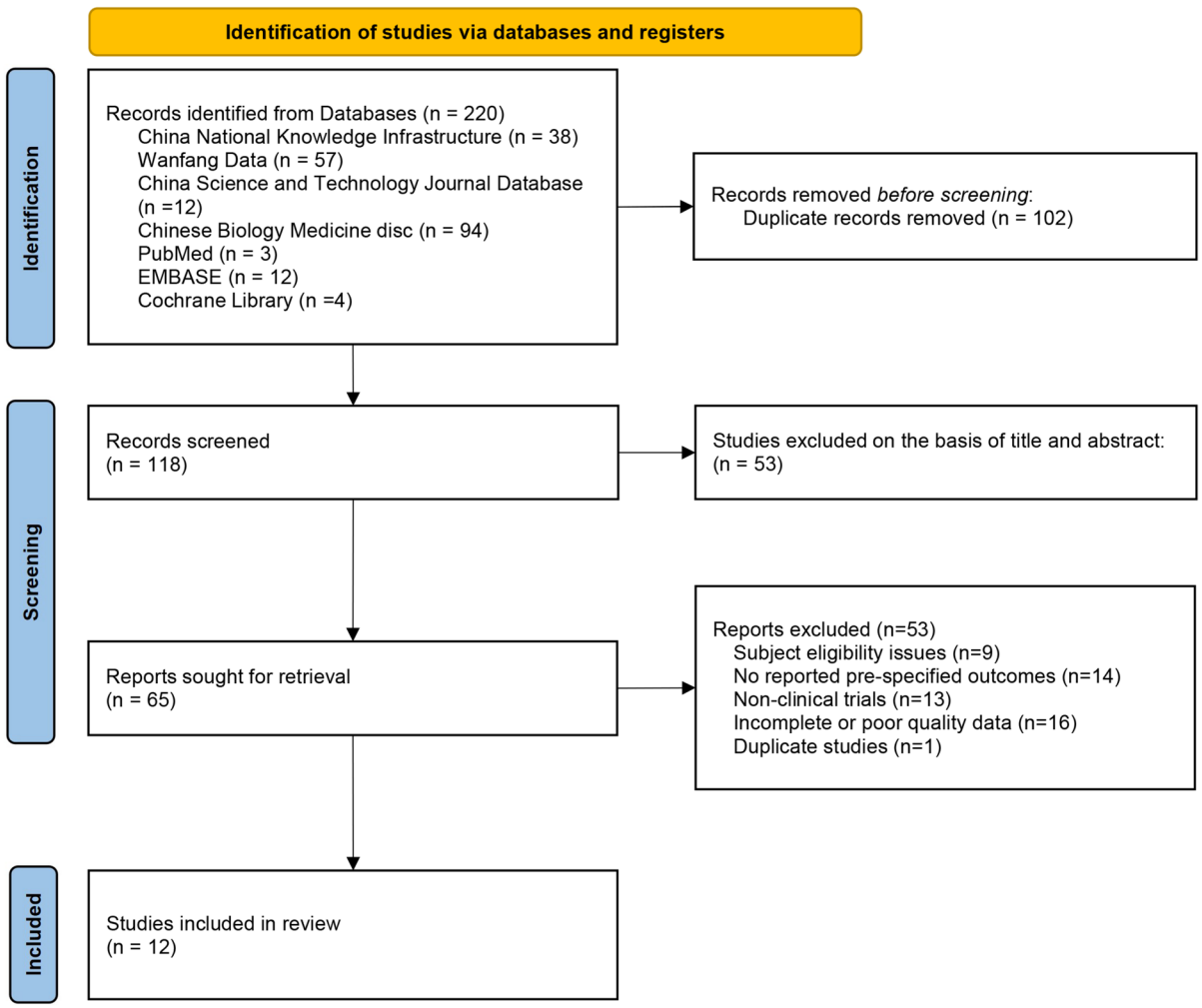


Fig. 1 Flow chart of literature screening

General characteristics of included studies

The baseline characteristics of the included studies are summarized in Table 1. In the Supplementary information, we provide the links, DOIs, and English titles of the studies included (as shown in Table 2). All 12 included studies [21–32] were RCTs conducted by investigators after the approval of conbercept. The earliest study was published in 2016 [22] and the most recent in 2022 [28]. A total of 864 patients were included, with 433 patients in the observation group and 431 patients in the control group.

Methodological quality evaluation

The results of the methodological quality assessment are shown in Fig. 2. In terms of selection bias, seven studies [23, 25–30] used a "random number table", while the remaining studies did not describe the specific method of random sequence generation. With regard to selection bias and performance bias, one study [25] was a double-blind trial, while patients in the other studies either signed an informed consent form or the consent process was not clearly described. For attrition bias and reporting bias, all outcome data were complete and were rated as "low risk". There was no other bias in any of the studies.

Primary outcomes

Central macular thickness

A total of five studies [21, 23, 24, 29, 31] reported central macular thickness after 6 months of treatment. Heterogeneity analysis ($P=0.54$, $I^2=0\%$) indicated no significant heterogeneity between studies, and a fixed-effects model was used to combine the effect sizes. A total of 357 patients were included, with 179 in the experimental group and 178 in the control group. At 6 months after treatment, the central macular thickness of patients in the experimental group was significantly lower than that of the control group (MD = −42.68, 95% CI = −55.04 ~ −30.32, $P<0.001$), as shown in Fig. 3.

To assess publication bias for central macular thickness, a funnel plot was generated. The asymmetry of the funnel plot suggests the presence of publication bias in this meta-analysis, as shown in Fig. 4.

Adverse events

This meta-analysis evaluated the incidence of adverse events after 6 months of treatment. Pooled data from these studies showed that the overall incidence of adverse events in the experimental group (Fig. 5A) was significantly lower than in the control group (RR = 0.26, 95% CI = 0.14 ~ 0.51, $P<0.001$). Specifically, the incidence of intraocular pressure elevation (Fig. 5B) (RR = 0.33, 95% CI = 0.12 ~ 0.94, $P=0.04$) and intraocular inflammation (Fig. 5C) (RR = 0.17, 95% CI = 0.03 ~ 0.97, $P=0.05$) was significantly lower in the experimental group than in the control group. However, there was no significant difference in the incidence of subconjunctival hemorrhage (Fig. 5D) (RR = 0.7, 95% CI = 0.14 ~ 3.5, $P=0.66$) and corneal edema (Fig. 5E) (RR = 0.2, 95% CI = 0.04 ~ 1.12, $P=0.07$) between the two groups.

Secondary outcomes

Clinical response rate

A total of three studies [22, 28, 30] reported clinical efficacy at 3 months of treatment. A total of 256 patients were included (128 in the experimental group and 128 in the control group). Heterogeneity analysis ($P=0.89$, $I^2=0\%$) showed low heterogeneity between studies, and a fixed-effect model was used to combine effect sizes. The results showed that the overall efficacy rate in the experimental group was significantly higher than that in the control group (RR = 1.25, 95% CI = 1.12 ~ 1.39, $P<0.001$), as shown in Fig. 6A.

Best-corrected visual acuity

Two studies [21, 31] reported the best-corrected visual acuity (BCVA) at 6 months of treatment. A total of 147 patients were included (74 in the experimental group and 73 in the control group). Heterogeneity analysis ($P=0.60$, $I^2=0\%$) showed low heterogeneity between the studies, and a fixed-effect model was used to combine the effect sizes. The results showed that the best-corrected visual acuity in the experimental group was significantly higher than that in

Table 1 Basic characteristics of the included studies

Study	Year	Country	Study type	No. of patients	Age(M ± SD) (years)	Treatments		Treatment duration	Follow-up time	Outcomes	Baseline results before treatment
				E/C	E/C	E	C				
Chen [21]	2018	China	RCT	36/36	70.5 ± 3.5 / 69.5 ± 3.5	Conbercept 0.05 ml	triamcinolone acetonide 0.05ml	6 months	6 months	①④	①: E, (384.69 ± 81.23) μm; C, (379.46 ± 90.27) μm ④: E, 0.16 ± 0.13; C, 0.17 ± 0.12
Dong et al. [22]	2016	China	RCT	37/37	66.3 ± 0.7 / 66.8 ± 0.5	Conbercept 0.05 ml	triamcinolone acetonide 0.1ml	3 months	3 months	②③④	①: E: (392.78 ± 107.21) μm; C: (391.65 ± 109.41) μm ④: E, 0.10 ± 0.01; C, 0.12 ± 0.08
Hong [23]	2017	China	RCT	37/37	68.5 ± 14.7 / 67.7 ± 14.4	Conbercept 0.1 ml	triamcinolone acetonide 0.1ml	NA	6 months	①	①: E, (392.17 ± 151.16) μm; C, (389.56 ± 146.28) μm ④: E, < 0.5; C, < 0.5
Hou et al. [24]	2018	China	RCT	60/60	64.58 ± 3.19 / 65.15 ± 2.37	Conbercept 0.1 ml	triamcinolone acetonide 0.1ml	6 months	6 months	①	①: E, (394.26 ± 54.34) μm; C, (387.71 ± 55.12) μm ④: E, < 0.5; C, < 0.5
Jiao et al. [25]	2018	China	RCT	30/29	73.60 ± 5.29 / 72.59 ± 5.30	Conbercept 0.1 ml	triamcinolone acetonide 0.1ml	3 months	3 months	②	①: E, (384.59 ± 60.47) μm; C, (385.30 ± 328.82) μm ④: E, 0.21 ± 0.001; C, 0.19 ± 0.006

Table 1 (continued)

Study	Year	Country	Study type	No. of patients	Age(M ± SD) (years)	Treatments		Treatment duration	Follow-up time	Outcomes	Baseline results before treatment
				E/C	E/C	E	C				
Jin et al. [26]	2020	China	RCT	43/43	71.59 ± 5.29 / 72.60 ± 5.19	Conbercept 0.1 ml	triamcinolone acetonide 0.1ml	3 months	3 months	②	①: E, (383.49 ± 60.37) μm; C, (384.32 ± 58.49) μm ④: E, 0.22 ± 0.01; C, 0.21 ± 0.06
Luo et al. [27]	2020	China	RCT	49/49	68.74 ± 4.52 / 68.36 ± 4.47	Conbercept 0.05 ml	triamcinolone acetonide 0.05ml	NA	3 months	②④	①: E, ≥ 300 μm; C, ≥ 300 μm; ④: E, < 0.5; C, < 0.5
Pan et al. [28]	2017	China	RCT	38/38	71.62 ± 5.27 / 71.59 ± 5.11	Conbercept 0.1 ml	triamcinolone acetonide 0.1ml	NA	6 months	①	①: E, (395.62 ± 55.43) μm; C, (389.27 ± 56.39) μm ④: E, < 0.5; C, < 0.5
Pan [29]	2022	China	RCT	43/43	61.59 ± 4.21 / 61.25 ± 4.15	Conbercept 0.1 ml	triamcinolone acetonide 0.1ml	3 months	3 months	③	①: E, ≥ 300 μm; C, ≥ 300 μm; ④: E, < 0.5; C, < 0.5
Pin [30]	2019	China	RCT	40/40	64.13 ± 10.9 / 63.1 ± 11.4	Conbercept 0.05 ml	triamcinolone acetonide 0.1ml	3 months	3 months	③④	①: E, ≥ 300 μm; C, ≥ 300 μm; ④: E, 0.21 ± 0.03; C, 0.22 ± 0.04
Zhang et al. [31]	2018	China	RCT	38/37	63.6 ± 6.7 / 64.2 ± 5.4	Conbercept 0.05 ml	triamcinolone acetonide 0.5ml	NA	6 months	①②④	①: E, (362.4 ± 76.1) μm; C, (356.5 ± 69.4) μm ④: E, < 0.5; C, < 0.5
Zhu et al. [32]	2017	China	RCT	25/25	66.82 ± 3.41 / 66.82 ± 3.41	Conbercept 0.1 ml	triamcinolone acetonide 0.1ml	NA	3 months	②④	①: ①: E, (4 22士 103.2) μm; C, (4 23士103.1) μm ④: E, < 0.5; C, < 0.5

E: Experimental group; C: Comparison group; RCT, randomized controlled trial; M:mean; SD: standard deviation; ①: Central Macular Thickness; ②: adverse events; ③: The total effective rate; ④: bestcorrected visual acuity

Table 2 Links to access to included studies

Study	Link	DOI	Title in english
Chen [21]	https://kns.cnki.net/kcms2/article/abstract?v=JgtjNxUAsgfu6W53jsLqDiEmdVDCa33wc1U_fx7ziM_UDh796rmgpSYwZnSclDoW_LGhdZKCeXrcAVuCD0fygkVAVQYT_WfgBbnzzTVux7YD8AS6EIutZz0xLOGHqyJwt9gvEDDmcr5iDRFKSi760o4YF8K1_ZEunx7dV98qsBZ815fx3SYZsHmMalorQNYMM_xWyQbjS6Iuw5vxgQvukQPw6KofY3tl1_Wnbpj1qKM=&uniplatform=NZKPT&language=CHS	10.14163/j.cnki.11–5547/r.2018.33.091	NA
Dong et al. [22]	https://kns.cnki.net/kcms2/article/abstract?v=JgtjNxUAsgeS1D2ASoU5IxqTer6MAS9yOPx8J-inhLPO0RqJ4qMDSRXvNAPuf-FOTeddsb0gvbn8k3NRHunBlyXXyNdDbGsuw3uDRV-cwYezgU4MfcmBNd-nf6h5ZLDwzlG6e-ZjNclXlf4iUh-LjjF5R8hexkuHchtHSe3w9Sn8ycxfT0BPzatEIqfcI1vO3bt8hmRHca7U9lpgIXq23IbgowezWglM&uniplatform=NZKPT&language=CHS	10.7501/j.issn.1674–5515.2016.03.021	NA
Hong [23]	https://kns.cnki.net/kcms2/article/abstract?v=JgtjNxUAsgfPgfJu1TUCyQafA86qVNUbcQBLvJZ66skEqZGMCUA71KTFpkjuEkynwmS5i2SnqbeG0aZ61zum5JLA40Aa-zlR3Nn7vbrlxYCLubcICkZ8JYMB_Xeyw3EDC-0daApB7UZGukiSDuRo58j18zl7zJWzvRBx1bjRJ4_RaHX5QdpPzjDiE8_VpfTJl2itDe2ClZ9xHt7F99R_GfLsTpHmqMoq&uniplatform=NZKPT&language=CHS	10.3969/j.issn.1009–4393.2017.19.031	NA
Hou et al. [24]	https://kns.cnki.net/kcms2/article/abstract?v=JgtjNxUAsgd7KmyzeJGuaPRdfbyoKP82WU_-7i4HZlz6w-s-uHcRcOcP7xP3VSuqDKDmtIzrQOoffsf19_5duyFTOnEGMJwtWGUGyYTti4XYlePTE3UFoLHtUY8NyO7-BcdDYvtLKBsh-22j71Jl7lm0ilujon__Hkmmqe3PQyT41qpjATeP1HJ3V5Cxlh4eO4bLfJuX9YwYpMTt78jDzLOaO_92cKTurgnIVkPfDM7k8N-UrsvX29nR80kOkxN208coIVVTzPe02vtaWSHTAI268-WDNUOowxdblqYGYVlyevZFE4bwr0B7yeSQrdHC9g7x3l0ouck3jC3C2XddaKjKX5IdBVVPGmWQ6XpiiLJXcwJ-1j8u1w==&uniplatform=NZKPT&language=CHS	NA	Clinical analysis of the Effect of Intravitreal Injection of Compactopril in the Treatment of Wettable Age

Table 2 (continued)

Study	Link	DOI	Title in english
Jiao et al. [25]	https://kns.cnki.net/kcms2/article/abstract?v=JgtjNxUAsgcJ7kUVYiwgaz45VQ61geBphHxh0LBvhehvydCF_oPlEMmsCpZpBfEFKoipzMNOzBtH0thZLhERGWD6i_IM3pdzNf_5a4w5BtTSEk05TxWdH9MbE0FVxSZrcrwfRMRPh0SbeHtfht31lFeuKb2QfHl3m689aZ89Dl88v6WLf26oVaBL70Gvisbhz-1KLygZZB-tKwYYU_CQ4oe0eomuSaaN8L_RMqqA2LsV_Lp3PWRU3MWikCHh4aB6ryPd_lAGWH4DBxorBoFpqiq6seVNOLcqYwHSHL9QsSGZOySJaxXoLdIfcvaPQzeACAAnFmBnYod6KvOXOsYw8B5gC2tqnWbgEHpT8fOPHYnYRq5UBLPMohUjhreMGXym7XLd9pMJ54cONORKhCahxEDfaNfcVWCj6AHFhM-_29paYHiN_6vcTw==&uniplatform=NZKPT&language=CHS	10.13493/j.issn.1672–7878.2018.03–018	NA
Jin et al. [26]	https://kns.cnki.net/kcms2/article/abstract?v=JgtjNxUAsgfyT0-mY95Q4ClEr1-medcCioPIFnUK55GZ7vw0AWVyD0Bz7EWeEUVEgKDoieStT_ac-KV0-g4nGMZQqORObYX3vApweywpZOaOt3wTTHs3HkHlz3XTAmC2TYYE2G-ogYdv_xugkx9QU-nJGMdhgfdhXbqVLZeh8_4waq7LehoHYKch-cMOn3QW6GvmtswG7gV0UGoe12DkALUb8YGF_XRMPTTXPb9vhJIeSZXuUBDK_hXz9hNrmJQIurZ7ITAH2s_9Z7SEZGegJnsU9yDKfkt0_LVif422pIsHWB5AJuz883mfM4vnFx5JykP6qiKFcNhlCi6vTrgeDcpGJpdGbZfaHTSVlkm2s767dTOPvaORFtybgkMRuD4qRKwubkwXCu-7sUBai-CZqvSg21v2iUcWIlrK9jGtNiwjKCdNryN9yQ==&uniplatform=NZKPT&language=CHS	10.3969/j.issn.1674–9316.2020.01.027	The Effect of Vitreous Cavity Injection of Compexip on ElderlyPatients With Wet Macular Degeneration
Luo et al. [27]	https://kns.cnki.net/kcms2/article/abstract?v=xpM8-w1VMS_srzsI4L3glUnX1I_GnsomjVEMg3AciQ5WecFPRvzLhofPIoINgl9-y92ODH5vd34u_K7WV_aBL0xKW_2D1hkjp31SRLhP25Nd7-G2IGJl2Vok-QQ1pehF7pbt2lHQ-8A_VFJ8gdfcE5bkNizkcXM2dvelZ5Pmtp9anpGxsk09AQH1n00CWkM0&uniplatform=NZKPT&language=CHS	10.3969/j.issn.1004-437X.2020.18.048	NA
Pan et al. [28]	https://d.wanfangdata.com.cn/periodical/ChlQZXJpb2RpY2FsQ0hJTmV3UzIwMjQwNzA0Eg96Z2x5eXgyMDE3MDIwNDUaCHB0NGJkNndv	10.13517/j.cnki.ccm.2017.02.044	NA

Table 2 (continued)

Study	Link	DOI	Title in english
Pan [29]	https://kns.cnki.net/kcms2/article/abstract?v=xpM8-w1VMS_Q4BJS1pFaOnL7KV4xuenK-Bqcn3JVBOHwhN7BLpJCyqil-oC3tDWzF_1y-yz9oy5us9ADeG197OMANVYOLm1bepYeAEKbl9vfxv3zounmZ4ieiH3A4nbuv9VFcJ8IRYwuSFWvb8vnIhgLdGq9WxLctRAERNUyH8I_xbwq44iAWc03WKB4Uidw&uniplatform=NZKPT&language=CHS	10.19528/j.issn.1003–3548.2022.07.041	NA
Pin [30]	https://kns.cnki.net/kcms2/article/abstract?v=xpM8-w1VMS_WFtFCfCE2FBO4iTb3stY_WUXPoM0YK7e5YhkBtgXnHfnQZliBUUVfwUkYmTYP_BDFnFLIO9N19_tUlP0BrlQdBxp18SdCmkVRTS8W5Y8D3IPeyB5o0wrrAUoFF9Jn_qTrxT6q45PFT55IRSlwj64FveAodqXTXQYEECFm3IyQQeUWiwQgfIV5&uniplatform=NZKPT&language=CHS	10.3969/j.issn.1004–4337.2019.07.050	NA
Zhang et al. [31]	https://kns.cnki.net/kcms2/article/abstract?v=xpM8-w1VMS9A4yITqZtKOlXw_dRyk_WFIeMsVTpJTf28oCbjADvRJnX398nRJavdI4HkAM_e2pJjn9Voi2gYW36dJYqwnng63CY6OAuinAp_DkwBi32N6WcfDup-tsrLVmWwVA3NkBvF4Xh-ec6_Dd3DKN9IlEjghxJ7bwDAKYrDO4qzN4GTNPN78IofowXW&uniplatform=NZKPT&language=CHS	10.7501/j.issn.1674–6376.2018.09.028	Changes of VEGF and PEDF concentrations in aqueous humor before and after intravitreal injection of Conbercept in patients with eAMD
Zhu et al. [32]	https://kns.cnki.net/kcms2/article/abstract?v=xpM8-w1VMS8eVeYDWB3mgPjVVj3eE60YBJ6aDGxPF_SBRPww23PYFJhDArVAeAcqxHY6ofXN93nutYjN45B-741Mhy2On20am2MvovjVen4k3cSudHmt4c1YRQL5za6_Knv9T0gyWX-b8YmhAsKQwh9FSqoqQ_Fk46p0CF9_scFLkJMlNfr_QshkDVZiGrcySd3fpQFqqAOzObrhH8PeyNl-SRSjZZpe94jbEAjGVJbDxoTVerFqebg8Fl2zefEgVRWHJVqc3-c=&uniplatform=NZKPT&language=CHS	10.3969/j.issn.1000–7377.2017.02.053	NA

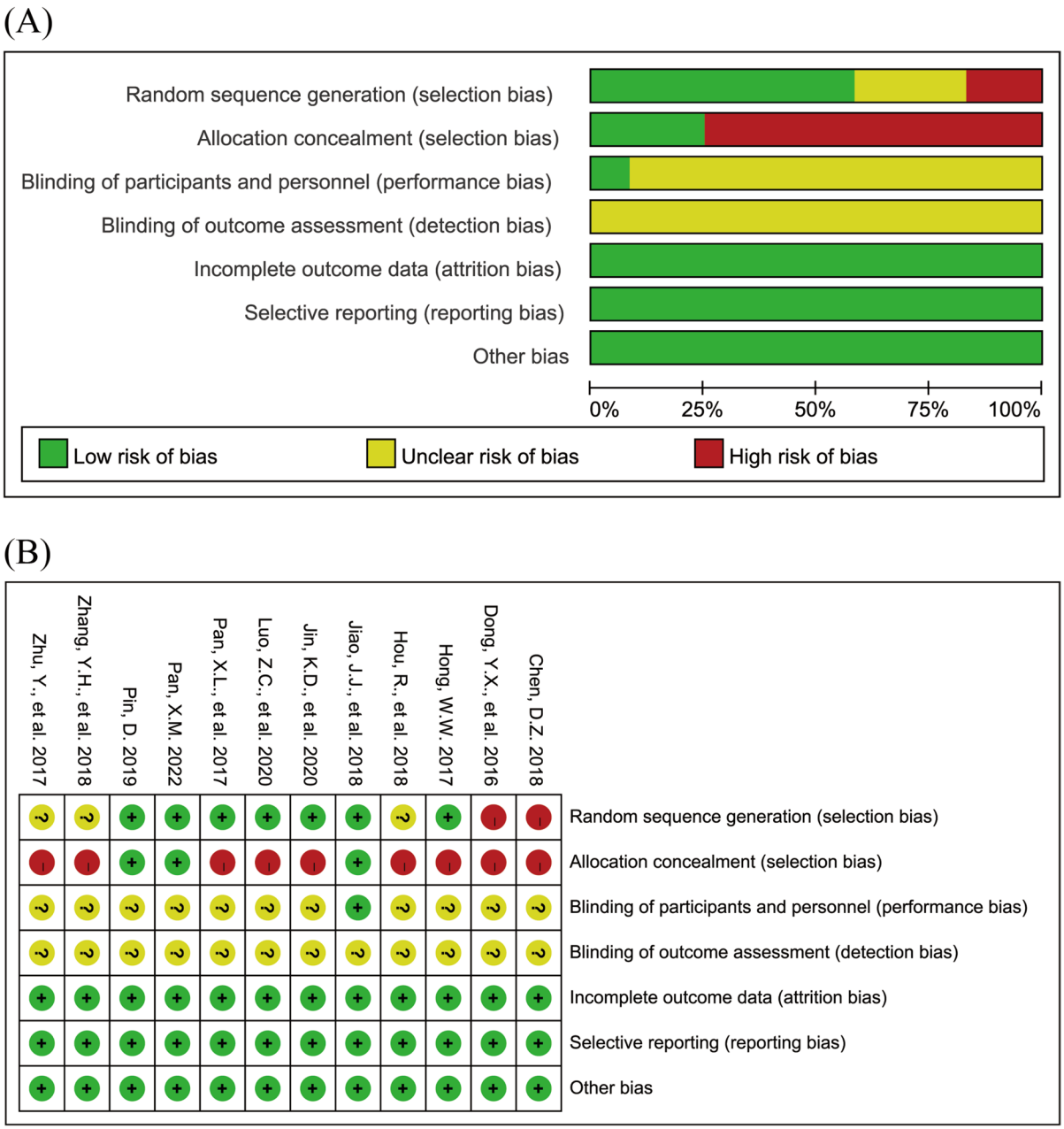


Fig. 2 Quality assessment of included studies (**A**: Risk of bias graph; **B**: Risk of bias summary)

the control group (MD = 0.16, 95% CI = 0.12 ~ 0.20, $P < 0.001$), as shown in Fig. 6B.

Sensitivity analysis

Sensitivity analyses were performed for Central Macular Thickness to test whether these results were stable. No significant changes in the pooled results were identified after removing the studies one by one, indicating that the conclusions of this meta-analysis had good stability, as shown in Fig. 7.

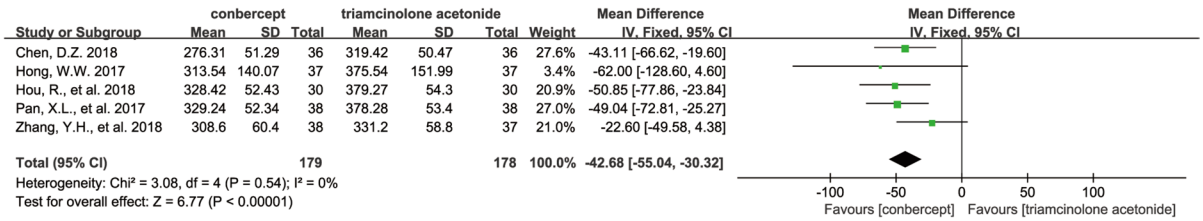


Fig. 3 Forest plots of central macular thickness

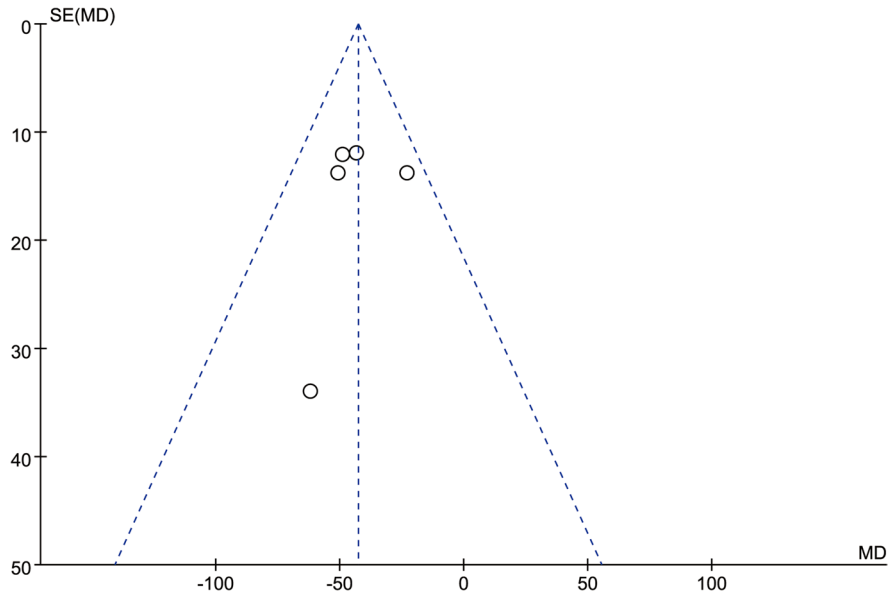


Fig. 4 Funnel plots of central macular thickness

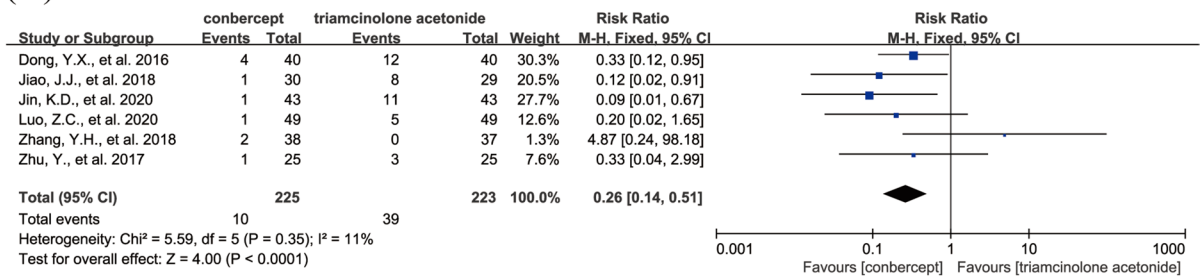
Discussions

This meta-analysis evaluated the efficacy of conbercept for wAMD. Compared with the control group, conbercept treatment for wAMD demonstrated a significant advantage in efficacy and a lower incidence of adverse events, with a significant impact on patients with wAMD.

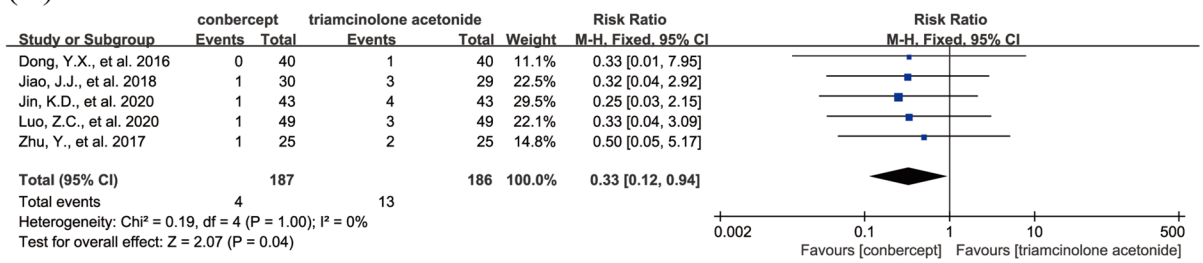
The mechanism of action of Conbercept may explain its efficacy in the treatment of wAMD. The main pathological feature of wAMD is the growth of choroidal neovascularization, which can lead to retinal exudation, hemorrhage, and fibrosis, resulting in progressive vision loss [33]. VEGF plays an important role in this process and is a major inducer of angiogenesis [34, 35]. Conbercept is a fusion protein of VEGF receptor and human immunoglobulin Fc fragment [36]. It binds to VEGF and competitively inhibits the binding of VEGF to its receptor, blocking the activation of the VEGF family of receptors and thus inhibiting endothelial cell proliferation and angiogenesis [37, 38]. This mechanism of action can effectively control the growth of neovascularization and slow down or stop vision loss caused by wAMD.

In terms of the results of data analysis, Conbercept effectively reduced the central subfoveal macular thickness in patients. Several theories can explain the observed findings. Firstly, Conbercept inhibits the growth of new vessels and reduces retinal edema caused by new vessel leakage by binding to VEGF and preventing it from binding to its receptor. With the inhibition of new vessels and the reduction of vascular leakage, the retinal structure is improved and the central subfoveal macular thickness is reduced. Secondly, Conbercept also has anti-inflammatory effects, which can reduce the inflammatory response associated with AMD, improve the microenvironment of the retina, and promote the absorption of

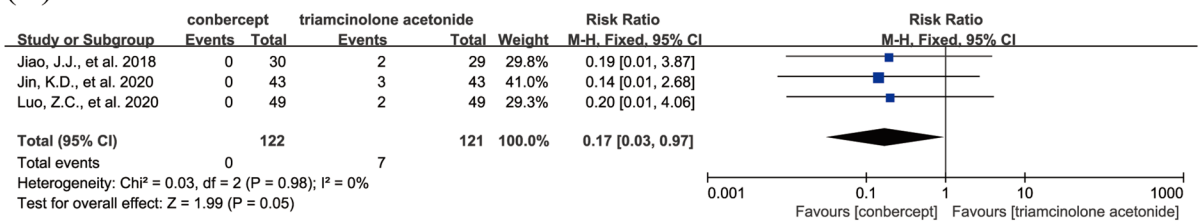
(A)



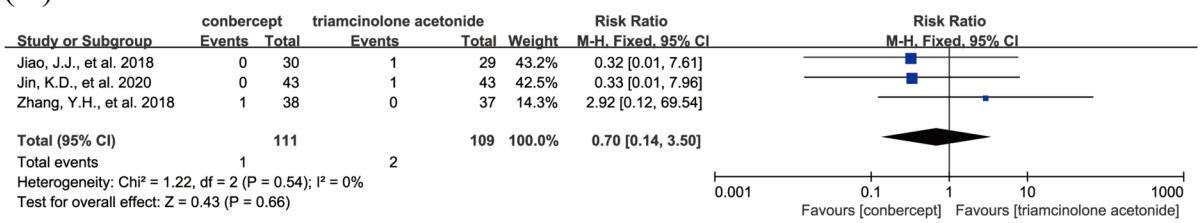
(B)



(C)



(D)



(E)

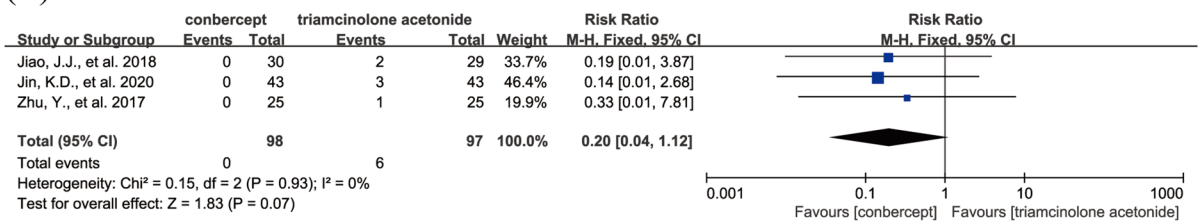


Fig. 5 Forest plots of **A** overall incidence of adverse events, **B** intraocular pressure elevation, **C** intraocular inflammation, **D** subconjunctival hemorrhage and **E** corneal edema

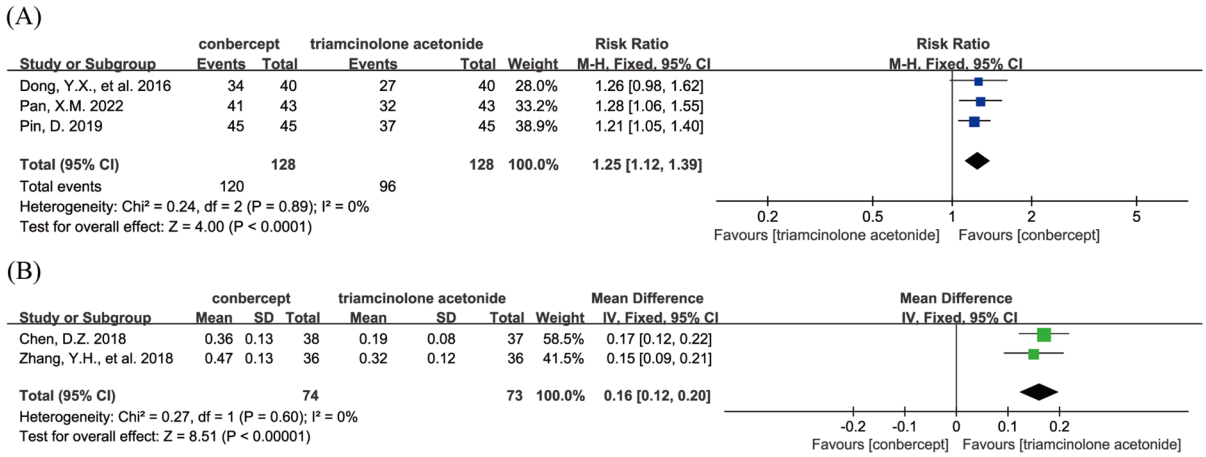


Fig. 6 Forest plots of **A** clinical response rate, **B** best-corrected visual acuity

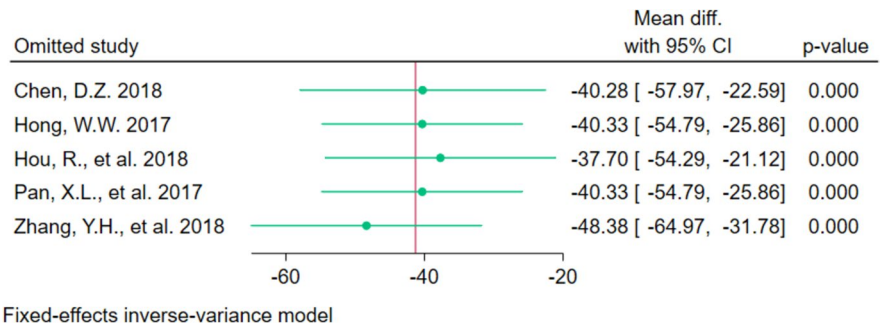


Fig. 7 Sensitivity analysis of central macular thickness

fluid accumulated under the retina, which also helps to reduce retinal thickness. In terms of the incidence of adverse reactions, Conbercept reduced the overall incidence of adverse reactions, the incidence of intraocular pressure elevation, and the incidence of endophthalmitis. However, there was no significant difference in the incidence of subconjunctival hemorrhage and corneal edema, which may be due to the fact that the mode of administration in both groups was intravitreal injection.

In recent years, Conbercept, as a novel anti-VEGF agent, has garnered widespread attention for its potential advantages in the treatment of wAMD. Conbercept significantly improves patients' visual acuity by effectively inhibiting pathological vascular growth and reducing retinal edema, with its therapeutic efficacy confirmed in multiple studies. The drug has shown a low incidence of side effects in clinical applications, and most patients can tolerate it well [39]. The treatment regimen can be personalized according to the specific conditions of the patient, including regimens such as 3+PRN and 3+Q3M. As a fusion protein, Conbercept is capable of simultaneously blocking multiple growth factors, which may enhance therapeutic outcomes and reduce the risk of resistance [40, 41]. In some regions, the economic benefits of Conbercept make it a strong choice for alleviating the financial burden on patients [42, 43]. Although the short-term therapeutic effects are remarkable, studies on the long-term effects of Conbercept are still relatively limited. Long-term use may induce resistance, affecting therapeutic outcomes [44]. The frequency of injections and related discomforts may impact patients' adherence to treatment. Although the incidence is low, side effects such as endophthalmitis and retinal detachment still require vigilance from medical professionals [45]. The clinical application of Conbercept is relatively new, and more randomized controlled trials are needed to verify its broad applicability. Direct comparative studies

with other anti-VEGF drugs are scarce, and there is a lack of data assessing its relative advantages and disadvantages. As an emerging anti-VEGF drug, further research is needed on the long-term effects, resistance risks, treatment adherence, and side effects of Conbercept. Physicians and patients should consider the potential advantages and disadvantages of Conbercept, as well as the individual needs of the patient, when choosing a treatment plan to formulate the best therapeutic strategy.

In the field of macular degeneration treatment, triamcinolone acetonide, while not the primary treatment option, is frequently used as a control group in clinical studies. As a synthetic glucocorticoid, triamcinolone acetonide exhibits significant anti-inflammatory effects, stabilizing the blood-retinal barrier and reducing retinal inflammatory responses. This mechanism has demonstrated good therapeutic efficacy in the treatment of wAMD. Furthermore, the selection criteria for the control group are typically based on the historical application effects, safety, and comparative effectiveness of the drug with new therapies. triamcinolone acetonide, with its long history of use and extensive research foundation, is often chosen as the control group to clearly assess the relative advantages and potential risks of new treatments. Existing data support that triamcinolone acetonide can significantly improve patients' visual function in randomized controlled trials, providing a basis for its reference value in clinical research. In China, medical policies and practices tend to favor proven treatment methods, making triamcinolone acetonide a common choice for the control group, aligning with clinical norms. Lastly, ethical considerations and patient choices are also significant factors in selecting triamcinolone acetonide as the control group. This choice ensures that trial participants do not receive ineffective treatments, protecting patients' rights and safety. The selection of triamcinolone acetonide as the control group not only provides clinical data support for the development of new therapies but also promotes a deeper understanding of the drug's mechanism of action, which is of great significance for future medical research.

This meta-analysis summarizes the current evidence on Conbercept versus Triamcinolone acetonide for the treatment of wAMD. It offers several advantages, including: 1. Choice of intervention: Currently, anti-VEGF drugs are the gold standard for treating wAMD. Conbercept, a Chinese-developed drug for wAMD, has improved drug accessibility for Chinese patients and offers a price advantage compared to imported drugs, covering a wider patient population. 2. Comprehensive literature search: We conducted an extensive search of Chinese and English databases, including only randomized controlled trials (RCTs) with rigorous designs and high credibility. While the number of included studies is still limited, it provides a foundation for further research. 3. Focused study population: The study population was exclusively wAMD patients, ensuring the results' high specificity and providing valuable guidance for clinical practice.

Several limitations of this meta-analysis should be considered. Firstly, as Conbercept is a drug developed in China, the majority of clinical trials have been conducted among the Chinese population, which may lead to potential racial bias in the final analysis [46]. Racial disparities in the prevalence of AMD have been noted, with studies indicating that the prevalence of AMD is higher in Caucasian populations compared to those of color [47]. A global meta-analysis revealed that the prevalence of AMD among Europeans (12.3%) is higher than that among Asians (7.4%) and Africans (7.5%), with no significant difference in prevalence between Asians and Africans. The prevalence of geographic atrophy (GA) is higher among Europeans compared to Africans and Asians, while the prevalence of neovascular AMD is similar across all races [48]. Additionally, there is a significant difference in the prevalence of polypoidal choroidal vasculopathy (PCV), a subtype of neovascular AMD, across different races, with more frequent reports in Asian regions [49]. The Beijing Eye Study reported a prevalence of PCV in China to be $0.3\% \pm 0.1\%$ [50], and in China, PCV accounts for 22.3–43.4% of neovascular AMD [51, 52]. The global therapeutic effect of Conbercept on AMD still needs to be explored. Second, most studies had relatively small sample sizes, which may limit the generalizability and applicability of the results. Small sample sizes may lead to inadequate statistical power, affecting the significance and reliability of the findings. Third, the follow-up periods of the studies were relatively short (maximum of six months), which may not be sufficient to observe long-term treatment effects and potential late-onset complications. Fourth, some studies employed non-rigorous randomized study designs, which may introduce bias and affect the objectivity and accuracy of the results. Fifth, the

studies did not adequately consider the influence of individual patient differences on treatment effects, including factors such as age, gender, disease stage, and comorbidities.

In conclusion, Conbercept was found to be more effective than Triamcinolone acetonide in the treatment of wAMD. Given the limitations of this meta-analysis, future research should employ larger sample sizes, longer follow-up periods, and more rigorous randomized controlled designs, while also considering individual differences and economic factors to provide more comprehensive and reliable evidence and further validate the findings of this study.

Author contributions Both authors contributed to the study conception and design, material preparation, data collection, and analysis. The first draft of the manuscript was written by FY. and was edited by RH. Both authors read and approved the final manuscript. Conceptualization: Fang Yang; Methodology: Ran Hu.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication Not applicable.

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