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ORIGINAL RESEARCH

One-Year Effectiveness Study of Intravitreously Administered Conbercept® Monotherapy in Diabetic Macular Degeneration: A Systematic Review and Meta-Analysis

Heping Wang · Jiashu Guo · Shanshan Tao · Xinyu Wang · Xinshu Liu · Tingting Li · Jue Wang · Xue Yang · Tongtong Niu · Dongning Liu

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ABSTRACT

Introduction: The evidence on efficacy of intravitreously administered Conbercept (IVC) monotherapy for diabetic macular degeneration was still limited.

Methods: A systematic review was conducted in November 2019 to summarize the current evidence on visual acuity (VA) changes with IVC monotherapy in the treatment of diabetic macular edema (DME) from Pubmed, ClinicalTrials.gov, EMbase, China National Knowledge Infrastructure (CNKI), Wanfang Database, Chin VIP Information (VIP), and Chinese Biomedical Database (CBM). Retrospective or prospective clinical studies which used IVC injection for the treatment of DME were included. Outcomes included in the analysis were change in best-corrected visual acuity (BCVA) and central macular thickness (CMT). A meta-regression was conducted to assess 1-year BCVA and CMT changes against numbers of injections.

Results: A total of 20 studies were included in current study. At 12-month follow-up, an overall increase of 0.67 logarithm of the minimum angle of resolution (logMAR) BCVA score [95% confidence interval (CI) 0.24–1.11; $P = 0.003$] and 1.03 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (95% CI 0.69–1.38; $P < 0.001$) was shown with IVC injection compared to baseline. Decrease in CMT was 142.79 μm (95% CI 112.71–172.87; $P < 0.001$) compared to baseline. The meta-regression showed a significant increase in effect size between number of injections and 12-month logMAR BCVA scale change as well as CMT.

Conclusion: Our findings suggest improved VA and CMT outcomes during 1-year follow-up in patients with DME who underwent IVC monotherapy. Increased injection frequency demonstrates a significant trend with improved outcomes at 12 months.

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H. Wang · J. Guo · X. Liu · T. Li · J. Wang · X. Yang · T. Niu (✉) · D. Liu (✉)
Department of Ophthalmology, The Fourth Hospital of Shenyang, Shenyang 110031, Liaoning, People's Republic of China
e-mail: ntt15840566565@163.com

D. Liu
e-mail: liudongning1976@126.com

S. Tao
Company, Chengdu Kanghong Biotechnology Inc, Chengdu 610091, Sichuan, People's Republic of China

X. Wang
China Medical University, Shenyang 110122, Liaoning, People's Republic of China

Keywords: Anti-VEGF therapy; Central macular thickness; Conbercept; Diabetic macular edema; Meta-analysis; Visual acuity

Key Summary Points
Why carry out this study?
The clinical efficacy of intravitreously administered Conbercept (IVC) has been reported in some prospective and retrospective studies to date. However, the evidence on efficacy of IVC monotherapy for DME was still limited
What was the evidence-based efficacy of IVC monotherapy for DME?
What was learned from the study?
Our findings suggest improved VA and CMT outcomes during 1-year follow-up in patients with DME who underwent IVC monotherapy
Increased injection frequency demonstrates a significant trend with improved outcomes at 12 months
IVC monotherapy as the initial treatment might be a treatment option for DME

INTRODUCTION

Currently, the prevalence of diabetes mellitus (DM) is rapidly increasing worldwide. Among the complications of diabetes, the most common diabetic eye disease is diabetic retinopathy (DR), and DR is also the most common cause of blindness in working-age populations in developed countries [1, 2]. Among patients with DR, visual function can be severely damaged by diabetic macular edema (DME), which is one of the most common complications of DR and significantly affects the quality of life among patients with diabetes [3].

DME is caused by the destruction of the internal and external barrier functions of the retinal blood vessels, leading to the extravasation of fluid and lipoproteins into the macular area [3]. Vascular endothelial growth factor (VEGF) has been shown to be the key promoter of damage to the blood-retinal barrier by increasing vascular permeability, leakage of retinal microvessels, and accumulation of retinal fluid in the macular region, which is currently the main pathogenesis of DME [4, 5]. Hence, the treatment strategy for DME has focused on anti-VEGF therapy, and intravitreal injection with an anti-VEGF agent has emerged as the first-line therapy for DME. There are a variety of anti-VEGF agents in the clinic such as bevacizumab (Avastin®) and ranibizumab (Lucentis®), which have been found to bind VEGFA only, or both; in addition, aflibercept (Eylea®), which is composed of the second domain of human VEGF receptor (VEGFR)-1 and the third domain of VEGFR-2, fused to the Fc domain of human immunoglobulin 1 (IgG1).

Conbercept (KH902; Chengdu Kanghong Biotech Co., Ltd., Sichuan, China), as a recent novel VEGF antagonist, is a 143-kDa humanized recombinant anti-VEGF fusion protein, consisting of extracellular domain 2 of VEGFR-1 and domains 3 and 4 of VEGFR-2, which bind to the Fc domain of human IgG1, and is a soluble receptor decoy that blocks all isoforms of VEGFA, VEGFB, VEGFC, and placenta growth factor (PIGF) [6]. Conbercept can effectively antagonize the effects of VEGF. It has the advantages of multiple targets, strong affinity, and a long half-life in vitreous [7, 8]. Previous studies revealed that intravitreally administered Conbercept (IVC) could significantly improve the vision and reduce central macular thickness (CMT) of patients with DME [9, 10]. However, these studies were conducted in single centers with small sample sizes and the results have not been systematically collected, sorted, or evaluated. Recently, a meta-analysis was performed to evaluate the efficacy of intravitreally administered ranibizumab (IVR) and IVC in patients with DME [11]. To date, no systematic review has reported on the effect and safety of IVC monotherapy in patients with DME. We performed a systematic review and meta-analysis to quantify the effect of IVC monotherapy on best

corrected visual acuity (BCVA) and CMT in patients with DME.

METHODS

Our systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12].

Compliance with Ethics Guidelines

The present study is based on previously reports and does not contain any studies with human participants or animals performed by any of the authors.

Search Strategy, Inclusion Criteria, Exclusion Criteria, and Data Collection

We performed a comprehensive systematic literature search using Pubmed, ClinicalTrials.gov, EMbase, Cochrane Library, China National Knowledge Infrastructure (CNKI), Chinese Biomedicine Literature Database (CBM-SinoMed), Chin VIP Information (VIP) Database for Chinese Technical Periodicals, and Wanfang Database for articles written in English or Chinese and published up to November 2019, and the references of all included studies were also traced. The search terms used were: "conbercept" OR "anti-VEGF" OR "anti-vascular endothelial growth factor" OR "Lumitin" OR "KH902" AND "diabetic macular edema" OR "diabetic macular oedema". Two authors, TTN and JSG, assessed all eligible studies and data independently. A consensus was reached if there were any cases of disagreement.

The inclusion criteria were studies that (1) provided sufficient data for a comparison of pre- and post-treatment BCVA and CMT of patients with DME given IVC; (2) human studies available in English or Chinese.

The exclusion criteria were (1) patients with DME received more than one type of therapy rather than IVC separately; (2) no sufficient data was available on the variation change in BCVA or CMT, e.g., the mean, standard deviation, or standard error; (3) animal or cell research, non-original research (reviews, editorials, or comments), abstracts, unpublished studies, and duplicated studies.

The primary outcome of this systematic analysis focused on assessing the effect of IVC therapy on BCVA and CMT from baseline to 1, 3, 6, or 12 months of treatment for DME. Additional outcomes included the relationship between the number of IVC injections and change in outcome, as well as the complications and serious adverse events (SAEs). BCVA was obtained using the logarithm of the minimum angle of resolution (logMAR) and Early Treatment Diabetic Retinopathy Study (ETDRS). CMT was demonstrated on optical coherence tomography (OCT).

Data Extraction and Risk of Bias Assessment

The relevant data from the articles were extracted using a standard data extraction form. The extracted data included the first author(s), publication date, study design, sample size, age, sex, interventions details, and follow-up periods. The literature quality was evaluated by using the Jadad scores (ranging from 0 to 5) [13]. Studies with a score of at least 3 were considered to be "high quality" studies.

Statistical Analysis

The meta-analyses were performed using the DerSimonian–Laird random-effects method regardless of the amount of heterogeneity between studies. The standardized mean difference (SMD) or weighted mean difference (WMD) with a 95% confidence interval [CI] was used to assess continuous variable outcomes. Heterogeneity between studies was based on the size of the I^2 value. Substantial heterogeneity was assumed if the I^2 value was above 50%. Meta-regression was used to examine the relationship in the various studies between the number of injections, baseline CMT, and the change in outcomes. Some studies provided data on different follow-up subgroups, rather than the same follow-up time. For these studies,

each subgroup was regarded as a separate study in all analyses. STATA 11.0 software was applied to integration analysis. A P value less than 0.05 was considered to be statistically significant.

RESULTS

Study Selection

There were 91 articles identified for the initial review. After further examination of all files, 42 articles satisfied the available information on BCVA and/or CMT, then these files went through a full-text review. After excluding studies which were not original regarding articles, we included 20 studies [9, 10, 14–31] (1244 participants, 1278 eyes) in this meta-analysis. The selection of studies is shown in the PRISMA flow diagram in Fig. 1. The characteristics of the 20 included studies are provided in Table 1.

Change in BCVA

Table 2 shows that compared with baseline data, logMAR BCVA scale was significantly improved at 1, 3, 6, and 12 months after IVC injection [SMD − 1.24 (− 2.09 to − 0.38, $P < 0.001$); − 2.30 (− 3.37 to − 1.23, $P < 0.001$); − 1.98 (− 2.88 to − 1.08, $P < 0.001$), and − 0.67 (− 1.11 to − 0.24, $P < 0.001$)]. Similar results were found to allow a quantitative synthesis that ETDRS BCVA scale was significantly improved at 1, 3, 6, 9, and 12 months after IVC injection [SMD 0.55 (0.11–0.98, $P = 0.014$); 0.56 (0.17–0.95, $P = 0.005$); 0.64 (0.31–0.97, $P < 0.001$); 0.51 (0.01–1.00, $P = 0.046$), and 1.03 (0.69–1.38, $P < 0.001$)]. There was still no evidence on the effects of IVC injection for DME with logMAR scale at 9 months and ETDRS scale at 2 months. Evidence of heterogeneity is shown in Table 2. A summary of the publication bias assessment using the Begg's and Egger's tests is provided in Table 3.

Change in CMT

The pooled results of the overall and subgroup by study design effects of IVC on changes in CMT at 1, 2, 3, 6, 9, and 12 months are shown in Table 4. The results from the various studies suggest that the overall CMT decrease was 141.48 μm (89.81–193.15, $P < 0.001$) at 1 month, 287.02 μm (251.71–322.34, $P < 0.001$) at 2 months, 182.70 μm (150.44–214.96, $P < 0.001$) at 3 months, 219.53 μm (165.33–273.73, $P < 0.001$) at 6 months, 113.40 μm (53.27–173.53, $P < 0.001$) at 9 months, and 142.79 μm (112.71–172.87, $P < 0.001$) at 12 months. Evidence of heterogeneity is shown in Table 4. A summary of the publication bias assessment using the Begg's and Egger's test is provided in Table 3.

Injection Frequency and BCVA Outcomes

Table 5 shows meta-regression results on the number of IVC injections for logMAR and ETDRS BCVA scale gain at 1, 3, 6, 9, and 12 months, which suggested a significant relationship with change in logMAR BCVA score at 12 months (Fig. S1 in the electronic supplementary material). An increase of one injection was associated with an increase of 1.19 (0.34–2.35, $P = 0.04$) logMAR BCVA score. However, a greater number of injections was not associated with a significant change in ETDRS BCVA scale at either 6 or 12 months. Insufficient data were available to properly evaluate this relationship at either 2 or 9 months for logMAR BCVA scale and at 1, 2, 3, or 9 months for ETDRS BCVA scale.

Injection Frequency and CMT Outcomes

The association between the number of IVC injections and the change in CMT within patients with DME at 1, 3, 6, and 12 months was examined by meta-regression (Table 6). The number of IVC injections had a significant impact on the change in CMT at 12 months, but the association was not deemed significant at 1, 3, or 6 months. An increase of one IVC injection was associated with a mean 20.26 μm

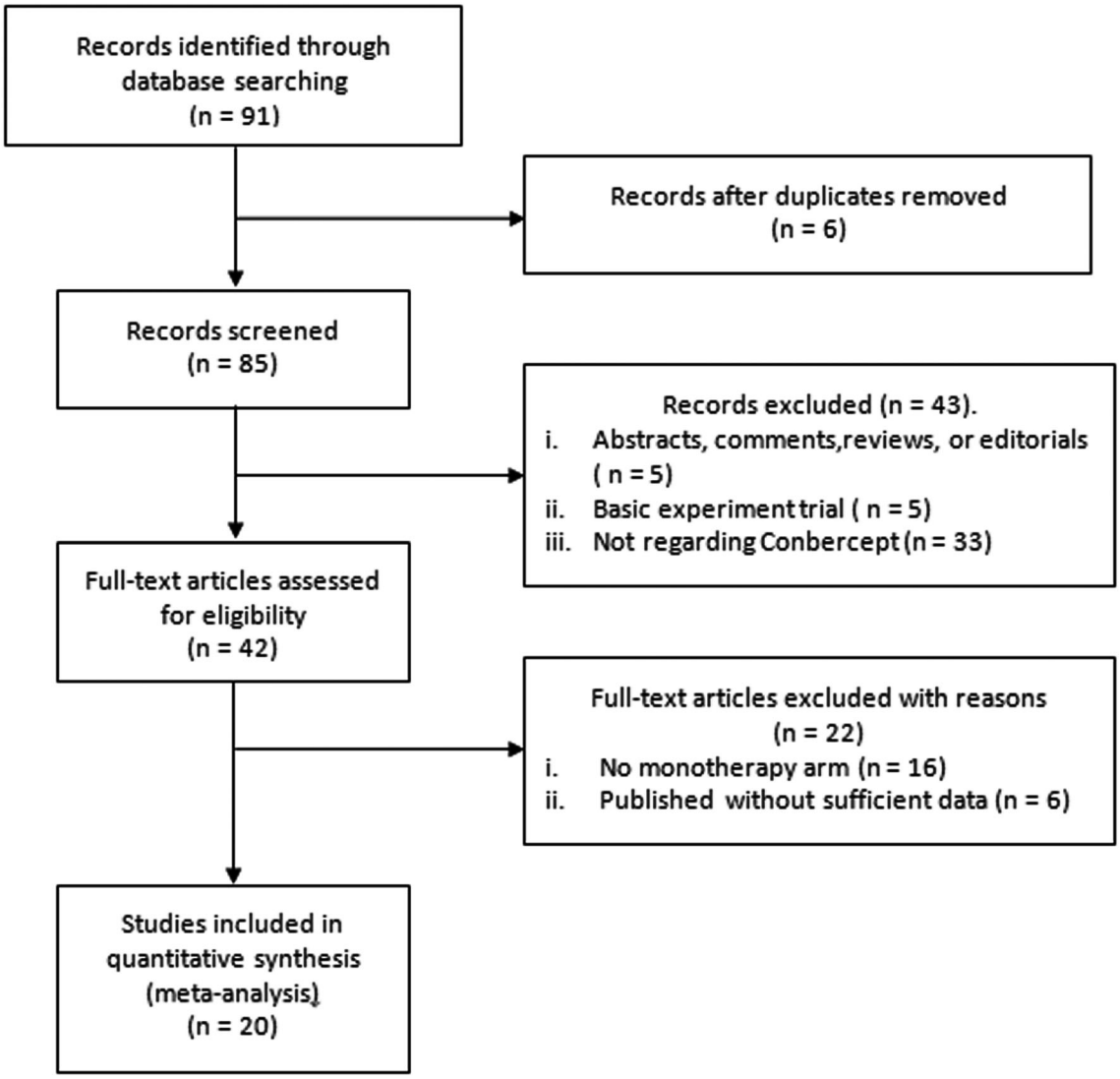

Fig. 1 Eligibility of studies for inclusion in meta-analysis

(0.87–39.66, $P = 0.04$) decrease in CMT (Fig. S2 in the electronic supplementary material).

Adverse Effects (AEs)

According to systematic review, patients with DME after IVC injection experienced ocular adverse events including conjunctival hemorrhage ($n = 29$), intraocular pressure increase ($n = 7$), transient anterior chamber inflammatory activity ($n = 3$), vitreous floaters ($n = 1$), vitreous hemorrhage ($n = 1$), and corneal abrasion ($n = 1$).

DISCUSSION

In this systematic review and meta-analysis, a total of 20 papers involving 1244 patients with DME were included. After pooled analysis, we found that IVC monotherapy led to significant visual acuity and CMT improvement in the treatment of DME. A significant relationship was found between the number of IVC injections and change in logMAR BCVA scale and CMT at 12 months. In addition, no serious AEs caused by the IVC injection were found.

Table 1 Characteristics of including studies

No.	Author (year)	Study design	DM type	DME type	Age (mean ± SD/ range, years)	Male/ female (*N*)	Patients (*N*)	Eyes (*N*)	No. of injections, mean (SD)	Treatment regimen	Jadad score
1	Liu et al. (2019) [14]	Retrospective	Type 2	DME	53.9 (34–69)	10/3	13	26	3	Monthly × 3	3
2	Li et al. (2019) [15]	Retrospective	NA	DME	50.5 ± 3.3 (44–62)	24/26	50	50	3	Monthly × 3	3
3	Chang et al. (2016) [16]	Retrospective	NA	CSME	49–62	11/10	21	22	3.05	1 + PRN	3
4	Jiang et al. (2017) [17]	Prospective	Type 2	CSME/CME/ DDME	54.10 ± 10.65	12/8	20	20	3.20 ± 0.52	3 + PRN	4
5	Guo et al. (2018) [18]	Retrospective	NA	DME	61.35 ± 7.58	28/27	55	55	3	Monthly × 3	3
6	Zhang et al. (2018) [19]	Prospective	NA	DDME	51.88 ± 10.18	13/12	25	25	1	Monthly × 1	4
7	Sun et al. (2018) [20]	Prospective	NA	DME	66.52 ± 8.39	13/16	29	30	3	Monthly × 3	3
8	Zhang et al. (2018) [21]	Prospective	NA	DDME	51.90 ± 10.90	NA	17	17	3	Monthly × 3	3
9	Ren et al. (2019) [22]	Prospective	NA	DDME	59.24 ± 8.61	NA	35	35	1	Monthly × 1	3
			NA	CME	62.51 ± 9.12		33	33	1	Monthly × 1	
			NA	SRD	60.86 ± 9.47		28	28	1	Monthly × 1	
10	Li et al. (2019) [23]	Retrospective	NA	DME	54 ± 5	24/16	19	21	1	Monthly × 1	4
11	Zhang et al. (2019) [24]	Prospective	NA	DME	NA	17/23	40	40	3	Monthly × 3	3

Table 1 continued

No.	Author (year)	Study design	DM type	DME type	Age (mean ± SD/ range, years)	Male/ female (*N*)	Patients (*N*)	Eyes (*N*)	No. of injections, mean (SD)	Treatment regimen	Jadad score
12	Xu et al. (2016) [25]	Retrospective	Type 1/Type 2	DDME	60.9 ± 12.9	12/14	26	31	5.6 ± 0.8	1 + PRN	3
13	Qian (2017) [26]	Retrospective	NA	DDME	NA	NA	33	40	5.8 ± 1.7	1 + PRN	3
14	Xu et al. (2017) [27]	Retrospective	Type 1/Type 2	CSME/ DDME	61.3 ± 14.9	18/14	32	36	6.6 ± 0.9	3 + PRN	3
15	Li et al. (2018) [28]	Retrospective	NA	DDME	NA	28/46	20	20	3.20 ± 0.4	1 + PRN	3
				CME			36	36	3.39 ± 0.95	1 + PRN	
				SRD			18	18	4.22 ± 1.55	1 + PRN	
16	Li et al. (2017) [10]	Retrospective	Type 2	DME	59.8 ± 9.8	NA	37	37	6.74	1 + PRN	3
			NA	DME	54.4 ± 6.3	NA	25	25	6.5	1 + PRN	
17	Niu and Ji (2018) [29]	Prospective	Type 2	DME	52.8 ± 14.0	15/8	23	23	2	1 + PRN	3
18	Xu et al. (2019) [30]	Retrospective	NA	CSME	60.55 ± 8.65	10/10	20	20	6.60 ± 3.02	3 + PRN	3
19	Zhou et al. (2019) [9]	Retrospective	NA	DME	59.6 ± 8.5	46/43	60	60	4.5 ± 1.0	3 + PRN	3
20	Li et al. (2019) [31]	Prospective	NA	DME	60.6 ± 12.3	19/13	32	32	8.58 ± 2.4	3 + PRN	4

CSME clinical significant macular edema, *CME* cystoid macular edema, *DME* diabetic macular edema, *DDME* diffuse diabetic macular edema, *SRD* serous retinal detachment, *PRN* pro re nata, *NA* not applicable

Table 2 Pooled visual acuity changes in patients with DME by IVC injection during 1-year follow-up

Subgroup restriction	Follow-up time	Number of studies	Visual testing scale	Pooled visual change (95% CI)	*P*	I^2 (%)	$P_{heterogeneity}$
Retrospective	1 month	3	logMAR	− 3.33 (− 5.83, − 0.84)	0.009	97.2	< 0.001
Prospective	1 month	6	logMAR	− 0.38 (− 0.90, 0.15)	0.159	81.3	< 0.001
Overall pooling	1 month	9	logMAR	− 1.24 (− 2.09, − 0.38)	0.005	94.7	< 0.001
Retrospective	2 months	2	logMAR	− 3.25 (− 8.07, 1.56)	0.185	97.5	< 0.001
Prospective	2 months	NA	logMAR	NA	NA	NA	NA
Overall pooling	2 months	2	logMAR	− 3.25 (− 8.07, 1.56)	0.185	97.5	< 0.001
Retrospective	3 months	4	logMAR	− 6.09 (− 10.53, − 1.65)	0.007	98.6	< 0.001
Prospective	3 months	9	logMAR	− 0.77 (− 1.38, − 0.17)	0.012	89.3	< 0.001
Overall pooling	3 months	13	logMAR	− 2.30 (− 3.37, − 1.23)	< 0.001	97	< 0.001
Retrospective	6 months	3	logMAR	− 8.58 (− 17.50, 0.34)	0.059	99.2	< 0.001
Prospective	6 months	10	logMAR	− 0.72 (− 1.29, − 0.15)	0.013	89.3	< 0.001
Overall pooling	6 months	13	logMAR	− 1.98 (− 2.88, − 1.08)	< 0.001	96.4	< 0.001
Retrospective	9 months	NA	logMAR	NA	NA	NA	NA
Prospective	9 months	NA	logMAR	NA	NA	NA	NA
Overall pooling	9 months	NA	logMAR	NA	NA	NA	NA
Retrospective	12 months	1	logMAR	− 0.33 (− 0.68, 0.033)	0.075	NA	NA
Prospective	12 months	4	logMAR	− 0.79 (− 1.33, − 0.24)	0.005	69.5	0.02
Overall pooling	12 months	5	logMAR	− 0.67 (− 1.11, − 0.24)	0.003	69.5	0.01
Retrospective	1 month	1	ETDRS	0.48 (− 0.116, 1.08)	0.114	NA	NA
Prospective	1 month	1	ETDRS	0.62 (− 0.02, 1.25)	0.058	NA	NA
Overall pooling	1 month	2	ETDRS	0.55 (0.11, 0.98)	0.014	0	0.768
Retrospective	2 months	NA	ETDRS	NA	NA	NA	NA
Prospective	2 months	NA	ETDRS	NA	NA	NA	NA
Overall pooling	2 months	NA	ETDRS	NA	NA	NA	NA

Table 2 continued

Subgroup restriction	Follow-up time	Number of studies	Visual testing scale	Pooled visual change (95% CI)	*P*	I^2 (%)	$P_{heterogeneity}$
Retrospective	3 months	NA	ETDRS	NA	NA	NA	NA
Prospective	3 months	2	ETDRS	0.56 (0.17, 0.95)	0.005	0	0.374
Overall pooling	3 months	2	ETDRS	0.56 (0.17, 0.95)	0.005	0	0.374
Retrospective	6 months	1	ETDRS	0.63 (0.03, 1.23)	0.041	NA	NA
Prospective	6 months	2	ETDRS	0.64 (0.25, 1.04)	0.001	0	0.356
Overall pooling	6 months	3	ETDRS	0.64 (0.31, 0.97)	< 0.001	0	0.653
Retrospective	9 months	0	ETDRS	NA	NA	NA	NA
Prospective	9 months	1	ETDRS	0.51 (0.01, 1.00)	0.046	NA	NA
Overall pooling	9 months	1	ETDRS	0.51 (0.01, 1.00)	0.046	NA	NA
Retrospective	12 months	6	ETDRS	1.12 (0.77, 1.48)	< 0.001	61.4	0.024
Prospective	12 months	1	ETDRS	0.51 (0.01, 1.01)	0.044	NA	NA
Overall pooling	12 months	7	ETDRS	1.03 (0.69, 1.38)	< 0.001	61.4	0.008

DME diabetic macular edema, *ETDRS* Early Treatment Diabetic Retinopathy Study, *IVC* intravitreally administered Conbercept, *logMAR* logarithm of the minimum angle of resolution, *NA* not applicable (no analysis performed because of an insufficient number of studies providing data), *CI* confidence interval

Table 3 Overall publication bias testing by Begg's test and Egger's test

Items	Follow-up time	Begg's test	Egger's test
logMAR BCVA scale	1 month	0.677	0.344
	2 months	NA	0.317
	3 months	0.11	0.016
	6 months	0.18	0.04
	9 months	NA	NA
	12 months	0.14	0.74
ETDRS BCVA scale	1 month	0.32	NA
	2 months	NA	NA
	3 months	0.32	NA
	6 months	0.12	0.36
	9 months	NA	NA
	12 months	0.65	0.11
CMT	1 month	0.48	0.049
	2 months	0.32	NA
	3 months	0.24	< 0.001
	6 months	0.21	0.04
	9 months	NA	NA
	12 months	0.17	0.28

ETDRS Early Treatment Diabetic Retinopathy Study, *logMAR* logarithm of the minimum angle of resolution, *CMT* central macular thickness, *NA* not applicable (no analysis performed because of an insufficient number of studies providing data)

Conbercept has been produced by the expression system of Chinese hamster ovary (CHO) cells and combines placental growth factor (PIGF) and all isoforms of VEGFA as well as VEGFB. Conbercept is alike in structure to aflibercept (Eylea, Regeneron Pharmaceuticals, Eastview, NY, USA). Many single-center, small-sized clinical trials showed that IVC injection for treatment of DME is significantly better than baseline in improving vision. Additionally, Conbercept has received marketing authorization in May 2019 by the China State Food and Drug Administration (CFDA) for the therapy of DME. As far as clinical practice is concerned, some patients with DME who were nonresponsive to intravitreal ranibizumab and bevacizumab therapy were still able to undergo effective treatment with Conbercept [32]. Nonetheless, large-scale, standard, and stringently controlled clinical trials are necessary to confirm these findings.

Previously, clinical trials on intravitreal anti-VEGF agent monotherapy in patients with DME showed that the mean improvement in BCVA was 0.81 logMAR after 3 months of treatment [33], and 0.3–3.85 logMAR after 12 months of treatment [34–36]. Our analysis of IVC monotherapy showed a mean logMAR BCVA scale improvement in which the largest change (6.09 logMAR) occurred at 3 months after treatment among retrospective studies ($n = 4$), which was higher than that previously reported. For ETDRS BCVA scale, the mean improvement with anti-VEGF agents was reported to be in the range of 5–13 letters after 12 months of treatment [34, 37–39]. Our results found that the largest mean change of ETDRS BCVA score was 1.12 (0.77–1.48) after pooling retrospective studies ($n = 6$), which was below the lower ends of the range of previous reports.

Additionally, there was some significant heterogeneity between included studies. This discrepancy could have occurred as a result of the heterogeneity of patient characteristics such as age and disease severity, comorbidities, methods for diagnosis and evaluation, treatment doses and interval, and study design features [40–43].

In a real-life clinical practice study, after 12-month follow-up, both IVC and IVR injection achieved similar clinical efficacy in the treatment of DME. However, in comparison to the IVR arm, IVC showed a longer treatment interval and fewer injections were needed [27]. Currently, there is still no evidence on the correlation between trends of efficacy and the number of IVC injections for DME. Hence, our meta-regression results revealed that there is a correlation between the frequency of IVC injections and efficacy (i.e., visual acuity gain and CMT decrease). We found that an increase of one injection was associated with an increase of 1.19 logMAR BCVA score at 12-month

Table 4 Pooled central macular thickness changes in patients with DME by IVC injection during 1-year follow-up

Subgroup restriction	Follow-up time	Number of studies	Pooled visual change (95% CI)	*P*	I^2 (%)	$P_{heterogeneity}$
Retrospective	1 month	5	− 213.92 (− 295.78, − 132.06)	< 0.001	92.3	< 0.001
Prospective	1 month	6	− 76.565 (− 97.29, − 55.84)	< 0.001	20.4	0.28
Overall pooling	1 month	11	− 141.48 (− 193.15, − 89.81)	< 0.001	93.1	< 0.001
Retrospective	2 months	2	− 287.02 (− 322.34, − 251.71)	< 0.001	0	0.951
Prospective	2 months	NA	NA	NA	NA	NA
Overall pooling	2 months	2	− 287.02 (− 322.34, − 251.71)	< 0.001	0	0.951
Retrospective	3 months	5	− 212.22 (− 289.28, − 135.16)	< 0.001	97.7	< 0.001
Prospective	3 months	11	− 168.80 (− 202.89, − 134.71)	< 0.001	84.5	< 0.001
Overall pooling	3 months	16	− 182.70 (− 214.96, − 150.44)	< 0.001	94.2	< 0.001
Retrospective	6 months	5	− 223.29 (− 330.63, − 115.95)	< 0.001	97.5	< 0.001
Prospective	6 months	11	− 217.36 (− 278.02, − 156.71)	< 0.001	95.4	< 0.001
Overall pooling	6 months	16	− 219.53 (− 273.73, − 165.33)	< 0.001	96.6	< 0.001
Retrospective	9 months	NA	NA	NA	NA	NA
Prospective	9 months	1	− 113.40 (− 173.53, − 53.27)	< 0.001	NA	NA
Overall pooling	9 months	1	− 113.40 (− 173.53, − 53.27)	< 0.001	NA	NA
Retrospective	12 months	6	− 160.82 (− 200.14, − 121.50)	< 0.001	77.6	< 0.001
Prospective	12 months	6	− 123.89 (− 165.55, − 82.23)	< 0.001	79.0	< 0.001
Overall pooling	12 months	12	− 142.79 (− 172.87, − 112.71)	< 0.001	80.8	< 0.001

DME diabetic macular edema, *IVC* intravitreally administered Conbercept, *NA* not applicable (no analysis performed because of an insufficient number of studies providing data), *CI* confidence interval

follow-up. The improvement in vision persisted till 12 months after first injection and the response had a dose–effect relationship between number of injections and visual gain. As a strong predictor of anatomical and functional outcome, CMT provides a measure of retinal recovery after treatment. Notably, our meta-analysis showed a significant decrease in CMT in patients with DME who underwent IVC injection. A significant effect was observed at 12-month follow-up, when an increase of one injection was associated with a 20.26-μm decrease in CMT.

According to the AEs reports, IVC injection was safe and well tolerated in the clinic. The ocular AEs were typical of complications with intravitreal injections such as intraocular pressure increase, conjunctival hemorrhage, etc. There were no reports of systemic AEs. The true incidence of ocular or systemic AEs requires a large-scale, real-life trial or observation for further assessment.

A strength of this study was that is was the first meta-analysis to evaluate the effect and safety of IVC injection for patients with DME. However, there were some limitations in this study: (1) As Conbercept has not yet been approved outside China, only Chinese patients were enrolled; (2) there were different follow-up times for observation; (3) only English or Chinese publications were evaluated; (4) there are no unpublished results; thus, publication bias cannot be fully excluded; (5) as the heterogeneity between study results was significant, it

Table 5 Meta-regression results for association between number of injections and visual acuity gain

Visual acuity testing scale	Follow-up time	Number of studies	Coefficient (95% CI)	*P*	Adjusted R^2
logMAR	1 month	9	− 0.16 (− 2.01, 1.68)	0.84	17.09%
	2 months	NA	NA	NA	NA
	3 months	13	0.01 (− 1.79, 1.81)	0.99	9.61%
	6 months	13	− 0.04 (− 2.66, 2.57)	0.97	10.08%
	9 months	NA	NA	NA	NA
	12 months	6	− 1.19 (− 2.35, − 0.34)	0.04	100%
ETDRS	1 month	NA	NA	NA	NA
	2 months	NA	NA	NA	NA
	3 months	NA	NA	NA	NA
	6 months	3	0.05 (− 0.74, 0.84)	0.6	0%
	9 months	NA	NA	NA	NA
	12 months	7	0.13 (− 0.42, 0.69)	0.56	20.79%

ETDRS Early Treatment Diabetic Retinopathy Study, *logMAR* logarithm of the minimum angle of resolution, *NA* not applicable (no analysis performed because of an insufficient number of studies providing data), *CI* confidence interval

Table 6 Meta-regression results for association between number of injections and CMT gain

Covariable	Follow-up time	Number of studies	Coefficient (95% CI)	*P*	Adjusted R^2
CMT	1 month	11	− 19.81 (− 81.77, 42.14)	0.49	6.04%
	2 months	NA	NA	NA	NA
	3 months	16	− 15.04 (− 55.96, 25.87)	0.44	4.14%
	6 months	16	− 3.78 (− 65.77, 58.19)	0.89	7.41%
	9 months	NA	NA	NA	NA
	12 months	12	− 20.26 (− 39.66, − 0.87)	0.04	36.85%

CMT central macular thickness, *NA* not applicable (no analysis performed due to an insufficient number of studies providing data), *CI* confidence interval

could be regarded as a weakness of the study. Multicenter, large-sample, double-blind randomized controlled trials are still needed to verify our findings.

CONCLUSIONS

In summary, the current systematic review and meta-analysis revealed that IVC injection alone was effective in the treatment of DME during 1-year observation. An increase of one injection was associated with an increase of 1.19 logMAR BCVA score and a decrease of 20.26 μm in CMT at 12-month follow-up. The current systematic review and meta-analysis showed that IVC monotherapy had significant visual and CMT outcomes in the treatment of DME.

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