ORIGINAL RESEARCH

# Therapeutic Efficacy of Intravitreal Conbercept Injections with or without Focal Macular Photocoagulation for Diabetic Macular Edema

Yu Mao, MD; Shuang Wang, MD; Xiwen Ji, MM; Kai Cao, MM; Simeng Hou, MM; Yuanyuan Xiao, BM


## ABSTRACT

**Objective** • This study aimed to investigate the effectiveness and safety of intravitreal conbercept injections with or without focal macular photocoagulation in the treatment of diabetic macular edema (DME).

**Methods** • This retrospective study included 60 DME patients (60 eyes) divided into two treatment groups. The conbercept group received monthly intravitreal injections for 5 consecutive sessions, while the combination therapy group received intravitreal injections and focal macular photocoagulation. Changes in best-corrected visual acuity (BCVA) and central macular thickness (CMT) were observed before and at months 1, 3, 6, 9, and 12 after treatment in both groups, along with the number of intravitreal conbercept injections administered.

**Results** • At 1, 3, 6, 9, and 12 months after treatment, both the conbercept and combined treatment groups showed improvement in best-corrected visual acuity (BCVA) and decrease in central macular thickness (CMT) compared to before treatment, with statistical significant differences ($P < .05$). However, the differences in BCVA and CMT between the two groups at each time point after treatment were not significant ($P > .05$). During the 1-year follow-up period, the mean number of injections in the combined treatment group was 6.3±0.8, which was less than that in the conbercept treatment group (7.6 ± 0.9), with a significant difference ($t = 5.556$, $P < .001$). The incidence of subconjunctival hemorrhage was 10.9% and 10.5% in the two groups, respectively, with no significant inter-group difference ($\chi^2 = 0.013$, $P = .908$). None of the patients exhibited serious treatment-related ocular and systemic complications during the treatment period.

**Conclusions** • Treatment of DME with intravitreal conbercept injections, whether with or without focal macular photocoagulation, is safe and effective in improving the patients' visual acuity and retinal anatomy. However, patients who receive combined treatment require fewer intravitreal injections than those who receive conbercept treatment alone. (*Altern Ther Health Med.* 2023;29(5):308-313).


**Yu Mao, MD,** Attending Doctor; **Xiwen Ji, MM,** Resident Doctor; **Simeng Hou, MM; Yuanyuan Xiao, BM;** Beijing Tongren Eye Center, Beijing Ophthalmology and Visual Science Key Lab, Beijing Tongren Hospital, Capital Medical University, Beijing, China. **Shuang Wang, MD,** Associate Chief Physician; **Kai Cao, MM,** Assistant Research Fellow; Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Ophthalmology and Visual Science Key Lab, Beijing Tongren Hospital, Capital Medical University, Beijing, China.

*Corresponding author: Yu Mao, MD*
*E-mail: 13810119694@163.com*

## INTRODUCTION

Diabetic macular edema (DME) is a significant cause of visual impairment in patients with diabetes.[1] Epidemiological data indicate that there are approximately 25 million patients with diabetic retinopathy (DR) in China, with 5.6 million suffering from DME.[2] The pathogenesis of DME involves the disruption of the blood-retinal barrier and increased vascular permeability, along with chronic inflammatory reactions, resulting in tissue ischemia and hypoxia. It leads to the release of large amounts of vascular endothelial growth factors (VEGFs). The efficacy of anti-VEGF drugs in treating DME has been well-established in previous studies, making them the first-line treatment option.[3-5] However, it is important to note that the duration of efficacy for anti-VEGF medication in DME treatment is relatively short, which requires multiple repeated injections. Therefore, there is a need to develop an improved treatment regimen for DME. In recent years, there has been a focus on clinical research to determine whether the combination of anti-VEGF drugs with macular laser treatment can help stabilize DME and reduce the number of anti-VEGF injections. This study aims to compare the efficacy and safety of conbercept injections

alone with conbercept injections combined with focal macular photocoagulation in treating DME, as detailed below.

## METHODS

### Study Design

This retrospective study aimed to compare the efficacy and safety of conbercept injections with or without focal macular photocoagulation in the treatment of diabetic macular edema (DME). The study included 60 patients (60 eyes) with DME who visited our hospital from July 2019 to September 2021. The patients were divided into two groups: the conbercept treatment group (30 patients, 30 eyes) who received only intravitreal conbercept injections, and the combined treatment group (30 patients, 30 eyes) who received intravitreal conbercept injections along with focal macular photocoagulation. The study design was retrospective in nature, and data were collected from medical records and analyzed to assess the efficacy and safety outcomes of the two treatment approaches.

### Baseline Clinical Parameters

In the conbercept treatment group, there were 17 men and 13 women with ages ranging from 48 to 70 years (mean age 59.2 ± 6.6 years). In the combined treatment group, there were 18 men and 12 women with ages ranging from 52 to 72 years (mean age 59.4 ± 5.3 years). There were no significant inter-group differences in terms of age, sex, duration of diabetes, glycosylated hemoglobin levels, and other general information ($P > .05$). Additionally, there were no significant differences between the two groups in terms of best-corrected visual acuity (BCVA) and central macular thickness (CMT) before treatment ($P > .05$).

### Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) Patients who were diagnosed with type 2 diabetes by endocrinology but had good glycemic control with a glycosylated hemoglobin level of ≤10%; (2) those who had center-involved diabetic macular edema (CI-DME) with a CMT of ≥300 μm as determined using optical coherence tomography (OCT), with a decrease in visual acuity; (3) FFA examination showing microangiomas and dilated capillaries within 500-3000 μm from the central fovea; (4) those who did not present with vitreous opacities, a symptom affecting fundus examination; (5) those who could cooperate with treatment and follow-up and whose clinical information was complete; and (6) those who voluntarily accepted treatment and signed an informed consent form.

The exclusion criteria were as follows: (1) patients who had undergone anti-VEGF therapy or macular laser treatment within three months before the current treatment; (2) those with other macular lesions such as epiretinal membrane, macular hole, and significant vitreomacular traction; (3) those with macular edema owing to other causes, such as uveitis and retinal vein occlusion; (4) those whose affected eyes had a prior history of vitreoretinal surgery; and (5) those who had the severe systemic disease and were unable to cooperate with treatment and follow-up.

### Treatment Regimens

In the early treatment stage, both groups of affected eyes received intravitreal conbercept injections once a month for five consecutive sessions (5+PRN regimen). Patients in the combined treatment group underwent focal macular photocoagulation within one week after the fifth injection. After five consecutive injections of conbercept, patients in both groups were treated on an as-needed basis according to the retreatment criteria. The retreatment criteria were as follows: (1) the BCVA decreased by ≥1 line since the previous follow-up examination; (2) OCT revealed a ≥50 μm increase in the CMT since the previous follow-up examination; and (3) OCT revealed new cystoid macular edema or subretinal fluid.

BCVA examination, slit-lamp microscopy, indirect ophthalmoscopy, fundus color photography, fundus fluorescein angiography (FFA), and OCT were performed in all patients to ensure accurate assessment and follow-up of their eye health and visual function. DR staging was conducted in both groups of patients. Patients who met the 4-2-1 rule started to undergo pan-retinal photocoagulation 1 week after the first conbercept injection.

### Intravitreal Conbercept Injections

The procedure for intravitreal conbercept injections was conducted in an operating room under aseptic conditions, including the use of sterile gloves and a sterile drape. After adequate topical anesthesia and insertion of an eyelid speculum, a single dose of 0.5 mg (0.05 ml) of conbercept (Chengdu Kanghong Biological Co., Ltd., Chengdu, China) was injected intravitreally, 3.5 to 4 mm posterior to the limbus, using a 30-gauge needle through the superotemporal quadrant. Levofloxacin eye drops were instilled into the eye postoperatively at a dose of four times per day for one week to prevent infection.

### Focal Macular Photocoagulation

Direct photocoagulation was performed on all leaking lesions, including microangioma and dilated capillaries, as revealed by fundus fluorescein angiography (FFA), within 500-3000 μm from the fovea centralis, using an ophthalmic multiwavelength laser emitter (Lumenis, USA) under the following operating conditions: laser spot diameter of 50-100 μm, exposure time of 0.1 s, and power of 50-150 mW, until the appearance of localized, pale white burns (with Grade-1 intensity) as the endpoint. The same physician performed all laser photocoagulation procedures.

### Follow-up and Observation Indicators

The BCVA and CMT were recorded before treatment and at 1, 3, 6, 9, and 12 months after treatment. The mean number of injections and any complications, such as injection site hemorrhage, endophthalmitis, and retinal detachment,

**Table 1.** Comparison of Baseline Information between the Two Groups of Patients

| Group | Sex (Number) | | Age | Duration Of Diabetes | Glycated Hemoglobin Levels | Pre-Treatment BCVA | Pre-Treatment CMT |
|---|---|---|---|---|---|---|---|
| | Male | Female | (years, $\bar{x} \pm s$) | (months, $\bar{x} \pm s$) | (%, $\bar{x} \pm s$) | ($\bar{x} \pm s$) | (μm, $\bar{x} \pm s$) |
| Conbercept Treatment (n = 30) | 17 | 13 | 59.2 ± 6.6 | 10.4 ± 5.9 | 7.2 ± 1.3 | 0.7 ± 0.2 | 561.7 ± 106.7 |
| Combined Treatment (n = 30) | 18 | 12 | 59.4 ± 5.3 | 10.8 ± 6.6 | 7.3 ± 1.3 | 0.7 ± 0.3 | 590.5 ± 128.5 |
| $t/\chi^2$ | | 0.06 | 0.08 | 0.26 | 0.35 | 0.77 | 0.94 |
| *P* value | | .79 | .93 | .78 | .72 | .44 | .34 |

Note: $\bar{x} \pm s$ represents mean ± standard deviation

**Abbreviations**: BCVA, best-corrected visual acuity; CMT, central macular thickness.

**Table 2**: Comparison of BCVA between the Two Groups at Each Time Point ($\bar{x} \pm s$)

| Group | Number Of Affected Eyes | Before Treatment | One Month After Treatment | Three Months After Treatment | Six Months After Treatment | Nine Months After Treatment | Twelve Months After Treatment |
|---|---|---|---|---|---|---|---|
| Conbercept Treatment | 30 | 0.70 ± 0.29 | 0.43 ± 0.32[a] | 0.40 ± 0.27[a] | 0.42 ± 0.27[a] | 0.39 ± 0.22[a] | 0.41 ± 0.23[a] |
| Combined Treatment | 30 | 0.76 ± 0.31 | 0.46 ± 0.32[a] | 0.39 ± 0.24[a] | 0.40 ± 0.25[a] | 0.39 ± 0.24[a] | 0.40 ± 0.23[a] |
| $t_{\text{inter-Group}}$ | | 0.77 | 0.31 | 0.20 | 0.27 | 0.00 | 0.16 |
| $P_{\text{inter-Group}}$ | | .44 | .75 | .84 | 0.78 | 1.00 | .86 |

[a]statistically significant ($P_a < .001$) comparison between the conbercept and combined treatment groups

Note: $\bar{x} \pm s$ represents mean ± standard deviation

**Abbreviations**: BCVA, best-corrected visual acuity; $t_{\text{intergroup}}$, *t* test for intergroup comparison; $P_{\text{intergroup}}$, *P* value for intergroup comparison.

after treatment in each group was recorded. The BCVA was measured using the Snellen chart, and Snellen visual acuity was converted to LogMAR visual acuity for analysis. Frequency domain OCT and FFA were performed using a Spectralis HRA+OCT device (Heidelberg, Germany). The CMT was measured using the analysis software that came with the device, and the results were manually calibrated.

### Statistical Analysis

Statistical analysis was performed using SPSS software version 23.0 (IBM, Chicago, Illinois, USA). A *P* value of less than .05 was considered indicative of a statistically significant difference. The measurement data were confirmed to be normally distributed using the W test and expressed as means ± standard deviations ($\bar{x} \pm s$). Intra-group comparison of BCVA and CMT at different time points was performed using paired t-test. Inter-group comparisons of BCVA and CMT at different time points and the mean number of injections were performed using independent samples *t* test. The incidence of adverse events in each group was assessed using the $\chi^2$ test.

## RESULTS

### Comparison of BCVA between Two Groups at Each Time Point

At 1, 3, 6, 9, and 12 months after treatment, the BCVA in both the conbercept treatment group and the combined treatment group showed significant improvement compared to the baseline BCVA (post- vs pre-treatment in the conbercept treatment group: $t = 3.44$, 4.24, 3.95, 4.55, and 4.63, respectively, with all $P < .001$; post- vs pre-treatment in the combined treatment group: $t = 7.37$, 8.93, 8.39, 8.42, and 8.49, respectively, with all $P < .001$). There was no significant difference in BCVA between the two groups at each time point ($t = 0.77$, 0.31, 0.20, 0.27, 0.00, and 0.16, respectively, with all *P* values >.05) (Table 2, Figure 1).

**Figure 1:** Mean Change in The Best-Corrected Visual Acuity (BCVA) Over 12 Months.

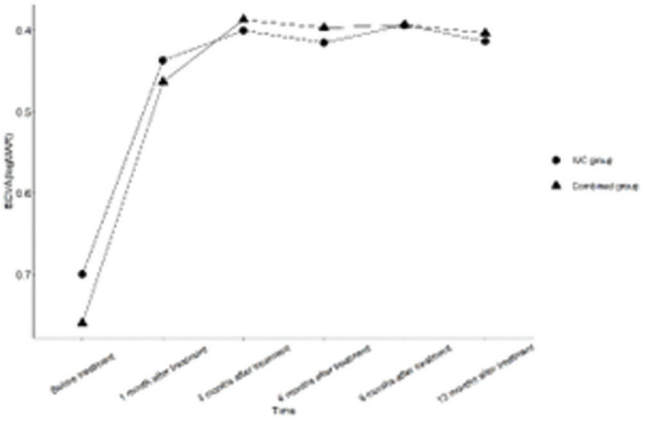


**Table 3.** Comparison of CMT between the two groups at each time point ($\bar{x}$ ± s, μm)

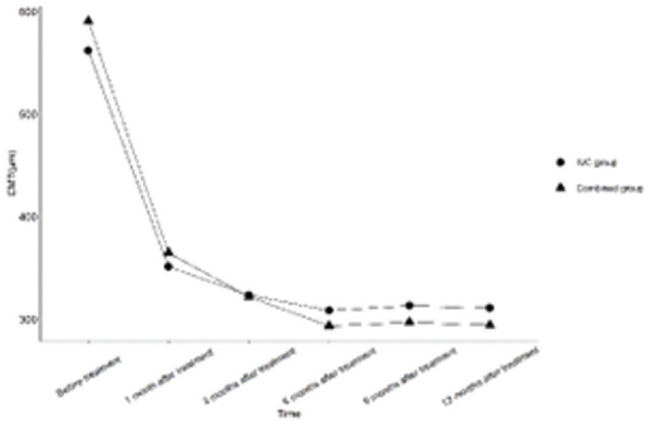
| Group | No of Affected Eyes | Before Treatment | One Month After Treatment | Three Months After Treatment | Six Months After Treatment | Nine Months After Treatment | Twelve Months After Treatment |
|---|---|---|---|---|---|---|---|
| Conbercept Treatment | 30 | 561.76 ± 106.73[a] | 351.17 ± 96.31[a] | 323.37 ± 78.11[a] | 308.47 ± 75.184[a] | 313.16 ± 64.32[a] | 310.9 ± 62.18[a] |
| Combined Treatment | 30 | 590.50 ± 128.59[a] | 364.67 ± 117.78[a] | 321.8 ± 95.63[a] | 293.46 ± 64.06[a] | 296.97 ± 61.35[a] | 294.10 ± 53.42[a] |
| $t_{\text{inter-group}}$ | | 0.94 | 0.48 | 0.06 | 0.82 | 0.99 | 1.12 |
| $P_{\text{inter-group}}$ | | .34 | .62 | .94 | .41 | .32 | .26 |

[a]statistically significant ($P_a < .001$) comparison between the conbercept and combined treatment groups.

Note: $\bar{x}$ ± s represents mean ± standard deviation.

**Abbreviations**: CMT, central macular thickness; $t_{\text{intergroup}}$, *t* test for intergroup comparison; $P_{\text{intergroup}}$, *P* value for intergroup comparison.

**Figure 2.** Mean Change in The Central Macular Thickness (CMT) Over 12 Months.




### Comparison of CMT between Two Groups at Each Time Point

At 1, 3, 6, 9, and 12 months after treatment, the CMT decreased significantly in both the conbercept treatment group and the combined treatment group compared to baseline (post- vs pre-treatment in the conbercept treatment group: $t = 12.08$, 14.88, 14.68, 15.79, and 12.15, respectively, with all $P < .001$; post- vs pre-treatment in the combined treatment group: $t = 9.13$, 11.62, 11.78, 11.79, and 12.67, respectively, with all $P < .001$). There was no significant difference in CMT between the two groups at each time point ($t = .94$, 0.48, 0.06, 0.82, 0.99, and 1.12, respectively, with all $P > .05$) (Table 3, Figure 2).

### Comparison of Number of Conbercept Injections between Two Groups

Patients in the combined treatment group were administered fewer injections within one year than those in the conbercept treatment group (6.3 ± 0.8 vs 7.6 ± 0.9), with a significant difference ($t = 5.556$, $P < .001$). After completing initial treatment with a 5+PRN regimen in both groups, all 30 eyes (100%) in the conbercept treatment group received additional injections. In the conbercept treatment group, 2 eyes received one additional injection (total of 6 injections), 14 eyes received two additional injections (total of 7 injections), 9 eyes received three additional injections (total of 8 injections), 3 eyes received four additional injections (total of 9 injections), and 2 eyes received five additional injections (total of 10 injections), resulting in a total of 229 injections. In the combined treatment group, 26 eyes (87%) received additional injections, with 14 eyes receiving one additional injection (total of 6 injections), 10 eyes receiving two additional injections (total of 7 injections), and 2 eyes receiving three additional injections (total of 8 injections), resulting in a total of 190 injections.

### Comparison of Complications in Both Groups

During the follow-up period, no treatment-related ocular or systemic complications, such as elevated intraocular pressure, iatrogenic cataract, vitreous hemorrhage, or retinal detachment, were observed in either the conbercept treatment group or the combined treatment group. Subconjunctival hemorrhage was observed in 25 cases (10.9%) out of 229 injections in the conbercept treatment group and in 20 cases (10.5%) out of 190 injections in the combined treatment group, with no significant difference ($\chi^2 = 0.013$, $P = .908$).

## DISCUSSION

CI-DME is a major cause of central vision loss in patients with DR, and its treatment has long been a major concern for ophthalmologists.[6] Currently, several authoritative guidelines have identified anti-VEGF therapy as the first-line treatment option for DME, with the wide acceptance of the concept of early intensive treatment.[7-9] However, even with the current standard anti-VEGF regimen, more than 30% of patients with DME develop residual edema or repeated recurrences after treatment,[10,11] making it necessary for ophthalmologists to explore more optimal treatment options. Macular laser photocoagulation was once the main treatment for DME; however, its effectiveness in improving visual acuity is poor, leading to a gradual decrease

in the use of this technique alone in clinical practices. In recent years, the focus of research has shifted towards investigating whether combining macular laser photocoagulation with the use of anti-VEGF drugs can help prevent the worsening of DME. To the best of our knowledge, this was the first study to compare a 5+PRN regimen of conbercept with a combined regimen of conbercept and focal macular photocoagulation in the treatment of DME. The results demonstrated that both regimens were effective in improving BCVA and reducing CMT in the affected eyes.

The existing studies on the combination of anti-VEGF drugs with laser photocoagulation for DME primarily focus on macular grid photocoagulation.[12-16] However, grid photocoagulation may cause damage to macular visual function and carries the risk of expanding scars.[17] Moisseiev et al.[18] reported that photocoagulation could reduce the number of anti-VEGF injections. However, data supporting the optimization of laser power and assessment of success rate are insufficient, making micropulse laser photocoagulation susceptible to under-treatment and treatment failure.[18,19]

An alternative option is focal macular photocoagulation, which involves FFA-guided photocoagulation of leaking macular lesions in patients who have residual edema after three to six consecutive anti-VEGF drug treatments or those with repeated recurrences during the follow-up period.[20] In this study, after adequate anti-VEGF therapy, focal macular photocoagulation was performed to directly photocoagulate the leaking microangiomas and capillaries revealed by FFA, effectively reducing macular edema and minimizing laser-induced damage. It is noteworthy that focal macular photocoagulation was initiated 1 week after the fifth conbercept injection in this study. This timing was chosen as by this time, the macular edema had significantly resolved with the administration of the anti-VEGF drug, thus avoiding the formation of a fluid barrier that could have been formed due to fluid accumulation in the macula. This approach facilitated the laser to exhibit its beneficial biological effect. This treatment protocol effectively combined the advantages of both treatment approaches, ensuring early initiation and adequate administration of anti-VEGF therapy, while also providing effective complementary therapy through focal macular photocoagulation, thereby optimizing the therapeutic efficacy.

Conbercept is a novel recombinant fusion protein developed in China as an anti-VEGF drug, which the Chinese Food and Drug Administration has approved for the treatment of DME since May 2019.[21-23] Conbercept exhibits high affinity and a long duration of action, as it can bind to multiple VEGF receptors. Its affinity for VEGF is 50 and 30 times higher than bevacizumab and ranibizumab, respectively.[24,25] Conbercept has a lower VEGF dissociation rate and isoelectric point than aflibercept, enabling it to have a longer effective duration of action in the vitreous cavity.[26] The SAILING study demonstrated that conbercept significantly improved visual acuity, reduced CMT (central macular thickness), and decreased the area of vascular leakage in patients with DME.[22]

Furthermore, a clinical study involving 68 affected eyes demonstrated that when the 3+PRN regimen was utilized in both the conbercept and ranibizumab groups, comparable visual acuity and retinal anatomy improvements were achieved at 12 months. However, the number of injections required was significantly lower in the conbercept treatment group compared to the ranibizumab group.[27] In the present study, both the conbercept and combined treatment groups demonstrated improved best-corrected visual acuity (BCVA) and reduced central macular thickness (CMT) at 1, 3, 6, 9, and 12 months after treatment when compared to baseline. However, there were no significant differences between the two groups. Moreover, no serious surgery-related complications were observed in either group during the 1-year follow-up period. These findings suggest that the treatment of DME with intravitreal conbercept injections, with or without focal macular photocoagulation, is both safe and effective in improving visual acuity and retinal anatomy in affected eyes. The combined treatment group required a significantly lower number of intravitreal injections ($6.3 \pm 0.8$) compared to the conbercept treatment group ($7.6 \pm 0.9$, $P < .001$), indicating that the addition of focal macular photocoagulation to conbercept therapy may help prevent DME worsening, reduce recurrence rate, prolong the duration of conbercept's efficacy, lower the number of injections, and reduce the financial burden on patients.

### Study Limitations

Limitations of the study should be considered. Firstly, the study design was retrospective, which may introduce data collection and analysis biases. Secondly, the sample size was small, which may restrict the generalizability of the findings to a larger population. Thirdly, a longer follow-up period is needed to assess the long-term effects of the treatment. Therefore, to further confirm the long-term therapeutic effectiveness and safety of combined anti-VEGF therapy with focal macular photocoagulation in the treatment of DME, a multicenter prospective study with a larger sample size is warranted.

## CONCLUSION

The findings of this study suggest that both intravitreal conbercept alone and in combination with focal macular photocoagulation are effective in treating diabetic macular edema, with a favorable safety profile. The combination therapy has the potential to reduce the number of intravitreal injections needed, which may have benefits in terms of treatment cost and financial burden on patients. However, it is important to acknowledge that this study has limitations, including its retrospective Design, small sample size, and the need for longer follow-up to assess long-term effects. Further research, preferably multicenter prospective studies with larger sample sizes, is warranted to confirm the long-term therapeutic effectiveness and safety of this combined treatment approach for DME.

## CONFLICT OF INTERESTS

The authors declared no conflict of interest.

## AUTHOR CONTRIBUTIONS

YM and SW designed the study and performed the experiments, XJ and KC collected the data, SH and YX analyzed the data, YM and SW prepared the manuscript. All authors read and approved the final manuscript.

## FUNDING

This study did not receive any funding in any form.

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