• Clinical Research •

Conbercept combined with 577 nm subthreshold micropulse laser for diabetic macular edema

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Abstract

● **AIM:** To evaluate the efficacy and safety of conbercept combined with 577 nm subthreshold micropulse laser (STML) for treatment of diabetic macular edema (DME).

● **METHODS:** A retrospective study was conducted. From October 2022 to March 2024, 72 patients diagnosed with DME at the outpatient clinic were enrolled. The patients were divided into two groups: the simple group (treated with conbercept alone) and the combination group (treated with 577 nm STML combined with conbercept). The following itmes were compared between the two groups: best corrected visual acuity (BCVA), central macular thickness (CMT), foveal avascular zone (FAZ), vessel density of the superficial capillary plexus (SCP) and deep capillary plexus (DCP), retinal mean sensitivity (RMS), injection numbers, and the number of cases with adverse effects.

● **RESULTS:** The mean age of patients was 57.13±8.76 (range 34-77)y with DR history of 0.89±0.55y. With the progression of treatment, both groups showed significant improvements in BCVA, CMT, DCP vessel density, and RMS compared to baselines (all, P<0.05). At 3 and 6mo after treatment, the combination group exhibited significantly better outcomes in BCVA, CMT, DCP vessel density, and RMS than the simple group (P<0.05). During the treatment period, neither group showed significant improvements in FAZ and SCP vessel density (P>0.05), and no significant differences in FAZ and SCP vessel density were observed between the two groups (P>0.05). The average number of injections required in the combination group was lower than that in the simple group (3.33±0.68 *vs* 4.06±0.96, P<0.05). No other serious ophthalmic adverse events were observed in either group.

● **CONCLUSION:** Conbercept combined with STML has better outcomes for treatment of DME and less intravitreal injections compared to conbercept monotherapy.

● **KEYWORDS:** 577 nm subthreshold micropulse laser; conbercept; diabetic macular edema; optical coherence tomography angiography

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INTRODUCTION

Diabetic retinopathy (DR) is a leading cause of blurry vision among individuals. The primary contributor to DR is diabetic macular edema (DME). The pathogenesis of DME greatly threatens the central vision of patients. In recent years, with the deepening of the understanding of DR and DME, the diagnostic and evaluation methods have been improved and the treatment methods have made great breakthroughs. Other effective methods for DME include laser photocoagulation, micropulse lasers, and anti-vascular endothelial growth factor (VEGF) drugs[1]. Despite the effectiveness of anti-VEGF treatment, it still has some limitations, including the increased risk of intraocular infection due to repeated invasive injection maneuvers, the heavy financial pressure on patients, and the insensitivity of a few patients to the drug. Therefore, finding a safer and more cost-effective way to treat DME is especially important.

The 577 nm subthreshold micropulse laser (STML) has been used clinically since 2009. It uses a yellow laser with a power of 200-400 mW and a wavelength of 577 nm. It is a high-frequency, short-duration, subthreshold, selective photocoagulation laser that reduces the spread of damage to

surrounding tissue layers. The advantages of STML are its highest oxyhemoglobin absorption, highest melanin absorption, and ability to penetrate the lens and superficial hemorrhage with low absorption by lutein, which not only reduces phototoxicity, but also meets the requirements of low scatter, low power consumption, high safety, and few side effects[2-3]. This research aims to assess the varying effectiveness between Conbercept combined with STML and conbercept intravitreal injection alone for DME treatment.

PARTICIPANTS AND METHODS

Ethical Approval The research rigorously followed the Declaration of Helsinki guidelines. Informed consent was obtained from all subjects. The research was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University. Ratification 2024-KY-1940-001.

Study Design and Participants This was a retrospective study. From October 2022 to March 2024, 72 patients diagnosed with DME at the outpatient clinic were separated into two groups based on different previous treatment plans: one group consisting of 36 eyes received only the conbercept injection (referred to as the simple group), while the other group, also comprising 36 eyes, underwent the micropulse and conbercept combination treatment group (referred to as the combination group). Inclusion Criteria were: 1) those who met the diagnostic criteria of DME diagnostic criteria; 2) with good glycemic control; 3) without any diagnosis and treatment before visiting our hospital; 4) central macular thickness (CMT) >250 μm; 5) no serious refractive media clouding. Exclusion criteria were: 1) presence of other retinal diseases, such as retinal vein occlusion or macular degeneration; 2) presence of ocular surface diseases affecting treatment and observation, such as conjunctivitis or keratitis; 3) presence of severe cardiovascular diseases and other systemic diseases; 4) allergy to medications used in the examination and treatment process; 5) CMT still exceeding 400 μm two weeks after the initial conbercept injection (at the first STML treatment); 6) patients have difficulty in completing follow-up visits.

Treatment Details

Intravitreal conbercept injection Patients received levofloxacin eye drops to prevent infection 2d before surgery. All patients were injected by the same ophthalmologist. The pupil of the operated eye was dilated 4 times 1h before surgery, preoperative preparation was completed, and then the patient was instructed to lie flat on the operating table, routine disinfection and towel spreading, proparacaine topical anesthesia, and irrigation of the conjunctival sac. The needle was inserted 3.5 mm posterior to the temporal limbus at a 90° angle perpendicular to the sclera. After confirming the needle tip was in the vitreous cavity, 0.05 mL of conbercept was slowly injected. After surgery, cotton swabs were pressed to stop bleeding, gatifloxacin ophthalmic ointment was applied, and the eye was patched. Monitoring of the intraocular pressure in the eye post-surgery was conducted on the surgery day and the initial day after the operation.

The 577 nm subthreshold micropulse laser treatment After the pupils were sufficiently dilated, topical anesthesia was induced with promethazine eye drops, and retinal laser photocoagulation was performed with the IQ 577 laser therapy device. Select the micropulse mode. The settings were: spot diameter of 200 μm, exposure time of 200ms, duty cycle of 5%, energy of 400 mW, photocoagulation area covering the entire retinal edema area, and leakage points, multipoint scanning in 7×7 matrix mode, and interspace scanning in the interspot area. At the end of the treatment, patients were asked to wait in the observation room for 20min and were allowed to leave if there was no visual impairment in the operated eye. Patients were given pranoprofen eye drops 4 times/d for 5d. All STMLs were done by the same ophthalmologist.

Group treatment The simple group received only conbercept treatment [3+*pro re nata* (PRN)], while the combination group received conbercept treatment (3+PRN) and STML treatment (1+PRN). All patients in both groups received 3 conbercept injections as a loading dose. At follow-ups, conbercept treatment continued if CMT>250 μm. In the combination group, the first STML treatment performed 2wk after the first injection of conbercept injection. At follow-ups, STML treatment administered when 250<CMT≤400 μm.

Outcomes Primary and Secondary Optical coherence tomography (OCT, Heidelberg, Germany), MP-3 microperimetry (Nidek, Japan), and optical coherence tomography angiography (OCTA, Intalight VG200D, China) were used to compare the amount of change in best corrected visual acuity (BCVA), central macular thickness (CMT), foveal avascular zone (FAZ), superficial capillary plexus (SCP), deep capillary plexus (DCP) vessel density, retinal mean sensitivity (RMS), injection frequency and cases of side effects in each group over 6mo.

Statistical Analysis SPSS26.0 statistical software was used. Data following a normal distribution were presented as mean±standard deviation (SD). For overall comparisons of all indicators at different follow-up time points between the two groups, a two-way repeated measures ANOVA was used. Post-hoc comparisons were performed using the LSD-*t* test. The independent samples *t*-test was used for between-group comparisons, and the Chi-square test for categorical variables. Data that did not follow a normal distribution were presented as the median (interquartile range), with comparisons conducted through non-parametric methods. $P<0.05$ was deemed statistically significant.

RESULTS

This study included 72 patients (35 men and 37 women).

Table 1 Comparison of general information before treatment mean±SD

Indicators	Simple group (*n*=36)	Combination group (*n*=36)	Statistical value	*P*
Age (y)	57.50±8.81	56.75±8.83	*t*=0.361	0.719
Gender (male/female)	16/20	19/17	χ^2=0.056	0.814
Eye (right/left)	17/19	16/20	χ^2=0.500	0.480
BCVA (logMAR)	0.60±0.15	0.60±0.13	*t*=0.155	0.877
CMT (μm)	394.92±63.92	399.56±52.70	*t*=-0.336	0.738
SCP vessel density (%)	30.49±2.94	30.51±3.30	*t*=-0.029	0.977
DCP vessel density (%)	32.22±2.97	32.84±2.52	*t*=-0.960	0.341
FAZ (mm^2)	0.482±0.102	0.486±0.092	*t*=-0.145	0.885
RMS (dB)	20.01±1.22	19.65±0.95	*t*=1.420	0.160
Follow-up time (mo)	6.06±0.21	6.05±0.22	*t*=0.330	0.742

BCVA: Best corrected visual acuity; CMT: Central macular thickness; SCP: Superficial capillary plexus; DCP: Deep capillary plexus; FAZ: Foveal avascular zone; RMS: Retinal mean sensitivity.

Table 2 Comparison of BCVA at different time points between the two groups mean±SD, logMAR

Groups	Different time points			
	Pretreatment	1mo	3mo	6mo
Simple group	0.60±0.15	0.41±0.10[a]	0.35±0.10[a]	0.30±0.10[a]
Combination group	0.60±0.13	0.38±0.11[a]	0.26±0.11[a,b]	0.20±0.07[a,b]

F_{time}=157.916, *P*<0.001; F_{group}=15.441, *P*<0.001; $F_{interaction}$=3.770, *P*=0.012. Compared with pre-treatment in the same group, [a]*P*<0.001; compared with the simple group at the same time point, [b]*P*<0.001. BCVA: Best corrected visual acuity.

Table 3 Comparison of CMT at different time points between the two groups mean±SD, μm

Groups	Different time points			
	Pretreatment	1mo	3mo	6mo
Simple group	394.92±63.92	288.53±51.45[a]	255.31±51.73[a]	226.72±45.36[a]
Combination group	399.56±52.70	282.00±49.71[a]	222.33±37.01[a,b]	192.92±36.70[a,b]

F_{time}=209.263, *P*<0.001; F_{group}=7.831, *P*=0.007; $F_{interaction}$=2.866, *P*=0.048. Compared with pre-treatment in the same group, [a]*P*<0.001; compared with the simple group at the same time point, [b]*P*<0.05. CMT: Central macular thickness.

Based on different treatment plans, patients were divided into the simple group (*n*=36) and the combination group (*n*=36). Comparative analysis showed no significant differences in age, gender, eye, BCVA, CMT, SCP vessel density, DCP vessel density, FAZ, RMS, and follow-up time between the two groups (*P*>0.05; Table 1).

In both groups, BCVA, CMT, DCP, and RMS showed significant improvement over time. There were significant differences between the two groups and a significant interaction effect between time and group (BCVA: P_{time}<0.001, P_{group}<0.001, $P_{interaction}$=0.012; CMT: P_{time}<0.001, P_{group}=0.007, $P_{interaction}$=0.048; DCP: P_{time}<0.001, P_{group}<0.001, $P_{interaction}$=0.002; RMS: P_{time}<0.001, P_{group}<0.001, $P_{interaction}$<0.001). Further simple effects analysis was conducted to explore the differences in treatment effects between and within groups. For intergroup comparisons, there were no significant differences in BCVA, CMT, DCP, or RMS before treatment and at 1mo after treatment (*P*>0.05; Tables 2, 3, 5, and 7). However, at 3 and 6mo after treatment, the combination group exhibited significantly better treatment outcomes than the simple group (*P*<0.05). For intragroup comparisons, both groups demonstrated significant after treatment improvements in BCVA, CMT, DCP, and RMS at all three time points (*P*<0.05). As time progressed, these parameters continued to improve in both groups (*P*<0.05).

No significant differences were found in SCP and FAZ between the two groups at different time points, and there were no significant interactions between time and group (SCP: P_{time}=0.084, P_{group}=0.923, $P_{interaction}$=0.992; FAZ: P_{time}=0.839, P_{group}=0.989, $P_{interaction}$=0.998) (Tables 4 and 6; Figures 1 and 2).

The mean number of injections in the simple and combination group was 4.06±0.96 and 3.33±0.68. The difference between the groups was statistically significant (*P*<0.05; Table 8).

During the 6mo, the simple group had increased intraocular pressure in 3 eyes and conjunctival hemorrhage in 1 eye; the combination group had increased intraocular pressure in 2 eyes and conjunctival hemorrhage in 2 eyes, and no other ophthalmologic serious adverse reactions occurred. No microscopic retinal damage was found in the patients on OCTA and RMS.

DISCUSSION

DR frequently arises as a complication in diabetes. The underlying causes of DME remain somewhat elusive, with prevailing theories suggesting they include alterations in hemodynamics due to hyperglycemia, decreased retinal perfusion, and blood-retinal barrier (BRB) disruption.

Table 4 Comparison of SCP vessel density at different time points between the two groups mean±SD, %

Groups	Different time points			
	Pretreatment	1mo	3mo	6mo
Simple group	30.49±2.94	31.17±3.16	29.86±2.84	29.99±3.51
Combination group	30.51±3.30	31.30±3.40	29.97±3.17	29.87±4.24

F_{time}=2.349, P=0.084; F_{group}=0.010, P=0.923; $F_{interaction}$=0.020, P=0.992. SCP: Superficial capillary plexus.

Table 5 Comparison of DCP vessel density at different time points between the two groups mean±SD, %

Groups	Different time points			
	Pretreatment	1mo	3mo	6mo
Simple group	32.22±2.97	34.63±2.96[a]	37.70±3.05[a]	39.58±3.16[a]
Combination group	32.84±2.52	34.96±2.27[a]	40.65±2.47[a,b]	42.55±2.26[a,b]

F_{time}=153.059, P<0.001; F_{group}=26.155, P<0.001; $F_{interaction}$=5.144, P=0.002. Compared with pre-treatment in the same group, [a]P<0.05; compared with the simple group at the same time point, [b]P<0.001. DCP: Deep capillary plexus.

Table 6 Comparison of FAZ at different time points between the two groups mean±SD, mm^2

Groups	Different time points			
	Pretreatment	1mo	3mo	6mo
Simple group	0.482±0.102	0.475±0.082	0.473±0.080	0.478±0.091
Combination group	0.486±0.092	0.474±0.086	0.471±0.073	0.478±0.089

F_{time}=0.281, P=0.839; F_{group}=0.001, P=0.989; $F_{interaction}$=0.012, P=0.998. FAZ: Foveal avascular zone.

Table 7 Comparison of RMS at different time points between the two groups mean±SD, dB

Groups	Different time points			
	Pretreatment	1mo	3mo	6mo
Simple group	20.01±1.22	21.44±1.29[a]	22.06±1.14[a]	22.66±1.23[a]
Combination group	19.65±0.95	21.46±1.18[a]	23.43±1.05[a,b]	24.03±1.32[a,b]

F_{time}=144.717, P<0.001; F_{group}=13.356, P<0.001; $F_{interaction}$=12.191, P<0.001. Compared with pre-treatment in the same group, [a]P<0.001; Compared with the simple group at the same time point, [b]P<0.001. RMS: Retinal mean sensitivity.

Table 8 Comparison of injection frequency mean±SD

Indicators	Simple group (n=36)	Combination group (n=36)	Statistical value	P
Total number of drug injection	4.06±0.96	3.33±0.68	t=3.705	<0.05

Presently, the primary therapeutic approach for DME involves anti-VEGF medications, proven through various research to diminish macular edema and enhance vision[4-8]. However, in clinical practice, there are still some limitations in the application of anti-VEGF therapy, such as multiple injections, which are economically burdensome; invasive treatment, which has a higher risk of adverse reactions; short duration of efficacy, which requires high patient compliance. Therefore, it is important to actively explore the feasibility of more DME treatments to achieve better therapeutic effects, which will improve the prognosis of patients, and reduce adverse reactions and economic burden.

More current studies have shown that STML can effectively treat macular edema caused by central serous chorioretinopathy (CSC), DR, and retinal vein occlusion (RVO) without causing permanent tissue damage[9-11]. Some previous studies indicated that micropulse laser selectively acts on retinal pigment epithelium (RPE) cells to restore the BRB function and RPE cell pump function by affecting the production of inflammatory biomarkers, growth factors [*e.g*., VEGF, pigment epithelium derived factor (PEDF), *etc*.], and heat-shock proteins (HSPs), to promote the absorption of subretinal fluid and reduce macular edema[12]. In patients with DME, micropulse laser may also restore retinal function and reduce macular edema by acting on Müller cells and improving their anatomical structure and physiological function.

In recent years, STML has been progressively applied to the treatment of a variety of fundus diseases and numerous research have validated the effectiveness and security of micropulse laser[13-16]. Recent research indicates that the use of anti-VEGF medications in conjunction with STML enhances the uptake of macular edema, reducing injection frequency and alleviating financial stress. By comparing the efficacy of the treatment of severe DME, Hosoya *et al*[17] found that both groups had the same effect in reducing CMT and increasing BCVA, but the combination group could relieve injection frequency. In a study by Wijeweera *et al*[16], it was found that the combined therapy group outperformed the laser-only group in relieving CMT and enhancing visual sharpness. This experiment also verified this result. The China 2022 Updated Clinical Guidelines for DR indicate that the impact of STML differs based on the intensity of DME. Individuals suffering from CMT smaller than 400 μm gained greater advantages from micropulse laser therapy; conversely, for those with

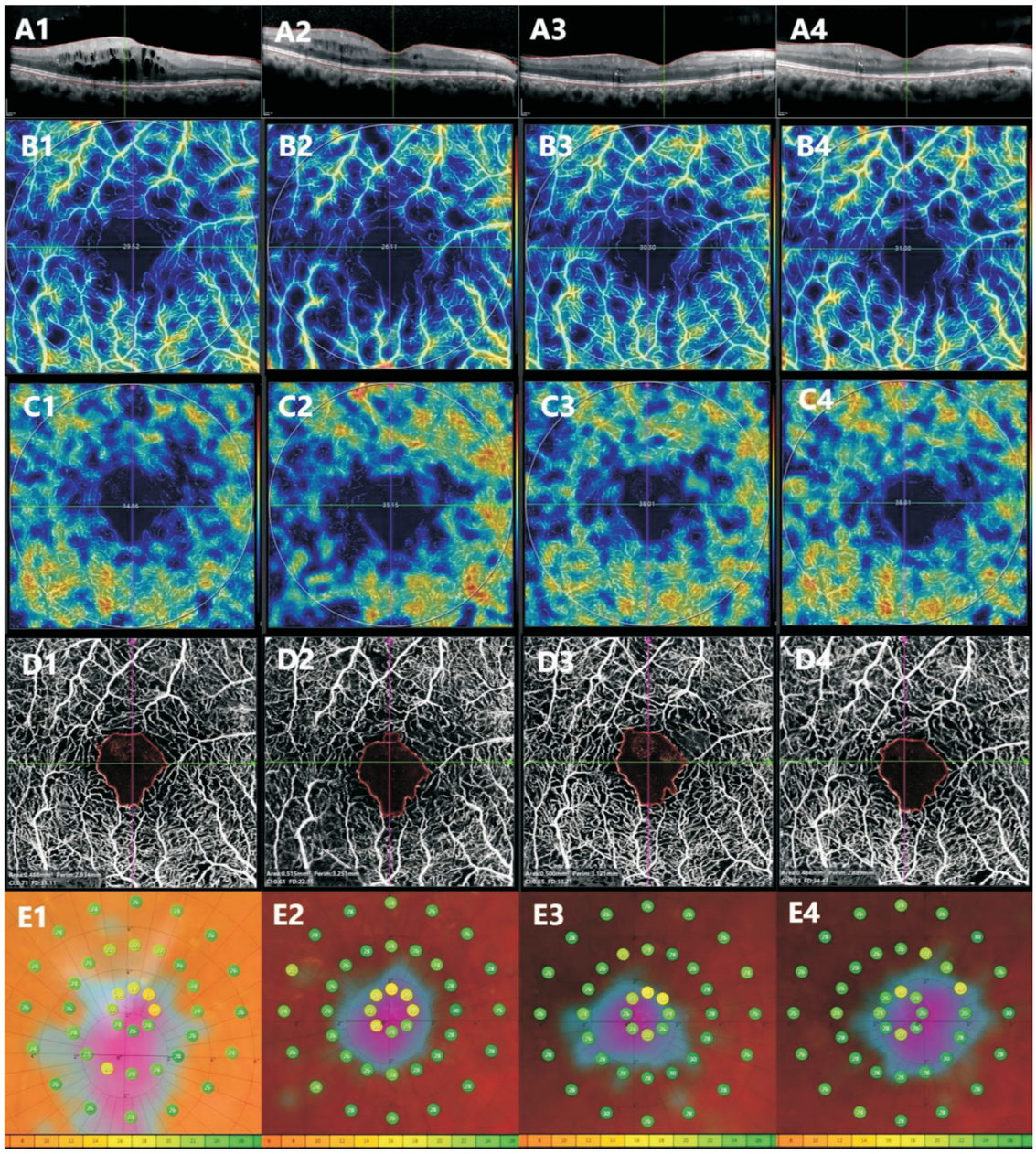

Figure 1 Comparison of OCT and OCTA images during follow-up of a patient in the simple treatment group A: OCT before treatment (A1), 1mo after treatment (A2), 3mo after treatment (A3), 6mo after treatment (A4); B: SCP blood flow density before treatment (B1), 1mo after treatment (B2), 3mo after treatment (B3), 6mo after treatment (B4); C: DCP blood flow density before treatment (C1), 1mo after treatment (C2), 3mo after treatment (C3), 6mo after treatment (C4); D: FAZ before treatment (D1), 1mo after treatment (D2), 3mo after treatment (D3), 6mo after treatment (D4); E: RMS before treatment (E1), 1mo after treatment (E2), 3mo after treatment (E3), 6mo after treatment (E4). OCT: Optical coherence tomography; OCTA: Optical coherence tomography angiography; SCP: Superficial capillary plexus; DCP: Deep capillary plexus; FAZ: Foveal avascular zone; RMS: Retinal mean sensitivity.

CMT larger than 400 μm, the onset of effect is longer, which may be due to the dispersion of the laser energy due to high edema, resulting in a limited effect of laser energy on the RPE layer, which reduces its therapeutic effect. Therefore, in this experiment, according to the latest guidelines for DR, three consecutive injections of anti-VEGF drugs (once a month) were given first, and later injections were given according to the PRN. The PRN criteria were: CMT>250 μm. For micropulse laser treatment, the "1+PRN" program was used, and the PRN criteria were: 250<CMT≤400 μm.

The changes in BCVA, CMT, and RMS within the two groups at 1mo were no notable statistical variance (P>0.05). The changes in BCVA, CMT, and RMS in the latter demonstrated significantly greater improvements than those in the former at 3 and 6mo (P<0.05). Anti-VEGF drugs reduce VEGF production and promote BRB repair and subretinal fluid absorption, further sensitizing the retina to light stimuli. The combination group had a more significant effect. On the one

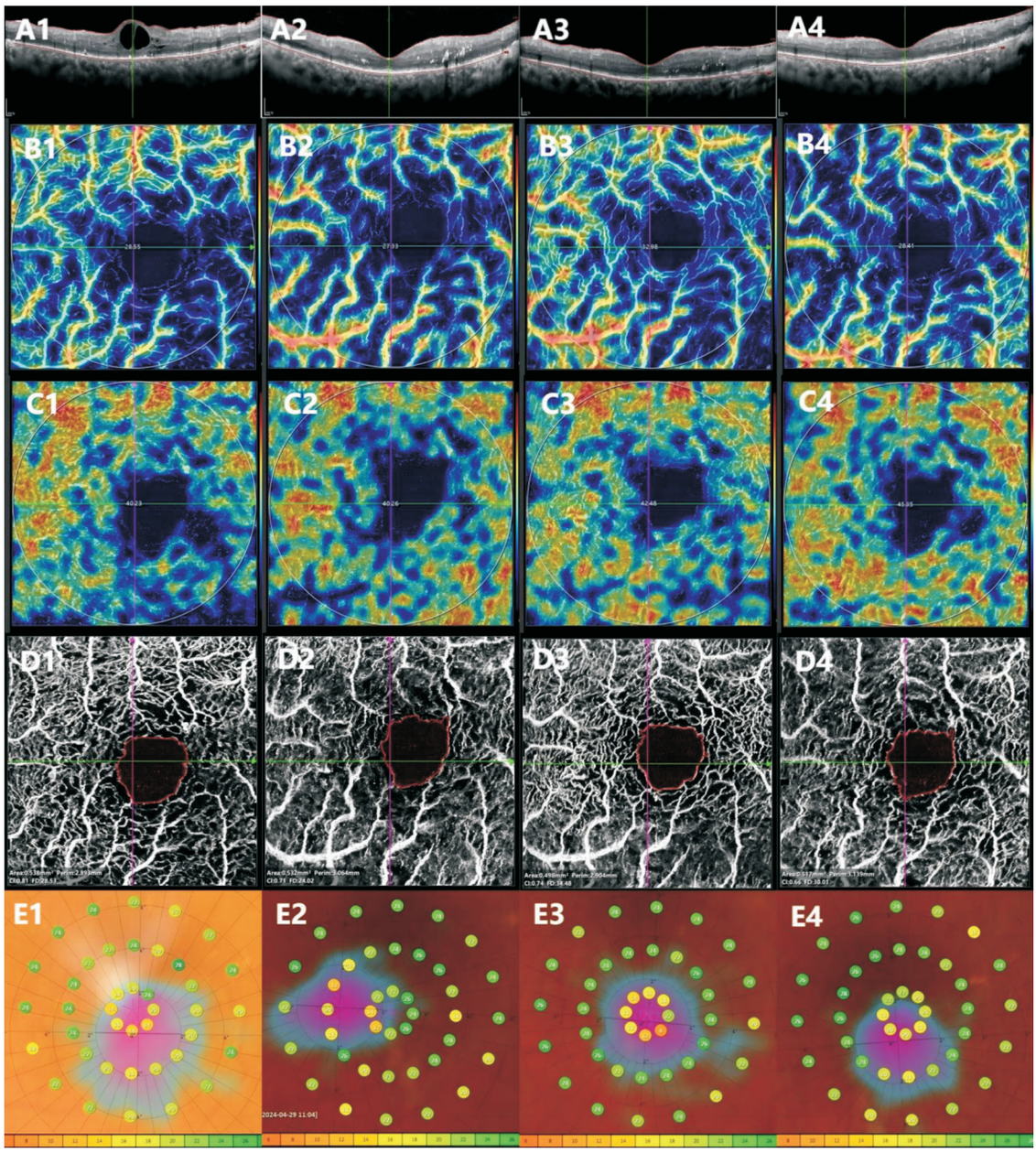

Figure 2 Comparison of OCT and OCTA images during follow-up of a patient in the combination treatment group A: OCT before treatment (A1), 1mo after treatment (A2), 3mo after treatment (A3), 6mo after treatment (A4); B: SCP blood flow density before treatment (B1), 1mo after treatment (B2), 3mo after treatment (B3), 6mo after treatment (B4); C: DCP blood flow density before treatment (C1), 1mo after treatment (C2), 3mo after treatment (C3), 6mo after treatment (C4); D: FAZ before treatment (D1), 1mo after treatment (D2), 3mo after treatment (D3), 6mo after treatment (D4); E: RMS before treatment (E1), 1mo after treatment (E2), 3mo after treatment (E3), 6mo after treatment (E4). OCT: Optical coherence tomography; OCTA: Optical coherence tomography angiography; SCP: Superficial capillary plexus; DCP: Deep capillary plexus; FAZ: Foveal avascular zone; RMS: Retinal mean sensitivity.

hand, the laser acted on the RPE layer, restored the dynamic balance between VEGF and PEDF, up-regulated the HSP, reduced the inflammatory reaction, promoted the repair of BRB, accelerated the recovery of CMT, and relieved the retinal compression more quickly, which not only alleviated the destructive effect but also made the light stimulation act on the RPE layer better with a lower CMT. On the other hand, micropulse laser may improve retinal blood flow density and correspondingly increase RMS and BCVA. No notable statistical variance at 1mo but differed at 3 and 6mo, probably because of the slow action of the micropulse laser. This result was further verified by Moisseiev *et al*[18], Khattab *et al*[19] and Kanar *et al*[20]. This suggests that combination therapy is superior to anti-VEGF therapy alone in improving CMT and improving BCVA.

In this study, some patients' macular edema subsided but BCVA and RMS were no improved. This may be because long-term repeated macular edema leads to the destruction of retinal

cell function and photoreceptors, and even though the edema subsides, its recovery still takes a long time or the permanent damage cannot be recovered. In our study, we also found very few patients had a significant improvement in RMS but no change in BCVA, which may be because the patient's baseline visual acuity was higher, the central visual acuity damage was less severe, the visual acuity improvement was smaller; or the follow-up time was shorter, and the change in BCVA had not yet been reflected. This further suggests that compared with BCVA, RMS can reflect retinal function more sensitively, and more clearly and accurately reflect the changes in condition and the effects of treatment, and that the quality of vision has changed despite the lack of change in BCVA. In addition, no micropulse-related adverse reactions were found in all patients, and there was no micropulse-related damage to the microfield, which further validated the safety of micropulse laser.

The study also found that patients showed different degrees of improvement in DCP (P<0.05), while FAZ and SCP did not improve (P>0.05). The changes in DCP within the two groups at 1mo were no statistical variance (P>0.05). The changes in DCP in the latter demonstrated significantly greater improvements than those in the former at 3 and 6mo (P<0.05); the amount of change in FAZ and SCP at 1, 3, and 6mo was no statistical variance (P>0.05). Preliminary consideration may be because the superficial capillary network is directly connected to small arteries with better perfusion and relatively less damage, while the deep capillary network, which part of the blood flow originates from the superficial capillaries, is prone to be damaged, and its response to hypoxia-ischemia and changes in the surrounding environment is more sensitive. After STML treatment, choroidal and retinal circulation improves, deep capillaries are rearranged, and vessel density increases, but this process is slow, and it takes time for the micropulse laser to take effect. Some scholars believe that SCP and DCP with preclinical DR have been significantly reduced, but others believe that only the DCP vessel density has been significantly reduced[21-23]. Mastropasqua *et al*[24] found that with the progression of DR, the vessel densities of DCP and SCP were gradually reduced but that the decrease in DCP occurred first and was more significant. A series of studies have demonstrated that the vessel density of DCP can more sensitively determine the severity of the disease, which is important for assessing the progression of DR. However, at present, different scholars have different views on the influence of anti-VEGF or micropulse laser on retinal vessel density. In the clinical observation, Yu *et al*[25] found that the improvement of BCVA and CMT in the combination group was highest, FAZ, SCP, and DCP vessel density with the other two groups having no notable statistical variance (P>0.05). The results of Zhu *et al*[26] showed a gradual increase in SCP and a trend of decrease in FAZ area after 6mo of continuous injection of conbercept treatment, but the mechanism of improvement was not clear. In this study, we did not obtain the results of SCP and FAZ improvement, and we considered that it might be because SCP was not sensitive enough compared with DCP, we did not obtain the results of the long-term efficacy of SCP and FAZ, and there might be an error in the fact that FAZ was measured manually. There was no difference in FAZ, which also verified the safety of STML. Some scholars believe that the restoration of perfusion to the ischemic retina may lead to ischemia-reperfusion injury and that the restoration of blood flow not only fails to restore the function of the retina but also leads to more serious functional metabolic disorders and structural damage[27]. Another part of the study supposed that although anti-VEGF drugs can relieve macular edema, they may aggravate retinal vascular occlusion and aggravate ischemia[28-29]. Less frequent injections of the latter than of the former (P<0.05), and no other ophthalmologic serious adverse reactions were observed in either group. This suggests that combination therapy may decrease injection frequency compared to the injection of anti-VEGF drugs alone, relieve economic stress, and not increase the incidence of complications.

In conclusion, both treatments can be effective in treating DME. The combination therapy significantly improves the visual acuity for a short period, reduces the macular edema, increases the density of vessels in the deep retina, reduces the number of injections, and does not increase FAZ and complication rates. However, this research still has limitations: some patients were lost; excluding patients difficult to follow up was a confounding factor; the follow-up time was short; a fixed energy setting was selected compared to titration; the sample size needed to be expanded; DME typing was not refined; and the type of anti-VEGF drug was not considered. Currently, there are fewer studies on the efficacy of anti-VEGF drugs and micropulse laser therapy in DR patients and a large number of basic experiments and clinical research are needed.

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