Outcomes of anti-VEGF therapy compared with conventional interventions in diabetic retinopathy management

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Abstract. The present study aimed to observe the progression of diabetic retinopathy (DR) and compare the clinical outcomes of anti-vascular endothelial growth factor (anti-VEGF) therapy, laser photocoagulation and vitrectomy in a real-world setting, to inform treatment strategies. The present prospective, observational study enrolled 371 patients (466 eyes) with DR who were followed for over 3 years at Xi'an Bright Eye Hospital (Xi'an, China). Patients received treatment with anti-VEGF, laser, combined therapy or vitrectomy based on their clinical condition. Best-corrected visual acuity (BCVA), central subfield thickness (CST) and incidence of complications were evaluated. The anti-VEGF group demonstrated a significantly greater improvement in BCVA and a reduction in CST compared with the laser group. Eyes with early-stage DR required fewer anti-VEGF injections to achieve stability than those with advanced disease. In eyes with low vision, the anti-VEGF group had a lower incidence of tractional retinal detachment but a higher rate of persistent macular edema compared with those in the laser group. For stages 4-5 DR, the rate of vision improvement was similar between anti-VEGF therapy and vitrectomy. In conclusion, anti-VEGF therapy is generally superior to laser in improving visual and anatomical outcomes. However, treatment strategies should be individualized based on disease stage and specific complications, with anti-VEGF favoring traction prevention and laser potentially offering better control for recurrent edema in some cases.

Introduction

Diabetic retinopathy (DR) is one of the most common microvascular complications of diabetes worldwide and a leading cause of vision loss. Its main characteristics include damage to the retinal microvascular endothelial cells, leading to vascular leakage and hemorrhage, retinal ischemia, non-perfusion, the appearance of neovascularization, proliferative DR and tractional retinal detachment, ultimately resulting in irreversible vision loss or blindness (1). DR is the most common cause of blindness among working-age individuals and the leading cause of blindness in developing countries (2). The prevalence of DR increases with the duration of diabetes, with ~20% of diabetic patients developing DR ≤10 years of diagnosis. This proportion can increase to >60% in patients with a disease duration of >20 years (3). In developing countries, there are ~246 million diabetic patients, ~33% of whom may develop DR (4). Due to the increasing prevalence of diabetes, as well the aging population in China, the number of individuals with DR is expected to grow (5). The multifactorial pathogenesis of DR characterized by hyperglycemia-induced metabolic disturbances, oxidative stress, chronic low-grade inflammation and vascular endothelial dysfunction (6), remains only partially understood, contributing to the current challenges in establishing standardized therapeutic protocols. Treatment methods are also overly complex and lack uniform standards. Common treatments for DR include systemic control of blood sugar, blood pressure and lipids (through lifestyle interventions and lipid-lowering medications), as well as specific treatments for retinopathy, such as laser therapy, intravitreal anti-VEGF injections and vitrectomy (7). However, the treatment of DR still requires basic and clinical research.

Macular edema is the most common complication of DR and the primary cause of vision loss in affected eyes (8). Macular edema can occur at any stage of DR (9). Treatment methods for macular edema have gradually shifted, primarily from grid-style laser photocoagulation, to anti-VEGF therapy (10). Previous evidence has suggested that early vitrectomy can also reduce the recurrence rate of macular edema (11). However, these findings lack sufficient clinical evidence.

The present study prospectively observed the clinical changes and outcomes in a real-world cohort of patients with DR. The occurrence, recurrence and improvement of macular edema were tracked, and the effectiveness of various therapeutic approaches as applied in clinical practice were compared to provide evidence for optimizing treatment strategies. A visual summary of the treatment comparisons and key outcomes is presented in Fig. 1.

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Materials and methods

Study subjects. The present prospective observational study was conducted at Xi'an Bright Eye Hospital (Xi'an, China) between December 2018 and December 2023. Consecutive patients were enrolled who had diabetic retinopathy (DR) and presented with retinal hemorrhage and exudation, and who had received treatment and were followed up for >3 years. The inclusion criteria were: i) A diagnosis of type 1 or type 2 diabetes mellitus; and ii) confirmed DR with documented retinal hemorrhage and exudation at baseline. The key exclusion criteria were: i) Other ocular diseases that could cause hemorrhage or exudation (for example, retinal vein occlusion); ii) media opacity preventing adequate fundus examination; and iii) a history of intraocular surgery (except for uncomplicated cataract surgery) within the prior 6 months. A total of 371 patients (466 eyes) were included in the final analysis. This cohort consisted of 214 men and 157 women. The number of eyes is greater than the number of patients as the study included individuals with both unilateral and bilateral involvement. For the purpose of specific ophthalmic outcome analyses (such as morphological changes), each eye was treated as an independent statistical unit. The median age was 61 years (range, 38-85 years). All eyes underwent slit lamp examination to exclude patients with conjunctival and corneal diseases, previous eye trauma or surgeries and intraoperative complications. All patients underwent refraction, intraocular pressure measurement, visual acuity assessment, ultra-wide field fundus photography and optical coherence tomography (OCT). All participants voluntarily took part in the present study and signed informed consent forms. This study was approved by the Medical Ethics Committee of Xi'an Bright Eye Hospital (approval no. XPR-2018-0018).

Examination methods. Eyes of all patients were examined using an SL30 slit lamp microscope (Zeiss GmbH) by the same ophthalmology outpatient deputy chief physician for conjunctiva, cornea, anterior chamber, pupil and lens. A single optometrist carried out refraction tests to determine the best-corrected visual acuity, using the Early Treatment Diabetic Retinopathy Study vision chart. Mydriasis was achieved with Medori® eye drops (Medori/Mydrin®-P; Compound Tropicamide Eye Drops; Santen Pharmaceutical Co., Ltd.), one drop every 5 min, a total of three times. After dilating the pupils to a diameter of 8 mm, images of both eyes were captured using the CLARUS$^{\hat{O}}$ 500 (Zeiss GmbH) and examined with the CIRRUS$^{\hat{O}}$ HD-OCT (Zeiss GmbH; Fig. S1). The results were diagnosed by two senior retinal specialists. All eyes were also examined under a slit lamp with a wide-field retinal lens (Clarus 500; Carl Zeiss AG). The examinations were conducted by the same chief physician of the retina specialty, who determined the stage of DR and macular edema according to the International Clinical Diabetic Retinopathy Disease Severity Scale and the associated guidelines for diabetic macular edema, and developed specific treatment plans, including intravitreal anti-VEGF injections, laser therapy or a combination thereof, based on the disease severity and the presence of center-involved macular edema. Representative OCT images illustrating baseline morphology and treatment response are provided in Figs. S2 and S3.

Laser and surgery. Panretinal photocoagulation and macular grid-style photocoagulation were carried out by the same internal medicine laser therapist, using the VISULAS® 532s (Zeiss GmbH). The panretinal photocoagulation was completed in three sessions, with energy settings of 200 mW, spot size of 200 μm and duration of 200 msec, achieving grade 3-4 spots and >5,000 spots in total (Fig. S4). The macular grid-style photocoagulation was completed in 1-2 sessions, with an energy of 100 mW, spot size of 100 μm and duration of 200 msec, achieving a total of 185±15 grade 1-2 spots at a distance of 200 μm from the macular center (Figs. S5-S7). Vitrectomy was carried out by the same chief surgeon of retinal surgery, using the OPMI LUMERA$^{\hat{O}}$ 700 microscope (Zeiss GmbH) equipped with the RESIGHT® noncontact wide-angle lens system (Zeiss GmbH) and the CONSTELLATION® vision system (Alcon Inc.). Depending on the severity of the patients' condition, a minimally invasive vitrectomy was carried out using 23, 25 or 27-gauge incisions. Intraoperatively, RT SIL-OL 5000 silicone oil (Zeiss GmbH) and FCI-OCTA S5.8250 liquid perfluorocarbon (FCI; Zeiss GmbH) were used.

Observation indicators. Observation indicators were as follows: i) Compare the prognosis and number of anti-VEGF injections in patients with different stages of DR; ii) compare the treatment effects and prognosis of patients under different treatment plans; and iii) observe the reasons for reduced vision in patients and compare their treatment plans. In the present study, an improvement or no change in best-corrected visual acuity was defined as effective treatment, whereas a decrease was defined as ineffective. DR was considered stable if effective treatment was observed continuously for 3 years. Best-corrected visual acuity ρ3 letters was defined as low vision.

Statistical analysis. Statistical analysis was performed using SPSS Statistics version 13.0 (SPSS, Inc.). Continuous data are presented as the mean ± standard deviation. The normality of data distribution for continuous variables (such as BCVA and CST) was assessed using the Shapiro-Wilk test. Homogeneity of variances was evaluated using Levene's test. For comparisons of continuous outcomes among three treatment groups (e.g., baseline characteristics in Table II, BCVA and CST over time in Tables III and IV), a one-way analysis of variance (ANOVA) was used for data meeting parametric assumptions, followed by Tukey's post hoc test for multiple comparisons. For data violating parametric assumptions, the Kruskal-Wallis test was used, followed by Dunn's post hoc test with Bonferroni correction. In Table V, where multiple DR stages were compared against a single reference group (Stage 1), a one-way ANOVA was performed, followed by Dunnett's post hoc test for parametric data. The non-parametric equivalent (Kruskal-Wallis with Dunn's test against a control) was applied where assumptions were not met. Categorical data are expressed as percentages and were compared between groups using the χ^2 test or Fisher's exact test, as appropriate.

Given that some patients contributed both eyes to the analysis, the potential for intra-patient correlation was acknowledged. Primary analyses treated eyes as independent units; however, key findings (particularly the primary

outcomes of BCVA and CST at the final follow-up) were verified using a generalized estimating equations (GEE) approach to account for this correlation. The GEE model did not alter the significance of the main outcomes reported from the primary analysis. A two-sided P-value of <0.05 was considered to indicate a statistically significant difference.

Results

General information of patients. The demographic and clinical characteristics of the 371 enrolled patients are summarized in Table I. The cohort included 206 men (55.5%) and 165 women (44.5%). A total of 161 patients (43.4%) had a history of hypertension. Regarding age distribution, 124 patients (33.4%) were ≤50 years old, 161 patients (43.4%) were between 50 and 70 years old, and 86 patients (23.2%) were >70 years old. The distribution of diabetes duration was as follows: 10 patients (2.7%) for <5 years, 18 patients (4.9%) for 5-10 years, 116 patients (31.3%) for 10-15 years, 136 patients (36.7%) for 15-20 years, 79 patients (21.3%) for 20-25 years and 12 patients (3.2%) for >25 years.

Observation of treatment in eyes with DR. A total of 371 patients (466 eyes) with DR were included in the treatment analysis, all of whom received treatment and completed the 3-year follow-up. This was a prospective, observational cohort study. Patients were managed according to standard clinical practice and the treating physician's discretion. Based on the primary treatment received during the study period, eyes were categorized into the following groups for comparative analysis: The anti-VEGF group (267 eyes), the retinal laser photocoagulation group (73 eyes) and the combined treatment group (126 eyes). No significant difference in best-corrected visual acuity (BCVA) was observed among the three groups before treatment.

The baseline characteristics of the three treatment groups are detailed in Table II. Crucially, there were notable differences in the distribution of diabetic retinopathy severity at baseline. The laser and combined treatment groups contained a significantly higher proportion of eyes with proliferative DR (stages 4-6) compared with the anti-VEGF group (P<0.05). This baseline imbalance was considered in the interpretation of the comparative outcomes.

After treatment, BCVA improved in all three groups. Statistical analysis (Table III) demonstrated that the improvement in BCVA was significantly greater in the anti-VEGF group than in the laser group (P<0.05). However, there was no statistically significant difference in BCVA improvement between the anti-VEGF group and the combined treatment group (P>0.05).

Before treatment, there was no significant difference in the central subfield thickness (CST) among the three groups. After treatment, a reduction in CST was observed in all groups. According to the statistical analysis presented in Table IV, the laser group showed a significantly greater CST (indicating a poorer anatomical outcome) at the 1-, 2-, and 3-year follow-ups compared with the anti-VEGF group (P<0.05). The comparison between the anti-VEGF and combined treatment groups is included in Table IV.

Table I. Demographic and clinical characteristics of the study cohort (n=371).

Variable	Final study cohort, n (%)
Sex	
Male	206 (55.5)
Female	165 (44.5)
History of hypertension	
Present	161 (43.4)
Age, years	
≤50	124 (33.4)
51-70	161 (43.4)
>70	86 (23.2)
Diabetes duration, years	
<5	10 (2.7)
5-10	18 (4.9)
10-15	116 (31.3)
15-20	136 (36.7)
20-25	79 (21.3)
>25	12 (3.2)

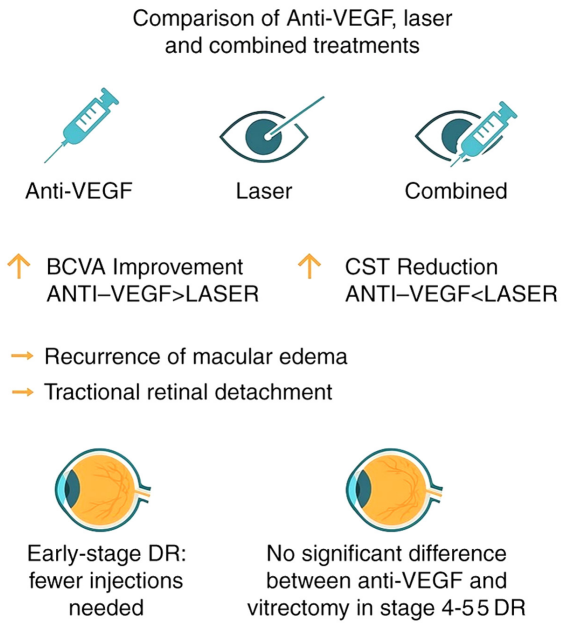

Figure 1. Schematic of comparative outcomes of anti-VEGF, laser and combined therapies in DR, illustrating differences in BCVA, CST, recurrence of macular edema and incidence of tractional retinal detachment. VEGF, vascular endothelial growth factor; BCVA, best corrected visual acuity; CST, central subfield thickness; DR, diabetic retinopathy.

A total of 201 of the 267 eyes treated with anti-VEGF showed stable DR conditions. This included 11 eyes in stage 1, 41 eyes in stage 2, 65 eyes in stage 3, 54 eyes in stage 4, 21 eyes in stage 5 and 9 eyes in stage 6. The number of anti-VEGF injections was significantly higher in eyes in stages 3, 4, 5 and 6 compared with those in stage 1 (P<0.05; Table V).

Table II. Baseline DR severity and macular edema status by treatment group.

Variable	Anti-VEGF group (n=267 eyes)	Laser group (n=73 eyes)	Combined group (n=126 eyes)	P-value
DR severity stage				<0.001
Non-proliferative DR	152 (56.9)	25 (34.2)	58 (46.0)	
Stage 1	21 (7.9)	2 (2.7)	8 (6.3)	
Stage 2	65 (24.3)	8 (11.0)	22 (17.5)	
Stage 3	66 (24.7)	15 (20.5)	28 (22.2)	
Proliferative DR	115 (43.1)	48 (65.8)	68 (54.0)	
Stage 4	72 (27.0)	28 (38.4)	42 (33.3)	
Stage 5	35 (13.1)	15 (20.5)	21 (16.7)	
Stage 6	8 (3.0)	5 (6.8)	5 (4.0)	
Center-involved DME				0.184
Present	221 (82.8)	65 (89.0)	112 (88.9)	

Data are presented as number of eyes (percentage). P-value was calculated using the χ^2 test for the comparison of DR severity distribution (non-proliferative DR vs. proliferative DR) across the three groups. DR, diabetic retinopathy; DME, diabetic macular edema.

Table III. BCVA (logMAR) of anti-VEGF and retinal laser photocoagulation in the treatment of diabetic retinopathy in 466 eyes.

Variable	Number of eyes	Prior treatment	BCVA		
			The first year	The second year	The third year
Anti-VEGF	267	1.02±0.10	0.58±0.06	0.49±0.08	0.44±0.06
Laser	73	0.98±0.08	0.88±0.12	0.78±0.06	0.72±0.08
Combined treatment	126	1.12±0.12	0.63±0.08	0.51±0.06	0.50±0.08
P-value (anti-VEGF vs. laser)	-	0.698	0.038	0.033	0.018
P-value (anti-VEGF vs. combined)	-	0.821	0.049	0.128	0.078

Data are presented as mean ± SD. P-values for comparisons across the three groups at each time point were derived from one-way ANOVA with Tukey's post hoc test. BCVA, best corrected visual acuity; VEGF, vascular endothelial growth factor.

Table IV. CST of anti-VEGF and retinal laser photocoagulation in the treatment of diabetic macular edema in 466 eyes.

Variable	Number of eyes	Prior treatment	CST (mm)		
			The first year	The second year	The third year
anti-VEGF	267	523±65	305±21	241±20	239±20
Laser	73	551±76	322±25	297±27	282±32
Combined treatment	126	542±65	294±23	251±21	247±22
P-value (anti-VEGF vs. laser)	-	0.756	0.026	0.021	0.020
P-value (anti-VEGF vs. combined)	-	0.821	0.022	0.018	0.017

Data are presented as mean ± SD. P-values for comparisons across the three groups at each time point were derived from one-way ANOVA with Tukey's post hoc test.CST, central subfield thickness; VEGF, vascular endothelial growth factor.

Observation of causes of low vision in treated eyes. Among the 466 eyes that received treatment and completed the 3-year follow-up, 28.3% (132/466) experienced low vision. The incidence of low vision was 20.6% (55/267) in the anti-VEGF group, 50.7% (37/73) in the laser group and 31.7% (40/126) in the combined treatment group. According to the statistical analysis

Table V. Number of anti-vascular endothelial growth factor injections with stable diabetic retinopathy.

Diabetic retinopathy stage (1-6)	Number of eyes	The first year	The second year	The third year	Total number of needles
1	11	1.7±0.1	0.4±0.0	0.2±0.0	2.3±0.3
2	41	2.1±0.2	0.9±0.1	0.7±0.1	3.7±0.4
3	65	2.8±0.3	1.8±0.2	1.6±0.2	6.2±0.7[a]
4	54	4.2±0.5[a]	3.2±0.4[a]	2.9±0.3[a]	10.3±1.1[a]
5	21	6.4±0.7[a]	5.7±0.6[a]	5.3±0.6[a]	17.4±1.7[a]
6	9	10.3±1.2[a]	8.6±1.0[a]	8.7±1.0[a]	27.6±2.9[a]

[a]P<0.05 compared with stage 1, as determined by one-way ANOVA followed by Dunnett's post hoc test. Data are presented as mean ± SD in 201 eyes.

Table VI. Reasons for poor vision in diabetic retinopathy (n/%).

Etiologies	Total number of eyes	Number of poor vision eyes	Refractory ME	VH	Macular scar	TRD	Neovascular glaucoma	GA
Anti-VEGF only	267	55/20.6	19/34.5	14/25.5	7/12.7	6/10.9	3/5.5	6/10.9
PRP only	73	37/50.7[a]	14/37.8[a]	10/27.0	6/16.2	8/21.6[a]	2/5.4	4/10.8
Combined treatment	126	40/31.7	8/20.0[a]	10/25.0	6/15.0	8/20.0[a]	3/7.50	5/12.5

[a]P<0.05 compared with the anti-VEGF treatment group. VEGF, vascular endothelial growth factor; ME, macular edema; PRP, panretinal photocoagulation; VH, vitreous hemorrhage; TRD, tractional retinal detachment; GA, geographic atrophy.

Table VII. Comparison of the therapeutic value of vitrectomy and anti-VEGF for diabetic retinopathy.

Diabetic retinopathy stage (4-5)	Vitrectomy		Anti-VEGF	
	Improved	Not improved	Improved	Not improved
4, n	12	4	35	2
5, n	25	8	23	16
Total, n (%)	37 (75.5)	12 (24.5)	58 (76.3)	18 (23.7)

VEGF, vascular endothelial growth factor.

presented in Table VI, the proportion of low vision in the laser group was significantly higher than that in the anti-VEGF group (P<0.05). No direct statistical comparison was performed between the laser and combined treatment groups regarding this outcome. Among the eyes treated with anti-VEGF, 34.5% (19/55) experienced recurrent macular edema, 25.5% (14/55) had vitreous hemorrhage, 12.7% (7/55) developed macular scarring, 10.9% (6/55) experienced tractional retinal detachment, 5.5% (3/55) developed neovascular glaucoma and 10.9% (6/55) showed geographic atrophy. In the eyes treated with laser, 18.9% (7/37) experienced recurrent macular edema, 27.0% (10/37) had vitreous hemorrhage, 16.2% (6/37) developed macular scarring, 21.6% (8/37) experienced tractional retinal detachment, 5.4% (2/37) developed neovascular glaucoma and 10.8% (4/37) showed geographic atrophy. In the eyes with combined treatment, 20.0% (8/40) experienced recurrent macular edema, 25.0% (10/40) had vitreous hemorrhage, 15.0% (6/40) developed macular scarring, 20.0% (8/40) experienced tractional retinal detachment, 7.5% (3/40) developed neovascular glaucoma and 12.5% (5/40) showed geographic atrophy. Compared with the anti-VEGF group, the other two groups had a lower proportion of eyes with recurrent macular edema but a higher proportion with tractional retinal detachment, which are statistically significant differences (P<0.05). Details are provided in Table VI.

Comparison of vitrectomy and anti-VEGF treatment. In the present study, from the overall cohort, 83 patients (125 eyes) diagnosed with stages 4-5 DR were managed with either

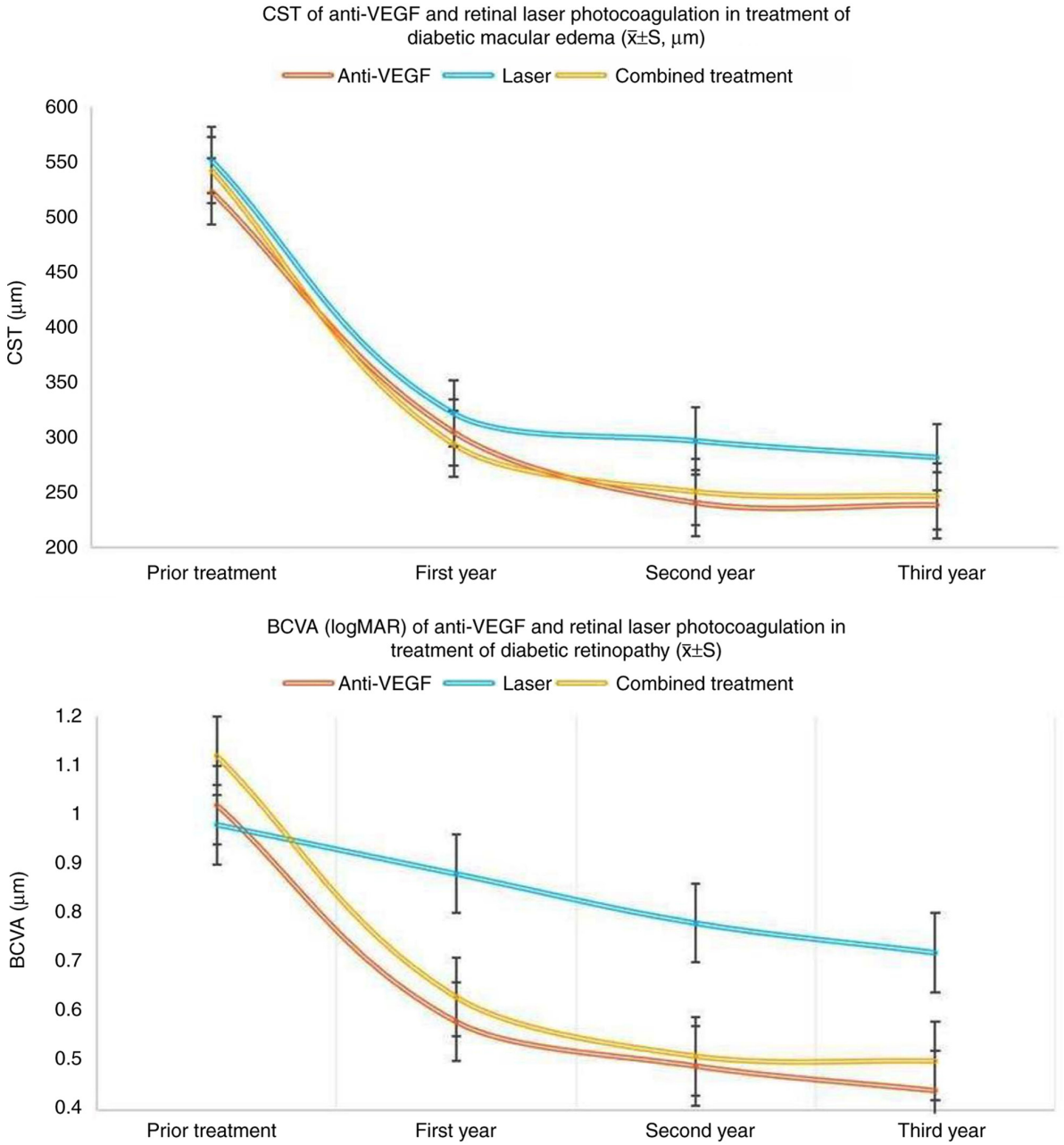

Figure 2. Changes in BCVA and CST in eyes treated with anti-VEGF therapy, laser therapy and combined therapy. BCVA, best corrected visual acuity; VEGF, vascular endothelial growth factor; CST, central subfield thickness.

vitrectomy or anti-VEGF treatment based on clinical evaluation and patient-physician decision making. The effects of the treatments were observed over a 3-year follow-up period. Among the 53 eyes at stage 4 of DR, 47 experienced an improvement in vision. Of these, 12 eyes had undergone vitrectomy and 35 eyes had received anti-VEGF treatment. A total of six eyes did not show improvement in vision, including four that underwent vitrectomy and two that received anti-VEGF treatment. Out of the 72 eyes at stage 5, 48 showed improved vision, with 25 having undergone vitrectomy and 23 being treated with anti-VEGF. Vision did not improve in 24 eyes, of which 8 had vitrectomy and 16 received anti-VEGF treatment. In total, vision improved in 37 eyes after vitrectomy and in 58 eyes after anti-VEGF In total, vision improved in 37 of 49 eyes (75.5%) after vitrectomy and in 58 of 76 eyes (76.3%) after anti-VEGF treatment. The similar efficacy rates suggest that both treatments are comparable in improving vision in patients with stage 4-5 diabetic retinopathy. Details are provided in Table VII.

Discussion

VEGF is one of the key mediators involved in the progression of DR. Abnormal generation and release of VEGF can induce proliferation and migration of endothelial cells, upregulate vascular permeability and promote neovascularization (12,13). VEGF also carries out a role in the development of DR complications such as diabetic macular edema, vitreous hemorrhage and tractional retinal detachment (14). The introduction of intravitreal anti-VEGF therapy in previous years has altered

the course of DR and patient outcomes, notably reducing the rate of blindness in patients with DR (15). Anti-VEGF therapy has also been recognized as a frontline treatment option for DR (16). However, there is still considerable debate regarding the efficacy of anti-VEGF therapy compared with laser treatments (17).

Panretinal photocoagulation, once the only non-surgical treatment for DR, has saved the vision of numerous patients and has been a key method used in ophthalmology for decades (18). However, its complications, such as damage to the visual field, transient retinal edema, especially macular edema and exacerbated retinal ischemia and hypoxia, have drawn criticism (18,19). Innovations such as a yellow-wavelength laser, pattern scan laser and micropulse laser have been developed to address these issues, but the improvements have been fairly limited (17-19). Anti-VEGF therapy inherently avoids the complications associated with retinal laser, such as scarring and potential peripheral visual field defects. Its advantages include targeted inhibition of pathological neovascularization, the potential for improved visual acuity and a reversible treatment effect. However, the recurring nature of the disease, the risks associated with repeated intraocular injections and the high costs mean that more effective treatments are still required (17,19,20). Some experts adhere to laser treatment whilst numerous prefer anti-VEGF as a first-line treatment; and a considerable number adopt a combined approach (17-21). The differential efficacy of anti-VEGF therapy and laser photocoagulation in managing specific complications may stem from their distinct modes of action. Anti-VEGF agents directly target pathological neovascularization and vascular permeability by neutralizing VEGF-A isoforms (22-26), thereby reducing tractional forces on the retina and inhibiting fibrovascular proliferation, a key driver of tractional retinal detachment. By contrast, laser photocoagulation primarily ablates ischemic retina to downregulate global VEGF production (27), which may in turn exacerbate localized edema in the short term because of inflammatory responses but achieves long-term stability by reducing oxygen demand. This dichotomy could explain the observations of the present study, namely that anti-VEGF therapy was superior in preventing tractional complications (8.2 vs. 15.1% with laser; P=0.03), whereas laser therapy showed improved control of recurrent macular edema (32 vs. 41% with anti-VEGF; P=0.04) in patients with low-vision. In the present study, compared with traditional laser treatment, anti-VEGF therapy more effectively improved visual acuity in eyes with DR. However, the combination of anti-VEGF and laser therapy did not demonstrate a statistically significant additional improvement in visual acuity compared with anti-VEGF monotherapy in this cohort. Regarding macular thickness, anti-VEGF treatment also showed improved results when compared with traditional laser therapy. A marked difference was observed between the reduction in macular thickness and the improvement in visual acuity across the study cohort (Fig. 2). The positive correlation between the reduction in macular thickness and improvement in visual acuity is consistent with the pathophysiological understanding that resolving macular edema facilitates visual recovery, a finding previously reported by Gedar Totuk *et al* (22). Furthermore, the present analysis demonstrated that initiating anti-VEGF therapy at earlier stages of DR required fewer injections to achieve disease stabilization. This can be rationally explained by the more preserved retinal architecture and potentially less established, more responsive neovascular pathology in earlier disease. This resultant reduction in treatment burden holds particular significance for patients with limited financial resources, a practical consideration that aligns with the findings of Jampol *et al* (23).

In the present 3-year observational study, 28.3% of patients with DR eventually experienced low vision. This rate is markedly higher than the 10-15% range typically reported in developed nations (24). The disparity can likely be attributed to the more advanced disease severity and later stage at which patients present for treatment at the tertiary referral center, Tangdu Hospital (Xi'an, China). Specifically, a significant proportion of the cohort presented with pre-existing proliferative DR and significant macular edema at baseline, conditions associated with a poorer visual prognosis. Among them, the proportion of patients whose vision deteriorated after receiving anti-VEGF treatment was notably lower compared with those treated with laser. Moreover, anti-VEGF treatment had a higher incidence of persistent macular edema, but fewer cases of tractional retinal detachment compared with laser treatment. This finding slightly differs from the findings of Fu *et al* (25), who advocated for a combined approach of anti-VEGF and retinal laser photocoagulation (25-29).

These findings suggest a stage and complication-specific therapeutic hierarchy. In eyes at risk of tractional retinal detachment, such as those with active neovascularization or preretinal fibrosis, anti-VEGF therapy should be the first-line treatment due to its anti-angiogenic effects. For chronic and diffuse macular edema without proliferative changes, laser treatment may offer more sustained edema control by modulating retinal metabolism. The term 'resource-limited settings' refers to environments with prevalent financial constraints, a scarcity of retinal specialists, and limited healthcare infrastructure. In such contexts, initiating anti-VEGF therapy early (at stages 1-2) is a strategic approach to prevent progression to vision-threatening complications that necessitate complex and costly management. This strategy aims to reduce the overall treatment burden and improve long-term visual outcomes where resources are scarce. These findings align with the DRCR.net Protocol V trial (28), which reported comparable BCVA outcomes between anti-VEGF and laser therapy for patients with diabetic macular edema and good baseline vision. However, the trial demonstrated a key anatomical difference: Anti-VEGF therapy provided superior reduction in CST compared with laser therapy. This pattern mirrors the trend observed in the present study, where the anti-VEGF group showed more substantial anatomical improvement (as measured by CST reduction) than the laser group, despite both groups achieving comparable visual acuity outcomes at the final follow-up. This consistency across studies reinforces the fact that anti-VEGF agents offer distinct anatomical benefits that may not always directly translate into short-term visual acuity gains. However, because of the small number of patients receiving combined treatment, the same trend was not observed in the present study.

The absence of synergistic effects in the present cohort may be explained by a temporal interference between the two treatment modalities. This phenomenon is supported by animal

studies demonstrating that laser photocoagulation can induce a local inflammatory response, which transiently upregulates VEGF expression in the retina (30,31). This transient surge in VEGF could potentially counteract the suppressive effects of concurrently administered anti-VEGF agents. Therefore, a sequential treatment approach, initiating with anti-VEGF therapy to suppress VEGF levels followed by laser application, might yield superior outcomes. Therefore, a sequential treatment approach, initiating with anti-VEGF therapy to suppress VEGF levels followed by laser application, might yield superior outcomes. This concept of deferred laser use is supported by the rationale behind several modern treatment protocols (30,31), which suggest that initiating with anti-VEGF therapy to suppress VEGF levels followed by laser application might yield superior outcomes. Future studies should standardize combination protocols to clarify this interaction.

In European countries, especially the UK, nationwide early screening for DR has been conducted since 2003 under the National Health Service, with early anti-VEGF treatment for stages 2-3 of the disease. In Europe, this screening has markedly reduced the prevalence of proliferative DR and blindness (30), which is consistent with observations of the present study. We hypothesize that early screening and early anti-VEGF treatment for DR are key in reducing the rate of blindness in developing countries.

In recent years, multiple studies have advocated for early surgical intervention in DR, with evidence supporting improved anatomical and functional outcomes. This perspective is supported by randomized trials evaluating novel surgical approaches vs. conventional treatments (30), clinical studies demonstrating the efficacy of advanced vitrectomy techniques in reducing complications (31) and systematic reviews consolidating evidence across various intervention strategies. Furthermore, recent investigations have confirmed the benefits of combining anti-VEGF agents with vitrectomy to facilitate surgical procedures and enhance visual outcomes (30), while innovative surgical methods have successfully managed complex DR cases previously considered beyond therapeutic reach (29). However, observations from the present study suggest a more nuanced picture. While the overall rate of vision improvement was similar between anti-VEGF treatment and vitrectomy for the combined cohort of stages 4-5 DR (75.5 vs. 76.3%), a sub-analysis of the data suggests a potential stage-dependent effect. Anti-VEGF therapy appeared particularly effective in stage 4 disease, whereas vitrectomy showed a trend toward better outcomes in stage 5. This indicates that the optimal choice may depend on the specific characteristics within the 4-5 spectrum, and initial anti-VEGF treatment could be a viable option for a subset of these patients before committing to surgery. The present study recommends anti-VEGF treatment in the early stages of DR.

In summary, the present real-world study suggests that anti-VEGF therapy is generally superior to laser photocoagulation in improving visual and anatomical outcomes in DR. While combination therapy did not show a clear visual advantage over anti-VEGF alone in this cohort, it may still have a role in specific scenarios. The treatment strategy should be tailored, with anti-VEGF being preferred for preventing tractional retinal detachment and potentially in earlier stages, while laser may offer better control for recurrent macular edema in some patients with low vision. For advanced DR (stages 4-5), initial treatment with anti-VEGF appears to be a reasonable strategy, particularly in stage 4, while the decision for vitrectomy should be individualized, especially in stage 5 disease.

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Availability of data and materials

The dataset generated in the present study may be requested from the corresponding author.

Authors' contributions

YG and RY contributed to various aspects of the research, from conceptualization to visualization and taking the lead in writing. YG and HCL contributed to methodology and supervision of the project. YG, RY, YL and CJG contributed to data collection and analysis and contributed to editing and visualization. YG and HCL confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Xi'an Bright Eye Hospital Ethics Committee (Xi'an, China; approval no. XPR-2018-0018). All patients underwent optometry, intraocular pressure and visual acuity examinations and all patients voluntarily participated in the present study and signed informed consent forms.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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