

The efficacy and safety of aflibercept and conbercept in diabetic macular edema

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Abstract: Diabetic macular edema (DME) has shown an increasing prevalence during the past years and is the leading cause of diabetic retinopathy blindness. Traditional treatment modalities include laser and corticosteroid therapy, which, however, either act through unclear mechanisms or cause cataracts and elevated intraocular pressure. In recent years, as the pathogenic role of VEGF in DME has been well-recognized, the intravitreal injection of anti-VEGF drugs has become the first-line treatment of DME due to their great efficacy in improving visual acuity and mitigating macular edema. Advantages have been shown for aflibercept and conbercept, the two recombinant decoy receptors that can bind VEGF with high specificity and affinity, in DME treatment in clinical trials conducted both worldwide and in People's Republic of China. This review introduces the structural characteristics and molecular mechanisms of action of these two anti-VEGF drugs, and summarizes the clinical trials evaluating their efficacy and safety, with the hope to provide clues for designing optimal and personalized therapeutic regimens for DME patients.

Keywords: diabetes, diabetic retinopathy, diabetic macular edema, therapy, aflibercept, conbercept, clinical trial, VEGF decoy receptor

Introduction

Diabetic macular edema (DME) has become the leading cause of vision loss in people with diabetes, and its prevalence is ascending on a global scale.¹ In the US, nearly 4% of diabetic patients aged over 40 years have DME.² Asia, the global epicenter of the diabetic epidemic,³ is also facing an increasing number of patients with DME. Moreover, vision loss substantially compromises patients' quality of life and capability of disease management.⁴ Therefore, effective treatments for DME are urgently needed. Three therapeutic modalities are available. First, laser therapy, including focal and grid laser, has been a standard treatment modality of DME for more than 3 decades.^{5,6} It reduces 50% of vision loss in patients with clinically significant DME,⁷ however, only 8.3%–25% of DME patients experience improvements in visual acuity (VA) following 2–3 years of laser treatment,⁸ and the mechanism of action of laser therapy remains elusive.⁹ Second, corticosteroid therapy, such as intravitreal injection of triamcinolone acetonide and long-acting dexamethasone implant,^{5,10–12} is an effective treatment modality for DME due to its anti-inflammatory functions.^{13,14} Nonetheless, the complications incurred limit its further applications.^{5,12,15}

With the advent of recombinant protein technology and the discovery of pathogenic mechanisms underlying DME, anti-VEGF drugs have emerged and have become the first-line treatment for DME in recent years as they restore and stabilize vision in most DME patients.^{16,17} Several types of anti-VEGFs acting via different mechanisms are

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clinically available, including the full-length monoclonal antibody (mAb) to VEGF, bevacizumab (Avastin®; Genentech, South San Francisco, CA, USA), the Fab fragment of the mAb to VEGF, ranibizumab (LUCENTIS®; Novartis International AG, Basel, Switzerland), and the recombinant decoy receptors such as aflibercept (EYLEA® or VEGF Trap-eye; Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA and Bayer, Berlin, Germany) and conbercept (Kanghong Biotech Company, Chengdu, Sichuan, People's Republic of China).¹⁸ Among these anti-VEGFs, the recombinant decoy receptors have shown remarkable efficacy and safety in clinical trials. This review aims to delineate structural and functional characteristics of aflibercept and conbercept, and to summarize and discuss the clinical data with regard to their efficacy and safety, as well as to compare the decoy receptor drugs with corticosteroid and anti-VEGF mAb drugs in the treatment of DME.

Structural, biochemical, and pharmacological characterization of aflibercept and conbercept

Aflibercept

Aflibercept is a 115 kDa recombinant protein that fuses the second extracellular domain of human VEGFR-1 and the third extracellular domain of human VEGFR-2 with the Fc portion of human immunoglobulin IgG1.¹⁹ It functions as a soluble decoy receptor that binds human VEGF-A, VEGF-B, and PlGF with high affinity (VEGF-A121, K_d = 0.36 pM; VEGF-A165, K_d = 0.50 pM; VEGF-B, K_d = 1.92 pM; PlGF, K_d = 38.9 pM).^{20,21} The experimental results suggest that aflibercept's binding affinity to VEGF-A165 is almost 100-fold greater than ranibizumab and bevacizumab, which might be ascribed to the 3-dimensional configuration of its Fab fragment that favors the creation of an almost irreversible "two-fist" grasp on the target.^{20,22,23} These structural characteristics may, at least from a theoretical perspective, enable aflibercept to suppress neovascularization and vascular permeability caused by VEGF overexpression. The mechanism of action of aflibercept is to competitively inhibit the binding of VEGF to its cognate receptors, VEGFR-1 and VEGFR-2.^{20,24,25}

The intravitreal half-life of aflibercept in humans has not been assessed, although the experiments in rabbits indicate a mean intravitreal half-life of 4.6 days, which is longer than that of ranibizumab (2.8 days) and bevacizumab (4.2 days) in the same animal model.^{26,27} On the other hand, a mathematical model predicts the intravitreal half-life of aflibercept in humans as approximately 4.8 days, which is

similar to that measured in rabbits and still longer than the predictive value of ranibizumab (3.2 days).²⁸

Ziv-aflibercept (Zaltrap®, Sanofi-Aventis, Bridgewater, NJ, USA, and Regeneron Pharmaceuticals, Inc.) bears an identical structure to aflibercept, and has been approved by the US Food and Drug Administration (FDA) to treat metastatic colon cancer. It is manufactured with larger dose, lower concentration, and higher osmolality than its counterpart for ocular administration.^{29,30}

Conbercept

Conbercept is a 143 kDa recombinant anti-VEGF fusion protein engineered from a full human cDNA sequence in Chinese hamster ovary cells. The Fab of conbercept comprises the second extracellular domain of VEGFR-1 and the third and fourth extracellular domains of VEGFR-2, which then fuses to the Fc of human IgG1.^{31–33} Conbercept also functions as a decoy receptor and binds all isoforms of VEGF-A (K_d for VEGF-A165 = 0.5 pM), VEGF-B, VEGF-C, and PlGF with high affinity, precluding the activation of downstream signaling mediated by the VEGF family members.³⁴ The structure of conbercept differs from aflibercept in that it incorporates the fourth extracellular domain of VEGFR-2 into the Fab. Although this domain is not directly involved in ligand binding, it facilitates receptor dimerization.³⁵ The dimerized receptor binds VEGF 100-fold more tightly than the monomeric counterpart.³⁶ Moreover, the fourth domain improves the receptor's 3-dimensional structure and enhances VEGF's association rate. Therefore, biochemical and pharmacological analyses indicate that conbercept's affinity to VEGF is 50-fold higher than that of bevacizumab. The structural characteristics provide a molecular basis for conbercept's anti-angiogenic functions in human umbilical vein endothelial cells.^{33,37,38}

Similar to aflibercept, the intravitreal half-life of conbercept in humans has not been reported. However, it is 4.2 days in rabbit eye, which is close to aflibercept (4.8 days) and bevacizumab (4.2–6.6 days), but longer than ranibizumab (2.8 days).^{39–42}

Clinical trials

Efficacy and safety of aflibercept and conbercept in the treatment of DME

Aflibercept

A self-controlled pilot study conducted by Do et al⁴³ was reported in 2009. Five DME patients received a single intravitreal injection of 4.0 mg aflibercept followed by 6-week observation. The results showed that aflibercept was

well-tolerated with no ocular toxicity. At the fourth week following the injection, the median best-corrected visual acuity (BCVA) improved by nine Early Treatment of Diabetic Retinopathy Study (ETDRS) letters read at 4 m distance (Snellen equivalent 20/50); the median excess central 1 mm foveal thickness (FTH) was reduced from 108 μ m at baseline to 59 μ m. At 6 weeks after the injection, four of the five patients showed improved BCVA (median improvement of three letters) and excess FTH (median 74 μ m; 31% reduction from baseline, $P=0.063$) (Table 1).

Another prospective study was reported by Campos et al⁴⁴ in 2018, which evaluated the efficacy of aflibercept. Fifteen anti-VEGF-naïve DME patients were recruited and received intravitreal injections of aflibercept (IVA) at 2 mg, 5-monthly doses followed by the same dose every 2 months for 1 year. BCVA improvement was observed at the second visit after the loading doses. At 12 months after the initial injection, the mean BCVA improved from 47.3 \pm 14.2 ETDRS letters at baseline to 62.2 \pm 13.9 ETDRS letters ($P<0.001$) (Table 1). All eyes (100%) gained ETDRS letters, 89.6% of the eyes gained ≥ 10 letters, 65.5% ≥ 15 letters, and 6.9% ≥ 20 letters. The central macular thickness (CMT) was significantly reduced from a mean of 460.5 \pm 11.8 μ m at baseline to 229.0 \pm 43.8 μ m ($P<0.001$) (Table 1). No adverse events occurred in this study.

In 2016, Andrade et al⁴⁵ reported a short-term, prospective clinical trial assessing the efficacy and safety of intravitreal injection of ziv-aflibercept (IVZA) in DME therapy. Seven patients with DME received IVZA every 4 weeks for 6 months. During the follow-up, the mean logarithm of the minimum angle of resolution (logMAR) of the BCVA improved 0.55 \pm 0.19 logMAR units ($P<0.001$) and the mean central retinal thickness (CRT) reduced 125.86 \pm 65.46 μ m ($P=0.002$), and there was no systemic or ocular complication (Table 1).

Conbercept

In 2018, a retrospective study⁴⁶ was reported which evaluated the therapeutic efficacy of conbercept for treatment of DME patients with different baseline VA. A total of 107 patients were divided into four groups according to their baseline BCVA: conbercept-treated subgroup with worse baseline VA (less than 69 letters), untreated subgroup with worse baseline VA, conbercept-treated subgroup with better baseline VA (78–69 letters), untreated subgroup with better baseline VA. Patients received one initial intravitreal injection of conbercept (IVC) followed by retreatment based on BCVA loss or CMT increase. At 12 m, the mean improvement in BCVA

was significantly greater in the conbercept-treated groups than that of the corresponding untreated controls (18.0 \pm 15.0 letters vs -4.0 ± 6.0 letters, $P<0.001$ for worse baseline BCVA groups; 7.0 \pm 1.0 letters vs -5.0 ± 5.0 letters, $P<0.001$ for better baseline BCVA groups) (Table 1). In addition, the mean CMT was significantly reduced in the conbercept treatment groups as compared to that of the corresponding untreated controls (-212.8 ± 11.9 vs -44.3 ± 35.3 μ m, $P<0.001$ for worse baseline BCVA groups; -116.1 ± 88.9 vs -33.7 ± 49.8 μ m, $P=0.001$ for better baseline BCVA groups) (Table 1). It is notable that the BCVA improvement and CMT reduction in the treated group with worse baseline VA were more prominent than that in the treated group with better baseline VA ($P<0.001$), however, the two groups had no significant difference in the number of injections (6.7 \pm 0.9 injections in the worse baseline VA group vs 6.5 \pm 1.1 injections in better baseline VA group, $P=0.350$) (Table 1).

Together, these studies have indicated that thus far all the VEGF decoy receptors, including aflibercept, ziv-aflibercept, and conbercept have shown safe and effective profiling in DME treatment. Conbercept may have better efficacy for eyes with worse baseline VA than those with better baseline VA with similar number of injections.

Comparison of aflibercept to laser therapy

The DA VINCI study⁴⁷ is a randomized, double-masked, multicenter, Phase II clinical trial that aimed to compare the efficacy of aflibercept at different dosing with traditional laser photocoagulation in eyes with DME. Two hundred and twenty-one diabetic patients with center-involved DME were enrolled and randomized into five groups: 0.5q4 group that received IVA 0.5 mg every 4 weeks; 2q4 group that received IVA 2 mg every 4 weeks; 2q8 group that received IVA 2 mg every 8 weeks after three initial monthly doses; 2PRN group that received IVA 2 mg as needed (PRN) after three initial monthly doses; and laser group that received macular laser photocoagulation. At 24 weeks, the mean VA improvements in the four aflibercept groups, ranging from 8.5–11.4 ETDRS letters, were significantly greater than that in the laser group (2.5 letters; $P=0.009$ for each IVA group vs laser group) (Table 2). Moreover, aflibercept maintained or augmented the VA improvements to the 52nd week (11.0, 13.1, 9.7, and 12.0 letters in 0.5q4, 2q4, 2q8, and 2PRN groups, respectively); in contrast, the VA in the laser group deteriorated 1.3 letters during the same period. The percentages of the patients with VA gain of 0, 10, and 15 letters were 93%, 64%, and 34% in the aflibercept groups as compared to 68%, 32%, and 21% in the laser group, respectively. The proportions

Table 1 Efficacy and safety of aflibercept and conbercept in DME treatment

Ref	Type of study	N (eyes)	Grouping	Regimen	Duration (m)	BCVA (logMAR units or ETDRS letters)			CRT/CMT (μm)		
						Baseline	Last follow-up	Change	Baseline	Last follow-up	Change
43	self-control	5	IVA	4mg	1.5	36		4W 9 6W 3	108		4W 59 6W 74
44	prospective	15	IVA	2q8	12	47.3 \pm 14.2	62.2 \pm 13.9 ^{***}		460.5 \pm 11.8	229.0 \pm 43.8 ^{***}	
45	single-center, prospective, single-treatment	7	IVZA	1.25q4	6	0.78 \pm 0.28		-0.55 \pm 0.19 ^{***}	392.0 \pm 69.57		-125.86 \pm 65.46 ^{**}
46	retrospective	107	IVC baseline VA < 69	0.5 mg +PRN	12	35 (18)	60 (15)	18 (15) ^{###}	490.4 \pm 93.2	277.6 \pm 61.8	-212.8 \pm 11.9 ^{###}
			IVC baseline VA 69-78			70 (4)	77 (3)	7 (1) ^{###}	389.2 \pm 64.2	273.1 \pm 47.6	-116.1 \pm 88.9 ^{###}
			Untreated baseline VA < 69			40 (14)	36.5 (14.5)	-4 (6)	499.4 \pm 94.6	455.1 \pm 100.0	-44.3 \pm 35.3
			Untreated baseline VA 69-78			69 (3)	65 (4)	-5 (5)	423.5 \pm 56.6	389.8 \pm 84.6	-33.7 \pm 49.8

Notes: ** $P < 0.01$ vs baseline, *** $P < 0.001$ vs baseline, ^{###} $P < 0.001$ vs corresponding untreated group. The BCVA data in reference 46 did not exhibit a normal distribution, hence were expressed as median (interquartile range).

Abbreviations: Ref, reference; DME, diabetic macular edema; IVZA, intravitreal injections of Ziv-aflibercept; IVA, intravitreal injections of aflibercept; IVC, intravitreal injections of conbercept; m, months; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; ETDRS, Early Treatment of Diabetic Retinopathy Study; CRT, central retinal thickness; CMT, central macular thickness; 1.25q4, 1.25 mg every 4 weeks; 0.5q4, 0.5 mg every 4 weeks.

Table 2 Comparisons of aflibercept with laser photocoagulation in DME treatment

Study	Ref	Duration (w)	Regimen	N (eyes)	BCVA (ETDRS letters)		CRT (μm)	
					Baseline	Change	Baseline	Change
DA VINCI	47	24	IVA 0.5q4	44	59.3 \pm 11.2	8.6**	426.1 \pm 128.3	-144.6***
			IVA 2q4	44	59.9 \pm 10.1	11.4****	456.6 \pm 135.0	-194.5****
			IVA 2q8	42	58.8 \pm 12.2	8.5**	434.8 \pm 111.8	-127.3**
			IVA 2PRN	45	59.6 \pm 11.1	10.3***	426.6 \pm 152.4	-153.3****
			Laser	44	57.6 \pm 12.5	2.5	440.6 \pm 145.4	-67.9
VISTA	50	52	IVA 2q4	154	58.9 \pm 10.8	12.5****	485 \pm 157	-185.9****
			IVA 2q8	151	59.4 \pm 10.9	10.7****	479 \pm 154	-183.1****
			Laser	154	59.7 \pm 10.9	0.2	483 \pm 153	-73.3
		100	IVA 2q4	154		11.5****		-191.4****
			IVA 2q8	151		11.7***		-191.1****
			Laser	154		6.3		-83.9
	51	148	IVA 2q4	154		10.4****		-200.4****
			IVA 2q8	151		10.5****		-190.1****
			Laser	154		1.4		-109.8
VIVID	50	52	IVA 2q4	136	60.8 \pm 10.7	10.5****	502 \pm 144	-195.0****
			IVA 2q8	135	58.8 \pm 11.2	10.7****	518 \pm 147	-192.4****
			Laser	132	60.8 \pm 10.6	1.2	540 \pm 152	-66.2
	16	100	IVA 2q4	136		11.8****		-211.8****
			IVA 2q8	135		10.6****		-195.8****
			Laser	132		5.5		-85.7
	51	148	IVA 2q4	136		10.3****		-215.2****
			IVA 2q8	135		11.7****		-202.8****
			Laser	132		1.6		-122.6

Note: ** $P<0.01$ vs laser, *** $P<0.001$ vs laser, **** $P<0.0001$ vs laser. The specific data of DA VINCI study at 52 week are not available from the literature (Ref 48), hence are not listed in this table.

Abbreviations: Ref, reference; w, weeks; BCVA, best-corrected visual acuity; EDTRS, Early Treatment of Diabetic Retinopathy Study; CRT, central retina thickness; IVA, intravitreal injections of aflibercept; 0.5q4, 0.5 mg every 4 weeks; 2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; 2PRN, 2 mg as needed.

of eyes with VA gain of more than 15 letters in individual aflibercept groups (40.9%, 45.5%, and 42.2% in 0.5q4, 2q4, and 2PRN groups, respectively) were significantly higher than that in the laser group (11.4%; $P=0.003$ for 0.5q4 vs laser; $P=0.001$ for 2q4 vs laser; $P=0.002$ for 2PRN vs laser) at the 52nd week (Table 2). Consistent with the VA improvements, the mean reductions in CRT in the aflibercept groups, ranging from 127.3–194.5 μm , were 2-fold greater than that in the laser group (67.9 μm , $P=0.007$ for each aflibercept group vs laser) after 24-week treatment,⁴⁸ and the superiority of aflibercept was sustained to the 52nd week (165.4, 227.4, 187.8, and 180.3 μm in 0.5q4, 2q4, 2q8, and 2PRN IVA groups, respectively; 58.4 μm in laser group; all $P<0.001$, each aflibercept group vs laser) (Table 2).⁴⁸

Moreover, a sub-study selected 46 patients from this clinical trial to evaluate retinal sensitivity.⁴⁹ Retinal sensitivity was measured by fundus-monitored microperimetry and compared in one (central), five (one central and four inner), and eight (four inner and four outer) subfields of optical coherence tomography (OCT). At the 52nd week, the mean VA improvements in the aflibercept groups, ranging

from 5.4–16.3 letters, were significantly greater than in the laser group (3.3 letters). The retinal sensitivity in the laser group was similar to the baseline level in the central OCT subfield and even reduced in the five and eight OCT subfields; in contrast, the 2q8 group and the pooled aflibercept group exhibited significantly higher retinal sensitivities in the five and eight OCT subfields than the laser group (both $P<0.050$). The results of DA VINCI study suggest that IVA can generate and maintain greater improvements in VA and CRT than laser photocoagulation; additionally, IVA, but not laser photocoagulation, improves retinal sensitivity in selected patients.

Another two similar clinical trials, the VISTA and VIVID studies,⁵⁰ were double-masked, randomized, Phase III trials. These trials were performed to compare the efficacy of aflibercept with laser in DME patients. Eight hundred and seventy-two DME patients with central involvement were included and received either IVA 2q4 or 2q8 after five initial monthly doses, or macular laser photocoagulation. After 52-week treatment, mean VA gains in the IVA groups (12.5 letters in 2q4, 10.7 in 2q8 in VISTA; 10.5 in 2q4, 10.7

in 2q8 in VIVID) were significantly greater than those in the laser group in both studies (0.2 letters in VISTA, 1.2 letters in VIVID, all $P < 0.001$ for IVA vs laser) (Table 2).⁵⁰ The greater VA benefits in the IVA groups were maintained to the 100th week (11.5, 11.1, and 0.9 letters in 2q4, 2q8, and laser groups, respectively, all $P < 0.001$ in VISTA; 11.4, 9.4, and 0.7 letters in 2q4, 2q8, and laser groups, respectively, all $P < 0.001$ in VIVID) (Table 2),¹⁶ and even to the 148th week (10.4, 10.5, and 1.4 letters in 2q4, 2q8, and laser groups, respectively, all $P < 0.001$ in VISTA; 10.3, 11.7, and 1.6 letters in 2q4, 2q8, and laser groups, respectively, all $P < 0.001$ in VIVID) (Table 2).⁵¹ Meanwhile, the proportions of eyes that gained more than 15 letters in the IVA groups (41.6% and 31.1% in 2q4 and 2q8 groups, respectively in VISTA; 32.4% and 33.3% in 2q4 and 2q8 groups, respectively in VIVID) were approximately 2–3-fold more than those in the laser groups (7.8% in VISTA; 9.1% in VIVID) at the 52nd week. The superiority was sustained until the 100th week (38.3%, 33.1%, and 13.0% in 2q4, 2q8, and laser, respectively, all $P < 0.001$ in VISTA; 38.2%, 31.1%, and 12.1% in 2q4, 2q8, and laser, respectively, all $P < 0.001$ in VIVID) and the 148th week (42.9%, 35.8%, and 13.6% in 2q4, 2q8, and laser, respectively, all $P < 0.001$ in VISTA; 41.2%, 42.2%, and 18.9% in 2q4, 2q8, and laser, respectively, $P < 0.001$ in VIVID). Anatomically, the mean reductions in CRT in the IVA groups (185.9 and 183.1 μm in 2q4 and 2q8, respectively in VISTA; 195.0 and 192.4 μm in 2q4 and 2q8, respectively in VIVID) were significantly greater than those in the laser group (73.3 μm , $P < 0.001$ in VISTA; 66.2 μm , $P < 0.001$ in VIVID) at the 52nd week (Table 2). Furthermore, IVA groups had substantially higher percentages of eyes gaining more than 2-step improvements in the Diabetic Retinopathy Severity Scale (DRSS) score than the laser group (37.0% in 2q4, 37.1% in 2q8, 15.6% in laser, all $P < 0.001$ in VISTA; 29.3% in 2q4, 32.6% in 2q8, 8.2% in laser, $P = 0.000$ in VIVID) (Table 2).¹⁶ This advantage in the aflibercept groups was maintained to the 148th week (29.9% in 2q4, 34.4% in 2q8, 20.1% in laser, $P = 0.035$ for 2q4 vs laser, $P = 0.0052$ for 2q8 vs laser in VISTA; 44.3% in 2q4, 47.8% in 2q8, 17.4% in laser, both $P < 0.001$ in VIVID) (Table 2).⁵¹

More recently, a Phase IV, ENDURANCE extension study was performed to determine whether the efficacy and safety achieved by 2.0 mg IVA for DME during the Phase III VISTA trial could be maintained by an individualized, PRN regimen.⁵² Sixty patients who completed VISTA were selected to receive IVA in the presence of clinically relevant DME. During the 12-month follow-up, mean values of 4.5 times IVA were

administered. Eighteen (30%) patients required no IVA, and mean values of 6.0 times IVA were administered to those in need. Both the BCVA and CRT were stable. The mean BCVA improvements were less than 1.5 letters from baseline at all the time points examined. In addition, 37 (62%) patients were also treated with laser, and there was no significant difference in the IVA frequency prior to and post-macular laser treatment.⁵²

Collectively, these series of studies are well-designed, stringently-controlled, large-scale, and long-term clinical trials that demonstrate superiority of IVA to laser therapy with convincing evidence. IVA was better than laser at improving BCVA, reducing CRT, and maintaining retinal sensitivity in DME patients. These advantages were sustained as long as 148 weeks. Besides, IVA generated a greater percentage of patients with high DRSS score than laser therapy, and it is also suitable for further maintenance therapy with a personalized PRN regimen.

Combination of conbercept with laser therapy

Up to date, there is no clinical trial comparing the therapeutic efficacy of conbercept with laser in the treatment of DME. However, a few clinical trials studying the therapeutic efficacy of combining conbercept with laser therapy have been reported. A retrospective study involving 51 patients was conducted in 2016 to compare the efficacy of IVC plus grid laser photocoagulation (GLP) with IVC alone in the treatment of diffuse DME.⁵³ At 12 months after therapy, the mean BCVA improved 9.1 ± 4.5 letter score in the IVC group and 7.5 ± 4.2 letter score in the combination group. The mean CRT reduced $145.1 \pm 69.9 \mu\text{m}$ in the IVC group and $168.5 \pm 53.6 \mu\text{m}$ in the combination group. Even though the differences in the BCVA improvement ($P = 0.164$) and CRT reduction ($P = 0.149$) between the two groups were not significant, the average injection frequency in the IVC group (5.6 ± 0.8 injections/eye) was significantly more ($P < 0.001$) than the combination group (3.3 ± 1.2 injections/eye). The results of this study indicate that the combinatorial therapy, IVC plus laser, might be a better modality than the solitary IVC. Although the combination therapy did not show significantly superior efficacy compared to mere IVC, the combined laser therapy did facilitate a reduction in injection frequency, which implicates that the combinatorial strategy may incur less adverse effects and costs than IVC alone.

A prospective, randomized controlled trial was performed to evaluate the therapeutic effects of panretinal

photocoagulation (PRP) therapy followed by IVC or posterior sub-Tenon's triamcinolone acetonide (STTA) therapy on DME at proliferative stage.⁵⁴ The DME patients at proliferative stage were initially treated with PRP, and then divided into two groups: group A was treated with IVC 0.5 mg, group B with STTA 40 mg (twice/2 weeks) during the first phase (1 month). The interventions were exchanged during the second phase (2 months) between the two groups. No treatment was given during the third phase (3–6 months). The results demonstrated that during the first phase, BCVA improved from 0.2 ± 0.2 to 0.4 ± 0.2 ($F=5.880$, $P=0.004$) in group A, and from 0.2 ± 0.2 to 0.3 ± 0.2 ($F=0.760$, $P=0.410$) in group B. The CMT reduced from 449.0 ± 155.1 to $304.1 \pm 84.7 \mu\text{m}$ ($F=14.900$, $P<0.01$) in group A, and from 463.8 ± 152.9 to $366.0 \pm 115.4 \mu\text{m}$ ($F=3.700$, $P<0.03$) in group B. The improvement in BCVA was better in group A ($P<0.05$) during this phase. In the second phase, the BCVA continued to rise to 0.5 ± 0.3 ($F=0.260$, $P<0.01$) in group A and to the same extent ($F=0.310$, $P<0.01$) in group B. The CMT was decreased to $260.7 \pm 63.0 \mu\text{m}$ ($F=-188.300$, $P<0.01$) in group A and to $261.9 \pm 50.2 \mu\text{m}$ ($F=-201.900$, $P<0.01$) in group B. No significant difference was found in the therapeutic effects between the two groups ($P>0.05$) during this phase. In the third phase, the improvements in BCVA and CMT were sustained in both groups, BCVA was 0.4 ± 0.3 ($F=0.220$, $P=0.001$), and CMT $267.8 \pm 58.3 \mu\text{m}$ ($F=-0.270$, $P<0.01$) in group A; these two parameters were 0.5 ± 0.3 ($F=-0.270$, $P<0.01$) and $272.7 \pm 49.2 \mu\text{m}$ ($F=-191.1$, $P<0.01$), respectively, in group B. Based on the results of this study, PRP plus IVC might be a better therapeutic strategy than PRP plus STTA in treating DME at proliferative stage.

Combination of ranibizumab or bevacizumab with laser therapy

Despite the fact that no study has reported on the efficacy of aflibercept combined with laser therapy in DME, several small-scaled clinical trials around the globe have examined the efficacy of combining ranibizumab with laser. However, the results are controversial. For example, in a single-arm, open-label, prospective clinical study conducted at four sites in Japan, DME patients were subjected to 2-monthly intravitreal injections of ranibizumab (IVRs) followed by PRN IVR in which IVR was performed when the CMT exceeded $300 \mu\text{m}$. One week after each IVR, short pulse focal/grid laser was delivered to treat residual leakage outside the fovea ($>500 \mu\text{m}$). Six months later, both the BCVA and CMT

in these patients were significantly improved, and it was also indicated that the laser photocoagulation could reduce the number of IVRs required to realize the functional and anatomical improvements.⁵⁵ In contrast, in a multicenter, prospective, randomized controlled clinical trial conducted in the US, angiography-guided macular laser photocoagulation was combined with a treat-and-extend regimen of IVR 0.3 mg. At the 1 year endpoint, the treat-and-extend regimen significantly reduced the number of IVRs compared with the monthly IVR 0.3 mg regimen, however, the laser modality neither improved the efficacy of IVR ($P=0.8$ for BCVA; $P=0.47$ for CRT), nor reduced the number of ranibizumab injections (10.7 for IVR treat and extend vs 10.1 for IVR treat and extend plus laser).⁵⁶ Such discrepancy might be due to the different dosing and regimens of IVR used in the trials, or due to the responses from distinct ethnic groups to the IVR and laser. It could also indicate that the combination of ranibizumab with laser might be more beneficial in short-term administration.

On the other hand, in a randomized three-arm clinical trial conducted in Egypt in 2010, the therapeutic modality combining intravitreal injection of bevacizumab (IVB) and sequential modified grid laser photocoagulation (MGP) appeared to be superior to IVB or MGP alone in reducing macular thickening and improving VA. Nonetheless, the BCVA improvements that had been generated by all the modalities disappeared at 6 months posttreatment.⁵⁷ Moreover, retrospective clinical research in the US showed that IVB alone at 24 months after the treatment was better than both GLP alone and IVB plus GLP at reducing CMT in the patients with diffuse DME.⁵⁸ Together, these results implicate that the combined modality of IVR or IVB plus laser might be used as a short-term (<6 months) therapeutic intervention for DME.

Comparison of aflibercept or conbercept to other drugs

Comparison of aflibercept to dexamethasone implant

The anti-VEGF drugs have shown superiority to laser therapy in the treatment of DME; however, due to the high prevalence of this disease, the costs involved during treatment have to be considered. A systematic review of literature reports that during a 3-year treatment period, the anti-VEGFs, such as ranibizumab and aflibercept, are more expensive than long-acting corticosteroid implants.⁵⁹ Therefore, an observational, retrospective study was conducted recently in Spain to

compare IVA vs sequential dexamethasone implant followed by IVA in naïve DME patients.⁶⁰ Fifteen patients in the IVA group were treated with aflibercept monthly for the first 5 months; whereas another 15 patients in the dexamethasone group were initially treated with a single dexamethasone implant (OZURDEX; Allergan plc, Dublin, Ireland), then both groups received IVA every 2 months. At the 12 months endpoint, the results showed that BCVA increased from 70.8±4.1 to 83.5±2.7 letters and from 75.6±2.7 to 86.5±2.5 letters in IVA and dexamethasone groups, respectively ($P=0.551$). CMT decreased from 411.0±26.1 to 288.1±10.5 μm and from 411.4±24.3 to 260.8±17.9 μm in IVA and dexamethasone groups, respectively. No statistical significance was found between the two groups in BCVA or CMT changes (both $P>0.05$). Therefore, the sequential treatment, dexamethasone implant followed by IVA, could serve as a more cost-effective yet equally efficacious alternative to the mere IVA regimen.⁶⁰

Comparison of aflibercept to bevacizumab and ranibizumab

In order to compare the clinical efficacy and safety of IVA, IVB, and IVR in the treatment of DME, a randomized controlled clinical trial called the DRCR.net Protocol T study⁶¹ was conducted by Wells et al in the US. Six hundred and sixty patients with DME from 89 clinical centers were randomly divided into three groups and received IVA (2.0 mg), IVB (1.25 mg), or IVR (0.3 mg) every 4 weeks, respectively. The results showed that all the anti-VEGF drugs improved the VA letter scores during the first year, and the mean score gains in the IVA group (13.3) were significantly greater than those in the IVB (9.7) and IVR (11.2) groups ($P<0.001$, IVA vs IVB; $P=0.03$, IVA vs IVR) (Table 3).

However, when taking the baseline VA letter score into account, the conclusion changed. In patients with mild baseline VA letter score (78–69; Snellen equivalent 20/32–20/40), the VA improvements were similar among the IVA (8.0 letter score), IVB (7.5 letter score), and IVR (8.3 letter score) groups both during the first and second year (IVA 7.8, IVB 6.8, and IVR 8.6 letter score, all $P>0.100$, for pair-wise comparisons) (Table 3).⁶² Furthermore, when patients with mild baseline VA were categorized by central subfield thickness (CST) at baseline, the IVB was significantly less beneficial than IVA and IVR during the first year in patients with CST more than 400 μm (IVA 9.5, IVB 5.4, and IVR 9.5 letter score) (Table 3).⁶³ On the other hand, in patients with worse baseline VA letter score (less than 69, Snellen equivalent 20/50 or worse), the IVA showed greater VA improvement

Table 3 Comparisons of aflibercept or conbercept with bevacizumab and/or ranibizumab in DME treatment

Ref	Duration (y)	Grouping	Regimen	N for BCVA (eyes)	BCVA (ETDRS letters)			N for CST (eyes)	CST (μm)			Eyes improved/total eyes		Score improvement	
					Baseline	Last follow-up	Change		Baseline	Last follow-up	Change	1y	2y	1y	2y
63	I	Letter score of 78 to 69 at baseline	IVA 2.0q4	106	73.5±2.6	81.4±8.3	8.0±7.6	104	373±108	242±57	-129±110				
			IVB 1.25q4	104	72.8±2.9	79.9±10.1	7.5±7.4	103	363±88	294±82	-67±65***				
			IVR 0.3q4	105	73.4±2.7	81.6±6.8	8.3±6.8	102	384±99	263±84	-119±109				
		Letter score of <69 at baseline	IVA 2.0q4	102	56.2±11.1	75.2±10.9	18.9±11.5	101	452±145	238±81	-210±151				
63	I	Letter score of 78 to 69 at baseline	IVB 1.25q4	102	56.6±10.6	68.5±13.6	11.8±12.0***	100	467±155	328±154	-135±152***				
			IVR 0.3q4	101	56.5±9.9	70.7±12.0	14.2±10.6***	99	431±138	252±92	-176±151				
		Letter score of 78 to 69 at baseline	IVA 2.0q4	33	73.2±2.7	82.6±8.4	9.5±8.4		≥400						
			IVB 1.25q4	31	72.4±2.7	76.1±15.6	5.4±8.6		≥400						
			IVR 0.3q4	43	72.8±2.7	82.3±6.1	9.5±6.7		≥400						
		CST ≥400 μm	IVA 2.0q4	72	73.6±2.5	80.7±8.2	7.2±7.2		<400						
		Letter score of 78 to 69, CST <400 μm	IVB 1.25q4	73	73.0±2.9	81.5±6.0	8.4±6.6		<400						
			IVR 0.3q4	61	73.7±2.7	81.3±7.3	7.6±6.8		<400						

62	2	Letter score of <69 at baseline, CST ≥ 400 μm	IVA 2.0q4 IVB 1.25q4 IVR 0.3q4	61 61 50	54.9 \pm 11.0 55.6 \pm 10.3 55.5 \pm 10.5	74.7 \pm 11.1 66.8 \pm 15.2 70.4 \pm 13.0	19.7 \pm 11.7 11.3 \pm 13.2 14.9 \pm 10.0		≥ 400 ≥ 400 ≥ 400							
		Letter score of <69 at baseline, CST <400 μm	IVA 2.0q4 IVB 1.25q4 IVR 0.3q4	40 39 49	59.0 \pm 10.0 59.4 \pm 9.7 57.7 \pm 9.1	76.6 \pm 10.1 71.0 \pm 10.7 71.1 \pm 11.1	17.5 \pm 11.3 11.6 \pm 8.8 13.3 \pm 11.3		<400 <400 <400							
		Letter score of 78 to 69 at baseline	IVA 2.0q4 IVB 1.25q4 IVR 0.3q4	103 93 97	73.5 \pm 2.6 73.0 \pm 2.9 73.4 \pm 2.7	81.2 \pm 8.3 79.8 \pm 11.4 82.0 \pm 6.8	7.8 \pm 8.4 6.8 \pm 8.8 8.6 \pm 7.0	101 93 95	373 \pm 108 360 \pm 82 377 \pm 97	237 \pm 50 291 \pm 95 250 \pm 81	-133 \pm 115 -68 \pm 98*** -125 \pm 118					
		Letter score of <69 at baseline	IVA 2.0q4 IVB 1.25q4 IVR 0.3q4	98 92 94	55.8 \pm 11.1 56.9 \pm 10.5 56.1 \pm 10.1	74.3 \pm 13.3 69.8 \pm 16.7 71.9 \pm 14.6	18.1 \pm 13.8 13.3 \pm 13.4* 16.1 \pm 12.1	97 89 91	450 \pm 142 471 \pm 153 430 \pm 135	236 \pm 82 282 \pm 108 253 \pm 115	-211 \pm 155 -185 \pm 158** -174 \pm 159					
64	2	Letter score of 78 to 69 at baseline	IVA 2.0q4 IVB 1.25q4 IVR 0.3q4	103			7.5 \pm 5.2 6.5 \pm 5.5 7.5 \pm 4.9									
		Letter score of <69 at baseline	IVA 2.0q4 IVB 1.25q4 IVR 0.3q4	98			17.1 \pm 9.7 12.1 \pm 9.4*** 13.6 \pm 8.5**									
65	2	NPDR at baseline	IVA 2.0q4 IVB 1.25q4 IVR 0.3q4	167 147 163	NPDR NPDR NPDR				NPDR NPDR NPDR			44/141 29/131 57/151	33/133 25/113 40/129	31.2 22.1** 37.7	24.8 22.1 31.0	
		PDR at baseline	IVA 2.0q4 IVB 1.25q4 IVR 0.3q4 IVC 0.5q4 IVR 0.5q4	30 38 32 36 32	PDR PDR PDR				PDR PDR PDR			22/29 11/35 16/29	19/27 10/33 9/24	75.9 31.4*** 55.2	70.4 30.3** 37.5*	
69	0.25					58.7 \pm 8.0 55.5 \pm 9.6	9.3 \pm 5.2 8.9 \pm 4.4			330.9 \pm 77.2 328.7 \pm 71.9	-138.4 \pm 97.7 -145.2 \pm 72.5					

Note: * $p < 0.05$ vs IVA, ** $p < 0.01$ vs IVA, *** $p < 0.001$ vs IVA.

Abbreviations: Ref, reference; y, years; BCVA, best-corrected visual acuity; EDTRS, Early Treatment of Diabetic Retinopathy Study; CST, central subfield thickness; PDR, proliferative diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; 2.0q4, 2.0 mg every 4 weeks; 1.25q4, 1.25 mg every 4 weeks; 0.5q4, 0.5 mg every 4 weeks; 0.3q4, 0.3 mg every 4 weeks; IVA, intravitreal injections of aflibercept; IVB, intravitreal injections of bevacizumab; IVR, intravitreal injections of ranibizumab; IVC, intravitreal injections of conbercept.

(18.9 letter score) than IVB and IVR (11.8 and 14.2 letter score, respectively; $P < 0.001$ for IVA vs IVB; $P = 0.003$ for IVA vs IVR) regardless of the baseline CST during the first year (Table 3).^{61,63} The IVA's superiority to IVB, but not IVR, was maintained during the second year (IVA 18.3, IVB 13.3, IVR 16.1 letter score; IVA vs IVB, $P = 0.020$; IVA vs IVR, $P = 0.180$) (Table 3).⁶² Anatomically, IVB reduced less CST than the other agents during the first year in the patients with worse baseline VA, but such difference was reduced during the second year (Table 3).⁶⁴

In 2017, the data of this clinical trial were reanalyzed, and the effects of these three drugs on severity of diabetic retinopathy (DR) were reported.⁶⁵ After 1-year treatment, 31.2%, 22.1%, and 37.7% of the eyes with non-proliferative DR that had been treated with IVA, IVB, and IVR, respectively, exhibited improvements in DR severity, with IVA and IVR being more beneficial than IVB ($P = 0.004$ for IVA vs IVB; $P = 0.010$ for IVR vs IVB). The amelioration of DR severity was sustained to the second year (24.8%, 22.1%, and 31.0% of eyes for IVA, IVB, and IVR, respectively), yet there was no significant difference among the groups. For the eyes with proliferative DR (PDR), aflibercept improved the disease severity more than the other drugs (IVA 75.9%, IVB 31.4%, and IVR 55.2%; $P < 0.001$ for IVA vs IVB; $P = 0.020$ for IVA vs IVR) during the first year, and this advantage was maintained during the second year (Table 3).

Results of this study suggest that all the three anti-VEGF drugs are effective in improving VA and DR severity in DME patients. Furthermore, aflibercept generates greater VA protective effects than bevacizumab and ranibizumab in DME patients with a baseline VA of less than 20/50, and it is also superior to mAbs in relieving disease severity in PDR patients. Nevertheless, it should be noted that the dosing of ranibizumab used in the US is 0.3 mg/injection, which is different than the dosing of 0.5 mg/injection in other countries. According to the pooled results of RISE and RIDE clinical trials,⁹ the two doses of ranibizumab have equivalent efficacy in the treatment of DME. Ranibizumab at 0.3 mg may result in lower drug concentration in systemic circulation, thereby reducing the risk of cardiovascular dysfunctions elicited by systemic inhibition of VEGF in patients with DME.⁶⁶ The FDA therefore approved 0.3 mg/injection as the standard, long-term administration of ranibizumab in DME treatment.⁹ However, the results of other clinical trials^{67,68} indicate that 0.5 mg ranibizumab used at a frequency less than once a month or in various PRN regimens could be considered, particularly in DME patients with a lower baseline VA.

Comparison of conbercept to ranibizumab

In 2017, Xu et al⁶⁹ reported a retrospective study comparing the efficacy of IVC with IVR in DME treatment. Sixty-two Chinese patients with DME were recruited, 32 of whom received IVC and the others IVR. The therapeutic regimen was once a month for 3 months followed by PRN therapy. After 1 year, both groups showed apparent BCVA improvements (IVC 9.3 ± 5.2 letter scores, IVR 8.9 ± 4.4 letter scores, $P = 0.756$) and CRT reductions (IVC $138.4 \pm 97.7 \mu\text{m}$, IVR $145.2 \pm 72.5 \mu\text{m}$, $P = 0.748$), however, no statistically significant differences were detected between the groups (Table 3). These data suggest that both conbercept and ranibizumab are effective in treating DME and can achieve similar efficacy. However, the number of injections in the IVR group was significantly more than that in the IVC group (IVR 7.2 ± 1.0 injections/eye, IVC 6.6 ± 0.9 injections/eye; $P = 0.027$, IVR vs IVC) (Table 3). The lower injection frequency of IVC may indicate a lower risk of injection-associated complications and greater cost-effectiveness of conbercept.

Discussion and conclusion

Aflibercept and conbercept both belong to the group of recombinant decoy receptors to VEGF. They sequester free VEGF from mediating signal transduction through its cognate receptors, thereby blocking the pro-inflammatory, hyper-permeable, and pro-angiogenic effects of VEGF in a similar manner. Both drugs have been shown to be effective and safe for DME treatment.

Aflibercept exhibits greater therapeutic efficacy, including greater VA improvement and anatomic restoration, than traditional laser therapy. Further, it displays advantages over mAb drugs, such as bevacizumab and ranibizumab, in improving VA and ameliorating macular edema particularly in patients with initial VA less than 20/50, as well as those with PDR. However, aflibercept is the most expensive among the three clinically available anti-VEGF drugs. During 1-year treatment of DME, the incremental cost-effectiveness ratio of aflibercept is higher than that of bevacizumab, though it is still lower than that of ranibizumab.⁷⁰ Treatment cost is another factor to consider especially when it is at odds with therapeutic efficacy. The sequential treatment of long-acting dexamethasone implant followed by IVA could be an option since it maintains similar efficacy as IVA alone, while reducing treatment cost.

On the other hand, conbercept, as a new anti-VEGF drug that is designed, developed, and manufactured in People's Republic of China, has not yet been widely applied in clinics

around the world. Even though the structural and functional merits of conbercept have been demonstrated in laboratories and it has been shown to be more cost-effective than ranibizumab in a small-sized clinical study,⁶⁹ its therapeutic equivalency or superiority to VEGF mAbs has not been demonstrated in large-scale clinical trials. Furthermore, a small-sized clinical trial conducted in People's Republic of China has compared the efficacy of the therapeutic modality combining laser with IVC with that of IVC alone.⁵³ The results suggest that the combinatorial therapy may be a promising modality for DME due to its cost-effectiveness and reduced risk of adverse events, while maintaining equal efficacy. Nonetheless, confirmation from large-scale, standard, and stringently-controlled clinical trials is necessary before laser and IVC combinatorial therapy can be applied routinely in clinics.

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Disclosure

The authors report no conflicts of interest in this work.

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