Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

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REVIEW

The clinical utility of aflibercept for diabetic macular edema

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Michael W Stewart

Department of Ophthalmology,
Mayo School of Medicine,
Jacksonville, FL, USA

Abstract: The treatment of center-involving diabetic macular edema (DME) has improved because of the proven efficacy of drugs that inhibit the effects of vascular endothelial growth factor (VEGF). The newest anti-VEGF drug, aflibercept, has recently been approved by the United States Food and Drug Administration for the treatment of center-involving DME and for diabetic retinopathy in eyes with DME. In the pivotal Phase III VISTA and VIVID trials, intravitreal aflibercept 2 mg injections every 4 or 8 weeks (after 5 monthly loading doses) produced superior gains in BCVA compared to laser/sham injections. In the Diabetic Retinopathy Clinical Research Network Protocol T trial, which featured monthly anti-VEGF monotherapy for 6 months, followed by monthly pro re nata anti-VEGF injections with laser rescue therapy from months 6 through 12, aflibercept 2 mg monthly was superior to bevacizumab 1.25 mg and ranibizumab 0.5 mg in eyes with BCVA of 20/50 or worse (aflibercept versus bevacizumab: $P<0.001$; aflibercept versus ranibizumab: $P=0.003$), but the three regimens were comparable for eyes with VA of 20/40 or better. Only in the 20/50 or worse subgroup did aflibercept achieve clinical superiority (>5 letter difference) to bevacizumab. Each treatment regimen led to significant macular thinning, with aflibercept being superior to bevacizumab in both visual acuity subgroups ($P<0.001$ for each), but it was not statistically superior to ranibizumab in either group. In diabetic patients, aflibercept has an excellent safety profile that does not appear to differ from laser/sham or other VEGF inhibitory drugs.

Keywords: aflibercept, bevacizumab, diabetic macular edema, ranibizumab, vascular endothelial growth factor

Introduction

Diabetes mellitus (DM) is responsible for 1% of worldwide blindness and is the leading cause of vision loss among working aged individuals in industrialized countries.[1–3] Diabetes adversely affects all parts of the eyes and visual pathways, but most vision loss results from diabetic retinopathy (DR).[4] A subclinical retinal neuropathy is the earliest manifestation of DR, and retinal vascular abnormalities due to progressive capillary endothelial cell damage frequently follow. Capillary closure results in retinal ischemia, which in severe cases produces retinal neovascularization and proliferative DR. Severe fibrovascular proliferation with traction retinal detachment and vitreous hemorrhage is the most common cause of severe vision loss among diabetics, but moderate vision loss from diabetic macular edema (DME) occurs more commonly.[5]

DME affects approximately 7.5% of diabetics (750,000 people in the United States).[6] Among Type 1 diabetics, 0% have DME at 5 years after being diagnosed with DM and 29% have it by 20 years, whereas among Type 2 diabetics, DME affects

Correspondence: Michael W Stewart
Department of Ophthalmology,
Mayo School of Medicine, 4500 San Pablo Road, Jacksonville, FL 32224, USA
Tel +1 904 953 2232
Fax +1 904 953 7040
Email stewart.michael@mayo.edu

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3% at 5 years and 28% at 20 years.[7,8] Other studies suggest that the 10-year incidence of DME varies from 20% to 40%, depending upon the patient's age and the type and severity of the diabetes.[9] Risk factors for DME include male sex, duration of diabetes, poor glucose control, use of insulin, diuretic use, systemic arterial hypertension, cardiovascular disease, hyperlipidemia, proteinuria, impaired renal function, and vitreomacular traction.[10–12] Risk factors for DME, such as serum lipid concentrations, may be different from those responsible for the development of DR.[13,14]

The incidence of blindness due to neovascular age-related macular degeneration (AMD) is falling because of the successful implementation of anti-vascular endothelial growth factor (VEGF) therapy.[15] Since the worldwide prevalence of DM is expected to increase from 4.0% in 1995 to 5.4% in 2025,[16] with the number of patients projected to reach 430 million by 2030,[17] the number of patients affected with DR and DME will increase significantly, thereby shifting the epidemiologic focus from AMD to DR. Improved treatment of DME with advanced pharmacotherapies will be critical in the fight against a diabetes-induced epidemic of worldwide blindness. This paper discusses the efficacy and safety of aflibercept, the newest anti-VEGF drug, in the treatment of DME.

Historical perspective and rationale for VEGF blockade

DME represents a collection of fundus abnormalities – microaneurysms, hemorrhages, and exudates, with associated thickening of the macula.[18] For most of the past three decades, center-threatening and center-involving DME – referred to as clinically significant macular edema (CSME) – has been diagnosed by binocular examination of the macula.[19] The recent introduction of optical coherence tomography (OCT) together with the widespread availability of anti-VEGF drugs for center-involving DME has made the use of the Early Treatment of Diabetic Retinopathy Study (ETDRS) classification system less useful and the current classification of DME is generally limited to center-involving or not center-involving edema.

Intraretinal fluid accumulation may reversibly decrease vision in the short term, but over longer time periods it causes permanent loss of vision.[20] To combat DME-related vision loss, the Early Treatment of Diabetic Retinopathy Study established focal/grid laser photocoagulation as the gold standard for the treatment of CSME.[21] Eyes with CSME had a 32% risk of moderate vision loss over 3 years, but this was reduced by 50% with the timely application of laser.[22,23] Unfortunately, only 3% of patients in the ETDRS trial improved by 15 letters, although subsequent analyses showed that 30% of eyes originally worse than 20/32 improved by 10 letters, with an average gain of +4 letters. In a more recent DRCR.net trial, 15% of laser-treated patients experienced 15 letter improvements.[24] The reason for the laser's efficacy remains unknown, but it may be due to improved retinal oxygenation.[25] Laser decreases hypoxia in an animal model of retinal vein occlusion,[26] and supplemental oxygen has been shown to decrease DME in human subjects.[27] Unfortunately, vision gains following macular laser are frequently disappointing, and photocoagulation may be complicated by "laser creep" and choroidal neovascularization,[28] both of which decrease visual acuity in the long term.

Disruption of the blood–retinal barrier by phosphorylation of junctional proteins represents a key event in the development of DME,[29,30] but despite a voluminous body of clinical knowledge regarding the formation and treatment of DME, the molecular trigger for its development long remained unknown. Michaelson[31] postulated the existence of an intraocular substance that promoted vascular growth and Folkman[32] proposed that a soluble vasoproliferative molecule was necessary for tumor growth. Critical advances in our understanding of ocular neovascularization began with the discovery (in 1983) of vascular permeability factor (VPF)[33] and the subsequent discovery of VEGF (in 1989) by two independent research groups.[34,35] Protein sequencing showed that VPF and VEGF were identical molecules, thereby enabling scientists to focus their initial development efforts on a single molecular target.

VEGF is a dimeric glycoprotein with a molecular weight of 36–46 kDa that segregates into seven families: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, and placental growth factor (PlGF).[36] Isoforms of VEGF-A, of which there are at least six major ($VEGF_{121}$, $VEGF_{145}$, $VEGF_{165}$, $VEGF_{183}$, $VEGF_{189}$, and $VEGF_{206}$) and eight minor,[37,38] are the most important promoters of intraocular neovascularization and hyperpermeability. $VEGF_{165}$ is the most abundant isoform and is the most important for neovascularization. Diffusible VEGF binds to and dimerizes three transmembrane receptors (VEGFR1, VEGFR2, and VEGFR3),[36] and although VEGFR1 binds $VEGF_{165}$ with greater affinity, VEGFR2 regulates the blood–retinal barrier and controls endothelial cell mitogenesis.[39]

VEGF upregulation occurs largely in response to localized oxidative stress with stabilization of hypoxia inducible factor-1α.[40] Several cells within the retina produce VEGF (capillary endothelial cells, pericytes, pigment epithelial cells, neurons, and astrocytes)[41,42] and though all cell types respond to VEGF, the capillary endothelial cell is its primary target. Hypoxia-induced upregulation of VEGF breaks down the blood–retinal barrier[43] and increases capillary permeability via VEGF-mediated downregulation of claudin-1. Blocking VEGF with ranibizumab restores claudin-1 levels within 24 hours.[44]

PlGF upregulation occurs in diabetic eyes,[45] but its role in the development of DR remains unclear. Neither PlGF-1 nor PlGF-2 disturb the blood–retinal barrier in vitro,[44] but animal models suggest that PIGF plays a critical role in the development of DR.[46] Genetic deletion of PIGF in a diabetic mouse strain prevents diabetes-induced retinal cell death, capillary degeneration, pericyte loss, and blood–retinal barrier breakdown.[47]

Several lines of evidence implicate VEGF in the development of DR. Intravitreal injections of VEGF produce the characteristic findings of DR (microaneurysms, hemorrhages, macular edema, and neovascularization),[48,49] and elevated intraocular VEGF levels have been detected in eyes with active DME.[50] Aqueous VEGF concentrations in patients with DME are three times those in the plasma,[51] and aqueous levels correlate with DME severity.[51]

Laser remained the standard of care for center-involving DME for over two decades, but investigators continually sought more effective therapies. Intensive research and innovative drug development produced five drugs (pegaptanib, Macugen®, Eyetech, New York, NY, USA; bevacizumab, Avastin®, Genentech, South San Francisco, CA, USA/Roche, Basel, Switzerland; ranibizumab, Lucentis®, Genentech/Roche; aflibercept, Eylea®, Regeneron, Tarrytown, NY, USA; and conbercept, Chengdu Kanghong Biotech, Chengdu, People's Republic of China) that specifically bind diffusible VEGF.

Pegaptanib (an aptamer to $VEGF_{165}$) improved BCVA better than sham/laser (10 letter improvement: 34% versus 10%, P=0.003; mean change in BCVA: +6.1 versus +1.3 letters) in a multicenter Phase II trial.[52] Patients receiving bevacizumab in the Bevacizumab or Laser Therapy in the Management of Diabetic Macular Edema (BOLT) trial improved by a mean of +8.6 ETDRS letters compared to −0.5 letters for those treated with laser.[53]

Small pilot studies of ten patients each showed that ranibizumab decreased DME and improved BCVA.[54,55] The value of anti-VEGF therapy in the treatment of DME emerged from the Phase II ranibizumab trials (RESOLVE and READ-2)[56–59] and was solidified in several Phase III trials (RESTORE, DRCR.net Protocol I, and RISE/RIDE).[60–64] The RISE and RIDE trials demonstrated that monthly injections of ranibizumab produced 2-year BCVA improvements of approximately +10 letters and accelerated a shift toward establishing intravitreal anti-VEGF injections as first-line therapy for center-involving DME. Unfortunately, treatment regimens that rely on monthly clinic visits and injections challenge patients' compliance and signal the need for strategies with lower injection frequencies.

Aflibercept structure and biochemistry

Aflibercept, previously referred to as the VEGF-Trap, is a 115 kD, recombinant, high-affinity, VEGF-binding fusion protein. It contains all human protein sequences with the second extracellular binding domain from VEGFR1 and the third extracellular binding domain from VEGFR2 fused to the Fc fragment of a human immunoglobulin IgG molecule.[65] Aflibercept attaches to the receptor binding sites of all isomers of VEGF-A, VEGF-B, and PlGF with a $VEGF_{165}$ binding affinity (0.45 pM) that is 100-fold greater than ranibizumab and bevacizumab.[66] This tenacious attachment results from its favorable three-dimensional configuration that brings each of its Fab binding segments into contact with each VEGF subunit, thereby creating a nearly irreversible two-fisted grasp.[67] In capillary endothelial cell assays, aflibercept inhibits cellular migration and calcium uptake 10–126 times more than ranibizumab and bevacizumab.[66]

Aflibercept has an intravitreal half-life of 4.7 days in rabbits[68] – longer than either ranibizumab (2.88 days)[69] or bevacizumab (4.32 days)[70] – but its half-life in human eyes has not been determined. Pharmacokinetic models suggest that the intraocular half-life of aflibercept in human eyes is intermediate between that of ranibizumab and bevacizumab (approximately 9 days).[71] After intravitreal injection, aflibercept (unaltered) passes into the systemic circulation where its half-life is approximately 6 days. Aflibercept binds plasma VEGF and lowers serum concentrations to below 10 pg/mL (the lower detectable limit of some assays) for at least 7 days.[72]

Clinical trials

Important findings from the key aflibercept DME trials are detailed in Table 1.

A Phase I study[25] assessed the safety and efficacy of aflibercept in five patients with DME. Subjects with central subfield thickness (CST) >250 μm and BCVA from 20/32 to 20/320 were enrolled. Single injections of 4 mg aflibercept were administered, followed by a 6-week observation period.

Table 1 Important aflibercept trials for the treatment of diabetic macular edema are listed with inclusion of study design and top-line results

Phase and enrollment	Study design	Important results
Key aflibercept trials for the treatment of DME		
Exploratory study		
Phase I[73] (5 eyes)	• Single injection of 4 mg IAI • 6-week follow-up	At 4 weeks: • Mean CPT decreased by 49 μm • 4 of 5 had decreased CPT (median 74 μm) at 6 weeks • 4 of 5 had improved VA (median 3 letters) at 6 weeks • No ocular or systemic toxicity noted
DA VINCI trial		
Phase II[74,75] (221 eyes)	5 treatment arms • Laser • 0.5 mg IAI q4wk • 2 mg IAI q4wk • 2 mg IAI q4wk ×3 then q8wk • 2 mg IAI q4wk ×3 then PRN	At primary endpoint (24 weeks) • Mean Δ VA (letters): +2.5, +8.6, +11.4, +8.5, +10.3 ($P \leq 0.0085$) At secondary endpoint (52 weeks) • Mean Δ VA (letters): −1.3, +11.0, +13.1, +9.7, +12.0 ($P \leq 0.0001$) • Improved by ≥15 letters: 11.4%, 40.9%, 45.5%, 23.8%, 42.2% • Mean Δ CRT (μm): −58.4, −165.4, −227.4, −187.8, −180.3 ($P \leq 0.0001$) • Ocular adverse events: conjunctival hemorrhage, eye pain, ocular hyperemia, increased intraocular pressure • Systemic adverse events: hypertension, nausea, congestive heart failure
VIVID and VISTA		
Phase III[76] (872 eyes)	Parallel, identical trials 3 treatment arms: • Laser/sham • 2 mg IAI q4wk • 2 mg IAI q4wk ×3 then q8wk	At 52 weeks • Mean Δ VA (letters): +0.2, +12.5, +10.7 VISTA +1.2, +10.5, +10.7 VIVID • Improved by ≥15 letters: 7.8%, 41.6%, 31.1% VISTA 9.1%, 32.4%, 33.3% VIVID • Mean Δ CRT (μm): −73.3, −185.9, −183.1 VISTA −66.2, −195.0, −192.4 VIVID • Incidences of ocular and nonocular adverse events and serious adverse events were similar among all groups
DRCR.net protocol T		
Phase III[78] (660 eyes)	3 treatment arms • IAI 2 mg • Bev 1.25 mg • Ran 0.3 mg Monthly for 24 weeks At week 24 • injections monthly PRN • laser q3mo PRN	At 1 year • Mean Δ VA (letters): +13.3, +9.7, +11.2 • Mean Δ VA (letters) baseline ≥20/40: +8.0, +7.5, +8.3 • Mean Δ VA (letters) baseline ≤20/50: +18.9, +11.8, +14.2 ($P \leq 0.003$) • Mean Δ CRT (μm): −169, −101, −147 • Mean number of injections: 9, 10, 10 • No significant differences in rates of serious adverse events, hospitalization, death, or major cardiovascular events

Note: The table includes the Phase I, Phase II (DA VINCI), and Phase III (VISTA and VIVID; DRCR.net Protocol T) trials.
Abbreviations: IAI, intravitreal aflibercept injection; CPT, central point thickness; VA, visual acuity; CRT, central retinal thickness; DME, diabetic macular edema; DA VINCI, DME and VEGF Trap-Eye: INvestigation of Clinical Impact study; VIVID, VEGF Trap-Eye in Vision Impairment due to DME; VISTA, Study of Intravitreal Administration of VEGF Trap-Eye in Patients with DME; q4wk, every 4 weeks; q8wk, every 8 weeks; PRN, pro re nata (as needed); Bev, bevacizumab; Ran, ranibizumab; q3mo, every 3 months.

Outcome measures included safety, change in BCVA, and change in CST. The injections were well tolerated by all patients without apparent ocular toxicity. One patient developed cellulitis that was believed to be unrelated to the injections. The most common ocular complications, minor irritation and conjunctival injection, were unrelated to the injections. By 4 weeks after the injections, the mean BCVA improved by 9 letters and the mean CST improved by 49 μm. At 6 weeks, four of five patients had mean CST improvements of 74 μm (P=0.0625) and four of five experienced improved BCVA (median of 3 letters). Fluorescein angiography at 6 weeks showed no change in leakage in three patients and decreased leakage in two others. The authors concluded that a single injection of aflibercept was well tolerated and further studies in patients with DME were warranted.

The Phase II DME and VEGF Trap-Eye: INvestigation of Clinical Impact (DA VINCI) study[73] determined whether different doses and dosing intervals of aflibercept are superior to laser. The 52-week (primary endpoint at 24 weeks), multicenter, randomized, double-masked trial enrolled 221 patients (200 completed the trial) from the United States, Canada, and Austria. Major inclusion criteria included CRT >250 μm and BCVA from 73 to 24 ETDRS letters; major ocular exclusion criteria included previous macular or panretinal laser photocoagulation, and intravitreal corticosteroids or antiangiogenesis drugs administered within 3 months of screening. Systemic exclusionary criteria included uncontrolled arterial hypertension, renal failure requiring dialysis, or a thromboembolic event within the previous 6 months. Patients were randomized to five treatment groups: 0.5 mg aflibercept q4wk, 2 mg q4wk, 2 mg q4wk ×3 followed by q8wk, 2 mg q4wk ×3 followed by pro re nata (PRN), and laser photocoagulation with sham injections. Patients in the PRN arm were eligible for repeat intravitreal injections if the CRT was >250 µm, the CRT increased by >50 µm compared to the previous least measurement, or the BCVA decreased by 5 ETDRS letters from the previous measurement with any accompanying increase in CRT. Patients in the laser/sham group were eligible for repeat laser every 16 weeks if CSME was detected.

The main outcome measures were changes in average BCVA and CRT at 24 weeks. Patients in the aflibercept groups experienced average gains of +8.5 to +11.4 ETDRS letters compared to +2.5 letters in the laser group ($P<0.0085$ for each aflibercept group compared to laser). The 2 mg q8wk group gained fewer letters than the q4wk group, but the groups experienced different BCVA gains after the first injections, suggesting that differences in the composition of the enrolled groups rather than the treatment regimens were responsible. Gains of +0, +10, and +15 letters were seen in up to 93%, 64%, and 34% of eyes in the aflibercept groups compared to 68%, 32%, and 21% of eyes in the laser group. Mean changes in CRT ranged from −127.3 to −194.5 µm in the aflibercept groups to only −67.9 µm in the laser arm ($P=0.0066$ for each aflibercept group versus laser). Patients in the 2 mg PRN arm received a mean of 1.5 (out of a possible 3) injections during the PRN phase and patients in the laser arm received a mean of 1.7 (out of a possible 2) procedures. Aflibercept was well tolerated with adverse event rates similar to those seen in other anti-VEGF trials. Two cases of endophthalmitis (one culture negative, one *Staphylococcus epidermidis*) occurred. Four patients (all receiving aflibercept) developed severe systemic arterial hypertension, though all carried previous diagnoses of hypertension. Three patients (all receiving aflibercept) had thromboembolic events.

The main 52-week outcomes of the DA VINCI trial[74] were the proportion of patients improving by 15 letters BCVA and the mean improvements in CRT. The proportion of eyes gaining 15 letters was 40.9%, 45.5%, 23.8%, and 42.2% respectively, compared to 11.4% for the laser group. The mean changes in BCVA in the aflibercept groups increased from +9.7 to +13.1 letters compared to −1.3 letters for the laser group ($P<0.0001$ versus laser). Mean changes in CRT were −165.4 to −227.4 µm versus −58.4 µm. DR severity scores improved in 40%, 31%, 64%, and 32% of patients respectively in the aflibercept groups but in only 12% of patients in the laser group; DR worsening was seen in 0%–13% of eyes treated with aflibercept and in 24% of eyes treated with laser/sham. Patients receiving 2 mg q8wk and 2 mg PRN received similar numbers of injections (7.2 and 7.4) as those in the RESTORE trial (7).[60] Eyes receiving aflibercept were eligible for rescue laser beginning at week 24. The mean number of lasers given to patients randomized to aflibercept was less than 1, whereas patients in the laser/sham group received a mean of 2.5 lasers. The incidence of endophthalmitis (2%) was similar to that in the RESOLVE trial.[56]

The Study of Intravitreal Administration of VEGF Trap-Eye in Patients with DME (VISTA; NCT01363440) and the VEGF Trap-Eye in Vision Impairment due to DME (VIVID; NCT01331681) trials[75] were similarly designed, double-blind, randomized, Phase III trials that enrolled 872 patients (eyes) (VISTA: 466; VIVID: 406) with center-involving DME. VISTA-DME was run in the United States, whereas VIVID-DME was run in Australia, Europe, and Japan. Eligible patients were Type I or II diabetics with BCVA of 73–24 letters (20/40–20/320) and CRT thickening on OCT. Eyes were randomized 1:1:1 to receive intravitreal aflibercept injection (IAI) 2 mg q4wk, IAI 2 mg q8wk after 5 monthly loading doses, or laser photocoagulation/sham injection. Patients were eligible for laser retreatment every 12 weeks if ETDRS-defined edema was present. All study eyes were eligible for additional (rescue) treatment beginning at 24 weeks if they lost ≥10 letters of BCVA on two consecutive visits or ≥15 letters at any visit from the previous best measurement, and BCVA was worse than baseline. For laser-treated eyes, additional treatment consisted of 5 monthly doses of 2 mg IAI, followed by injections every 8 weeks, and for IAI-treated eyes, active laser therapy was performed. The primary temporal endpoint was at 52 weeks, but patients receiving IAI will be treated through 148 weeks. Patients randomized to laser/sham will be eligible to crossover to IAI during year 3.

The primary efficacy endpoint was the mean improvement in ETDRS BCVA at 52 weeks. Secondary efficacy endpoints included the proportion of patients gaining ≥15 letters, the proportion of patients gaining ≥10 letters, the proportion of eyes experiencing a two-step improvement in the ETDRS Diabetic Retinopathy Severity Scale (DRSS) score, the mean changes in central retinal thickness (CRT) as measured by

OCT, the change from baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) near activities subscale score, and the change from baseline in the NEI VFQ-25 distance activities subscale score. VISTA enrolled a greater proportion of Black patients and VIVID enrolled a greater proportion of Asian patients. More eyes in VISTA, compared to VIVID, had previously received anti-VEGF injections (42.9% versus 8.9%).

Mean BCVA changes from baseline to 52 weeks for the groups receiving IAI 2 mg q4wk, IAI 2 mg q8wk, and laser/sham were +12.5, +10.7, and +0.2 letters ($P<0.0001$) in VISTA and +10.5, +10.7, and +1.2 letters ($P<0.0001$) in VIVID. When eyes receiving additional therapy were included in the analysis, those in the IAI groups changed by +10.7 to +12.4 letters from baseline, whereas those in the laser groups changed by +4.2 and +3.5 letters. Visual acuity gains were significantly greater in the IAI groups in both patients who had and had not received prior anti-VEGF therapy. The corresponding proportions improving by ≥10 letters were 64.9%, 58.3%, and 19.5% respectively ($P<0.0001$) in VISTA and 54.4%, 53.3%, and 25.8% respectively ($P<0.0001$) in VIVID. The corresponding proportions improving by ≥15 letters were 41.6%, 31.1%, and 7.8% ($P<0.0001$) in VISTA and 32.4%, 33.3%, and 9.1% ($P<0.0001$) in VIVID. The corresponding proportions that lost ≥15 letters were 0.6%, 0.7%, and 9.1% respectively ($P<0.0001$) in VISTA and 0.7%, 0%, and 10.6% respectively ($P<0.0001$) in VIVID. Compared to laser, most patients receiving IAI did not lose any letters from baseline: 94.2%, 92.7%, and 57.1% in VISTA, and 94.1%, 91.9%, and 62.9% ($P<0.0001$) in VIVID. Significantly more patients treated with IAI q4wk and q8wk than laser experienced a two-step improvement in DRSS in both VISTA (33.8% and 29.1% versus 14.3%) and VIVID (33.3% and 27.7% versus 7.5%). Mean changes in CRT were −185.9, −183.1, and −73.3 μm in VISTA and −195.0, −192.4, and −66.2 μm in VIVID. The mean ± SD in NEI VFQ-25 scores for the IAI q4wk groups were significantly different from the laser groups only for the near activities subscale scores in VISTA (9.0±20.6 versus 5.4±20.4; $P=0.0168$). For patients treated with laser/sham, the mean numbers of procedures were 2.7 and 2.1 in VISTA and VIVID, respectively. More patients in the laser group than the IAI groups received additional (rescue) therapy (VISTA: 31.2% versus 0.7% and 2.6%; VIVID: 24.1% versus 4.4% and 8.1%).

Incidences of ocular and nonocular adverse events and serious adverse events including Anti-Platelets Trialists Collaborative defined vascular events and deaths were similar among all groups. The incidences of ocular and nonocular adverse events were similar across all treatment groups. Serious nonocular adverse events were uncommon (hypertension: 9.7%; cerebrovascular accidents: 1.1%; and myocardial infarction: 1.1%). Incidences of intraocular inflammation were 0.2% (4/1,832 injections), 0.1% (1/1,284 injections), and 0.5% (1/212 injections) in VISTA and 0.2% (4/1,566 injections), 0.4% (5/1,186 injections), and 0.7% (1/135 injections) in VIVID. Both laser patients that developed inflammation did so before receiving aflibercept. There were no incidences of endophthalmitis. The incidences of congestive heart failure and anemia were higher in the aflibercept groups, and the incidences of myocardial infarction and osteoarthritis were higher in the laser groups. The total numbers of vascular deaths were 2, 2, and 2, and the total numbers of deaths were 2, 4, and 2 due to additional deaths from B-cell lymphoma and lung carcinoma in the 2 mg q8wk group.

A Bayesian network meta-analysis was used to indirectly compare the literature-reported efficacies of ranibizumab and aflibercept on the treatment of DME. For 10 letter gains, the results slightly favored ranibizumab (relative risk: 1.59, 95% credible interval: 0.61–5.37).[76]

The only trial to directly compare IAI with bevacizumab or ranibizumab for the treatment of DME was the recently reported DRCR.net Protocol T trial.[77] This prospective, comparison trial randomized 660 patients at 89 sites to receive 1.25 mg bevacizumab, 0.3 mg ranibizumab, or 2 mg aflibercept. Entry criteria included BCVA from 20/32 to 20/320 with center-involving DME by clinical examination and OCT. Patients were treated every 4 weeks unless the BCVA reached 20/20 or better with a CST below the eligibility threshold, or there was no BCVA change of 5 letters or more or a 10% change in CST over the past two injections. Beginning at week 24, injections were withheld if the BCVA change was <5 letters and the CST change was <10% over two injections irrespective of BCVA. Laser photocoagulation was performed at or after 24 weeks for persistent edema.

Mean numbers of injections were 9 (aflibercept), 10 (bevacizumab), and 10 (ranibizumab) ($P=0.045$). Laser photocoagulation was performed in 37%, 56%, and 46% of eyes respectively ($P<0.001$). Mean changes in BCVA at 1 year were +13.3 letters (aflibercept), +9.7 letters (bevacizumab), and +11.2 letters (ranibizumab) ($P<0.001$: aflibercept versus bevacizumab; $P=0.03$: aflibercept versus ranibizumab). Subgroup analysis was critical in uncovering significant differences in efficacy among the drugs. For eyes with baseline BCVA of 20/32 to 20/40, mean changes were +8.0 (aflibercept), +7.5 (bevacizumab), and +8.3 letters (ranibizumab). When baseline VA was ≤20/50, mean changes in BCVA were +18.9 (aflibercept), +11.8 (bevacizumab), and +14.2 letters (ranibizumab). The average changes in CST were −169, −101, and −147 μm respectively. Only two eyes developed endophthalmitis. There were no significant differences in the rates of serious adverse events (P=0.40), hospitalization (P=0.51), death (P=0.72), or major cardiovascular events.

Analysis and future considerations

Aflibercept has been approved by the United States Food and Drug Administration (FDA) for the treatment of neovascular AMD and macular edema due to retinal vein occlusions. The FDA also approved aflibercept for the treatment of center-involving macular edema due to DME (2014) and DR with associated DME (2015). In 2014, the European Union approved aflibercept for the treatment of DME. Ongoing aflibercept trials for the treatment of DR include VIVID-Japan, a Phase III, open-label study evaluating the safety and tolerability of intravitreal aflibercept in Japanese patients with DME, the ACT trial, a two-dose trial evaluating the effects of intravitreal aflibercept on proliferative DR, and DRCR.net Protocol V, that compares aflibercept with laser photocoagulation for eyes with DME but excellent BCVA.

Apart from the recently published DRCR.net Protocol T trial,[77] no randomized trials have compared aflibercept with other anti-VEGF drugs for the treatment of DME. Physicians will be tempted to compare the results of the pivotal VISTA/VIVID[75] trials with other completed Phase III trials (particularly RISE/RIDE[61]), but should do so with caution because of differences in patient populations and treatment strategies. VISTA/VIVID enrolled a large Asian subpopulation (20%) compared to RISE/RIDE (5%) and also studied an active laser control group (treated at baseline), whereas RISE/RIDE used a sham control group that was eligible for laser only after 3 months. Ranibizumab-treated patients in RISE/RIDE were eligible for laser after 3 months, whereas IAI-treated patients could not receive laser for at least 24 weeks.

Patients receiving aflibercept in VISTA but not VIVID reported significant improvements in near visual function on the NEI VFQ-25 questionnaires. The differences in visual outcomes in VISTA and VIVID were similar, so these reported quality differences may have been due to the different study populations. The North America–based VISTA trial had a significant proportion of African–American subjects (11.1%), whereas the eastern hemisphere-based VIVID trial had a large proportion of Asian subjects (19.3%).

Patients receiving IAI q8wk in VIVID/VISTA developed a saw tooth pattern of CRT measurements after the five loading doses, but there were no corresponding changes in BCVA. The CRT patterns suggest that 8 weeks approaches the average effective treatment interval for DME and AMD study populations. Unfortunately, VIVID and VISTA were not able to determine if this saw tooth pattern of macular thickening causes long-term compromise of macular morphology or visual acuity. Physicians should be aware that carefully selected individual patients may be extended to much longer intervals, whereas others will require more frequent injections. Study developers required five monthly doses of aflibercept before extending the intertreatment interval to 8 weeks. Unfortunately, we do not know if a shorter initiation sequence is sufficient or if a longer sequence is required for optimal results.

Aflibercept possesses a much longer systemic half-life than ranibizumab, causing serum accumulation and depression of VEGF levels after intravitreal injections.[72] Some investigators worry that aflibercept's longer half-life may increase its risk of VEGF-associated vascular occlusive events such as stroke, but pivotal trials with both aflibercept and ranibizumab were underpowered to detect infrequent complications, so results vary and firm conclusions cannot be reached. Ranibizumab was associated with a dose-dependent increase in stroke rate compared to the sham/laser group in RISE/RIDE, but the results from Protocol T suggested that there were no differences in stroke rates among the anti-VEGF drugs.

Treatment guidelines for DME are evolving rapidly and experts frequently disagree on optimal strategies, but the Phase III trials suggest that several principles are reasonable to follow. RISE/RIDE and VISTA/VIVID were designed according to the pharmacokinetic profiles of ranibizumab and aflibercept to optimize visual outcomes. Excellent visual results were obtained with monthly ranibizumab injections through 2 years and monthly or bimonthly (following 5 monthly injections) injections through 52 weeks. Mean improvements in BCVA with monthly injections are slightly better than those achieved in the more flexible RESTORE and DRCR.net Protocol I trials, but comparing the results from these different trials must be done carefully because of their different entry criteria. Regimens with monthly injections impose significant hardships upon both patients and physicians, and so the bimonthly injection regimen from VIVID/VISTA provides some relief without compromising visual outcomes. More flexible treatment regimens with reinjections based on visual acuity (RESTORE) or visual acuity together with OCT findings (Protocol I) allow for fewer injections while still producing excellent visual outcomes. Whether or not flexible treatment regimens limit BCVA gains remains to be determined.

The need for macular laser photocoagulation in patients receiving monthly anti-VEGF injections is not clear. VIVID and VISTA allowed for laser photocoagulation at 6 months in eyes with incomplete responses to pharmacotherapy, but eyes receiving ranibizumab monotherapy in RESTORE had excellent visual acuity results. Hopefully, future studies will better characterize the need for laser photocoagulation in patients receiving aflibercept.

The aggregate results from Protocol T suggest that small but statistically different BCVA improvements result from the use of the three anti-VEGF drugs, but important additional conclusions were gleaned from the subgroup analyses. For eyes with reasonably good baseline VA ($\geq$20/40), monthly injections of bevacizumab, ranibizumab, or aflibercept can be expected to produce excellent improvements in BCVA (approximately +8 letters). For eyes with VA $\leq$20/50, monthly aflibercept provides a clear advantage over bevacizumab (Δ of 7.1 letters) and ranibizumab (Δ of 4.7 letters). A tiered approach to eyes with DME based on initial BCVA would appear prudent.

For patients with poor VA ($\leq$20/50) and increased CRT, a cost-effective analysis prior to the completion of VISTA/VIVID and Protocol T recommended that intravitreal pharmacotherapy with triamcinolone and less expensive anti-VEGF injections (bevacizumab) should be considered.[78] Not surprisingly, less frequently administered (q8wk) aflibercept is more cost-effective than monthly injections since it reduces cost by 39%. The recently published results of VISTA/VIVID and particularly Protocol T invite an updated analysis. The treatment of eyes with good VA ($>$20/32) has not been systematically studied with anti-VEGF agents, and at this time, the less expensive laser photocoagulation may be the best choice. DRCR.net Protocol V is currently evaluating the administration of aflibercept for eyes with good VA.

Conclusion

Intravitreal aflibercept is superior to laser photocoagulation for eyes with center-involving DME and may be more effective than bevacizumab and ranibizumab for eyes with BCVA $\leq$20/50.

Disclosure

Michael W Stewart is solely responsible for the preparation of this manuscript. He serves on advisory boards for Allergan and Regeneron, which also provide institutional research support. He also serves as a consultant for Boehringer-Ingelheim. The author reports no other conflicts of interest in this work.

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