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Review Article

Aflibercept for diabetic macular edema: a concise review

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ABSTRACT

Diabetic retinopathy and diabetic macular edema are associated with loss of vision in patients with diabetes worldwide. The treatment requires a multidisciplinary interventional approach. Among the available management options for DME, laser photocoagulation has been the standard of care. Due to its slow progression and inability to reverse the vision loss, an alternative treatment is needed. The role of vascular endothelial growth factors (VEGF) and inflammatory mediators led to the development of anti-VEGF agents, that stimulates retinal vasculogenesis and angiogenesis. Intravitreal aflibercept is an anti-angiogenic soluble decoy receptor with trap technology employed by fusion of multiple endogeneous receptor component, approved for the treatment of DME. Clinical trials of aflibercept comparing it with laser photocoagulation and other anti-VEGF have shown reliable efficacy, providing significantly positive visual and anatomical results. However, treatment regimens with monthly clinical visits and injections, challenge the patients comfort, thereby requiring the need to identify better strategies to lower injection frequencies.

Keywords: Aflibercept, Drug, Diabetic Retinopathy, Diabetic macular edema, New therapy

INTRODUCTION

Diabetic retinopathy (DR), a leading cause for visual impairment is a specificmicrovascular complication of the retina among patients with diabetes mellitus. DR currently affects approximately 150 million people globally, and the World Health Organization projects that the number of people affected will double by the year 2025.[1] Diabetic retinopathy progresses to microvascular alterations such as retinal ischemia, retinal permeability, retinal neovascularization, proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME) creating an economic impact on society and healthcare systems.[2] Visual loss from DME is five times greater than that from proliferative diabetic retinopathy.[3] DME is an ocular manifestation of the disease causing visual deterioration and 5.4% are estimated to be visually impaired due to DME in Europe.[4] DME results in thickening of retinal capillary basement membrane and produces impaired oxygen diffusion, which stimulates production of VEGF.[5] VEGF is elevated in vitreous and retina and is over expressed among diabetic retinopathy patients, and thus plays a pivotal role in the progression of DME. Focal or grid laser photocoagulation was the first modality and was the preferred choice for a decade. However, its effects were not sustained for longer duration and patients continued to have diminished visual acuity. This led to the development of new treatment

approaches with vasoactive and pro-inflammatory molecules such as VEGF inhibitors.[6] As VEGF is responsible for blood retinal barrier breakdown, VEGF intra-vitreal VEGF inhibitors are a paragon component to treat DME by counteracting VEGF overexpression.

MECHANISM OF ACTION

Aflibercept is a 115-kDA high affinity human recombinant fusion protein with antiangiogenic effects consisting of extracellular domain of human VEGF receptors (VEGFR)-1 and (VEGFR)-2 fused to the Fcdomain fragment region of human immunoglobulin IgG1 molecule. It functions as decoy soluble receptor there by blocking the VEGF signalling pathway. Aflibercept acts like a VEGF trap by binding to circulating VEGFs and by inhibiting vascular endothelial growth factor such as VEGF-A, VEGF-B and placental growth factor that blocks retinal cell migration and proliferation. VEGF trap attaches to receptor binding site of isomers of VEGF-A, VEGF-B and placental inhibitor growth factor(PIGF) with higher binding affinity of 0.45pM that is 100-fold greater than ranibizumab and bevacizumab (anti-VEGF antibodies). Clinical studies have demonstrated that the aflibercept binds to VEGF-A with higher affinity and faster association rate than other anti-VEGF antibodies. With consistent binding kinetics, VEGF trap illustrates increased potency relative to ranibizumab and bevacizumab and additionally it has the unique ability to bind VEGF-B and PIGF.[7]

EFFICACY

The efficacy of aflibercept were evaluated in multicenter randomized, double masked, phase 2 and phase 3 clinical trials for the treatment of DME. The primary endpoints involved change in best corrected visual acuity and the secondary outcomes involved the change from baseline in central retinal thickness (CRT) and proportion of patients gaining at least 15 letters at week 24. In the phase II DAVINCI study compared between 4 different dosing regimens and laser coagulations, the visual gains were lower in the 0.5 mg and 2q8 group and higher in 2q4 and PRN group.[8,9] The low visual gain was consistent for the 2q8 at an earlier stage compared with other groups symbolizing the poor baseline criteria. The baseline characteristics were identical for all groups except 2q8 group with higher percentage of type I DM with proliferative diabetic retinopathy and additionally higher percentage (66%) had received laser grid compared with another group.

Table 1: The major randomized clinical trials involving aflibercept.

Study design/ study topic	Patients	Inter-vensions	Primary outcome	Mean change in BCVA letters at month 12	Mean CRT	Gains from baseline
Multicenter, phase II, double blinded/ Davinci	221	0.5q4,2q4,2q8, 2PRN, laser group	Mean change in VA and central macular thickness at 24 weeks	+8.6, +11.4, +8.5, +10.3, +2.5	-165.4, -227.4, -187.8, -180.3 and -58.4	Gains of +0, +10 and +15 letters were seen in 83%,64% and 34% in aflibercept groups and 68%,32% and 21% in the laser groups.
Randomized, double blinded, phase III/ Vivid	466	2q4,2q8, laser group	Change from baseline in BCVA in EDTRS letters at week 52.	+10.5, +10.7, +1.2 (p<0.0001)	-195.0, -192.4 and -66.2	32.4%,33.3% and 9.1% improved by ≥15 letters
Randomized, double blinded, phase III/ Vista	406	2q4,2q8, laser group	Change from baseline in BCVA in EDTRS letters at week 52.	+12.5, +10.7, +0.2 (p<0.0001)	-185.9, -183.1, -73.3	41.6%,31.1% and 7.8% improved by ≥15 letters
Multicentre, randomized/ protocol T (aflibercept arm)	660 (224 AFL)	IAI 2 mg, BEV 1.25 mg, Ran 0.3 mg	Comparison of the change in VA at 1 year between different drugs	+13.3, +9.7, +11.2	-169, -101, -147	Mean VA with 20/30-20/40 at baseline: +8.0, +7.5, +8.3 Mean VA with 20/50 at baseline: +18.9, +11.8, +14.2

Abbreviations: BCVA, best-corrected visual acuity; CRT, central retinal thickness; IAI, intravitreal aflibercept injection; VA, Visual acuity; 0.5q4-0.5 mg every 4 weeks, 2q4-2 mg IAI every 4 weeks, 2q8-2 mg IAI every 8 weeks, 2PRN-2 mg IAI for three months initially, then as needed

In the phase III VIVID/VISTA of similar design, except majority of patients in VISTA study received anti-VEGF than VIVID (42.9% versus 8.9%); the VA gain were significantly greater in the AFL group in both patient's groups with or without receiving prior anti-VEGF therapy.[10] In contrast to DAVINCI study, the 2q4 and 2q8 (Table 1) had similar visual gains, that depicted the poor baseline criteria previously. DRCR protocol T is the first major RCT that used spectral domain-optical coherence tomography (OCT) along with VA in their assessment to determine the efficacy and safety of intra-vitreous aflibercept compared with other drugs such as bevacizumab and ranibizumab. The mean improvement in VA was significantly greater in aflibercept than ranibizumab and bevacizumab. In the BOLT study, 1.25 mg dose of bevacizumab showed no significant difference or improvement in DME compared with 2.5 mg.[11,12] The READ study that compared ranibizumab 0.5 mg and 2 mg, revealed higher visual gain in 0.5 mg arm.[13] Additionally, the RISE/RIDE study with 0.3 mg and 0.5 mg dose of ranibizumab, showed no improvement in the treatment of DME illustrating the fact that doubling the dose of ranibizumab does not increase the efficacy of the drug.[14] Comparing with laser photocoagulation and the other anti-VEGF agents, aflibercept proves to be an effective primary treatment for patients with VA 20/50 or worse in DME and significantly greater reduction of CRT (Table1) and the proportion of patients that gained ≥ letters were maximum in the aflibercept group.[15]

PHARMOKINETICS

Aflibercept is administered intravitreally to the patients, prescribed at a dose of 2 mg every month for 5 months, followed by 2mg every other month. After subsequent absorption of drug into the systemic circulation a portion of the administered drug binds with endogenous VEGF in the eye, forming inactive aflibercept VEGF complex (Unbound to VEGF) and are present in a stable inactive form.[15] The mean c-max of free aflibercept in the plasma was 0.05 mcg/ml and was attained in 1-3 days. Aflibercept is a therapeutic protein undergoes elimination through both target mediated disposition via binding to free endogenous VEGF and metabolism via proteolysis.[16] The terminal elimination half-life (t1/2) of free aflibercept in plasma was approximately 5 to 6 days.[17]

SAFETY

The rates of systemic adverse events were similar across all the AFL group evaluated and tolerated by the patients. The most commonly related ocular adverse events include conjunctival hemorrhage, ocular hyperemia, increased intraocular pressure and systemic adverse events includes hypertension, nausea, congestive heart failure. The most reported side effects include eye pain, cataract and vitreous floaters. patients with active ocular infection are not advised for the treatment of AFL.[18]

CURRENT STATUS AND FUTURE DIRECTION

Aflibercept has been approved by the USFDA and the European union in the year 2014. Protocol I study suggested that treatment of DME is effective using a PRN strategy. In relation to the anatomical outcomes or changes in the DAVINCI or VIVID/VISTA group, a fluctuation in macular thickness (see-saw pattern) was observed in bimonthly dosing regimen and not found to be in the PRN arms of the DAVINCI and protocol T group, hence supporting the PRN dosing regimen of aflibercept for treating DME. Longer half-life of aflibercept than ranibizumab causes serum accumulation and suppresses the plasma free VEGF levels after intravitreal injections.[19] Patients with late switching of aflibercept showed anatomic improvement but failed to improve visual gains concluding these patients belong to late responder group and might respond with continuous treatment.[20] Switching to aflibercept from other anti-VEGFs certainly be a good option for the treatment of DME. However, the exact efficacy and timing of switching the drugs between the patients must be evaluated.

CONCLUSION

Aflibercept is an anti-VEGF agent that is approved for the treatment of DME at a dose of 2 mg intravitreal injection. Considering the limited alternative options for the treatment of DME, the entry of aflibercept is certainly welcome. The long-term safety of this medication in these patients needs to be established from future post marketing studies as most of the earlier studies were performed in trials with smaller sample sizes. The demand for macular laser photocoagulation (first line therapy) in patients receiving anti-VEGF is uncertain. Thus future studies to evaluate the need for laser photocoagulation in patients receiving intravitreal aflibercept is to be undertaken.

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