MODULE 9.2
Biology and Pharmacology of Anti-VEGF Therapies

Vascular endothelial growth factor (VEGF) is known to play a key role in the development of diabetic macular edema (DME).[1,2] VEGF acts on proteins in tight junctions (TJs), thus causing the breakdown of the blood-retinal barrier (BRB).[3] The mechanisms by which VEGF induces neovascularization in proliferative diabetic retinopathy (PDR) are multifactorial; however, several critical factors have been identified[2]:

- Activation of protein kinase C beta-2 (PKC-b2) isoform
- Induction of serine protease, tissue-type plasminogen activator, and metalloproteinase expression
- Decreased inhibitors of metalloproteinases TIMP-1 and TIMP-2
- Enhancement of intercellular adhesion molecule 1 (ICAM-1) and vascular adhesion molecule 1 (VCAM-1)

Concentrations of VEGF are known to be elevated in the aqueous humor and vitreous humor of patients with DR and DME compared with that of individuals without diabetes.[4-6] These higher VEGF concentrations appear to be correlated with macular leakage in patients iwth diabetes.[7] Elevated concentrations of VEGF can contributeto a worsening of retinal perfusion in DME.[8]

These findings and others have led to the development of anti-VEGF therapeutic agents for DME.

Ophthalmologists now have several anti-VEGF agents to choose from when treating their patients with DME, namely bevacizumab, ranibizumab, and aflibercept (Table 1). Bevacizumab is a full-length murine monoclonal, anti-VEGF antibody[2] approved for numerous cancer indications but not for any ocular conditions. Ranibizumab is an affinity-enhanced antibody fragment developed from bevacizumab. The FAB fragment of ranibizumab allows for monovalent binding to VEGF, versus the bivalent binding of bevacizumab, with higher affinity.[9] Aflibercept was designed as an in-line fusion protein of VEGFR-1 and VEGFR-2 extracellular ligand–binding domains that is linked to the Fc portion of human immunoglobulin G1 (IgG1).[10] Aflibercept has the highest binding affinity to VEGF of the 3 agents.[11]

Responses to anti-VEGF therapy include:

- Reduced vascular permeability
- Decreased thickening of the macula and retina
- Improved visual acuity

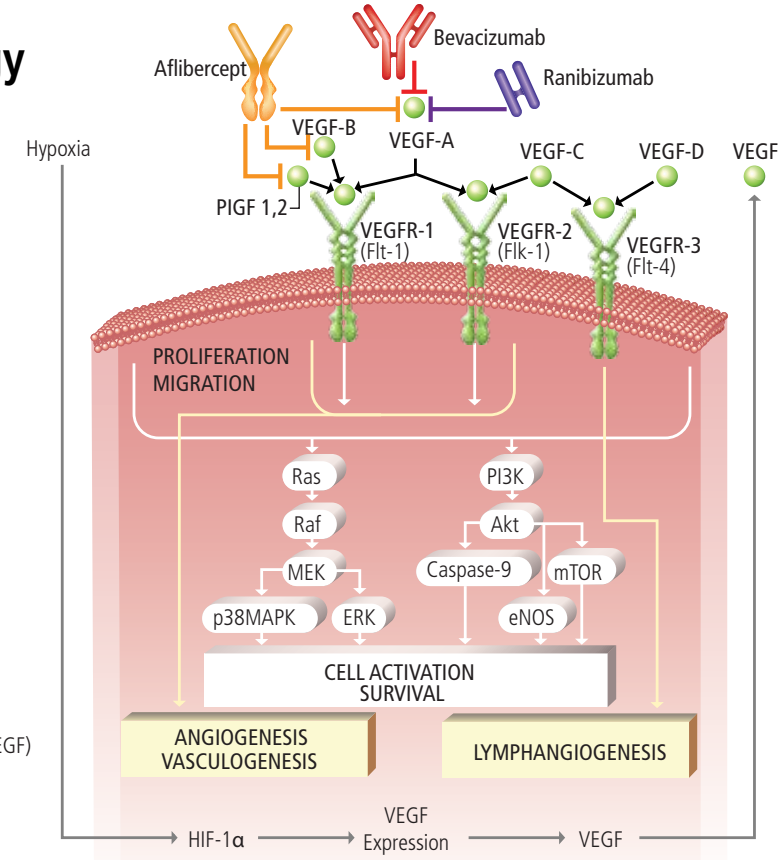
Biology and Pharmacology of Anti-VEGF Treatmets

There are three major responses to anti-VEGF therapy:

1) Reduced vascular permeability
2) Decreased thickening of the macula and retina
3) Improved visual acuity

Once the over-expression of VEGF is halted, its effects subside and leaking blood vessels diminish, reducing DME.

Currently two agents, ranibizumab (Lucentis) and aflibercept (Eylea), are approved to treat DME in the United States and the European Union. Trials are ongoing and further data is needed to understand the role and limitations of other agents. Strategies for managing DME will continue to evolve as more data is collected from these trials.

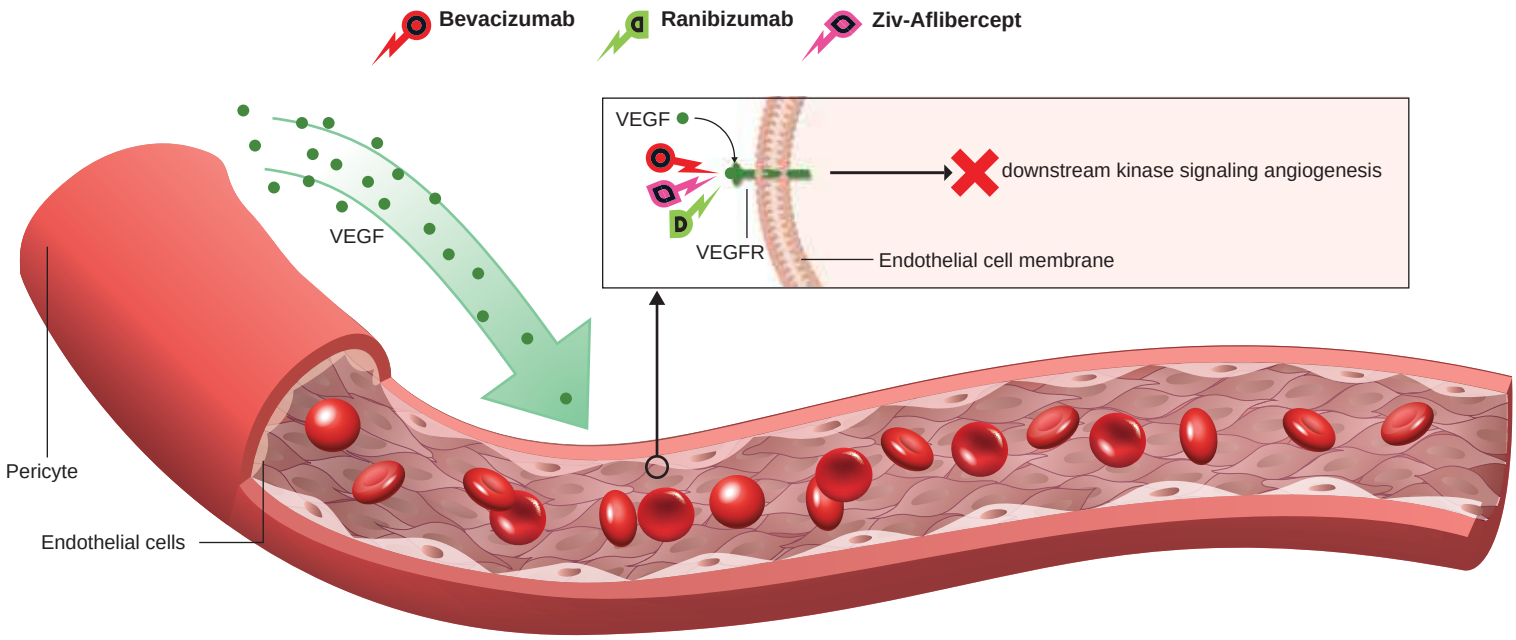


ENDOTHELIAL CELL The vascular endothelial growth factor (VEGF) family (A-D) binds to receptors VEGFR-1, VEGFR-2, VEGFR-3, activating signal transduction to promote angiogenesis, vasculogenesis, and lymphangiogenesis.

Table 1. Characteristics of Anti-VEGF Agents in the Treatment of Diabetic Retinopathy

From Simo et al, 2014[2]

	Ranibizumab	Aflibercept	Bevacizumab
	Affinity enhanced antibody fragment developed from bevacizumab: lacks the Fc portion and monovalent binding to VEGF	In-line fusion protein of VEGFR-1 and VEGFR-2 extracellular ligand–binding domains linked to the Fc portion of human IgG1	Full-length humanized, murine monoclonal, anti-VEGF antibody
MOA / Class	Anti-VEGF-A antibody fragment (targets all VEGF-A isoforms)	Anti-VEGF-A/ placental growth factor (PIGF)/ VEGF-B recombinant fusion protein (targets all VEGF-A isoforms, VEGF-B and PIGF)	Anti-VEGF-A full-length antibody (targets all VEGF-A isoforms)
Molecular Weight	48 kDa	97-115 kDa	149 kDa
Half-life in the Rabbit Eye	2.88 days	4-6 days	4.32 days
Systemic Elimination Half-Life	~2 hours	4-5 days	20 days
Licensed Indications	Wet age-related macular degeneration (AMD), visual impairment due to DME, visual impairment due to macular edema (ME) secondary to retinal vein occlusion (RVO) (branch RVO [BRVO] and central RVO [CRVO])	Wet AMD, ME secondary to CRVO	Metastatic colorectal cancer, non–small cell lung cancer, glioblasto-ma, metastatic kidney cancer
Formulation / Administration	Intravitreal injection from a single-use vial	Intravitreal injection from a single-use vial	For licensed indications: intravenous infusion from a single-use vial
KD for $VEGF_{16}$	46 pM	0.49 pM	58 pM
Structure	Image	Image	Image



Several studies have been conducted to evaluate the efficacy and safety of anti-VEGF agents in comparison to sham injections or laser treatment. Some of these studies have assessed the effectiveness of different dosing strategies in an attempt to lessen the treatment burden to the patient. You will learn more about these studies in Module 10.

The Protocol T study from the Diabetic Retinopathy Clinical Research Network (DRCRN; NCT01627249) was designed to compare the efficacy and safety of intravitreal aflibercept (2.0 mg), bevacizumab (1.25 mg), and ranibizumab (0.3 mg) for the treatment of central-involved DME in eyes with visual acuity of 20/32 to 20/320.[17] You will learn more about Protocol T in Module 10.

Previous clinical trial results have demonstrated anti-VEGF therapy is extremely effective and improves vision for patients with DME.[18,19]

The dosing regimen for DME is somewhat different from that for age-related macular degeneration (AMD). For example, in the DRCRN study, the average number of intravitreal injections for the deferred laser group was 9 in the first year but decreased to 3 in the third year of the study.[18] PRN dosing requires monthly monitoring, and studies are exploring the use of treat-and-extend (TE) protocols to reduce this treatment burden on patients. The RETAIN study evaluated the noninferiority/superiority of a TE regimen of ranibizumab, with/without laser, to a PRN regimen in patients with visual impairment due to DME.[20] Efficacy of ranibizumab using the TE regimen was noninferior to that with the PRN dosing regimen over 24 months. There was an approximate 40% reduction in patient visits scheduled with the TE regimen, and approximately 70% of TE patients had a monitoring interval of ≥2 months.

Another study, published in the New England Journal of Medicine, found that diabetic patients without any history of myocardial infarction had as high a risk of myocardial infarction as nondiabetic patients with previous myocardial infarction.[22]

Studies have evaluated the predictors of visual acuity and/or response in DME patients who have received intravitreal anti-VEGF therapy, including age, best-corrected visual acuity and presence of subretinal fluid at baseline presentation.[23,24]

Investigators conducting a longitudinal cohort study at a tertiary care referral center found that the organization of the retinal inner layers in the foveal area is associated with visual acuity (VA).[25] Disorganization of the retinal inner layers (DRIL) was predictive of future changes in VA. Early changes in DRIL prospectively identified eyes with a high risk of either subsequent VA improvement or deterioration. Interestingly, there is evidence that poor response to anti-VEGF therapy is correlated with sleep apnea. A recent study found that DME patients who were poor responders to anti-VEGF therapy had a significantly higher risk of obstructive sleep apnea compared with age-matched controls.[26] The study authors went on to propose that these patients should also be screened for apnea.

Long-term outcomes from anti-VEGF therapy are beginning to emerge, and are discussed in Module 10. Because of the favorable efficacy and safety profiles of the newer anti-VEGF agents, treatment paradigms for DME are changing. A literature search by Mitchell and Wong[27] advised “further research is needed to clarify if specific features (eg, intraretinal cysts or disruption of the inner segment/outer segment junction) and quantitative measures (eg, volume of thickening) are useful in assessing the need for anti-VEGF treatment or in predicting outcomes.”

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