

## Anti VEGF for Posterior Segment in Eye

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### Review Article

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### Abstract

Various vasoactive factors are responsible for structural and functional changes in diseases like diabetic retinopathy. It includes vascular endothelial growth factor (VEGF), protein kinase C (PKC), heparin, angiotensin II, pigment epithelium derived factor (PEDF), platelet derived growth factor (PDGF), matrix metalloproteinase (MMPs).

**Keywords:** VEGF; Angiogenesis; DME; Retina

**Abbreviations:** VEGF: Vascular Endothelial Growth Factor; PKC: Protein Kinase C; PEDF: Pigment Epithelium Derived Factor; PDGF: Platelet Derived Growth Factor; MMPs: matrix metalloproteinase; PDF: Placental Growth Factor; AMD: Age Related Macular Degeneration; RAP: Retinal Angiomas Proliferation; CNV: Choroidal Neovascularisation; PRP: Pan Retinal Photocoagulation; TRD: Tractional Retinal Detachment; CRVO: Central Retinal Vein Occlusion; CVOS: CRVO Study; BRVO: Branched Retinal Vein Occlusion.

### Introduction

VEGF-A is most potent factor responsible for promoting angiogenesis. It belongs to a gene family which includes placental growth factor (PDF), VEGF-B, VEGF-C, VEGF-D. VEGF-A exist in six major isoforms- 121, 145, 165, 183, 189, 206. VEGF-165 isoform is most important factor responsible for diabetic macular edema DME. VEGF-A is a ligand for two receptor tyrosine kinases, VEGFR-1 and VEGFR-2. It is produced by RPE cells, ganglion cells, Muller cells, pericytes, endothelial cells, glial cells, neurons and smooth muscle cells of retina. VEGF produces conformational changes in the tight junction of retinal vascular endothelium leading to increased permeability. VEGF inhibition has been achieved by PKC inhibitors, aptamers (protein kinase C

inhibitor, pegatinib) and antibodies (Ranibizumab, bevacizumab) targeted against VEGF-A [1].

### Types of Anti VEGFS

#### PKC Inhibitors

VEGF increase vascular permeability directly and indirectly by activating PKC isoforms [2]. Ruboxistaurin (RBX) [3] is a selective protein kinase C inhibitor. It inhibits the increase in leucocyte entrapment in the retinal microcirculation during early diabetes. Entrapment of leucocytes leads to vascular non perfusion and vascular leakage. It is in clinical trial phase III.

#### VEGF Aptamer

Macugen (pegaptanib) is a 28 base RNA oligonucleotide that selectively binds to heparin binding domain of VEGF 165. Approved by FDA in 2004. It functions as high affinity inhibitor of specific protein target. 0.3 mg of macugen should be administered once every 6 weeks by intravitreal injection. Its half-life is 10 days. It is supplied in prefilled syringe and formulated as 3.47mg/ml solution. Active ingredient is 0.3 mg of free acid form of oligonucleotide is equivalent to 1.6 mg of pegatinib sodium.

### Anti VEGF Antibody

**Bevacizumab (Avastin):** It is a humanized monoclonal antibody approved by FDA in 2004 for use of metastatic colorectal cancer. Its use in ophthalmology is “off label” since it is not approved by FDA for ophthalmic use. Intravitreal avastin has become a widely accepted practice because of easy dispensing and relative low cost. It is given in a dose of 1.25 mg in 0.05 ml as intravitreal injection. Half-life of avastin is 15 to 20 days.

**Ranibizumab (Iucentis):** It is a humanized monoclonal antibody fragment (fab fragment) directed against VEGF-A. It is a non-selective inhibitor of all isoforms of VEGF –A and bioactive proteolytic products. Fc fragment of antibody is missing so it cannot incite immune response against complement C<sub>3</sub> and Fc gamma receptors. It was found to be superior to Macugen for treatment of AMD. 0.3 mg of Ranibizumab is recommended every 6 weeks. Its half-life is approximately 5 days. Iucentis is sterile pale solution in a single use glass vial providing 0.05 ml of 100mg/ml.

### VEGF Trap

It is a cytokine trap solution. It is known as Eylea or Regeneron. High affinity recombinant fusion trap consist of immunoglobulin domain 2 of VEGF R1 receptor and domain 3 of VEGF R2 receptor fused to crystallisable fragment of human IgG. Each arm of VEGF trap binds to binding interface on each pole of VEGF and PlGF dimer, forming a stable inert complex thereby preventing it from binding to native receptors. VEGF Trap has longer duration of action of 25 days making it more efficacious than ranibizumab.

### Blocking VEGF Receptors

PTK 787 OR Vatalanib is an orally administered drug under trial which acts by inhibiting receptor phosphorylation. It blocks VEGF and PlGF receptors. AG013958 inhibits VEGF R2 signalling through inhibition of tyrosine kinase domain. Its route of administration is subtenon.

### Silencing VEGF Production

A more effective way of inhibiting proteins is to prevent their production. RNA interference is the silencing of gene production by activation of innate cellular defence mechanism by double stranded RNA. There are two si RNA molecules undergoing trials – C and 5, si RNA027. C and 5 is si RNA against all isoforms of VEGF and si RNA 027 is against VEGF receptor 1. si RNA can be delivered in drops form.

### Squalamine Lactate (Evizon)

Systemically administered anti-angiogenesis compound that belongs to amino sterol class and has multifaceted action. It has more generalized effect on cellular signalling cascade that is common to both VEGF and other growth factors. Because of systemic administration, both eyes are treated simultaneously with single dose of medication allowing bilateral therapy and potentially imparting a prophylactic benefit on fellow eyes with non-exudative age related degeneration. 0.25 mg/ml of solution given intravenously over a period of 10 to 40 minutes.

### Anecortave Acetate (Retaane)

Newly developed angiostatic cortisone which lacks glucocorticoid activity which is delivered as juxta scleral depot by curved blunt tipped cannula which has been designed for administration in macular region.

### Indications and Uses of Anti VEGFs

1. Choroidal neovascularisation: Most common cause of choroidal neovascularisation is exudative age related macular degeneration (AMD). MARINA trial evaluates the efficacy and safety of ranibizumab in minimally classic and occult AMD. ANCHOR compared the safety and efficacy of 0.3 mg and 0.5mg Ranibizumab in classic AMD. VISION compared intravitreal pegatinib with sham injections in ocular neovascularisation.
2. Retinal angiomatous proliferation: a variant of exudative AMD characterised by intra retinal, sub retinal and choroidal neovascularisation. Studies evaluated the improvement in vision in patients with retinal angiomatosis proliferation (RAP).
3. Choroidal neovascularisation (CNV) secondary to pathological myopia: Studies have shown that intravitreal bevacizumab is safe and efficacious in patients with choroidal neovascularisation secondary to pathological myopia.
4. Other causes of choroidal neovascularisation like angoid streaks, Best disease, Central serous retinopathy etc. have also responded to anti VEGF.
5. Retinal neovascularisation: It is a potential sequel of vascular compromise and can lead to vitreous haemorrhage or tractional retinal detachment.
6. Proliferative diabetic retinopathy: Persistent neovascularisation after laser treatment and media opacity are the cases which require anti VEGF. It can be given in combination with Pan retinal photocoagulation (PRP) to prevent secondary macular edema. Anti VEGF given in preop prior to PPV in complicated cases like

vitreous haemorrhage and Tractional retinal detachment (TRD).

7. Sickel cell retinopathy: Anti VEGF is found useful in cases of persistent neovascularisation despite PRP and in cases of vitreous haemorrhage precluding sectoral PRP.
8. Retinopathy of prematurity: Single injection results in regression of retinal neovascularisation, iris engorgement, reduction of retinal vessel engorgement.
9. Diabetic macular edema: Anti VEGFs are requiring in patients with leaking micro aneurysms lying close to fovea which cannot be treated with photocoagulation. Extensive macular edema decreasing penetration and effectiveness of laser also require anti VEGF. CME and serous retinal detachment not responding to laser need anti VEGF.
10. Central retinal vein occlusion CRVO: No proven therapy exists for macular edema from CRVO. CRVO Study (CVOS) showed that laser treatment was not effective in treating macular edema following CRVO.
11. Branched retinal vein occlusion (BRVO): use of intravitreal injection is considered after 3 month period of observation where standard laser treatment cannot be applied (media opacity) or when edema is refractory to laser.

### Side Effects and Complications

#### Systemic Side Effects

It includes fatigue, Gastro Intestinal upset, hypertension, proteinuria, stroke myocardial infarction.

#### Ocular Side Effects:

- Injection related complications: endophthalmitis, retinal detachments, iatrogenic traumatic cataract, raised intra ocular pressure,
- Drug related complications: Nodular episcleritis, intraocular inflammation and uveitis, RPE tears, subretinal bleed.

**Contraindications:** Any history of recent ocular inflammation and glaucoma. Patient with known hypersensitivity to drug.

### References

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