New frontiers in Anti VEGF Therapy

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Anti VEGF therapy is one of the most talked and most sought therapy in current ophthalmic clinical practice. It has been seen to have widespread implications along with burgeoning scope of development and research.

HISTORY

In 1983, Senger& colleagues discovered a protein secreted from a guinea pig tumor cell line which induced vascular leakage & named it vascular permeability factor (VPF)

In 1989,Napoleon Ferrara & colleagues identified a molecule in conditioned media from bovine pituitary follicular cells that prompted proliferation of endothelial cell & called it Vascular Endothelial derived Growth Factor (VEGF).

What is VEGF?

VEGF is an angiogenicpeptide derived from a single gene.Four alternatively spliced messenger RNAs code for proteins of VEGF – A 121,165,189 & 206 AA, they are efficiently secreted but differ in their affinity for heparin.

In 1992 VEGF was 1st identified in retina

Physiological roles of VEGF:

- Wound healing
- Vasodilative
- Neuroprotective
- Maintains coronary artery

Pathological roles of VEGF :

- Diabetic Retinopathy
- Retinal Venous Occlusions
- Retinopathy of Prematurity
- Age Related Macular Degeneration
- Neovascular Glaucoma
- Intraocular tumors
- Corneal neovascularization

Evolution of Anti VEGF Therapy

The first commercial use was with Macugen (Pegaptanib sodium, Eyetech/Pfizer) followed by Off-label use of Avastin (Bevacizumab, Genentech) and finally came Lucentis (Ranibizumab, Genentech), widely popular as Accentrix today.

Molecular properties of Bevacizumab and Ranibizumab

- Bevacizumab is a full-length recombinant humanized monoclonal IgG antibody (3 × larger than ranibizumab)[1,2]
- Includes both Fc and Fab regions
- Produced in mammalian expression system (glycosylated molecule)
- Ranibizumab is a recombinant humanized monoclonal antibody fragment(Fab)[3,4]
- Produced in an *Escherichia coli* expression system (and thus not glycosylated)
- Genetically engineered to increase its affinity for binding and inhibition of VEGF
- Shorter systemic half-life than full-length antibody

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	Ranibizumab	Bevacizumab
Company	Genentech/Novartis	Genentech/Roche
MOA / class	Anti-VEGF-A antibody fragment [targets all VEGF-A isoforms][1]	Anti-VEGF-A full-length antibody [targets all VEGF-A isoforms][4]
Molecular weight	48 kDa[2]	149 kDa[4]
Half-life in the rabbit eye	2.88 days[3]	4.32 days[4]
Systemic elimination half-life	~2 hours[2]	20 days[4]
Licensed indications	Wet AMD, visual impairment due to DME, visual impairment due to ME secondary to RVO (BRVO and CRVO)[1]	Metastatic colorectal cancer, non-small cell lung cancer, glioblastoma, metastatic kidney cancer[4]
Formulation/ administration	Intravitreal injection from a single-use vial[1]	For licensed indications: intravenous infusion from a single-use vial[4]

INDICATIONS

Licensed indications of Ranibizumab are:

1. Neovascular (wet) AMD
2. Visual impairment due to DME
3. Visual impairment due to macular edema secondary to RVO (BRVO and CRVO)
4. Visual impairment due to Myopic CNV

- Ranibizumab is designed and manufactured to the appropriate standards for intraocular use
- It is presented in single use vials for intravitreal injection

Licensed indications of Bevacizumab are:

- Intravenous infusion treatment for patients with metastatic colorectal cancer, non-small cell lung cancer, metastatic renal cell cancer or glioblastoma[5]
- **Bevacizumab is neither licensed nor indicated for any ocular conditions**
- Bevacizumab vials are intended for single use as an intravenous infusion[5]
- For unlicensed intraocular use in neovascular AMD, multiple doses vials[6]
- Vials contain no preservatives and have limited stability[5,7]
- Risk of contamination (particulate or microbial)[8]
- Potential for human error (incorrect dose or incorrect drug)
- **It is not licensed for compounding into smaller doses for ocular use**

Bevacizumab doesn't meet the standards for ophthalmic solutions because of the following

reasons:

- Requirements for particle counts in ophthalmic solutions are clearly defined in US Pharmacopoeia
- USP chapter 789 limits for ophthalmic products: maximum of 50 particles of ≥10 μm permitted in a volume of 1 mL[9]
- USP chapter 788 limits for intravenous medications: maximum of 3000 particles of ≥10 μm per container[10]
- Significant increases in particle density 14 days following preparation have been seen in repackaged bevacizumab from a number of compounding pharmacies ($p<0.03$ for all comparisons)[11]

SIDE EFFECTS

There may be potential adverse effects of anti VEGF action:

- Adverse effects from lack of VEGF signaling, such as:[12]
- Slowed or poor wound healing
- Difficulty growing new blood vessels to replace blocked areas
- There is a theoretical risk of arterial thromboembolic events (ATEs) following intravitreal use of any VEGF inhibitor
- The bevacizumab label states that intravenous use has been associated with serious arterial thromboembolic events (ATEs) including myocardial infarction (sometimes fatal)[13]

Why so much of interest in Anti VEGF?

- We still don't have an ideal anti VEGF
- Global market of anti VEGF is 10 billion US$ per year
- Annual Accentrix sale in India last year was Rs 96 crores.

UPCOMING AGENTS

Few upcoming anti VEGF agents are:

AFLIBERCEPT (Bayer, Regeneron)

- Eylea, instead of being an antibody to VEGF molecule, is a fusion protein consisting of portion of VEGF receptors fused with Fc portion of IgG1.
- Recommended dose is 2 mg (0.05 ml)
- Specially used for cases refractory to Avastin or Lucentis
- Supported by VIVID, VISTA and PROTOCOL T trials

ANECORTAVE ACETATE Retaane (Alcon labs)

- It inhibits the expression of urokinase plasminogen activator (uPA) and matrix metalloproteinases (MMP)
- It prevents the breakdown of basement membrane and extracellular matrix, preventing the migration of VECs
- 15 mg suspension tried as posterior juxtascleral depot
- Also found safe with PDT
- Trials mainly done for wet AMD

Anti PDGF drug FOVISTA (Ophthotech)

- In a large phase 2 study, combination of Fovista and Ranibizumab was 62% more efficacious than Ranibizumabmonotherapy.
- It targets PDGF and causes pericyte stripping from the newly formed blood vessels
- The dose is 1.5 mg

DARPin (Designed Ankyrin Repeat Proteins) Allergan

- Drug developed with Molecular Partners, showed efficacy in treating wet AMD as monotherapy in a phase 2a study.
- The priority now is to combine the DARPin with an anti-PDGF in a dual-acting combination therapy.
- The DARPin is also being tested in combination with Ranibizumab.
- Abiciparpegol 2 mg is the latest drug being worked upon.
- Phase 3 trials started in 2015

Allegro Ophthalmics' **Integrin peptide** (ALG-1001 Luminate)

- Integrin Peptide Therapy turns off the production, reduces the leakage of and inhibits the growth of aberrant blood vessels by acting against integrin alpha(v) and beta(3&5)
- This new approach has the potential as a monotherapy or used in combination with existing drugs
- The drug showed good efficacy in DME and AMD

KALA's **MPP** (Mucus-Penetrating Particle)

- Kala's product candidate KPI-121 is a novel nanoparticle formulation of loteprednoletabonate for the treatment of ocular inflammation, dry eye and meibomian gland disease.
- Kala is also advancing small molecule receptor- tyrosine kinase inhibitor (RTKi) for topical treatment of wet age-related macular degeneration (AMD)

Pill for Dry AMD

- Acucela's drug Emixustat (formerly known as ACU-4427) entered a phase 2/3 trial for the treatment of dry AMD.
- It works by inhibiting RPE65 and reducing A2E
- Results announced on 25.5.2016 for phase 3 (ENVISION)

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