Theme Article

Anti VEFG Agents In Retinal Diseases

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Abstract

Anti-vascular endothelial growth factor (Anti VEGF) agents are emerging as the most vital tool in the prevention of blindness due to ocular neovascularization in modern medicine. VEGFs are glycoproteins specific to endothelial cells, acting as key regulators of angiogenesis, vasculogenesis, and increasing vascular permeability. These are indicated in conditions such as diabetic macular edema (DME), vascular occlusions (RVO), Retinopathy of prematurity (ROP), neovascular age-related macular degeneration (nAMD), etc. The cost effect, need for frequent dosage, and side effects of increased IOP, infection, and cataract adds to the economic and disease burden. The newer research is now focused beyond anti-VEGF such as Angiopoietin and tyrosine kinase for vasculogenesis. This article reviews various anti-VEGF and angiogenic agents available in clinical practices.

Delhi J Ophthalmol 2022; 32; 93-96; Doi http://dx.doi.org/10.7869/djo.755

Keywords: *Anti Vegf , Antiangiogemic Agents*

Introduction

A diffusible glycoprotein" factor X" was identified by Michelson I.C. in 1980 which showed angiogenic properties resulting in proliferation and increased permeability of the vascular endothelium.[1] Decades later, this 40kDa molecule was recognized as VEGF. VEGF is released in response to hypoxia of the retinal vasculature. It is released by the retinal endothelial cells, Muller cells, and retinal pigment epithelium.

Abnormal angiogenesis may occur in a plethora of conditions such as diabetic retinopathy, hypertensive retinopathy, retinopathy of prematurity, Coat's disease, macular edema secondary to vascular occlusions, wet age-related macular degeneration (AMD). The development of anti-VEGFs has made a breakthrough in the treatment of retinal and choroidal pathologies.

Table 1: Receptors and Functions of various VEGF released intraocular.

VEGF	Receptors	Function
VEGF A	VEGFR1 VEGFR2	Angiogenesis and chemotaxis
A121		Endothelial cell proliferation Sequestered in the extracellular matrix due to the presence of a heparin-binding domain
A145		cell migration, angiogenesis, and increases vascular permeability Fibroblast proliferation Sequestered in the extracellular matrix due to presence of a heparin-binding domain
A165		
A189		
A206		
VEGF B	VEGFR1	Specific to myocardial tissue Helps in embryonic angiogenesis
VEGF C	VEGFR3, a weak affinity for VEGFR2	Lymphangiogenesis
VEGF D	VEGFR3, a weak affinity for VEGFR2	Lymphatic development, Specific to the pulmonary system
VEGF E (orf Viral gene) VEGF F	VEGFR 2	Angiogenesis, usually not found in humans
PIGF	VEGFR1	Inflammation and vasculogenesis

In humans, the VEGF family consists of 7 components namely, VEGF A to F and Placental growth factors (PIGF). Each member has certain functions as stated in (Table 1).[2] VEGF bind to specific Tyrosine kinase (TKR) VEGF receptors to initiate vasculogenesis and angiogenesis. These are VEGFR1 (Flt1), VEGFR2 (KDR), VEGFR3 (Flt4). The receptors consist of an ecto-domain and an endo-domain. The VEGF Fab portion binds to the ecto-domain which in turn activates the endo-domain and initiates the vasculogenic cascade via associated tyrosine kinase activity.

VEGF A has numerous isoforms which result from alternate splicing and processing of the VEGF gene. These are classified based on the number of amino acids present such as VEGF A121, A145, A165, A189, and A206. VEGF A165 is the most abundant form (Table 1).

Indications[3]

1. Diabetic macular edema
2. Retinal vascular occlusions
3. Neovascular age-related macular degeneration/ choroidal neovascular membrane
4. Retinopathy of prematurity
5. Vasculitis such as Eale's disease
6. Myopic Choroidal neovascularization
7. Ocular tumor, Neovascular glaucoma
8. Preoperative- in diabetic, vasculitic Vitreous haemorrhage, Tractional retinal detachment

Anti-VEGF Agents

The first anti-VEGF agent Pegaptinib sodium was approved by FDA in 2004 for its use in colon cancer.

The introduction of anti-VEGF in ophthalmology has set high expectation in treating all neovascular conditions. Pegaptanib was the first FDA-approved anti-VEGF agent used to treat ocular neovascularization. Currently, the commonly available anti VEGFs in ophthalmology are Pegaptanib sodium, Ranibizumab, aflibercept. Bevacizumab is used "off-label" in ophthalmic conditions. Bevacizumab and aflibercept are the two anti-VEGF available as systemic therapy also. Direct drug delivery into the vitreous helps in increased efficacy of the drug with a reduced burden of systemic adverse effects.

Anti-angiogenic effect can be brought by blocking the VEGF receptors by antibodies against the VEGF molecule, VEGF receptors and decoy proteins that compete with VEGF binding to the VEGF receptors, inhibitors specific to tyrosine kinase.

Humanized monoclonal Immunoglobulin G antibodies consist of Fc and Fab parts. The Fab portion binds to the target while the Fc portion carries out the effector function by activation or deactivation of the intrinsic cascade.[4]

Pegaptanib Sodium (MacugenTM): approved by FDA in December 2004 for use in neovascular AMD. It is a highly selective oligonucleotide ligand (RNA aptamer) having an affinity to the VEGF A165 isoform.[5] It is the first Anti-VEGF drug approved for ocular use.

Efficacy: VEGF inhibition Study in Ocular Neovascularization (VISION)

Bevacizumab (Avastin™ by Genentech, San Francisco)

Full-length humanized IgG1 monoclonal antibody of 145kDa (Figure1) molecular weight blocks all the isoforms of anti-VEGF. It is cost-effective and thus used off-label in nAMD and DR.

Side effects: Uncontrolled hypertension, proteinuria, thromboembolism, gastrointestinal bleeding, and perforation. It has been discontinued due to these side effects.[6]

Ranibizumab (Lucentis™ By Genentech/Roche, Usa)

It is made up of Fab moiety of monoclonal human immunoglobulin IgG1 produced from E. coli by insertion of complementary determining sequences (CDR) of murine anti-VEGF A molecule with amino acid sequence alteration for its stability and immunogenicity. It has more affinity to the receptors as compared to bevacizumab and more diffusion into the retina and choroid. Ranibizumab avoids binding of VEGF A to VEGR receptors 1 and 2 present on the endothelial cell surface and thus inhibited vasculogenesis and inflammation.[7]

AFLIBERCEPT/ VEGF Trap (Eyelea/Zaltraptm Regeneron, New York)

Fully humanized fusion protein Ig of 115 kDa approved for AMD in 2011 and retinal vein occlusions in 2012. It blocks VEGF A, VEGF B, Placental growth factor (PIGF) 1 and 2. [8]
It binds to VEGF from both sides of the VEGF molecule, unlike bevacizumab and Ranibizumab which binds from one single side. However, single molecule bevacizumab can bind to multiple VEGF molecules (Figure1). Aflibercept was considered superior to the other two drugs considering improvement of visual acuity in Protocol T of DRCR.network study for DME.[9]

Table 2: molecular structure and pharmacodynamics of commercially available Anti VEGF agents

S.NO.	Anti- VEGF	Commercially Available as	FDA Approval	Structure	Molecular Weight	T1/2	Dose	Mechanism of action	Pharmacokinetics
1	PEGAPTANIB SODIUM	MACUGEN Single prefilled syringes	December 2004	Aptamer	50kDa	10 Days	0.3mg, 6weekly injections	Angiogenesis and increased vascular permeability	Slow metabolism Excretion: Kidney
2	BEVACIZUMAB	AVASTIN		Humanized monoclonal antibody	148kDa	20 Days	1.25mg IN 0.05ml		
3	RANIBIZUMAB	LUCENTIS	June 2006	Monoclonal antibody fragment	48kDa	9 Days	0.5mg in 0.05ml		Clearance faster X100 times
4	AFLIBERCEPT	EYELEA	2011	Recombinant fusion protein	115kDa		2mg in 0.5ml		

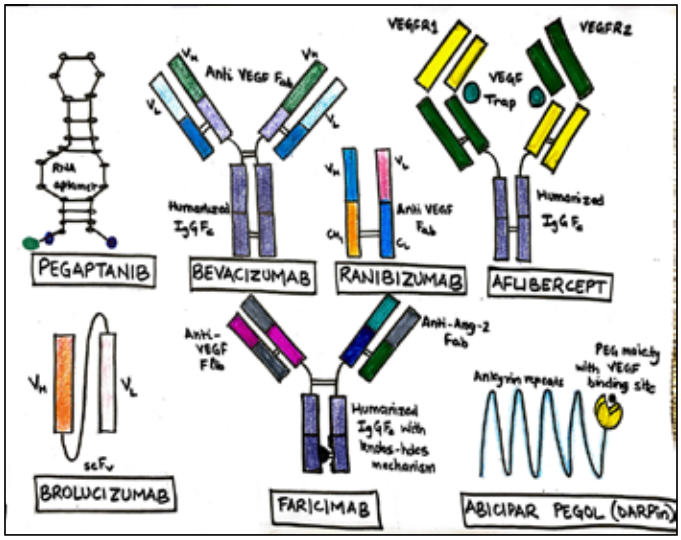

Figure 1: *Diagram showing structures of the various anti-VEGF molecules*

Summary Of Pharmacology of AntiVEGF Biosimilars

These are biotherapeutic products that are similar to the pre-existing generic molecule with comparable efficacy, pharmacodynamics, immunogenicity, and safety profiles. The biosimilars are however not the same as the originator generic drug. These are larger molecules with a different structure and a chemical formula not predefined by the original fixed formulated molecule. Stability and its efficacy is difficult to attain due to a different molecular structure as compared to the generic drug.[10]
At present, Mvasi (Amgen) and Zirabev (Pfizer) are commercially available biosimilars for **Bevacizumab,** and ONS-5010 (Outlook Therapeutics) is under research.

Razumab (Intas Pharmaceuticals Ltd., Ahmedabad, India) was approved in India in 2015 after a clinically registered trial on 104 patients of wet AMD. RE-ENACT (REal life assessmENt of safety And effectiveness of Razumab) study showed similar results in DME, nAMD, RVO, and myopic CNVM. Another retrospective analysis to evaluate the "Clinical Efficacy and Safety of Razumab" (CESAR) showed equivalent results in vision improvement as shown in RE-ENACT along with no ocular side effects and immunogenicity.[11]

Other biosimilars under study are: Ranizurel (Reliance life science, India), FYB201, SB11 Byooviz and CKD-701(South Korea), LUBT010 (Lupin India).[12]

Newer Anti-VEGF

CONBERCEPT (Lumitin, Sichuan)

A recombinant human fusion protein of extracellular (Ig) domains of VEGFR1, the third and fourth domain of VEGFR2, and a portion of Fc IgG1. Conbercept 0.5 mg varies from aflibercept with the addition of VEGFR2 domain 4, which allows for tighter binding to VEGFA, VEGFB, and PGF.

In a phase III prospective PHOENIX trial conducted in China, the Conbercept group showed a significant improvement in visual acuity compared to sham groups in wet AMD.[13]
The phase III trials PANDA-1 and PANDA-2 were quadruple-blinded multicentric randomized trials evaluating the BCVA at the end of 36weeks, with 0.5 mg and 1 mg Conbercept, and 2 mg Aflibercept.[14]

Brolucizumab

It is a humanized monoclonal antibody fragment that acts against VEGF A. It has a molecular weight of 26kDa (Figure1). It is highly stable and soluble thus allowing it to be available at 120mg/ml concentration. The dose of 6mg/0.5ml is considered 10 times more effective than the routing dose of aflibercept and 20 times more effective than Bevacizumab and Ranibizumab. Being the smallest of all anti-VEGF it has a better penetrance, faster clearance, and lower systemic side effects.

Efficacy and safety of Broculizumab were found to be non-inferior to aflibercept in nAMD was analysed by a 2year multicentric randomized trial HAWK and HARRIER. Another similar study OSPREY is in its Phase II trial.[15] Occlusive vasculitis and vitreous inflammation are the major side effects noted.

Abicipar Pegol

Abicipar (Allergan) is a designed ankyrin repeat protein, directed to all VEGF A isoforms similar to Ranibizumab (Figure 1). However, it differs from Ranibizumab in its higher affinity to bind to the receptors and also in t1/2 being longer thus, less frequent dosing is required.

Various study groups have found longer effects with 1mg and 2mg Abicipar in nAMD (BAMBOO and CYPRESS study). REACH study gave comparative results between Ranibizumab and different doses of Abicipar. Phase III SEQUOIA ad CEDAR study has shown non-inferiority to Ranibizumab in treating nAMD with a lesser frequency of intravitreal injection advised.[16] The drug is under regulatory review by FDA at present.

Faricimab

A bispecific intravitreal anti-VEGF binds and neutralizes Ang 2 and VEGF A. Angiopoietin 1 and 2, angiopoietin-like proteins, and tyrosine kinase (Ang 2-Tie) help in mediating vascular growth and inflammation. Faricimab targets this alternative biological pathway of Ang 2-Tie complex thus, inhibiting this pathway provides a better long-term prognosis.[17] (Figire 1)
Patients with DME (BOULEVARD study)[18] and nAMD (AVENUE and STAIRWAY study)[19] 6mg of Faricimab showed significant visual improvement, was considered equally safe and efficacious compared to Ranibizumab. It is indicated in cases of DME and nAMD. Ongoing trials in eyes with DME (YOSEMITE and RHINE) and nAMD (TENAYA and LUCERNE) are aimed at assessing the safety durability and effect of the drug.[20]

Port Delivery System

PDS is surgically fitted drug delivery system fitted in the sclera or at the pars plana level. In Phase III trial of Ranibizumab (ARCHWAY study) permanent implant with refill of 100mg/ml every 24 weeks at fixed dose interval was given in eyes with nAMD. These reservoir implants helped in delaying the need for repeated injection with the advantage of continued drug delivery into the eye by passive diffusion along the concentration gradient into the vitreous cavity. LADDER study employed an additional step of ablation of the choroid at the pars plana dissection site which helped decrease the risk of haemorrhage.[15]

Other Drugs

1. OPT-302: 2mg drug injected intravitreal, targets VEGF C and D.
2. KSI-301: Antibody biopolymer conjugate (abc) indicated in retinal vascular disease and nAMD.
3. X-82: Tyrogenex: Oral route of delivery, binds and inhibits VEGF A and PDGF. Ongoing APEX trial is testing 50mg, 100mg and 200mg of the drug.
4. ICON-1 is a recombinant factor VIIIa modified protein with Fc portion of a human Ig G1.

Adverse Effects Of Intravitreal Injection

1. Sub conjunctival hemorrhage,
2. ocular pain,
3. short-term and long-term increase in ocular pressure
4. Floaters
5. Endophthalmitis
6. Vitreous hemorrhage
7. Retinal detachment
8. Systemic side effects are rare such as thromboembolic events.[21]

Contraindications

1. Ocular/periocular infection
2. High intraocular pressure
3. Hypersensitivity
4. Tachyphylaxis [21]

References

1. Tah V, Orlans HO, Hyer J, et al. Anti-VEGF Therapy and the Retina: An Update. J Ophthalmol. 2015;2015:627674. doi:10.1155/2015/627674
2. S. L. (2008). Therapeutic Anti-VEGF Antibodies. In H. B. Lowman (Ed.), Handbook of Experimental Pharmacology (Vol. 181, pp. 131-150). Springer Berlin Heidelberg.
3. Yorston D. Anti-VEGF drugs in the prevention of blindness. Community Eye Health. 2014;27(87):44-46.
4. Holash J, Davis S, Papadopoulos N, et al. VEGF-Trap: a VEGF blocker with potent antitumor effects. Proc Natl Acad Sci U S A. 2002;99(17):11393-11398. doi:10.1073/pnas.172398299
5. Ng, E., Shima, D., Calias, P. et al. Pegaptanib, a targeted anti-VEGF aptamer for ocular vascular disease. Nat Rev Drug Discov 5, 123–132 (2006). https://d oi.org/10.1038/nrd1955
6. Short-term safety and efficacy of intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Rich RM, Rosenfeld PJ, Puliafito CA, Dubovy SR, Davis JL, Flynn HW Jr, Gonzalez S, Feuer WJ, Lin RC, Lalwani GA, Nguyen JK, Kumar G. Retina. 2006 May-Jun; 26(5):495-511.
7. Krispel C, Rodrigues M, Xin X, Sodhi A. Ranibizumab in diabetic macular edema. World J Diabetes. 2013;4(6):310-318. doi:10.4239/wjd.v4.i6.310
8. Park YG, Rhu HW, Kang S, Roh YJ. New Approach of Anti-VEGF Agents for Age-Related Macular Degeneration. J Ophthalmol. 2012;2012:637316. doi:10.1155/2012/637316
9. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med. 2015;372(13):1193-203.
10. Sharma A, Reddy P, Kuppermann BD, Bandello F, Lowenstein A. Biosimilars in ophthalmology: "Is there a big change on the horizon?". Clin Ophthalmol. 2018;12:2137-2143. Published 2018 Oct 24. doi:10.2147/OPTH.S180393
11. Sharma S, Khan M, Chaturvedi A; RE-ENACT 2 Study Investigators Group. A Multicenter, Retrospective Study (RE-ENACT 2) on the Use of Razumab™ (World's First Biosimilar Ranibizumab) in Wet Age-Related Macular Degeneration. Ophthalmol Ther. 2020;9(1):103-114. doi:10.1007/s40123-019-00228-7
12. Kapur M, Nirula S, Naik MP. Future of anti-VEGF: biosimilars and biobetters. Int J Retina Vitreous. 2022;8(1):2. Published 2022 Jan 4. doi:10.1186/s40942-021-00343-3
13. Liu K, Song Y, Xu G, Ye J, Wu Z, Liu X, et al. Conbercept for treatment of neovascular age-related macular degeneration: results of the randomized phase 3 PHOENIX study. Am J Ophthalmol 2019;197:156-67.
14. Efficacy and safety trial of conbercept intravitreal injection for neovascular age-related macular degeneration (PANDA-1) - full text view -ClinicalTrials.gov. Clinicaltrialsgov 2020; https://clinicaltrials.gov/ct2/show/NCT03577899
15. Chandrasekaran PR. Newer anti-vascular endothelial growth factor agents. TNOA J Ophthalmic Sci Res 2020;58:268-73.
16. Samanta A, Aziz AA, Jhingan M, Singh SR, Khanani AM, Chhablani J. Emerging Therapies in Neovascular Age-Related Macular Degeneration in 2020. Asia Pac J Ophthalmol (Phila). 2020;9(3):250-259.
17. Khan M, Aziz AA, Shafi NA, Abbas T, Khanani AM. Targeting Angiopoietin in Retinal Vascular Diseases: A Literature Review and Summary of Clinical Trials Involving Faricimab. Cells. 2020;9(8):1869. Published 2020 Aug 10. doi:10.3390/cells9081869
18. Simultaneous Inhibition of Angiopoietin-2 and Vascular Endothelial Growth Factor-A with Faricimab in Diabetic Macular Edema: BOULEVARD Phase 2 Randomized Trial. Sahni J, Patel SS, Dugel PU, Khanani AM, Jhaveri CD, Wykoff CC, Hershberger VS, Pauly-Evers M, Sadikhov S, Szczesny P, Schwab D, Nogoceke E, Osborne A, Weikert R, Fauser S Ophthalmology. 2019 Aug; 126(8):1155-117.
19. Efficacy of Every Four Monthly and Quarterly Dosing of Faricimab vs Ranibizumab in Neovascular Age-Related Macular Degeneration: The STAIRWAY Phase 2 Randomized Clinical Trial.Khanani AM, Patel SS, Ferrone PJ, Osborne A, Sahni J, Grzeschik S, Basu K, Ehrlich JS, Haskova Z, Dugel PU JAMA Ophthalmol. 2020 Sep 1; 138(9):964-972.
20. ClinicalTrials.gov A Study to Evaluate the Efficacy and Safety of Faricimab in Participants With Neovascular Age-Related Macular Degeneration (TENAYA). ClincalTrials.gov. [(accessed on 5 August 2020)]; Online Resources. Available online: https://clinicaltrials.gov/ct2/show/NCT03823287.
21. Vaidyanathan U, Moshirfar M. Ranibizumab. [Updated 2021 Jul 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan.

Cite This Article as: Khushboo Chawla, AntiVEFG Agents In Retinal Diseases. Delhi J Ophthalmol 2022 32 (3) 93-96.

Acknowledgments: Nil

Conflict of interest: None declared

Source of Funding: None

Date of Submission 02 Mar 2022
Date of Acceptance: 21 Mar 2022

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