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Guest Editorial

An overview on Anti-Vegf and in search for an ideal anti VEGF agent

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Looking back, if we see what we could do for a patient with AMD before the 1980s, the story was quite dismal because there is actually no treatment and most of the patients with wet AMD would lose their central vision, the Ophthalmologist would be helpless. We started applying ablative thermal laser in the 80's and this went on till about 2000 when photodynamic therapy was introduced. Laser and photodynamic therapy could only halt the disease progression but there was no significant effect on visual improvement.

The management scenario for nAMD and subsequently for DME and other vascular retinopathies started changing from 2005 onwards with the introduction of Anti-VEGF agents. The development of these pharmacological treatments for retinal diseases, along with the introduction of OCT, has completely revolutionized the field of ophthalmology, especially treatment of all kinds of vascular retinopathies, improving vision outcomes and quality of life for millions of people.

The Anti-VEGF story starts in the early 1970s with the proposal by Judah Folkman that tumor growth and progression is dependent on the ability of the tumor to recruit and support formation of a vasculature.[1] In 1994, The American Journal of Pathology published an article which stated that hypoxic retina produces vascular endothelial growth factor (VEGF), suggesting a role for VEGF in ocular neovascularization.[2]

In the early 2000's, Anti-VEGF compounds began to be used therapeutically. The first was Intra-Venous Bevacizumab, FDA-approved for the treatment of colon cancer in Feb. 2004. BUT not approved for eye treatment. Soon after, an Anti-VEGF was approved for eye: Pegaptanib, in 2004 for wet AMD. After a few years this drug was discontinued because of its poor performance.

Ranibizumab was first approved on 2006 for nAMD, 2012 for DME, 2016 for CNV and it is also indicated for RVO's. Ranibizumab is a monoclonal antibody fragment targeted against VEGF-A. It is the first approved Anti-VEGF agent for the treatment of retinopathy of prematurity (ROP). In 2011, Aflibercept was approved for wet AMD based on the results of the VIEW trials[3] that showed aflibercept dosed every two months was not inferior to ranibizumab dosed monthly. Ranibizumab and aflibercept were later approved for the treatment of diabetic macular edema (DME) and macular edema from retinal vein occlusions (RVO).

If we try to analyze the pathogenesis of nAMD, firstly we have to look at the normal retina - in physiologic conditions, a flow of oxygen and nutrients raises from the choroid to the outer retina. The RPE produces physiologic levels of VEGF to sustain the proximity of choroidal vessels and maintenance of a normoxic status. In early AMD, the disruption of cellular mechanisms damages RPE cells leading to the formation of sub-RPE drusen and thickening of Bruch's membrane. This results in relative hypoxia in the outer retina. The hypoxic state causes the RPE

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cells to upregulate production of VEGF & other mediators leading to choroidal neovascularization and ultimately a dystrophic RPE layer (disciform scar). Vigorous research into angiogenesis have led to the identification of various molecules that serve as proangiogenic factors where VEGF is the most important. But there are other factors as well - Basic fibroblast growth factor, Placental-like growth factor (PLGF), Angiopoietin 2 (Ang 2), Transforming growth factor-b, Platelet-derived growth factor (PDGF), Interleukin-8, nitric oxide synthetase and pleiotrophin among others.

If we look at Diabetic Macular Edema (DME) – Hyperglycemia causes biochemical and molecular abnormalities leading to release of reactive oxygen species, inflammation and hypoxia and these leads to upregulation of VEGF, Ang 2, TNF-a, Interleukin-8, ICAM-1 and a host of other Kallikrinin-Kinins. These factors cause endothelial cell junction breakdown, loss of pericytes, thickening of basement membrane and leucostasis causing alteration of blood retinal barrier and increased vascular permeability leading to DME. Later with increasing hypoxia and further upregulation of VEGF and other factors, retinal angiogenesis progresses to Proliferative Diabetic Retinopathy.

Now the question is – "Is VEGF the only factor". Of course VEGF is a key factor but we have to recognize the others as well.

Comparing the major Anti-VEGF agents available we can see that-

Ranibizumab : is a recombinant humanized monoclonal antibody and VEGF-A antagonist**.** Ranibizumab binds to VEGF-A with high affinity as well as its biologically active forms, such as $VEGF_{165}$, $VEGF_{121}$, and $VEGF_{110}$. Its molecular weight is ≈ 48 kDa.

Dose[3]**:** 0.5 mg (0.05 mL) and is administered once a month.

Aflibercept: is a recombinant fusion protein that acts as a decoy receptor for the ligands, VEGF-A, VEGF-B and placental growth factor. Its molecular weight is 97-115 kDa.

Dose[3]: nAMD 2 mg (0.05 mL) once a month for the first 3 injections, followed by every 2 months.

DME 2 mg (0.05 mL) once a month for the first 5 injections, followed by every 2 months.

Brolucizumab: a monoclonal antibody which is a vascular endothelial growth factor (VEGF) inhibitor which targets the major VEGF-A isoforms: $VEGF_{110}$, $VEGF_{121}$, and $VEGF_{165}$. Its molecular weight is 26 kDa.

Dose[3]: nAMD 6 mg (0.05 mL) once a month x3 doses, THEN 6 mg every 2 months.

DME 6 mg (0.05 mL) q6Weeks for first 5 doses, THEN 6 mg q8-12 weeks.

Bivacizumab: continues to be used off label. It is a humanized monoclonal antibody and VEGF-A antagonist. Its molecular weight is ≈ 149 kDa.

Dose[3]: 1.25 mg (0.05 mL) and is administered once a month.

Faricimab: is a bispecific antibody (bsAb) based on human IgG_1 comprising two different heavy and two different light chains capable of simultaneously binding to both VEGF-A and Ang-2. Its molecular weight ≈150 kDa.

Dose[3]- For nAMD

6 Mg (0 05 mL by intravitreal injection q4Weeks for first 4 doses.

Followed by one of the following regimens after OCT & Visual Acuity exam 8-12wks later

1. 6 mg by intravitreal injection at Weeks 28 and 44, OR
2. 6 mg by intravitreal injection at Weeks 24, 36, and 48, OR
3. 6 mg by intravitreal injection at Weeks 20, 28, 36, and 44

For DME – one of the following regimen

1. Regimen 1
   (a) 6 mg (0.05 mL) by intravitreal injection q4 weeks for at least 4 doses
   (b) If after at least 4 doses, edema resolves based on central subfield thickness (CST) of macula as measured by OCT, then dosing may be modified by extending the interval up to 4-week increments or reducing up to 8-week increments based on CST and visual acuity evaluations through week 52,
2. Regimen 2
   (a) 6 mg (0.05 mL) by intravitreal injection q4 weeks for 6 doses; followed by 6 mg by intravitreal injection q8Weeks over the next 28 weeks.

It transpires that all of the available Anti-VEGF agents binds to VEGF receptors and some to other receptors as well. The drug availability per administration is different as well as the dosing schedule. Brolucizumab and Faricimab are the last Anti-VEGF agents to be introduced. The different clinical trials and studies show that among all licensed anti-VEGF treatments, Brolucizumab showed superior reduction in retinal thickness and comparable BCVA gains and discontinuation rates, despite having the lowest injection frequency.[4,5]

The last Anti-VEGF to be available is Faricimab which is the first bispecific antibody designed for the eye. It targets and inhibits two disease pathways linked to a number of vision-threatening retinal conditions by neutralising angiopoietin-2 (Ang-2) and vascular endothelial growth factor-A (VEGF-A). In the global phase III studies, TENAYA and LUCERNE,Faricimab meets primary endpoint, and shows potential to extend time between treatments up to 16 weeks for people with neovascular age-related macular degeneration.[6]

Newer molecules continue to be developed with better efficacy and extended dosing schedules, but we are still looking for an ideal Anti-VEGF molecule. We must consider the top clinical reasons for switching Anti VEGF therapies, which are insufficient fluid resolution, to extend intervals between doses, no improvement or worsening of BCVA. On the other hand, the unmet needs from the Physicians' perspective was also studied and the major unmet needs are as follows - improved efficiency, reduced treatment burden, improved safety, sustained delivery and new treatment mechanism of action.

The luminous study[7] showed in Real-world evidence that over 70% of patients with nAMD are undertreated in the 1^{st} year of therapy.

Taking into consideration of all the factors we can hope that one day we will have an ideal Anti-VEGF. So, What can be the characteristics if this dream Anti–VEGF ?

1. Should be an eye drop
2. Less frequency of administration
3. Affordable
4. Easy availability - Patient can easily access it from anywhere
5. Can work with multiple receptors
6. Small molecule
7. Better vascular penetration
8. Minimal side effect

In conclusion, we can say that, Anti-VEGF injections has provided a medical option to patients with certain posterior segment issues that simply didn't exist before. Anti-VEGF caused a revolution and changed the history or retinal disease management. In many cases where legal blindness was obvious, now we can control it and treat it. We believe there is still long way to go to get to our dream molecule, and we all need to work together and look ahead for the day.

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