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Review Article

Optimising multi pronged drug intercepts in AMD

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ABSTRACT

Age-related macular degeneration (AMD) is the most common cause of blindness in the elderly population worldwide. The clinical spectrum of AMD comprises of drusen, hyperplasia of the retinal pigment epithelium (RPE), atrophy and choroidal neovascularization (CNV). These changes affect the macula of the retina and subsequently may affect central or reading visual acuity. The pharmacological therapies include photodynamic therapy (PDT), steroids, vascular endothelial growth factor (VEGF) inhibitors, extracellular matrix(ECM) modifiers, gene therapy and nutrition supplements.

1. Introduction

Age-related macular degeneration(AMD) is a progressive disease which can lead to diminished visual acuity and loss of central vision. In advanced disease people retain their peripheral vision but are legally blind due to a loss of central vision. Advanced stages of AMD, including choroidal neovascularization (CNV), are responsible for the majority of vision loss associated with AMD. The degenerative changes associated with both forms (dry and wet AMD) occur in the central part of retina, the macula, but the exact aetiology is still not fully understood. The pathogenesis of AMD includes lipofuscine genesis, drusogenesis, and local inflammatory state, as well as neoangiogenesis. Age-related macular degeneration (AMD), a progressive condition that is untreatable in up to 90% of patients.[1,2] The disease almost always begins as a non-neovascular form of AMD and it may progress to the neovascular form in one or both eyes. The World Health Organization (WHO) estimates that wet AMD affects 3 million people globally, accounting for 8.7 percent of all blindness and 50 percent of blindness in industrialized countries.[3] Data on AMD in India show prevalence ranging from 1.8% to 4.7%.[4] The pathophysiology of AMD includes diffuse thickening of the inner aspect of Bruch's membrane associated with soft drusen and may be accompanied by abnormalities of the retinal pigment epithelium (RPE) with focal hyperpigmentation.[5] Early AMD is often asymptomatic. Some patients notice mild central distortion, particularly when reading, and reduced reading ability with low light. Late AMD affects central vision and can progress rapidly (weeks or months) in the neovascular form, and more slowly (years or decades) in the atrophic form. There are two types of AMD: dry (atrophic) and wet (neovascular or exudative). Most AMD starts as the dry type and in 10-20% of individuals, it progresses to the wet type. Age-related macular degeneration is always bilateral (i.e., occurs in both eyes), but does not necessarily progress at the same pace in both eyes. It is therefore possible to experience the wet type in one eye and the dry type in the other Symptom of early wet AMD is that straight lines appear wavy. Blind spots or blurriness may develop near central

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field of vision. Other symptoms include difficulty adjusting to low light and a decrease in the intensity of colors.[6] There is a strong genetic component to AMD and over the past decade more than 50 gene variants have been found to be associated with increased risk for AMD. Most recently, reported a novel major AMD locus on chromosome 15q21 Three other genes, Fibulin 5,APOE and Complement Factor H have been reported to be associated with AMD phenotypes.[7] A total of 13 studies found a statistically significant association between smoking and AMD with increased risk of AMD of two- to three-fold in current-smokers compared with never-smokers.[8] People with a family history of AMD are at a higher risk of developing AMD. Obesity and high-fat diets containing cholesterol and saturated fats increase the risk of AMD while taking antioxidants in the early stages of the disease may play a role in curbing its progression.[9] The prevalence of AMD increases with age [Figure 1]

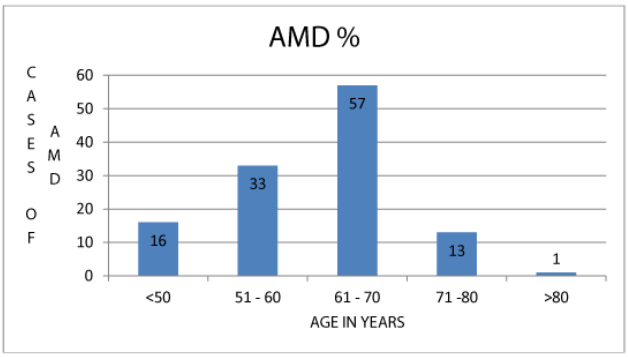

Fig. 1:

2. Therapeutic Interventions for AMD

At present there is no treatment for dry AMD. It may be possible to see better with the help of special magnifiers and good lighting. The process of angiogenesis in wet AMD is induced by generation of vascular endothelial growth factor (VEGF) from the RPE cells which binds to tyrosine kinase receptors (VEGFR) on the cell surface and the signalling cascade leading to angiogenesis is triggered. Platelet-derived growth factor (PDGF) is one of the numerous growth factors that regulate cell growth and division and play role in angiogenesis.

2.1. Prevention and Delay of AMD Progression

Clinical trials have shown high-dose zinc and anti-oxidant vitamin supplements can slow theprogression from early-stage to late-stage AMD by about 20%. High-dose statin therapy isbeing investigated to delay progression, but at this point evidence remains unconclusive.

2.2. Treatment of Atrophic AMD

Though there are no effective therapy for atrophic AMD, several agents are being investigated in clinical trials, especially drugs targeting the complement pathway related toinflammation. Use of stem-cell-based therapies is being explored for potentially replacingdead or dysfunctional retinal pigment epithelium with healthy retinal pigment epithelium.

2.3. Treatment of Neovascular AMD

Lifestyle changes demonstrated to be beneficial in reducing occurrence and progression of AMD include cessation of smoking and antioxidant vitamin and mineral supplementation. A modest benefit of antioxidant vitamin and mineral supplementation in people with moderate to severe signs of AMD was the conclusion of the Cochrane review. Effective treatment for neovascular AMD is based on inhibition of the angiogenic protein vascular endothelial growth factor (VEGF), which is produced in the retina and induced by hypoxia and other conditions. VEGF increases retinal vascular permeability and promotes formation of new blood vessels - neovascularization.[10]

VEGF regulates the growth of abnormal new blood vessels in the eye—known as neovascularization—that can lead to wet AMD.

AMD cannot be cured, but its progression may be retarded with the use of intravitreal) anti-VEGF injections. These injections may preserve, and even recover, vision. Retinal disease management, might see a big change in the coming few years as more and more biosimilars are approved for the clinical use in both developing and developed world, which would be more cost effective Innovator companies have realized that entry of biosimilars could significantly impact their sales and margins; hence, they are gearing up for the competition with strategies such as sustained drug delivery device for ranibizumab which can be a game changer for them.[11,12]

3. Role of VEGF in Retinal Disease

VEGF is a member of the platelet-derived growth factor (PDGF) family. The VEGF gene family consists of VEGF-A, VEGF-B, VEGF-C, VEGF-D and placental growth factor (PlGF), located on chromosome 6p12. The binding of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel growth and therefore plays a key role in angiogenesis. There are nine VEGF-A isoforms: $VEGF_{121}$, $VEGF_{145}$, $VEGF_{148}$, $VEGF_{162}$, $VEGF_{165}$, $VEGF_{165b}$, $VEGF_{183}$, $VEGF_{189}$ and $VEGF_{206}$. The most abundant isoform found in the eye is $VEGF_{165}$. VEGF-A levels have been found to be elevated in the vitreous of patients with neovascular (wet) age-related macular degeneration (AMD),]diabetic macular edema, and retinal vein occlusion. Choroidal

Table 1: Summary of currently available intravitreal anti-VEGF therapies.

Agent	Manufacturer	Mechanism of action	Clinical Development Status
Pegaptanib (Macugen)	OSV/Eyetech; Pfizer	Anti-VEGF-A aptamer targeting VEGF 165	FDA approval in 2004
Bevacizumab (Avastin)	Genetech/Roche	Humanized anti-VEGF-A antibody binding all isoforms and biologically active degradation products	Off-lable use; ongoing Phase III CATT trial
Ranibizumab (Lucentis)	Genenetech/Roche	Humanized anti-VEGF-A antibody-binding fragment targeting all isoforms and biologically active degradation products	FDA approval in 2006
Afibercept VEGF Trap-Eye (Eylea)	Regenron Pharmaceuticals Sanofi-Aventis	Chimeric protein binding all isomers of the VEGF-A family, VEGF-B and PIGF	FDA approval in 2011

AMD: Age-related macular degeneration;
FDA: Food and drug administration;
PIGF: Placental growth factor

neovascularization (CNV) in AMD may be instigated by several events, such as accumulation of lipid metabolic byproducts, oxidative stress, reduction in choriocapillaris blood flow, and alterations in Bruch's membrane.

3.1. Anti VEGF Drugs:

3.1.1. Bevacizumab

Lower price, bevacizumab, a VEGF inhibitor closely related to ranibizumab and marketed for the treatment of various malignancies, is sometimes used off label for intravitreal injection in AMD. In six randomised trials including a total of about 3200 patients, funded independently of the pharmaceutical industry, bevacizumab (1.25 mg per dose) was about as effective as ranibizumab (0.5 mg per injection): visual acuity stabilised or improved in 90% to 95% of patients after one to two years of treatment. These trials confirmed the known adverse effect profile of bevacizumab, which is similar to that of ranibizumab and includes serious ocular as well as extraocular adverse effects, in particular cardiac disorders. . Efficacy and safety of triple therapy consisting single-session photodynamic therapy (PDT), intravitreal bevacizumab (IVB) and intravitreal triamcinolone (IVTA) for treatment of neovascular age-related macular degeneration (AMD). Short-term results of single session triple therapy suggested that it might be a useful treatment option for neovascular AMD based on its low retreatment rates, sustainable CNV (Choroidal neovascularization) eradication result and visual gain achievement.[13] In a retrospective study of 1173 patients receiving intravitreal bevacizumab injections, the reported systemic events included acute blood pressure elevations (0.59%), cerebrovascular accidents (0.5%), myocardial infarction (0.4%), iliac artery aneurysms (0.17%), and death (0.42%).[14]

3.1.2. Ranibizumab

In humans, ranibizumab was well tolerated in single intravitreal doses to 500μg in a study involving 27 subjects with doses ranging from 150–1000μg. The Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab (formerly, RhuFab) in the Treatment of Neovascular AMD (MARINA) was a phase III randomized, prospective, double-blind, placebo-controlled comparison of ranibizumab against sham controls. Investigators enrolled 716 patients to receive 24 monthly intravitreal injections (0.3 mg or 0.5 mg) or sham injections. At 12-month follow-up, 95% of those treated with monthly ranibizumab injections had improved or stable vision versus 62% of control subjects receiving sham treatment (P< 0.001). The ANCHOR study compared the efficacy and safety of ranibizumab versus PDT in patients with predominantly classic, subfoveal choroidal neovascularization (CNV) secondary to AMD. At 12 months, the visual acuity (VA) benefit of ranibizumab over PDT was reflected in corresponding changes, on average, in several anatomic features of the lesions. At month 24, 65.7% of patients treated with PDT, 90.0% of those treated with 0.3 mg ranibizumab, and 89.9% of those treated with 0.5 mg ranibizumab lost fewer than 15 letters compared with baseline. These results were very similar 1 Year.[15]

3.1.3. Aflibercept

The VIEW Phase III studies, the largest controlled trials of anti-VEGF agents in AMD ever performed, demonstrated that 8-weekly 2 mg aflibercept dosing after three initial monthly doses (2q8) provided gains in VA that were equivalent to those achieved with monthly ranibizumab over 1 year. Despite fewer injections being required, aflibercept was as effective as ranibizumab in increasing VA and reducing retinal thickness and CNV size over 2 years. Mean VA improvement from baseline to month 24 was 6.0 letters, increasing from a mean VA of 61.4 letters (~20/60) at

baseline to 67.4 letters (~20/45) at the 2-year visit, in a study of treat-and-extend aflibercept therapy in 136 eyes from 123 patients with nAMD completing 24 months of follow-up in routine clinical practice.[16].

Aflibercept was able to completely inhibit VEGF detection for 6 h at a minimal concentration of 0.031 μg/ml, in contrast to bevacizumab (3.9 μg/ml) and ranibizumab (0.244 μg/ml). Inhibition of VEGF after a single aflibercept application of 125 μg/ml could be found over the course of 7 days, with some VEGF detectable at the 7th day. In contrast, VEGF was detectable after 72 h of ranibizumab treatment and some VEGF could already be found 12 h after bevacizumab treatment. Aflibercept displays a prolonged VEGF inhibition, confirming its effectiveness but also raising concerns about possible side effects of long-term usage.[17]

3.1.4. Brolucizumab-dbll

The HAWK/HARRIER Phase 3 trials that led to the medication's approval showed that both 3mg and 6mg regimens of brolucizumab were noninferior to aflibercept in best-corrected visual acuity change from baseline at 48 weeks. The trials also revealed a 4% rate of intraocular inflammation and a 1% rate of retinal artery occlusion. At the 16-week analysis, investigators found rates of disease activity and need for 8-week dosing was significantly lower among brolucizumab groups in both HAWK (brolucizumab 3mg=28.1%; brolucizumab 6mg=24.0% vs aflibercept=34.5%; P <.03 for both) and HARRIER (brolucizumab 6mg=22.7% vs aflibercept=32.2%; P=.002) versus aflibercept.[18,19]

3.2. Mode of action of VEGF (Inhibitors)

VEGF inhibitors prevent the binding and activation of VEGF receptors leading to a decrease in the neovascularization and vascular permeability associated with neovascular AMD and macular edema following macular edema following retinal vein occlusion (RVO) diabetic retinopathy (DR) and diabetic macular edema (DME).

Ranibizumab (molecular weight = 48 kD) is an affinity-matured, humanized immunoglobulin G1 monoclonal antibody fragment that binds to the receptor-binding site of active VEGF-A. Thus, ranibizumab inhibits the interaction of VEGF-A with its receptors on endothelial cells, preventing endothelial proliferation, vascular permeability, and neovascularization. VEGF-A plays a significant role in vascular leak and angiogenesis in the development of NVAMD. Ranibizumab is an antigen-binding fragment (Fab) derived from bevacizumab and has a higher affinity to VEGF-A. Additionally, ranibizumab has one binding site for VEGF, allowing two molecules of ranibizumab to bind to one VEGF dimer. The small size of ranibizumab allows for enhanced diffusion into the retina and choroid,[20,21]Figures 2 and 3 Intraocular injection of ranibizumab was linked to a significant increase in nonocular hemorrhagic events, including ecchymosis, gastrointestinal hemorrhages, hematoma, vaginal hemorrhages, and subdural hematomas

3.3. Aflibercept

Has a unique binding action and binds to both sides of the VEGF dimer, forming an inert 1:1 complex, also termed a VEGF trap. Aflibercept is the only drug in its class to bind to PIGF-2 (Placental growth factor) . Placental growth factor (PGF) is a protein-coding gene and a member of the vascular endothelial growth factor (VEGF) family. Another differentiating feature of aflibercept is that the binding affinity for VEGF is 0.5 pM Kd, which is considerably stronger than ranibizumab, bevacizumab, or native VEGF receptors. This allows for effective blocking of VEGF, even at low concentrations, which may translate into a longer duration of action and extended dosing intervals In clinical trials, VEGF Trap-Eye has been shown to be as effective in the treatment of neovascular AMD as other anti-VEGF therapies and possibly to have a longer duration of drug activity.

Although anti-VEGF treatments represent the mainstay of treatment, the progressive decline in their biological efficacy, as a result of tachyphylaxis, is quite concerning as they may only be beneficial on a short-term basis with no long term efficacy. Many studies reported that aflibercept was effective for non responders and patients having tachyphylaxis to ranibizumab. Aflibercept may treat SRD (serous retinal detachment) more efficiently in patients with DME compared to Ranibizumab with fewer injections. Figure 4 [21a, b] The most common adverse reactions (≥5%) reported in patients receiving Aflibercept were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure.

Conbercept is an anti-VEGF recombinant fusion protein that was approved in China in 2013. Like Aflibercept , Conbercept targets VEGF-A and -B and PLGF (placental growth factor). Preclinical studies have shown it has a greater affinity for binding to vascular endothelial growth factor than Ranibizumab . Two global Phase III trials in nAMD (neovascular AMD) started recruiting in the past year: PANDA-1 and PANDA-2. Each trial is evaluating 1,140 patients randomized to conbercept, 0.5 or 1 mg, or Aflibercept 2 mg,. Trial results may come in subsequent years[22]

3.4. New Anti VEGF agents

Abicipar pegol is a designed ankyrin repeat protein (DARPin) that binds to all forms of VEGF-A. (as shown in figure 4) As a member of this new class of binding

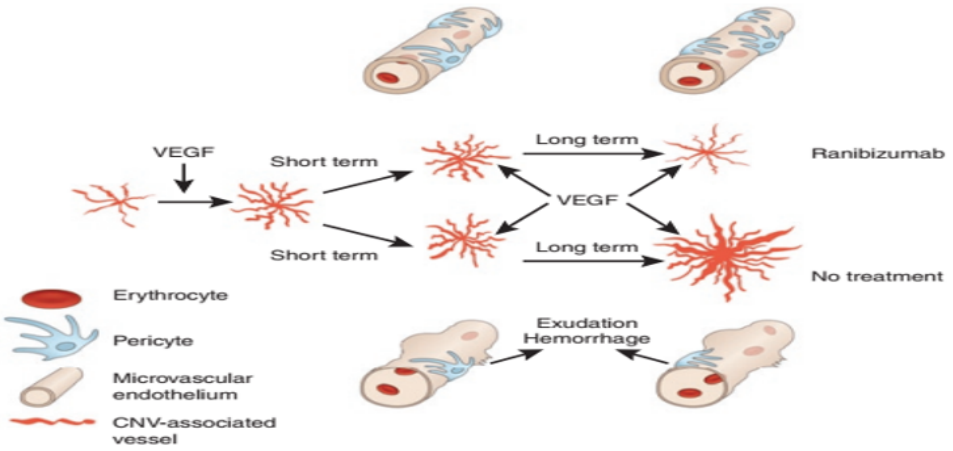

Fig. 2: Role of VEGF in AMD

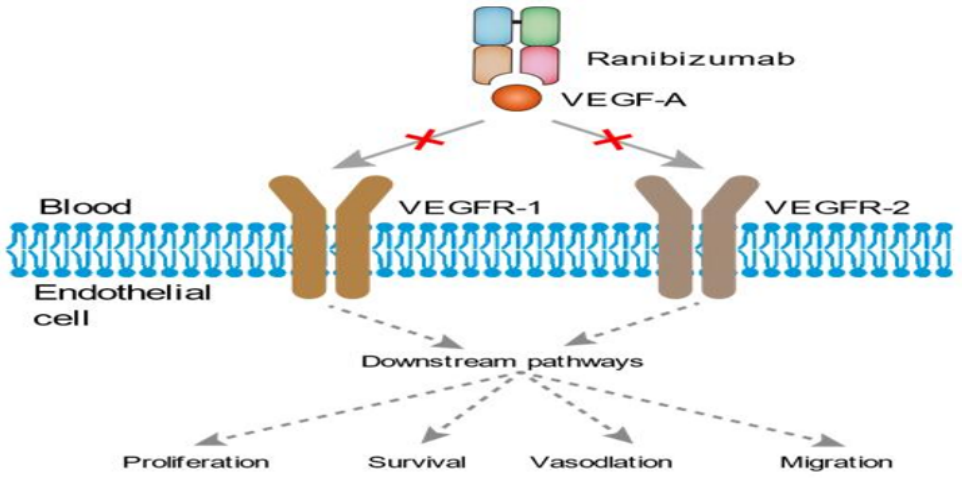

Fig. 3:

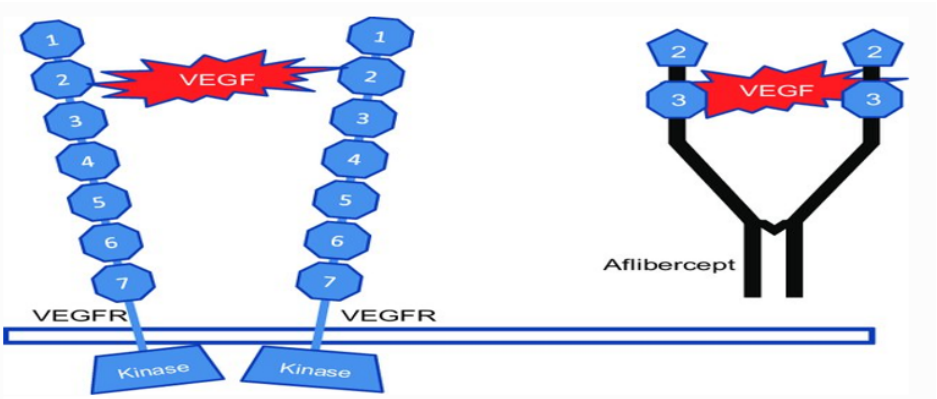

Fig. 4:

proteins, abicipar offers an alternative to antibody-based drugs for inhibition of VEGF. With an extended half-life of 6 to 7 days, abicipar may offer extended treatment intervals for patients with wet AMD. In CEDAR and Trials, researchers found that treatment every 8 or 12 weeks with abicipar was noninferior to monthly ranibizumab. Open-label MAPLE study was undertaken to explore whether a new manufacturing method could lower rates of ocular inflammation observed in the two phase 3 studies and subsequently found that the new formulation of abicipar was associated with a lower rate of intraocular inflammation.

KSI-301 binds to VEGF-A as the other primary anti-VEGF agents. What makes KSI-301 unique is the projected durability of this effect inside of the eye. The antibody biopolymer conjugate platform on which KS-301 is based has been engineered specifically for increased durability. It has two components, a specific anti-VEGF IgG1 antibody with an inert immune effector function that is covalently and stably linked to an intentionally high molecular weight, optically clear phosphorycholine biopolymer. Durability of KSI-301 in phase 1b trial was encouraging. The DAZZLE study, which will compare KSI-301 to aflibercept for the treatment of wet AMD.[23]

3.4.1. Pegatanib

Works as an antagonist to VEGF, which when injected into the eye blocks the actions of VEGF. This then reduces the growth of the blood vessels located within the eye and works to control the leakage and swelling. Clinical trials showed that pegaptanib stabilized vision and reduced the risk of severe visual loss in the majority of patients with AMD, with some patients showing visual improvement. Pegaptanib has maintained a good safety profile with only occasional adverse effects. Pegaptanib has since fallen out of favourafter other anti-VEGF agents demonstrated meaningful improvement in vision,[24]

3.5. Anti integrin

Risuteganib is a novel anti-integrin peptide targeting four different integrin heterodimers ($\alpha V\beta 3$, $\alpha V\beta 5$, $\alpha 5\beta 1$, and $\alpha M\beta 2$) involved in the pathogenesis of AMD and DME. Risuteganib helps reduce the cellular burden of oxidative stress and restores retinal homeostasis. Risuteganib is arginylglycylaspartic acid, small molecular-weight peptide that has a long retinal half-life of about 21 days . The drug demonstrated a good safety profile, with no drug-related serious adverse events. At 28 weeks, 48% of risuteganib patients gained eight or more letters of BCVA (Best corrected visual acuity) compared with 7.1% of patients in the sham cohort, a statistically significant difference (P = .013).[25]

3.5.1. Mammalian Target of Rapamycin (mTOR) Inhibitors

Although several mTOR inhibitors are undergoing clinical trials, the mTOR inhibitor everolimus is the only class of this drug undergoing a Phase II clinical trial related to its efficacy in neovascular AMD. Wet age-related macular degeneration refractory to aflibercept is usually responsive to systemic everolimus[26]

3.6. Drug Delivery Systems to extend patent process

3.6.1. Ranibizumab Port

The ranibizumab port delivery system is a refillable implant that is placed beneath the conjunctiva and is designed to provide sustained release of ranibizumab into the vitreous . The port delivery system has the potential to greatly reduce the burden of frequent injections. LADDER study is proposed to assess the safety and efficacy of ranibizumab delivered via the port delivery system compared to the standard of care intravitreal injections of ranibizumab.[27]

3.7. Angiopoietin neutralizer or Faricimab: structure shown below

Faricimab, the first bispecific antibody designed for intraocular use, simultaneously and independently binds and neutralizes angiopoietin 2 (Ang-2) (Tie 2 site) and vascular endothelial growth factor A (VEGF-A)., shown in Figure 5. It is suggested that Tie1 signalling promotes vascular integrity while Tie2 (Tyrosine protein kinase) is important in angiogenesis, particularly for vascular network formation. Patients on faricimab, whether treatment naïve or previously treated with anti-VEGF, were more likely to gain 10 letters or more in vision: 70.5 and 61.2 percent in the 6- and 1.5-mg faricimab groups, respectively, vs. 57.1 percent for the ranibizumab patients in the treatment-naïve group; and 65.2 percent in the faricimab 6-mg group vs. 42.9 percent of ranibizumab patients who had previous anti-VEGF treatment.[28]

3.7.1. Combined Therapy

PDT (Photodynamic therapy) in combination with anti-VEGF and steroids is currently used as a second-line therapy in patients not responding to monotherapy with anti-VEGF agents or in whom the treatment burden of monthly injections is too great. Combination therapy with anti-VEGF therapy and ionizing radiation offers another option to reduce treatment frequency. Radiation was never widely adopted because it did not provide a significant, reproducible effect on visual acuity, while difficulty delivering targeted doses led to complications in some patients.[29]

3.7.2. Platelet-derived growth factor inhibitors

Pegpleranib is a pegylated DNA aptamer that selectively binds to PDGF-BB and PDGF-AB homodimers and

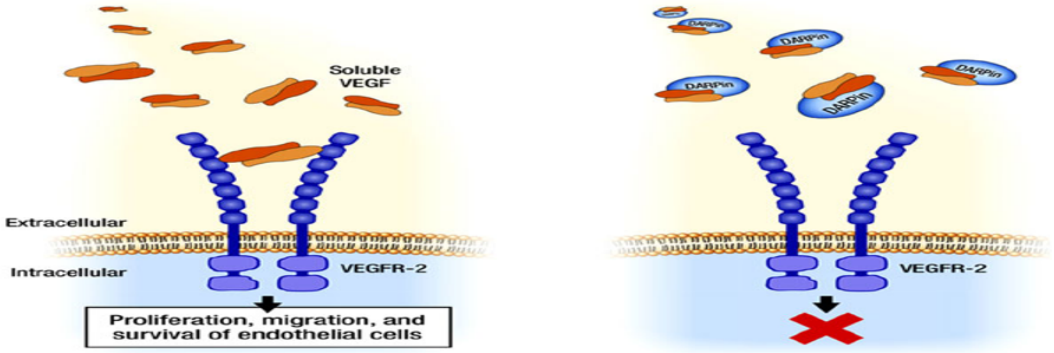

Fig. 5:

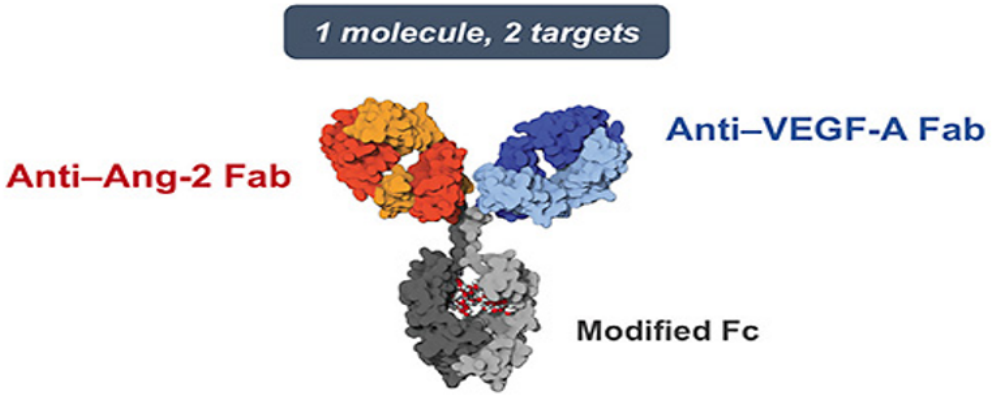

Fig. 6:

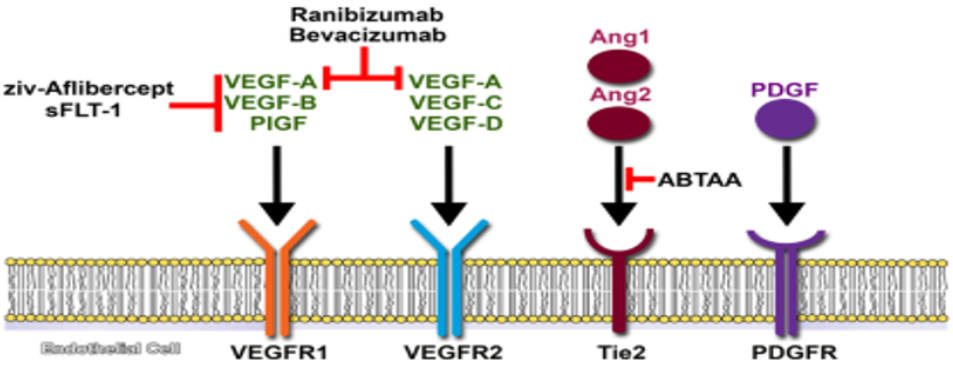

Fig. 7:

heterodimers, interrupting the interaction with their associated tyrosine kinase receptors. These receptors are commonly expressed on pericytes, which stabilize newly formed vessels. By disrupting the effect of PDGF on pericytes, the angiogenic process is negatively affected. In a phase 2B trial of 449 patients with neovascular AMD, pegpleranib in association with ranibizumab was compared with ranibizumab monotherapy. The study showed that the combination of pegpleranib 1.5 mg and ranibizumab 0.5 mg yielded a 62% relative benefit measured as Early Treatment Diabetic Retinopathy Study visual acuity over ranibizumab monotherapy.[30]

3.7.3. Use of steroids in AMD

Corticosteroids, such as dexamethasone, in combination with anti-VEGFs may be useful in treating frequent immune response reoccurrences and tachyphylaxis. In addition to the anti-inflammatory effects, corticosteroids can directly and indirectly reduce the permeability of choroidal endothelial cells and the outer blood retina barrier, inhibit the activation of matrix metalloproteinase, and suppress vascular endothelial growth factor (VEGF) . Dexamethasone is regarded as one of the most potent corticosteroid agents. Several reports have shown that dexamethasone can be combined with verteporfin photodynamic therapy (PDT) and anti-VEGF agents to treat CNV lesions from AMD. expression.

3.7.4. Daclizumab

A pilot prospective study evaluated the use of systemic daclizumab in four patients with neovascular AMD for 6 months. The results showed that daclizumab appeared to decrease the need for anti-VEGF intravitreal injections by approximately half.[31]

4. Conclusion

AMD is common across the world and the pathogenesis of this severe condition is not fully understood. Anti-VEGF therapies can slow the progression of wet AMD and in some cases improve vision. Multiple studies have proven bevacizumab to have comparable efficacy and safety to the registered anti-VEGF drugs, and there is also evidence that bevacizumab is the most costeffective drug for wet AMD Agents such as Ranibizumab and Aflibercep thave been well established as first-line therapies for Diabetic Macular Edema by the US FDA. Although used off-label, Bevacizumab has shown similar results and is also widely used.

5. Conflict of Interest

None.

6. Source of Funding

None.

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